Published in final edited form as:

J Neurol Neurosurg Psychiatry. 2016 January ; 87(1): 86–92. doi:10.1136/jnnp-2014-310065.

Dietary cholesterol, fats and risk of Parkinson's disease in the Singapore Chinese Health Study

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Abstract

Background—Prospective studies on lipids and risk of Parkinson's disease (PD) in Asian populations are sparse. This study prospectively examined the associations between dietary cholesterol and major fatty acids, and risk of PD among the Chinese in Singapore.

Methods—This study used data from the Singapore Chinese Health Study, a population-based prospective cohort of 63 257 men and women aged 45–74 years in Singapore enrolled in 1993–1998. Dietary intakes of cholesterol and fatty acids were derived from a validated semiquantitative food frequency questionnaire and the Singapore Food Composition Table. Incident PD cases were identified either through follow-up interviews or record linkage analysis with hospital discharge and PD outpatient registries.

Results—After an average of 14.6 years, 218 men and 193 women in the cohort developed PD. Dietary cholesterol was associated with statistically significantly lower risk of PD in a dose–dependent manner among men after adjustment for established risk factors for PD and intakes of major fatty acids. Compared to the lowest quartile, HR (95% CI) for the highest quartile was 0.53 (95% CI 0.33 to 0.84) (P for trend=0.006). Among women, dietary monounsaturated fatty acid

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Competing interests None.

Ethics approval Institutional Review Boards of the National Healthcare Group, National University of Singapore, Singapore Health Services and the University of Pittsburgh.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data is stored with the PIs of the original study according to the governance of their respective institutions and IRBs.

was inversely associated with PD risk (P for trend=0.033). Compared to the lowest quartile, HR for the highest quartile was 0.44 (95% CI 0.22 to 0.88). There was no statistically significant association between dietary saturated, n-3 and n-6 fatty acids and PD risk.

Conclusions—Higher intakes of cholesterol and monounsaturated fatty acids may reduce risk of PD in men and women, respectively.

INTRODUCTION

Parkinson's disease (PD) is a debilitating neurodegenerative disorder that is caused by selective degeneration of the dopaminergic neurons in the substantia nigra. The exact mechanism underlying this process is unclear, but oxidative stress, mitochondrial dysfunction and inflammation are thought to play major roles in aetiology of PD.[1]

Fatty acids (FAs) are major components in neuronal cell membranes and synapses, and essential for maintaining their structure and function. FAs have also been found to have anti-inflammatory, antioxidative and neuroprotective properties.[2–5] The FA composition of cell membranes is affected by diet. In infants and young animals, dietary deficiency of monounsaturated FAs (MUFA) and polyunsaturated FAs (PUFA) have been reported to lead to poorer brain function.[45]

Cholesterol also plays an important role in the central nervous system. Although the brain makes up only 2–5% of body mass, approximately 25% of total cholesterol in the body resides in the brain.[6] The majority (70–90%) of the cholesterol in the central nervous system constitutes the myelin that surrounds axons and facilitates neurotransmission.[6] α-Synuclein, a major constituent of Lewy bodies that is the hallmark of PD pathology, contains two cholesterol-binding domains. It has been shown cholesterol and other lipids modulate α-synuclein aggregation and have therefore been implicated in PD pathogenesis.[67]

A number of retrospective case–control[7–13] and prospective cohort studies[14–17] have investigated the associations between intakes of dietary lipids (ie, fats and cholesterol) and risk of PD. However, few studies have analysed specific subtypes of major dietary fats including saturated FA (SFA), MUFA, and PUFA including n-3 FA and n-6 FA. Among four prospective cohort studies, two found an association between higher intake of unsaturated FA and reduced risk of PD[1417] while two others did not find any significant association.[1516] There have been no prospective studies showing any statistically significant relationship between dietary cholesterol intake and the risk of PD. In the present study, we examined prospectively the associations between dietary intakes of cholesterol and major FAs and risk of PD in a prospective cohort of middle-aged and elderly Chinese men and women in Singapore.

MATERIALS AND METHODS

Study population

The Singapore Chinese Health Study is a population-based prospective cohort that recruited 63 257 Singapore Chinese who were of ages 45–74 years between April 1993 and December 1998. The recruitment only included citizens or permanent residents who were residing in

government-built housing estates, where 86% of the Singapore population lived during the enrolment period. We restricted study participants to the two major dialect groups of Chinese in Singapore—the Hokkiens who originated from the southern part of Fujian Province and the Cantonese who came from the central region of Guangdong Province.[18] About 42% and 15% of the resident Chinese population in Singapore belonged to the Hokkien and Cantonese group, respectively, during the period of recruitment.[19] This study was approved by the Institutional Review Boards of the National Healthcare Group, National University of Singapore, Singapore Health Services, and the University of Pittsburgh. All participants gave informed consent.

Baseline exposure assessment

At recruitment, participants were interviewed in their homes by trained interviewers using a structured questionnaire to obtain information on demographics, smoking, current physical activity, menstrual and reproductive histories (women only), occupational exposure and medical history. We used a 165-item semi-quantitative food frequency questionnaire (FFQ) that was specifically developed for and validated in this study population to assess usual dietary intake over the past 12 months[18] at the baseline interview. The 165 listed food items were commonly consumed in this population and belonged to food categories such as rice and noodle, meats, vegetables, fruits, soy foods, legumes, nuts and seeds, dairy products, beverages, condiments and preserved foods. The study participants were instructed to select, for each food item, from eight intake frequency categories (ranging from ‘never or hardly ever’ to ‘two or more times a day’) in combination with three portion sizes (small, medium, large) with the aid of food photographs. The intake of each nutrient from diet for every cohort participant was calculated based on the participant's response to all 165 food items with the Singapore Food Composition Table that was created specifically for this study and described previously.[18] This Food Composition Table contained approximately 100 nutritional and non-nutritional values per 100 g of the edible raw and cooked foods for each food item or mixed dish.[18] The FFQ had been validated previously using 24 h recalls and readministration of the FFQ among a subset of 810 participants. The validation study by these two methods showed similar distributions with most mean pairs for energy and nutrients within 10% of each other's values. The correlation coefficient by these two methods for each dietary component ranged between 0.24 and 0.79, which is comparable with previous validation study in diverse populations.[18]

Case ascertainment and follow-up

Identification of potential PD cases among cohort participants was described previously.[20] Briefly, PD cases were identified from three independent sources. (1) Two follow-up interviews were conducted on all surviving cohort participants in 1999–2004 and in 2006–2010. The response rates of follow-up I and II were 90% and 76% among surviving participants, respectively. Participants were asked if they had ever been told by a physician to have PD, and if yes, age at which diagnosis was ascertained (source 1). (2) A computer-assisted record linkage analysis of the cohort database with the nationwide hospital discharge database was carried out to identify all diagnoses with the International Classification of Disease V.9 (ICD-9) code 332 PD from 1990 to 2010 in public and private hospitals (source 2). (3) A computer-assisted record linkage analysis of the cohort database

with hospital-based PD registries until 31 December 2010 was carried out. These PD registries recorded patients with PD diagnosis and were followed up primarily as outpatients in PD centres housed in the two largest public hospitals in Singapore (source 3).

Of the PD cases ascertained from the three sources, 151 cases were identified from source 1, 429 cases from source 2, and 195 cases from source 3. All available medical records of these 775 identified cases were reviewed by a movement disorder fellow (KM) and specialist (LCT) to verify the date of diagnosis and confirm that the diagnosis was primary PD made according to the criteria defined by the Advisory Council of the USA National Institute of Neurological Disorders and Stroke (NINDS).[21] Of the 775 cases, the dates of first diagnosis on 53 patients occurred before their dates of cohort enrolment (ie, these were prevalent cases of PD) and one patient had incomplete medical records to ascertain date of first diagnosis, and these were excluded from this study. Among the remaining 721 cases, 285 patients did not meet our diagnostic criteria of PD and were not counted as cases. The remaining 436 patients were verified as incident cases of PD in this study. Among them, 242 (56%) satisfied NINDS's definition for probable PD, and 177 (41%) satisfied NINDS's definition for possible PD. Of the remaining 17 PD cases, eight patients exhibited rigidity and/or asymmetrical onset in addition to resting tremor and/or bradykinesia, a substantial and sustained response to levodopa or dopa-mine agonist, or an inadequate trial of levodopa or dopamine agonist and absence of other cause of parkinsonism. Nine patients had clear documentation by a certified internist to have PD but the accessible medical records did not allow for the above evaluation.

Statistical analysis

We further excluded participants with a baseline history of cancer due to the consideration of their change in dietary habits after cancer diagnosis (n=1931), and further excluded those who had extreme values of daily calorie consumption (<700 or >3700 kcal/day for men (n=459) and<600 and >3000 kcal/day for women (n=564)). The vital status of cohort participants was ascertained by a routine record linkage analysis of the cohort database with the Singapore Registry of Births and Deaths. The final analysis included 60 249 eligible study participants that included 411 incident PD cases.

For each study participant, person-years were counted from the date of baseline interview to the date of PD diagnosis, date of death, or 31 December 2010 whichever occurred first. The χ^2 test (for categorical variables) or student's t test (for continuous variables) was used to examine the differences in distributions of characteristics between study participants who developed PD and those who remained free of PD. Energy-adjusted intake of FA (g/day) and cholesterol (mg/day) were calculated by means of the residual method.[22] This method is used to control for confounding by total energy intake and to remove extraneous variation due to total energy intake, thus allowing the variation due to the nutrient composition of the diet (as opposed to the combination of dietary composition and total amount of food) to be evaluated directly.[22] The quartile levels of each energy-adjusted nutrient were derived from the respective distributions among all participants in the cohort. The correlation between intake of two nutrients was measured by the Spearman correlation coefficient.

Proportional hazards regression methods were used to examine the associations between dietary intakes of cholesterol and major FA group and risk of PD with adjustment for potential confounders. The strength of a given association was measured by the HR and its corresponding 95% CI and two-sided p value. The selection of potential confounders was based primarily on prior consideration of their associations with risk of PD in this population. All regression models were adjusted for age at recruitment (years), year of interview (1993–1995, 1996–1998), gender (whole cohort analysis), dialect group (Cantonese, Hokkien) and level of education (no formal education, primary school, secondary school or higher), body mass index (<20, 20–<24, 24–<28, 28+ kg/m^2), cigarette smoking (never, former, current), black tea intake (non/monthly, weekly, daily), caffeine intake (quartiles). Additional analysis included further adjustment for cholesterol and major FA groups (quartiles). Quartile categories were drawn up based on intake within the whole cohort. Tests for trend were performed by using the ordinal values of intake in the quartile categories as continuous variables in the Cox regression models. For example, participants in the lowest quartile intake were assigned an ordinal value of one and those in the highest quartile intake were assigned a value of four. Heterogeneity of the diet-PD risk associations between men and women was tested by including a product term, which is a product between gender and ordinal values of the nutrient intake in quartiles, as an interaction term in the Cox model.

All statistical analysis was conducted using SAS V.9.2 (SAS Institute, Inc., Cary, North Carolina, USA). All reported p values are two sided; $p<0.05$ was considered statistically significant.

RESULTS

The present analysis was based on 411 cases among 60 249 participants after a mean follow-up of 14.0 SD, 3.7) years. The mean age at diagnosis for the incident PD cases was 70.5 (SD, 7.5) years and the mean time interval between cohort enrolment and PD diagnosis was 8.4 years (SD, 4.4 years). The incidence rates of PD, adjusted to the age structure of the whole cohort (ages 45 to 74 years) were 61.3/100 000 person-years in men and 40.0/100 000 person-years in women.

The PD cases were significantly older at recruitment compared to the rest of the cohort. There was a significantly greater proportion of men than women among PD cases compared to non-PD cases. PD cases were less likely to smoke cigarettes and consumed lower caffeine than non-cases (table 1). Compared to participants without PD, PD cases had lower energy-adjusted intake of cholesterol, total fats, SFA and MUFA (table 1).

Dietary intake of cholesterol was moderately correlated with intake of FAs; the correlation coefficients ranged from 0.19 with n-6 FA to 0.53 with MUFA (table 2). Within major FA groups, the correlation coefficient was highest between SFA and MUFA (r=0.69), followed by correlation between n-3 FA and n-6 FA (r=0.48). Poultry and red meat including pork, beef and lamb accounted for 10.5%, 12.1% and 13.9% of SFA, MUFA and cholesterol, respectively. Up to 42% of cholesterol came from seafood and eggs. Cooking fats, oil and

butter/margarine spread accounted for 29.4% and 35.1% of SFA and MUFA, but only 2.7% of cholesterol intake, respectively.

Dietary intake of cholesterol was associated with reduced risk of PD in all participants, and the inverse relationship was statistically borderline significant (p=0.046) after adjustment for established risk/protective factors for PD in this study population. The inverse cholesterol-PD risk was apparent in men but not in women (P for interaction=0.19). Among men, HR of PD for the highest quartile intake was 0.62 (95% CI 0.42 to 0.93) compared with the lowest quartile (P for trend=0.018) (table 3). Simultaneous adjustment for intakes of SFA, MUFA, n-3 FA and n-6 FA did not change the association between dietary cholesterol intake and PD risk in both genders (table 4). The cholesterol-PD risk association could be subjected to reverse-causality bias since some PD cases could be undiagnosed at enrolment due to the lag period between onset and diagnosis of PD. To overcome this bias, we excluded PD cases diagnosed within 4 years postenrolment and the corresponding observed person-years. The results remained essentially unchanged (table 4).

After adjusting for established risk factors for PD, dietary intake of MUFA was inversely associated with PD risk in women but not in men (P for interaction=0.11) (table 3). Compared to the lowest quartile, the HR for the highest quartile intake in women was 0.57 (95% CI 0.36 to 0.90, P for trend=0.029) (table 3). Further adjustment for dietary cholesterol and other major FA group did not materially alter the inverse MFA-PD risk association in women (table 4). The inverse relationship between MFA intake and PD risk in women was slightly diminished after excluding PD cases diagnosed within 4 years post enrolment and the corresponding observed person-years (P for trend=0.058) (table 4).

For the other major FA, overall, there was no statistically significant association between intakes of total fat, SFA, n-3 FA and n-6 FA, and risk of PD in men and women combined or in either gender alone (table 3). The results were essentially the same using gender-specific cut-points for the definition of quartiles for the food and nutrient variables included in this study (data not shown).

DISCUSSION

The present study suggested that among Singapore Chinese, higher intakes of dietary cholesterol and MUFA were associated with reduced risk of PD among men and women, respectively.

A novel finding in this study is that higher intake of dietary cholesterol is associated with a lower risk of PD among men. Previous retrospective case–control studies have shown inconsistent results; higher intake of dietary cholesterol was associated with increased risk of PD in two studies,[10,23] but reduced risk in one other study in men only.[24] Of the two prospective cohorts that studied the association of cholesterol and PD,[16,17] one showed a trend for an inverse relationship between cholesterol and the risk of PD[17] while the other study found a null association.[16] More compelling support for our findings may be found in the literature on studies comparing serum cholesterol with the risk of PD. At least two case–control studies[25,26] and three prospective studies[27–29] have found that higher serum

cholesterol levels were associated with a reduced risk of PD. In addition, a secondary analysis of the DATATOP (Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism) trial in patients with PD found that higher serum cholesterol levels were associated with a slower disease progression to a surrogate end point, which is clinical disability requiring levodopa therapy.[30] The effects of cholesterol in PD have also been demonstrated in high-resolution MRI studies which found that higher serum cholesterol levels were associated with lower iron content in the substantia nigra and globus pallidus in patients with PD.[31] Iron accumulation has been found in the brains of patients with PD and is thought to play a pathogenic role.[31] The results of these publications support our finding that higher dietary intakes of cholesterol could reduce the risk of developing PD.

Dysregulation of cholesterol homeostasis in the brain has been linked to chronic neurodegenerative disorders, including Alzheimer's disease, Huntington's disease and PD.[6] Biochemical studies showed that α-synuclein, the major component of Lewy bodies found in PD brains, binds to cholesterol with high affinity, and its aggregation is modified by cholesterol.[67] A recent study has shown that lanosterol, a cholesterol precursor, was significantly reduced in the nigrostriatal region of 1-methyl-4-phenyl-1236-tetrahydropyridine (MPTP) treated mice, an animal model of PD. Remarkably, exogenous addition of lanosterol rescued dopaminergic neurons from 1-methyl-4-pheylpyridium (MPP +) induced cell death in culture, suggesting a neuroprotective effect.[32] It has also been found that there is significantly lower cholesterol biosynthesis in patients with PD than controls.[33] While these findings suggest an important role of cholesterol in the pathogenesis or in providing neuroprotection in PD, it is important to note that because plasma lipoproteins do not cross the intact blood-brain barrier, nearly all cholesterol in the brain is synthesised in situ.[34] Despite this, it is possible that dietary and serum cholesterol may have some effect on brain cholesterol production and/or metabolism as cholesterol and lipid transport are complex, and dysfunction of the blood-brain barrier has been found in PD that could result in transportation of lipoproteins between plasma and brain.[35] Furthermore, cholesterol turnover in the brain is increased in neurodegenerative disorders and large amounts of cholesterol turnover occur among glial cells and neurons in the central nervous system during neuron repair and remodelling.[34] Higher intake of cholesterol may therefore be beneficial in facilitating central nervous system repair, thereby lowering the risk of developing PD.

A number of retrospective case–control studies have shown either a positive correlation[101126] or no association[891213] between dietary fat and PD. However, these studies did not analyse specific subtypes of fat and carry inherent methodological limitations such as recall bias and temporal bias. Our findings are consistent with that in the Rotterdam study, a prospective cohort study, which found that higher intakes of MUFA were significantly associated with a lower risk of PD.[17] A recent case–control study also revealed that higher dietary adherence to the Mediterranean-type diet, which is rich in unsaturated FAs, was associated with a reduced risk for PD.[36]

The relative brain content of FAs such as MUFA depends heavily on nutritional intake in mammals.[537] MUFA have been shown to have anti-inflammatory and immune-modulating properties[538] and might protect against oxidative stress.[245] In addition, it has been suggested

that low MUFA in the brain cell membranes may result in greater degeneration in PD. Patients with PD who took higher cumulative doses of levodopa, a marker of more severe PD, had lower MUFA in the brain cortex on postmortem.[39] These findings together, suggest an important role that MUFA may play in reducing the risk of PD.

The study of the dietary effects of lipids is complicated by gender differences in lipoprotein metabolism and dietary responses. Lipoprotein metabolism is accelerated approximately twofold in women compared with men due to the stimulatory effects of oestrogen in women and the inhibitory effects of androgen in men.[40] Studies have found that following dietary cholesterol intake, serum low-density lipoprotein (LDL)-cholesterol increases were significantly higher in men than women, especially in participants 50 years of age and older.[4041] The relatively attenuated rise in serum LDL-cholesterol following dietary cholesterol intake in women may be one of the possible explanations for a lack of association between dietary cholesterol intake and PD risk in women in the present study. The complex interaction between sex-hormones and lipid metabolism may be another possible explanation for the differential association between dietary MUFA intake and PD risk that was found in women only. Nevertheless, we acknowledge that the lack of consistency between men and women in the analyses of cholesterol and MUFA may be chance findings. Further studies are warranted to further unravel gender differences in lipid metabolism.

To the best of our knowledge, this is the first prospective cohort study in an Asian population that has comprehensively examined specific major types of dietary FAs, cholesterol and risk of PD. Strengths of the study include its population-based design and the presumed lack of recall bias in exposure data since they were obtained many years before diagnosis of PD. We restricted study participants to the two major dialect groups of Chinese in Singapore—the Hokkiens, who originated from the southern part of Fujian Province, and the Cantonese who came from the central region of Guangdong Province. For our cohort participants, most of their parents would have come from the same province in China and thus belonged to the same dialect group. Hence, in all our analyses, we have included dialect group as a covariate to account for any possible genetic heterogeneity between these two dialect groups. Our previous results using the same cohort have shown that the method of case ascertainment using three different sources is relatively complete.[20] Another strength is the use of a FFQ that was created for and validated in our study population.[18]

A major limitation of this study is that diet assessment was only conducted at study recruitment. Dietary changes over time after baseline interview may also lead to non-differential misclassification of intake, which would result in an underestimation of the true effect size of dietary cholesterol and FAs and risk of PD. A second limitation is the use of the FFQ to measure dietary intake in this population. Although the FFQ is a convenient and cost-effective method for dietary assessment in large epidemiological studies, increasing concern has been raised about measurement errors associated with its use.[42] However, this would most likely result in non-differential misclassification with respect to disease status and likely underestimation of risk. In addition, the self-reported lifestyle-related data and baseline comorbidity status may also result in some misclassification and residual confounding. Another potential limitation is the lack of systematic screening for PD at

baseline and hence the possibility of prevalent cases being included as incident cases. Another limitation of the study is the lack of information on the use of cholesterol-lowering drugs, such as statins, in the study population. We also cannot exclude the possibility that our positive findings could be chance findings, given that multiple comparisons were made.

In conclusion, we report for the first time in a prospective study that an increased intake of dietary cholesterol is associated with a reduced risk of PD. These results lend weight to the increasing evidence that cholesterol may lower the risk or modify the progression of PD. Our study also supports previous reports that a higher intake of MUFA is associated with a reduced risk of PD. As fats and cholesterol are intimately associated with the central nervous system, these findings warrant further investigation to understand the underlying pathogenic mechanisms of PD. This in turn may lead to the development of compounds that can reduce the risk or progression of PD.

Acknowledgements

The authors thank Siew-Hong Low of the National University of Singapore for supervising the field work of the Singapore Chinese Health Study, Renwei Wang of the University of Pittsburgh Cancer Institute for the management of the cohort study database, and Irene Seah of the National Neuroscience Institute for management of the Parkinson's disease (PD) database. The authors also thank the Ministry of Health in Singapore for assistance with the identification of PD cases via record linkage analysis with various databases. The authors acknowledge the following doctors for their assistance to access medical records: Drs David Ng (National Healthcare Group Polyclinics), Ngiap-Chuan Tan (Singhealth Polyclinics), Kay-Yaw Tay (Khoo Teck Puat Hospital), and Keng-Bee Yap (Alexandra Hospital—Jurong Health Services). Finally, the authors acknowledge the founding principal investigator of the Singapore Chinese Health Study—Mimi C Yu.

Funding This study was supported by the National Institutes of Health, USA (R01 CA144034 and UM1 CA182876); National Medical Research Council, Singapore; and Singapore Millennium Foundation.

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Table 1

Baseline characteristics of cohort members without PD and PD cases (mean (SD) or per cent), The Singapore Chinese Health Study

	PD cases (n=411)	Non-PD participants (n=59 838)	p Value
Age (years) at recruitment	61.5 (7.2)	56.5 (8.0)	<0.0001
Body mass index (kg/m^2)	23.0 (2.9)	23.1 (3.3)	0.35
Sex (%)			
Males	218 (53.0)	26 591 (44.4)	0.0005
Females	193 (47.0)	33 247 (55.6)	
Dialect (%)			
Cantonese	176 (42.8)	27 723 (46.3)	0.15
Hokkien	235 (57.2)	32 115 (53.7)	
Level of education (%)			
No formal education	111 (27.0)	16 149 (27.0)	0.032
Primary school (1-6 years)	205 (49.9)	26 614 (44.5)	
Secondary school and above	95 (23.1	17 075 (28.5)	
Smoking status (%)			
Never smoker	296 (72.0)	41 577 (69.5)	0.007
Former smoker	57 (13.9)	6513 (10.9)	
Current smoker	58 (14.1)	11 748 (19.6)	
Black tea intake (%)			
Non/monthly	302 (73.5)	42 987 (71.8)	0.12
Weekly	76 (18.5)	10 182 (17.0)	
Daily	33 (8.0)	6669 (11.2)	
Total energy (kcal/day)	1529 (554)	1548 (520)	0.46
Dietary intake (energy-adjusted)			
Caffeine (mg/day)	125.5 (102.2)	148.5 (106.2)	<0.0001
Total fatty acids (g/day)	42.4 (9.6)	43.8 (10.3)	0.003
Saturated fatty acids (g/day)	14.8 (4.3)	15.5 (4.6)	0.001
Monounsaturated fatty acids (g/day)	14.3 (3.5)	14.8 (3.8)	0.003
n-3 Polyunsaturated fatty acids (g/day)	0.88 (0.3)	0.89 (0.3)	0.63
n-6 Polyunsaturated fatty acids (g/day)	7.8 (3.0)	7.9 (3.1)	0.73
Cholesterol (mg/day)	157.7 (65.5)	173.0 (74.3)	<0.0001

p Value by χ^2 or student's t test.

PD, Parkinson's disease

Table 2

Spearman correlation coefficients between diet fat and cholesterol (energy-adjusted) in the Singapore Chinese Health Study

	Total FAs	Saturated FAs	MUFAs	n-3 PUFAs	n-6 PUFAs	Cholesterol
Total FAs	1.00	0.73	0.87	0.52	0.50	0.51
Saturated FAs		1.00	0.69	0.32	0.03	0.46
MUFA			1.00	0.42	0.40	0.53
n-3 PUFAs				1.00	0.48	0.29
n-6 PUFAs					1.00	0.19
Cholesterol						1.00

FAs, fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

Table 3

Dietary cholesterol and fatty acids in relation to risk of Parkinson's disease, The Singapore Chinese Health Study 1993–2010

Energy-adjusted intake by quartile	Total Cases	HR (95% CI)	Men Cases	HR (95% CI)	Women Cases	HR (95% CI)
Cholesterol (mg/day)						
1st (<130.7)	130	1.00	82	1.00	48	1.00
2nd (130.7–166.5)	115	0.96 (0.74 to 1.23)	56	0.94 (0.67 to 1.32)	59	1.00 (0.68 to 1.47)
3rd (166.5–206.4)	91	0.84 (0.64 to 1.10)	44	0.83 (0.57 to 1.19)	47	0.87 (0.58 to 1.31)
4th (>206.4)	75	0.77 (0.58 to 1.02)	36	0.62 (0.42 to 0.93)	39	0.98 (0.64 to 1.5)
P for trend		0.046		0.018		0.72
Total fatty acids (g/day)						
1st (<38.4)	117	1.00	74	1.00	43	1.00
2nd (38.4–44.3)	114	1.03 (0.79 to 1.34)	62	1.17 (0.83 to 1.64)	52	0.86 (0.58 to 1.29)
3rd (44.3–50.0)	111	1.10 (0.85 to 1.44)	46	1.03 (0.71 to 1.49)	65	1.10 (0.75 to 1.62)
4th (>50.0)	69	0.80 (0.59 to 1.08)	36	0.92 (0.61 to 1.37)	33	0.66 (0.41 to 1.04)
P for trend		0.30		0.69		0.24
Saturated fatty acids (g/day)						
1st (<12.8)	124	1.00	79	1.00	45	1.00
2nd (12.8–15.5)	111	0.98 (0.75 to 1.26)	57	1.04 (0.74 to 1.46	54	0.91 (0.61 to 1.35)
3rd (15.5–18.3)	97	0.94 (0.71 to 1.22)	41	0.85 (0.58 to 1.24)	56	0.99 (0.66 to 1.47)
4th (>18.3)	79	0.89 (0.67 to 1.19)	41	0.96 (0.65 to 1.41)	38	0.80 (0.52 to 1.25)
P for trend		0.39		0.59		0.45
Monounsaturated fatty acids (g/day)						
1st (<12.8)	116	1.00	69	1.00	47	1.00
2nd (12.8–14.9)	121	1.10 (0.85 to 1.42)	63	1.27 (0.9 to 1.79)	58	0.88 (0.6 to 1.29)
3rd (14.9–17.0)	102	1.01 (0.77 to 1.33)	45	1.05 (0.72 to 1.53)	57	0.90 (0.61 to 1.33)
4th (>17.0)	72	0.80 (0.60 to 1.08)	41	1.03 (0.7 to 1.52)	31	0.57 (0.36 to 0.90)
P for trend		0.16		0.99		0.029
n-3 Polyunsaturated fatty acids (g/day)						
1st (<0.72)	120	1.00	77	1.00	43	1.00
2nd (0.72–0.85)	101	0.87 (0.66 to 1.13)	44	0.78 (0.54 to 1.13)	57	0.93 (0.63 to 1.39)
3rd (0.85–0.99)	85	0.74 (0.56 to 0.99)	42	0.80 (0.55 to 1.17)	43	0.68 (0.44 to 1.04)
4th (>0.99)	105	0.95 (0.72 to 1.23)	55	1.04 (0.73 to 1.47)	50	0.85 (0.56 to 1.28)
P for trend		0.45		0.96		0.23
n-6 Polyunsaturated fatty acids (g/day)						
1st (<6.0)	102	1.00	64	1.00	38	1.00
2nd (6.0–7.4)	111	1.12 (0.86 to 1.47)	57	1.22 (0.85 to 1.75)	54	0.97 (0.64 to 1.48)
3rd (7.4–9.3)	104	1.10 (0.83 to 1.45)	45	1.09 (0.74 to 1.6)	59	1.03 (0.68 to 1.55)
4th (>9.3)	94	0.99 (0.74 to 1.32)	52	1.20 (0.83 to 1.74)	42	0.77 (0.49 to 1.2)
P for trend		0.91		0.43		0.31

Adjusted for age at recruitment (years), year of interview (1993–1995, 1996–1998), gender (whole cohort analysis), dialect group (Cantonese, Hokkien) and level of education (no formal education, primary school, secondary school or higher), body mass index (<20, 20-<24, 24-<28, 28+ kg/m^2), cigarette smoking (never, former, current), black tea intake (non/monthly, weekly, daily) and caffeine intake (quartiles).

Table 4

Dietary cholesterol and monounsaturated fatty acids in relation to risk of Parkinson's disease, The Singapore Chinese Health Study 1993–2010

	Total		Men		Women	
Energy-adjusted intake by quartile	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**
Cholesterol (mg/day)						
Whole cohort						
1st (<130.7)	130	1.00	82	1.00	48	1.00
2nd (130.7–166.5)	115	0.96 (0.74 to 1.25)	56	0.87 (0.61 to 1.25)	59	1.10 (0.74 to 1.64)
3rd (166.5–206.4)	91	0.85 (0.63 to 1.15)	44	0.73 (0.49 to 1.10	47	1.05 (0.67 to 1.63)
4th (>206.4)	75	0.79 (0.57 to 1.11)	36	0.53 (0.33 to 0.84)	39	1.29 (0.78 to 2.12)
P for trend		0.13		0.006		0.41
More than 4 years of follow-up						
1st (<130.7)	107	1.00	66	1.00	41	1.00
2nd (130.7–166.5)	86	0.84 (0.62 to 1.13)	41	0.77 (0.51 to 1.15)	45	0.94 (0.61 to 1.46)
3rd (166.5–206.4)	77	0.82 (0.59 to 1.13)	39	0.75 (0.49 to 1.17)	38	0.92 (0.57 to 1.50)
4th (>206.4)	60	0.70 (0.48 to 1.02)	30	0.50 (0.30 to 0.84)	30	1.06 (0.61 to 1.85)
P for trend		0.07		0.012		0.91
Monounsaturated fat (g/day)						
Whole cohort						
1st (<12.8)	116	1.00	69	1.00	47	1.00
2nd (12.8–14.9)	121	1.12 (0.84 to 1.51)	63	1.46 (0.98 to 2.16)	58	0.80 (0.52 to 1.23)
3rd (14.9–17.0)	102	1.05 (0.73 to 1.51)	45	1.32 (0.80 to 2.19)	57	0.75 (0.44 to 1.28)
4th (>17.0)	72	0.84 (0.53 to 1.33)	41	1.40 (0.76 to 2.57)	31	0.44 (0.22 to 0.88)
P for trend		0.42		0.38		0.033
More than 4 years of follow-up						
1st (<12.8)	88	1.00	51	1.00	37	1.00
2nd (12.8–14.9)	97	1.18 (0.85 to 1.65)	51	1.58 (1.01 to 2.47)	46	0.79 (0.49 to 1.29)
3rd (14.9–17.0)	86	1.16 (0.77 to 1.74)	41	1.62 (0.93 to 2.81)	45	0.73 (0.40 to 1.33)
4th (>17.0)	59	0.90 (0.54 to 1.50)	33	1.53 (0.77 to 3.04)	26	0.46 (0.21 to 0.98)
P for trend		0.68		0.26		0.058

Adjusted for age at recruitment (years), year of interview (1993–1995, 1996–1998), gender (whole cohort analysis), dialect group (Cantonese, Hokkien) and level of education (no formal education, primary school, secondary school or higher), body mass index (<20, 20–<24, 24–<28, 28+ kg/m^2), cigarette smoking (never, former, current), black tea intake (non/monthly, weekly, daily), caffeine intake (mg/1000 kcal/day), and energy-adjusted dietary intakes of cholesterol, saturated fatty acids, monounsaturated fatty acids, n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids (all in quartiles).