Epidemiology of Parkinson's disease

Lonneke M L de Lau, Monique M B Breteler

The causes of Parkinson's disease (PD), the second most common neurodegenerative disorder, are still largely unknown. Current thinking is that major gene mutations cause only a small proportion of all cases and that in most cases, non-genetic factors play a part, probably in interaction with susceptibility genes. Numerous epidemiological studies have been done to identify such non-genetic risk factors, but most were small and methodologically limited. Larger, well-designed prospective cohort studies have only recently reached a stage at which they have enough incident patients and person-years of follow-up to investigate possible risk factors and their interactions. In this article, we review what is known about the prevalence, incidence, risk factors, and prognosis of PD from epidemiological studies.

Lancet Neurol 2006; 5: 525–35

Department of Epidemiology & Biostatistics (L M L de Lau MD, M M B Breteler MD) **and Department of Neurology** (L M L de Lau), **Erasmus Medical Centre Rotterdam, Netherlands**

Correspondence to:
Prof M M B Breteler, Department of Epidemiology & Biostatistics, Erasmus Medical Centre, PO Box 1738, 3000 DR Rotterdam, Netherlands
m.breteler@erasmusmc.nl

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and is expected to impose an increasing social and economic burden on societies as populations age. In recent years, the interest of the scientific community in PD has grown substantially, triggered by the discovery of several causative monogenetic mutations. However, these mutations likely only explain a small proportion of all PD and about 90% of cases are apparently sporadic. Despite insights derived from genetic research, the exact pathogenetic mechanisms underlying the selective dopaminergic cell loss in PD are still not understood. Current thinking is that mitochondrial dysfunction, oxidative stress, and protein mishandling have a central role in PD pathogenesis,[1] and that in sporadic PD these processes are induced by non-genetic factors, probably in interaction with susceptibility genes. Insight in non-genetic causes is needed to further the understanding of the pathogenesis of the disease and to develop effective therapeutic strategies. Large, well-designed, prospective population-based cohort studies are the only studies suited to examine the effects of multiple potential risk factors and their interactions, as well as effects that develop over a longer period.

In the past, numerous methodologically limited epidemiological studies on PD have been done, mostly small case-control or register-based studies, many based on prevalence. Only in the past 5–7 years have larger prospective studies reached a stage where they have identified sufficient numbers of patients with PD to examine incidence and potential risk factors of the disease. In this article, we will review what is known about the prevalence, incidence, risk factors, and prognosis of PD from epidemiological studies. Special attention will be given to methodological issues, as the usefulness of epidemiological data and interpretation of findings are largely dependent on the quality of the studies they were obtained from.

Diagnosis of PD in epidemiological research

A reliable and easily applicable diagnostic test or marker for PD is not yet available. Sophisticated imaging with single-photon-emission CT or PET may be helpful to diagnose PD in specialised settings, but although these techniques have become more widely available and easier to use, their usefulness for population-based epidemiological research is still limited. Thus, a diagnosis of PD in epidemiological studies is primarily based on clinical symptoms. Current criteria for a diagnosis of parkinsonism require the presence of at least two of the symptoms resting tremor, bradykinesia, rigidity, or postural imbalance. A diagnosis of PD requires that potential causes of secondary parkinsonism have been excluded. Asymmetric symptom onset and a good response of the symptoms to levodopa are supportive for a diagnosis of PD and were found to be the most important features to discriminate PD from other diagnoses.[2]

Clinical criteria at best lead to a diagnosis of probable PD, while a definite diagnosis requires post-mortem confirmation. Clinicopathological studies have shown that in 80–90% of the cases the clinical diagnosis of PD was confirmed at autopsy.[2] The relevance of such pathological validation studies for early diagnosis of PD is, however, limited by the lack of universally accepted neuropathological criteria for PD[2] and the fact that the time from initial diagnosis of the disease until death can be long. Moreover, atypical cases from specialised clinics are likely to be overrepresented in these studies. Little is known about the accuracy of the clinical diagnosis of PD by general neurologists in a representative sample from the general population. The clinical diagnosis of PD is especially difficult in the early stages of the disease and when assessed at one single point in time.[3] Long-term follow-up of patients will improve diagnostic accuracy, as diagnoses may be revised on the basis of information on disease course and progression, appearance of additional symptoms and responsiveness to levodopa therapy.

Prevalence and incidence

Methodological considerations

Estimates of the prevalence and incidence of PD may vary according to applied methodology, which complicates comparison across studies.[3–5] Not surprisingly, the use of stricter diagnostic criteria yields lower estimates of

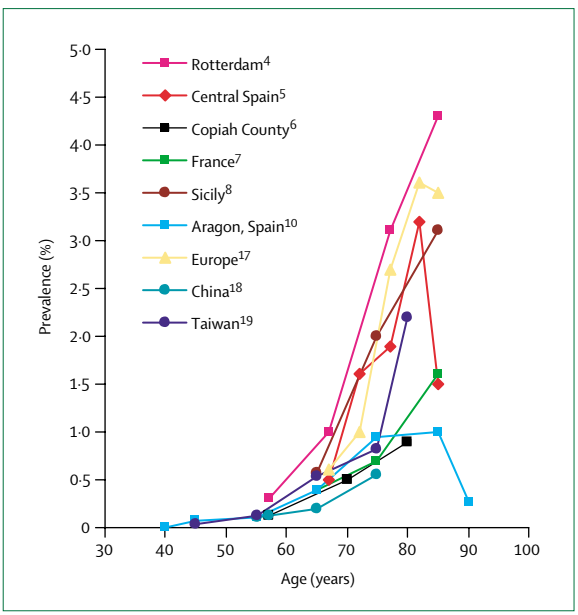

Figure 1: **Population-based prevalence studies of Parkinson's disease**

prevalences and incidence.[3] Estimates are influenced even more by case-finding strategies. Record-based studies and studies done in clinical settings do not include patients who have not sought medical attention, and thus underestimate the prevalence or incidence of PD in the general population: in several door-to-door prevalence surveys, the proportion of patients who were first identified with PD through the screening ranged from 24% to 42%.[4–10] Most incidence studies with in-person examination also yielded higher incidence rates than record-based studies did, with proportions of incident cases first identified through the screening ranging from 39% to 53%.[11,12]

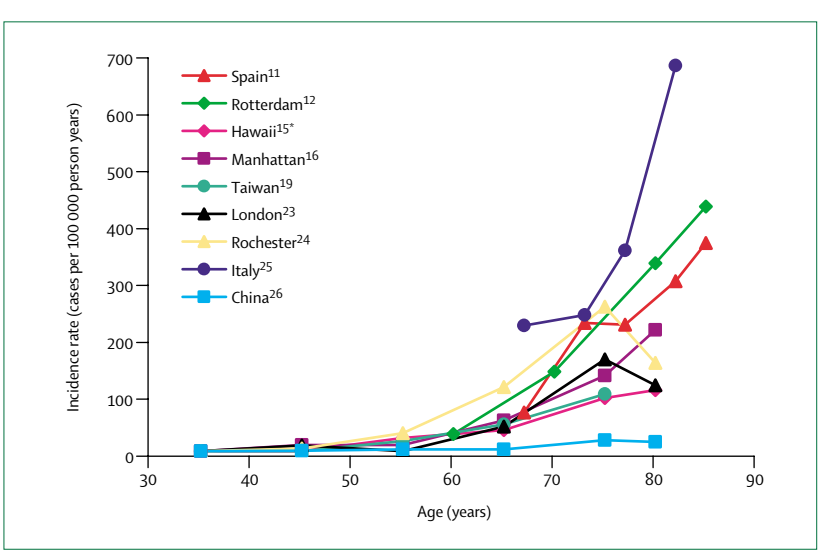

Figure 2: **Prospective population-based incidence studies of Parkinson's disease**
*Study restricted to men.

Incidence rates are theoretically not affected by differences in survival of patients and therefore better measures of the risk of disease than prevalence estimates.[13] However, population-based incidence estimates are much harder to obtain than record-based data, as they require large cohorts and long follow-up periods. Also, if the follow-up of a cohort is incomplete, substantial misclassification may occur, which will typically lead to underestimation of disease risk.

Several authors present crude estimates of the prevalence or incidence for an entire population or a section of the population above a certain age. These are of little use, because they strongly depend upon the underlying age distribution. Age-standardised rates are also of limited value, as differences in age distributions used for standardisation may hamper comparison.

Prevalence

The prevalence of PD in industrialised countries is generally estimated at 0·3% of the entire population and about 1% in people over 60 years of age.[14] Cross-cultural variations in the prevalence of PD are potentially interesting from an aetiological point of view, as they might result from differences in environmental exposures or distribution of susceptibility genes.[13] Only a few methodologically very distinct studies addressed the issue of ethnicity in relation to occurrence of PD. PD might be less common in black and Asian people than in white people, yet results are conflicting and reported differences may result from differences in response rates, survival, and case-ascertainment rather than from real differences in PD prevalence across ethnic groups.[6,13,15,16] In figure 1 [4–8,10,17–19] we summarise age-specific prevalence rates obtained from population-based surveys. PD clearly is an age-related disease: it is rare before age 50 years and the prevalence increases with age,[4–8,10,16–18,20] up to 4% in the highest age groups.

Some studies reported a higher prevalence of PD in men than in women,[5,10,16,18,21] although other studies found no significant differences in PD prevalence between men and women.[4,7–9] Neuroprotective effects of oestrogens have been suggested as a possible explanation for a higher risk of PD in men than in women, but their role is still controversial.[22]

Incidence

Reported standardised incidence rates of PD are 8–18 per 100 000 person-years. Figure 2[11,12,15,16,19,23–26] shows age-specific incidence rates from prospective population-based studies with either record-based or in-person case-finding. Onset of PD is rarely before age 50 years and a sharp increase of the incidence is seen after age 60 years. Some studies observed a decline in incidence in the highest age groups[15,27] but this is likely an artifact caused by increased diagnostic uncertainty due to comorbid disorders, diagnostic nihilism, and selective loss to follow-up.[17]

Studies with in-person screening found higher estimates of the incidence rates for all age categories (figure 2).[11,12,25] As in prevalence studies, several of the prospective studies found evidence for a higher incidence of PD in men than in women (table 1).[11,12,16,19,21,24–27]

	Study population size	PD cases	Ratio* (95% CI)
Rochester[24]	53 885	138	1·6 (1·3–1·9)
China[26]	3 869 162	566	0·9 (0·6–1·4)
Manhattan[16]	213 000	83	1·6 (1·3–2·1)
Taiwan[19]	11 411	37	1·1 (0·5–2·7)
Central Spain[11]	5160	30	2·6 (1·2–5·4)
Rotterdam[12]	6566	67	1·5 (1·0–2·5)
Italy[25]	4341	42	2·1 (1·1–4·1)

*Derived from prospective incidence studies.

Table 1: **Studies of age-adjusted male-to-female ratios for the incidence of PD**

Non-genetic risk factors

Methodological considerations

Many environmental risk factors for PD have been proposed on the basis of presumed pathogenetic mechanisms of the disease. Most of these risk factors were examined in retrospective case-control studies, which are prone to several kinds of bias, especially recall bias, selection of inappropriate controls, or inaccurate ascertainment of PD resulting in selected case series. An important caveat in the interpretation of case-control studies is reversed causality, which may particularly play a part in studies on dietary factors. Dopamine shortage can affect food preferences,[28] and altered intake of certain nutrients in patients with PD may thus erroneously be thought to have an aetiological role.

Even prospective cohort studies with exposure assessment before onset of PD may be subject to bias, especially when case-finding is register-based and patients with PD outside medical care—most likely the ones with early or mild disease—are not included. Furthermore, reversed causality may also play a part in prospectively designed studies. Because the exact duration of the preclinical period in PD is unknown, some of the participants who seem disease-free at the start of the study may already have changes due to presymptomatic dopaminergic degeneration, which might theoretically influence study results. Finally, the critical time period during which patients are at risk of PD is unknown, and therefore whether early, late, cumulative, or average lifetime exposures should be studied is unknown.

Occupational exposures: pesticides, herbicides, and heavy metals

The discovery in 1983 that several people developed typical signs of PD after intravenous injection of drugs contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and the subsequent finding that MPTP selectively damages dopaminergic cells in the substantia nigra[29] led to the hypothesis that exposure to environmental toxins might be related to the risk of PD. Since then, many epidemiological studies have been done to examine the association between exposure to pesticides and herbicides, as well as hypothesised surrogate measures, such as farming, living in rural areas, and drinking of well water, and the risk of PD. Most of these studies were retrospective case-control studies, and thus subject to most of the methodological limitations that were mentioned above. Evidence fairly consistently points towards a positive association between pesticide exposure and PD risk, although results were statistically significant in only half of the studies.[30] In a meta-analysis of 19 peer-reviewed studies on pesticide exposure and the risk of PD done between 1989 and 1999, Priyadarshi and colleagues[31] found significant heterogeneity among studies and calculated a pooled odds ratio of 1·94 (95% CI 1·49–2·53),[31] which fits the results of more recent case-control studies.[32,33] The relation between (self-reported) pesticide exposure and plantation work and PD has only been examined prospectively in one large study among men. A significantly increased risk of PD was found among men who worked for more than 10 years on a plantation, and a non-significant association for men exposed to pesticides.[34]

MPTP as well as the herbicide paraquat and the pesticide rotenone are selective complex-I inhibitors and induce dopamine depletion in animal studies.[35] The relevance of this is highlighted by the finding of complex I defects in the substantia nigra of patients with sporadic PD.[1]

Welding and exposure to heavy metals such as iron, manganese, copper, lead, amalgam, aluminium, or zinc have also been hypothesised to increase the risk of PD through accumulation of metals in the substantia nigra and increased oxidative stress.[30] Some case reports and a few case-control studies have been published, but epidemiological evidence for an association between metal exposure and risk of PD is still inconclusive.[30,36]

Tobacco, coffee, and alcohol

Smoking

Smoking of cigarettes is among the most studied risk factors for PD, and one of the few for which very consistent results were obtained. Many epidemiological studies have shown a reduced risk of PD among cigarette smokers. The vast majority of these were case-control studies, but some large prospective cohort studies confirmed their results.[37–39] In a large meta-analysis based on 44 case-control studies and four cohort studies from 20 countries, a pooled relative risk of PD of 0·59 was calculated for ever smokers, and a relative risk of 0·39 for current smokers. In pursuit of completeness, many

	Study size	PD cases	RR (95% CI)	Category of comparison
Honolulu Asia Aging Study[37]	8004 men	58	0·39 (0·22–0·70)	Ever *vs* never smoking
			0·25 (0·14–0·46)	Current *vs* never smoking
			0·50 (0·28–0·87)	Former *vs* never smoking
Leisure World Cohort Study[38]*	13 979	395	0·42 (0·25–0·69)	Current *vs* never smoking
			0·92 (0·73–1·16)	Former *vs* never smoking
Nurses' Health Study[39]	121 700 women	153	0·59 (0·43–0·81)	Ever *vs* never smoking
			0·40 (0·20–0·70)	Current *vs* never smoking
			0·70 (0·50–1·00)	Former *vs* never smoking
Health Professionals Follow-up Study[39]	51 529 men	146	0·49 (0·35–0·69)	Ever *vs* never smoking
			0·30 (0·10–0·80)	Current *vs* never smoking
			0·50 (0·40–0·70)	Former *vs* never smoking

RR=relative risk. *Nested case-control study.

Table 2: **Population-based prospective studies of smoking and the risk of PD**

meta-analyses apply rather broad eligibility criteria, and results might in part be driven by studies of poor methodological quality. However, the pooled effect estimate for all case-control studies in this meta-analysis was only modestly different from the association for all cohort studies.[40] Our overview in table 2[37–39] is restricted to population-based prospective studies. All of them showed a significant inverse association between smoking and PD, with more or less similar effect estimates. The biological basis that might underlie this association is still poorly understood. The observations could result from bias due to selective mortality of smokers among people without PD, inaccurate recording of PD diagnoses in smokers, and confounding by unknown factors.[40] Although these factors may have played a part in some of the methodologically weaker studies, the consistency of findings across different study designs—including carefully done large prospective studies—argues against bias as the sole explanation.

Several mechanisms have been proposed to explain the potential neuroprotective effect of cigarette smoking. The most likely explanations involve nicotine, as nicotine may stimulate dopamine release, act as an antioxidant, or alter activity of monoamine oxidase B.[41] Given the role of dopaminergic pathways in reward mechanisms, it has also been hypothesised that patients with PD might be less prone to addictive behaviours, either as a consequence of dopamine shortage or due to their genetic make-up.[40,41]

Coffee consumption

Several studies assessed coffee consumption in relation to PD risk, with fairly consistent results. Again, findings from case-control studies have been confirmed in several large follow-up studies (table 3).[38,42–44] A meta-analysis based on eight case-control studies and five cohort studies showed a significantly decreased PD risk for coffee drinkers (pooled relative risk 0·69) that was not attenuated when analyses were adjusted for smoking.[40] Caffeine is generally thought to be the active component, given that total caffeine intake and intake of caffeine from non-coffee sources were found to be inversely related to PD risk, whereas no association was seen between other components in coffee and the risk of PD.[42] Caffeine is an inhibitor of the adenosine A_2 receptor and improves motor deficits in a mouse model of PD.[42] Interestingly, in two cohort studies of only men, there was a strong and significant inverse association,[42,43] whereas in a cohort of only women this association was weaker and only borderline significant.[43] Furthermore, in postmenopausal women from this latter cohort the effect of caffeine consumption on PD risk seemed dependent on the use of oestrogen-replacement therapy. Because oestrogen is a competitive inhibitor of caffeine metabolism, interactions between the two may explain why the effect of caffeine consumption on PD risk in women is dependent on the use of oestrogen replacement.[45,46] These interesting observations await confirmation in other studies.

Alcohol consumption

The findings on smoking and coffee consumption and the hypothesised role of dopaminergic reward systems have led some researchers to examine the association between alcohol consumption and the risk of PD. However, results of a number of case-control studies and some prospective cohort studies (table 4)[38,47] have not been very straightforward, with inverse associations in some studies[38,48] but no significant association in others.[46,49–51]

Dietary factors

Various food groups and specific nutrients have been investigated as potential risk factors that are either related to a high or low risk of PD. In most epidemiological studies, dietary habits are assessed by means of a food-

	Study size	PD cases	RR (95% CI)	Category of comparison
Honolulu Asia Aging Study[42]	8004 men	102	0·45 (0·30–0·71)	Coffee *vs* non-coffee drinkers
Leisure World Cohort Study[38]*	13 979	395	0·64 (0·48–0·84)	Two or more cups of coffee/day *vs* no coffee consumption
Nurses' Health Study[43]	121 700 women	153	0·80 (0·60–1·00)	Coffee *vs* non-coffee drinkers
Health Professionals Follow-up Study[43]	51 529 men	146	0·70 (0·50–0·90)	Coffee *vs* non-coffee drinkers
Framingham Study[44]	6048	58	0·89 (0·49–1·63)	Coffee *vs* non-coffee drinkers

RR=relative risk. *Nested case-control study.

Table 3: **Population-based prospective studies of coffee consumption and the risk of PD**

	Study size	PD cases	RR (95% CI)	Category of comparison
Leisure World Cohort Study[38]*	13 979	395	0·73 (0·56–0·96)	Two or more drinks/day *vs* no alcohol consumption
Nurses' Health Study[47]	88 722 women	167	1·00 (0·40–2·20)	Highest *vs* lowest category
Health Professionals Follow-up Study[47]	47 367 men	248	0·60 (0·40–1·10)	Highest *vs* lowest category

RR=relative risk. *Nested case-control study.

Table 4: **Population-based prospective studies of alcohol consumption and the risk of PD**

frequency questionnaire, which unavoidably leads to a certain amount of error and thus misclassification of intake. Moreover, intakes of many nutrients are highly correlated and specific associations are therefore not always easily identified. Most epidemiological research on dietary factors comprised case-control studies. Only a few population-based prospective cohort studies have been done (tables 5[52,53] and 6[54–58]).

Antioxidants

The focus in nutritional epidemiology has been mainly on antioxidants, given the presumed central role of oxidative stress in the pathogenesis of PD. Antioxidants, such as vitamins E and C, might protect cells against oxidative damage by neutralising free radicals. Clinical trials of vitamin E supplementation have shown no effect on primary endpoints, such as the need to start levodopa therapy.[59] However, these trials were done in patients with clinically manifest PD, in whom a substantial proportion of the dopaminergic neurons have already degenerated, whereas neuroprotection from antioxidants is more likely to be effective at very early, presymptomatic stages of the disease. Although high vitamin E intake has been associated with a significantly lower risk of PD in some case-control studies,[60,61] prospective studies did not confirm this finding.[52,53] No significant association between vitamin C intake and PD risk was observed in several case-control studies[62–64] and one prospective study.[52]

Fat and fatty acids

The relation between dietary fat and PD is unclear. Diets with high lipid content could theoretically increase the amount of oxygen radicals by lipid peroxidation and thus increase the risk of PD.[65] Some case-control studies indeed reported higher intakes of total fat in patients with PD,[62,63,66] but in prospective studies either no significant association[54] or a significant inverse association between total fat intake and PD risk was observed.[56] The positive relation between total calorie intake and PD that was found in some case-control studies,[62,63,67] was not confirmed in any of the prospective studies either.[54–56] Positive associations for consumption of dairy products and milk have been observed in prospective studies, although the active component is unknown.[57,58]

More attention has recently been given to unsaturated fatty acids as they may have neuroprotective and anti-inflammatory properties.[68] Within the Honolulu Asia Aging Study, a significantly reduced risk of PD was observed with higher intake of polyunsaturated fatty acids,[55] a finding that was recently confirmed in the Rotterdam Study.[56] In contrast, in the Health Professionals Follow-up Study and Nurses' Health Study only intake of arachidonic acid was associated with a lower risk of PD.[54]

Dietary iron

Iron may induce free radical formation and increased iron levels have been found in the substantia nigra of

	Study size	PD cases	Intake	RR (95% CI)	Category of comparison
Vitamin E					
Health Professionals Follow-up Study[52]	47 331 men	161	Total vitamin E intake	0·89 (0·58–1·34)	Highest *vs* lowest quintile
			Dietary intake only	0·65 (0·40–1·05)	Highest *vs* lowest quintile
Nurses' Health Study[52]	76 890 women	210	Total vitamin E intake	0·58 (0·36–0·92)	Highest *vs* lowest quintile
			Dietary intake only	0·71 (0·44–1·14)	Highest *vs* lowest quintile
Honolulu Asia Aging Study[53]	8006 men	84		0·83 (0·57–1·19)	Per ln of vitamin E intake
Vitamin C					
Health Professionals Follow-up Study[52]	47 331 men	161	Total vitamin C intake	1·08 (0·66–1·78)	Highest *vs* lowest quintile
			Dietary intake only	1·55 (0·98–2·46)	Highest *vs* lowest quintile
Nurses' Health Study[52]	76 890 women	210	Total vitamin C intake	0·88 (0·52–1·49)	Highest *vs* lowest quintile
			Dietary intake only	0·87 (0·54–1·42)	Highest *vs* lowest quintile
Beta carotene					
Health Professionals Follow-up Study & Nurses' Health Study[52]	124 221	371	Pooled data	0·90 (0·63–1·30)	Highest *vs* lowest quintile

RR=relative risk; Ln=natural logarithm.

Table 5: **Population-based prospective studies of dietary antioxidants and the risk of PD**

patients with PD.[30] Two case-control studies found a positive association between iron intake and PD,[63,69] but two others reported no association.[62,66] Results of prospective studies on the relation between dietary iron and the risk of PD have not been published.

Dietary factors related to homocysteine metabolism

Because of the potential neurotoxic effects of homocysteine, intakes of nutrients that influence homocysteine concentration (vitamin B6, vitamin B12, and folate) have been investigated in relation with PD. In one large US-based prospective study no significant associations were observed.[70] However, considering the food fortification with folic acid, the USA may not be the ideal setting to assess this association. Results from the Rotterdam Study show a significantly decreased risk of PD with higher intake of vitamin B6 in the absence of an association for vitamin B12 and folate.[71]

Inflammation

The role of inflammation in the pathogenesis of PD is unknown. Upregulation of cytokines was found in the brains and cerebrospinal fluid of patients with PD, and activated glial cells have been observed in post-mortem material.[72] However, whether this immune response is the cause or rather a consequence of neurodegeneration is unclear, because no prospective studies have investigated inflammatory markers in relation to PD. However, in two large prospective epidemiological studies, the use of non-steroidal anti-inflammatory drugs

	Study size	PD cases	RR (95% CI)	Category of comparison
Total calories				
Health Professionals Follow-up Study[54]	47 331 men	191	1·11 (0·73–1·69)	Highest *vs* lowest quintile
Nurses' Health Study[54]	88 563 women	168	0·91 (0·54–1·51)	Highest *vs* lowest quintile
Honolulu Asia Aging Study[55]	8006 men	137	No association	No RR estimate given
Rotterdam Study[56]	5298	51	1·11 (0·81–1·50)	Per SD
Total fat				
Health Professionals Follow-up Study	47 331 men	191	1·38 (0·87–2·18)	Highest *vs* lowest quintile
Nurses' Health Study	88 563 women	168	0·86 (0·52–1·43)	Highest *vs* lowest quintile
Rotterdam Study	5298	51	0·69 (0·52–0·91)	Per SD
Saturated fat				
Health Professionals Follow-up Study	47 331 men	191	1·44 (0·92–2·25)	Highest *vs* lowest quintile
Nurses' Health Study	88 563 women	168	0·65 (0·37–1·16)	Highest *vs* lowest quintile
Rotterdam Study	5298	51	0·82 (0·61–1·10)	Per SD
Animal fat				
Health Professionals Follow-up Study	47 331 men	191	1·42 (0·91–2·20)	Highest *vs* lowest quintile
Nurses' Health Study	88 563 women	168	0·65 (0·36–1·16)	Highest *vs* lowest quintile
Cholesterol				
Health Professionals Follow-up Study	47 331 men	191	1·10 (0·68–1·76)	Highest *vs* lowest quintile
Nurses' Health Study	88 563 women	168	0·79 (0·47–1·33)	Highest *vs* lowest quintile
Honolulu Asia Aging Study	8006 men	137	No association	..
Rotterdam Study	5298	51	0·81 (0·59–1·10)	Per SD
MUFA				
Health Professionals Follow-up Study	47 331 men	191	1·00 (0·63–1·61)	Highest *vs* lowest quintile
Nurses' Health Study	88 563 women	168	0·78 (0·45–1·35)	Highest *vs* lowest quintile
Honolulu Asia Aging Study	8006 men	137	No association	..
Rotterdam Study	5298	51	0·68 (0·50–0·94)	Per SD
PUFA				
Health Professionals Follow-up Study	47 331 men	191	0·82 (0·53–1·27)	Highest *vs* lowest quintile
Nurses' Health Study	88 563 women	168	0·92 (0·56–1·49)	Highest *vs* lowest quintile
Honolulu Asia Aging Study	8006 men	137	Significant inverse association	No RR estimate given
Rotterdam Study	5298	51	0·66 (0·46–0·96)	Per SD
Dairy products				
Health Professionals Follow-up Study	47 331 men	210	1·8 (1·2–2·8)	Highest *vs* lowest quartile
Nurses' Health Study	88 563 women	184	1·1 (0·7–1·7)	Highest *vs* lowest quartile
Milk				
Honolulu Asia Aging Study	7504 men	128	2·3 (1·3–4·1)	Highest *vs* lowest group

RR=relative risk; SD=standard deviation; MUFA=monounsaturated fatty acids; PUFA=polyunsaturated fatty acids.

Table 6: **Population-based prospective studies of dietary fat and fatty acids and the risk of PD**

was associated with a low risk of PD, which may indicate a potential neuroprotective role.[73,74]

Oestrogens

The role of oestrogens in PD is disputed. The higher prevalence and incidence of PD in men in various epidemiological studies have prompted the hypothesis that female sex hormones would somehow protect against neuronal cell death. Animal studies have provided evidence for a potential beneficial effect of oestrogens on PD, possibly through antioxidant properties.[22] In a small trial in postmenopausal women with PD, significant improvement of motor function was seen in patients who received oestrogens.[75] Case-control studies on the relationship between use of oestrogens or length of the reproductive period and PD risk show conflicting results.[76–79] Large observational studies that prospectively study the effect of oestrogen concentrations or hormone therapy on the risk of PD are needed, but no such study has been reported.

PD and cancer

Some epidemiological evidence suggests a low incidence of many common types of cancers in individuals with PD.[80–82] The initial hypothesis that this finding might have resulted from the inverse association between smoking and PD did not hold, because a low incidence has been described for both smoking-related and non-smoking-related cancers.[81,83] An alternative hypothesis that was brought up recently states that a specific genetic background that can protect from cancer might also predispose an individual to neurodegeneration in PD, or vice versa.[83] Some of the genes that cause familial PD (*PINK1*, *UCHL-1*, *LRRK-2*, and *DJ-1*) seem to have a peripheral role in the cell cycle and mutations in these genes might theoretically influence cancer risk.[83] However, the evidence for an inverse association between PD and cancer is rather weak, and in at least one large study the incidence of cancer was significantly higher in patients with PD than in contols matched for age and sex.[84] More research is needed to confirm the existence of a link between cancer and PD and to clarify the remaining questions.

Miscellaneous

Several other factors have been investigated in relation to PD. Physical activity was related to a low risk of PD in men in one large prospective cohort study.[85] Several case-control studies showed a positive association between head trauma and subsequent PD, although this relation is still controversial.[30] Other factors that have been linked to a high risk of future PD include olfactory disturbances, a certain risk-avoiding personality type, depression, and anxiety.[86]

Genetic risk factors

Causative genes

Monogenetic causes do not seem to have a primary role in most cases of PD. Although in several studies a positive family history has been associated with a high risk of PD, in most cases a clear mode of inheritance could not be established.[87] A significant effect of genetic factors was found in a study among almost 20 000 male twins, but predominantly in PD with onset before age 50 years.[88] Since 1997, several families have been identified with parkinsonism with clear mendelian inheritance, and monogenetic forms are now estimated to cause about 10% of PD cases. Current knowledge of PD genetics has recently been extensively reviewed,[87,89] therefore only an updated overview of the genes and loci believed to cause familial PD is presented in table 7.[87,89–92] These monogenetic diseases might make up a distinct category of parkinsonian syndromes. Many of the familial forms display clinical features that are considered atypical for PD, such as young onset, dystonia, or early occurrence of dementia. However, some are clinically indistinguishable from idiopathic PD, although classic histological features are absent. Genetic advances have thus contributed to

Gene	Chromosome	Inheritance	Clinical features	Protein	Protein function
α synuclein (*PARK1*)[87,89]	4q21	AD	Similar to IPD, young onset, rapid progression	α synuclein	Lewy-body component
Parkin (*PARK2*)[87,89]	6q25·2–27	AR	Young onset, slow progression, early dystonia, and dyskinesia	Ubiquitin ligase	UPS component
UCHL-1 (*PARK5*)[87,89]	4p14	AD	Similar to IPD	UCHL-1	UPS component
DJ-1 (*PARK7*)[87,89]	1p36	AR	Young onset, levodopa-responsive	DJ-1	Protection against oxidative stress
PINK1 (*PARK6*)[87,90]	1p35–36	AR	Young onset, benign course, levodopa-responsive	PTEN-induced kinase	Protection against mitochondrial dysfunction
LRRK2 (*PARK8*)[91]	12p11·2–q13·1	AD	Similar to IPD	Dardarin	Unknown
NR4A2 (*NURR1*)[89,92]	2q22–q23	AD*	Late-onset PD	Nuclear receptor	Differentiation or survival of dopaminergic neurons
PARK3[87]	2p13	AD	Similar to IPD, levodopa-responsive		
PARK4[87]	4p16	AD	Similar to IPD, plus dementia and dysautonomia, young onset		
PARK9[89]	1p36	AR	Parkinsonism with spasticity, dementia, and supranuclear palsy		
PARK10[87]	1p32	Unknown	Similar to IPD		
PARK11[89]	2q36–37	Unknown	No definite phenotype reported		

AD=autosomal dominant; AR=autosomal recessive; IPD=idiopathic PD; UPS=ubiquitin proteasome system. *As yet unclear whether causal or susceptibility gene.

Table 7: **Gene mutations involved in familial PD**

	Location (country)	Type of study	Source of study	Cases	Type of cases	Follow-up (years)	HR (95% CI)
Morens[15] (1996)	Honolulu (USA)	Cohort study	Population	92	Incident	29·0	2·50*
Louis[102] (1997)	New York (USA)	Case-control	Hospital	180	Prevalent	3·0	2·70 (1·7–4·4)
Hely[101] (1999)	Sydney (Australia)	Case series	Hospital	130	Prevalent	10·0	1·58 (1·.21–2·02)†
Berger[103] (2000)	Europe (five countries)	Five cohort studies	Population	252	Prevalent	Variable	2·30 (1·80–3·00)
Morgante[104] (2000)	Sicily (Italy)	Case-control	Population	59	Prevalent	8·0	2.30 (1·60–3·39)
Guttman[105] (2001)	Ontario (Canada)	Case-control	Register	15304	Prevalent	6·0	2·50 (2·40–2·60)
Elbaz[100] (2003)	Olmsted (USA)	Case-control	Register	196	Incident	7·2	1·60 (1·20–2·14)
Fall[106] (2003)	Ostergotland (Sweden)	Case-control	Population	170	Prevalent	9·4	2·40 (1·9–3·0)
Herlofson[107] (2004)	Rogaland (Norway)	Case series	Population	245	Prevalent	8·7	1·52 (1·29–1·79)*
Hughes[108] (2004)	Leeds (UK)	Case-control	Hospital	90	Prevalent	11·0	1·64 (1·21–2·23)
de Lau[109] (2005)	Rotterdam (Netherlands)	Cohort study	Population	166	Both	6·9	1·83 (1·47–2·26)

*In people age 70–89 years, 95% CI not given; †Standardised mortality ratio. HR=mortality hazard ratio.

Table 8: **Studies of mortality hazard ratios for PD**

the recent conceptualisation of PD as several neurodegenerative diseases with clinical and pathological overlap.

Susceptibility genes

Sporadic cases of PD are generally thought to result from complex interactions between environmental and genetic factors. Numerous association studies have been done on candidate genes that were hypothesised to contribute to the risk of sporadic PD. The most commonly studied candidate genes include genes involved in dopamine metabolism, mitochondrial metabolism, detoxification, other neurodegenerative diseases, and familial PD and genes associated with putative risk factors for PD (lipoproteins, hormonal factors, homocysteine metabolism).[93–98] Studies on susceptibility genes differ considerably with respect to recruitment of patients, PD diagnosis, or the selection of controls, and most found either no effects or weak associations that could not be reproduced in a different setting. Insufficient statistical power is a major drawback in most of these studies. Given the supposed multifactorial causes underlying PD, the effect of each individual susceptibility gene is expected to be small and large numbers of case-control pairs are required to detect these small effects. Moreover, certain polymorphisms (eg, those involved in toxin metabolism) might only increase PD risk in combination with particular environmental exposures that are commonly not assessed.[94]

Several meta-analyses have been done to increase statistical power.[94–96] Only a few polymorphisms (in the genes *NAT2, MAOB, GSTT1*,[94] the *APOE* ε2 allele,[95] and the tau H1 haplotype[96]) appeared significantly associated with PD, but the pathophysiological significance of all these polymorphisms is unknown. More recent approaches focused on polymorphisms in mitochondrial DNA, suggesting that some of these variants may modify susceptibility to PD.[99]

Prognosis

Methodological considerations

Several studies investigated the life expectancy and occurrence of dementia in patients with PD. Most of these studies were done in patient groups from specialised centres or used medical records to find cases. Patients with relatively mild symptoms are likely to be under-represented in these studies and results therefore are not representative of the general population. Besides, many of these studies did not account for duration of disease at the time of enrolment. Population-based cohorts likely yield more accurate results, in particular when based on incident cases. In several prospective epidemiological studies, mortality rates in patients and controls diverged with increasing time since diagnosis.[100,101] A long delay between diagnosis and inclusion in a prognostic study of PD may therefore lead to overestimation of mortality risk.

Mortality and dementia

Most epidemiological studies suggest that PD reduces life expectancy with fairly consistent results despite different methodologies. Mortality hazard ratios were between 1·5 and 2·7 (table 8).[15,100–109] About 25–40% of the patients with PD eventually develop dementia, due to spread of degeneration and Lewy bodies to the cerebral cortex and limbic structures.[110] Epidemiological studies have reported that the risk of dementia is 1·7–5·9 times higher in patients with PD than in healthy people.[110–114] Factors that seem to influence the risk of dementia, although not consistent across studies, include age at onset of PD, disease duration or severity, and *APOE* genotype.[109,112,114] Dementia seems largely responsible for the reduced life expectancy of patients with PD, as mortality risk is only moderately increased in those who do not develop dementia.[114]

Conclusions

PD is a common disease, especially beyond age 60 years. In sporadic cases, the causes and aetiology are still largely

Search strategy and selection criteria

References for this review were identified by searches of MEDLINE and PubMed and from the reference lists of relevant papers. The search terms used were "Parkinson disease", "PD", "parkinsonism", "epidemiology", "cohort study", "prevalence", "incidence", "risk factors", "pesticide", "diet", "coffee", "smoking", "alcohol", "estrogen", "inflammation", "cancer", "susceptibility genes", "mortality", "dementia", and "prognosis". Only papers published in English between 1969 and February 2006 were reviewed. Abstracts and reports from meetings were included only when they related directly to previously published work.

unknown. For most of the factors, evidence is still inconclusive and, thus far, older age and smoking habits are the only risk factors for PD that have consistently been found across studies. Many of the initial studies on the epidemiology of PD were too small or had methodological limitations that hampered the interpretability of their findings. The paucity of well-designed and sufficiently large studies has been a serious limiting factor in epidemiological research of PD in the past. Only recently have several prospective cohort studies reached a stage where they have enough incident patients and person-years of follow-up to investigate possible risk factors for PD. The potential yield of these cohort studies is of extreme importance, not only for the identification of new risk factors, but also for promising research areas, such as proteomics and the presymptomatic detection of PD, and to establish the population effect of findings from mechanistic and genetic studies. In the coming years, and possibly through pooling of studies to further increase statistical power, we will gain a better insight into the role of environmental factors in the pathogenesis of this devastating disease.

Contributors

Both authors contributed equally to the paper.

Conflicts of interest

We have no conflicts of interest.

Acknowledgments

This study was supported by a grant (015 000 083, MMBB) of the Netherlands Organization for Scientific Research (NWO).

References

1 Greenamyre JT, Hastings TG. Biomedicine: Parkinson's—divergent causes, convergent mechanisms. *Science* 2004; **304:** 1120–22.
2 Litvan I, Bhatia KP, Burn DJ, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord* 2003; **18:** 467–86.
3 de Rijk MC, Rocca WA, Anderson DW, Melcon MO, Breteler MM, Maraganore DM. A population perspective on diagnostic criteria for Parkinson's disease. *Neurology* 1997; **48:** 1277–81.
4 de Rijk MC, Breteler MM, Graveland GA, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. *Neurology* 1995; **45:** 2143–46.
5 Benito-Leon J, Bermejo-Pareja F, Rodriguez J, Molina JA, Gabriel R, Morales JM. Prevalence of PD and other types of parkinsonism in three elderly populations of central Spain. *Mov Disord* 2003; **18:** 267–74.
6 Schoenberg BS, Osuntokun BO, Adeuja AO, et al. Comparison of the prevalence of Parkinson's disease in black populations in the rural United States and in rural Nigeria: door-to-door community studies. *Neurology* 1988; **38:** 645–46.
7 Tison F, Dartigues JF, Dubes L, Zuber M, Alperovitch A, Henry P. Prevalence of Parkinson's disease in the elderly: a population study in Gironde, France. *Acta Neurol Scand* 1994; **90:** 111–15.
8 Morgante L, Rocca WA, Di Rosa AE, et al. Prevalence of Parkinson's disease and other types of parkinsonism: a door-to-door survey in three Sicilian municipalities. *Neurology* 1992; **42:** 1901–07.
9 de Rijk MC, Tzourio C, Breteler MM, et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; **62:** 10–15.
10 Claveria LE, Duarte J, Sevillano MD, et al. Prevalence of Parkinson's disease in Cantalejo, Spain: a door-to-door survey. *Mov Disord* 2002; **17:** 242–49.
11 Benito-Leon J, Bermejo-Pareja F, Morales-Gonzalez JM, et al. Incidence of Parkinson disease and parkinsonism in three elderly populations of central Spain. *Neurology* 2004; **62:** 734–41.
12 de Lau LM, Giesbergen PC, de Rijk MC, Hofman A, Koudstaal PJ, Breteler MM. Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. *Neurology* 2004; **63:** 1240–44.
13 Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am J Epidemiol* 2003; **157:** 1015–22.
14 Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. *N Engl J Med* 2003; **348:** 1356–64.
15 Morens DM, Davis JW, Grandinetti A, Ross GW, Popper JS, White LR. Epidemiologic observations on Parkinson's disease: incidence and mortality in a prospective study of middle-aged men. *Neurology* 1996; **46:** 1044–50.
16 Mayeux R, Marder K, Cote LJ, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. *Am J Epidemiol* 1995; **142:** 820–27.
17 de Rijk MC, Launer LJ, Berger K, et al. Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts. *Neurology* 2000; **54** (11 suppl 5): S21–23.
18 Li SC, Schoenberg BS, Wang CC, et al. A prevalence survey of Parkinson's disease and other movement disorders in the People's Republic of China. *Arch Neurol* 1985; **42:** 655–57.
19 Chen RC, Chang SF, Su CL, et al. Prevalence, incidence, and mortality of PD: a door-to-door survey in Ilan county, Taiwan. *Neurology* 2001; **57:** 1679–86.
20 Errea JM, Ara JR, Aibar C, de Pedro-Cuesta J. Prevalence of Parkinson's disease in lower Aragon, Spain. *Mov Disord* 1999; **14:** 596–604.
21 Fall PA, Axelson O, Fredriksson M, et al. Age-standardized incidence and prevalence of Parkinson's disease in a Swedish community. *J Clin Epidemiol* 1996; **49:** 637–41.
22 Saunders-Pullman R. Estrogens and Parkinson disease: neuroprotective, symptomatic, neither, or both? *Endocrine* 2003; **21:** 81–87.
23 MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000; **123:** 665–76.
24 Rajput AH, Offord KP, Beard CM, Kurland LT. Epidemiology of parkinsonism: incidence, classification, and mortality. *Ann Neurol* 1984; **16:** 278–82.
25 Baldereschi M, Di Carlo A, Rocca WA, et al. Parkinson's disease and parkinsonism in a longitudinal study: two-fold higher incidence in men. ILSA Working Group. *Neurology* 2000; **55:** 1358–63.
26 Wang YS, Shi YM, Wu ZY, He YX, Zhang BZ. Parkinson's disease in China. Coordinational Group of Neuroepidemiology, PLA. *Chin Med J (Engl)* 1991; **104:** 960–64.
27 Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. *Neurology* 1999; **52:** 1214–20.
28 Wang GJ, Volkow ND, Fowler JS. The role of dopamine in motivation for food in humans: implications for obesity. *Expert Opin Ther Targets* 2002; **6:** 601–09.

29 Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983; **219:** 979–80.

30 Lai BC, Marion SA, Teschke K, Tsui JK. Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism Relat Disord* 2002; **8:** 297–309.

31 Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S. A meta-analysis of Parkinson's disease and exposure to pesticides. *Neurotoxicology* 2000; **21:** 435–40.

32 Baldi I, Cantagrel A, Lebailly P, et al. Association between Parkinson's disease and exposure to pesticides in southwestern France. *Neuroepidemiology* 2003; **22:** 305–10.

33 Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT Jr, Checkoway H. Pesticides and risk of Parkinson disease: a population-based case-control study. *Arch Neurol* 2005; **62:** 91–95.

34 Petrovitch H, Ross GW, Abbott RD, et al. Plantation work and risk of Parkinson disease in a population-based longitudinal study. *Arch Neurol* 2002; **59:** 1787–92.

35 Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci* 2000; **3:** 1301–06.

36 Jankovic J. Searching for a relationship between manganese and welding and Parkinson's disease. *Neurology* 2005; **64:** 2021–28.

37 Grandinetti A, Morens DM, Reed D, MacEachern D. Prospective study of cigarette smoking and the risk of developing idiopathic Parkinson's disease. *Am J Epidemiol* 1994; **139:** 1129–38.

38 Paganini-Hill A. Risk factors for parkinson's disease: the leisure world cohort study. *Neuroepidemiology* 2001; **20:** 118–24.

39 Hernan MA, Zhang SM, Rueda-deCastro AM, Colditz GA, Speizer FE, Ascherio A. Cigarette smoking and the incidence of Parkinson's disease in two prospective studies. *Ann Neurol* 2001; **50:** 780–86.

40 Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* 2002; **52:** 276–84.

41 Quik M. Smoking, nicotine and Parkinson's disease. *Trends Neurosci* 2004; **27:** 561–68.

42 Ross GW, Abbott RD, Petrovitch H, et al. Association of coffee and caffeine intake with the risk of Parkinson disease. *JAMA* 2000; **283:** 2674–79.

43 Ascherio A, Zhang SM, Hernan MA, et al. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. *Ann Neurol* 2001; **50:** 56–63.

44 Fink JS, Bains, LA, Beiser A, Seshadri S, Wolf PA. Caffeine intake and the risk of incident Parkinson's disease: the Framingham Study. *Mov Disord* 2001; **16:** 984.

45 Ascherio A, Weisskopf MG, O'Reilly EJ, et al. Coffee consumption, gender, and Parkinson's disease mortality in the cancer prevention study II cohort: the modifying effects of estrogen. *Am J Epidemiol* 2004; **160:** 977–84.

46 Xu K, Xu Y, Brown-Jermyn D, et al. Estrogen prevents neuroprotection by caffeine in the mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. *J Neurosci* 2006; **26:** 535–41.

47 Hernan MA, Chen H, Schwarzschild MA, Ascherio A. Alcohol consumption and the incidence of Parkinson's disease. *Ann Neurol* 2003; **54:** 170–75.

48 Fall PA, Fredrikson M, Axelson O, Granerus AK. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. *Mov Disord* 1999; **14:** 28–37.

49 Jimenez-Jimenez FJ, Mateo D, Gimenez-Roldan S. Premorbid smoking, alcohol consumption, and coffee drinking habits in Parkinson's disease: a case-control study. *Mov Disord* 1992; **7:** 339–44.

50 Benedetti MD, Bower JH, Maraganore DM, et al. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study. *Neurology* 2000; **55:** 1350–58.

51 Checkoway H, Powers K, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD. Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake. *Am J Epidemiol* 2002; **155:** 732–38.

52 Zhang SM, Hernan MA, Chen H, Spiegelman D, Willett WC, Ascherio A. Intakes of vitamins E and C, carotenoids, vitamin supplements, and PD risk. *Neurology* 2002; **59:** 1161–69.

53 Morens DM, Grandinetti A, Waslien CI, Park CB, Ross GW, White LR. Case-control study of idiopathic Parkinson's disease and dietary vitamin E intake. *Neurology* 1996; **46:** 1270–74.

54 Chen H, Zhang SM, Hernan MA, Willett WC, Ascherio A. Dietary intakes of fat and risk of Parkinson's disease. *Am J Epidemiol* 2003; **157:** 1007–14.

55 Abbott RD, Ross GW, White LR, et al. Environmental, life-style, and physical precursors of clinical Parkinson's disease: recent findings from the Honolulu-Asia Aging Study. *J Neurol* 2003; **250** (suppl 3)**:** III30–39.

56 de Lau LM, Bornebroek M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study. *Neurology* 2005; **64:** 2040–45.

57 Chen H, Zhang SM, Hernan MA, Willett WC, Ascherio A. Diet and Parkinson's disease: a potential role of dairy products in men. *Ann Neurol* 2002; **52:** 793–801.

58 Park M, Ross GW, Petrovitch H, et al. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. *Neurology* 2005; **64:** 1047–51.

59 Stocchi F, Olanow CW. Neuroprotection in Parkinson's disease: clinical trials. *Ann Neurol* 2003; **53** (suppl 3)**:** S87–97.

60 de Rijk MC, Breteler MM, den Breeijen JH, et al. Dietary antioxidants and Parkinson disease: The Rotterdam Study. *Arch Neurol* 1997; **54:** 762–65.

61 Golbe LI, Farrell TM, Davis PH. Follow-up study of early-life protective and risk factors in Parkinson's disease. *Mov Disord* 1990; **5:** 66–70.

62 Logroscino G, Marder K, Cote L, Tang MX, Shea S, Mayeux R. Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study. *Ann Neurol* 1996; **39:** 89–94.

63 Johnson CC, Gorell JM, Rybicki BA, Sanders K, Peterson EL. Adult nutrient intake as a risk factor for Parkinson's disease. *Int J Epidemiol* 1999; **28:** 1102–09.

64 Scheider WL, Hershey LA, Vena JE, Holmlund T, Marshall JR, Freudenheim. Dietary antioxidants and other dietary factors in the etiology of Parkinson's disease. *Mov Disord* 1997; **12:** 190–96.

65 Farooqui AA, Horrocks LA. Lipid peroxides in the free radical pathophysiology of brain diseases. *Cell Mol Neurobiol* 1998; **18:** 599–608.

66 Anderson C, Checkoway H, Franklin GM, Beresford S, Smith-Weller T, Swanson PD. Dietary factors in Parkinson's disease: the role of food groups and specific foods. *Mov Disord* 1999; **14:** 21–27.

67 Hellenbrand W, Boeing H, Robra BP, et al. Diet and Parkinson's disease. II: a possible role for the past intake of specific nutrients—results from a self-administered food-frequency questionnaire in a case-control study. *Neurology* 1996; **47:** 644–50.

68 Youdim KA, Martin A, Joseph JA. Essential fatty acids and the brain: possible health implications. *Int J Dev Neurosci* 2000; **18:** 383–99.

69 Powers KM, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD, Checkoway H. Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes. *Neurology* 2003; **60:** 1761–66.

70 Chen H, Zhang SM, Schwarzschild MA, et al. Folate intake and risk of Parkinson's disease. *Am J Epidemiol* 2004; **160:** 368–75.

71 De Lau LM, Koudstaal PJ, Witteman J, Hofman A, Breteler MM. Dietary folate, vitamin B12, and vitamin B6 and the risk of Parkinson disease. *Neurology* (in press).

72 McGeer PL, McGeer EG. Inflammation and neurodegeneration in Parkinson's disease. *Parkinsonism Relat Disord* 2004; **10** (suppl 1)**:** S3–7.

73 Chen H, Zhang SM, Hernan MA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. *Arch Neurol* 2003; **60:** 1059–64.

74 Chen H, Jacobs E, Schwarzschild MA, et al. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. *Ann Neurol* 2005; **58:** 963–67.

75 Tsang KL, Ho SL, Lo SK. Estrogen improves motor disability in parkinsonian postmenopausal women with motor fluctuations. *Neurology* 2000; **54:** 2292–98.

76 Currie LJ, Harrison MB, Trugman JM, Bennett JP, Wooten GF. Postmenopausal estrogen use affects risk for Parkinson disease. *Arch Neurol* 2004; **61:** 886–88.

77 Benedetti MD, Maraganore DM, Bower JH, et al. Hysterectomy, menopause, and estrogen use preceding Parkinson's disease: an exploratory case-control study. *Mov Disord* 2001; **16:** 830–37.

78 Marder K, Tang MX, Alfaro B, et al. Postmenopausal estrogen use and Parkinson's disease with and without dementia. *Neurology* 1998; **50:** 1141–43.

79 Ragonese P, D'Amelio M, Salemi G, et al. Risk of Parkinson disease in women: effect of reproductive characteristics. *Neurology* 2004; **62:** 2010–14.

80 Gorell JM, Johnson CC, Rybicki BA. Parkinson's disease and its comorbid disorders: an analysis of Michigan mortality data, 1970 to 1990. *Neurology* 1994; **44:** 1865–68.

81 Vanacore N, Spila-Alegiani S, Raschetti R, Meco G. Mortality cancer risk in parkinsonian patients: a population-based study. *Neurology* 1999; **52:** 395–98.

82 D'Amelio M, Ragonese P, Morgante L, et al. Tumor diagnosis preceding Parkinson's disease: a case-control study. *Mov Disord* 2004; **19:** 807–11.

83 West AB, Dawson VL, Dawson TM. To die or grow: Parkinson's disease and cancer. *Trends Neurosci* 2005; **28:** 348–52.

84 Elbaz A, Peterson BJ, Bower JH, et al. Risk of cancer after the diagnosis of Parkinson's disease: a historical cohort study. *Mov Disord* 2005; **20:** 719–25.

85 Chen H, Zhang SM, Schwarzschild MA, Hernan MA, Ascherio A. Physical activity and the risk of Parkinson disease. *Neurology* 2005; **64:** 664–69.

86 Wolters EC, Francot C, Bergmans P, et al. Preclinical (premotor) Parkinson's disease. *J Neurol* 2000; **247** (suppl 2)**:** II103–09.

87 Hardy J, Cookson MR, Singleton A. Genes and parkinsonism. *Lancet Neurol* 2003; **2:** 221–28.

88 Tanner CM, Ottman R, Goldman SM, et al. Parkinson disease in twins: an etiologic study. *JAMA* 1999; **281:** 341–46.

89 Healy DG, Abou-Sleiman PM, Wood NW. PINK, PANK, or PARK? A clinicians' guide to familial parkinsonism. *Lancet Neurol* 2004; **3:** 652–62.

90 Valente EM, Abou-Sleiman PM, Caputo V, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science* 2004; **304:** 1158–60.

91 Gilks WP, Abou-Sleiman PM, Gandhi S, et al. A common LRRK2 mutation in idiopathic Parkinson's disease. *Lancet* 2005; **365:** 415–16.

92 Le WD, Xu P, Jankovic J, et al. Mutations in NR4A2 associated with familial Parkinson disease. *Nat Genet* 2003; **33:** 85–89.

93 Tan EK, Drozdzik M, Bialecka M, et al. Analysis of MDR1 haplotypes in Parkinson's disease in a white population. *Neurosci Lett* 2004; **372:** 240–44.

94 Tan EK, Khajavi M, Thornby JI, Nagamitsu S, Jankovic J, Ashizawa T. Variability and validity of polymorphism association studies in Parkinson's disease. *Neurology* 2000; **55:** 533–38.

95 Huang X, Chen PC, Poole C. APOE-epsilon2 allele associated with higher prevalence of sporadic Parkinson disease. *Neurology* 2004; **62:** 2198–202.

96 Healy DG, Abou-Sleiman PM, Lees AJ, et al. Tau gene and Parkinson's disease: a case-control study and meta-analysis. *J Neurol Neurosurg Psychiatry* 2004; **75:** 962–65.

97 Maraganore DM, Farrer MJ, McDonnell SK, et al. Case-control study of estrogen receptor gene polymorphisms in Parkinson's disease. *Mov Disord* 2002; **17:** 509–12.

98 de Lau LM, Koudstaal PJ, van Meurs JB, Uitterlinden AG, Hofman A, Breteler MM. Methylenetetrahydrofolate reductase C677T genotype and PD. *Ann Neurol* 2005; **57:** 927–30.

99 van der Walt JM, Nicodemus KK, Martin ER, et al. Mitochondrial polymorphisms significantly reduce the risk of Parkinson disease. *Am J Hum Genet* 2003; **72:** 804–11.

100 Elbaz A, Bower JH, Peterson BJ, et al. Survival study of Parkinson disease in Olmsted County, Minnesota. *Arch Neurol* 2003; **60:** 91–96.

101 Hely MA, Morris JG, Traficante R, Reid WG, O'Sullivan DJ, Williamson PM. The Sydney multicentre study of Parkinson's disease: progression and mortality at 10 years. *J Neurol Neurosurg Psychiatry* 1999; **67:** 300–07.

102 Louis ED, Marder K, Cote L, Tang M, Mayeux R. Mortality from Parkinson disease. *Arch Neurol* 1997; **54:** 260–64.

103 Berger K, Breteler MM, Helmer C, et al. Prognosis with Parkinson's disease in Europe: a collaborative study of population-based cohorts. *Neurology* 2000; **54** (11 suppl 5)**:** S24–27.

104 Morgante L, Salemi G, Meneghini F, et al. Parkinson disease survival: a population-based study. *Arch Neurol* 2000; **57:** 507–12.

105 Guttman M, Slaughter PM, Theriault ME, DeBoer DP, Naylor CD. Parkinsonism in Ontario: increased mortality compared with controls in a large cohort study. *Neurology* 2001; **57:** 2278–82.

106 Fall PA, Saleh A, Fredrickson M, Olsson JE, Granerus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. *Mov Disord* 2003; **18:** 1312–16.

107 Herlofson K, Lie SA, Arsland D, Larsen JP. Mortality and Parkinson disease: A community based study. *Neurology* 2004; **62:** 937–42.

108 Hughes TA, Ross HF, Mindham RH, Spokes EG. Mortality in Parkinson's disease and its association with dementia and depression. *Acta Neurol Scand* 2004; **110:** 118–23.

109 de Lau LM, Schipper CMA, Hofman A, Koudstaal PJ, Breteler MMB. Prognosis of Parkinson disease: risk of dementia and mortality: The Rotterdam Study. *Arch Neurol* 2005; **62:** 1265–69.

110 Emre M. Dementia associated with Parkinson's disease. *Lancet Neurol* 2003; **2:** 229–37.

111 Hobson P, Meara J. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. *Mov Disord* 2004; **19:** 1043–49.

112 Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol* 2003; **60:** 387–92.

113 Marder K, Tang MX, Cote L, Stern Y, Mayeux R. The frequency and associated risk factors for dementia in patients with Parkinson's disease. *Arch Neurol* 1995; **52:** 695–701.

114 Levy G, Tang MX, Louis ED, et al. The association of incident dementia with mortality in PD. *Neurology* 2002; **59:** 1708–13.