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Dietary Fat Intake, Pesticide Use, and Parkinson's Disease

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Abstract

Background—Dietary fat intake may modify Parkinson's disease (PD) risk directly or by altering the response to environmental neurotoxicants including pesticides.

Methods—We conducted a case-control study of PD nested in the Agricultural Health Study (AHS), a cohort of pesticide applicators and spouses. We evaluated diet and pesticide use before diagnosis in 89 PD cases, confirmed by movement disorder specialists, or a corresponding date in 336 frequency-matched controls. Associations were evaluated using multivariate logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results—In the AHS, PD was inversely associated with N-3 polyunsaturated fatty acids (PUFAs) (OR 0.4,95% CI 0.2-0.8 for highest vs lowest tertile) and the N-3 precursor α-linolenic acid (0.4, 0.2-0.8). In a meta-analysis of nine studies, including the present one, PD was inversely associated with α-linolenic acid (0.81, 0.68-0.96). In the AHS, associations of PD with the pesticides paraquat and rotenone were modified by fat intake. The OR for paraquat was 4.2

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(1.5-12) in individuals with PUFA intake below the median but 1.2 (0.4-3.4) in those with higher intake (p-interaction=0.10). The OR for rotenone was 5.8 (2.3-15) in those with saturated fat intake above the median but 1.5 (0.5-4.2) in those with lower intake p-interaction=0.02).

Conclusions—PUFA intake was consistently associated with lower PD risk, and dietary fats modified the association of PD risk with pesticide exposure. If confirmed, these findings suggest that a diet high in PUFAs and low in saturated fats might reduce risk of PD.

Keywords

Parkinson's disease; dietary fat; polyunsaturated fatty acids; pesticides

INTRODUCTION

Dietary fat may modify PD risk directly or by altering the response to environmental neurotoxicants including pesticides. Epidemiological studies of the relationship of dietary fat to Parkinson's disease (PD) have however been inconsistent, with some suggesting that increased fat intake is associated with PD risk [1,2] while others have reported no or even an inverse association [3-10]. Some inconsistencies may be explained by differences in study design or the type of fat considered. In addition, study populations may vary in genetic susceptibility, other aspects of diet, lifestyle characteristics, or exposure to environmental neurotoxicants, any of which could modify the response to dietary fat. Experimental animal models have provided similarly inconsistent results concerning the relationship of PD to dietary fat, although there is a growing consensus that N-3 polyunsaturated fatty acids (PUFAs) may be protective [11].

Mechanisms potentially involved in both PD pathophysiology and pesticide neurotoxicity include oxidative stress and neuroinflammation [12]. Dietary fat may also affect these mechanisms: saturated fats increase oxidative stress [13], while PUFAs may attenuate the inflammatory response [11]. The brain is enriched in PUFAs, and accumulating evidence suggests that the anti-inflammatory effects of N-3 PUFAs underlie their protective effects on neurodegeneration [11].

The Agricultural Health Study (AHS) is a prospective cohort study of licensed pesticide applicators and their spouses. In a case-control study nested in the AHS we found that PD risk was associated with the pesticides paraquat and rotenone [14]. In the present study we used data from the same study to investigate the association of PD with dietary fat intake. Because dietary fat and pesticides may affect common cellular mechanisms, we also evaluated associations of PD with paraquat or rotenone in individuals with high or low dietary fat intake.

METHODS

Study population

Recruitment of study participants has been described previously [14]. In brief, the Farming and Movement Evaluation (FAME) study is a case-control study of PD nested in the AHS, a prospective cohort that includes licensed private pesticide applicators and the spouses of married applicators, recruited in Iowa or North Carolina in 1993 to 1997. Suspect PD cases were identified by self-report or from state mortality files. Potential controls randomly selected from the cohort were frequency-matched to cases (3:1) by age, gender, and state. During home visits, neurologists examined living suspect cases and 5% of controls, and neurologist-trained technicians examined the remaining controls. Case status based on established criteria for PD [15] was determined by agreement of two movement disorder

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specialists using information from medical records, the in-home examination, and a videotaped movement evaluation conducted during the home visit. FAME included 115 confirmed PD cases and 383 controls. The analyses reported here are based on the 89 cases and 336 controls who provided diet information. Within the subset with diet data, the ratio of controls to cases was approximately 4:1; more cases than controls lacked diet data because we did not collect this information from proxies. The 73 individuals (26 cases and 47 controls) without diet information were similar to the 425 included in the analysis in terms of age, gender, and smoking, but more individuals from North Carolina than Iowa lacked diet data.

FAME was approved by institutional review boards for the Parkinson's Institute, NIH, Social and Scientific Systems, Inc, the University of Iowa, and Battelle, Inc. All participants provided written informed consent.

Exposure assessment

Exposures were evaluated with respect to a reference age; the reference age for cases was the age at PD diagnosis, and the reference age for controls was the mean age of PD diagnosis for cases within the corresponding age-gender-state stratum. Food intake was assessed using the Diet History Questionnaire version I, a self-administered 144-item food frequency questionnaire developed by the National Cancer Institute (http://riskfactor.cancer.gov/DHQ/). Participants reported frequency of consumption and portion size for each food consumed during a 12 month period occurring ten years before their reference age. Total energy and dietary fats were estimated using Diet*Calc software version 1.4.3. Occupational exposure to paraquat and rotenone was assessed using structured telephone interviews. We collected a complete occupational history and asked about pesticide use in each farm job from 14 years of age onward. Pesticide use falling outside U.S. Environmental Protection Agency (EPA) approval dates was not included. Only pesticide exposures occurring before the reference age were evaluated. Information on cigarette smoking and education was also collected in the interviews. Information on height and weight at age 40 was collected during the home visit and used to calculate body mass index.

Statistical analysis

We evaluated the relationship of dietary fat to PD using multivariate logistic regression in SAS 9.2 (Cary, NC) to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Daily intakes of total fat, saturated fat, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), and individual PUFAs were expressed as a percentage of total energy (nutrient density) [16] and then categorized in tertiles based on distributions in the control group; the lowest tertile was used as the referent group. The matching variables reference age (40-57, 58-65, 66-87), gender, and state (Iowa or North Carolina) were included in all models. Models also included ever smoking (100 lifetime cigarettes), which is inversely associated with PD, and total energy intake (kilocalories per day, including carbohydrate, fat, protein, and alcohol), because a negative energy balance is a feature of PD [17] and therefore adjustment for total energy is recommended [16].

We conducted additional analyses to determine whether dietary fat intake altered the association of pesticide exposure with PD. Fat variables were dichotomized (high intake, low intake) based on the median of the control group, and pesticide exposure was dichotomized (no, yes) based on ever use in any farm job. We then created a four level fat–pesticide variable (high fat–no pesticide, high fat–yes pesticide, low fat–no pesticide, and low fat–yes pesticide), using the high fat–no pesticide group, assumed to have the lowest risk, as the referent group. We calculated a p-value for interaction from models including the

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fat and pesticide variables and their product; we used p≤0.10 as a cutoff for this hypothesis generating study. Analyses were restricted to men for paraquat, because no women used this chemical, but analyses for rotenone included both men and women.

Meta-analysis

We conducted a meta-analysis of dietary fat intake and PD risk. We searched MEDLINE using one of the MeSH terms dietary fats, fatty acids, essential nutrients, N-3, or N-6 together with *Parkinson disease* or *parkinsonism*. Studies were included if ORs, hazard ratios, or relative risks (RRs) were reported. We excluded two papers [1,2] because only animal fat was reported. Thus, our meta-analytic data comprised eight published studies (Supplemental Table 1) plus the present study.

We calculated pooled estimates for each dietary fat category using STATA 11.2. Since PD is a rare disease, and the number of available studies was small, we pooled OR and RR estimates. In all studies, diet information was ascertained from food frequency questionnaires; recall periods varied from 24 hours to lifetime. In most studies, dietary fat variables were treated as categorical variables. The one exception [7] used continuous variables to estimate increased risk per standard deviation of fat intake. We generated pooled estimates using effect measures comparing the highest fat category with the lowest together with the continuous variable used by de Lau et al [7]. We examined heterogeneity across reported effect measures using Cochran's Q statistic. Because this test indicated that effect size was homogeneous, we report results from fixed rather than random effect models.

RESULTS

The study population consisted of 89 cases and 336 controls, with a mean age of 68 years in cases and 69 in controls. Cases and controls were well-matched for age, gender, and state (Table 1). As expected, cases were less likely to smoke than controls. The mean body mass index (BMI) at age 40 was 25 kg/m^2 for both case and control groups. Mean total energy intake was slightly greater in cases than controls (2394 kcal/d for and 2197 kcal/d, respectively) but not statistically different. Overall fat consumption of FAME participants was similar to that of the US population evaluated in NHANES (Supplemental Table 2) [18].

After adjustment for age, gender, state, smoking, and total energy, intake of all types of fat was inversely associated with PD (Table 2). Associations were stronger for PUFAs as a group and for subtypes of PUFAs, and associations and dose-response trends were statistically significant for N-3 PUFAs as a group and for α-linolenic acid. Results were similar for men and women (Supplemental Table 3), for cases with median time from diagnosis to enrollment in FAME below or above the median (Supplemental Table 4), and when individuals with Cognitive Abilities Screening Instrument (CASI) scores ≤80 were excluded (Supplemental Table 5).

Our meta-analysis included eight published studies (Supplemental Table 1) plus the present study. Two studies presented data for men and women separately [6,9]; we included both sets of data in the meta-analysis. High fat intake was inversely associated with PD for all six fat categories (Table 3). The inverse association was strongest for α-linolenic acid and weakest for saturated fat. Most studies collected diet information for a period before diagnosis (Supplemental Table 1). After excluding three case-control studies which collected diet information for a period up to or after diagnosis [4,9,10] the inverse associations of PD with dietary fat were stronger (Supplemental Table 6).

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Dietary fats modified associations of PD with paraquat and rotenone (Table 4). For both pesticides, associations with PD were stronger in those with high intake of saturated fat, although the interaction was statistically significant only for rotenone (p=0.02); a similar although less pronounced interaction was evident for total fat and MUFAs for rotenone but not for paraquat. In contrast, for both pesticides associations with PD were stronger in those with low intake of grouped PUFAs and PUFA subtypes; for paraquat, the interactions for PUFAs, N-6 PUFAs, and linoleic acid were significant (p≤0.10). Results for dietary fats and rotenone were similar for men alone (data not shown).

DISCUSSION

Our results indicate that PD is inversely associated with higher intake of dietary fats, particularly PUFAs. Notably, associations of PD with N-3 PUFAs were stronger than those with other fat types and were also statistically significant. Dietary fat also modified associations of PD with pesticide use; high levels of PUFA intake attenuated the association of PD with paraquat, while high levels of saturated fat intake intensified the association of PD with both paraquat and rotenone. These findings are consistent with the hypothesis that oxidative stress and neuroinflammation play a role in PD pathophysiology [12].

Previous reports of the relationship of PD to dietary fat have not been consistent. Two early studies suggested that higher intake of saturated fat or fat from animal sources might increase risk of PD [1,2], but more recent studies have generally not supported these findings. Four prospective cohort studies reported decreased risk of PD associated with fat intake [5-8]. Results of case-control studies were more variable, with some showing an inverse and others a positive association [3,4,9,10]. Despite differences among studies, which may reflect differences in populations or study design, our meta-analysis found an inverse association of PD with dietary fats, particularly α-linolenic acid, an N-3 PUFA.

Experimental studies have also investigated effects of dietary fat in animal models of PD. Docosahexaenoic acid, a 22-carbon N-3 PUFA, protected mice against motor impairments and memory deficits following treatment with MPTP [19], and a diet high in N-3 PUFAs prevented MPTP-induced decreases in tyrosine hydroxylase labeled cells and in dopamine transporter and *Nurr1* mRNA levels [20]. Some experimental evidence, however, indicates that higher fat intake may increase PD risk. A high fat diet leading to insulin resistance in rats impaired nigrostriatal dopamine function [21], and a similar diet causing obesity in mice increased vulnerability of dopamine neurons to MPTP [22]. High fat diets may increase vulnerability to PD by contributing to obesity or insulin resistance, which may in turn increase PD risk [23], potentially explaining previous epidemiologic findings that animal and saturated fat were associated with an increase in PD risk [1,2]. Other processes may also mediate effects of dietary fats on PD risk. PUFAs bind α-synuclein and may promote its oligomerization to a putatively more toxic form, but this phenomenon has been observed chiefly using free PUFAs in cell-free systems and may not reflect the actions of esterified membrane-bound PUFAs in vivo [24]. Furthermore, although PUFA content in cerebral cortex as a whole was increased in PD patients compared to controls, PUFAs were dramatically decreased in lipid rafts, the normal site of presynaptic localization of α-synuclein, potentially expelling the protein from the lipid rafts and facilitating its neurotoxic aggregation in addition to compromising its role in synaptic vesicle trafficking [25].

We previously reported that both paraquat and rotenone were associated with PD in this population, consistent with other epidemiologic studies and experimental research [14]. In the present study we found that dietary fat modified associations of PD with paraquat and rotenone. Saturated fat increased both associations, potentially indicating that saturated fat and neurotoxicants have synergistic effects on PD risk, and that elevated risk is observed

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primarily when both are present. This could explain why findings for either factor alone are sometimes inconsistent; for example, an increased vulnerability to neurotoxic agents may underlie previous observations that animal and saturated fat were associated with an increase in PD risk [1,2]. Both grouped PUFAs and subtypes of PUFAs decreased the associations of PD with paraquat, and there was a similar although less pronounced effect for rotenone, again suggesting that PD risk may depend on a combination of factors.

Oxidative stress potentially mediates the association of pesticide exposure with PD. Paraquat may increase oxidative stress directly, while rotenone may contribute to oxidative stress through a pathway involving mitochondrial dysfunction [12]. Dietary fats may also affect oxidative stress. Saturated fats, for example, increase oxidative stress [13] and may therefore exacerbate the toxic effects of paraquat and rotenone, as suggested by our results. Oxidation of brain PUFAs may be associated with PD [26], suggesting that higher PUFA intake might also increase pesticide toxicity. However, not all studies find an association of lipid peroxidation with PD [27], and other evidence indicates that diets rich in N-3 PUFAs may reduce oxidative stress, possibly by mobilizing antioxidant defenses [28]. Our results are more consistent with the latter findings.

Neuroinflammation plays an important role in PD pathophysiology, potentially mediating the effects of pesticide exposure and other insults [12]. Accumulating evidence indicates that pre-existing neuroinflammation increases vulnerability to environmental toxicants, including pesticides. In mice, pretreatment with lipopolysaccharide increased sensitivity to paraquat, while inhibition of microglial activation prevented paraquat-induced loss of dopaminergic nigral neurons [29]. Similarly, treatment of primary mesencephalic cultures from mouse brain with lipopolysaccharide increased sensitivity to the neurodegenerative effects of rotenone [30]. PUFAs play a significant role in the inflammatory response; the anti-inflammatory effects of N-3 PUFAs likely mediate their protective effects on neurodegeneration [11]. This anti-inflammatory effect may underlie our findings that PUFAs reduce the association of PD with paraquat and possibly with rotenone.

Differences in the interactions of fat intake with paraquat compared to rotenone may reflect the relative importance of different mechanisms underlying the effects of the two pesticides on PD pathophysiology. The anti-inflammatory effects of N-3 PUFAs may be of greater significance to the association of PD with paraquat, while the pro-oxidant effect of saturated fats may be more relevant to rotenone action. Little evidence, however, supports such a distinction, and the interactions of both fat types with pesticides were qualitatively similar in most cases; apparent differences may be due to chance.

Our study was potentially limited by its small size; statistical power was limited, particularly for interactions of fats with pesticides, and many comparisons were made; thus this hypothesis-generating study requires replication. We were, however, able to detect associations of PUFAs with PD and interactions of dietary fats with pesticide exposure. The retrospective design was another potential limitation. However, although bias due to differential recall by cases and controls can be an issue in retrospective studies, our results on dietary fat are consistent with published studies, including prospective ones, and the meta-analysis reinforces our findings. We found that the association of PD with PUFA intake was qualitatively similar among those with a shorter or longer interval between diagnosis and FAME interview, suggesting that neither the length of the recall period nor secular trends in fat consumption completely account for our results. Exclusion from the meta-analysis of three case-control studies that considered diet up to or after diagnosis [4,9,10] strengthened the inverse associations of PD with dietary fat, suggesting that retrospective studies like ours can provide useful information by focusing on periods sufficiently long before diagnosis. We relied on self-reports of pesticide use, but farmers

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report pesticide use reliably [14]. Finally, although our study is potentially limited by its focus on an agricultural population, the similarity of fat intake between FAME participants and the US population suggests that our results may have more general applicability.

Study strengths include the strict diagnostic criteria employed to identify cases, reducing the potential for misclassification, and the detailed information we collected on pesticide exposure. A further strength is the nesting of the case-control study within an occupational cohort so that the internal control group had similar lifestyle characteristics and exposure opportunities as the cases, reducing the likelihood of confounding. BMI and total energy intake were similar for case and control groups, allaying concern that high caloric intake coupled with weight loss in PD cases could confound associations between dietary nutrients and PD [17]. A notable strength of our study is the availability of information on both diet and pesticide use; few other studies have comparable information.

In conclusion, we found that higher intake of dietary fats, particularly N-3 PUFAs, was inversely associated with PD. These findings are consistent with results from other epidemiologic research as well as experimental studies, and may be related to the ability of N-3 PUFAs to limit the inflammatory response. Of particular interest was the greater increase in PD risk associated with pesticide use in individuals with lower intake of PUFAs, or higher intake of saturated fat, suggesting that individuals with such diets may be more vulnerable to neurotoxicants. These results are preliminary and require confirmation in additional studies. However, if replicated, our findings suggest that a diet high in PUFAs and low in saturated fats might reduce risk of PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1
Characteristics of Parkinson's disease cases and controls in the FAME Study

		Cases		Controls			
Characteristic		**N**	**%**	**N**	**%**	**OR[a]**	**95% CI**
Age at enrollment in the AHS (years)	40 - 57	32	36	108	32	1.0	Referent
	58 - 65	34	38	134	40	0.9	0.5 1.6
	66 - 87	23	26	94	28	0.9	0.5 1.8
Gender	Men	67	75	246	73	1.0	Referent
	Women	22	25	90	27	0.8	0.4 1.5
State	Iowa	65	73	251	75	1.0	Referent
	North Carolina	24	27	85	25	1.2	0.7 2.1
Ever smoke	No	65	73	202	60	1.0	Referent
	Yes	24	27	134	40	0.5	0.3 0.9
BMI at age 40 (kg/m^2)	0 - 23.6	29	33	110	33	1.0	Referent
	23.7 - 25.9	29	33	113	34	0.9	0.5 1.7
	≥ 26.0	30	34	112	33	0.9	0.5 1.7
Total energy (kcal/d)	≤1685	28	31	112	33	1.0	Referent
	1686 - 2399	23	26	112	33	0.8	0.4 1.6
	≥ 2400	38	43	112	33	1.4	0.7 2.5

[a] Adjusted for age, gender, state, smoking, and total energy intake

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Table 2
Parkinson's disease and dietary fat intake in the FAME Study

Type of fat	% energy	Cases		Controls		OR[a]	95% CI		p-trend
		N	%	N	%				
Total	0-34.20	33	37	112	33	1.0	Referent		0.23
	34.21-38.98	31	35	111	33	0.9	0.5	1.6	
	≥38.99	25	28	113	34	0.7	0.4	1.3	
Saturated	0-11.42	33	37	112	33	1.0	Referent		0.56
	11.43-13.41	29	33	112	33	0.8	0.4	1.4	
	≥13.42	27	30	112	33	0.8	0.5	1.5	
MUFA[b]	0-12.84	32	36	112	33	1.0	Referent		0.51
	12.85-14.75	29	33	112	33	0.8	0.5	1.5	
	≥14.76	28	31	112	33	0.8	0.4	1.5	
PUFA[b]	0-6.35	34	38	112	33	1.0	Referent		0.10
	6.36-7.76	33	37	111	33	1.0	0.6	1.7	
	≥7.77	22	25	113	34	0.6	0.3	1.1	
N-6 PUFA[b]	0-5.67	33	37	111	33	1.0	Referent		0.15
	5.68-6.92	33	37	112	33	1.0	0.5	1.7	
	≥6.93	23	26	113	34	0.6	0.3	1.2	
Linoleic Acid	0-5.63	33	37	111	33	1.0	Referent		0.12
	5.64-6.87	34	38	112	33	1.0	0.6	1.8	
	≥6.88	22	25	113	34	0.6	0.3	1.1	
N-3 PUFA[b]	0-0.671	45	51	112	33	1.0	Referent		0.006
	0.672-0.846	21	24	112	33	0.4	0.2	0.7	
	≥0.847	23	26	112	33	0.4	0.2	0.8	
α-Linolenic Acid	0-0.597	38	43	111	33	1.0	Referent		0.010
	0.598-0.725	34	38	113	34	0.8	0.5	1.4	
	≥0.726	17	19	112	33	0.4	0.2	0.8	

[a] Adjusted for age, gender, state, smoking, and total energy intake

[b] MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids

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Table 3
Meta-analysis of Parkinson's disease and dietary fat intake

			Homogeneity Test		Fixed Effects		
Type of fat	**N studies** [ab]	**N cases** [b]	**Q**	**p**	**OR**	**95% CI**	
Total	11	1839	11.7	0.31	0.84	0.72	0.98
Saturated	10	1497	9.1	0.43	0.88	0.75	1.03
MUFA [c]	9	1371	5.9	0.66	0.83	0.71	0.98
PUFA [c]	9	1371	11.1	0.20	0.85	0.72	1.00
Linoleic acid	9	1371	8.1	0.42	0.86	0.72	1.02
α-Linolenic acid	8	1214	9.7	0.20	0.81	0.68	0.96

[a] The meta-analysis included data from 8 published studies plus the FAME Study. Two studies presented data for men and women separately.

[b] Some studies did not report data for some fats, so Ns vary.

[c] MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

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Table 4

Pesticide exposure and dietary fat consumption in the FAME Study [a]

Fat consumption	Pesticide use	Paraquat(n=300)[b]							Rotenone (n=413)[b]						
		Case		Control		OR[c]	95% CI		Case		Control		OR[c]	95% CI	
		N	%	N	%				N	%	N	%			
Total fat															
high	no	19	31	96	40	1.0	Referent		31	36	154	47	1.0	Referent	
high	yes	7	11	31	13	1.4	0.5	3.7	7	8	10	3	**4.3**	**1.4**	**12.7**
low	no	24	39	97	41	1.3	0.7	2.7	37	43	141	43	1.4	0.8	2.4
low	yes	11	18	15	6	**4.7**	**1.7**	**12.6**	11	13	22	7	**2.6**	**1.1**	**6.2**
p-interaction		0.18							0.24						
Saturated fat															
high	no	18	30	98	41	1.0	Referent		29	34	149	46	1.0	Referent	
high	yes	10	16	25	10	**3.1**	**1.2**	**8.0**	12	14	11	3	**5.8**	**2.3**	**14.6**
low	no	25	41	95	40	1.5	0.8	3.1	39	45	146	45	1.3	0.7	2.2
low	yes	8	13	21	9	2.3	0.8	6.4	6	7	21	6	1.5	0.5	4.2
p-interaction		0.29							0.02						
MUFA [d]															
high	no	20	33	100	42	1.0	Referent		32	37	154	47	1.0	Referent	
high	yes	8	13	29	12	1.6	0.6	4.3	7	8	10	3	**4.1**	**1.4**	**12.2**
low	no	23	38	93	39	1.3	0.7	2.7	36	42	141	43	1.3	0.8	2.3
low	yes	10	16	17	7	**3.8**	**1.4**	**10.4**	11	13	22	7	**2.6**	**1.1**	**6.1**
p-interaction		0.42							0.29						
PUFA [d]															
high	no	15	25	70	29	1.0	Referent		30	35	149	46	1.0	Referent	
high	yes	7	11	30	13	1.2	0.4	3.4	6	7	17	5	2.0	0.7	5.8
low	no	28	46	123	51	1.1	0.5	2.3	38	44	146	45	1.4	0.8	2.4
low	yes	11	18	16	7	**4.2**	**1.5**	**11.6**	12	14	15	5	**4.1**	**1.7**	**9.9**
p-interaction		0.10							0.57						

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Fat consumption	Pesticide use	Paraquat(n=300)[b]							Rotenone (n=413)[b]						
		Case		Control		OR[c]	95% CI		Case		Control		OR[c]	95% CI	
		N	%	N	%				N	%	N	%			
N-6 PUFA [d]															
high	no	16	26	72	30	1.0	Referent		30	35	150	46	1.0	Referent	
high	yes	7	11	30	13	1.2	0.4	3.3	6	7	17	5	2.1	0.7	5.9
low	no	27	44	121	51	1.0	0.5	2.1	38	44	145	44	1.4	0.8	2.4
low	yes	11	18	16	7	**4.0**	**1.5**	**10.9**	12	14	15	5	**4.1**	**1.7**	**10.0**
p-interaction		0.08							0.59						
Linoleic acid															
High	no	16	26	71	30	1.0	Referent		30	35	149	46	1.0	Referent	
High	yes	7	11	29	12	1.2	0.4	3.3	6	7	17	5	2.1	0.7	5.9
Low	no	27	44	122	51	1.0	0.5	2.0	38	44	146	45	1.4	0.8	2.4
Low	yes	11	18	17	7	**3.8**	**1.4**	**10.3**	12	14	15	5	**4.1**	**1.7**	**10.0**
p-interaction		0.09							0.58						
N-3 PUFA [d]															
High	no	12	20	71	30	1.0	Referent		21	24	143	44	1.0	Referent	
High	yes	3	5	23	10	1.0	0.2	4.0	7	8	20	6	2.8	1.0	7.7
Low	no	31	51	122	51	1.8	0.8	3.8	47	55	152	46	**2.4**	**1.3**	**4.5**
Low	yes	15	25	23	10	**4.6**	**1.8**	**11.8**	11	13	12	4	**7.0**	**2.6**	**18.7**
p-interaction		0.23							0.97						
α-Linolenic acid															
high	no	17	28	73	31	1.0	Referent		26	30	146	45	1.0	Referent	
high	yes	5	8	27	11	1.1	0.4	3.6	10	12	18	6	**3.5**	**1.4**	**8.6**
low	no	26	43	120	50	1.0	0.5	2.1	42	49	149	46	1.6	0.9	2.8
low	yes	13	21	19	8	**3.3**	**1.3**	**8.2**	8	9	14	4	**3.3**	**1.2**	**8.9**
p-interaction		0.16							0.43						

[a] Statistically significant associations (p<0.05) are shown in bold.

[b] Paraquat models included only men because no women used paraquat. Rotenone models included both men and women.

[c] Models were adjusted for age, state, smoking, and energy; rotenone models were additionally adjusted for gender.

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[d] MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.