RESEARCH ARTICLE

Relationship between high dietary fat intake and Parkinson's disease risk: a meta-analysis

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Abstract

OBJECTIVE: To assess whether dietary fat intake influences Parkinson's disease risk.
DATA SOURCES: We systematically surveyed the Embase and PubMed databases, reviewing manuscripts published prior to October 2018. The following terms were used: ("Paralysis agitans" OR "Parkinson disease" OR "Parkinson" OR "Parkinson's" OR "Parkinson's disease") AND ("fat" OR "dietary fat" OR "dietary fat intake").
DATA SELECTION: Included studies were those with both dietary fat intake and Parkinson's disease risk as exposure factors. The Newcastle-Ottawa Scale was adapted to investigate the quality of included studies. Stata V12.0 software was used for statistical analysis.
OUTCOME MEASURES: The primary outcomes included the relationship between high total energy intake, high total fat intake, and Parkinson's disease risk. The secondary outcomes included the relationship between different kinds of fatty acids and Parkinson's disease risk.
RESULTS: Nine articles met the inclusion criteria and were incorporated into this meta-analysis. Four studies scored 7 and the other five studies scored 9 on the Newcastle-Ottawa Scale, meaning that all studies were of high quality. Meta-analysis results showed that high total energy intake was associated with an increased risk of Parkinson's disease (P = 0.000, odds ratio (OR) = 1.49, 95% confidence interval (CI): 1.26–1.75); in contrast, high total fat intake was not associated with Parkinson's disease risk (P = 0.123, OR = 1.07, 95% CI: 0.91–1.25). Subgroup analysis revealed that polyunsaturated fatty acid intake (P = 0.010, OR = 1.03, 95% CI: 0.88–1.20) reduced the risk of Parkinson's disease, while arachidonic acid (P = 0.026, OR = 1.15, 95% CI: 0.97–1.37) and cholesterol (P = 0.002, OR = 1.09, 95% CI: 0.92–1.29) both increased the risk of Parkinson's disease. Subgroup analysis also demonstrated that, although the results were not significant, consumption of n-3 polyunsaturated fatty acids (P = 0.071, OR = 0.88, 95% CI: 0.73–1.05), α-linolenic acid (P = 0.06, OR = 0.86, 95% CI: 0.72–1.02), and the n-3 to n-6 ratio (P = 0.458, OR = 0.89, 95% CI: 0.75–1.06) were all linked with a trend toward reduced Parkinson's disease risk. Monounsaturated fatty acid (P = 0.450, OR = 1.06, 95% CI: 0.91–1.23), n-6 polyunsaturated fatty acids (P = 0.100, OR = 1.15, 95% CI: 0.96–1.36) and linoleic acid (P = 0.053, OR = 1.11, 95% CI: 0.94–1.32) intakes were associated with a non-significant trend toward higher PD risk. Saturated fatty acid (P = 0.619, OR = 1.01, 95% CI: 0.87–1.18) intake was not associated with Parkinson's disease.
CONCLUSION: Dietary fat intake affects Parkinson's disease risk, although this depends on the fatty acid subtype. Higher intake of polyunsaturated fatty acids may reduce the risk of Parkinson's disease, while higher cholesterol and arachidonic acid intakes may elevate Parkinson's disease risk. However, further studies and evidence are needed to validate any link between dietary fat intake and Parkinson's disease.

Key Words: *nerve regeneration; dietary fat; Parkinson's disease risk; meta-analysis; total energy intake; polyunsaturated fatty acids; arachidonic acid; cholesterol; α-linolenic acid; linoleic acid; n-3/n-6 polyunsaturated fatty acid intake ratio; monounsaturated fatty acids; neural regeneration*

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Introduction

Parkinson's disease (PD) is a neurodegenerative disease that is progressive and has a high incidence rate, with characteristic substantia nigra dopaminergic neuron depletion that gives rise to striatal dopamine depletion (Zecca et al., 2004; Sampaio et al., 2017; Martinez et al., 2018; Qu et al., 2019). PD development is influenced by both environmental and genetic mechanisms (Di Monte et al., 2002; Ma et al., 2015a, b, c; Liu et al., 2018), and it is a multi-factorial disease that arises from a combination of family history, age, ethnicity, occupation, and diet (Chaturvedi et al., 1995; Logroscino et al., 1998; Taylor et al., 1999; Kirkey et al., 2001; Priyadarshi et al., 2001; Zorzon et al., 2002; Li et al., 2005). There is evidence that, rather than a single disease, PD is actually a set of individual illnesses with a similar presentation (Dick et al., 2007). Although the mechanisms of PD development and progression are incompletely understood, inflammation, oxidative stress, and impaired mitochondrial function are all known to contribute to this disease (Jenner, 2003; Wullner and Klockgether, 2003; Schapira, 2007; Wang et al., 2017). Oxidative damage readily impacts the brain, because it requires substantial oxygen and iron availability (Noseworthy and Bray, 1998).

Dietary fat intake refers to the sum of fats from the various foods we eat every day, including simple lipids, complex lipids, terpenoids and steroids and their derivatives, derived lipids, and binding lipids. As well as providing energy to or-

ganisms, different fats have specific functions. Fatty acids are essential for brain function, and studies in rats have demonstrated that brains are dependent on dietary fatty acid intake (Ikemoto et al., 2001; Bowen and Clandinin, 2002; Hashimoto et al., 2002; Levant et al., 2007). Epidemiological evidence also suggests that dietary fat consumption may be linked with PD risk, but research results have to date been inconsistent (Hellenbrand et al., 1996; Noseworthy and Bray, 1998; Schatzkin et al., 2001; Chen et al., 2003; de Lau et al., 2005; Gao et al., 2007; Powers et al., 2009; Miyake et al., 2010; Kyrozis et al., 2013; Kamel et al., 2014). In recent years, increasing numbers of PD animal models and epidemiological investigations have shown that polyunsaturated fatty acids (PUFAs) play an important role in cell membrane sequencing, gene transcription, cell signal transduction, and protease activation of glial and neuronal cells, thereby influencing PD progress (Logroscino et al., 1996; Akbar and Kim, 2002; Akbar et al., 2005; Calon et al., 2005). Furthermore, in a PD autopsy report, docosahexaenoic acid levels were markedly decreased in the substantia nigra pars compacta and frontal cortex lipid raft (Dalfo et al., 2005; Fabelo et al., 2011).

Daily dietary fat intake may influence PD development, but further exploration of this association is needed. In the present meta-analysis, we conducted a systematic review with the aim of summarizing the available evidence regarding links between fat consumption and PD risk.

A systematic review was performed using the Embase and PubMed database, and relevant observational studies assessing the link between lipid or dietary fat content and PD risk were identified. Reference review of identified papers was also used to identify additional relevant publications. Only human studies were considered, and all studies were published in English.

The Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed to design, implement, analyze, and report the results of this meta-analysis. The MOOSE guidelines were described in JAMA (Stroup et al., 2000) and propose a common methodology for meta-analyses.

Data and Methods

Search strategy

Embase and PubMed were searched for the following terms: ("Paralysis agitans" OR "Parkinson disease" OR "Parkinson" OR "Parkinson's" OR "Parkinson's disease") AND ("fat" OR "dietary fat" OR "dietary fat intake"). Manuscripts published prior to October 2018 were reviewed. Two authors (YQ and XC) independently conducted the literature search.

Selection criteria

A total of 343 references were screened, using the following inclusion criteria: (1) the study could be defined as epidemiological, including case-control, nested case-control, cohort, and prospective studies; (2) dietary fat intake was the exposure of interest; (3) PD risk was the outcome of interest; (4) the study reported the odds ratio (*OR*) or relative risk (*RR*) and 95% confidence interval (*CI*), or the reported data were sufficient to be able to calculate these.

Articles that did not involve humans or that were not original, such as reviews, editorials, meta-analyses, or commentaries, were excluded. We also excluded studies of other exposures or endpoints.

Data extraction

Two authors (YQ and XC) independently collected detailed information from each identified article, with any discrepancies being resolved *via* discussion with the third author (MMX). The following data were extracted: (1) basic information: authors, year of publication, study population, age, sex, sample size, diagnoses, and case number; (2) study characteristics: study name and design, study location, follow-up duration; (3) variables adjusted during analysis; (4) outcome assessment method; (5) risk estimates and corresponding 95% *CI*s. If multiple multivariate-adjusted models were used for risk extraction, we extracted the confound-adjusted *OR* estimate.

Data regarding dietary intake in non-overlapping individuals were derived from questionnaires, which had high heterogeneity (I^2 = 75.9%).

Quality assessment

The Newcastle-Ottawa Scale (Cota et al., 2013) was adapted to investigate the quality of included studies. Case-control and cohort studies were investigated separately (**Additional Tables 1** and **2**). A total score of 0–3, 4–6, or 7–9 indicated a study of low, intermediate, or high quality, respectively.

Both authors (YQ and XC) independently used this scale to establish the quality of each study (Fang et al., 2015).

Outcome measures

The primary outcomes included high total energy intake, high total fat intake, and sex. The secondary outcomes included different kinds of fatty acids.

Statistical analysis

The *OR* and corresponding 95% *CI* were used as risk estimates for studies that satisfied the inclusion criteria. Dietary fat intake was determined based on Etminan's classification, as follows: high fat intake was within the 4th quartile or 5th quintile, while moderate fat intake was within the 2nd, 3rd, or 4th quintile or the 2nd and 3rd quartile. A random-effects (Der Simonian and Laird) model was used to pool these *OR*s, with the model combining heterogeneity within and between studies. The *RR* values of the four cohort analyses were converted to the corresponding *OR* values (Zhang et al., 1998). The values used in statistical analyses were all *OR* values.

Subgroup analysis was carried out to investigate significant differences in *OR*s, and whether results were influenced by residual confounding factors adjusted for sex, geographical location, numbers of participants, follow-up duration, and study quality.

The I^2 statistic was used as a measure of heterogeneity of the included studies, with I^2 values of 25%, 50%, or 75% re-

spectively indicating low, intermediate, or high heterogeneity.

Both a funnel plot and Egger's test were used to assess the potential for publication bias. Studies that were identified as having a high risk of bias were subjected to both Egger's and Begg's tests. $P < 0.05$ was considered to indicate significant publication bias. Two-tailed statistical tests were performed using Stata 12.0 software (Stata Corporation, College Station, TX, USA), with $P < 0.05$ as the significance threshold.

Results

Search results

We retrieved 259 PubMed articles and 173 Embase articles, all of which were published before October 2018 (**Figure 1**). Nine articles (four cohort studies and five case–control studies) met the inclusion criteria and were incorporated into this meta-analysis.

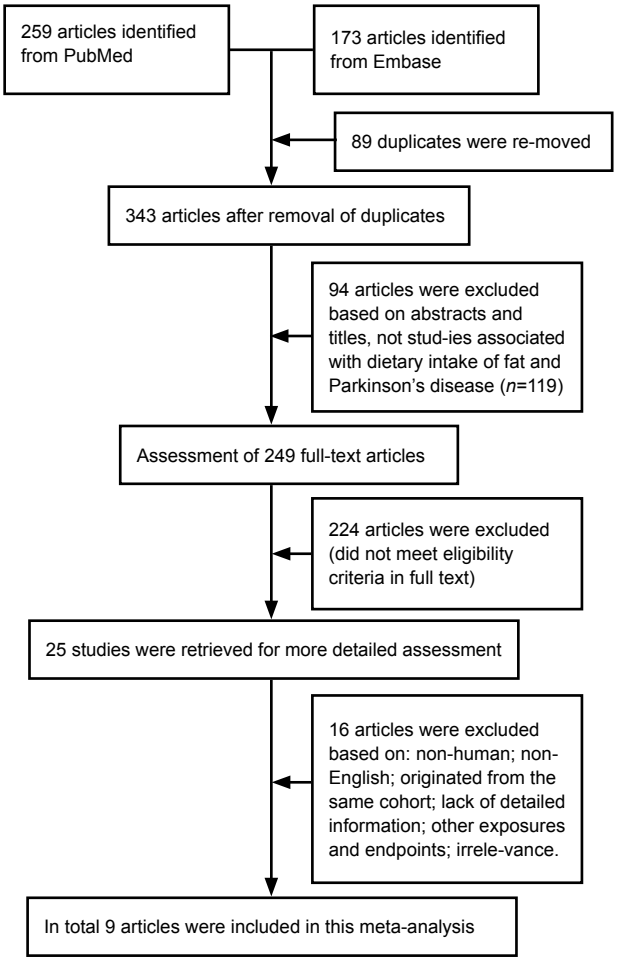

Figure 1 Flow chart depicting the literature search and selection strategy.

Study characteristics

Basic parameters of the included studies are summarized in **Tables 1** and **2**. A total of 778,571 participants were included in the nine studies, including 5751 PD cases. There was a range of follow-up durations from 2–14 years. Four studies (Chen et al., 2003; Gao et al., 2007; Kyrozis et al., 2013; Dong et al., 2014) were cohort studies, while five studies (Hellenbrand et al., 1996; Logroscino et al., 1996; Powers et al., 2009; Miyake et al., 2010; Kamel et al., 2014) were case-control studies. Four studies scored 7 on the Newcastle-Ottawa Scale, and the other five studies scored 9, meaning that all studies were of high quality (**Additional Tables 1** and **2**).

Meta-analysis results

Primary outcomes

To assess the link between different factors of interest and the exposure assessments, we performed separate analyses. The pooled *OR* for PD in those with a high total energy intake was 1.49 ($P = 0.000$, *OR* = 1.49, 95% *CI*: 1.26–1.75), while it was 1.07 ($P = 0.123$, *OR* = 1.07, 95% *CI*: 0.91–1.25) in those with high total fat intake, and 1.02 ($P = 0.005$, *OR* = 1.02, 95% *CI*: 0.79–1.30) in men. The overall pooled *OR* was 1.21 ($P = 0.000$, *OR* = 1.21, 95% *CI*: 1.09–1.34; **Figure 2**). However, fat included many subtypes, and different food sources may have different amounts of fat subtypes, which may have led to the high heterogeneity observed in these results ($I^2 = 75.9\%$), so we carried out subgroup analyses and a sensitivity analysis simultaneously.

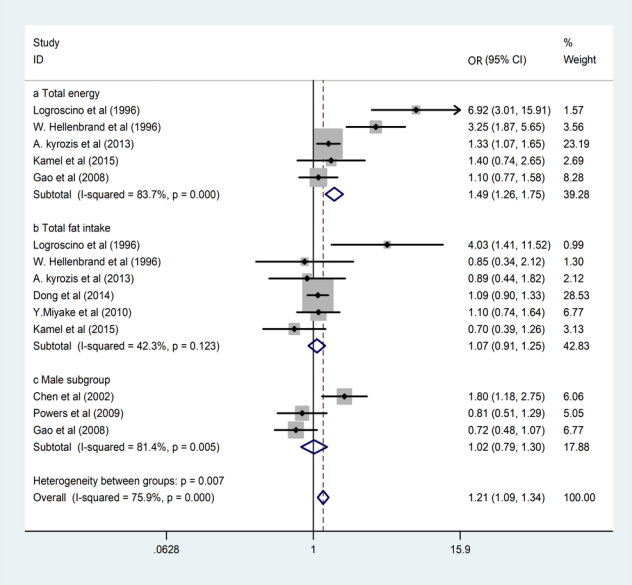

Figure 2 Forest plots of total energy intake, total fat intake, and male subgroup associations with Parkinson's disease (PD) risk.
High total energy intake and sex were both linked with elevated PD risk, while total fat intake was not associated with PD risk.

Subgroup analyses

The subgroup analyses were conducted based on fat subtypes (PUFA, arachidonic acid, cholesterol, n-3 PUFA, n-6 PUFA, α-linolenic acid, linoleic acid, monounsaturated fatty acid [MUFA], saturated fatty acids, and n-3 to n-6 PUFA ratio) to further explore the source of heterogeneity. An association was found between high PUFA intake and reduced PD risk ($P = 0.010$, *OR* = 1.03, 95% *CI*: 0.88–1.20). In contrast, ara-

chidonic acid (*P* = 0.026, *OR* = 1.15, 95% *CI*: 0.97–1.37) and cholesterol (*P* = 0.002, *OR* = 1.09, 95% *CI*: 0.92–1.29) intakes were linked with an elevated PD risk. Moreover, although the results were not significant, consumption of n-3 PUFA (*P* = 0.071, *OR* = 0.88, 95% *CI*: 0.73–1.05), α-linolenic acid (*P* = 0.06, *OR* = 0.86, 95% *CI*: 0.72–1.02), and the n-3 to n-6 PUFA ratio (*P* = 0.458, *OR* = 0.89, 95% *CI*: 0.75–1.06) were all linked with a non-significant trend toward reduced PD risk, while MUFA (*P* = 0.450, *OR* = 1.06, 95% *CI*: 0.91–1.23), linoleic acid (*P* = 0.053, *OR* = 1.11, 95% *CI*: 0.94–1.32), and n-6 PUFA (*P* = 0.100, *OR* = 1.15, 95% *CI*: 0.96–1.36) intakes were associated with a non-significant trend toward higher PD risk. Saturated fatty acid intake (*P* = 0.619, *OR* = 1.01, 95% *CI*: 0.87–1.18) was not associated with PD (**Figure 3**).

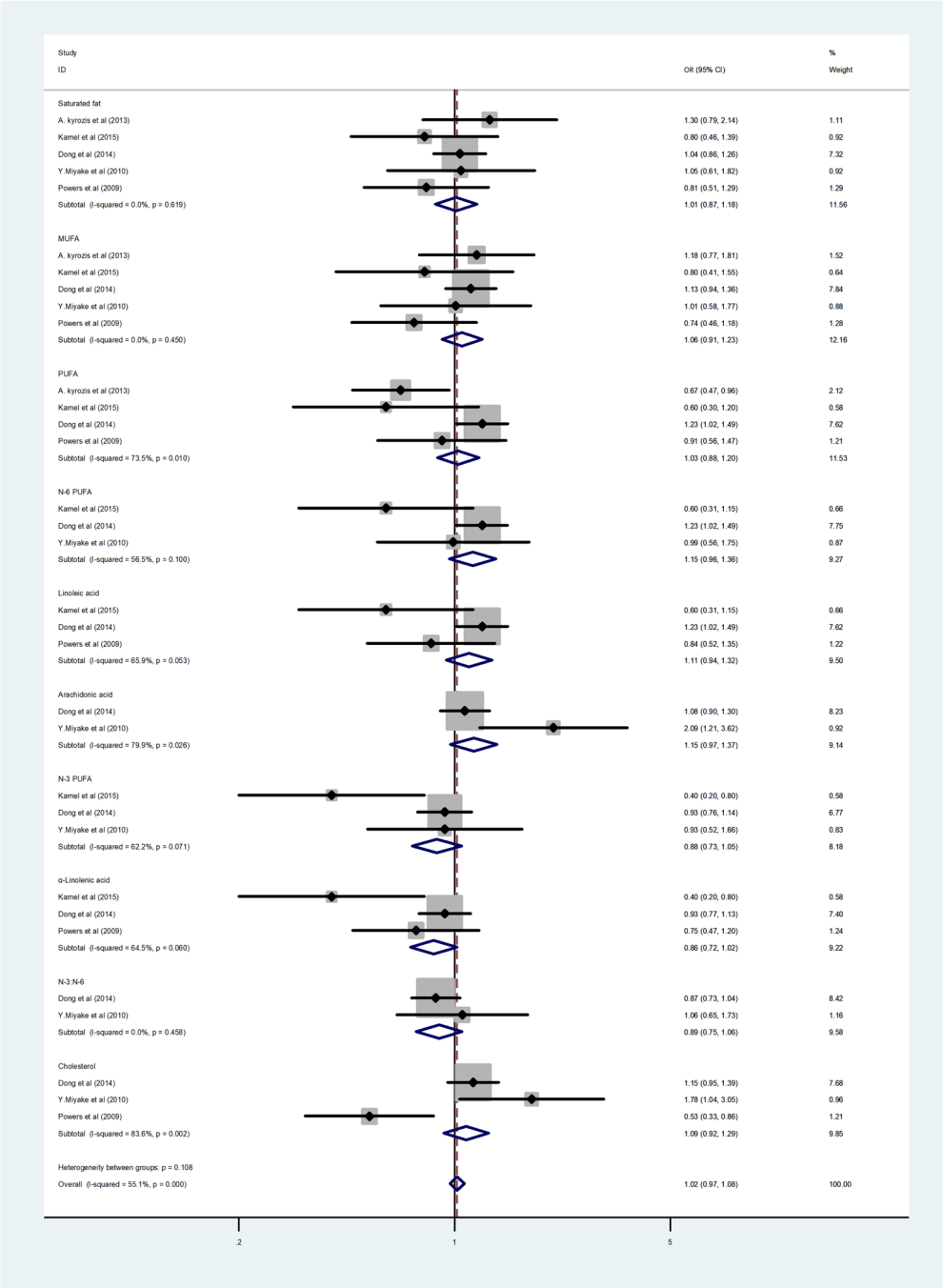

Figure 3 Forest plots of saturated fatty acids, monounsaturated fatty acid (MUFA), high polyunsaturated fatty acids (PUFA), arachidonic acid, n-3 PUFA, α-linolenic acid, n-6 PUFA, linoleic acid, the ratio of n-3 to n-6 PUFA, and cholesterol intake associations with Parkinson's disease (PD).

There was a consistent link between PUFA consumption and lower PD risk, while higher cholesterol and arachidonic acid intakes were linked with elevated PD risk. Although the results were not significant, consumption of n-3 PUFA, α-linolenic acid, and the n-3 to n-6 PUFA ratio were all linked with a trend toward reduced PD risk, while MUFA, linoleic acid, and n-6 PUFA intakes were associated with a trend toward higher PD risk. Saturated fatty acid intake was not associated with PD.

Publication bias

We did not detect publication bias for studies of either high total energy intake and PD risk or high total fat intake and PD risk, based on a fully adjusted model ($P = 0.114$). There are two articles that seem farther outside the funnel, possibly caused by the high heterogeneity of both articles. These studies were not excluded, however, because they met the inclusion criteria and Egger's test gave $P > 0.05$ (**Figure 4**).

Discussion

High dietary fat intake and Parkinson's disease risk

We found that high total energy intake was linked with elevated PD risk, whereas total fat intake was not. However, we revealed an association between high PFUA and reduced PD risk; in contrast, arachidonic acid and cholesterol intakes were linked with an elevated PD risk. Although the results were not significant, consumption of n-3 PUFA, α-linolenic acid, and the n-3 to n-6 PUFA ratio was all linked with a trend toward reduced PD risk, while MUFA, linoleic acid, n-6 PUFA intakes were associated with a trend toward higher PD risk. Saturated fatty acids were not associated with PD.

Elevated PD risk may result from the consumption of dietary fat, because of its effects involving increased oxidative stress and neuroinflammation, which potentially exacerbate neurotoxin-induced dopaminergic neuron loss. PUFAs are primarily found in the SN2 position of phosphoglycerates in neural cell membranes where, in response to lipid peroxida-

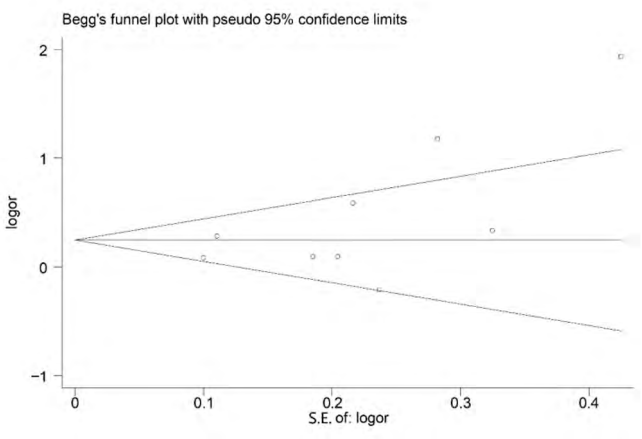

Figure 4 Publication bias measured by a funnel plot and Egger's test ($P = 0.114$).
Two articles are farther outside the funnel; they may have only represented a trend.

Table 1 Characteristics of the included studies ($n = 9$) regarding the association between dietary fats intake and Parkinson's disease

Author	Type of study	Study design	Location	No. of participants (case/control)	Gender	Ages for cases and controls (range or mean ± SD, years)	Clinical diagnostic criteria	Exposure assessment
Hellenbrand et al. (1996)	NA	Case-control study	German	342/342	Male/female	56.2±6.7/56.1±6.9	UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria	FFQ
Logroscino et al. (1996)	Community study	Case-control study	United States	110/287	Male/female	< 70, 70–80, > 80	Published criteria; DSM-III-R; the Hoehn and Yahr scale; direct interview	A semiquantitative food-frequency questionnaire
Chen et al. (2002)	HPFS NHS	Retrospective cohort study	United States	51529 (394 cases)*	Male/female	40–75	NA	FFQ, disease history, life style
Gao et al. (2008)	HPFS NHS	Retrospective cohort study	United States	131368 (508 cases)*	Male/female	40–75	NA	FFQ
Powers et al. (2009)	SMMSE	Case-control study	United States	420/560	Male/female	29–88	NA	FFQ
Miyake et al. (2010)	NA	Case-control study	Japan	249/368	Male/female	NA	UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria	DHQ
Akyrozis et al. (2013)	EPIC-Greece	Retrospective cohort study	Greece	26173 (120 cases)*	Male/female	20–86	UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria	A questionnaire
Dong et al. (2014)	NIH-AARP Diet and Health Study	Prospective cohort study	United States	566398 (3519 cases)*	Male/female	50–71	NA	FFQ, questions on demographics and life style
Kamel et al. (2015)	AHS, FAME, NIH	Case-control study	United States	89/336	Male/female	68/69	NA	DHQ

*Cohort study (participants/Parkinson's disease onset). DHQ: Self-administered, semi-quantitative, comprehensive, diet history questionnaire; FFQ: the Willett food frequency questionnaire; NA: not available; HPFS: the Health Professionals Follow-up Study; NHS: the Nurses' Health Study; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders; AHS: Agricultureral Health Study; FAME: the Farming and Movement Evaluation.

Table 2 Characteristics of included studies

Study	Case ascertainment	Comparison	Multivariates controlled	NOS score
Hellenbrand et al. (1996)	Attending neurologists were asked to verify inclusion and exclusion criteria according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria	Energy intake, carbohydrate intake, monosaccharide intake, disaccharide intake, polysaccharide intake; individual amino acid intake, total protein intake; antioxidant vitamin intake, ascorbic acid intake, beta-carotene intake, alpha-tocopherol intake; thiamine intake, various B vitamins intake; niacin intake	Age, sex, body mass index, smoking status, disease duration; education	9
Logroscino et al. (1996)	Confirmed by three experienced neurologists according to published criteria	Calories, fat intake	Age, sex, education, ethnic	7
Chen et al. (2002)	Confirmed by neurologists	Food groups low to high, man *vs*. woman	Age, lengths of follow-up, body mass index, smoking status, energy intake, caffeine intake, physical activity, alcohol consumption	7
Gao et al. (2008)	Identified by biennial self-reported questionnaires	Prudent dietary pattern, western dietary pattern	Age, weight, height, smoking status, physical activity, body mass index, use of nonsteroidal anti-inflammatory drugs, total energy intake, caffeine intake, alcohol intake, urate index and iron intake	7
Powers et al. (2009)	Confirmed by medical records	The lowest and highest quartiles of iron; low SatFat, low Fe *vs*. high SatFat, high Fe *vs*. low SatFat, high Fe; low cholest, low Fe *vs*. high cholest, high Fe *vs*. low cholest, high Fe	Age, gender, smoking, ethnicity, education	9
Miyake et al. (2010)	NA	Arachidonic acid intake, cholesterol intake, total fat intake, individual fat intake	Sex, age, region of residence, pack-years of smoking, years of education, intake of vitamin E, iron, alcohol and body mass index	9
Akyrozis et al. (2013)	Diagnosed according to UKBB-based questionnaire	Dairy total intake, milk intake, Yoghurt intake, cheese intake; fat total intake; individual fat intake	Age, gender, marital status, farm occupation, height, weight, body mass index, physical activity, energy intake, alcohol intake, smoking status, caffeinated coffee, tea consumption, years of education	9
Dong et al. (2014)	Confirmed by self-reported, completed a diagnostic questionnaire and provide a copy of the patient's medical records.	Total fat intake, individual fat intake, total energy intake, protein intake, carbohydrate, cholesterol,	Age, gender, race/ethnicity caffeine intake, total energy intake, smoking status, diabetes, and self-reported health status	9
Kamel et al. (2015)	Confirmed by movement disorder specialists or a corresponding dates	High fat no pesticide; high fat yes pesticide; low fat no pesticide; low fat yes pesticide	Age, gender, state, smoking, total energy intake	7

NA: Not available; NOS: Newcastle-Ottawa Scale.

tion, they can give rise to oxygen free radicals (Choi et al., 2005; Shchepinov et al., 2011; Bousquet et al., 2012). PUFAs are also necessary for appropriate glial cell membrane formation, and can further regulate the generation of inflammatory cytokines and prostaglandins (Laye, 2010). Dietary n-3 and n-6 α-linoleic acids are used to synthesize PUFA in cell membranes, and can also give rise to long-chain PUFA *via* desaturation and elongation (Youdim et al., 2000). In particular, n-3 PUFAs play anti-inflammatory roles, while n-6 PUFAs serve as inflammatory prostaglandin precursors (Dong et al., 2014). Arachidonic acid, one of the major types of PUFA present in the brain, is one of several key types of n-6 PUFAs (Porter et al., 1995; Simopoulos, 1999; Hadders-Algra, 2008), and linoleic acid is also a subtype of n-6 PUFA. In the present study, PUFAs were linked with a decreased risk of PD, in contrast to the expected increased risk, and this result suggests that the n-3/n-6 ratio might be an important factor when assessing PD development risk. If intake of n-3 is greater than n-6 intake, the risk of PD may be reduced. Although our study revealed that there was no significant relationship between n-3/n-6 PUFA ratio and PD risk, there was a non-significant trend toward reduced risk of PD when the n-3/n-6 PUFA ratio was higher.

The brain contains the most cholesterol of any organ, and it is capable of synthesizing cholesterol (Noguchi et al., 2014). However, few studies have reported that cholesterol-rich diets drive neurotoxin-induced dopaminergic neuron loss (Choi et al., 2005; Bousquet et al., 2012). Elevated cholesterol levels can contribute to oxidative stress (Pappolla et al., 2002; Thirumangalakudi et al., 2008; Prasanthi et al., 2010) and neuroinflammation (Thirumangalakudi et al., 2008; Ullrich et al., 2010; Pirchl et al., 2012). In addition,

high levels of cholesterol can cause mitochondrial dysfunction and influence α-synuclein aggregation (Bar-On et al., 2008). Therefore, cholesterol may be a risk factor for neurodegenerative disease in general (Vance, 2012; Martin et al., 2014), which is consistent with our results.

There are many factors that affect the results of our analysis. Some come from the original literature, and were possibly caused by defects in research design. Of the reviewed references, only Kamel et al. (2014) provided evidence that α-linolenic acid and linoleic acid intakes decreased PD risk. Others reported that a moderately reduced PD risk was not associated with α-linolenic acid or linoleic acid intake (Porter et al., 1995; Youdim et al., 2000; Ikemoto et al., 2001; Levant et al., 2007; Hadders-Algra, 2008; Laye, 2010; Shchepinov et al., 2011). In addition, only Dong et al. (2014) provided evidence for a positive relationship between dietary PUFA intake and PD risk. Some PUFA are associated with specific functions of the human body, and although N-3 must be obtained from the diet, other fatty acids can be synthesized in the body; thus, we cannot rule out the effects of self-synthesized fatty acids on our results. Moreover, exposure assessments in the included references were all obtained *via* different questionnaires, such as diet history questionnaires and food frequency questionnaires. This may have led to variation in survey accuracy, because dietary consumption does not necessarily translate to biological nutritional status.

Limitations

This study has certain limitations. First, a more careful analysis of other dietary PUFA fats is needed to confirm the protective PUFA concentrations that are necessary to reduce PD risk, and to confirm the adverse results of eating other types of fats. Second, we did not pool vitamins or other types of nutrition in this study, and therefore potentially overlooked their roles as antioxidants in protecting against PD. Third, the food sources of each fat were not considered, which may have led to the high heterogeneity that we found. Fourth, we did not consider the contributions of regionalism and dietary customs, which also may have influenced our results.

Conclusions and future directions

This meta-analysis revealed that higher energy intake is linked with elevated PD risk. We also demonstrated that high PUFA was associated with reduced PD risk; in contrast, arachidonic acid and cholesterol intakes were linked with an elevated risk of PD. Although the results were not significant, consumption of n-3 PUFA, α-linolenic acid, and the n-3/n-6 PUFA ratio were all linked with a trend toward reduced PD risk, while MUFA, linoleic acid, and n-6 PUFA intakes were associated with a trend toward higher PD risk. Saturated fatty acids were not associated with PD risk.

Further research is necessary to confirm the link between dietary fat and PD risk, and other nutritional antioxidants such as vitamins should also be considered in this context. New studies should focus on the dietary sources of each fat (such as the intake of the various PUFAs, and the n-3/n-6 intake ratio), as well as how regional dietary variations may influence these outcomes, to avoid high heterogeneity.

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Peer review: *Externally peer reviewed.*

Open peer reviewer: *Anupom Borah, Assam University, India.*
Additional files:
Additional Table 1: *Newcastle-Ottawa Scale Assessment of Case-Control Studies.*
Additional Table 2: *Newcastle-Ottawa Scale Assessment of Cohort Studies.*
Additional file 1: *Open peer review report 1.*

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