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Dietary fat intake and risk for Parkinson's disease

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Abstract

BACKGROUND—Previous epidemiological studies have generated inconsistent results regarding the associations between dietary fat intakes and risk for Parkinson's disease (PD). We therefore prospectively examined these associations in the NIH-AARP Diet and Health Study.

METHODS—A 124-item food frequency questionnaire was administered at baseline in 1995–1996, and PD diagnosis was self-reported at the follow-up survey in 2004–2006. A total of 1,087 cases with a PD diagnosis between 2000 and 2006 and 299,617 controls were included in the analyses.

RESULTS—Overall, intakes of fats and other macronutrients were not associated with PD risk. However, we found a weak positive association between n-6 polyunsaturated fatty acids (PUFA) and the risk for PD. After adjusting for potential confounders, the odds ratio (OR) and 95% confidence interval (CI) between extreme quintiles of n-6 PUFA intake was 1.23 (95% CI=1.02–1.49, *P* for trend=0.02). A similar association was observed for the intake of linoleic acid. Results were similar among men and among women.

CONCLUSIONS—Our study suggests that fat intake in general is not related to the risk for PD. The weak positive association between intake of n-6 PUFA and PD risk needs further investigation.

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Disclosure statement

The authors have no conflicts of interest.

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Keywords

Dietary fat intake; Parkinson's disease; cohort study

Parkinson's disease (PD) is the second most common neurodegenerative disease and affects more than one million Americans [1]. Although the exact mechanisms underlying PD pathogenesis are yet to be defined; oxidative stress, mitochondrial dysfunction, and inflammation may contribute to this process[2–4]. The brain is particularly susceptible to oxidative damage because of its high demand for oxygen and the presence of abundant iron and unsaturated fatty acids [5]. In addition, polyunsaturated fatty acids (PUFA), which are essential components of neuronal and glial cell membranes, regulate the production of pro/anti-inflammatory cytokines that may also contribute to neurodegenerative diseases such as PD [6].

Murine studies have shown that brain concentrations of fatty acids, such as PUFA, may be affected by dietary intake[7, 8]. Epidemiological studies on dietary fat intake and PD have generated inconsistent results, ranging from positive associations [9–12], to null [13, 14] or even inverse associations [15–20]. We therefore prospectively examined the relationships between PD risk and intakes of total fat, specific types of fat, and other macronutrients in the NIH-AARP Diet and Health Study.

Patients and Methods

Study population and PD case identification

The details of the NIH-AARP Diet and Health Study have been described previ-ously[21]. Briefly, in 1995–1996, a total of 566,398 members of AARP (formerly known as the American Association of Retired Persons), aged 50 to 71 years, were recruited into a large prospective study to evaluate roles of diet and lifestyle in the development of cancers and other chronic diseases. Participants were from six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). At enrollment, they reported a wide range of dietary intakes of macro- and micronutrients [21]. From 2004 to 2006, a follow-up survey was conducted among surviving participants to update lifestyle exposures and to ascertain the occurrence of major chronic diseases, including PD. Participants were asked whether they had been diagnosed with PD by a physician and, if so, the year of diagnosis in the following categories: before 1985, 1985–1994, 1995–1999, or during or after 2000. A total of 318,257 men and women responded to the follow-up survey and 2,432 participants reported a PD diagnosis.

Between 2007 and 2010, we contacted surviving PD patients to confirm self-reported PD diagnoses. Detailed procedures were published previously [22]. Briefly, we first asked patients who self-reported PD to confirm their reports. We then asked their treating physician to complete a diagnostic questionnaire and to provide a copy of the patient's medical records. The medical records were subsequently reviewed by a movement disorder specialist (X. H.). A case was confirmed if one of the following criteria was met: (1) the diagnosis was

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confirmed by the treating physician, (2) the medical record included a final diagnosis of PD, or (3) at least two cardinal signs were present with one being resting tremor or bradykinesia, the disease course was progressive, and there was an absence of unresponsiveness to levodopa or other features suggesting an alternative diagnosis. Of the 1,069 physician responses received, 940 (87.9%) PD diagnoses were confirmed. The confirmation rate was similar across years of diagnosis: 83.3% for cases diagnosed before 1985, 92.8% for cases diagnosed in 1985–1994, 87.9% for cases diagnosed in 1995–1999, and 87.2% for cases diagnosed after 2000.

We excluded 15,760 subjects whose baseline questionnaires were completed by proxy from the 566,398 members of the cohort, and then subjects who reported extreme intakes (>2 times the interquartile range above the 75th percentile or below the 25th percentile of log-transformed intake) of total energy (n=3,726) and total fat (n=631). Inclusion of participants with extreme intakes however had little effect on the results (data not shown).

After these exclusions, a total of 546,281 baseline enrollees left and 309,619 of them also participated in the follow-up survey and therefore eligible for the current analyses. We further removed subjects who didn't answer the questions about PD status in the follow-up questionnaire (n=7,054) or were reporting errors and misdiagnoses (n=905), and PD patients whose diagnosis were denied by themselves or treat physicians in the disease validation process (n=48). Because PD may take years to develop and our previous studies indicated dietary and behavioral changes 2–4 years prior to disease diagnosis [23, 24], we further excluded 908 self-reported cases diagnosed before 2000. This left us with a total of 1,087 cases diagnosed between 2000 and 2006, and 299,617 controls in the primary analyses.

Exposure assessment

All study participants completed a mailed questionnaire at baseline that included a validated 124-item food-frequency questionnaire (FFQ) and questions on demographics and lifestyle. The FFQ asked participants to report their typical consumption frequency and portion size of 124 food items during the past year. Consumption frequency allows for 10 categories, ranging from never to two or more times per day for solid foods and never to six or more times per day for drinks. The portion size had three categories-small, medium, and large. Nutrient intakes were calculated from the 1994–1996 U.S. Department of Agriculture Continuing Survey of Food Intake by individuals [25]. The FFQ was calibrated against two nonconsecutive 24-hour dietary recalls that were administered by telephone within a year of the baseline questionnaire (n =2,053) [21]. The estimated energy-adjusted Pearson correlation coefficients for men and women, respectively, were 0.72 and 0.62 for total fat, 0.76 and 0.69 for saturated fat, 0.71 and 0.62 for monounsaturated fat and 0.53 and 0.56 for polyunsaturated fat [21, 26]. Caffeine intake was estimated from consumption of coffee and other caffeine-containing drinks and foods as reported on the FFQ [27]. For smoking status, participants were asked whether they had ever smoked more than 100 cigarettes during their lifetime. Ever smokers were further asked about typical number of cigarettes smoked per day, current smoking status, and, for past smokers, the number of years since they last smoked[27]. Both current smoking and higher caffeine intake was associated with lower risk of PD in this cohort as expected[22, 27].

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Statistical analysis

Our primary exposures of interest were dietary intakes of total fat, individual types of fat and individual types of fatty acids. We calculated total n-6 PUFA intake as the sum of intakes of 18:2 and 20:4 fatty acids and total n-3 PUFA intake as the sum of intakes of 18:3, 18:4, 20:5, 22:5, and 22:6 fatty acids [28]. To account for total energy intake in the analyses, we used the multivariate nutrient density method [29]. Exposures of interest were first expressed as percentage of total energy intake and then categorized into quintiles with the lowest quintile as the reference group. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from multivariate logistic regression models, adjusting for age (year, continuous variable), gender, race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian, Pacific Islander, or American Indian/Alaskan Native and Unknown), caffeine intake (mg/day, continuous variable), smoking status (never, ever and current), and total energy intake (Kcal/day, continuous variable).

Only 56.2% of the original cohort enrollees participated in the cohort's follow-up survey and their baseline population characteristics were significantly different from those excluded from the analysis (data not shown). We therefore conducted additional analyses using the inverse probability weighting method to examine potential selection biases from death or non-participation in the follow-up survey [30]. In doing this, we used a directed acyclic graph [31] to analyze the following potential confounders identified from previous publications: age, gender, race/ethnicity, smoking status, caffeine intake, physical activity, body mass index (BMI), education, marital status, total energy intake, vitamin E intake, iron intake, alcohol use, non-steroidal anti-inflammatory drug use, diabetes diagnosis, and self-reported health status. As a result, we identified two minimally sufficient adjustment sets: (1) age, gender, physical activity, race/ethnicity, smoking, caffeine intake, diabetes, alcohol, BMI, and total energy intake; (2) age, gender, physical activity, race/ethnicity, smoking, caffeine intake, diabetes, and self-reported health status (Supplementary Figure 1). We used the second minimally sufficient adjustment set as the final model because it had less missing data on covariates than the first.

We then used the stabilized inverse probability weights to adjust for covariates in the second minimally sufficient adjustment set and to account for non-participation in the follow-up survey [30, 32]. We calculated separate stabilized weights to adjust for potential confounders and potential selection bias, respectively. For stabilized confounding weights, we calculated the numerators of these weights as predicted probabilities of exposure from an intercept only model and the denominators of these weights as predicted probabilities of exposure from a model including the covariates in the second minimally sufficient adjustment set as explanatory variables. For stabilized selection weights, we calculated the numerators of these weights as predicted probabilities of not dropping out of the cohort conditional on the exposure of interest and the denominators of these weights as predicted probabilities conditional on the exposure of interest and the covariates in the second minimally sufficient adjustment set. We then calculated the overall stabilized weight as the product of the two weights. The overall stabilized weight was finally applied to logistic regression models for PD risk that contained the exposure of interest as the only explanatory variable [30]. We used

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robust variance estimates to calculate 95% CIs because using weights induced within-subject correlation [33].

In addition to the primary analyses, we also conducted stratified analyses according to age (< 62 and ≥ 62), sex, smoking status (never and ever) and caffeine intake (< 234 and ≥ 234 mg/day). Statistical interactions were tested by adding a multiplicative interaction term to the logistic regression model. All statistical analyses were performed using Stata 12.0 (College Station, TX, USA) and $P < 0.05$ was considered as statistically significant.

Standard protocol approvals, registrations and patient consent

Participants consented to the study by returning survey questionnaires. The study protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences and the Special Studies Institutional Review Board of the National Cancer Institute.

Results

Characteristics of study population

Table 1 presents the baseline characteristics of the study population according to quintiles of total fat intake. The median intakes of total fat as percentages of energy intake ranged from 20.1% in the lowest quintile to 39.5% in the highest quintile. Participants with higher fat intake were more likely to be men, non-Hispanic Whites and current smokers. They also were more likely to report higher intakes of caffeine, total energy, and cholesterol, but lower intake of carbohydrate. Further, they on average had a higher BMI and were more likely to report diabetes and poorer health status.

Associations between dietary fat intake and PD risk

After adjusting for potential confounders, intakes of total energy and total fat each showed a weak positive association with PD risk with borderline significant dose-response relationship (Table 2). In the inverse probability weighted analyses, the association with total energy intake was slightly stronger whereas the one for total fat intake was modestly attenuated. Among individual types of fat, there were weak positive associations between PD risk and intakes of total PUFA and n-6 PUFA. For example, compared with the lowest quintile, the OR was 1.23 (95% CI=1.02–1.49, *P* for trend=0.02) for the highest quintile of n-6 PUFA intake. The association was also borderline statistically significant in the inverse probability weighted analyses (*P* for trend=0.03). When we examined the n-3 to n-6 ratio in relation to PD risk, we found that participants in the fourth quintile had a lower risk for PD as compared with those in the first quintile (OR=0.81, 95% CI=0.38–0.98), but the *P* for trend was not statistically significant (*P* for trend=0.12). None of these associations remained statistically significant after Bonferroni correction for multiple comparisons. Intake of other types of fat or macronutrients was not associated with PD risk.

We further examined specific types of PUFA in relation to PD risk (Table 3). As expected, intake of linoleic acid showed a weak positive association with the risk for PD. No other n-6 fatty acids or n-3 fatty acids were associated with the risk for PD.

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Interaction analyses

Overall, we did not observe significant interactions between intakes of these fatty acids and age, sex, smoking or caffeine intake (Supplementary Table 1). The positive associations observed in the main analyses were however apparently limited to never smokers and heavy coffee drinkers.

Discussion

In this large prospective study among older US adults, we found that overall fat intake was not associated with the risk for PD. There were weak positive associations of PD risk with higher intakes of the n-6 PUFA and linoleic acid; however these associations did not persist adjustments for multiple comparisons. To the best of our knowledge, this study is to date the largest prospective analysis on dietary fat and PD risk. Further, we excluded PD cases diagnosed prior to 2000 from the analysis with the hope to reduce concern about reverse causation due to changing dietary habits of PD patients in the years leading to a PD diagnosis.

Dietary fat intake may affect PD risk because fats, particularly PUFA, may contribute to oxidative stress and neuroinflammation. Neural membranes are rich in PUFA and are therefore sources of oxygen radicals through lipid peroxidation [34]. Oxidation of membrane PUFA may cause mitochondrial dysfunction and damage cellular components, thus contribute to neuronal degeneration [35]. In addition, PUFA are essential components of glial cell membranes and regulate the production of prostaglandins and proinflammatory cytokines [6]. Exacerbated or prolonged inflammatory processes in the brain may play a key role in neurodegeneration [36]. Furthermore, PUFA may promote α-synuclein oligomerization and aggregation in cultured dopaminergic cells and increase its deposit into intraneuronal Lewy-like inclusions [37]. The majority of membrane PUFA is synthesized from dietary n-6 linoleic and n-3 α-linoleic acids, which are also precursors for the synthesis of long chain PUFA by desaturation and elongation reactions [38]. The n-3 PUFA are anti-inflammatory, while n-6 PUFA are precursors of proinflammatory prostaglandins. Therefore our finding that n-6 PUFA intake was associated with higher PD risk is biologically plausible.

To the best of our knowledge, the associations between dietary fat intake and PD have been investigated in approximately a dozen epidemiological studies, including both case-control studies and prospective studies. Several earlier case-control studies reported a positive association with intake of total fat [9, 11] or animal/saturated fat [9, 10], but these findings were largely not confirmed in later studies [12, 13, 18, 19]. For specific types of dietary fats, the findings are largely null [12, 18], although some interactions were reported between specific types of dietary fats (saturated or PUFA) and iron intake [18] or pesticide exposure [19]. Most of these case-control studies used prevalent PD cases that had the diseases for years at the time of the study [9–13, 18, 19] and a couple of studies did not specifically query dietary intake prior to disease diagnosis [12], therefore these findings might have been affected by recall bias and reverse causation that dietary intakes might have changed as a result of the disease.

Prospective cohort studies assessed diet prior to disease diagnosis and thus are relatively less prone to reverse causality and recall bias. However, diet in prospective studies is often

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evaluated at one point in mid- or late- adulthood, which may not capture the time windows that are relevant to disease etiology. Further, prospective studies may not be immune from reverse causation because patients may suffer from premotor symptoms which may affect dietary intakes. Some cohort studies, but not all, suggested lower risk of PD with higher intakes of one or more types of fatty acids, although the results were not always statistically significant nor consistent for specific types of fatty acids [14–17, 20]. Only one previous study evaluated the dietary intake repeatedly and conducted lag analyses that excluded the first several years of follow-up [16]. The Health Professionals Follow-up Study and the Nurses' Health Study included 359 incident PD cases, nearly the total number of cases of the other four cohorts combined [16]. This study did not identify associations between PD risk and total fat or individual types of fatty acids with the exception of a borderline inverse association with arachidonic acid [16].

Compared to previous prospective studies, our current study was substantially larger with 1,087 PD cases and 299,617 controls. This large sample size provided better power to detect associations and facilitated adjustment for multiple covariates and gender-specific analyses. Our analyses only included PD cases diagnosed after 2000, at least four to five years after exposure assessment, which might have further alleviated concern about reverse causality. This large population also encompassed a large range of fat intakes. Fat intakes in this cohort have been associated with the risk of various types of chronic diseases, such as prostate cancer, chronic liver disease and hepatocellular carcinoma and pancreatic cancer in a manner consistent with their metabolic effects [28, 39, 40].

Our study also had several limitations. First, PD cases were self-reported and thus reporting and diagnostic errors were inevitable. We confirmed 88% of diagnoses in patients for whom we obtained medical information from their treating neurologists and we further removed patients with identified reporting errors and misdiagnoses from the analyses. However, we were unable to include PD cases who did not report their diagnosis on the follow-up questionnaire as cases in the analysis, and this might have biased the analyses if fat intakes of these cases were systematically different from cases who did report their diagnoses. Further, as the exact date of diagnosis was only available for some cases, we were unable to perform time to event survival analyses. Secondly, fat intakes were assessed as part of a dietary history questionnaire at study baseline; we could not exclude the possibility of measurement errors and residual confounding. Thirdly, PD may have a long prodromal period and we only had dietary assessment once at baseline. Although we only included PD cases diagnosed after 2000, we could not exclude the possibility of reverse causality if some PD patients' dietary habits had been affected early in the prodromal period. Fourthly, the analysis was performed among participants of the follow-up survey, and therefore the possibility of selection bias cannot be excluded. Nevertheless, we used the inverse probability weighting analysis to account for this potential selection bias and found similar results. Finally, the cohort was predominantly non-Hispanic white, so results may not be readily generalizable to other populations.

In summary, we conducted the largest prospective study to date examining the associations between dietary fat intake and PD risk. Dietary intakes of fat in general were not found to be

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associated with the risk for PD. The weak positive association between intake of n-6 PUFA and PD needs confirmation and further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Baseline characteristics by quintiles of total fat intake as percentages of energy among participants in NIH-AARP Diet and Health Study.

Characteristics	Q1	Q2	Q3	Q4	Q5
N participants	60,141	60,141	60,141	60,141	60,140
Total fat intake (Median), % of total energy	20.1	26.0	30.0	34.0	39.5
Age, years (Mean ± SD)	61.6 ± 5.3	61.5 ± 5.3	61.5 ± 5.3	61.4 ± 5.3	61.2 ± 5.4
Men, N (%)	33,481 (55.7)	33,485 (55.7)	35,140 (58.4)	36,420 (60.6)	35,765 (59.5)
Race, N (%)					
Non-Hispanic White	55,001 (91.5)	55,677 (92.6)	55,741 (92.7)	55,890 (92.9)	56,098 (93.3)
Other	4,481 (7.5)	3,898 (6.5)	3,805 (6.3)	3,640 (6.1)	3,377 (5.6)
Caffeine intake, mg/day (Mean ± SD)	297.7 ± 339.6	331.1 ± 350.9	355.2 ± 356.7	386.1 ± 373.3	429.7 ± 398.7
Smoking status					
never	23,584 (41.1)	23,863 (41.5)	23,628 (41.1)	22,975 (39.9)	21,237 (36.9)
past	29,845 (52.0)	29,344 (51.0)	28,729 (50.0)	28,254 (49.0)	27,282 (47.4)
current	3,922 (6.8)	4,327 (7.5)	5,156 (9.0)	6,379 (11.1)	9,064 (15.7)
Total energy intake, Kcal/day (Mean ± SD)	1,737.6 ± 839.7	1,710.4 ± 703.7	1,792.7 ± 725.7	1,892.5 ± 780.1	2,005.5 ± 870.5
Carbohydrate intake, % of energy, (Mean ± SD)	61.4 ± 11.4	56.4 ± 7.5	52.8 ± 6.3	49.4 ± 5.39	43.7 ± 5.6
Protein intake, % of energy (Mean ± SD)	14.7 ± 3.6	15.6 ± 3.1	15.6 ± 3.0	15.6 ± 2.9	15.6 ± 2.9
Cholesterol intake, mg/day (Mean ± SD)	121.5 ± 71.2	162.0 ± 83.0	194.0 ± 97.1	228.6 ± 115.3	280.2 ± 150.7
Body mass index, kg/m^2 (Mean ± SD)	25.8 ± 4.4	26.6 ± 4.7	27.0 ± 4.8	27.4 ± 5.0	27.9 ± 5.5
Self-reported diabetes, N (%)					
No	57,428 (95.5)	56,612 (94.1)	55,950 (93.0)	55,389 (92.1)	53,768 (89.4)
Yes	2,713 (4.5)	3,529 (5.9)	4,191 (7.0)	4,752 (7.9)	6,372 (10.6)
Self-reported health status, N (%)					
Excellent	14,026 (23.3)	12,079 (20.1)	10,904 (18.1)	10,046 (16.7)	9,482 (15.8)
Very good	22,712 (37.8)	23,246 (38.7)	22,866 (38.0)	22,401 (37.2)	20,983 (34.9)
Good	17,946 (29.8)	19,119 (31.8)	20,360 (33.9)	21,092 (35.1)	21,900 (36.4)
Fair	4,195 (7.0)	4,468 (7.4)	4,721 (7.9)	5,354 (8.9)	6,295 (10.5)
Poor	444 (0.7)	436 (0.7)	494 (0.8)	537 (0.9)	737 (1.2)

Numbers may not add up to the total due to missing.

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TABLE 2

Associations between dietary intakes of fats and other macronutrients and PD risk.

Type of fat	% Total energy	Case, N	Age and sex adjusted [a]		Multivariate adjusted[b]		Inverse probability weighting[c]	
			OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend
Total fat	≤ 23.5	213	ref	0.17	ref	0.06	ref	0.25
	23.5–28.1	198	0.94 (0.77–1.14)		0.95 (0.78–1.15)		0.93 (0.76–1.13)	
	28.1–32.0	218	1.02 (0.84–1.23)		1.04 (0.86–1.26)		0.98 (0.81–1.20)	
	32.0–36.4	231	1.08 (0.89–1.30)		1.11 (0.92–1.34)		1.07 (0.88–1.30)	
	≥ 36.4	227	1.08 (0.90–1.31)		1.14 (0.94–1.38)		1.06 (0.87–1.28)	
Saturated fat	≤ 6.81	220	ref	0.34	ref	0.12	ref	0.3
	6.81–8.38	192	0.89 (0.73–1.08)		0.90 (0.74–1.10)		0.89 (0.73–1.09)	
	8.38–9.84	221	1.02 (0.84–1.22)		1.04 (0.86–1.26)		1.02 (0.84–1.24)	
	9.84–11.62	243	1.12 (0.93–1.35)		1.16 (0.97–1.39)		1.12 (0.93–1.35)	
	≥ 11.62	211	0.99 (0.82–1.19)		1.04 (0.86–1.27)		0.99 (0.82–1.21)	
Monounsaturated fatty acids	≤ 8.6	211	ref	0.24	ref	0.1	ref	0.26
	8.6–10.5	194	0.92 (0.76–1.12)		0.94 (0.77–1.14)		0.92 (0.75–1.12)	
	10.5–12.1	229	1.07 (0.89–1.29)		1.09 (0.91–1.32)		1.04 (0.86–1.26)	
	12.1–13.9	221	1.02 (0.85–1.24)		1.06 (0.87–1.28)		1.02 (0.84–1.24)	
	≥ 13.9	232	1.08 (0.90–1.30)		1.13 (0.94–1.37)		1.08 (0.89–1.30)	
Polyunsaturated fatty acids (PUFA)	≤ 5.2	199	ref	0.05	ref	0.03	ref	0.05
	5.2–6.2	216	1.09 (0.90–1.32)		1.10 (0.91–1.33)		1.07 (0.88–1.31)	
	6.2–7.3	214	1.07 (0.88–1.30)		1.08 (0.89–1.31)		1.08 (0.90–1.32)	
	7.3–8.6	227	1.14 (0.94–1.38)		1.15 (0.95–1.40)		1.16 (0.96–1.41)	
	≥ 8.6	231	1.20 (0.99–1.45)		1.23 (1.01–1.48)		1.19 (0.98–1.44)	
N-6 PUFA	≤ 4.6	196	ref	0.03	ref	0.02	ref	0.03
	4.6–5.5	214	1.09 (0.90–1.33)		1.10 (0.91–1.34)		1.08 (0.89–1.32)	
	5.5–6.5	213	1.08 (0.89–1.31)		1.09 (0.90–1.32)		1.09 (0.90–1.33)	
	6.5–7.7	234	1.19 (0.99–1.44)		1.20 (0.99–1.46)		1.22 (1.00–1.48)	
	≥ 7.7	230	1.21 (1.00–1.46)		1.23 (1.02–1.49)		1.20 (0.99–1.46)	
N-3 PUFA	≤ 0.5	218	ref	0.73	ref	0.59	ref	0.86

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Type of fat	% Total energy	Case, N	Age and sex adjusted [a]		Multivariate adjusted[b]		Inverse probability weighting[c]	
			OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend
	0.5–0.6	212	0.98 (0.81–1.82)		0.98 (0.81–1.19)		1.00 (0.82–1.21)	
	0.6–0.7	214	0.99 (0.82–1.20)		1.00 (0.83–1.21)		1.01 (0.84–1.23)	
	0.7–0.9	258	1.22 (1.01–1.46)		1.22 (1.02–1.47)		1.24 (1.03–1.49)	
	≥ 0.9	185	0.91 (0.75–1.11)		0.93 (0.76–1.14)		0.89 (0.73–1.09)	
n-3:n-6 PUFA ratio	≤ 0.10	254	ref	0.13	ref	0.12	ref	0.07
	0.10–0.11	212	0.86 (0.71–1.03)		0.85 (0.71–1.02)		0.87 (0.72–1.05)	
	0.11–0.12	213	0.87 (0.72–1.04)		0.87 (0.72–1.04)		0.88 (0.73–1.06)	
	0.12–0.14	198	0.82 (0.68–0.99)		0.81 (0.38–0.98)		0.80 (0.66–0.97)	
	≥ 0.14	210	0.88 (0.73–1.05)		0.87 (0.73–1.05)		0.85 (0.71–1.03)	
Total energy, Kcal/day	≤ 1,200.5	196	ref	0.24	ref	0.09	ref	0.04
	1,200.5–1,524.3	191	0.90 (0.74–1.10)		0.90 (0.74–1.11)		0.88 (0.71–1.08)	
	1,524.3–1,860.1	206	0.92 (0.76–1.12)		0.93 (0.76–1.13)		0.92 (0.75–1.13)	
	1,860.1–2,346.2	250	1.07 (0.88–1.29)		1.09 (0.90–1.32)		1.12 (0.92–1.37)	
	≥ 2,346.2	244	1.04 (0.85–1.26)		1.09 (0.90–1.33)		1.12 (0.92–1.37)	
Protein	≤ 12.9	212	ref	0.98	ref	0.83	ref	0.19
	12.9–14.6	239	1.12 (0.93–1.35)		1.12 (0.93–1.35)		1.16 (0.96–1.41)	
	14.6–16.1	221	1.04 (0.87–1.27)		1.04 (0.86–1.26)		1.06 (0.87–1.29)	
	16.1–17.9	208	1.01 (0.84–1.23)		1.00 (0.82–1.21)		0.97 (0.80–1.19)	
	≥ 17.9	207	1.05 (0.87–1.28)		1.04 (0.85–1.26)		0.95 (0.78–1.16)	
Carbohydrate	≤ 44.9	217	ref	0.77	ref	0.61	ref	0.53
	44.9–50.3	216	1.02 (0.84–1.23)		0.99 (0.82–1.20)		0.99 (0.81–1.22)	
	50.3–55.1	239	1.15 (0.96–1.39)		1.11 (0.92–1.34)		1.11 (0.91–1.36)	
	55.1–60.7	219	1.08 (0.89–1.30)		1.02 (0.84–1.24)		1.01 (0.82–1.24)	
	≥ 60.7	196	1.00 (0.82–1.21)		0.93 (0.76–1.13)		0.92 (0.74–1.14)	
Cholesterol	≤ 0.07	203	ref	0.99	ref	0.52	ref	0.94
	0.07–0.09	235	1.17 (0.97–1.41)		1.19 (0.98–1.43)		1.16 (0.95–1.40)	
	0.09–0.11	237	1.20 (1.00–1.45)		1.26 (1.02–1.48)		1.18 (0.97–1.43)	
	0.11–0.14	198	1.01 (0.83–1.22)		1.04 (0.85–1.27)		1.00 (0.82–1.22)	

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Type of fat	% Total energy	Case, N	Age and sex adjusted [a]		Multivariate adjusted[b]		Inverse probability weighting[c]	
			OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend
	≥ 0.14	214	1.08 (0.90–1.31)		1.15 (0.95–1.39)		1.07 (0.88–1.30)	

Abbreviations: OR: odds ratios; CI: confidence intervals; MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids

[a] Adjusted for age and sex

[b] Adjusted for age, sex, race, smoking status, caffeine intake and total energy intake.

[c] Adjusted for inverse probability weights with 95% CIs calculated from robust variance estimates.

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TABLE 3

Associations between dietary intakes of specific n-6 and n-3 PUFA and PD risk.

Type of fat	% Total energy	Case, N	Age and sex adjusted [a]		Multivariate adjusted[b]		Inverse probability weighting[c]	
			OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend
n-6 PUFA								
Linoleic acid (18:2)	≤ 4.5	196	ref	0.04	ref	0.03	ref	0.04
	4.5–5.5	215	1.10 (0.91–1.34)		1.11 (0.91–1.34)		1.09 (0.90–1.33)	
	5.5–6.4	214	1.09 (0.89–1.32)		1.09 (0.90–1.33)		1.10 (0.90–1.34)	
	6.4–7.6	233	1.19 (0.98–1.44)		1.20 (0.99–1.45)		1.21 (1.00–1.47)	
	≥ 7.6	229	1.20 (0.99–1.46)		1.23 (1.01–1.48)		1.19 (0.98–1.45)	
Arachidonic acid (20:4)	≤ 0.03	226	ref	0.75	ref	0.56	ref	0.71
	0.03–0.04	222	0.97 (0.81–1.17)		0.98 (0.82–1.18)		0.99 (0.82–1.20)	
	0.04–0.05	209	0.92 (0.76–1.11)		0.94 (0.77–1.13)		0.94 (0.78–1.14)	
	0.05–0.07	206	0.94 (0.77–1.13)		0.95 (0.79–1.15)		0.91 (0.75–1.10)	
	≥ 0.07	224	1.05 (0.87–1.27)		1.08 (0.90–1.30)		1.00 (0.83–1.21)	
n-3 PUFA								
α-Linolenic acid (18:3)	≤ 0.5	225	ref	0.88	ref	0.68	ref	1
	0.5–0.6	212	0.95 (0.79–1.15)		0.96 (0.79–1.16)		0.97 (0.80–1.18)	
	0.6–0.7	206	0.93 (0.77–1.13)		0.94 (0.78–1.14)		0.94 (0.78–1.15)	
	0.7–0.8	255	1.17 (0.98–1.40)		1.18 (0.99–1.42)		1.19 (0.99–1.43)	
	≥ 0.8	189	0.90 (0.74–1.10)		0.93 (0.76–1.12)		0.89 (0.73–1.08)	
Eicosapentaenoic acid (20:5)	≤ 0.005	214	ref	0.16	ref	0.22	ref	0.13
	0.005–0.009	197	0.95 (0.79–1.16)		0.96 (0.79–1.17)		0.90 (0.74–1.10)	
	0.009–0.014	215	1.02 (0.85–1.24)		1.03 (0.85–1.24)		1.01 (0.83–1.23)	
	0.014–0.025	221	1.04 (0.87–1.26)		1.04 (0.86–1.26)		1.02 (0.85–1.24)	
	≥ 0.025	240	1.11 (0.92–1.34)		1.10 (0.91–1.32)		1.10 (0.91–1.33)	
Docosapentaenoic acid (22:5)	≤ 0.000	214	ref	0.34	ref	0.53	ref	0.59
	0.000–0.005	221	1.07 (0.88–1.29)		1.01 (0.82–1.24)		1.12 (0.93–1.37)	
	0.005–0.007	208	1.00 (0.82–1.21)		0.97 (0.80–1.18)		0.99 (0.81–1.21)	
	0.007–0.010	204	0.99 (0.82–1.20)		0.96 (0.79–1.16)		0.97 (0.79–1.18)	

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Type of fat	% Total energy	Case, N	Age and sex adjusted [a]		Multivariate adjusted[b]		Inverse probability weighting[c]	
			OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend	OR (95% CI)	*P* for trend
	≥ 0.010	240	1.14 (0.95–1.38)		1.09 (0.91–1.32)		1.13 (0.94–1.37)	
Docosahexaenoic acid (22:6)	≤ 0.016	228	ref	0.22	ref	0.27	ref	0.3
	0.016–0.024	200	0.89 (0.74–1.08)		0.90 (0.74–1.08)		0.91 (0.75–1.11)	
	0.024–0.034	208	0.94 (0.77–1.13)		0.94 (0.78–1.14)		0.95 (0.79–1.16)	
	0.034–0.052	209	0.95 (0.79–1.14)		0.95 (0.78–1.14)		0.96 (0.79–1.16)	
	≥ 0.052	242	1.10 (0.92–1.32)		1.09 (0.91–1.31)		1.09 (0.90–1.31)	

Abbreviations: OR: odds ratios; CI: confidence intervals; MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids

[a] Adjusted for age and sex

[b] Adjusted for age, sex, race, smoking status, caffeine intake and total energy intake.

[c] Adjusted for inverse probability weights with 95% CIs calculated from robust variance estimates