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A systematic review of nutritional risk factors of Parkinson's disease

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A wide variety of nutritional exposures have been proposed as possible risk factors for Parkinson's disease (PD) with plausible biological hypotheses. Many studies have explored these hypotheses, but as yet no comprehensive systematic review of the literature has been available. MEDLINE, EMBASE, and WEB OF SCIENCE databases were searched for existing systematic reviews or meta-analyses of nutrition and PD, and one meta-analysis of coffee drinking and one meta-analysis of antioxidants were identified. The databases were searched for primary research articles, and articles without robust methodology were excluded by specified criteria. Seven cohort studies and thirty-three case–control (CC) studies are included in the present systematic review. The majority of studies did not find significant associations between nutritional factors and PD. Coffee drinking and alcohol intake were the only exposures with a relatively large number of studies, and meta-analyses of each supported inverse associations with PD. Factors that were reported by at least one CC study to have significantly increased consumption among cases compared with controls were: vegetables, lutein, xanthophylls, xanthins, carbohydrates, monosaccharides, junk food, refined sugar, lactose, animal fat, total fat, nuts and seeds, tea, Fe, and total energy. Factors consumed significantly less often among cases were: fish, egg, potatoes, bread, alcohol, coffee, tea, niacin, pantothenic acid, folate and pyridoxine. In three cohort studies, two reported borderline decreased relative risks and one a significant increased risk with vitamin C intake. One cohort reported an inverse association between caffeine intake and PD. Three cohorts reported significant positive association in men between dairy products and PD.

Parkinson's disease: Nutrition: Systematic review: Antioxidant risk

Introduction

The specific contributions of genetic and environmental factors to the aetiology of Parkinson's disease (PD) remain largely unknown, nearly 200 years after PD was first recognised by James Parkinson (Parkinson, 1817). As the elderly proportion of the world's population increases, questions surrounding ageing disorders become increasingly pertinent. PD is the second most common neurological disorder and its worldwide prevalence is estimated to be approximately 2 % in those over 65 years (Zhang & Roman, 1993; de Rijk *et al.* 1997*c*).

Concordance rates from monozygotic and dizygotic twin studies are similarly low, which indicates that genetics cannot fully explain the aetiology of PD (Tanner, 2003). Specific causal genes have been identified in familial PD, but these genes are relatively rare in sporadic PD (de Silva *et al.* 2000; Gwinn-Hardy, 2002). Therefore it is probable that environmental factors contribute to the aetiology.

The possible role of nutrition in the aetiology of PD has been examined in many epidemiological studies; however, the implicated foods and nutrients vary between studies. Most have been retrospective case–control (CC) studies; therefore exposure measurement may not reflect the premorbid diet. Many were exploratory, testing multiple nutritional risk factors with the purpose of generating hypotheses.

Specific foods, macronutrients and micronutrients could contribute to the cause of PD either by direct or indirect effects, as with amyotrophic lateral sclerosis–Parkinsonism dementia complex, which is caused by neurotoxic cycad seeds (Calne *et al.* 1986; Cox & Sacks, 2002). This exposure is uncommon in other parts of the world, but it does highlight food consumption as a possible risk factor for PD.

Nutrition may influence neurodegeneration by indirect effects on the body. The most relevant biological mechanism for the role of nutrition in PD is oxidative stress, which is defined as increasing production of reactive oxygen or nitrogen species and/or decreasing levels of antioxidant defences (Foley & Riederer, 2000; Bharath *et al.* 2002; Butterfield *et al.* 2002; Koutsilieri *et al.* 2002; Rao & Balachandran, 2002; Jenner, 2003). There is an ongoing

Abbreviations: CC, case–control; HPFS, Health Professionals' Follow-up Study; NCC, nested case–control; NHS, Nurses' Health Study; OR, odds ratio; PD, Parkinson's disease; RR, relative risk.

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debate as to whether oxidative stress is a cause or consequence of neurodegeneration. The brain is susceptible to oxidative damage because of its high O_2 utilisation, high Fe content and the presence of excess unsaturated fatty acids, which are targets for lipid peroxidation (Halliwell, 1992; Bharath *et al.* 2002).

Preliminary evidence that alcohol may contribute to oxidative stress through production of alkaloids, which may be toxic, is inconclusive (Collins, 2002). If this is the case, then there should be an increased risk of PD in individuals who have ever consumed alcohol, and a dose–response effect.

A systematic search of the published literature for all studies reporting on the association between nutritional risk factors and PD has been conducted. To date there have not been any comprehensive systematic reviews on this topic. The evidence for the association of PD with various foods and nutrients is presented.

Methods

Search strategy

To determine if previous systematic reviews or meta-analyses of nutritional risk factors for PD existed, a search for all reviews of PD and risk factors was conducted using MEDLINE, EMBASE and WEB OF SCIENCE databases from 1989 through to September 2004. Systematic reviews or meta-analyses were assessed on their search methodology, inclusion criteria, and presentation of results. If the review met the assessment criteria, then review results were reported along with additional relevant results.

To identify original contributions to the topic, the same three databases were searched based on published sources (Oxman, 1994; Glasziou *et al.* 2001; Scottish Intercollegiate Guidelines Network, 2002; Khan, 2003), and by using index terms from databases within MEDLINE and EMBASE. The MEDLINE search used the following medical subject headings terms and free text with '*' as the wildcard symbol: Parkinson's disease and one or more of the following (nutrition; diet*; food; food additives; food, fortified; ascorbic acid; vitamin; antioxidant*; antioxidants; oxidat*; iron; mineral; metal*; fat*; caffeine; alcohol; beverage*). EMBASE was searched for terms similar to MEDLINE using EMBASE index terms. WEB OF SCIENCE did not have an index of terms; therefore terms from MEDLINE and EMBASE were used.

Bibliographies from the primary search and reviews were scanned and additional relevant references were obtained. No attempt was made to solicit unpublished results, either directly from key investigators or through conference abstracts.

Inclusion and exclusion criteria

Inclusion: (1) articles published in all languages; (2) primary research that examined the relationship between specific foods, food groups or nutrients and PD; (3) PD as the outcome of interest; (4) reported odds ratios (OR) or relative risks (RR) and 95 % CI, or provided enough information to calculate values; (5) 'ever *v.* never', semi-quantitative or quantitative measures of exposure; (6) an attempt to assess the exposure information before the onset of disease.

Exclusion: (1) cross-sectional studies without CC design; (2) for articles that presented the same data in multiple publications, all but the most recent publication were excluded; (3) used a subjective measure of exposure (for example, of a husband and wife pair, which ate more than the other).

Studies without either specified diagnostic criteria, in medical records or upon examination by a neurologist, or a physician-verified diagnosis were excluded. Ecological studies are not included because exposure is not necessarily related to disease in the same individuals. The present review will specifically look at associations between nutrition and PD in man. An extensive literature base in animals does exist.

Data extraction

The Newcastle-Ottawa scale and other guidelines for assessing the quality of non-randomised studies in meta-analyses were used to identify study characteristics for data extraction (Liddle, 1996; Glasziou *et al.* 2001; Wells *et al.* 2003). Subjective quality scoring was not conducted. One author (L. I.) extracted data from studies. Only objective study characteristics that could contribute to heterogeneity in results were extracted and summarised in tables.

Summary tables

Figures for alcohol and an overall summary table are presented. Tables for other food groups are available online at http://www.iph.cam.ac.uk/~lsi20/NRR_tables.htm

The tables include the most adjusted OR and RR estimates from each study. Factors are organised by categories within each broad classification of exposure (for example, carbohydrates and fats). CC studies are presented first, followed by nested CC (NCC) and cohort studies, each in the order of ascending publication date.

The adjustment column includes the matching variables, if used in the analysis, and adjustments made during the analysis. The number of cases and controls, or the cohort size, are reported.

Calculation of missing odds ratios and confidence intervals

If the OR and/or 95 % CI were not presented in the original study, the values were calculated from available information. Studies without sufficient information to calculate both the OR and 95 % CI were not included in the present review.

The STATA statistical package (StataCorp LP, College Station, TX, USA) was used. The crude OR and 95 % CI for CC studies were calculated with the STATA cci command. The STATA mcci command was used for matched CC studies.

For coffee and alcohol, when possible, the quantitative measures were also calculated as OR or RR, yes *v.* no, to increase the comparability of estimates between studies. The CC OR were calculated as described above. The cohort

RR and 95 % CI were calculated using the STATA iri function.

Meta-analysis

A pooled risk estimate was calculated only for variables investigated by more than five studies with homogeneous exposure measurement. This was decided after data extraction was completed. The STATA meta command was used to produce random and fixed effect estimates and to conduct a test of heterogeneity.

Results

Literature search

The titles and abstracts of possible systematic reviews and meta-analyses were reviewed, and one meta-analysis each for coffee drinking and antioxidants were identified (Hernan *et al.* 2002; Etminan *et al.* 2005).

After applying inclusion and exclusion criteria, there were a total of seven cohorts and thirty-three CC studies included in the systematic review from primary and secondary searches. All primary articles were found in either MEDLINE or EMBASE. No unique articles were identified through WEB OF SCIENCE. Additional studies were added after searching the bibliographies of primary articles and reviewing other environmental risk factor publications.

One cross-sectional study is included because the methods were similar to the CC studies, and because it was included in one of the published meta-analyses (de Rijk *et al.* 1997*a*). The quality of evidence is not as strong, but results are presented as supporting evidence.

Study characteristics and methods

Cohort study populations. There were six prospective cohorts from the USA and one cohort from the Netherlands (Table 1). There were two prospective NCC studies, one from the Honolulu Heart Study cohort (Morens *et al.* 1996; Paganini-Hill, 2001). The Health Professionals' Follow-up Study (HPFS) and the Nurses' Health Study (NHS) recruited participants in healthcare occupations through a mailed survey. Both are selective populations and may not be representative of the general population, but they had relatively good response and follow-up rates. The Honolulu Heart Study is a male-only selective population originally chosen to study heart disease among Japanese immigrants in Hawaii. It has since expanded to look at other outcomes including age-related diseases, and is now known as the Honolulu Aging Study. The Iowa cohort of women did not describe methods for recruitment. The remaining cohorts, Rotterdam, Framingham and Leisure World, were community based.

Case–control selection. The methods for case and control selection were heterogeneous (Table 2). Cases were selected from hospitals, neurology clinics, patient support groups, and pharmacy databases. The source of cases was most often neurology and movement disorders clinics, which may

Table 1. Cohort and nested case–control study characteristics

Cohort name	Authors	Location	Start date	Population source	Age at baseline (years)	
					Mean	Range
Honolulu Heart, Honolulu Aging Study	Grandinetti *et al.* (1994), Davis *et al.* (1996), Morens *et al.* (1996)*, Ross *et al.* (2000), Park *et al.* (2005)	USA	1965	All male Oahu residents of Japanese or Okinawan ancestry listed in selective service records and born between 1900 and 1919	54	45–68
Nurses' Health Study	Ascherio *et al.* (2001), Chen *et al.* (2002), Zhang *et al.* (2002), Chen *et al.* (2003), Hernan *et al.* (2003), Chen *et al.* (2004)	USA	1976	Female registered nurses in eleven large states mailed questionnaire		30–55
Health Professionals' Follow-up Study	Ascherio *et al.* (2001), Chen *et al.* (2002), Zhang *et al.* (2002), Chen *et al.* (2003), Hernan *et al.* (2003), Chen *et al.* (2004)	USA	1986	Male health professionals mailed questionnaire		40–75
Iowa Women's Health Study	Cerhan *et al.* (1994)	USA	1986	Women from the state of Iowa		55–69
Leisure World Cohort	Paganini-Hill (2001)*	USA	1981	All residents in a retirement community	75 ± 6·1	
Rotterdam Study	Willems-Giesbergen *et al.* (2000)	The Netherlands	1990	Community-based recruitment in Rotterdam		55 +
Framingham Study	Fink *et al.* (2001)	USA	N/A	Framingham Heart Study, Massachusetts follow-up	69	

N/A, not applicable.
* Nested case–control studies. Morens *et al.* (1996) matched by year of birth ±2 years; Paganini-Hill (2001) matched by sex, birth date ±2 years, vital status, and death date ±1 year.

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Table 2. Case–control study characteristics

Author	Location	Source of cases	Exclusion criteria	Selection of controls	Exclusion criteria	Matching specifications
Anderson *et al.* (1999)	USA	Neurology practices; databases	MMSE < 24	Community	Neurodegenerative disease; dementia	None
Behari *et al.* (2001)	India	Consecutive movement disorders patients	Dementia or information unreliable	Hospital, other neurological diseases	Dementia	Age ±3 years
Benedetti *et al.* (2000)	USA	PD records linkage system	Males	Community – random	PD, Parkinsonism, or tremor; males	Age ±1 year and sex
Butterfield *et al.* (1993)	USA	Referrals; support groups	Not young YOPD*	Volunteers with rheumatoid arthritis	N/A	Frequency matched for sex, birth and diagnosis year
Chan *et al.* (1998)	Hong Kong	Two hospitals	N/A	Hospitals	Any signs of PD or Parkinsonism	10-year age group, sex and hospital
Checkoway *et al.* (2002)	USA	Diagnosis logs and pharmacy database	Used medication known to cause Parkinsonism	Health cooperative enrolees	No history of PD or other progressive neurological disorders	Frequency matched by age, sex, clinic, and year of GHC enrolment
De Rijk *et al.* (1997*a*)†*	The Netherlands	Volunteers from among all county residents	Age < 55 years; demented; not living independently	Community	PD; age < 55 years; demented; not living independently	None
Fall *et al.* (1999)	Sweden	Prescription records; GP reports	Age < 40 or > 75 years; incomplete information	Randomly drawn from the population register	Residence	None
Gorell *et al.* (1999)	USA	Health system database	Age < 50 years no recent physician visit; MMSE < 24	Health system database	Age < 50 years age; no recent visit to physician; MMSE < 24; Parkinsonian signs	Frequency matched by sex and age ±5 years
Haack *et al.* (1981)	USA	Neurology clinics	N/A	Door-to-door in neighbourhood	N/A	Age ±5 years; sex; race
Hellenbrand *et al.* (1996*a*,*b*)	Germany	Multiple neurology clinics	Age > 67 years age; long disease duration; FFQ incomplete; dementia	Two random community controls per case	N/A	Region; sex and age ±3 years
Ho *et al.* (1989)	Hong Kong	Hospital and survey	Past cerebrovascular accident	Three controls from hospital or elderly homes	PD and dementia	Age ±3 years; sex; residence
Jimenez-Jimenez *et al.* (1992)	Spain	Consecutive movement disorders clinic patients	N/A	Recruited from hospital	Neurological complaints	Age; sex
Johnson *et al.* (1999)	USA	Health system database	Age < 50 years; no recent visit to physician; MMSE < 24; disease duration > 10 years; non-English speaker or medically unable	Randomly selected from same database	Age < 50 years; no recent visit to physician; MMSE < 24; Parkinsonian signs; non-English speaker or medically unable	Frequency matched by sex, age, and race

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Table 2. *Continued*

Author	Location	Source of cases	Exclusion criteria	Selection of controls	Exclusion criteria	Matching specifications
Liou *et al.* (1997)	Taiwan	Movement disorder clinic	Not born in Taiwan; had exposure to neuroleptics or previous brain diseases	Neurology or outpatient clinics at the same hospital	Not born in Taiwan; exposure to neuroleptics or previous brain diseases	Sex and age ±2 years
Logroscino *et al.* (1996, 1998)	USA	Registry: hospital, GPs, senior centres, and government health agencies	Residence; cognitive impairment or dementia	Random sample of Medicare recipients from the same region	Residence; clinical evidence of PD, dementia or other major disease	Frequency matched for age, ethnicity and sex
Mayeux *et al.* (1994)	USA	Registry: hospital, GPs, senior centres, health agencies	Residence; dementia	Consecutive controls at the same time cases found	Residence; evidence of PD, dementia or other major diseases	None
Morano *et al.* (1994)	Spain	Neurology out-patients	N/A	Subjects presenting to the emergency room	Neurological ailments	Age and sex
Nefzger *et al.* (1968)	USA	Veterans' hospitals	Died; discharged	Next hospital patient	Died; discharged; psychiatric or extrapyramidal disease	None
Nelson *et al.* (1999)	USA	Healthcare database	N/A	Randomly selected from same database	N/A	Frequency matched for age, sex, self or proxy
Powers *et al.* (2003)	USA	Diagnosis logs; neurologist referrals; pharmacy database	MMSE $<$ 24	Health cooperative enrolees	MMSE $<$ 24; no past history of PD or progressive neurological disorders	Frequency matched to cases by age, sex, clinic, and year
Preux *et al.* (2000)	France	Hospital in-patients and out-patients	Had not lived in region for at least 20 years	Hospital in-patients and out-patients	Residence; history of neurological disorder	Age ±5 years and sex
Ragonese *et al.* (2003)	Italy	Consecutive out-patients at neurological clinics	MMSE $<$ 24; had neuroleptic treatment in the past 6 months	Random selection using population records of the municipality	MMSE $<$ 24; presence of neurological or other chronic disease	Sex, age ±2 years and place of residence
Scheider *et al.* (1997)	USA	All eligible hospital and community survey	Demented; MMSE $\leq$ 23	Chosen from lists provided by cases	MMSE $\leq$ 23	Age ±5 years, sex and clinic
Smargiassi *et al.* (1998)	Italy	Consecutive cases from neurology institute	N/A	Out-patient centres of the same hospital	N/A	None
Tan *et al.* (2003)	Singapore	Randomly selected movement disorders database	Not Chinese race; dementia	Participants in community health screening programme	Presence of Parkinsonian features	Age ±0·5 years, sex, and race
Taylor *et al.* (1999)	USA	Movement disorders clinic	N/A	Chosen from lists provided by cases	PD diagnosis or signs	None

Table 2. *Continued*

Author	Location	Source of cases	Exclusion criteria	Selection of controls	Exclusion criteria	Matching specifications
Tsai *et al.* (2002)	Taiwan	Hospital movement disorder data bank	Extensive neurological disease; family history; not YOPD*	Volunteers working in or attending the same hospital	Presence of Parkinsonian features; residence	Age and sex
Wang *et al.* (1993)	China	Randomly selected neurology out-patients	MMSE ≤ 12 of 21; other serious illnesses	Randomly selected neurology out-patients	MMSE ≤ 12 of 21; PD and other serious illnesses	Sex, age ±3 years and same hospital
Yang *et al.* (1994)	China	Not specified	N/A	Community	Extrapyramidal symptoms	Sex, age ±5 years; residence
Zayed *et al.* (1990)	Canada	Neurologist patients; volunteers	Dementia	Two randomly selected using municipal phonebook	Parkinsonian symptoms	Age ±3 years; sex

MMSE, mini mental status examination; PD, Parkinson's disease; YOPD, young-onset PD; N/A, not applicable; GHC, Group Health Cooperative of Puget Sound; GP, general practitioner; FFQ, food-frequency questionnaire.
* Individuals were excluded if they were not YOPD cases.
† Cross-sectional study.

be a selected group of PD patients. Controls were selected from among spouses, the patients' communities, hospitals, and healthcare databases. Most of the studies matched controls to the cases by age and sex, either directly or by frequency matching, with the exception of six (Nefzger *et al.* 1968; Mayeux *et al.* 1994; Smargiassi *et al.* 1998; Anderson *et al.* 1999; Fall *et al.* 1999; Taylor *et al.* 1999). Other matching criteria included ethnicity, hospital or clinic, and geographical region.

A common exclusion criterion was dementia, usually indicated by a mini mental status examination (Folstein *et al.* 1975) score below twenty-four, because subjects with dementia would be unable to provide reliable information. Other exclusion criteria related to age, disease duration, practical considerations such as location and language, and medical history, especially diseases that may have a role in PD aetiology.

Exposure measurement. Food and nutrient intake can be assessed using different instruments, including the 24 h dietary recall and semi-quantitative food-frequency questionnaire. Food-frequency questionnaires and study-specific questionnaires were the most commonly used instruments in CC and cohort studies (Table 3).

Exposure measurement may be qualitative, semi-quantitative, or quantitative. The simplest qualitative measure of consumption is the 'ever *v.* never' or 'yes *v.* no' question. Another qualitative measure is a relative measure, such as asking whether the case ate more or less of a food item than his/her spouse before PD onset. The results from relative comparisons are excluded because they do not provide estimates of consumption differences between cases and controls.

A semi-quantitative measurement asks about the average or usual number of times a food is consumed during a given time period. The approximate serving size may be specified.

Quantitative measurements are more precise about serving sizes and frequency of intake. The subjects may be given graphs with serving sizes to estimate the amounts of food. A more precise measure called 'weighed intake' requires subjects to weigh all foods consumed. This is not economical and is rarely seen in epidemiological studies, except as a means of validation on a sub-sample of the study population.

Risk estimates were calculated for semi-quantitative and quantitative measures as: above *v.* below the median; highest *v.* lowest tertiles, quartiles, and quintiles; number of servings or times consumed in a given time period; continuous measures using logistic regression.

Diagnostic criteria. The diagnosis of Parkinsonism is based on clinical signs because there is currently no conclusive diagnostic test available (Tanner & Ben Shlomo, 1999). The gold standard is a post-mortem pathological examination. PD clinical characteristics manifest only when the substantia nigral cell loss has reached a threshold of 60 to 80 %, and most Parkinsonian symptoms are not specific to PD (Lang & Lozano, 1998; Ben-Shlomo, 1998; Tanner & Ben Shlomo, 1999). PD is underdiagnosed in the population because of mis- and late diagnosis (Hughes *et al.* 1992*b*; Ben-Shlomo, 1998).

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Table 3. Exposure measurement and diagnostic criteria for all studies

Reference	Exposure measurement	Time period before outcome	Method of diagnosis	Diagnostic criteria*
Retrospective case–control studies				
Anderson *et al.* (1999)	Trained nurse; interview; SFFQ	20–30 years	Neurologist diagnosis; medical record	1, 3
Behari *et al.* (2001)	Trained investigator; questionnaire	Lifetime	Clinical examination	2, 3, 4, 5
Benedetti *et al.* (2000)	Questionnaire	Lifetime	Medical records	1, 3, 4
Butterfield *et al.* (1993)	Mailed questionnaire	Lifetime or 10 years	Medical records; telephone; neurologist	1, 3, 5
Chan *et al.* (1998)	Person interview; questionnaire	N/A	Geriatrician or neurologist examination	1, 3, 4 (Maraganore *et al.* 1991)
Checkoway *et al.* (2002)	Nurse; structured questionnaire	Lifetime	Diagnosis logs; pharmacy database	1, 3
De Rijk *et al.* (1997*a*)†	Interview and SFFQ	Past 1 year	Screening questionnaire and neurological examination	1, 3
Fall *et al.* (1999)	Mailed questionnaire	15 years	Neurologist examination	At least one sign from 2 and 3, 4, 5
Gorell *et al.* (1999)	Self report	Age 18 until time of interview	Documented by neurologists	1, 3 (Gorell *et al.* 1997)
Haack *et al.* (1981)	Trained interviewer	Lifetime	Medical records; neurologist confirmed	2
Hellenbrand *et al.* (1996*a*,*b*)	Trained interviewers. Self-administered FFQ with photographs	Before PD diagnosis; 1 year before interview	Neurologist examination	8
Ho *et al.* (1989)	Interview; structured questionnaire	Lifetime	Neurology student examination; medical records	6
Jimenez-Jimenez *et al.* (1992)	Interview	Lifetime	Neurologist diagnosis	Not specified
Johnson *et al.* (1999)	FFQ	Past 1 year	Neurologist records	1, 3 (Gorell *et al.* 1997)
Liou *et al.* (1997)	Blinded interviewers, questionnaire	Lifetime	Neurologist examination	1, 3, 4
Logroscino *et al.* (1996, 1998)	Trained interviewers; questionnaire; SFFQ; serum	Past 1 year	PD case registry; neurologist confirmed	3; 8
Mayeux *et al.* (1994)	Trained interviewers, questionnaire	Lifetime	PD case registry; neurologist confirmed	3; 8
Morano *et al.* (1994)	Questionnaire	Lifetime	Diagnosis in records; neurologist examination	Weiner & Lang (1989)
Nefzger *et al.* (1968)	Interview	Lifetime	Medical records	Not specified
Nelson *et al.* (1999)	Structured interview; FFQ	Lifetime	Medical record review	Modified core assessment programme for intracerebral transplantations (Langston *et al.* 1992; Hughes *et al.* 1992*a*)
Powers *et al.* (2003)	FFQ administered by a nurse practitioner	Adult life	Diagnosis logs; pharmacy database; chart reviews	1, 3
Preux *et al.* (2000)	Open-ended and structured interview	Lifetime history; adult years	Neurological examination	8
Ragonese *et al.* (2003)	Structured questionnaire	Lifetime history; adult years	Neurological examination	1, 3, 4, 5
Scheider *et al.* (1997)	Structured interview; questionnaire	20 years before interview date	Interview or current patient; confirmed by neurologist	1, 3, 4
Smargiassi *et al.* (1998)	Trained interviewer using a structured questionnaire	Lifetime or 10 years before onset	Neurologist examination	8
Tan *et al.* (2003)	Interviewer; questionnaire	Lifetime	Neurologist examination	8

Table 3. *Continued*

Reference	Exposure measurement	Time period before outcome	Method of diagnosis	Diagnostic criteria*
Taylor *et al.* (1999)	Trained interviewers using a structured questionnaire	Lifetime	Neurologist examination	Ward & Gibb (1990)
Tsai *et al.* (2002)	Structured interview	Lifetime	Medical records	2, 3
Wang *et al.* (1993)	Interview by trained neurologists; blood	Lifetime	Neurologist examination	1, 3
Yang *et al.* (1994)	Questionnaire	Lifetime	Neurologist examination or record review	Not specified
Zayed *et al.* (1990)	Interview with questionnaire	Lifetime	Neurologist examination	7, 3
Nested case–control studies				
Morens *et al.* (1996)	Dietitians; 24 h dietary recall with photographs	27–30 years	Hospital or neurologist records; death certificates; re-screening	Confirmed by neurologist or 2, 3, 4
Paganini-Hill (2001)	Questionnaire	Up to 17 years of follow-up until end of study or death	Death certificates, hospital discharge; questionnaire	N/A
Cohort studies				
Ascherio *et al.* (2001)	Questionnaire; SFFQ	On average, HPFS 9·2 years; NHS 15·5 years	Questionnaires; death index; medical records	No specified criteria or 1, 4
Chen *et al.* (2002, 2003, 2004); Zhang *et al.* (2002)	Questionnaire; SFFQ	HPFS 12 years; NHS 18 years	See Ascherio *et al.* (2001)	No specified criteria or 1, 4
Davis *et al.* (1996)	Measured serum uric acid level	30 years	See Morens *et al.* (1996)	Confirmed by neurologist or 2, 4
Fink *et al.* (2001)	Questionnaire	10 years	N/A	2; 3
Grandinetti *et al.* (1994)	Questionnaire; serum cholesterol	26 years	See Morens *et al.* (1996)	Confirmed by neurologist or 2, 4
Hernan *et al.* (2003)	SFFQ	HPFS 14 years; NHS 18 years	See Ascherio *et al.* (2001)	No specified criteria or 1, 4
Park *et al.* (2005); Ross *et al.* (2000)	Dietitian-assisted 24 h dietary recall	30 years	See Morens *et al.* (1996)	None specified or 1, 3, (4 or asymmetry of signs), 5
Cerhan *et al.* (1994)	Mailed questionnaires	6 years	Self report	N/A
Willems-Giesbergen *et al.* (2000)	Interview and FFQ	6 years	Screening; neurologist examination	1, 3

SFFQ, semi-quantitative food-frequency questionnaire; N/A, not applicable; PD, Parkinson's disease; FFQ, food-frequency questionnaire; HPFS, Health Professionals' Follow-up Study; NHS, Nurses' Health Study.

* 1, At least two of four cardinal signs (bradykinesia, resting tremor, rigidity, and postural reflex impairment); 2, at least two of three symptoms (bradykinesia or akinesia, rigidity, resting tremor); 3, exclusion of known causes or secondary Parkinsonism or atypical features; 4, good response to levodopa; 5, progressive course; 6, at least three of five symptoms (bradykinesia or akinesia; resting tremor; cogwheel or lead-pipe rigidity; stooped posture with generalised flexion of limb, neck, trunk ± postural instability; shuffling and/or festinating gait) or two of the five symptoms and two of these symptoms (no arm swinging during walking; glabellar tap; mask face ± infrequent blinking; micrographia or voice diminished and monotonous); 7, at least three of the major criteria (bradykinesia or akinesia; rest tremor; rigidity – cogwheel or plastic resistance; postural instability; start hesitation – small step), and two of the accessory criteria (reduced or absence of arm swing; masked facies and minimal eye-blinking; micrographia; monotone voice and weak volume); 8, United Kingdom Parkinson's Disease Society Brain Bank Criteria (Hughes *et al.* 1992*b*).

† Cross-sectional study.

Methods and criteria can significantly impact PD diagnosis (de Rijk *et al.* 1997*b*). Both varied between the reviewed studies and their characteristics are reported as possible sources of heterogeneity that could influence risk estimates (Table 3).

Methods of diagnosis used in the studies included medical record review, interview, physician examination and neurological examination. Death certificates were not considered an acceptable method of PD case ascertainment because PD is often not the primary cause of death. Medical record review and interview only identify previously diagnosed cases. Clinical or neurological examinations can potentially identify new cases of PD and exclude secondary causes of PD. The misdiagnosis rate of PD in a clinicopathological study was 24 % by neurologists; therefore it is possible that non-neurologically trained clinicians would have a higher misdiagnosis rate (Hughes *et al.* 1992*b*).

Diagnostic criteria are often based upon the presence of four cardinal signs of Parkinsonism: bradykinesia or akinesia, resting tremor, rigidity, and postural reflex impairment. Secondary Parkinsonism, caused by known sources such as neuroleptic drugs or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure, should be excluded. Exclusion criteria based on secondary Parkinsonism and known causes were specified by studies; however, they are not undisputed. For example, stroke was excluded as a known cause in some studies, but examined as a risk factor in others. Levodopa response is often used as supporting evidence for PD although not all patients take this drug. Other features of Parkinsonism such as micrographia, unilateral onset, progressive course, shuffling gait, reduced arm swing and masked facies may be used as supporting evidence.

The reviewed studies used a combination of the symptoms and supporting features mentioned above to diagnose PD (Table 3). Some studies did not specify diagnostic criteria and accepted the medical diagnosis by a neurologist or other clinician. The most commonly used set of criteria was from the United Kingdom Parkinson's Disease Society Brain Bank (Hughes *et al.* 1992*a*,*b*) (Appendix 1).

Fruits, vegetables and antioxidants

Fruits and vegetables have relatively high contents of nutrients such as vitamin C, vitamin A, and β-carotene. They were used in previous studies to approximate antioxidant intake. Higher intake of fruits and vegetables is hypothesised to be protective for PD because of the nutrient-rich content, but there is also the possibility that the use of pesticides on raw produce may increase risk (Ho *et al.* 1989).

Intake was measured as: fruits, vegetables, combined fruits and vegetables, raw vegetables, and tomatoes only. Exposure was reported as 'yes or no' (Ho *et al.* 1989), consumption less than or greater than or equal to one time per week (Chan *et al.* 1998), and quartiles of consumption (Hellenbrand *et al.* 1996*b*; Anderson *et al.* 1999; Chen *et al.* 2002). For tomatoes, intake was recorded as seldom/never, each month, each week or daily (Fall *et al.* 1999).

There were no clear differences between CC and cohort risk estimates for fruits and vegetables. The only significantly increased OR was found for raw vegetables by the CC study with the smallest sample size (Ho *et al.* 1989). The study was conducted in Hong Kong, as was a larger study by Chan *et al.* (1998), which reported a non-significant increased OR for raw vegetable consumption. The German study (Hellenbrand *et al.* 1996*b*) found a non-significant inverse association. The exposure was binary compared with the two CC studies with null findings, which used quantitative measures. Hellenbrand reported OR by quartiles and Chan by greater or less than one serving per d. Studies were adjusted for age, except for the two studies from Hong Kong. The NHS and HPFS cohorts reported sex-specific risk estimates, which suggested that men but not women have a lower risk of PD with higher fruit and vegetable intake, although the results were not significant (Chen *et al.* 2002).

Vitamin A and carotenoids. Vitamin A and carotenoids have been shown to have antioxidant properties in animal studies but their effects in man have not been consistently demonstrated (Institute of Medicine, 2001; US Department of Agriculture, 2004). β-Carotene is a provitamin A carotenoid. Lycopene, lutein, zeaxanthin, and xanthophyll are carotenoids, but they are not converted to vitamin A.

Vitamin A exposure was measured as: consumption of foods high in vitamin A, retinol, dietary and total intake. The exposure was reported in quartiles (Anderson *et al.* 1999; Johnson *et al.* 1999) or tertiles (Cerhan *et al.* 1994; Paganini-Hill, 2001). The two CC studies did not find an association between vitamin A intake and PD; however, Anderson reported the only estimate below unity for foods containing vitamin A (Anderson *et al.* 1999; Johnson *et al.* 1999). The female cohort (Cerhan *et al.* 1994) and NCC studies (Paganini-Hill, 2001) reported borderline significant increased risks for total vitamin A intake. In these two studies, the risk estimates of the sub-categories dietary vitamin A (Paganini-Hill, 2001) and retinol (Cerhan *et al.* 1994) were calculated, and they remained elevated but not significant.

Other antioxidant exposures included total antioxidants, β-carotene, α-carotene, total carotenes, lutein, lutein and zeaxanthin, lycopene and other xanthins. Intake was classified by quartiles (Hellenbrand *et al.* 1996*a*; Anderson *et al.* 1999; Johnson *et al.* 1999; Powers *et al.* 2003), quintiles (Zhang *et al.* 2002), median intake (Scheider *et al.* 1997), or specified amounts of intake (de Rijk *et al.* 1997*a*).

There was no association found between total antioxidant intake and PD in one CC study comparing highest and lowest quartiles (Anderson *et al.* 1999). There was no significant association between PD and flavonoid intake reported by one cross-sectional study (de Rijk *et al.* 1997*a*).

The cross-sectional study reported a non-significant inverse association for β-carotene. A meta-analysis (Etminan *et al.* 2005) for β-carotene intake reported non-significant inverse pooled estimates for one cross-sectional (de Rijk *et al.* 1997*a*) and three CC studies (Hellenbrand *et al.* 1996*a*; Scheider *et al.* 1997; Johnson *et al.* 1999).

Only one CC study measured total carotenes, above and below the median, and reported a non-significant positive association (Scheider *et al.* 1997). Results for α-carotene were not significant. The cohort study (Zhang *et al.* 2002) reported an inverse relationship with PD, and the CC study (Scheider *et al.* 1997) found a positive association with α-carotene intake. Both studies adjusted for age, sex, smoking and energy intake.

Two CC studies and one cohort study reported non-significant associations for lycopene. The larger CC study found an increased OR (Powers *et al.* 2003). The cohort study reported a decreased RR (Zhang *et al.* 2002).

Three CC studies found positive associations between PD and lutein, and two were significant (Scheider *et al.* 1997; Johnson *et al.* 1999; Powers *et al.* 2003). The OR decrease with more recent publication date, and the non-significant estimate comes from the largest study. All were adjusted for age and sex. The only cohort study reported a non-significant decreased risk for intake of lutein and zeaxanthin combined (Zhang *et al.* 2002).

Total xanthophylls and other xanthins showed a significant positive association with PD, comparing above and below the median in one CC study (Scheider *et al.* 1997). The same study found a non-significant increased risk among those consuming high amounts of cryptoxanthin. A cohort study found a nearly significant inverse association between β-cryptoxanthin and PD (Zhang *et al.* 2002).

In summary, there were no significant associations reported between vitamin A intake and PD for CC studies but an NCC study and a female cohort study reported borderline significant increased RR. Alpha-, β- and total carotenes were not associated with PD. Lycopene had a borderline significant increased OR in one CC study, but no association in one cohort and one CC study. Higher intakes of lutein were associated with PD in CC studies, but not in two cohorts. Only one study examined other carotene-related nutrients, and significantly increased OR were found for xanthins and xanthophylls, but not for cryptoxanthin and β-cryptoxanthin.

Vitamin C. Vitamin C (ascorbic acid) has antioxidant properties (Ensminger, 1994; US Department of Agriculture, 2004). Vitamin C intake was assessed by: intake of foods containing vitamin C, total intake, dietary intake and use of supplements. The risks are reported for quintiles (Zhang *et al.* 2002), quartiles (Hellenbrand *et al.* 1996*a*; Anderson *et al.* 1999; Johnson *et al.* 1999; Powers *et al.* 2003), tertiles (Cerhan *et al.* 1994; Paganini-Hill, 2001) and median intake (Scheider *et al.* 1997).

There were no significant associations between PD and vitamin C, with the exception of the NCC. The cross-sectional study reported no association between vitamin C per 1000 mg/d and PD. One CC study found a decreased OR for higher consumption of foods with vitamin C (Anderson *et al.* 1999). Of four CC studies, two reported an increased risk and two a decreased risk with higher intake of vitamin C. The highest estimate was from the smallest study, and the estimates decreased with increasing sample size. All studies were adjusted for age and sex. There were no clear differences between the adjustment factors for studies reporting opposing estimates. The estimates did not follow a trend for date of publication.

In the cohort studies, men had an increased risk of PD and women a decreased risk with increasing vitamin C intake (Zhang *et al.* 2002). The other female cohort reported a decreased risk for total vitamin C intake (Cerhan *et al.* 1994).

Dietary intake was examined as a sub-category of total vitamin C intake by the NCC study and the NHS and HPFS cohorts. The NCC study reported a significantly increased risk of PD. The cohort studies reported decreased risks for men and women, separately and combined. All adjusted for age and sex, and the cohort estimates were further adjusted.

A meta-analysis (Etminan *et al.* 2005) of dietary vitamin C intake reported non-significant inverse pooled estimates for five CC (Hellenbrand *et al.* 1996*a*; Scheider *et al.* 1997; Anderson *et al.* 1999; Johnson *et al.* 1999; Paganini-Hill, 2001), one cohort (Zhang *et al.* 2002), and one cross-sectional study (de Rijk *et al.* 1997*a*).

The NHS and HPFS cohorts examined the association between vitamin C supplement use and PD (Zhang *et al.* 2002). There were no significant RR when comparing past use with never in men. However, for women there was a borderline increased risk of PD. In contrast, when current use for 10 years or more was compared with never users, men had an increased risk and women a decreased risk, although both were not significant. Comparing highest with lowest quintiles of vitamin C supplements, men had a slightly increased risk and women a decreased risk, although neither was significant.

Overall, there was no consistent evidence for an association between vitamin C intake and PD. The borderline significant estimates were in opposition. The Iowa women's cohort reported a decreased risk of PD with increased vitamin C intake, whereas the NCC study reported a significantly increased risk for dietary intake. The NHS women's cohort found an increased risk of PD with past use of vitamin C supplements compared with never use.

Vitamin E. α-Tocopherol is the most active form of vitamin E and the most powerful antioxidant (US Department of Agriculture, 2004). There has been some research involving vitamin E as a possible treatment for PD, but its effects are questionable (Fariss & Zhang, 2003).

Vitamin E intake was assessed in three ways: intake of foods containing vitamin E, dietary intake, and total intake including supplements. The risks are reported for quartiles (Hellenbrand *et al.* 1996*a*; Anderson *et al.* 1999; Johnson *et al.* 1999; Powers *et al.* 2003), above *v.* below the median value (Scheider *et al.* 1997), quintiles (Zhang *et al.* 2002), and for a continuous variable in mg (Morens *et al.* 1996).

The CC study of consumption of foods with vitamin E reported a non-significant increased risk of PD (Anderson *et al.* 1999). There was a significant inverse association in the cross-sectional study between PD and vitamin E intake per 10 mg/d (de Rijk *et al.* 1997*a*). There were no significant risks reported by five CC studies of total vitamin E. There were no clear trends with publication date or sample size. The Honolulu Heart Study reported vitamin E intake above and below the RDA, OR 0·64 (95 % CI 0·35, 1·17), and above and below the median, OR 0·90 (95 % CI 0·54, 1·48) (Morens *et al.* 1996).

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The NHS and HPFS cohort studies examined vitamin E intake (Zhang *et al.* 2002). For total vitamin E intake, there was a slightly increased risk for men and decreased risk for women, but both were not significant. There was a significantly decreased risk of PD in women consuming the highest amounts of dietary vitamin E compared with the lowest quintile (Zhang *et al.* 2002). The decreased risk for men was not significant.

A recent meta-analysis (Etminan *et al.* 2005) reported a significantly decreased pooled risk for PD with moderate vitamin E intake. Five CC (Morens *et al.* 1996; Hellenbrand *et al.* 1996*a*; Scheider *et al.* 1997; Anderson *et al.* 1999; Johnson *et al.* 1999), one cohort (Zhang *et al.* 2002) and one cross-sectional study (de Rijk *et al.* 1997*a*) reported data for moderate intake but only four of these studies were pooled to assess high intake. The pooled estimates were 0·81(95 % CI 0·67, 0·98) for moderate intake (second and third quartile or third and fourth quintile) and 0·78 (95 % CI 0·57, 1·06) with high intake (fourth quartile or fifth quintile).

Total intake of vitamin E and foods with vitamin E were not significantly associated with PD in CC studies. The cohort studies indicated a slightly increased risk of PD in men and a lower risk in women with higher vitamin E intake. This was significant only for dietary vitamin E intake in women.

Carbohydrates

Carbohydrates contain sugars, starch, cellulose, gums and related substances (Ensminger 1994). The specific biological hypothesis for an association between carbohydrates and PD is unclear.

Carbohydrate consumption was reported as: total carbohydrates, disaccharides, monosaccharides, and lactose, and by measuring intake of specific foods that are high in carbohydrates, such as breads, potatoes, cereals and 'other starch foods'. The risk estimates were reported as quartiles (Hellenbrand *et al.* 1996*a*,*b*; Logroscino *et al.* 1996; Anderson *et al.* 1999; Johnson *et al.* 1999; Chen *et al.* 2002) and quintiles (Chen *et al.* 2003).

Of three CC studies that measured total carbohydrate consumption, one found a significantly increased OR for PD (Hellenbrand *et al.* 1996*a*). The remaining two CC studies failed to find significant associations and reported estimates in opposite directions. All studies adjusted for age, sex, education, and energy intake.

The NHS and HPFS cohort studies reported an increased risk of PD for women and a decreased risk for men with higher total carbohydrate consumption (Chen *et al.* 2003). Neither estimate was statistically significant.

A German CC study found increased adjusted OR for the highest quartiles of disaccharide and monosaccharide intake, although only the estimate for monosaccharides was significant (Hellenbrand *et al.* 1996*a*).

The HPFS male cohort reported a significantly increased RR for lactose intake of 25 mg or more from diary products, adjusted for Ca, vitamin D, fat and protein (Chen *et al.* 2002).

There were no significant risks reported for cereals or 'other starch foods'. A non-significant decreased OR was reported by one CC study for combined bread and cereal intake (Anderson *et al.* 1999). Two sex-specific cohort studies measured cereal intake and other starch foods, but did not find significant associations (Chen *et al.* 2002). One CC study reported a significantly decreased unadjusted OR for individuals consuming French loaf or wheat bread, daily *v.* never (Fall *et al.* 1999). Another CC study found a significantly decreased risk for PD among individuals consuming the highest quartile of potatoes (Hellenbrand *et al.* 1996*b*). All studies were adjusted for age, sex, and other covariates.

Higher intake of total carbohydrates and sugars was associated with PD in some CC studies. The finding was not confirmed in cohort studies, which found no significant effects, with the exception of a positive association with lactose intake in men. Specific foods high in carbohydrates were not associated with PD except for potatoes and French or wheat bread, which were inversely associated with PD.

Fats and cholesterol

Fats and oils are lipids, which are involved with fat-soluble vitamin transport among other functions. The intake of excess fats may be relevant to PD aetiology because unsaturated fatty acids are the targets of lipid peroxidation, which can generate free radicals and cause oxidative stress (Ensminger, 1994). Other functions of the fatty acids, such as the role of arachidonic acid in inflammatory response, may also be involved in PD. The biological relationship of cholesterol to PD aetiology is not clear.

Fish oils are a rich source of *n*-3 long-chain PUFA, including EPA and DHA. DHA may play a role in neurological function and/or neuroprotection, although its specific function is undefined (Salem *et al.* 2001). Arachidonic acid may have anti-inflammatory effects, as shown in studies of rheumatoid arthritis patients (Cleland *et al.* 2003).

Fat intake was measured as total, animal, dairy, vegetable, saturated, monounsaturated, polyunsaturated, and *trans*-unsaturated. Specific fatty acids were examined in the NHS and HPFS cohorts: arachidonic, docosahexaenoic, eicosapentaenoic, linoleic, linolenic, oleic, and *n*-3 (Chen *et al.* 2003). The risk estimates for fats were reported as quartiles (Logroscino *et al.* 1996; Hellenbrand *et al.* 1996*a*; Anderson *et al.* 1999; Johnson *et al.* 1999; Powers *et al.* 2003), quintiles (Chen *et al.* 2003), and one or more servings *v.* none (Morens *et al.* 1996). Total intake of cholesterol was measured by three studies (Johnson *et al.* 1999; Chen *et al.* 2003).

Of four CC studies examining total fat intake, only one found a significant positive association with PD (Hellenbrand *et al.* 1996*a*; Logroscino *et al.* 1996; Johnson *et al.* 1999; Powers *et al.* 2003). All studies adjusted for age, sex, and energy intake. There was no trend in the estimates with publication date; however, the two studies with smaller sample sizes reported positive associations with fat consumption, whereas the two larger studies reported inverse associations. The NHS and HPFS cohorts reported an increased risk of PD with higher fat consumption for men, and a reduced risk for women. Neither result was significant.

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In addition to total fat, studies examined the relationship between specific subtypes of fat and PD. Only the HPFS cohort reported fat intake categorised by dairy and non-dairy sources. Both RR were non-significant, adjusted for Ca, vitamin D, protein and lactose (Chen *et al.* 2002). Two CC studies measured intake of animal fat and both found significant positive associations, adjusted for age, sex, energy intake, and other covariates. One male NCC study reported a non-significant estimate in the same direction, adjusted for smoking and coffee (Morens *et al.* 1996). The NHS and HPFS cohorts found an increased RR for PD in men and a decreased risk in women comparing highest and lowest quintiles of animal fat intake, although neither result was significant (Chen *et al.* 2003).

The only CC study to report an OR for fats from vegetables found no difference in intake between cases and controls (Logroscino *et al.* 1996). A male NCC study found a non-significant reduced risk with at least one serving of vegetable oil compared with none (Morens *et al.* 1996). The HPFS cohort found a non-significant reduced risk of PD for men consuming vegetable fat in the highest quintile (Chen *et al.* 2003). The NHS cohort found a non-significant increased RR for women in the highest quintile (Chen *et al.* 2003).

Two CC studies reported OR in opposite directions for saturated fat intake. The larger of the two found a significantly reduced OR, whereas the study with approximately half the number of cases found a non-significant increased OR (Johnson *et al.* 1999; Powers *et al.* 2003). Both studies, conducted in the USA, were adjusted for age, sex, race, smoking and energy intake, but other covariates differed. The HPFS and NHS cohort studies reported an increased risk of PD for men and a decreased risk for women, and both were non-significant (Chen *et al.* 2003).

Only the HPFS and NHS cohorts examined the relationships of monounsaturated, polyunsaturated and *trans*-unsaturated fat with PD (Chen *et al.* 2003). None of the RR were significant. For monounsaturated fat, men appeared to have a slightly increased risk and women a decreased risk for the highest intake.

The NHS and HPFS cohorts reported inverse relationships between arachidonic acid intake and PD in men and women, although only the pooled estimate reached statistical significance (Chen *et al.* 2003). The RR for DHA, EPA, and *n*-3 fatty acids were below unity but non-significant.

The NHS and HPFS cohorts reported a non-significant inverse relationship between PD and linoleic acid intake (Chen *et al.* 2003). One CC study also measured linoleic acid intake and reported no association with PD (Johnson *et al.* 1999). The same CC study reported a non-significant increased OR for oleic acid intake. The RR from the NHS and HPFS for linolenic acid intake was above unity for women and below for men, although neither was statistically significant (Chen *et al.* 2003).

The CC study that estimated cholesterol intake found a non-significant positive association with PD (Johnson *et al.* 1999). The HPFS and NHS studies reported non-significant RR in opposite directions (Chen *et al.* 2003). The Honolulu Heart Study measured serum cholesterol (mg) in men at baseline and found no significant difference in the RR of PD. This measure may not be directly related to cholesterol consumption as the body also produces cholesterol (Grandinetti *et al.* 1994).

Two cohort studies and one NCC study did not find significant associations between PD and fat or specific types of fat. Two CC studies found significantly increased OR for the highest levels of total and/or animal fat intake. The risk estimates for specific fatty acids were not significant. There was no evidence to suggest that cholesterol intake is related to PD.

Proteins

Proteins are complex organic molecules made up of amino acids. Some functions of proteins are cell maintenance, regulation, and energy formation. The specific biological hypothesis for an association between proteins and PD is unclear.

Protein intake was measured as total protein and by foods that are mainly composed of protein. The risk estimates for proteins were reported as quartiles (Hellenbrand *et al.* 1996*a*; Logroscino *et al.* 1996; Anderson *et al.* 1999; Johnson *et al.* 1999; Chen *et al.* 2002), quintiles (Chen *et al.* 2003), and by frequency of consumption (Fall *et al.* 1999).

Total protein intake was measured by three CC studies, and none found a significant OR (Hellenbrand *et al.* 1996*a*; Logroscino *et al.* 1996; Johnson *et al.* 1999). The two larger studies reported an inverse association with PD, whereas the smaller study reported a two-fold increased risk. The smaller study matched controls by frequency, whereas the other two matched each individual case. All adjusted for age and sex. The HPFS and NHS cohorts reported non-significant RR for protein intake (Chen *et al.* 2003).

A CC study reported an inverse association between PD and total meat intake (Anderson *et al.* 1999). The same study found a positive association for red meat consumption. The HPFS cohort reported non-significant increased RR in men for total meat and red meat (Chen *et al.* 2003). In contrast, the NHS cohort reported non-significant decreased risks in women (Chen *et al.* 2003).

One unmatched, unadjusted CC study reported non-significant decreased OR for both fried and broiled meat, and smoked ham and meat, comparing daily consumption with never (Fall *et al.* 1999). The study found a significantly decreased risk of PD for individuals consuming eggs daily compared with never.

The HPFS and NHS cohorts found no significant association between PD and chicken consumption, although estimates indicated a protective effect with higher intake (Chen *et al.* 2003). The RR for fish consumption was similar to chicken in men, but in women the RR was non-significantly increased for the highest quartile of consumption. A CC study measuring combined chicken and fish consumption reported a non-significant decreased OR (Anderson *et al.* 1999). The same study found no association for fish intake alone. The cohort studies and CC study were adjusted for age, sex, energy intake and other covariates.

In general there were no significant associations or patterns for the relationship between protein intake and PD. The cohort RR were close to unity, and the CC study OR were in both directions. The most extreme estimates, nearly reaching significance, were for inverse associations between

PD and fried and broiled meat consumption, and PD and smoked ham and meat consumption. However, the estimates were from one unadjusted CC study; therefore they must be interpreted with caution.

Dairy products

Dairy is comprised of all products made from milk. Milk contains carbohydrates, proteins, minerals, fat and vitamins. There are no specific *a priori* hypotheses for dairy products.

One CC and three cohort studies examined the association of PD with total dairy product or milk intake (Anderson *et al.* 1999; Chen *et al.* 2002; Park *et al.* 2005). More specific dairy product analyses were conducted in the HPFS male cohort only (Chen *et al.* 2002). There were no significant risk estimates for the highest compared with the lowest quartiles of total dairy consumption in the CC study or the female NHS cohort, although the estimates were in opposite directions. The risk was significantly elevated in men consuming the highest amount of total dairy products in both the HPFS and Honolulu male cohorts. Ca had no apparent association with PD after adjustment for milk consumption (Park *et al.* 2005). For the sub-categories high-fat and low-fat dairy, both the HPFS and NHS cohorts had increased but non-significant RR with higher consumption. The PD risk estimates for specific dairy products in HPFS men were not significant, with the exception of an elevated risk in men consuming cream cheese at least once per week compared with never.

Dairy product intake was examined by only four studies, and a significant association between total dairy intake and PD was found in the two male cohorts only. A sub-analysis of specific dairy products in the HPFS cohort suggested that cream cheese and sour cream intake more than once per week compared with never might increase risk of PD.

Alcohol intake

Alcohol is usually consumed in the form of ethanol. Alcohol is included in the present review as a beverage type. Alcohol is combined with O_2 in the liver, where alcohol is changed into the toxic chemical acetaldehyde. This is converted to acetate in the liver and other cells. Acetate is oxidised to CO_2 and water to produce heat and energy (Ensminger, 1994).

The brain is very sensitive to alcohol. At low levels in the blood it may act as a stimulant, but its main effect is as a depressant. Alcoholism can cause premature ageing of the brain, which may cause temporary or permanent damage to cognitive function (Ensminger, 1994). It is also possible that alcohol contributes to oxidative stress, which may affect the brain (Collins, 2002). However, alcohol has been discussed as a protective factor for neurodegeneration and vascular disease, although the mechanisms are unknown (Desagher *et al.* 1996; Gonthier *et al.* 2004).

The intake of alcohol was measured as: 'ever *v.* never'; 'yes *v.* no'; ex- or current drinker *v.* never drinkers; heavy or moderate intake *v.* never drinkers; quantitative comparisons using estimated alcohol or ethanol consumed (g) per d; and durations of exposure.

The binary measures were combined and summarised using a meta-analysis comparing drinkers with non-drinkers. Information was available from thirteen CC studies (Haack *et al.* 1981; Ho *et al.* 1989; Jimenez-Jimenez *et al.* 1992; Mayeux *et al.* 1994; Liou *et al.* 1997; Smargiassi *et al.* 1998; Gorell *et al.* 1999; Nelson *et al.* 1999; Benedetti *et al.* 2000; Behari *et al.* 2001; Checkoway *et al.* 2002; Tsai *et al.* 2002; Ragonese *et al.* 2003) and four cohort studies (Grandinetti *et al.* 1994; Willems-Giesbergen *et al.* 2000; Hernan *et al.* 2003).

The meta-analysis results are reported for the fixed effects models, as the random and fixed effects estimates were similar. The CC pooled OR was 0·81 (95 % CI 0·70, 0·92) (Fig. 1). The estimates for Tsai and Nelson were for current drinkers *v.* never, as overall estimates could not be calculated (Nelson *et al.* 1999; Tsai *et al.* 2002). The pooled estimate excluding these two studies was 0·86 (95 % CI 0·74, 1·00). The cohort pooled RR estimate was 0·73 (95 % CI 0·57, 0·92) (Fig. 2). Two of the four cohorts were

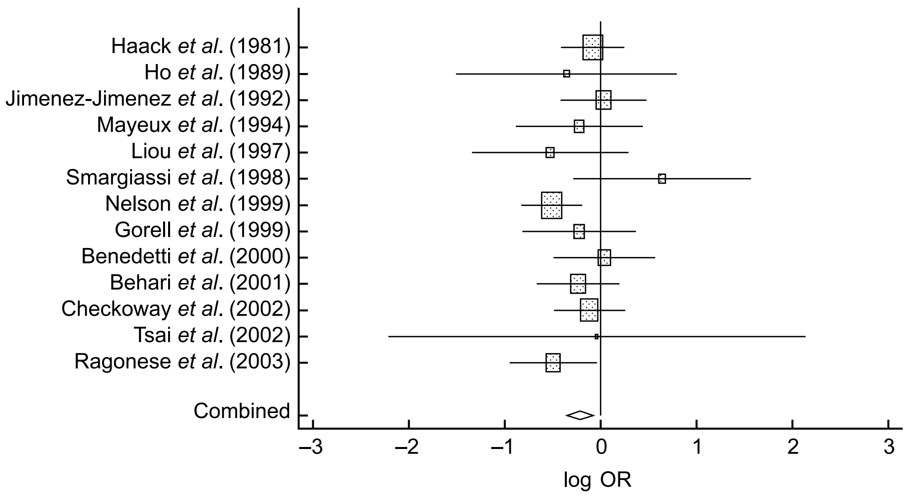

Fig. 1. A meta-analysis of the association between ever drinking alcohol and Parkinson's disease in thirteen case–control studies. For Nelson *et al.* (1999) and Tsai *et al.* (2002), the estimates represent current *v.* never drinking alcohol, as the overall estimate could not be calculated.

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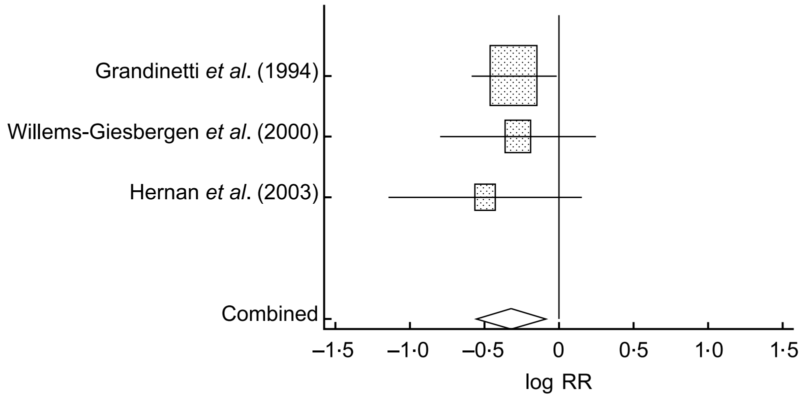

Fig. 2. A meta-analysis of the association between ever drinking alcohol and Parkinson's disease in three cohort studies. Hernan *et al.* (2003) is a pooled estimate of the Nurses' Health Study and Health Professionals' Follow-up Study sex-specific cohorts.

sex specific but a pooled estimate was available and used for the meta-analysis (Hernan *et al.* 2003).

In general the OR estimates indicated an inverse association, although only two were significant (Nelson *et al.* 1999; Ragonese *et al.* 2003). Three non-significant OR indicated a positive relationship between alcohol drinking and PD, two of which were in women only (Jimenez-Jimenez *et al.* 1992; Smargiassi *et al.* 1998; Benedetti *et al.* 2000). The four cohort studies reported inverse associations, but only the unadjusted estimate from the male HPFS cohort reached borderline significance.

The five CC studies using semi-quantitative measures, which estimated ethanol intake (g) or number of drinks, reported a general inverse relationship with PD (Jimenez-Jimenez *et al.* 1992; Wang *et al.* 1993; Hellenbrand *et al.* 1996*b*; Checkoway *et al.* 2002; Ragonese *et al.* 2003). The estimates from two of the studies reached statistical significance. The NCC study and two cohorts reported the same inverse relationship but only the NCC study was significant (Paganini-Hill, 2001; Hernan *et al.* 2003).

One CC study reported OR for alcohol drinking stratified by the number of years drinking compared with non-drinkers. There was a non-significant inverse association between PD and drinking for less than or equal to 20 years. The relationship was reversed for those consuming alcohol for more than 20 years (Behari *et al.* 2001).

Alcohol intake was categorised in several studies by specific types of alcoholic beverages: beer, wine and spirits or liquor.

Two CC studies reported significant inverse associations between PD and beer intake. One measured consumption in quartiles (Hellenbrand *et al.* 1996*b*) and the other stratified beer intake by strength, medium and strong, and compared the number of bottles consumed with the reference category of one or less bottle of beer per d and week, respectively (Fall *et al.* 1999). The HPFS and NHS cohorts reported a significant inverse association between PD and the consumption of one or more beers per week compared with less than one per month (Hernan *et al.* 2003). However, the RR for the male and female cohorts separately were not significant.

The measurement of wine consumption differed between studies and the estimates were similarly variable. The larger of two CC studies reported a non-significant increased OR for PD comparing highest and lowest quartiles of wine consumption (Hellenbrand *et al.* 1996*b*). The other study, unmatched and unadjusted, reported a significantly decreased risk for drinking two to six bottles of wine per week compared with non-drinkers (Fall *et al.* 1999). The pooled RR for the HPFS and NHS cohorts was non-significantly increased for drinking wine at least five times per week compared with less than once per month. The risk was increased in women and decreased in men, but neither was significant.

Hard liquor, liquor and spirits were considered the same exposure. All three CC studies reported significant inverse associations between PD and liquor consumption (Wang *et al.* 1993; Hellenbrand *et al.* 1996*b*; Fall *et al.* 1999). The two smaller studies measured liquor as a binary exposure, yes or no, and by the number of bottles consumed per week (Wang *et al.* 1993; Fall *et al.* 1999). The largest study compared the highest and lowest tertiles of intake (Hellenbrand *et al.* 1996*b*). The pooled RR for the NHS and HPFS cohorts was non-significant comparing individuals consuming liquor five or more times per week with less than once per month (Hernan *et al.* 2003). The cohorts reported non-significant risks for men and women separately.

Overall there is some evidence for an inverse association between alcohol and PD; however, the majority of studies failed to reach statistical significance. Of thirteen CC studies comparing drinkers with non-drinkers, ten showed an inverse association, two of which were significant. The four cohort studies all showed inverse associations, although only an unadjusted estimate for men was borderline significant. When alcohol was measured quantitatively, all OR for five CC studies were below one, two of which were significant. The NCC showed a significant inverse association, and the two cohorts reported non-significant inverse associations.

Coffee, tea and caffeine

Caffeine is a drug with primarily stimulatory effects (Ensminger, 1994). Caffeine is mainly metabolised by the CYP1A2 isoenzyme of the p450 family (Fredholm *et al.*

1999; Pollock *et al.* 1999). The effects of caffeine include stimulation of the central nervous system (Weinreb *et al.* 2004).

A meta-analysis of eight CC studies (Nefzger *et al.* 1968; Haack *et al.* 1981; Jimenez-Jimenez *et al.* 1992; Morano *et al.* 1994; Fall *et al.* 1999; Benedetti *et al.* 2000; Preux *et al.* 2000; Paganini-Hill, 2001) and four cohort studies (Ross *et al.* 2000; Ascherio *et al.* 2001; Fink *et al.* 2001) that investigated the association between coffee drinking and PD reported a pooled estimate of 0·74 (95 % CI 0·67, 0·81) for the fixed effects model and 0·72 (95 % CI 0·64, 0·81) for the random effects model (Hernan *et al.* 2002). These estimates were corrected after the original publication (MA Hernan, personal communication). The pooled RR per three additional cups of coffee per d was 0·75 (95 % CI 0·64, 0·86) in CC studies (Nefzger *et al.* 1968; Jimenez-Jimenez *et al.* 1992; Benedetti *et al.* 2000; Ahmadi *et al.* 2000), and 0·68 (95 % CI 0·46, 1·00) in cohort studies (Ross *et al.* 2000; Willems-Giesbergen *et al.* 2000; Ascherio *et al.* 2001).

Coffee drinking overall was found to be protective for PD. The pooled estimates for CC and cohort studies were not significantly different from each other. None of the individual studies reported increased risks, but some of the protective risk estimates were not statistically significant.

The inclusion and exclusion criteria for the meta-analysis were similar to the criteria set out for the present systematic review. Two studies not included in the meta-analysis were identified from the specified time period (Zayed *et al.* 1990; Hellenbrand *et al.* 1996*b*). Hellenbrand was mentioned but not included because the data did not provide enough information to calculate OR. Zayed reported a non-significant inverse relationship for the binary and quantitative measures of coffee intake (Zayed *et al.* 1990; Hellenbrand *et al.* 1996*b*).

Three additional CC studies were published after the meta-analysis inclusion period (Checkoway *et al.* 2002; Ragonese *et al.* 2003; Tan *et al.* 2003). Tan would not have been included because the exposure, thirty cup-years, cannot be calculated in binary terms. The other two studies reported inverse associations between PD and coffee drinking, but only Ragonese was significant. The additional studies would not significantly change the pooled estimates from the 2002 meta-analysis.

The quantitative measurements compare the highest and lowest categories of coffee consumption in seven CC, five cohort and one NCC studies. All but two specified the number of cups per d (Hellenbrand *et al.* 1996*b*; Ross *et al.* 2000). Hellenbrand compared quartiles and Ross computed an RR using ounces of coffee consumed. Zayed used a combined measure of coffee and tea consumption (Zayed *et al.* 1990). All risk estimates supported the inverse relationship between coffee and PD. Three CC (Hellenbrand *et al.* 1996*b*; Fall *et al.* 1999; Benedetti *et al.* 2000), one cohort (Ross *et al.* 2000) and the NCC (Paganini-Hill, 2001) study reported significant inverse associations.

Two age- and sex-matched CC studies measured coffee cup-years and reported OR significantly below unity (Ragonese *et al.* 2003; Tan *et al.* 2003). The OR for individuals consuming greater than thirty cup-years, estimating three cups per d for 10 years, was 0·79 (95 % CI 0·66, 0·93) (Tan *et al.* 2003). The analysis was adjusted for covariates including smoking, alcohol and tea. The other study reported OR of 0·36 (95 % CI 0·05, 1·86), 0·19 (95 % CI 0·08, 0·43) and 0·20 (95 % CI 0·08, 0·47) for one to thirty-eight, thirty-nine to eighty and eighty-one to 288 cup-years, respectively (Ragonese *et al.* 2003). The estimates were adjusted for education but not for smoking. The results support the inverse association between coffee drinking and PD.

Two studies reported non-significant OR for the relationship between decaffeinated coffee and PD. The CC study did not find an association between PD and regular or decaffeinated coffee. The decaffeinated OR was 1·10 (95 % CI 0·7, 1·8) (Checkoway *et al.* 2002). The NCC study found a significant inverse relationship between PD and the consumption of two or more cups of regular coffee compared with non-drinkers (Paganini-Hill, 2001). This same comparison with decaffeinated coffee produced a null result, RR 0·94 (95 % CI 0·72, 1·23). If this result is replicated it might indicate that caffeine is the exposure affecting the outcome of PD.

Tea drinking exposure was measured as yes or no (Ho *et al.* 1989; Yang *et al.* 1994; Morano *et al.* 1994; Preux *et al.* 2000), cups per d (Chan *et al.* 1998; Fall *et al.* 1999; Paganini-Hill, 2001; Checkoway *et al.* 2002) and cup-years (Tan *et al.* 2003). The risk estimates for PD and tea consumption are inconsistent. The only NCC study reported a non-significant increased OR comparing drinking at least two cups of tea per d to none (Paganini-Hill, 2001).

Four CC studies measured tea consumption as a binary variable, and there were two OR estimates in each direction (Ho *et al.* 1989; Yang *et al.* 1994; Morano *et al.* 1994; Preux *et al.* 2000). The only estimate reaching significance reported a positive association between tea drinking and PD (Preux *et al.* 2000).

All four CC studies with quantitative measures of tea drinking reported significant inverse associations with PD (Chan *et al.* 1998; Fall *et al.* 1999; Checkoway *et al.* 2002; Tan *et al.* 2003). The NCC found a non-significant positive association.

There is no clear trend of the risk estimates with publication date or geographical location. Of the three studies that reported increased risk of PD with tea drinking, one was unadjusted and two were adjusted for age and sex. Of the six studies reporting a decreased risk, three were unadjusted and three were adjusted for age, sex and other covariates.

One CC study investigated the association between cola intake and PD, and the risk estimate was 0·60 (95 % CI 0·30, 1·40), adjusted for age, sex and clinic (Checkoway *et al.* 2002).

The Honolulu Heart Study male cohort used dietary food and beverage consumption to estimate total caffeine intake and caffeine from non-coffee sources. The RR for caffeine in the highest *v.* lowest quintile was 0·20 (95 % CI 0·08, 0·48). For caffeine from non-coffee sources the RR was 0·37 (95 % CI 0·19, 0·71). Both estimates were adjusted for age and smoking (Ross *et al.* 2000).

All ten CC, one NCC and four cohort studies reported inverse relationships between PD and ever drinking coffee. Four of the CC estimates were significant, as were those from the NCC and the male HPFS cohort. All OR and RR

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using quantitative measures were less than or equal to unity, with the one NCC, four of seven CC, and one of five cohort studies reporting significant associations.

There were two OR estimates in each direction for the binary measure of tea drinking, and only one suggesting a positive association with PD was significant. All CC studies measuring tea consumption quantitatively reported significant inverse associations.

Overall the evidence points to an inverse association between PD and caffeine or caffeinated beverages, although not entirely.

Other foods

Three studies examined the association between junk foods and PD. One CC study found a non-significant decreased OR for higher junk food intake (Anderson *et al.* 1999). A larger CC study reported significantly increased OR for higher consumption of sweets, chocolate, and desserts (Hellenbrand *et al.* 1996*b*). The HPFS and NHS cohorts did not find significant risks for increased consumption of 'chocolate, candies or brownies' or 'other sweets or desserts' (Chen *et al.* 2002).

The OR for the associations between PD and other miscellaneous foods were mostly non-significant. The intake of nuts and seeds was positively associated with PD in a CC study, but the HPFS and NHS cohorts combined reported a significantly decreased risk for higher nut intake (Butterfield *et al.* 1993; Zhang *et al.* 2002).

Calcium

Ca is an essential element whose absorption depends on dietary factors such as vitamin D, lactose, protein and acid medium. Ca plays a role in nerve impulse transmission (Ensminger 1994). No *a priori* hypotheses appear to be discussed for Ca.

Ca intake was measured as total dietary Ca and Ca supplements. Two CC studies reported non-significant increased OR comparing the highest with lowest quartiles of dietary Ca intake (Johnson *et al.* 1999; Powers *et al.* 2003). The HPFS male cohort reported a non-significant protective effect of Ca supplement intake above 200 mg/d compared with none (Chen *et al.* 2002).

Overall, there were no significant associations between Ca intake and PD.

Iron

Fe is an essential mineral and is a component of proteins involved in O_2 transport and metabolism (Institute of Medicine, 2001). The role of Fe in PD has been investigated because its levels are increased in the PD substantia nigra, and it has the capacity to enhance the production of oxygen free radicals (Berg *et al.* 2001).

Fe intake was measured as: foods with Fe, dietary Fe and total Fe including supplements. Of four CC studies, two reported borderline positive associations with PD. The smallest study reported a non-significant inverse association between PD and the consumption of foods with Fe (Anderson *et al.* 1999). Another small study reported a nearly significant positive association between PD and dietary Fe intake. However, when dietary Fe and supplements were considered together, the OR was non-significant and less than unity. Two larger CC studies considering the total intake of Fe reported positive associations, one of which was nearly significant.

The two smallest studies reported estimates in opposite directions for dietary intake without supplements. The first study was unmatched but adjusted for age, sex and other covariates (Anderson *et al.* 1999). The second study was frequency matched for age, ethnicity and sex, but unadjusted in the analysis (Logroscino *et al.* 1998).

For total Fe intake including supplements, two studies reported increased OR (Johnson *et al.* 1999; Powers *et al.* 2003) and one reported a decreased OR (Logroscino *et al.* 1998). The two positive studies were larger, frequency-matched for age and sex, and adjusted for various covariates.

There is a possible positive association between Fe and PD. Two CC studies reported borderline significant positive associations between Fe intake and PD, although one found a null result for dietary and supplemental Fe combined. The two remaining studies reported non-significant estimates in opposite directions.

Multivitamins or total vitamins

Multivitamin intake is a heterogeneous exposure and intake was measured as: vitamins, vitamin or cod liver oil supplement, and multivitamins. One CC study reported a non-significant increased OR for PD with the intake of vitamin or cod liver oil supplements at least once per week (Chan *et al.* 1998). Another CC study reported no association with vitamin intake (Taylor *et al.* 1999). The HPFS and NHS cohort studies analysed multivitamin intake for men and women, separately and pooled (Zhang *et al.* 2002). None of the comparisons were significant.

Overall, there were no significant associations between vitamin or multivitamin use and PD. The results from the analyses of past or current use in the NHS and HPFS cohorts indicate that past use but not current use for greater than 10 years may be protective for PD in men, and the opposite relationship is indicated for women.

B vitamins

B vitamins are often referred to by their most common forms: vitamin B_1 (thiamin); vitamin B_2 (riboflavin); vitamin B_3 (niacin); vitamin B_5 (pantothenic acid); vitamin B_6 (pyridoxine); and vitamin B_{12} (cobalamin).

B_6 is a water-soluble vitamin whose major function is in amino acid metabolism, and extremely high intakes have been associated with neurological damage (Bender, 1989).

Folate and folic acid are different forms of a water-soluble B vitamin (Herbert, 1999). Levels of folate and homocysteine are inversely related (Verhoef *et al.* 1996). Low folate status may play a role in depression, cognitive impairment and/or dementia, although evidence is inconsistent and the causal relationship has not been proven (Morris, 2002). A study in mice found that folate deficiency caused increased susceptibility to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a chemical known to cause Parkinsonian signs (Miller, 2002). Folate also plays a role in the formation of purines and pyrimidines necessary for RNA and DNA synthesis. Vitamin B_{12}, or cobalamin, is necessary for DNA synthesis (Herbert, 1996).

Two CC and two cohort studies examined the intake of various B vitamins (Hellenbrand *et al.* 1996*a*; Johnson *et al.* 1999; Chen *et al.* 2004). The NHS and HPFS cohorts measured folate, vitamins B_6 and B_{12} as total, dietary and supplement intake. Total and dietary intakes were divided into quintiles. Supplemental intake was divided into three categories and compared non-users with users above and below specified amounts of intake (Chen *et al.* 2004).

The relationship between thiamin intake and PD was examined by one CC study (Johnson *et al.* 1999). The adjusted OR was non-significant, comparing highest and lowest quartiles.

The CC studies reported estimates in opposite directions comparing the highest and lowest quartiles of riboflavin, folate and pyridoxine intake, separately. The US study estimates were above one and non-significant, whereas the German study OR were significantly less than one for all three vitamins (Hellenbrand *et al.* 1996*a*; Johnson *et al.* 1999). The two cohort studies reported non-significant RR for total, dietary and supplemental folate and vitamin B_6 intake (Chen *et al.* 2004).

Both CC studies reported decreased OR for niacin, although only the larger study was significant. Hellenbrand found a significantly decreased OR for pantothenic acid and a non-significant decreased OR for cobalamin. The two cohort studies reported non-significant RR for total, dietary and supplemental cobalamin intake (Chen *et al.* 2004).

The CC studies were matched for age and sex, and adjusted for multiple covariates including energy intake. The German study (Hellenbrand *et al.* 1996*a*) was twice as large as the American study (Johnson *et al.* 1999). Both studies measured nutrient intake with a food-frequency questionnaire and specified PD diagnostic criteria. One difference in case selection was that Hellenbrand chose individuals under 67 years, and Johnson chose individuals greater than 50 years of age. The sex-specific cohort studies adjusted for age, sex, and total energy and other factors.

In summary, two CC and two cohort studies examined the association between B vitamins and PD. The cohort studies reported no significant associations comparing the highest and lowest quintiles of folate, vitamin B_6 or vitamin B_{12} intake. In the CC studies, there were no significant associations between PD and thiamin, riboflavin, and cobalamin. The German study reported an inverse relationship between niacin and PD, which was supported by the non-significant finding in the US study. The CC studies had estimates in opposite directions for pyridoxine and folate. The German study reported significant inverse associations, and the US study reported non-significant positive associations. The German study found a significant inverse relationship between pantothenic acid and PD.

Total energy

It has been observed that PD patients consume more energy than unaffected individuals while still losing body weight (Davies *et al.* 1994). This may be due to their using more energy for activities of daily living; however, it is possible that this difference could also have existed in the premorbid diet. No hypotheses have been discussed for the role of energy intake in PD. Six studies compared the energy intake between PD cases and unaffected individuals (Hellenbrand *et al.* 1996*b*; Logroscino *et al.* 1996; Anderson *et al.* 1999; Johnson *et al.* 1999; Chen *et al.* 2003).

The four CC studies compared the highest and lowest quartiles of energy intake. Three reported increased OR, of which two were significant. The fourth study reported a non-significant estimate below unity. All were adjusted for age and sex, as well as other factors.

The NHS and HPFS cohort studies reported a pooled adjusted RR of one comparing the highest and lowest quintiles of energy intake. The NHS was slightly below, and the HPFS slightly above null, but neither was significant.

Overall, the CC studies suggested a positive association between energy intake and PD, but this was not supported by the null findings in the two cohort studies.

Miscellaneous nutrients

Only nutrients that were reported by at least three unrelated studies were summarised in separate sections and the rest are reported below.

K maintains cellular osmotic pressure and acid–base balance. Na is associated with muscle contraction and nerve function, and it plays a role in carbohydrate absorption. P is involved in almost all metabolic functions and is a component of nucleic acids (Ensminger 1994).

One CC study reported a non-significant reduced OR for K, and a non-significant increased OR for Na and P (Johnson *et al.* 1999). All estimates were adjusted for age, sex, race, total energy and smoking.

Cu is a constituent of enzyme systems that relate to brain cell and spinal cord function. Cu deficiency can lead to disorders including dymelination and degeneration of the nervous system. Mg is an essential mineral required for the activation of enzymes involved with the phosphorylation of ADP to ATP (Ensminger 1994). Mg releases nerve impulses and is involved with muscle contraction (US Department of Agriculture, 2004). Zn is an essential mineral necessary for synthesis and metabolism of proteins and nucleic acids. Se is an essential trace mineral; it is an important part of antioxidant enzymes (Combs & Gray, 1998). Mn is involved in cholesterol synthesis and the metabolism of carbohydrates, fats, proteins and nucleic acids (Ensminger, 1994).

One CC study reported no significant associations between PD and Cu, Mg, Mn, Se or Zn intake, comparing the highest and lowest quartiles of intake (Powers *et al.* 2003). One female cohort study examined Mn intake and reported a significant inverse association comparing highest and lowest tertiles (Cerhan *et al.* 1994). This estimate was in the opposite direction of the other study. Both studies were adjusted for age and education, and the CC study was further adjusted.

It has been hypothesised that uric acid might have a role in protecting against free radical oxidation (Ames *et al.* 1981; Tohgi *et al.* 1993; Church & Ward, 1994; Davis *et al.* 1996). The Honolulu Heart Study male cohort reported a non-significant reduced risk for PD for higher levels of serum uric acid, adjusted for age and smoking (Davis *et al.* 1996). The biological measure was objective and is assumed to reflect intake.

Vitamin D, or calciferol, is a fat-soluble vitamin whose primary function is to maintain Ca and P levels in the blood (Institute of Medicine, 1999).

A CC study reported a non-significant increased OR for the highest *v.* lowest quartile of intake for foods with vitamin D, with and without supplements (Anderson *et al.* 1999). The HPFS male cohort study reported a non-significant result in the same direction for supplement intake of greater than 10 μg (400 IU) compared with none. The RR was the same for 0·025 to 9·975 μg (1 to 399 IU), indicating a lack of dose response (Chen *et al.* 2002).

Discussion

Systematic review methods

The searches for previous systematic reviews on the topic of nutritional risk factors for PD were limited to the years 1989 until 2004. Before 1989, systematic reviews were not widely conducted, and older reviews would need to be updated with literature from more than 15 years. One meta-analysis including articles published between 1966 and 2002 reported an inverse association between coffee drinking and PD (Hernan *et al.* 2002). A systematic review of β-carotene, vitamin E, and vitamin C from literature published between 1996 and 2005 reported no associations between PD and vitamin C or β-carotene, but a significant inverse association between vitamin E intake and PD (Etminan *et al.* 2005).

The MEDLINE, EMBASE and WEB OF SCIENCE databases were used to search for original contributions to the topic. Additional articles were gathered by scanning the bibliographies of the primary articles. No attempt was made to obtain unpublished results. The quality of unpublished results cannot be easily assessed, and the value of obtaining such data was believed to be limited, although publication bias does make it probable that a substantial proportion of negative studies would exist.

Inclusion and exclusion criteria for the review were clearly specified to ensure the quality of included articles. Cross-sectional studies were to be excluded but the results are reported from one study because the methods were similar to CC studies (de Rijk *et al.* 1997*a*).

Data extraction was conducted using a standardised form by one author (L. I.). Qualitative details were recorded using recommended methods. The quality scores were not used for qualitative analysis but to determine the study characteristics that could be the sources of heterogeneity (Tables 1–3).

Most data are presented as a systematic review and summary of results rather than a meta-analysis. This was due to the heterogeneity in exposure measurement and other study design characteristics, and the limited numbers of studies examining specific exposures.

Study methods

Subject selection. The selection of cohorts is important because the study population can determine both the validity and generalisability of the findings. A specific group of individuals may have better response and follow-up rates at the cost of generalisability to the total population of interest, and vice versa.

Case and control selection influence the validity and generalisability of results (Table 2). The PD patients were recruited through sources, most of which relied on the presence of a PD diagnosis. The movement disorders clinics and neurology practices may treat a higher proportion of severe PD patients than those identified from records. Secondary and drug-induced Parkinsonism were for the most part excluded; however, this is dependent on the clinical history, and cases that have been classified as PD may affect the risk estimates.

Controls were matched in most of the studies. PD is a disease related to ageing; therefore matching by age is important. Preliminary findings in the literature suggest a male preponderance; therefore sex might also be a key matching criterion. Matching by other variables may reduce additional confounding.

The selection and response rate of controls must be considered for generalisability to the overall population. The most unbiased method of selection is random selection from the community. Hospital controls and elderly home residents may be more ill than the general population. Friends or spouses may be too similar in environmental exposures (for example, smoking, alcohol, caffeine) to examine differences.

Some studies excluded individuals with cognitive impairment and/or dementia. This criterion may exclude older and more severe PD cases, since PD is a risk factor for dementia (Aarsland *et al.* 2003). Other studies restricted the age group for cases. This could be useful if the early- and late-onset cases differ in aetiology. There is some evidence that this is the case because genes implicated in early-onset familial PD are not found in later-onset sporadic PD (Gwinn-Hardy, 2002). Another way to examine the effect of age would be to stratify analyses rather than exclude individuals.

Study size and power. There were very few significant results reported amongst the many nutritional factors tested for association with PD. Some of the CC study populations were very small, and therefore the power was low. Minor differences in dietary intake between cases and controls would not be detected by small studies. However, the cohort studies generally had a sufficient number of cases and still reported null results. Therefore if true differences do exist between affected and unaffected individuals, either exposure measurement must be more precise or population sizes need to be even larger to detect differences.

Both misdiagnosis of PD and underdiagnosis of early disease could weaken the effect measures, problems which are unavoidable without biological markers.

Exposure measurement. Nutritional exposures were assessed using the 24 h dietary recall, semi-quantitative food-frequency questionnaire and other types of interviews or questionnaires. More specific nutrition information is available at http://www.nal.usda.gov/fnic/foodcomp/ Most of the studies did not specifically state that the interviewers were blinded to CC status; therefore interviewer bias may have been introduced.

The shortest type of measurement instrument is the 24 h recall, which is meant to estimate current dietary intake and assumes minimal day-to-day variation. Food-frequency questionnaires have been validated and are considered acceptable approximations for dietary intake for a period of time (Willett *et al.* 1985). Other studies had their own structured questionnaires and the validation was often not described.

The qualitative measures, most often 'ever *v.* never' or 'yes or no', may be too simplistic to detect subtle differences between PD patients and unaffected individuals. However, in the case of alcohol and coffee intake, significant differences were detected. These exposures may be more likely than foods to have extreme amounts of consumption.

The validity of measuring nutritional intake retrospectively is often debated because it may not be representative of premorbid dietary intake. Recall bias cannot be avoided in a retrospective CC study, but results must then be interpreted with caution and verified in cohort studies. In cohort studies, the time period between exposure and outcome should be long enough for the disease to have developed after the exposure. The length of the latent period before the onset of PD symptoms is unknown, but it may be longer than 10 years.

The nutritional exposures were grouped into similar food groups and nutrients, but even within the categories there was heterogeneity. The measures are not truly comparable, although concordant results within a category may indicate an association. Foods have many components, and if an effect is found, the component responsible will need to be identified from amongst many nutrients.

The qualitative measures were often binary, but some studies classified exposure as above or below the median, or in quantiles. A larger number of quantiles would create more extreme comparisons between the highest and lowest categories, which would make it more likely to find a significant difference between the groups, assuming a reasonable population size. However, the numbers in each category would become less, which would widen the CI.

Comparisons between OR and RR reported by different studies will have to be interpreted with caution because they used different methods of measurement and calculation. Many of the studies adjusted for a number of possible confounders but most did not state how they choose the variables. The only estimate in common is a crude estimate. A solution in future studies may be to present an estimate adjusted for the minimum core confounders such as age, sex, and smoking, which have strong evidence to suggest confounding effects. Another approach would be to present stratified results, which some cohorts have done for men and women, but with small numbers this can be problematic.

Diagnostic criteria. At the moment, there are no alternatives to relying on a clinical diagnosis of PD, so it is assumed that some proportion of cases will be misdiagnosed (Hughes *et al.* 1992*b*). Both misdiagnosis of PD and underdiagnosis of early disease could weaken the effect measures, but the problems are unavoidable.

The methods of diagnosis included neurologist examination, medical record review, diagnosis logs, pharmacy databases, and telephone and mail questionnaires. Mailing questionnaires or searching records is less costly but also less comprehensive than conducting neurological examinations. Pharmacy records are a good confirmation of PD because many drugs are disease specific; however, not all patients with diagnosed PD take anti-Parkinsonian medication.

The methods of diagnosis and criteria can greatly impact which individuals are classified as affected with PD (de Rijk *et al.* 1997*b*). Neurological examination of all individuals to diagnose or exclude PD would be preferred, although in the absence of validated biomarkers (Michell *et al.* 2004) there would still be a possibility of misdiagnosis. Examinations are not always practical or possible; therefore medical records and databases have been utilised.

Summary of results

The majority of studies, even those testing many variables, did not find significant associations between nutritional factors and PD (summarised in Table 4). With the exception of coffee and alcohol, there were six or less of each study type, CC or cohort, examining each broad nutrition group. For the few nutrients and total energy intake that were found to be significantly associated with PD in CC studies, the findings were not consistently replicated in cohort studies.

The updated meta-analysis of the association between coffee drinking and PD in CC studies was similar to the past estimate (Hernan *et al.* 2002). There were no new cohort studies to be assessed. The meta-analyses of alcohol drinking and PD showed a significant inverse association in both the cohort and CC study pooled estimates.

Conclusions and recommendations

The aetiology of idiopathic PD probably involves both genetic and environmental factors. Few, if any, environmental exposures have been conclusively associated with PD. Nutrition is a challenging exposure to measure because of issues with recall and validation, but it is important to continue research in this area because of the possible effects on PD.

Retrospective measurement of dietary intake is problematic. Associations found in CC studies but not replicated in cohort studies are questionable. Prospective studies are necessary to support past findings and to examine new hypotheses. There were no conclusive associations between PD and any of the foods and nutrients in the present review. Coffee and alcohol intake are the only two exposures that have a relatively large number of studies in agreement that there may be inverse associations with PD. However, there are also studies with estimates in the opposite direction and null findings.

The main *a priori* hypotheses regarding nutritional factors and PD were not strongly supported by past study findings. The proposed protective effects of antioxidants, and conversely the harmful effects of oxidative stress, were not strongly supported by the null findings from most studies examining fruits and vegetables, vitamins, fats and Fe. The hypothesis that alcohol might cause oxidative stress

Table 4. Summary of evidence of association between nutritional factors and Parkinson's disease (PD) from nutritional factor studies

	Case–control studies			Cohort studies*		
Food or nutrient	Null	Increase†	Decrease‡	Null	Increase	Decrease
Fruit	4	–	–	2	–	–
Vegetables	3	1	–	2	–	–
Vitamin A	2	–	–	2	–	–
Carotenes	5	–	–	2	–	–
Lutein	1	2	–	2	–	–
Lycopene	1	(1)	–	2	–	–
Xanthophylls, xanthins	–	1	–	–	–	–
Vitamin C	5	–	–	3	1	–
Vitamin E	5	–	–	2	–	1
Carbohydrates	2	1	–	2	–	–
Fats	3	2	–	3	–	–
Cholesterol	1	–	–	2	–	–
Protein, meat	5	–	–	2	–	–
Fish	1	–	1	2	–	–
Egg		–	1	–	–	–
Dairy	1	–	–	1	2	–
Alcohol (binary)	11	–	2	3	–	1
Alcohol (quantitative)	3	–	2	2	–	1
Beer	–	–	2	2	–	–
Wine	1	–	1	2	–	–
Liquor	–	–	3	2	–	–
Coffee (binary)	6	–	4	3	–	2
Coffee (quantitative)	4	–	3	4	–	2
Tea	3	1	4	1	–	–
Cola	1	–	–	–	–	–
Caffeine	–	–	–	–	–	1
Junk food	1	1		2	–	–
Legumes	–	–	–	–	–	1
Nuts, seeds	–	1	–	1	–	1
Ca	2	–	–	1	–	–
Fe	2	(2)	–	–	–	–
Multivitamins	2	–	–	2	–	–
Thiamin	1	–	–	–	–	–
Riboflavin	2	–	–	–	–	–
Niacin	1	–	1	–	–	–
Pantothenic acid	–	–	1	–	–	–
Pyridoxine	1	–	1	2	–	–
Folate	1	–	1	2	–	–
Cobalamin	1	–	–	2	–	–
Total energy	2	2	–	2	–	–
Cu	1	–	–	–	–	–
Mg	1	–	–	–	–	–
Mn	1	–	–	–	–	–
P	1	–	–	–	–	–
K	1	–	–	–	–	–
Se	1	–	–	–	–	–
Na	1	–	–	–	–	–
Uric acid	–	–	–	1	–	–
Vitamin D	1	–	–	1	–	–
Zn	1	–	–	–	–	–

* Cohort and nested case–control studies.
† Increase indicates a significant positive association between factor and PD. Values in parentheses represent borderline significant results.
‡ Decrease indicates a significant inverse association between factor and PD.

was opposed by the consistent reporting of a protective association between PD and alcohol intake.

In general, *a priori* hypotheses about the involvement of certain nutritional factors in PD were not specified. Instead, what appeared to be the total or majority of factors from the questionnaire were included in the analysis. Future research on this topic should involve setting out *a priori* hypotheses regarding specific nutrients and their possible role in PD, rather than unjustified multiple testing. Many of the studies tested all available data from food-frequency questionnaires without hypotheses and even if there were some positive results, this could always be due to chance. False positive results are less likely with larger population sizes, but confirmation in multiple unrelated studies is more convincing evidence that an association is real. The methods for analysis should also be specified before viewing the data. This would involve deciding how to calculate the risk estimates.

Conducting epidemiological studies is difficult and an ideal study is usually impossible; however, the study methodology should be as robust as possible. The specified diagnostic criteria should be well recognised, and exclude secondary Parkinsonism. Adjustments in the analyses should be appropriate, and the steps taken to select adjustment factors should be reported. A crude association was the only estimate common across studies. An agreed minimum set of adjustments such as age, sex and smoking would be helpful for comparisons across studies with further adjustment depending on the specific model. Another option is stratification, but this is difficult to synthesise into a systematic review.

Systematic review of the literature is valuable to suggest new areas of research and to evaluate whether there is enough quality evidence to set aside hypotheses. The strongest associations were found with alcohol, caffeine and dairy products and biological research in the future will hopefully be able to elucidate their role in PD. There were a limited number of studies examining other nutrients and foods; therefore more evidence is needed to decide whether to pursue research in those areas.

Areas of future interest include studying the interaction of diet and PD with other factors. The gene–diet interaction (Mattson, 2003) has been explored in animals and needs to be confirmed in human subjects. Studying the effects of dietary patterns on disease outcomes may reveal nutrient interactions. The interaction between nutrition, vascular disease, and PD is interesting because nutritional factors have been implicated in both diseases, and vascular disease is a cause of at least one type of Parkinsonism (Foltynie *et al.* 2002). Large cohort studies may be able to take the approach that has been used in dementia and nutrition studies, and use blood biomarkers prospectively, but large numbers will be necessary.

Conflict of interest

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Appendix 1

United Kingdom Parkinson's Disease Society Brain Bank Criteria (Hughes et al. *1992*a*)*

Step 1 – Diagnosis of Parkinsonian syndrome:
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following;
Muscular rigidity;
4–6 Hz rest tremor;
Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.
Step 2 – Exclusion criteria for Parkinson's disease:
History of repeated strokes with stepwise progression of Parkinsonian features;
History of repeated head injury;
History of definite encephalitis;
Oculogyric crises;
Neuroleptic treatment at onset of symptoms;
More than one affected relative;
Sustained remission;
Strictly unilateral features after 3 years;
Supranuclear gaze palsy;
Cerebellar signs;
Early severe autonomic involvement;
Early severe dementia with disturbances of memory, language, and praxis;
Babinski sign;
Presence of cerebral tumour or communicating hydrocephalus on computed tomography scan;
Negative response to large doses of levodopa (if malabsorption excluded);
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure.
Step 3 – Supportive prospective criteria (three or more required for diagnosis of definite Parkinson's disease):
Unilateral onset;
Rest tremor present;
Progressive disorder;
Persistent asymmetry affecting side of onset most;
Excellent response (70–100 %) to levodopa;
Severe levodopa-induced chorea;
Levodopa response for 5 years or more;
Clinical course of 10 years or more.