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Dietary Fats, Cholesterol and Iron as Risk Factors for Parkinson's Disease

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Abstract

Background—Epidemiologic findings suggest that dietary components may contribute to the etiology of Parkinson's disease (PD). This population-based case-control study evaluated PD risk and dietary intake of fats, cholesterol and iron.

Methods—Newly diagnosed case (n = 420) and age/gender/ethnicity-matched unrelated controls (n = 560) were identified between 1992 and 2006 from the Group Health Cooperative health maintenance organization in western Washington State, and the University of Washington neurology clinic. In-person interviews elicited data on food frequency habits during most of adult life. Nutritional intakes were calculated and analyzed, with adjustments made for total energy intake (the 'nutrition density' technique).

Results—Cholesterol intake in the highest quartile compared with the lowest quartile was associated with a decreased risk of PD in men (odds ratio (OR)=0.53, 95% CI: 0.33, 0.86). The highest versus the lowest quartile of dietary iron increased PD risk in men (OR=1.82, 95% CI: 1.11, 2.99). When the lowest quartile of cholesterol and the highest quartile for iron were compared to the highest quartile of cholesterol and the lowest quartile of iron, no association was seen in women, but for men PD risk was increased (OR=2.70, 95% CI: 1.26, 5.76). Saturated fat intake below the median in combination with iron intake above the median also increased PD risk (OR=1.50, 95% CI: 1.07, 2.11) in both genders combined.

Conclusions—A low intake of cholesterol, particularly in the presence of high iron, may be associated with an increased risk for PD.

Introduction

Although the etiology of Parkinson's disease (PD) etiology is poorly understood, epidemiologic evidence suggests that dietary factors may contribute to the development of PD [1]. Dietary influences on PD risk may be mediated by oxidative stress, which can lead to dopaminergic cell loss. The cells in the substantia nigra are normally subject to a high degree of oxidative stress, due in part to the metabolism of dopamine and subsequent creation of hydroxyl radicals

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via the Fenton reaction [2]. Dietary intake of iron, a catalyst in the Fenton reaction, has been shown to increase PD risk either in association with animal fat [3], or alone [4,5]. Dietary fats, including cholesterol, have been associated with PD in some studies, and are thought to contribute to oxidative stress, but results have been conflicting [3-10]. Findings regarding PD risk related specifically to dietary cholesterol have indicated either no association [6,8,9], or an increased risk [4]. Elevated serum levels of cholesterol have recently been related to a decreased PD risk [11,12]. In a previously reported analysis from this study, saturated fat and total fat showed no association with PD risk, but individual fatty acids and cholesterol were not analyzed at that time [5]. Here, we examine levels of dietary fat and cholesterol as well as iron intake, and their associations with PD risk.

Methods

Study Subjects

Patients newly diagnosed with idiopathic PD were identified during 1992 through 2006 from clinics of Group Health Cooperative (GHC) in western Washington and the University of Washington (UW) Neurology clinic. Cases were identified from either neurologist referral at both institutions or from GHC outpatient diagnoses or prescriptions written for PD medications (e.g., levodopa) in the GHC pharmacy database. Prescriptions alert of a possible PD diagnosis. Medical records for cases not diagnosed by neurologists were reviewed by three neurologists among the authors (G.M.F., W.T.L, and P.D.S.) to verify PD diagnosis, indicated by the presence of at least two of the four cardinal signs of PD: bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment. Exclusion criteria for a primary diagnosis of PD were use of specific medications (e.g. phenothiazines, haloperidol, metoclopramide) during the 12 months preceding symptom onset; clinical, MRI, or CT evidence of multiple cerebrovascular events prior to PD symptom onset; evidence of another known cause of parkinsonism (e.g., history of brain tumor, encephalitis, normal-pressure hydrocephalus); or atypical PD presentation that may involve severe dementia, early marked autonomic disturbance (e.g., excessive sweating), corticospinal tract dysfunction signs (e.g., Babinski signs), or marked supranuclear palsy. Control subjects were GHC enrollees without histories of PD or other progressive neurologic disorders (e.g., Alzheimer's disease, Multiple Sclerosis), as determined from chart and subject interviews. Subjects with a score less than 24 on the Standardized Mini-Mental State Examination (SMMSE) [13], a brief cognitive screen to establish competence for providing accurate responses, were excluded from the study.

The control group was frequency-matched to cases in 10-year categories, gender, original year of GHC enrollment, and GHC clinic (representing a geographical area). Human Subjects committees at the GHC Center for Health Studies and the UW reviewed and approved the study. Case and control demographic characteristics are summarized in table 1. Of the 450 probable PD cases, 30 were excluded from the analysis. The proportion of cases participating was somewhat higher (73 percent) than for the controls (61 percent). Cases included 266 men and 154 women, median age 69 years. Controls included 351 men and 209 women, median age of 71 years. Both educational level and smoking were significantly different between cases and controls. Body Mass Index (BMI) was only available for the most recently enrolled 78 cases and 87 controls. No difference in BMI calculated from self-reported values at the time of the interview was found between cases (mean ($\bar{x}$) = 27.4 ± 4.4 (std)) and controls ($\bar{x}$ = 27.0 ± 4.9).

Data collection

A modified version of the Willet food frequency questionnaire (FFQ) was administered to assess dietary intake throughout most of adult life [14]. The FFQ version as of 1991 was used, but the portion sizes were modified to match the Nutritionist Pro database (Version 1.1 2001,

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First Databank, Inc., San Bruno, CA) for nutrient content analysis. The interviewer asked for eating habits "during your life" before each food list in order to determine past dietary habits. The same nurse practitioner (JP) administered the FFQ in person to all subjects. A set script was used in asking the questions to avoid any bias in the answers between subjects. The questionnaire also elicited information on demographic variables, medical history, and lifestyle factors, including smoking. Subjects were first presented with an informed consent form, and then the questionnaire and the SMMSE.

Data analysis

Nutrient content of each food was obtained from the program Nutritionist Pro, from which kilocalories (Kcal) per day were determined. We focused the analysis on fats (total, saturated, and unsaturated), cholesterol, and iron. The sum of each nutrient from each food was calculated to determine the total nutrient/day value. Every nutrient was divided by the Kcal for each person to obtain variables representing nutrient/day/Kcal [14]. The Kcal values for case ($\bar{x}$=2007 ±557 std) and control ($\bar{x}$=2051 ±614 std) subjects were similar. We defined nutrient quartiles based on the distributions of the control group, assuming the controls' values are representative of the source population.

Logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) associated with each level of intake for each nutrient by gender. Joint effects of saturated fat and iron, as well as cholesterol and iron were calculated with dichotomous variables constructed based on the median of each nutrient among controls. The lowest and highest quartiles of iron and saturated fat in addition to the lowest and highest quartile of iron and cholesterol were also compared to assess joint effects. Adjustments for age, gender, education (≤12 or >12 years), ethnicity (non-Hispanic white or other), caffeine, alcohol, Kcals, and pack-years of smoking were included in the model. For trend tests, quartile categories of each nutrient were assigned scores of 1, 2, 3 or 4 and entered into each equation as a linear term. The p-value from the Wald statistic for this linear term was used as a test for linear trend in OR. Analysis was conducted using SPSS statistical software version 12.0 2000 (Chicago, IL). Significance was set at $p < 0.05$, two-tailed. The crude and adjusted ORs were similar; therefore, only adjusted results are shown. Due to the largely exploratory nature of associations with diet in this study, we did not make corrections for multiple comparisons.

The quartile and median cut-points used in this analysis are based on the nutrient weight/day/Kcal intake for each person. These quartile values need to be described based on a fixed number of Kcal in order to obtain a mg quantity for each nutrient. The numbers in the tables are given only as a guide as they are specifically for a 2000 Kcal/day diet, and energy intakes differ from person to person.

Results

The relations between PD and fats and cholesterol are shown in table 2. Total fat, saturated fat, and the other fatty acids listed (monounsaturated, polyunsaturated, oleic acid, linoleic acid, linolenic acid, eicosapentaenoic acid and docosahexaenoic acid) showed no consistent associations with PD. Cholesterol intake in the highest quartile compared with the lowest quartile was associated with a decreased risk of PD in men (OR=0.53, 95% CI: 0.33, 0.86), trend p=0.007 but not in women (OR=1.13, 95% CI: 0.59, 2.19), trend p=0.819.

An increased risk from dietary iron intake, exhibiting a dose-response gradient was found in men (OR highest quartile=1.82, 95% CI: 1.11, 2.99), trend p=0.013, but not in women (OR highest quartile=1.12, 95% CI: 0.59, 2.12), trend p=0.314 (table 3). We also performed an analysis of dietary iron intake stratified on intake of multivitamins or iron supplements (<1/day vs. ≥1/day). The reference group was defined as persons with iron intake below the median

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of controls and <1/day multivitamin or iron supplement intake. Compared with this reference group, we found PD risk increased (OR=1.46, 95% CI: 0.99, 2.15), for above-median dietary iron intake in subjects with <1/day multivitamin or iron supplement. There was only a weak association for ≥1/day multivitamin or iron supplement in persons with below-median iron intake (OR=1.26, 95% CI: 0.85, 1.87), which was similar to those with ≥1/day multivitamin or iron supplement and above-median dietary iron intake (OR=1.17, 95% CI: 0.82, 1.67).

Joint effects of dietary saturated fat and iron, as well as cholesterol and iron are shown in table 4. Because saturated fat intake tended to decrease PD risk and iron intake increased PD risk, the reference group used was high saturated fat (above the median) and low iron (below the median). Using this reference combination, a modest increase in PD risk was seen for the combination of low saturated fat and high iron intake (OR=1.50, 95% CI: 1.07, 2.11) for all subjects combined. A non-significant increased PD risk was observed for low saturated fat and high iron when men and women where analyzed separately. Joint effects of cholesterol and iron were analyzed using a reference group of high cholesterol (above the median) and low iron (below the median). Increase in the risk for PD risk was observed in the low cholesterol, and high iron combination, but the association was stronger in men (OR=1.96, 95% CI: 1.25, 3.06) than in women (OR=1.35, 95% CI: 0.75, 2.44).

In order to compare quartile distributions, a reference group combining the highest quartile of saturated fat and the lowest quartile of iron was defined. Compared to this reference, the lowest saturated fat and the highest iron showed a modest increase in PD risk for both genders combined (OR=1.41, 95% CI: 0.81, 2.47), with the risk slightly higher in men (OR=1.60, 95% CI: 0.79, 3.22) than in women (OR=1.10, 95% CI: 0.42, 2.93). Using this quartile stratification with cholesterol, the risk of PD from the lowest cholesterol in combination with the highest iron increased in men (OR=2.70, 95% CI: 1.26, 5.76) but not in women (OR=0.70, 95% CI: 0.25, 1.91).

Discussion

We observed a moderately reduced PD risk associated with the highest levels of dietary cholesterol intake, although this association was limited to men. The highest levels of iron intake were found to increase PD risk in men, but not in women. When combining low dietary cholesterol and high dietary iron, the risk was even greater than each factor alone, although this association was also limited to men. In addition, the combination of low saturated fats and high iron conferred moderate PD risk elevations in men and women combined, although effects were considerably stronger in men.

The nutritional values obtained from this analysis are within normal limits. The upper quartile of iron for this population (>15.7 mg for a 2000 Kcal/day diet) is within a normal range, as the recommended intake for iron is 8 mg/day for adults over 50 years of age and the Tolerable Upper Intake Level (UL) is 45 mg/day for age 14 and over [15]. The median for total fat (69g, or 31% of total Kcal/day for a 2000 Kcal/day diet) is also within the Acceptable Macronutrient Distribution Range (AMDR) for adults of 20–35 % of total Kcal total fat [16]. Since the body can synthesize cholesterol, no recommended intake is determined [16].

In contrast to our findings, PD and diet have demonstrated an increased risk of PD from cholesterol [4] or no association [6,8,9]. Of interest though is that eggs, which are high in cholesterol, were observed to decrease PD risk in one study from Sweden [17]. The lack of association between PD and saturated fat in our study is in agreement with others [6,9], although an increase in PD risk has also been found from saturated fat intake [4,8]. The increased risk for PD from dietary iron found here agrees with our previous findings [5] as well as with findings from studies in New York [3] and Michigan [4]. The study in New York also found

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that the iron effect disappeared when animal fat was considered [3], indicating that PD risk from iron was reduced with higher levels of animal fat. This also agrees with our observation of a lower risk of PD from high iron with high levels of saturated fat. The different associations that we observed in men and women are difficult to explain, but a previous study by de Lau [11] has also shown gender-specific associations; a reduced PD risk from serum cholesterol was found only in women.

Iron catalyzes the Fenton reaction converting hydrogen peroxide (H_2O_2) to the highly reactive hydroxyl radical. Oxidative stress is thought to occur in idiopathic PD as part of a cascade of events involved in dopaminergic cell death [2]. An increase in oxidative stress from the Fenton reaction is coherent mechanistically with the increased risk seen from elevated iron intake. Cholesterol as a protective factor for PD has recently been suggested from a large study in Rotterdam, where it was found that higher levels of serum total cholesterol lowered the risk of PD, although this was restricted to women [11]. Another recent cohort study found a modest decreased PD risk with increasing serum cholesterol levels for men and women [18]. It has also been reported that the best predictor of the potent anti-oxidant coenzyme Q_{10} (CoQ_{10}) in serum is serum cholesterol [19]. Thus, elevated cholesterol per se may not reduce risk, but instead may be a marker of CoQ10. Cholesterol and CoQ10 share a common pathway for synthesis [20]; and increasing cholesterol may have feedback on the production of CoQ_{10}, either increasing or decreasing synthesis. Higher levels of CoQ_{10} might be beneficial by reducing oxidative stress due to H_2O_2 generated by dopamine metabolism [21]. CoQ_{10} as a therapeutic agent for PD is also under current investigation [22]. Cholesterol may have direct neuroprotective effects due to its requirement for cell membrane structure and function, and its role in myelin synthesis [23]. Cholesterol has also been found to induce the formation of synapses in cultured neurons by as much as seven times [24]. Although cholesterol is the brain is mostly from in situ synthesis and not transported from the circulation [23], it is still possible that plasma cholesterol may have some effect on brain cholesterol production or metabolism as cholesterol and lipid transport are complex. Cholesterol turnover in the brain is increased in neurodegenerative disorders, and large amounts of cholesterol turn over among both glial cells and neurons in the central nervous system during neuron repair and remodeling [25].

Possible relations between PD and oxidative stress and lipid peroxidation [4] led us to investigate various fatty acids, but our null results for fatty acids do not support these mechanistic hypotheses.

A limitation of this study is the reliance upon questionnaires, administered later in life, to elicit dietary habits throughout adult life, as there is potential for bias towards current dietary habits. This limitation is common to case-control studies of diet and has been addressed by validating the FFQ for periods as long as 20 years [26], and 24 years [27]. There is controversy regarding the period of life over which PD develops [28]. For this reason, we elicited data regarding typical dietary habits during most of adult life. The difference in time between PD onset and diagnosis should therefore be less problematic when dietary habits are considered over a wide time frame of adult life. An additional limitation of this study, as well as other retrospective studies of PD, is distinguishing the temporal relation between dietary habits and disease onset. Food choices may change due to the early manifestations of PD, possibly due to dopamine depletion [29]. Because of this, failure to take into account the temporal relations between changes in dietary habits and PD onset symptoms can be a source of bias. Our non-significant finding for iron intake in women may be due to a difference in iron status between men and women, which we could not investigate because serum iron levels were not available. In addition, BMI would also be most accurate if it had been measured rather than self reported. Our finding of no detectable difference in BMI between PD cases and controls is not in agreement with others who have found PD cases to lose weight of about 5 pounds on average in the 10 years before diagnosis [30], although our sample of subjects with BMI data is small.

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An important strength of our study is the identification of a large number of incident rather than prevalent PD cases. Prevalent cases, used in most other epidemiologic studies, can introduce bias if the exposures of interest are related to the progression of the disease. In addition, our subjects were selected from a well-defined population, in an institution providing medical care to approximately 400,000 people in western Washington State.

Our finding of an increased risk of PD from a dietary intake of low cholesterol in the presence of high iron may be part of the chain of events leading to death of dopaminergic neurons. It is possible that increased cholesterol intake may increase either the level of cholesterol in the brain, or the level of the antioxidant CoQ_{10}. Cholesterol and iron may have different mechanisms in relation to PD pathogenesis, and thus their effects would be expected to be independent. Other corroborative studies of PD risk related to dietary intakes of cholesterol and iron would add support to our observed associations. Public health recommendations arising from this and future research on dietary fats and PD need to be developed with careful consideration given to prevention of prevalent conditions, such as cardiovascular disease.

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Table 1

Demographic characteristics of Parkinson's disease cases and controls

Characteristic	Cases (N=420)	Controls (N=560)
Gender, %		
Men	63.3	62.7
Women	36.7	37.3
Age, median (range) *	69 (29-88)	71 (38-87)
Ethnicity, %		
Non-Hispanic Caucasian	93.3	92.5
Other	6.7	7.5
Education, % *		
Some College or more	85.2	79.5
High School or less	14.8	20.5
Pack-years of Smoking, % *		
0	56.4	42.7
>0-19	24.5	25.0
20-39	10.2	18.0
>40	8.8	14.3

* Significantly different between cases and controls

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Table 2

Associations of Parkinson's disease with lipids (fat and cholesterol)

Nutrient Quartiles	g/day/2000Kcal	Men				Women			
		Cases n=266	Controls n=351	OR*	95%CI*	Cases n=154	Controls n=209	OR*	95%CI*
Total Fat									
1	0-60.8	85	80	1.0	---	48	60	1.0	---
2	60.8-69.2	62	84	0.76	0.48, 1.22	36	56	0.77	0.42, 1.39
3	69.2-77.9	54	95	0.62	0.39, 1.00	33	45	0.91	0.50, 1.66
4	> 77.9	65	92	0.81	0.51, 1.29	37	48	1.03	0.57, 1.87
p for trend					0.269				0.855
Saturated Fat									
1	0-19.9	75	87	1.0	---	46	53	1.0	---
2	19.9-23.7	69	95	0.88	0.56, 1.39	36	45	0.87	0.47, 1.62
3	23.7-27.5	61	77	0.99	0.61, 1.59	37	63	0.66	0.37, 1.18
4	> 27.5	61	92	0.82	0.51, 1.31	35	48	0.81	0.44, 1.50
p for trend					0.511				0.313
Monounsaturated Fat									
1	0-22.2	87	77	1.0	---	44	63	1.0	---
2	22.2-26.0	59	87	0.66	0.41, 1.05	44	53	1.21	0.67, 2.15
3	26.0-30.0	55	95	0.63	0.39, 1.01	29	45	0.94	0.50, 1.74
4	> 30.0	65	92	0.74	0.46, 1.17	37	48	1.23	0.67, 2.25
p for trend					0.187				0.694
Polyunsaturated Fat									
1	0-9.8	77	75	1.0	---	35	65	1.0	---
2	9.8-12.3	70	92	0.94	0.59, 1.49	52	48	2.14	1.19, 3.85
3	12.3-15.1	54	94	0.70	0.43, 1.13	23	46	1.03	0.52, 2.01
4	> 15.1	65	90	0.91	0.56, 1.46	44	50	1.92	1.04, 3.52
p for trend					0.462				0.179
Oleic Acid									
1	0-20.2	80	79	1.0	---	44	61	1.0	---
2	20.2-24.2	74	89	0.92	0.58, 1.45	43	51	1.14	0.64, 2.04
3	24.2-27.8	47	90	0.61	0.37, 1.00	27	50	0.77	0.41, 1.45

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Nutrient Quartiles	g/day/2000Kcal	Men				Women			
		Cases n=266	Controls n=351	OR*	95%CI*	Cases n=154	Controls n=209	OR*	95%CI*
4	> 27.8	65	93	0.85	0.53, 1.35	40	47	1.31	0.72, 2.37
p for trend					0.252				0.659
Linoleic Acid									
1	0-8.3	77	76	1.0	---	37	64	1.0	---
2	8.3-10.7	73	93	0.94	0.59, 1.49	50	47	1.85	1.03, 3.32
3	10.7-13.7	55	91	0.72	0.44, 1.17	25	49	0.96	0.50, 1.85
4	> 13.7	61	91	0.84	0.52, 1.35	42	49	1.67	0.91, 3.06
p for trend					0.310				0.318
Linolenic Acid									
1	0-9.1	90	85	1.0	---	38	55	1.0	---
2	9.1-1.0	67	95	0.72	0.46, 1.14	39	45	1.52	0.81, 2.85
3	1.0-1.1	54	84	0.71	0.44, 1.14	36	56	1.04	0.56, 1.95
4	> 1.1	55	87	0.75	0.47, 1.21	41	53	1.23	0.66, 2.28
p for trend					0.234				0.796
Eicosapentaenoic Acid (EPA)									
1	0-0.05	47	87	1.0	---	37	53	1.0	---
2	0.05-0.08	77	89	1.59	0.97, 2.59	37	51	1.02	0.54, 1.90
3	0.08-0.11	66	84	1.39	0.84, 2.30	38	56	0.84	0.46, 1.55
4	> 0.11	76	91	1.34	0.81, 2.20	42	49	1.30	0.70, 2.43
p for trend					0.440				0.563
Docosahexaenoic Acid (DHA)									
1	0-0.08	54	89	1.0	---	36	51	1.0	---
2	0.08-0.12	75	81	1.46	0.90, 2.35	37	59	0.88	0.47, 1.64
3	0.12-0.17	67	89	1.16	0.71, 1.88	42	51	1.07	0.58, 1.98
4	> 0.17	70	92	1.05	0.65, 1.72	39	48	1.25	0.66, 2.37
p for trend					0.872				0.407
Cholesterol (mg/day/2000Kcal)									
1	0-192	80	76	1.0	---	52	64	1.0	---
2	192-243	63	75	0.84	0.52, 1.35	43	65	0.88	0.50, 1.53

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Nutrient Quartiles	g/day/2000Kcal	Men				Women			
		Cases n=266	Controls n=351	OR*	95%CI*	Cases n=154	Controls n=209	OR*	95%CI*
3	243-312	66	93	0.70	0.44, 1.10	31	47	0.90	0.49, 1.66
4	> 312	57	107	0.53	0.33, 0.86	28	33	1.13	0.59, 2.19
p for trend					0.007				0.819

* odds ratio (OR) adjusted for age, education, ethnicity, caffeine, alcohol, Kcal and smoking Variables are adjusted for total energy intake (weight/day/Kcal).

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Table 3

Associations of Parkinson's disease with iron from food by gender

Iron Quartiles	mg/day/2000Kcal	Men				Women			
		Cases n=266	Controls n=351	OR*	95%CI*	Cases n=154	Controls n=209	OR*	95%CI*
1	0 - 11.9	49	86	1.0	---	35	54	1.0	---
2	11.9-13.9	60	83	1.23	0.74, 2.04	34	57	0.81	0.44, 1.52
3	13.9-15.7	72	96	1.47	0.90, 2.42	48	44	1.56	0.84, 2.91
4	> 15.7	85	86	1.82	1.11, 2.99	37	54	1.12	0.59, 2.12
p for trend					0.013				0.314

*odds ratio (OR) adjusted for age, education, ethnicity, caffeine, alcohol, Kcal and smoking Iron is adjusted for total energy intake (weight/day/Kcal).

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Table 4

Joint effects of saturated fat and cholesterol with iron from food by gender

Nutrient Split at median		All subjects				Men				Women			
		Cases n=420	Controls n=560	OR*	95%CI*	Cases n=266	Controls n=351	OR*	95%CI*	Cases n=154	Controls n=209	OR*	95%CI*
High SatFat, Low Fe		109	169	1.0	---	64	96	1.0	---	45	73	1.0	---
Low SatFat, Low Fe		69	111	0.92	0.62, 1.37	45	73	0.86	0.52, 1.43	24	38	1.00	0.52, 1.93
High SatFat, High Fe		85	111	1.28	0.87, 1.88	58	73	1.30	0.80, 2.12	27	38	1.22	0.64, 2.33
Low SatFat, High Fe		157	169	1.50	1.07, 2.11	99	109	1.43	0.91, 2.24	58	60	1.66	0.96, 2.85
High Cholest, Low Fe		96	159	1.0	---	64	108	1.0	---	32	51	1.0	---
Low Cholest, Low Fe		82	121	1.10	0.74, 1.64	45	61	1.26	0.75, 2.12	37	60	0.95	0.51, 1.79
High Cholest, High Fe		86	121	1.33	0.90, 1.96	59	92	1.25	0.78, 1.99	27	29	1.71	0.83, 3.51
Low Cholest, High Fe		156	159	1.65	1.16, 2.35	98	90	1.96	1.25, 3.06	58	69	1.35	0.75, 2.44
Quartiles: Comparison of the lowest and highest quartiles													
SatFat	Fe												
High	Low	36	62	1.0	---	23	45	1.0	---	13	17	1.0	---
Middle	Middle	326	426	1.34	0.86, 2.11	206	260	1.60	0.92, 2.80	120	166	0.90	0.40, 1.99
Low	High	58	72	1.41	0.81, 2.47	37	46	1.60	0.79, 3.22	21	26	1.10	0.42, 2.93
Cholest	Fe												
High	Low	33	56	1.0	---	19	41	1.0	---	14	15	1.0	---
Middle	Middle	331	452	1.18	0.74, 1.89	207	281	1.53	0.85, 2.77	124	171	0.72	0.32, 1.60
Low	High	56	52	1.63	0.90, 2.95	40	29	2.70	1.26, 5.76	16	23	0.70	0.25, 1.91

* odds ratio (OR) adjusted for age, education, ethnicity, caffeine, alcohol, Kcal and smoking (and gender for all subjects combined) Variables are adjusted for total energy intake (weight/day/Kcal). Median cut-points based on the nutrient weight/day/Kcal intake for each person need to be described based on a fixed number of Kcal in order to obtain a mg quantity for each nutrient. For an individual with a 2000Kcal/day diet the median for iron is 13.9 mg, the median for saturated fat is 23.7 g, and the median for cholesterol is 243 mg. Quartile cut-points are listed in tables 2 and 3.