SUPPLEMENT

Epidemiology and etiology of Parkinson's disease: a review of the evidence

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Abstract The etiology of Parkinson's disease (PD) is not well understood but likely to involve both genetic and environmental factors. Incidence and prevalence estimates vary to a large extent—at least partly due to methodological differences between studies—but are consistently higher in men than in women. Several genes that cause familial as well as sporadic PD have been identified and familial aggregation studies support a genetic component. Despite a vast literature on lifestyle and environmental possible risk or protection factors, consistent findings are few. There is compelling evidence for protective effects of smoking and coffee, but the biologic mechanisms for these possibly causal relations are poorly understood. Uric acid also seems to be associated with lower PD risk. Evidence that one or several pesticides increase PD risk is suggestive but further research is needed to identify specific compounds that may play a causal role. Evidence is limited on the role of metals, other chemicals and magnetic fields. Important methodological limitations include crude classification of exposure, low frequency and intensity of exposure, inadequate sample size, potential for confounding, retrospective study designs and lack of consistent diagnostic criteria for PD. Studies that assessed possible shared etiological components between PD and other diseases show that REM sleep behavior disorder and mental illness increase PD risk and that PD patients have lower cancer risk, but methodological concerns exist. Future epidemiologic studies of PD should be large, include detailed quantifications of exposure, and collect information on environmental exposures as well as genetic polymorphisms.

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Abbreviations

AHS	Agricultural Health Study
BMI	Body mass index
CI	Confidence interval
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DLB	Dementia with Lewy bodies
GIS	Geographical information system
GWAS	Genome-wide association study
HDL	High-density lipoprotein
HR	Hazard ratio

IOM	Institute of Medicine
JEM	Job exposure matrix
LDL	Low-density lipoprotein
LPS	Lipopolysacharide
MSA	Multiple system atrophy
MET	Metabolic equivalent task
MPTP	1-methyl-4-phenyl-1, 2, 3, 6,-tetrahydropiridine
NAS–NRC	National Academy of Sciences–National Research Council
NSAID	Non-steroid anti-inflammatory drugs
OR	Odds ratio
PD	Parkinson's disease
PET	Positron emission tomography
PMR	Proportionate mortality ratio
POR	Prevalence odds ratio
PSP	Progressive supranuclear palsy
RBD	REM sleep behavior disorder
RR	Relative risk
SPECT	Single photon emission computed tomography
SIR	Standardized incidence ratio
SHR	Standardized hospitalization ratio
SMR	Standardized mortality ratio
TIA	Transient ischaemic attack

Introduction

Parkinson's disease (PD), the second most common neurodegenerative disorder after Alzheimer's disease, was originally described in 1817 by James Parkinson in the classic "Essay on the Shaking Palsy". All the cardinal signs of PD relate to motor dysfunction and include resting tremor, bradykinesia, rigidity and postural reflex impairment. Other manifestations include psychiatric symptoms such as anxiety and depression and dysautonomic symptoms such as hypotension and constipation, paresthesias, cramps, olfactory dysfunction, and seborrheic dermatitis. As the disease progresses, decreased cognitive ability may appear [1]. PD symptoms, usually described as "parkinsonism", can also be components of syndromes that share some or most of the signs of PD plus other signs or symptoms that are not characteristic of PD. The term "parkinsonism" typically is used for syndromes with known etiology, such as parkinsonism due to ischemic injuries, exposure to toxins or neuroleptic medications.

The main pathological finding associated with the motor deficits of PD is degeneration of the dopaminergic neurons of the pars compacta of the substantia nigra leading to loss of dopamine in the striatum. Symptoms do not develop until about 50–60% of the nigral neurons are lost and about 80–85% of the dopamine content of the striatum is depleted [1]. Catecholaminergic and serotoninergic brain-stem neurons may also degenerate. Lewy bodies—eosinophilic inclusion bodies containing many different proteins—are present mainly in the surviving neurons [2, 3]. The identification of several genes related to PD has provided clues about the molecular mechanisms involved in its pathogenesis. These mechanisms may include defective handling of proteins, mitochondrial dysfunction, oxidative stress, and inflammation. Although knowledge has grown rapidly, the molecular mechanisms in the pathogenesis of PD are still largely unknown.

The etiology of PD is complex, involving both genetic and environmental factors. Here, we review the literature on the epidemiology of PD, including descriptive and genetic epidemiology, as well as risk and protective factors.

Diagnosis of PD

Due to lack of biomarkers or specific neuroimaging findings, the diagnosis of PD is based on clinical criteria, chiefly parkinsonian symptoms and no signs of other neurological damage and no history of provoking drugs, toxins or infections [1]. Most diagnostic criteria were based on the experiences of the respective authors and have not been validated. The first set of criteria, proposed by Hoehn and Yahr in 1967 [4], was modified by Marttila and Rinne in 1976 [5]. They suggested the term idiopathic PD in the presence of two or more of the cardinal symptoms: resting tremor, rigidity, hypokinesia, and impaired postural reflexes. As a prerequisite, essential tremor has to be ruled out. Patients with a history of encephalitis were classified as postencephalitic PD whilst arteriosclerotic PD was not accepted as a subgroup [4, 5].

In 1985, Schoenberg et al. [6] proposed the terms probable and possible PD based on additional exclusion criteria, such as drug-induced syndromes and parkinsonian symptoms due to other diseases. Calne et al. [7] added the category clinically definite idiopathic parkinsonism, which required three of the four cardinal symptoms originally listed [4] or alternatively, two of these, with one displaying asymmetry. The UK Brain Bank criteria [2] suggested the diagnosis of parkinsonian syndrome be assigned when bradykinesia is present, plus at least one of rigidity, rest tremor and postural instability. A large number of exclusion criteria also were listed (notably, history of repeated strokes indicating atherosclerotic parkinsonism and severe autonomic involvement indicating the diagnosis of multiple system atrophy—MSA); as supportive criteria, progressive disorder and l-dopa response were added.

Based on a literature review, Gelb et al. [8] developed a set of diagnostic criteria that, similarly to the set proposed by

Calne et al. [7], used three levels of confidence: possible, probable and definite PD (the latter requiring histopathological confirmation). These authors emphasized asymmetric onset of symptoms and response to l-dopa or dopamine agonist treatment, whereas postural reflex impairment was not listed as a cardinal symptom. In addition to progression, response to l-dopa and asymmetry of signs were criteria originally proposed by Ward and Gibb [9] based on histopathological data from the UK Brain Bank (see below) and a literature review.

Few studies attempted to validate the diagnostic criteria for PD with histopathological examinations. In one study, 31 of 41 (75%) patients with clinically diagnosed PD (by two of the three cardinal signs rest tremor, rigidity and bradykinesia) had histopathological signs of PD at autopsy [10]. Among 100 cases with clinically diagnosed PD, 76 fulfilled pathological criteria for PD, whilst 24 were misdiagnosed [11]. When the UK Brain Bank diagnostic criteria [2] were retrospectively applied, diagnostic accuracy increased to 82%. Asymmetrical onset, no atypical clinical features and no other cause of parkinsonian syndrome were the best predictors of histopathological confirmation of PD [12]. In a more recent sample of 100 cases with clinically diagnosed PD, 90 cases fulfilled neuropathological criteria for PD, leading the authors to suggest greater awareness among clinicians regarding diagnosis of PD [13]. A study based on cases diagnosed at a movement disorder clinic reported that 72 of 73 clinically diagnosed PD cases had a neuropathological diagnosis of PD. However, 7 of 79 cases that fulfilled neuropathological criteria for PD had clinical diagnoses other than PD [14].

In a study that attempted to define criteria for differentiating between PD and dementia with Lewy bodies (DLB), clinical diagnoses were assigned by six raters based on medical records for 105 patients with histopathological diagnoses of PD, DLB, or other neurodegenerative disorders. Median specificity was 92% and median sensitivity was 80% for the diagnosis of PD, with a positive predictive value of 46%. For the diagnosis of DLB, median specificity was 97%, but sensitivity was as low as 29%, with a positive predictive value of 56%. The authors concluded that PD was overdiagnosed whilst DLB was underdiagnosed. Asymmetry of signs and response to l-dopa were the variables that best discriminated PD from other forms of parkinsonism [15].

Descriptive epidemiology

Methodological considerations

When interpreting the vast number of published studies, methodological issues need consideration such as completeness of case ascertainment (case-finding strategy, diagnostic procedures, criteria, etc) and demographic characteristics of the source populations. Studies based solely on registry diagnoses depend on the completeness of the registry used, diagnostic criteria are not uniform, and, clearly, they cannot include cases without a diagnosis. Hospital-based registries have the additional disadvantage of failing to identify cases treated in outpatient care only.

The most complete case-finding strategy is the door-to-door survey (in which an entire population is screened), followed by clinical examinations of suspected cases. Using this design, previously undiagnosed cases can be ascertained, a proportion that ranged between 24% and 48% of the total number of cases in such studies [16–23]. However, non-participation, either in the screening phase or in the diagnostic phase, is a potential problem and can result in serious selection bias if participation is associated with health status. Another important issue is the validity of screening [24]. Comparisons across studies are also influenced by the way the data are presented. Age distribution differences in the underlying population may be dealt with by reporting standardized incidence or prevalence rates. But as different studies use different standard populations, comparisons still may not be straightforward.

A few studies have examined the impact of different diagnostic criteria on measures of occurrence of PD. Using data from three community studies, one study reported that different combinations of at least two cardinal signs did not markedly influence prevalence. Additional requirements such as disease duration, asymmetry of signs, or response to medication reduced prevalence. Further, three cardinal signs also resulted in lower prevalence, but the inclusion of impaired postural reflexes only altered this estimate slightly [25]. A study that compared data from several prevalence studies that applied different diagnostic criteria showed that in some instances, differences largely disappeared when diagnostic criteria were identical [26].

Another study investigated the influence of strict, intermediate, and broad diagnostic criteria on the estimated incidence rate of PD [27]. In addition to cases classified as PD based on strict criteria, intermediate diagnostic criteria classified cases as PD that were originally classified as unspecified parkinsonism (for example due to several possible causes of parkinsonism, uncertain chronology of causative events, or with insufficient clinical documentation). Broad diagnostic criteria included all PD cases classified as PD by the intermediate criteria, plus those originally classified as parkinsonism in dementia. Compared to the strict criteria, incidence rates were almost doubled when the broad diagnostic criteria were applied.

In men, incidence increased with age with all sets of criteria. Above 80 years, however, incidence decreased with strict criteria, remained unchanged by intermediate

criteria, and continued to increase with broad criteria. The influence of diagnostic criteria on incidence was less apparent in women. Incidence was higher in men than in women using all sets of diagnostic criteria, but the sex difference was more striking in older age groups using the intermediate and the broad criteria. The authors proposed that the decline in incidence in older age groups seen in several studies (see below) may be the result of difficulties in assigning a PD diagnosis in patients with extensive comorbidities [27].

Incidence

Compared to prevalence studies, there are relatively few incidence studies of PD. Incidence studies that reported results by age group are summarized in Table 1 [5, 28–49].Other incidence studies of PD are listed in Supplemental Appendix 1. Overall, incidence rates for PD in studies that reported results for all age groups ranged between 1.5 and 22 per 100,000 person-years. Studies restricted to older populations (above 55 or 65 years) [28, 29, 33] reported overall incidence rates between 410 and 529 per 100,000 person-years. A review [50] identified five studies with similar methodology, which reported age-standardized incidence rates between 16 and 19 per 100,000 person-years. Based on 8 high-quality studies, Hirtz et al. [51] estimated the median standardized incidence rate in developed countries at 14 per 100,000 person-years. In studies restricted to individuals 65 years or above, the median incidence rate was considerably higher: 160 per 100,000 person-years, predicting an estimated 59,000 new cases per year in the US [51].

Variations in PD incidence across ethnic groups might give clues about etiology, including differential environmental exposures or susceptibility genes. However, comparison among incidence studies of PD is hampered by differences in methodology and reporting. For example, some studies provided crude incidence rates, others incidence rates adjusted to different standard populations. Most incidence studies were conducted in Europe, with overall incidence rates between 9 and 22 per 100,000 person-years [5, 31, 35–39, 44, 47–49, 52, 53]. As noted above, European studies based on populations above 55 or 65 years showed relatively little variation, with overall incidence rates between 410 and 529 per 100,000 person-years [28, 29, 33]. In North American studies, overall incidence rates ranged between 11 and 13 per 100,000 person-years [30, 40, 45, 54]. One recent North American study reported an incidence rate of 224 per 100,000 person-years in individuals 65 years or above [34]. Asian studies reported overall incidence rates between 1.5 and 17 per 100,000 person-years [32, 42, 46]. An additional study in Singapore reported an incidence rate of 32 per 100,000 person-years

among individuals 50 years or above [43]. In this study, incidence among Indians was higher than that among Chinese and Malays, but numbers were small.

In general, few studies examined whether incidence differed by ethnicity although in a male North American population, incidence of PD was higher among Blacks [40]. In a multi-ethnic population in California [45], incidence of PD was highest among Hispanics, followed by non-Hispanic Whites, Asians and Blacks. In sum, although incidence data for PD are limited (especially for populations other than White), there are indications of ethnic differences.

There are no or very few cases occurring before 40 years. Also, the incidence of PD clearly increases with age steeply after age 60. However, several studies reported that incidence rates dropped in older age groups [5, 30–32, 34, 37, 41, 42, 44, 46–49, 52]. It is still a matter of debate whether this decline is real or due to underdiagnosis. A study that included individuals with dementia as well as PD reported that incidence increased slightly with age but still dropped after 89 years [34]. Nevertheless, several studies reported increasing incidence rates up to 85 years [29, 33, 34, 40, 44, 45].

The incidence of PD seems to be higher in men than in women. A meta-analysis of 7 door-to-door incidence studies showed a male to female ratio of 1.49 (95% confidence interval (CI) 1.24–1.95) [55]. Similarly, another meta-analysis based on 17 incidence studies of PD reported a pooled age-adjusted male to female ratio of 1.46 (95% CI 1.24–1.72) with significant heterogeneity between studies [56]. Suggested explanations for the male preponderance include protective effects of estrogens, higher frequency of intensity of occupational toxin exposure as well as minor head trauma in men, and recessive susceptibility genes on the X chromosome [55, 56].

A few studies estimated cumulative incidence of PD adjusted for the competing risk of death (lifetime risk). Based on data from the Rochester Epidemiology Project [54], the lifetime risk was estimated at 2% in men and 1.3% in women. From age 40, the remaining lifetime risk was 1.7% overall. Men had a higher incidence, but the gender difference decreased with increasing age, as men had higher mortality rates than women [54]. A considerably higher lifetime risk was reported by the Physicians Health Study (6.7% after age 45) [34]. This finding was interpreted as probably due to the longevity of the Physicians Health Study cohort. Another possible explanation is overdiagnosis.

Prevalence

The prevalence of PD has been estimated in more than 80 studies around the world. Studies employing door-to-door surveys followed by clinical examinations of suspected

Table 1 Incidence studies for Parkinson's disease

Study [reference]	Population	Ascertainment	No. of incident cases	Age group (years) Incidence/100,000 person-years	Diagnostic criteria
Brewis [31]	UK	Medical records	60	<39: 0; 40–49: 7; 50–59: 20; 60–69: 43; 70–79: 65; 80+: 37	Not stated
Marttila [5]	Turku, Finland	Hospital and practice records, insurance records, nursing homes, clinical exam	179	0–39: 0.1; 40–49: 2.6; 50–59: 19.8; 60–69: 62.3; 70–79: 92.6; 80+: 49.4	2 of 4[a]
Granieri [37]	Ferrara, Italy	Hospital and practice records, drug prescriptions, telephone surveys of general practitioners, clinical exam	394	35–39: 1; 40–44: 4; 45–49: 7; 50–54: 14; 55–59: 21; 60–64: 44; 65–69: 29; 70–74: 33; 75+: 13	2 of 4[a]
Wang [46]	China	Screening and clinical exam	58	30–39: 0; 40–49: 1; 50–59: 3; 60–69: 3; 70–79: 19; 80+: 17	3 of 3[b]
Mayeaux [40]	Manhattan, USA	Hospital and practice records, nursing homes, clinical exam	83	45–64: 11; 65–74: 54; 75–84: 133; 85+: 213	UK Brain Bank
Fall [35]	Östergötland, Sweden	Drug prescriptions, hospital records, survey of practices and nursing homes, clinical exam	49	30–39: 2; 40–49: 3; 50–59: 9; 60–69: 22; 70–79: 59; 80–89: 80	1 of 3[b] + progression, no neuroleptic treatment, no atypical signs, effect of l-dopa
Morens [41]	Hawaii (Honolulu Heart Study)	Hospital records, death certificates, medical records, screening and clinical exam	92	45–49: 0; 50–54: 6; 55–59: 34; 60–64: 28; 65–69: 45; 70–74: 67; 75–79: 139; 80–84: 117; 85–94: 84	Ward and Gibb [9]
Bower [30]	Olmstead County, Rochester, USA	Medical records	154	30–49: 1; 50–59: 17; 60–69: 53; 70–79: 93; 80+: 79	2 of 4[a]
Baldereschi [28]	Italian Longitudinal Study on aging	Screening and clinical exam	42	65–69: 221; 70–74: 239; 75–79: 353; 80–84: 678	2 of 4[a] without antiparkinson medication, or 1 of 4 plus improvement by antiparkinson medication
MacDonald [39]	UK, General Practice Linkage Scheme	Multiple record-based methods	Not stated	45–49: 20; 55–59: 0; 60–64: 50; 65–69: 37; 70–74: 222; 75–79: 100; 80–84: 0; 85+: 116	Not stated
Chen [32]	Ilan County, Taiwan	Health insurance records and medical records	15	40–49: 0; 50–59: 19; 60–69: 47; 70–79: 100; 80+: 0	2 of 4[a]
Morioka [42]	Wakayama, Japan	Survey of hospitals	232	40–49: 1; 50–59: 10; 60–69: 36; 70–79: 95; 80+: 81	Japanese Research Committee
Leentjens [38]	The Netherlands	General practitioners records	139	<40: 0.5; 40–49: 0.3; 50–59: 16; 60–69: 39; 70–79: 134; 80+: 279	3 of 3[b]

Table 1 continued

Study [reference]	Population	No. of incident cases	Age group (years) Incidence/100,000 person-years	Ascertainment	Diagnostic criteria
Van den Eeden [45]	California, USA	588	<30: 0; 30–39: 5; 40–49: 3; 50–59: 10; 60–69: 39; 70–79: 107; 80–89: 119	Medical care program records, drug prescriptions and practice referrals	CAPIT/UK Brain Bank
Benito-Leon [29]	Spain	30	65–69: 0; 70–74: 113; 75–79: 159; 80–84: 100; 85+: 305	Screening and clinical exam	UK Brain Bank
De Lau [33]	Rotterdam, the Netherlands	132	55–65: 30; 65–75: 140; 75–85: 330; 85+: 430	Screening and clinical exam	2 of 4[a] without antiparkinson medications, or 1 sign if on medications
Foltynie [36]	Cambridgshire, UK	201	30–39: 0.9; 40–49: 2.0; 50–59: 9.6; 60–69: 41.2; 70–79: 75.5; 80+: 86.2	General practitioners, neurology or geriatrician practice records, hospital records, clinical exam	UK Brain Bank
Taylor [44]	Aberdeen, UK	50	0–39: 0; 40–49: 3.1; 50–59: 19.6; 60–69: 5.3; 70–79: 147.3; 80–89: 317.2; 90–99: 108.0	General practitioners and hospital records, referral letters	2 of 4[a]
Tan [43]	Singapore	12	50–59: 10; 60–69: 54; 70–79: 56; 80+: 0	Phone screening, medical and hospital records	Gelb [8]
Driver [34]	Physician's Health Study, USA	563	40–44: 0; 45–49: 6; 50–54: 17; 55–59: 39; 60–64: 67; 65–69: 134; 70–74: 190; 75–79: 255; 80–84: 355; 85–89: 615; 90–99: 446	Self-report and medical records	2 of 4[a]
Hristova [49]	Plovdiv, Bulgaria	244	0–39: 0; 40–44: 0.7; 45–49: 2.0; 50–54: 3.3; 55–59: 9.9; 60–64: 27.7	Questionnaires to general practicioners and neurologists, hospital, outpatient and nursing home records; clinical exam	UK Brain Bank
Linder [47]	Umeå, Sweden	60	30–39: 2.5; 40–49: 2.8; 50–59: 27.9; 60–69: 54.3; 70–79: 138.3; 80–89: 124.3; 90+: 0	Review of referral letters to neurological department, letter asking for referral of suspected cases to practitioners in catchment area; clinical exam	UK Brain Bank
Winter [48]	Moscow, Russia	308	0–44: 0; 45–49: 2.1; 50–54: 3.7; 55–59: 5.6; 60–64: 18.0; 65–69: 25.6; 70–74: 80.4; 75–79: 70.0; 80+: 61.6	Referral to neurology department, primary care and hospital records; clinical exam	UK Brain Bank

[a] Referring to the four cardinal signs resting tremor, bradykinesia, rigidity and postural reflex impairment

[b] Referring to the three cardinal signs resting tremor, bradykinesia and rigidity

cases that reported age-specific prevalence are summarized in Table 2 [6, 16, 20, 22, 23, 32, 46, 57–69]. Studies primarily using other ways of ascertainment, such as hospital or general practitioner records, drug prescription records, etc are listed in Supplemental Appendix 2. Although there are large variations, door-to-door surveys usually reported higher prevalence compared to registry-based studies or studies using other ways of ascertainment. Overall prevalence in door-to-door studies ranged from 167 to 5,703 per 100,000, with those studying an elderly population (above 60 or 65 years) reporting the highest figures [17, 18, 23, 57, 69]. In studies using registries or other case-finding strategies, overall prevalence ranged between 31 and 970 per 100,000, although most studies reported prevalence between 100 and 300 per 100,000. A review based on 12 high-quality US and European studies estimated the PD prevalence among people 65 years or older at 950 per 100,000, equivalent to 349,000 affected individuals in the US [51]. Another study that used data from six European prevalence studies and country-specific population structure data estimated the number of individuals above age 50 with PD in the world at between 4.1 and 4.6 million in 2005. By year 2030 the number was projected to more than double to between 8.7 and 9.3 million [70].

Several studies reported lower prevalence of PD in Africa [21, 40, 71–73], Asia [32, 46, 62, 65–67, 74] and South America [63, 64] compared to Europe [16, 17, 19, 22, 25, 58, 60, 61, 75]. To facilitate comparison among 25 studies conducted in different countries, Zhang et al. [76] calculated age-standardized prevalence proportions using the US population in 1970 as the standard. They reported a 13-fold difference in age-standardized prevalences with an average prevalence of 103 per 100,000. Regions with comparatively low estimated prevalence included Japan, China, Libya, Sardinia and Poland [76]. In contrast, a Chinese study that directly examined 29,454 individuals (94% of the study population) reported a prevalence of 1,700 per 100,000 in individuals above 65 years [23] whilst a prevalence of 3,300 per 100,000 above 65 years was found in Brazil [57]. Thus, these results were similar to European countries, questioning whether the low prevalences in China and South America resulted from differences in methodology, rather than true ethnic differences.

The low prevalence in Africa may be due to population structure (shorter life expectancy compared to developed countries) [77]. In fact, the crude prevalence of PD in Africa is lowest in the eastern and western countries, where life expectancy is lowest, whereas prevalence proportions in northern African countries [78, 79] are similar to those in developed countries [80]. Another suggested explanation for the low prevalence in Africa is that hospital-based ascertainment used in some studies [40, 71–73] may be biased by socioeconomic and cultural factors [77].

In line with incidence studies, prevalence of PD clearly increases with age. However, some studies reported a decline in prevalence in the oldest age group (above 80 or more) [16, 31, 46, 58, 61, 63, 65, 81–86] perhaps due to underdiagnosis of PD because of comorbidity (as discussed above) [27], non-response [26], and unstable estimates due to small numbers in old age groups.

Several studies reported higher prevalence in men than in women [16, 19, 35, 40, 62, 68], although other studies found no gender difference [20, 22, 23, 25, 60].

Mortality

Studies performed after the late 1960s—when treatment with l-dopa was introduced—reporting mortality of patients with PD compared to that of persons without the disease are summarized in Table 3 [32, 41, 87–102]. These studies quite consistently reported about a two-fold increased mortality rate among patients with PD than in the general population, although the range was between 1.3 and 5.7. One large study (15,304 cases), that identified patients with parkinsonism (not PD per se) by health insurance records and drug prescriptions, reported a mortality ratio of 2.5 (95% CI 2.4–2.6) [103]. Thus, despite large variation in the methodology (study design, case ascertainment, length of follow-up, adjustment for confounders, etc), the results were relatively similar. When registry-based studies were compared with studies based on population samples, there were no apparent differences, although one might expect higher mortality rates among cases ascertained by registries, due to more severe disease at the time of enrolment.

Data from six European mortality studies showed a decreased life expectancy in all age groups, more pronounced among patients with early onset of PD [104]. For PD patients diagnosed between age 25 and 39 mean life expectancy was 38 years versus 49 years for the general population; for PD patents with onset between age 40 and 64, life expectancy was 21 years versus 31 years for the general population and for PD patients with onset 65 years or above, 5 years versus 9 years [104].

Nevertheless, results are somewhat conflicting regarding the association between age of PD onset and mortality. Late age of onset was associated with higher excess mortality in some studies [89, 100, 102], but similar to Ishihara et al. [104] (see above), others reported the opposite effect [93, 96, 105]. It has been suggested that shorter life expectancy in PD cases with early onset may be attributed to the longer disease duration [104].

Most mortality studies have been based on prevalent cases, and few adjusted for disease duration at the time of

Table 2 Prevalence studies for Parkinson's disease

Study [reference]	Population	Ascertainment	No. of prevalent cases	Age group (years) / Prevalence/100,000 persons	Diagnostic criteria
Li [62]	Six cities, China	Screening and clinical exam	28	50–59: 92; 60–69: 145; 70+: 615	Progressive rest tremor plus 1 or more of rigidity and bradykinesia
Schoenberg [6]	Copiah County, Mississippi	Screening and clinical exam	31	40–64: 128; 65–74: 550; 75+: 958	2 of rest tremor, bradykinesia, rigidity, parkinsonian gait or posture, retropulsion, masked facies, micrographia
Okada [65]	Izumo, Japan	Screening, public financial assistance register and clinical exam in a subset of cases	66	30–39: 23; 40–49: 20; 50–59: 64; 60–69: 339; 70–79: 479; 80–89: 336	2 of 4[a]
Wang [46]	29 provinces, China	Screening and clinical exam	566	<50: 0.7; 50–59: 23; 60–69: 89; 70–79: 158; 80+: 132	3 of 3[b]
Morgante [20]	Sicily, Italy	Screening and clinical exam	63	0–49: 0; 50–59: 116; 60–69: 621; 70–79: 1,978; 80–89: 3,055; 90–99: 0	2 of 4[a]
Tison [22]	Gironde, France	Screening and clinical exam	60	65–69: 500; 70–74: 1,800; 75–79: 1,800; 80–84: 2,200; 85–89: 2,200; 90+: 2,200	2 of 4[a]
De Rijk [60]	Rotterdam	Screening and clinical exam	97	55–64: 300; 65–74: 1,000; 75–84: 3,100; 85–94: 4,300	2 of 4[a] without antiparkinson medications, or 1 sign if on medications
Wang [67]	Kinmen, China	Screening and clinical exam	23	50–59: 273; 60–69: 535; 70–79: 565; 80+: 1,839	2 of 4[a], or 1 sign if on medications
Melcon [63]	Junin, Argentina	Screening and clinical exam	51	40–49: 0; 50–59: 153; 60–69: 637; 70–79: 1,727; 80+: 657	2 of 4[a]
Chen [32]	Ilan County, Taiwan	Screening and clinical exam	37	40–49: 38; 50–59: 123; 60–69: 547; 70–79: 820; 80+: 2,198	2 of 4[a]
Kis [61]	South Tyrol, Italy	Screening and clinical exam	12	60–64: 510; 65–69: 976; 70–74: 649; 75–79: 6,542; 80–85: 1,136	2 of 4[a], or 1 sign if on medications
Benito-Leon [16]	Spain	Screening and clinical exam	81	65–69: 500; 70–74: 1,600; 75–79: 1,900; 80–84: 3,200; 85+: 1,500	2 of 4[a] without antiparkinson medications, or 1 sign if on medications
Nicoletti [64]	Cordillera Province, Bolivia	Screening and clinical exam	5	40–49: 133; 50–59: 371; 60+: 443	2 of 4[a], at least one resting tremor or bradykinesia
Bergareche [58]	Bidasoa, Spain	Screening and clinical exam	18	65–74: 328; 75–84: 2,537; >84: 2,069	2 of 4[a], or 1 of 4 + improvement with antiparkinson treatment
Tan [66]	Singapore	Screening and clinical exam	46	50–59: 50; 60–69: 280; 70–79: 510; 80+: 1,250	Gelb [8]

Table 2 continued

Study [reference]	Population	Ascertainment	No. of prevalent cases	Age group (years) / Prevalence/100,000 persons	Diagnostic criteria
Chan [59]	Sydney, Australia	Screening and clinical exam	36	50–59 1639; 60–69 1159; 70–79 3,951; 80+ 9,191	2 of 3[b]
Zhang [23]	Bejing, Xian Shanghai, China	Screening and clinical exam	277	55–64 210; 65–74 939; 75–84 2,420; 85+ 2,721	Calne [7]
Barbosa [57]	Bambui, Brazil	Screening and clinical exam	39	64–69 800; 70–74 2,900; 75–79 2,800; 80–84 8,500; 85+ 14,300	Bradykinesia + 1 of rest tremor, rigidity or postural instability
Wirdefeldt [68]	Sweden	Screening and clinical exam	132	50–59 99; 60–69 506; 70–79 1,063; 80–89 1,508	Gelb [8]
Racette [69]	USA (Amish community)	Screening and clinical exam	15	60–69 1,515; 70–79 8,235; 80–89 1,2820; 90+ 16,666	3 of 4[a], or 2 of 4[a] with 1 displaying asymmetry

[a] Referring to the four cardinal signs resting tremor, bradykinesia, rigidity and postural reflex impairment

[b] Referring to the three cardinal signs resting tremor, bradykinesia and rigidity

enrolment. Estimation of mortality from date of enrolment rather than date of diagnosis may overestimate relative mortality, as differences in mortality rates compared with the general population increase with increasing disease duration. In a study based on the Rochester Epidemiology Project, survival curves for incident cases and non-cases started to diverge after about 5 years [93], whilst in another study relative mortality rates did not increase during the first 3 years of follow-up [95]. Other studies also reported an association between disease duration at the time of enrolment and mortality [88, 90].

Other predictors of excess mortality in PD are disease severity (most commonly measured by the Hoehn and Yahr scale) [4, 89, 92, 106, 107], dementia [90, 92, 95, 96, 107], and, as indicated, early age at enrolment [89, 100]. Comparing PD cases with and without dementia versus non-demented persons, one study reported an almost doubled mortality ratio for PD cases with dementia versus PD cases without dementia [98]. Another study [108] found that incident dementia in PD patients was associated with increased mortality, even after adjusting for severity of motor symptoms as measured by the United Parkinson's Disease Rating Sscale [109].

Studies investigating causes of death in PD cases and non-cases show that pneumonia is the most significant cause of death relative to non-cases [89, 94, 95, 100, 107, 110, 111]. Other conditions possibly related to PD, such as cachexia, dementia and "weakness due to old age" were also significant causes of death in PD patients relative to non-cases in some studies [89, 94]. Several studies showed considerable underreporting of PD on death certificates [93, 94, 112].

Genetic epidemiology

Twin studies

Twin and family aggregation studies are frequently used to study possible familial components (genetic or shared environmental) in the etiology of a disease. As monozygotic twins are genetically identical, dizygotic twins share on average half of their genome, while both share rearing environment, it is possible to differentiate between genetic and shared environmental effects in a twin study. In a classic twin study design, concordance rates in monozygotic and dizygotic twins are compared; if concordances are higher in monozygotic twins, genetic factors are indicated.

Early PD twin studies reported low concordance rates that did not differ by zygosity [113–116]. One study [117], re-evaluated 8 years after the initial investigation, found no difference in concordance between monozygotic and

Table 3 Mortality of Parkinson's disease patients relative to mortality in the general population

Study [reference]	Population	Study design	Ascertainment	No. of cases	Follow-up (years, average or median)	Hazard ratio (95% confidence interval)
Martilla [99]	Turku, Finland	Case series	Hospital	349 prevalent	3.1	SMR[a] 1.85
Ebmeier [92]	Aberdeen, Scotland	Matched cohort	GP and hospital records + clinical exams	216 prevalent	3	4.1 (2.40–7.22)
Vanacore [101]	Italy	Cohort	Death certificates	Not stated	8	SMR[a] 5.73
Morens [41]	Hawaii (Honolulu Heart Study	Cohort	Hospital records, death certificates, medical records, screening + clinical workup	92 incident	29	2.5[b]
Louis [98]	Manhattan, New York	Matched cohort	Hospital + practice records, nursing homes + clinical exams	288 prevalent	3	4.9 (3.4–7.1)[c] 2.7 (1.7–4.4)[d]
Hely [95]	Sydney, Australia	Case-series	Hospital-based multicentre study	130 prevalent	10	SMR[a] 1.58 (1.21–2.02)
Berger [87]	European multicentre	Cohort	Screening + clinical exam	139 prevalent	6	2.32 (1.80–3.00)
Morgante [100]	Sicily, Italy	Matched cohort	Screening + clinical exam	59 prevalent	8	2.3 (1.60–3.39)
Chen [32]	Ilan County, Taiwan	Cohort	Screening + clinical exam + Health insurance records	52 incident and prevalent	7	3.38 (2.05–4.34)
Elbaz [93]	Olmstead County, Rochester, USA	Matched cohort	Medical records	196 incident	7.2	1.60 (1.20–2.14)
Fall [94]	Östergötland, Sweden	Matched cohort	Drug prescriptions, hospital records, survey of practices + nursing homes + clinical exam	170 prevalent	9.4	2.4 (1.9–3.0)
Herlofson [96]	Rogaland, Norway	Case series	Hospital + GP practice records + district nurses + nursing homes	245 prevalent	8	SMR[a] 1.52 (1.29–1.79)
Hughes [97]	Leeds, UK	Matched cohort	Hospital + practice records	90 prevalent	11	1.64 (1.21–2.23)
De Lau [90]	Rotterdam, The Netherlands	Cohort	Screening + clinical exam	166 incident and prevalent	6.9	1.8 (1.5–2.3)
Chen [88]	Health Professionals Follow-up study, USA	Cohort	Self-report + medical records	288 incident	6.7	1.6 (1.3–2.0) 1.8 (1.5–2.2)
D'Amelio [89]	Sicily, Italy	Matched cohort	Screening + clinical exam	59 prevalent	13.5	2.1 (1.4–3.1)
Driver [91]	Physician's Health Study, USA	Matched cohort	Self-reported PD (validation by medical records for a subset)	560 incident	5.8	2.32 (1.85–2.92)
Diem-Zangerl [102]	Innsbruck, Austria	Case series	Hospital records	238 prevalent	Not stated	SMR[a] 1.3 (1.1–1.5)

[a] SMR = standardized mortality ratio

[b] For ages 70–89 years

[c] PD and dementia versus non-demented controls

[d] PD without dementia versus non-demented controls

dizygotic pairs. However, these studies were all small, and most of them used advertisements and contacts with movement disorder clinics to recruit twins, resulting in possible ascertainment bias (monozygotic and concordant pairs may be more likely to participate). Only one of them [114] used a population-based twin cohort, in which PD cases were identified through the Finnish national hospital discharge register. Methodological concerns of the early twin studies were raised in a review [118].

The National Academy of Sciences/National Research Council (NAS-NRC) World War II Veteran Twins Registry reported a study including 193 twins with PD diagnoses assigned by neurological examination or by medical records and interview with a proxy [119]. Concordance rates were 20% in monozygotic and 12% in dizygotic twins overall. In cases diagnosed before age 50, however, concordance rates were 100% in monozygotic versus 17% in dizygotic twins, although the estimates were unstable due to small numbers. This study, including men only, suggested that among males with late-onset PD, environmental factors are most important, while in early-onset PD, genetic factors seem to be substantial.

A study based on the population-based Swedish Twin Registry identified 247 twins with self-reported PD or a PD diagnosis in the Swedish national hospital discharge register and 517 twins who reported parkinsonian symptoms or use of anti-parkinson medication [120]. For self-reported PD or a hospital discharge diagnosis, there were only two concordant pairs, both female dizygotic. Similarly, concordances were low in all zygosity groups when the definition of affected was expanded to include twins with parkinsonian symptoms or use of anti-parkinson medication. Thus, these results were similar to the early twin studies in PD [113–116]. The NAS-NRC study reported higher concordance rates both in monozygotic and dizygotic twins, a finding that may partially be explained by higher prevalence of PD (867 per 100,000 men in the NAS-NRC study [119], versus 547 per 100,000 men in the Swedish study [68]). Nevertheless, although the NAS-NRC study reported higher concordance rates among monozygotic twins versus dizygotic twins for young onset cases, concordance rates overall did not differ by zygosity [119]. Hence, at the population level genetic effects conferred by highly penetrant genes appear to be of little importance in PD.

A limitation of twin studies conducted to date is their cross-sectional design. Concordance rates reflect the status at a certain time point. With follow-up a certain proportion of discordant pairs may become concordant. Studies using positron emission tomography (PET) scanning have demonstrated that the onset of PD symptoms is preceded by a period—estimated at 5–6 years on average—of impaired dopaminergic function in the striatum [121]. When the procedure was applied in a twin study to assess nigrostriatal dysfunction instead of clinically diagnosed PD, concordance rates were 45% in monozygotic twins versus 29% in dizygotic twins [122]. When the same authors followed another twin sample for 7 years, concordance rates for nigrostriatal dysfunction increased from 55% at baseline to 75% in monozygotic twins and from 18 to 22% in dizygotic twins, suggesting a significant genetic component [123]. Two additional PET studies reported impaired fluorodopa metabolism in asymptomatic twin partners of twins with PD compared to healthy subjects [124, 125]. Altogether, these results indicate that susceptibility to impaired nigrostriatal dysfunction is influenced by genetic factors to a greater extent than PD. Interactions between genetic and environmental factors may contribute to the development of PD from nigrostriatal dysfunction.

Family studies

Typically, familial aggregation studies attempt to estimate the importance of genetic factors in disease etiology by comparing the proportions of affected relatives among individuals with and without PD. Although familial aggregation has been investigated in a large number of studies, most of them were hospital-based [126–154]. The relative risk (RR) of PD when having a first-degree relative with PD compared to having no first-degree relative with PD in these studies ranged between 1.6 and 10.4, although one study reported an odds ratio (OR) of 41.7 [147]. In general, population-based studies [155–163] reported lower RRs, with a range between 1.5 and 7.5. A study that included both a clinic-based sample and a population-based sample [161] reported a higher RR estimate together with lower age of PD onset in the clinic-based sample than in the population-based sample, indicating that the type of sampling strategy influences results.

The familial aggregation was stronger for early-onset compared to late-onset PD, although definitions of early and late varied across studies [134, 138, 148, 149, 157, 158, 161–163]. Most studies that examined different types of relationships (siblings or parent–child) reported that PD in a sibling was associated with a higher risk compared to PD in a parent or child [131, 161–164], indicating recessive genetic or shared environmental effects.

Beside the method of case ascertainment, several other methodological issues may affect results of familial aggregation studies. One issue is ascertainment of relatives. In the most robust so-called family study method, relatives of the proband are evaluated individually. This method can be compared to the family history method, in which all information regarding PD in the family is collected through the proband or a proxy [165]. Most studies used the family history method, although it is prone to information bias; PD patients (or their proxies) report other cases of PD among

their relatives with higher sensitivity than controls, leading to overestimation of the familial aggregation [166].

A meta-analysis estimated the RR of PD for having a first-degree relative with PD at 2.9 (95% CI 2.2–3.8) based on studies using the most rigorous methods [167]. Non-population-based studies, not confirming the PD diagnosis in relatives, not enumerating the relatives (classifying them in aggregate) and using a case-control rather than a cohort design were all associated with higher RR estimates [167]. In sum, despite the methodological difficulties, family studies indicate that family history is a strong risk factor for PD, indicating genetic or shared environmental effects, or both.

PD genes

Genes and loci in familial PD

To date (2010), 11 genes and an additional 3 genetic loci have been associated with PD [168–184]; two additional loci await to be confirmed [185, 186]. The PD genes and loci are described in Table 4. Typically, these findings were based on family data using linkage analysis, in which a disease locus is located in the genome on the basis of co-segregation with a genetic marker. Most of the genes were identified in families with several affected as well as unaffected individuals, with autosomal recessive or autosomal dominant inheritance, often with early age of onset. A few gene loci were also identified using sets of affected sib pairs or families of smaller size. In many cases, clinical features of the affected individuals were typical for PD, while atypical features were present in some cases.

Genes associated with autosomal dominant PD

α-Synuclein (SNCA) (PARK1)   The first PD mutation was identified in 1997, in a large kindred of Italian/American origin and three unrelated Greek families, all with autosomal dominant inheritance [178]. Two other extremely rare [187] missense mutations have been identified [188, 189]. In the Italian/American kindred, the disease was typical for PD with neuronal loss in the substantia nigra and Lewy bodies, but relatively early onset, rapid course and less tremor [190]. In other families, α-Synuclein mutations were associated with a phenotype similar to LBD [191].

Table 4 Parkinson's disease genes and loci

Gene/locus	Chromosomal location	Mode of inheritance	Distinctive clinical features	Study [reference]
SNCA (PARK1/ PARK4)	4q21	Dominant	Relatively early onset, less tremor, rapid progression	Polymeropoulos [178]
				Singleton [181]
Parkin (PARK2)	6q25	Recessive	Early-juvenile onset, dyskinesia, dystonia, slow progression	Kitada [171]
PARK3	2p13	Dominant	Dementia	Gasser [169]
UCH-L1 (PARK5)	4p14	Dominant	None	Leroy [173]
PINK1 (PARK6)	1p35-36	Recessive	Early onset, slow progression	Valente [183]
DJ-1 (PARK7)	1p36	Recessive	Early onset, dystonia, psychiatric symptoms	Bonifati [168]
LRRK2 (PARK8)	12q12	Dominant	None	Paisan-Ruiz [175]
				Zimprich [184]
ATP13A2 (PARK9)	1p36	Recessive	Early onset, rapid progression, pyramidal signs, dementia	Ramirez [179]
PARK10	1p32	–	None	Hicks [170]
GIGYF2 (PARK11)	2q36-37	–	None	Pankratz [176]
				Pankratz [675]
				Pankratz [177]
				Lautier [172]
PARK12	Xq21-25	–	None	Pankratz [177]
Omi/HtrA2 (PARK13)	2p12	Dominant	None	Strauss [182]
PLA2G6 (PARK14)	22q12-13	Recessive	Early onset, dystonia, pyramidal signs	Paisan-Ruiz [174]
FBXO7 (PARK15)	22q12-13	Recessive	Early onset, pyramidal signs	Shojaee [180]
PARK16	1q32	–	None	Satake [262]

Apart from point mutations, PD can be caused by increased gene dosage of the α-Synuclein gene. In a family with early-onset autosomal dominant PD and dementia, the disease segregated with a triplication of a genomic region containing 17 genes (initially referred to as the *PARK4* locus), one of which was the α-Synuclein gene [181]. Subsequently, several other PD families both with duplications and triplications including the α-Synuclein locus were described in different populations [192–195]. A Swedish/American family showed a duplication in the Swedish branch and a triplication in the American branch [193]. The severity of the phenotype seems to be related to gene dosage. Clinical characteristics of patients with duplications were rather typical for PD [192, 194], while patients with triplications had lower age at onset,rapid progression, and more often dementia [196]. Most commonly, the duplications and triplications occurred de novo [196]. α-Synuclein duplications were also identified in apparently sporadic cases [197–199]. The α-Synuclein protein is the major component of Lewy bodies and so-called Lewy neurites, both in PD and in LBD [200, 201].

PARK3 Linkage to chromosome 2p (*PARK3*) was reported in six families primarily of German-American and Danish-American origin with autosomal dominant PD in 1998 [169]. The phenotype was similar to typical PD with an average age of onset of 59 years, although dementia was present in two families. Autopsies of affected individuals from three families showed neuronal degeneration and Lewy bodies in the substantia nigra, but there were also findings more typical for Alzheimer's disease. To date, the *PARK3* gene has not been identified. The candidate region was, however, refined to a physical distance of 2.5 Mb with 14 candidate genes sequenced but no mutations were found [202]. Linkage to the *PARK3* locus was confirmed in two US studies of sib pairs and smaller multiplex families that modeled age of onset instead of susceptibility to disease [203, 204], as well as in one study that included mostly European small multiplex pedigrees with PD [205]. Haplotype analysis indicated that the region contained the Sepiapterin Reductase gene [206, 207], but the role of the *PARK3* locus is still controversial.

Ubiquitin-carboxy-terminal hydrolase L1 (UCH-L1) (PARK5) A point mutation in the UCH-L1 gene was identified in two siblings from a family with autosomal dominant PD [173]. The transmitting parent was unaffected and all other affected family members were deceased. The clinical phenotype resembled typical PD with onset at ages 49 and 51. To date, no other mutations in UCH-L1 have been found. No neuropathological data have yet been reported. The UCH-L1 protein is involved in the ubiquitin-dependent protein degradation pathway [173].

LRRK2 (PARK8) Two research groups independently found mutations in the LRRK2 gene in several families with autosomal dominant PD of different origin [175, 184]. Previously, linkage to chromosome 12, where LRRK2 is situated, was demonstrated in a Japanese family [208]. In all families, the disease was similar to typical PD with relatively late onset, but there was a wide range of neuropathological findings. A large number of genetic variations have since then been discovered in different populations, not only in familial but also in apparently sporadic cases [209–211]. Relatively few of these variants are considered as established pathogenic mutations. Nevertheless, the LRRK2 gene is the most common PD gene known, accounting for up to 10% of autosomal dominant PD and about 4% of sporadic PD [212]. The frequency of the most common mutation, G2019S, varies across populations, is most common in North African and Jewish populations [210, 213], while it seems to be rare in Asian [214, 215] and South African populations [216]. Studies that examined the origin of the mutation by haplotype analyses reported only three haplotypes, indicating founder effects [212]. Penetrance of the G2019S mutation is age-dependent. An international consortium analyzing 1,045 individuals with LRRK2 mutations estimated penetrance of 28% at age 59, 51% at age 69, and 74% at age 79. Compared to idiopathic PD, the disease was more benign in LRRK2 carriers [217].

Genes associated with autosomal recessive PD

Parkin (PARK2) In 1998, deletions in the Parkin gene were reported in a set of Japanese families with autosomal recessive early-onset parkinsonism [171] with atypical features such as frequent dystonia, slow progression and hyperreflexia [218]. Neuropathological examination showed selective degeneration of nigrostriatal neurons, but no Lewy bodies [219]. Subsequently, Lewy bodies were demonstrated in two patients with Parkin mutations [220, 221], possibly reflecting mutations that did not result in complete loss of Parkin activity. To date, hundreds of cases with a wide variety of Parkin mutations, from large exon rearrangements to single base pair deletions and insertions, have been reported. Mutations have been found in nearly every ethnicity studied [222]. Although they are more frequent among early-onset and familial cases, they have also been detected among late-onset cases [223].

Parkin mutations account for about half of cases with autosomal recessive early onset (<50 years) PD, 10–20% of non-familial PD cases with early onset and 0.4–0.7% of all non-familial PD in the general population [222, 224]. Many mutations are homozygous or compound heterozygous, but there also exist cases with one single Parkin mutation [222, 225], although it is controversial whether

these are disease-causing mutations or merely polymorphisms [226]. Several studies found earlier age of onset in individuals with two compared to those with only one Parkin mutation [223, 227, 228]. Parkin is an E3 ubiquitin ligase with several substrates, one being the glycosylated form of α-Synuclein [229]. Similar to UCH-L1, the function of Parkin highlights protein degradation as a molecular pathway that may play a role in PD pathogenesis of PD.

PINK1 (PARK6) Two homozygous point mutations in the PINK1 (PTEN-induced putative kinase 1) gene were reported in two Italian and one Spanish family with autosomal recessive parkinsonism [183]. The clinical picture was similar to typical PD apart from early onset and slow progression with sustained response to levodopa [230]. No neuropathological data were available. When 100 patients with sporadic early-onset (<50 years) PD were screened for PINK1 mutations, two patients had two mutations and five patients had one mutation. Thus, similar to Parkin, it seems as haploinsufficiency of the PINK1 gene may cause susceptibility to sporadic PD. All mutations were point mutations or substitutions of a few nucleotides [231]. Other studies that screened PD patients (most often with early onset) from different populations reported PINK mutations in 0.5–9% of cases [232–236]. Thus, PINK1 mutations seem to be more rare compared to Parkin mutations. Located to mitochondria, the PINK protein may protect neurons from mitochondrial dysfunction caused by protease inhibitors [183].

DJ-1 (PARK7) Two different homozygous mutations (one point mutation, one large deletion) were found in the DJ-1 gene in a Dutch and an Italian family with autosomal recessive early-onset parkinsonism [168]. The region was originally mapped using homozygosity mapping. Several other DJ-1 mutations (including point mutations and large deletions) were subsequently reported in different populations, both in homozygous and heterozygous state, but DJ-1 mutations seem to account for a smaller proportion of cases than both Parkin and PINK1 [237–241]. The function of the DJ-1 protein is not completely known, but the protein may be involved in the oxidative stress response pathway as an antioxidant protein [242] or as a scavenger [243].

ATP13A2 (PARK9) Kufor-Rakeb syndrome is an autosomal recessive atypical parkinsonian syndrome characterized by early onset, rapid progression, dementia, supranuclear upgaze paresis, and pyramidal signs [244]. In 2006, mutations were identified in the ATP13A2 gene in a Jordanian and a Chilean family, one homozygous and one compound heterozygous [179]. A homozygous mutation was also identified in a Japanese patient with clinical features similar to Kufor–Rakeb syndrome but later onset [245]. Mutation screening of PD cases with early onset, but otherwise no atypical signs similar to Kufor–Rakeb syndrome, showed a few other mutations, both homozygous and heterozygous [246, 247]. The ATP13A2 protein is a lysosomal ATPase [179], indicating that the lysosomal degradation pathway may play a role in the pathogenesis of PD.

PD loci in families with unclear mode of inheritance

PARK10 In 2002, linkage to the chromosome 1p32 locus (PARK10) was demonstrated in a genome wide linkage scan using 51 Icelandic families [170]. Identified by linkage of a population-based register of PD patients and a nation-wide genealogical database in Iceland, these families had typical PD with average age of onset 66 years. The PARK10 locus was also linked to age at onset for PD in a US sample [248]. Association between SNPs in the candidate gene ELAVL4 and age at onset for PD or susceptibility to PD were reported in Caucasian populations [249–251], but have not been confirmed in other populations.

PARK11 Linkage to the PARK11 locus at chromosome 2q36-37 was identified in 116 American sibling pairs with typical PD and average age at onset 60 years [176]. When the same authors doubled their sample of sibling pairs with PD, linkage to PARK11 was confirmed [177]. A genome-wide association study also confirmed the locus [252], but it was not confirmed in a European linkage study [253]. In 2008, 7 different heterozygous mutations were identified in the GIGYF2 gene (located at the linkage peak) in French and Italian PD cases with family history of PD [172]. However, when 96 PD cases from the original linkage study [176] were screened for GIGYF2 mutations, no mutations were found that consistently segregated with PD [254]. A Belgian study found two heterozygous mutations in three sporadic PD cases (out of altogether 305 sporadic and familial cases), but the pathogenicity of these mutations was not clear [255]. Another study of North American and Portuguese PD cases found two of these mutations, but only in healthy persons [256], and a study of primarily Italian cases found no mutations [257], casting doubt whether the GIGYF2 is a causative PD gene. In a large sample of US and Norwegian PD cases (in total 1,139 cases), one of the originally reported [172] mutations was identified in three US sporadic cases, but none of the other mutations were found [258].

PARK12 In the two American sibling pair studies in which linkage to the PARK11 locus was demonstrated [176, 177], a locus on chromosome Xq21-25 was also linked to PD (designated PARK12). This locus was previously reported as linked to PD in two other genome screens [170, 259] but no gene has yet been identified.

PARK13 A German study screened PD cases for mutations in the Omi/HtrA2 gene because Omi/HtrA2 is associated with a parkinsonian phenotype in mice [182]. One heterozygous mutation was detected in four of 518 PD cases, and in vitro studies indicated that the mutation resulted in impaired protein function. These results have not yet been confirmed in other populations.

PARK14 In two unrelated families from Pakistan with autosomal recessive l-dopa-responsive parkinsonism, dystonia and pyramidal tract signs, two different homozygous mutations in the PLA2G6 gene were found [174]. Mutations in the same gene, a phopholipase, causes two childhood neurological diseases, infantile neuroaxonal dystrophy and neurodegeneration with brain iron accumulation [260].

PARK15 A homozygous mutation in the FBXO7 gene was identified in an Iranian family with early-onset autosomal recessive parkinsonism and pyramidal tract signs [180]. Another homozygous mutation and a compound heterozygous mutation were found in Italian and Dutch families with similar phenotypes [261]. Whether the PLA2G6 and the FBXO7 genes are implicated in typical PD is yet unknown.

PARK16 A Japanese genome-wide association study (GWAS) including two replication stages (in total 2,011 cases and 18,381 controls) identified a susceptibility locus for PD at chromosome 1q32 [262]. Association with this locus was also reported by another (two-stage) genome-wide association study of 5,044 PD cases and 8,551 controls from Germany, UK, and USA [263] and a replication study of a Chinese sample [264]. The region of interest contains five genes [262, 263].

In sum, although no less than 11 PD genes exist, most of them are associated with autosomal dominant or recessive PD rather than the more common form of sporadic PD. Available data indicate that the proportion of all PD attributable to highly penetrant genes is small.

Susceptibility genes

Beside highly penetrant mutations, specific variants in a gene may be associated with susceptibility to disease although they cannot alone explain disease status in a given individual. Typically, these variants are more common and the corresponding risks smaller compared to the highly penetrant mutations. To date (2010), no less than about 760 genetic association studies in PD have been published [265]. We are unable to review this enormous body of literature completely, but we will bring some points to attention.

The PD gene database [265] provides continuously updated meta-analyses of all published genetic association studies in PD. As of September, 2010, the meta-analyses yielded a significant association for at least one variant within 34 genes. Pooled ORs ranged between 0.71 and 3.16, but were above 2 only for variants in two genes, glucocerebrosidase (GBA) and LRRK2 [265].

Homozygous mutations in the GBA gene (a lysosomal enzyme) cause Gaucher's disease with multiple organ involvement including parkinsonian and other neurological features [266]. The disease is especially common among persons with Ashkenazi Jewish descent. A recent multicentre study of 5,691 PD cases and 4,898 controls (most of them non-Ashkenazi Jewish) reported an OR for any GBA mutation in cases versus controls of 5.43 (95% CI 3.89–7.57) [267]. Thus, while homozygous GBA mutations cause Gaucher's disease, heterozygous GBA mutations appear to increase risk of PD. Heterozygous GBA mutations have also been identified in patients with DLB [268, 269].

A few of the *PARK* genes contain variants that appear to act as susceptibility factors. Based on meta-analyses of 12 and 14 studies respectively, the R1628P and Gly2385variants in the LRRK2 gene both increased PD risk about twofold, an effect especially prominent in Asian populations [265]. The Japanese GWAS mentioned above [262] reported a strong association with LRRK2, while the GWAS including individuals of European descent [263] reported a suggestive association with LRRK2. Based on 28 studies, variants of the Rep1 repeat polymorphism in the α-Synuclein promoter also increased risk (OR 1.25 for the 263 basepair vs. 261 basepair allele, 95% CI 1.11–1.40), while variants in the PINK1 and UCHL1 genes decreased risk of PD (OR 0.90, 95% CI 0.83–0.98 for a PINK1 variant based on 8 studies; OR 0.92, 95% CI 0.86–0.98 for a UCHL1 variant based on 22 studies) [265]. Both GWAS mentioned above [262, 263] as well as a replication study of a Chinese sample [264] reported strong associations with α-Synuclein. Two studies reported an interaction between the α-Synuclein Rep1 polymorphism and smoking [270, 271]. One study reported an interaction between the α-Synuclein Rep1 polymorphism and pesticides, more prominent in early-onset cases [271], but another study [272] reported no such interaction. In the same sample, there was no interaction between the α-Synuclein Rep1 polymorphism and alcohol use [273].

Beside the *PARK* genes, others have been studied based on a candidate gene approach; only the most extensively studied are mentioned here. Because of its role in Alzheimer's disease, one such gene is the APOE gene. Meta-analysis of 40 studies showed a slightly increased PD risk for the epsilon 2 versus 3 allele (OR 1.14, 95% CI 1.03–1.27), but no association for the epsilon 4 allele implicated in Alzheimer's disease [265]. One study reported an interaction between APOE and coffee intake; the inverse association with coffee was stronger among

carriers of the epsilon 2 allele, however, the main effect of APOE was not significant [270].

The CYP2D6 gene codes for an enzyme that metabolizes xenobiotic substances, notably organophosphate pesticides and 1-methyl-4-phenyl-1, 2, 3, 6,-tetrahydropiridine (MPTP). Based on 35 studies, homozygosity for an allele (associated with the so-called poor metabolizer phenotype) increased PD risk (OR 1.13, 95% CI 1.01–1.25) [265]. A French study [274] reported that risk of PD for professional pesticide use was more than doubled in slow metabolizers compared to other individuals, whereas, in the absence of pesticide exposure, slow metabolizers had no increased risk [274]. These results were supported by an Australian study [275] but not by a European multicentre study [276].

Meta-analysis of 27 studies of a variant in the microtubule-associated protein tau (MAPT) gene, mutated in the syndrome frontotemporal dementia with parkinsonism syndrome [277], yielded an OR of 0.76 (95% CI 0.71–0.81) [265]. One study [270] assessed possible gene-environment interactions for this variant; no evidence for interactions with smoking or coffee intake was found. The GWAS including individuals of European descent [263] reported a strong association with MAPT, but this finding was not replicated in the Japanese GWAS [262], indicating genetic heterogeneity specific to populations.

Based on meta-analysis of 28 studies, a polymorphism in the X-linked monoamine oxidase B (MAOB) gene increased risk (OR 1.10, 95% CI 1.01–1.20) [265]. For this polymorphism, an interaction with smoking was reported in two studies [278, 279] (the inverse association with smoking was limited to a specific allele), but was absent in another study [280].

Findings from genetic association studies often fail to replicate, most likely because of small sample size. However, when applying meta-analysis methods, there is fairly consistent evidence that some genes confer susceptibility to PD.

Occupational and environmental exposures

Pesticides

The interest in the relationship between pesticides and PD was raised in the 1980s, when it was discovered that exposure to 1-methyl-4-phenyl-1, 2, 3, 6,-tetrahydropyridine (MPTP), a substance structurally similar to the herbicide paraquat, resulted in chronic parkinsonism and degeneration of dopaminergic neurons in humans [281]. An ecological study reported high prevalence of PD in rural agricultural regions in Canada [282]. In case reports, parkinsonism was attributed to different pesticides [283–288]. Studies examining the association between pesticides

overall, herbicides, insecticides, and fungicides are summarized in Supplemental Tables 1–4.

Case-control studies

Pesticide exposure overall   In most studies of pesticides in relation to PD exposure was assessed retrospectively as a broad category, rather than examining specific substances. Of 38 case-control studies, 19 reported increased risk of PD [147, 154, 156, 289–304] with ORs ranging between 1.3 and 3.7 for most studies. One study reported an OR of 7.0 (*P* value < 0.05) [289] and another an OR of 10.9 (95% CI 2.5–48.0) [301]. The remaining 19 case-control studies that analyzed results from pesticide exposure overall reported no association [131, 136, 137, 141, 142, 144, 145, 305–317].

Most studies assessed exposure to pesticides as a dichotomous variable (exposed or not exposed according to different definitions), but some attempted to examine duration or frequency of exposure or both (cumulative exposure). A hospital-based study found an increased risk of PD with overall pesticide or herbicide use (OR 2.89, 95% CI 2.28–3.66); the risk increased with longer duration of exposure (OR 6.72, 95% CI 2.62–12.21 for more than 20 years of exposure vs. none) [293]. One population-based study reported increased risk of PD following occupational exposure to pesticides (OR 2.25, 95% CI 1.27–3.99) without a dose-response relationship [290]. Another—that assessed pesticide exposure by a job exposure matrix (JEM)—found elevated PD risk associated with overall pesticide exposure (OR 2.20, 95% CI 1.11–4.34) and increasing risk with higher level of exposure up to the third quartile, with a decline in the fourth quartile (OR 0.7, 95% CI 0.1–3.7) [297].

A large (5 country) study with a mixture of hospital- and population-based controls reported increased PD risk for high exposure (OR 1.39, 95% CI 1.02–1.89) but not for low exposure to pesticides (OR 1.09, 95% CI 0.77–1.55) [300]. A family-based study that used siblings, parents and spouses as controls reported increased risk of PD with overall exposure to pesticides (OR 1.61, 95% CI 1.13–2.29) with a dose-response relationship for cumulative exposure (*P* for trend 0.002) [302]. The association was restricted to cases without family history of PD and significant both for insecticides and herbicides [302]. One hospital-based study reported a marginally increased risk with increasing duration of pesticide exposure [144].

One of the largest population-based studies reported no associations for occupational exposure (only men) or home-based exposure to pesticides, after adjusting for age, sex and smoking [316, 317]. In many populations, farmers smoke less than the general population, and since smoking is inversely related to PD risk, an association between pesticides and PD may be overestimated. On the other

hand, smoking may be associated with higher exposure to pesticides (for example, one study showed that smoking was associated with higher levels of polychlorinated biphenyls and organochlorine pesticides in breast milk samples [318]), which would confound an association between pesticides and PD towards the null. Adjustment for smoking, however, gave lower risk estimates for pesticides than unadjusted analyses in several of the studies [144, 147, 293, 319]. A substantial proportion of the studies that observed no association between pesticides and PD did not adjust for smoking in the analyses [131, 136, 141, 142, 145, 305–309, 311, 314, 315].

A meta-analysis of 19 case-control studies published between 1989 and 1999 reported a pooled risk of PD related to exposure to pesticides overall at 1.94 (95% CI 1.49–2.53), with no dose-response relationship [320].

Herbicide exposure Some case-control studies reported results for specific categories of pesticides, such as herbicides, insecticides, or fungicides, rather than pesticides overall. Of 18 studies that analyzed exposure to herbicides, 10 found increased risk of PD, either for herbicides as a group of substances, or for specific herbicides, such as paraquat, nitrile herbicides or 2,4-Dichlorophenoxyacetic acid [153, 154, 290, 293, 302, 304, 321–324], with ORs ranging between 1.6 and 5.8. The other 8 studies reported no association between herbicides and PD [131, 143, 292, 299, 301, 315, 316, 325].

Among studies that found an increased risk, one hospital-based study reported increased risk of PD with overall herbicide use (OR 1.7, 95 % CI 1.0–2.7) and a trend with longer duration of exposure using regional controls (*P* for trend 0.001) but not using neighborhood controls [154]. Another hospital-based study among young-onset PD cases and patients with reumathoid arthritis as controls reported an increased risk with herbicide exposure more than 10 times a year (OR 3.22, *P* value 0.03) [153]. A population-based study reported increased risk with any occupational exposure to herbicides (OR 4.10, 95% CI 1.37–12.24), but no associations following agricultural or recreational herbicide exposure [321, 322]. Another population-based study also reported an increased risk with occupational exposure to herbicides (OR 3.06, 95% CI 1.34–7.00) [290]. A family-based study that found a dose-response relationship between overall pesticide exposure and PD reported an increased risk related to herbicides (OR 1.59, 95% CI 1.00–2.54) but could not examine dose-response [302].

The hospital-based study that reported a dose-response relationship for overall pesticide or herbicide use [293] also reported a relationship for paraquat. Four other studies that assessed paraquat specifically, however, found no association [292, 301, 304, 316, 317], although one [304] reported

increased risk of PD following exposure to 2,4-Dichlorophenoxyacetic acid (OR 2.59, 95% CI 1.03–6.48). A population-based Californian study [323] assessed historical pesticide residential exposure through a combination of interviews, geographical information system (GIS), and California Pesticide Use Reports. Combined exposure to maneb and paraquat (OR 1.75, 95% CI 1.13–2.73), but not to paraquat alone (OR 1.01, 95% CI 0.71–1.43) was associated with increased risk [323]. Another study was performed among farmers, taking advantage of the French health insurance system for agriculture workers (Mutualite Sociale Agricole-MSA) [324]. Exposure to pesticides was assessed in two phases, using questionnaires followed by home interviews by health insurance physicians for professional users of pesticides. For professional herbicide use overall and for paraquat, no associations were detected. However, there was an increased risk of PD associated with nitrile herbicides (OR 5.8, 95% CI 1.1–29.0) [324]. In contrast to the Californian study [323], this study found a stronger association in individuals with late age at onset (>65 years) [324].

The largest among the "negative" studies was a hospital-based study comprising 377 prevalent cases of PD and controls with neurological diseases other than PD that adjusted for multiple variables in the analyses [143]. Similar to overall pesticide exposure, the population-based study of 250 incident cases mentioned above [316] found no association for occupational (men only) or home-based (men and women) exposure to herbicides. The other studies that found no association [131, 292, 299, 301, 315, 325] were all smaller (100–150 cases); several did not adjust for smoking [292, 299, 301, 315].

Insecticide exposure Of 17 studies, 9 reported increased risk of PD either for insecticides as a group, or for specific insecticides [153, 154, 156, 290, 302, 306, 321, 322, 324], with ORs ranging from 1.2 to 5.8. The other 8 studies, all mentioned above, reported no association for insecticides as a group or for specific insecticides [143, 292, 299, 301, 304, 315, 316, 325].

One of the "positive" studies was the hospital-based study mentioned above [154] that, similar to herbicides, found a dose-response relationship for exposure to insecticides using regional controls (*P* for trend 0.001) but not using neighborhood controls. Although estimates were unstable, there was an increased risk associated with organochlorines using regional controls (OR 5.8, 95% CI 1.1–30.1) but not using neighborhood controls [154]. The population-based study mentioned above [321, 322] reported higher risk with longer duration of occupational insecticide exposure. However, similar to herbicides, there were no associations for agricultural, recreational or residential insecticide exposure [321, 322]. Another population-based

study reported increased risk with occupational exposure to insecticides (OR 2.05, 95% CI 1.03–4.03) [290]. Exposure to insecticides more than 10 times a year was associated with increased risk in the study of young-onset PD [153] (OR 5.75, $P = 0.001$).

The MSA study reported a dose-response relationship between cumulative hours of exposure to insecticides and PD risk in men older than 65 years (P for trend 0.04) [324]. When insecticides and fungicides were included in the same statistical model, insecticides, but not fungicides, were still significant [324], specifically organochlorine insecticides and arsenic insecticides. Organochlorine insecticide use was also associated with increased risk in the family-based study mentioned above [302] (OR for ever use 1.99, 95% CI 1.09–3.64). Further, this study reported increased risk associated with organophosphorus insecticides (OR 1.89, 95% CI 1.11–3.25) [302].

Two other "positive" studies were small. One population-based study of 36 cases found increased risk with any exposure to insecticides although no P value was provided [156]. Another hospital-based study of 34 cases reported increased risk with a few specific pesticides, one of which was pentachlorophenol, without providing P values [306].

In a postmortem study that compared levels of highly persistent organochlorines more PD cases than controls had detectable levels of dieldrin (P value 0.03) in the frontal or occipital cortex [326]. Another postmortem study reported higher levels of both dieldrin and lindane in PD cases than controls in the substantia nigra [327]. A small (31 cases) case-control study found similar serum concentrations for all 31 organochlorines analyzed, except for DDE (a metabolite of DDT), which was detected in higher concentrations in cases than controls (P value 0.005) [328].

One nested case-control study [329] analyzed organochlorine pesticides in serum samples collected around 1970, several years before onset of PD. Among never smokers, higher levels of dieldrin was associated with increased risk (OR per interquartile range 1.95, 95% CI 1.26–3.02), but overall, the association was non-significant (OR per interquartile range 1.28 (95% CI 0.97–1.69). No other organochlorine pesticide was associated with PD risk [329]. Because exposure correlation could not be ruled out, confounding by compounds other than dieldrin that could not be assessed due to their non-persistence is possible.

Fungicide exposure Relatively few studies investigated fungicides in relation to PD risk. None of five such studies reported an association for exposure to fungicides overall [290, 292, 316, 321, 324]. The MSA study [324] reported a significant dose-response relationship between cumulative hours of fungicide exposure in men above 65 years (P for trend 0.02). In men, this study also found increased risk associated with the specific groups amide fungicides (OR

3.1, 95% CI 1.2–8.3) and dithiocarbamate fungicides (OR 2.1, 95% CI 1.0–4.3) [324].

Prospective studies

Other than the case-control study nested within the Finnish Mobile Clinic Health Examination Survey [329], four prospective studies have investigated the role of pesticides in PD, the largest based on the Cancer Prevention Study II Nutrition Cohort in the US [330]. Exposure to pesticides in general or herbicides was associated with increased risk of PD with a RR of 1.7 (95% CI 1.2–2.3) but no dose-response relationship [330]. The Honolulu-Asia Aging study, a cohort of men in Hawaii, reported an increased risk of PD with increasing years of work on a plantation, with a RR for the highest category (more than 20 years) versus not having worked on a plantation of 1.9 (95% CI 1.0–3.5, P for trend 0.006) but no significant dose-response relationship between self-reported pesticide use and PD [331]. A small prospective study used a JEM to assess occupational exposure to pesticides and found an increased risk of PD in men (OR 5.63, 95% CI 1.47–21.58) but not in women [319].

In the Agricultural Health Study (AHS) [332], a cohort of individuals who applied for license to use restricted pesticides in Iowa and North Carolina in 1993–1997, data on pesticide use and medical history were collected at enrollment and at 5 years of follow-up. Based on self-report, 83 prevalent PD cases and 78 incident PD cases were identified. Increasing cumulative lifetime days of pesticide use was associated with increasing risk of incident PD (OR 2.3, 95% CI 1.2–4.5 for highest versus lowest category of exposure, P for trend 0.009) but not in prevalent PD. When exposure to pesticides was analyzed as a dichotomous variable (ever vs. never), no significant associations were detected. In analyses of specific pesticides among incident cases, ORs above 1.4 (although non-significant) were obtained for dicamba, trifuralin, butylate, and 2,4,5-trichlorophenoxyacetic acid (herbicides), for lindane and phorate (insecticides), for chlorothalonil and benomyl (fungicides), and for methyl bromide (fumigant) [332]. Exposure to paraquat was associated with non-significantly increased PD risk in prevalent but not in incident cases [332].

Methodological considerations

Such a complex exposure as pesticides is challenging to assess in epidemiologic studies. In many studies of PD, pesticides exposure was categorized as a dichotomous variable (exposed or not) and assessed as a broad category, rather than examining specific substances. Lack of detailed exposure assessment in combination with low frequency and intensity of exposure hampers analyses of dose-response relationships and specific pesticides.

Only the AHS [332] and the MSA [324] studies performed in-depth assessment of pesticide exposure in populations with high exposure prevalence. However, despite collection of detailed information regarding frequency, duration, use of specific pesticides as well as protection equipment, misclassification of exposure may still occur. Within the AHS, an algorithm was developed to estimate average lifetime exposure to specific pesticides [333]. When this algorithm was validated against urine concentrations of pesticides, moderate correlations were found with data from field observers, but for self-reported data correlations were low. Results differed by formulation of exposure (granular vs. liquid), highlighting the importance of collecting information on type of pesticide [334]. To date (2010), only one study used prospectively assessed biomarkers [329]. Misclassification of exposure may be differential or non-differential, potentially leading to spurious associations or bias towards the null. In prospective studies, misclassification of exposure is likely non-differential, whereas in case-control studies (the study design that most epidemiologic evidence on pesticides and PD is derived from), information bias is an important concern.

Most case-control studies used prevalent rather than incident cases and a hospital-based rather than population-based design. Only about half of the studies adjusted for confounders, notably smoking. Although frequency of exposure usually differs between men and women, analyses were not always gender-specific. Further, many studies were small, resulting in unstable relative risk estimates.

Ecologic studies

Beside the Canadian prevalence study [282], other prevalence studies [335–337] and an incidence study [338] reported higher occurrence of PD in rural than in urban areas. However, one study found lower prevalence of PD among farmers [339] and another study found slightly higher incidence in urban than in rural areas [52]. One study reported higher mortality rates due to PD in urban areas than in rural [340], whereas another study [341] found no difference in mortality rates from PD between urban and rural areas. Differences in case ascertainment may, at least partially, explain the divergent results. A study conducted in Nebraska [342]—based on a combination of mortality data, information on anti-parkinson drug sales, and census data on pesticide use by county—found a correlation between anti-parkinson drug sales and acres of fertilizer used, weeds sprayed, and hay insect sprayed. However, there was no association between PD mortality and anti-parkinson drug sales or pesticide use variables [342]. Similarly, a California study [343] used a combination of mortality data and ecologic data obtained both from pesticide use reports and an agricultural census.

Individuals with ischaemic heart disease as their cause of death were chosen for comparative purposes. The prevalence odds ratio (POR) for PD was 1.45 (95% CI 1.32–1.59) for high pesticide use versus none. Further, higher proportion of county land treated with insecticides was associated with increasing PD mortality (POR 2.41, 95% CI 1.77–3.27 for above 90th percentile versus below 50th percentile) [343].

Farming, rural living, well water use

Several case-control studies that investigated pesticides in relation to PD also analyzed variables related to pesticides, most commonly farming, rural living, and well-water use. Of the 34 case-control studies that investigated the association between farming and PD, 7 reported an increased risk [290, 293, 298, 303, 321, 322, 344] with ORs that ranged between 1.3 and 5.2. Most studies observed no association [143, 144, 147, 154, 156, 292, 293, 295, 296, 302, 304–306, 309, 310, 312, 314–317, 345–350] and one study found a significantly decreased risk [351]. In a case series study, farming occurred three times more frequently among PD patients than expected [352]. A mortality study including 26 US states found increased proportional mortality due to PD among livestock farmers, but not among crop farmers [353]. A study based on the Swedish national population reported a weak, although significant, association between farming and hospital-based PD in men (RR 1.08, 95% CI 1.02–1.15). A similar Danish study also reported a weak association (standardized hospitalization ratio, SHR, 1.30, 95% CI 1.03–1.63) [354].

Among 29 case-control studies that studied rural living as an exposure, 11 reported an increased risk of PD [136, 141, 142, 147, 153, 289, 293, 303, 305, 309, 314] with ORs ranging between 1.5 and 4.9. One study reported an inverse association [350], whereas the others found no association [131, 143–146, 154, 291, 307, 311, 312, 315, 316, 321, 325, 356–358].

Of the 34 case-control studies that evaluated the relationship between well water use and PD, 9 reported an increased risk [140, 142, 147, 305, 309, 312, 316, 346, 355]. Most of these studies reported ORs ranging between 1.7 and 2.8. Two reported statistically imprecise ORs at 10.9 (95% CI 1.8–67.5) [355] and 8.7 (95% CI 1.5–52.0) [312]. Of the remaining 25 studies that examined well water in relation to PD, three reported a decreased risk [131, 141, 146], whereas the others found no association [136, 143–145, 154, 289, 292, 293, 300, 302, 307, 310, 311, 314, 315, 321, 325, 350, 351, 356–358].

A Californian study [359] assessed exposure to specific pesticides in well water through a combination of interviews, GIS, and California Pesticide Use Reports. High possible well water exposure to the insecticides methomyl

(OR 1.67, 95% CI 1.00–2.78), chlorpyrifos (OR 1.87, 95% CI 1.05–3.31) and propargite (OR 1.92, 95% CI 1.15–3.20) were associated with increased PD risk. Further, risk of PD increased with exposure to increasing number of pesticides in well water [359]. An ecologic study reported a correlation between well water use and PD mortality in Michigan [360].

Only a few studies attempted to determine whether farming, rural living, and well water use can be considered as independent risk factors for PD, or whether they are correlated with pesticide exposure. One population-based study found that occupational exposure to herbicides or insecticides and farming were to some extent independently associated with PD risk [321]. In contrast, another population-based study reported that the increased risk observed with occupational exposure to herbicides did not remain after adjusting for occupational exposure to insecticides and farming, suggesting that these exposures were inter-related [290]. A hospital-based study found that the increased risks observed for farming and rural living .were partly explained by occupational exposure to pesticides [293]. Thus, these results are not consistent.

Molecular mechanisms

Experimental and animal studies have examined the effects of different pesticides on nigrostriatal dopaminergic system degeneration, as well as cellular effects, such as mitochondrial dysfunction, oxidative stress, and α-Synuclein aggregation. Several authors have reviewed this literature [361–366]. In rats, chronic infusion of rotenone, an insecticide that inhibits complex I in the respiratory chain, resulted in selective nigrostriatal dopaminergic degeneration, cytoplasmic inclusions similar to Lewy bodies, and motor symptoms [367]. Paraquat injected intraperitoneally repeatedly in mice caused dose-dependent degeneration of dopaminergic neurons in the substantia nigra, but striatal dopamine levels were normal [368]. In another study, combined intraperitoneal administration of paraquat and maneb in mice, but not either alone, lead to degeneration of nigral dopaminergic neurons, loss of striatal dopamine and reduced motor activity [369]. In vitro, dieldrin (an organochlorine) caused increased α-Synuclein fibril formation [370] and in mice, dieldrin exposure lead to increased α-Synuclein expression and alterations in the dopaminergic system [371]. Although experimental evidence indicates that several pesticides can exert a neurotoxic effect to dopaminergic neurons, doses and routes of administration were not comparable to the conditions present in pesticide users, making it difficult to generalize the results to humans.

In sum, there is epidemiologic evidence that pesticides, or a subgroup of them, may increase the risk of PD. Most studies suffered from lack of detailed exposure assessment and low frequency or intensity of the exposure, precluding analyses of particular pesticides and dose-response relationships. Recent studies conducted in populations highly exposed to pesticides [324, 332] represent an improvement. As indicated in reviews covering the area [362–365, 372–374] however, causation has not been established between pesticides and PD. Furthermore, if the association is causal, it remains to be established what specific compounds are implicated.

Metals

By the beginning of the nineteenth century, it was noted that high manganese exposure caused parkinsonian symptoms, although clinically distinct from PD [375]. There are also case reports on parkinsonism induced by lead exposure [376]. Iron has been hypothesized to play a role in PD based on its involvement in oxidative stress, and increased iron levels were demonstrated in the substantia nigra of PD patients compared to controls, although iron levels were also increased in patients with progressive supranuclear palsy (PSP) and MSA [377, 378]. Copper and zinc are important as co-factors for the enzyme superoxide dismutase (SOD), and alterations in nigral levels of these metals have also been reported [378, 379].

One early case-control study that measured levels of mercury in blood, urine, and hair reported increased risk of PD in relation to increased mercury levels (OR 9.4, 95% CI 2.5–35.9 for the highest tertile of blood mercury vs. the lowest) [380]. An ecologic study reported a correlation between iron industries and PD mortality per county (Spearman rank correlation 0.29, P value 0.008), although there was no correlation between industries using copper and PD mortality [360].

Most case-control studies that investigated the role of metals in PD focused on occupational exposures. Some studies assessed metal exposure overall through questionnaires without collecting information on occupational history, an approach that also captures recreational metal exposure. Of studies that examined exposure to heavy metals overall, only one reported an increased risk (OR11.84, 95% CI 1.08–130.37) [358], whereas the others found no association [293, 313, 381]. Another study found no association for residential proximity to steel plants [146].

A German hospital-based case-control study [154] and two US population-based studies [317, 322, 382] found no associations between occupational exposure to lead and PD. However, in one of the latter studies, exposure for more than 20 years was related to increased risk (OR 5.25, P value 0.006) [322]. The combination of exposure to lead and iron showed no increased risk compared to exposure to lead alone [322]. Using the same subjects, these authors

assessed whole body lifetime lead exposure by measurements of bone lead stores in combination with occupational history and reported an increased risk of PD for the 4th quartile of whole body lifetime lead exposure compared to the 1st quartile (OR 2.27, 95% CI 1.13–4.55) [383].

No associations for occupational exposure to copper overall were observed in the two US population-based studies [317, 322, 382], but one of them [322, 382] reported increased risk for more than 20 years of exposure (OR 2.49, P value 0.037). In a European multicentre study, there was no association between exposure to copper and PD [300]. Similarly, this study reported no association between iron exposure and PD [300], as did one of the US studies [382]. Studies that assessed occupational exposure to mercury [132, 154, 382] and zinc [154, 382] found no relation to PD.

Four case-control studies found no association between exposure to manganese and PD [132, 292, 300, 317]. Similarly, one small study (29 cases) found no association between serum or urinary levels of manganese and PD [384]. One of the US case-control studies mentioned above reported an increased risk after more than 20 years of exposure (OR 10.63, P value 0.044) but no association overall [322]. A cohort study among workers in ship building companies in South Korea measured airborne manganese levels and detected PD cases by a national insurance register and medical records [385]. No differences in incidence between exposed and non-exposed workers were found [385]. An ecologic study conducted in Canada showed no association between neighborhood levels of airborne manganese and risk of PD based on register and drug prescription data [386].

Welders have been of specific interest as they are exposed to manganese-containing fumes. A Danish [387] and a Swedish study [388] based on cohorts of male iron and metal goods manufacturing workers both reported no association between being a welder and hospitalization due to PD. Similarly, no association between welding and PD was observed in a US study based on occupational and mortality data from the National Center for Health Statistics database [389] nor in a case-control study based on medical insurance records for employees at a Caterpillar plant in Pittsburgh [390].

One study found no association between number of blood donations (an indirect marker of iron stores) and PD [391]. Another study that examined serum levels of different measures of systemic iron metabolism reported that transferrin receptor concentration predicted mortality in PD patients but not in controls [392].

In sum, there is no convincing epidemiologic evidence that exposure to specific metals causes PD. Besides the German study [154], the European multicentre study [300] and one US study [317] the relevant studies were small and prospective data are lacking for most metals.

Organic solvents

The role of organic solvents in PD has been studied as part of the general proposal that PD may be caused by an environmental toxin. Occupational exposure to organic solvents was associated with increased risk of PD in two case-control studies [154, 309] whilst in another study, the increased risk was confined to men [292]. Six other case-control studies, including the large (767 cases) European multicentre study [300], observed no association between organic solvents and PD [300, 308, 310, 313, 317, 393]. One case-control study found an increased risk with longer duration of exposure (OR 3.59, 95% CI 1.26–19.26 for 20–30 years of exposure vs. not exposed, P for trend 0.04) although no association was observed overall [381]. Another case-control study found no association between residential exposure to paint plants and PD (OR 3.0, 95% CI 0.20–45.7) [146]. The only published prospective study reported no association between organic solvents and PD [330].

Other chemicals

Chemicals other than pesticides and organic solvents have been evaluated either as a combination of occupational and residential exposure, or through assessment of occupational history only. The former group of studies, which should be more informative, is examined. One case-control study assessing residential exposure to rubber plants, industrial chemical plants, and printing plants, observed no association with PD for any variable [146]. Another study found an excess risk following exposure to chemical substances, such as methanol, toluene, cyanide, mercury or petroleum products (OR 5.87, 95% CI 1.48–27.23) [145]. The prospective study based on the Cancer Prevention II Nutrition Cohort in the US [330] reported no associations between risk of PD and exposure to asbestos, coal or stone dust, asphalt, diesel engine or gasoline exhaust, dyes, formaldehyde, textile dust, wood dust or radioactive material. Similarly, a population-based case-control study found no association of PD with exposure to asbestos, paints, cleaning products, petroleum derivatives, glues, or printing products [299].

Magnetic fields

Exposure to magnetic fields has been assessed primarily by the application of JEMs to occupational history. A study of workers in electric utility companies in North Carolina found no association [394]. Similarly, a Danish study of workers in utility companies found no association between exposure to magnetic fields and hospitalization due to PD [395]. A US study combined occupational and industry codes with JEM to assess exposure to magnetic fields [396]. For the highest category exposure versus the lowest

according to the JEM, the OR for PD mortality was 1.50 (95% CI 1.02–2.19). Increased risk of PD mortality was also observed for having an electrical occupation versus not having an electrical occupation (OR 1.55, 95% CI 0.98–2.45) and for definite or probable magnetic field exposure versus no magnetic field exposure according to the combination of occupation and industry codes (OR 1.76, 95% CI 1.17–2.65) [396].

Occupational history

Several studies investigated possible associations between a broad range of occupations and PD. A Swedish population-based study [295] reported excess risk among carpenters (OR 6.7, 95% CI 1.76–30) and cleaners (OR 2.8, 95% CI 0.89–8.7, women only). A Canadian hospital-based case-control study reported that being a teacher, medical worker, forestry, logging, mining or oil field worker, as well as social science or law worker was associated with a increased risk of PD, with the highest risk observed for the category that included forestry, logging, mining or oil field worker (OR 3.79, 95% CI 1.72–8.37) [348]. Further, being a construction worker, management or administration worker, or clerical worker was associated with decreased risk of PD. That teachers and medical workers have an increased risk of PD was not confirmed in a Danish study based on census job codes and hospital discharge PD diagnosis [354]. However, being a paint and wallpaper dealer, psychologist or welfare worker, lawyer, railway and transport worker, or bus driver was associated with increased risk of PD in men. In women, working with laundry and dry-cleaning or cleaning was associated with increased risk. In men, being a construction worker was associated with a decreased risk [354]. In contrast, a US multi-centre study reported increased risk of PD associated with being a construction worker [304]. This study also reported increased risk of PD for legal occupations [304].

Similar to the Canadian [348] and the Danish [354] studies, a US population-based case-control study [345] observed a decreased risk of PD for male construction workers (OR 0.3, 95% CI 0.1–0.7). As in the Canadian study [348], an increased risk was also observed for being a physician (OR 3.7, 95% CI 1.0–13.1) [345]. A case-series study that included more than 2,200 patients with PD or parkinsonism from three movement disorders clinics in New York, Atlanta, and Sunnyvale compared occupational frequencies between patients and the general population [352]. Among patients, more physicians and teachers than expected were observed, but for medical occupations other than physician, fewer cases than expected were observed [352].

A nationwide Swedish study [397] based on census data and hospital discharge PD diagnoses reported that being a

teacher, religious, social, or law worker, administrator, sales agent, painter, wall paper hanger, or wood worker was associated with slightly increased risk of PD in men. In women, being an assistant nurse was associated with increased risk [397].

Although there were mutually compatible findings in some of the studies mentioned above, the results overall are not consistent. Methodological limitations include for example use of hospital-based rather than population-based samples that may leave room for selection bias and lack of adjustment for possible confounders, such as smoking and education. Among the occupations with a possible link to PD a few may be associated with environmental exposures, such as organic solvents for painters and wood dust for wood workers. On the other hand, occupations such as teacher, medical worker or administrative worker are not clearly associated with any specific exposure. It has been proposed that the increased risk observed among teachers and medical workers may be due to higher exposure to viral infections in these occupations [348]. The decreased risk observed among construction workers has been hypothesized to be due to higher level of physical activity [345].

Lifestyle factors

Smoking

Smoking is one of the most extensively studied lifestyle exposures in relation to PD. An inverse association between smoking and PD was first reported in studies that examined general mortality in smokers, with standardized mortality ratio (SMR) estimates of 0.36 [398], 0.23 [399], 0.76 [400] and 0.43 [401]. These studies relied on information on death certificates regarding the PD diagnosis, which may be problematic in several ways [402, 403]. Quality of PD diagnoses on death certificates is questionable, and as PD is a chronic disease, it may not always be noted on the death certificate. Underreporting of PD diagnosis on death certificates may be more extensive in smokers, for whom smoking-related causes of death and diseases may dominate. This would lead to underestimation of PD occurrence among smokers and a spurious or exaggerated protective effect. Most of these studies included men only.

Case-control studies

Few studies within this area were published during the 1960s and 1970s, but from the 1980s and onwards, a large number of primarily case-control studies were performed in different parts of the world. Most studies used prevalent PD cases. Choice of control group, diagnostic criteria and adjustment for possible confounders varied, although

almost all studies adjusted for age and gender in the analyses. Study size varied from below 50 cases to about 500 cases. Of 44 case-control studies, 30 reported an inverse association between smoking and PD [127, 131, 136, 137, 140, 143, 145, 153, 293, 295, 298, 309, 310, 325, 344, 358, 404–417]. The other studies found no significant association, although several of them reported RR estimates below unity [132, 141, 146, 296, 303, 306, 315, 380, 418–424]. The inverse relationship was generally stronger for current smokers than for past smokers. The RRs for PD in ever smokers (current and past smokers combined) versus never smokers ranged between 0.32 and 0.77 in studies reporting an association. An inverse dose-response relationship between amount of cigarettes smoked (in pack-years) and PD risk was reported in several studies [298, 310, 358, 413, 415–417].There was no evidence for gender differences regarding the inverse association between smoking and PD.

Two small co-twin controlled studies reported a statistically non-significant inverse association between smoking and PD [425, 426]. A somewhat larger co-twin controlled study reported that in twin pairs discordant for PD, the unaffected twin smoked more (in pack-years) than the affected twin [427].

Prospective studies

Prospective studies of smoking in relation to PD that did not use only death certificates as source of diagnostic information are listed in Table 5. Of these 9 studies, five were large cohort studies, four of which were conducted in the US [428–430] and one was conducted in Singapore [431]. The Honolulu Asia-Aging cohort of men was somewhat smaller (58 PD cases) [432]. Three case-control studies were nested within the Harvard College and University of Pennsylvania Alumni cohort, USA [433], Leisure World cohort, California, USA [434] and the Swedish Twin cohort [435]. The results from these 9 prospective studies were similar. In fact, all reported an inverse relationship of smoking with PD.

In the five large cohort studies, RRs for PD in current smokers versus never smokers ranged between 0.27 and 0.56; and in past smokers versus never smokers, between 0.50 and 0.78 [428–431]. The Honolulu Asia study did not report RR for current and past smokers other than in a figure, but their RR for ever versus never smokers was 0.44 (95% CI 0.26–0.75) [432]. The nested case-control studies reported somewhat higher relative risk estimates both for current versus never smokers and for past versus never smokers [433–435]. A significant inverse dose-response relationship was detected in all prospective studies except the Harvard College and University of Pennsylvania Alumni study [433], which was one of the smallest (76

cases). The inverse association persisted when possible confounders such as coffee and alcohol consumption were adjusted for.

Meta-analyses

A meta-analysis including 44 case-control and four cohort studies reported a pooled RR of 0.59 (95% CI 0.54–0.63) for ever versus never smokers, 0.39 (95% CI 0.32–0.47) for current versus never smokers, and 0.80 (95% CI 0.69–0.83) for past versus never smokers [436]. In an earlier meta-analysis that included 46 studies (with high degree of overlap with the Hernan study [436]) the summary estimate was 0.57 (95% CI 0.52–0.63) for ever versus never smokers [437]. Hernan et al. [436] noted that the inverse association between smoking and PD was stronger in cohort studies than in case-control studies, especially for the comparison of past versus never smokers. Further, these authors found low heterogeneity between studies and no evidence for publication bias. A meta-analysis of six prospective studies (including early mortality studies) reported a pooled RR of 0.51 (95% CI 0.43–0.61) for ever smokers versus never smokers [438].

Another meta-analysis calculated a pooled relative risk of PD related to smoking in patients with and without family history of PD [439]. For ever versus never smokers, they reported a pooled RR of 0.82 (95% CI 0.44–1.53) in individuals with positive family history of PD, and a pooled RR of 0.77 (95% CI 0.59–1.01) in individuals with negative family history of PD [439]. However, these estimates were based on few studies.

A meta-analysis that included 11 US studies (8 case-control and three cohort studies) addressed the importance of smoking intensity versus duration, age of starting or quitting smoking, time interval after smoking cessation, and type of tobacco in relation to risk of PD [440]. For ever versus never smokers, this study reported a pooled RR of 0.70 (95% CI 0.63–0.78) for case-control studies and 0.54 (95% CI 0.45–0.65) for cohort studies. In both case-control and cohort studies the inverse association was stronger among current than among past smokers. There was a significant inverse dose-response trend with increasing pack-years of smoking as well as with shorter time since cessation of smoking. Still, in individuals who quit smoking for up to 25 years before, there was an inverse association. In men, an inverse association was observed for cigar or pipe smoking (OR 0.46, 95% CI 0.28–0.76) [440].

The largest cohort study [430] also addressed the importance of smoking intensity versus duration. At fixed duration, number of cigarettes smoked per day was not related to PD risk. However, within categories of fixed intensity of smoking (number of cigarettes smoked per day), increasing duration was associated with lower PD

Table 5 Prospective studies of smoking and PD

Study [reference]	Study design	Population	No. of PD cases/ population	Ascertainment	Relative risk (RR) or odds ratio (OR) (95% confidence interval)
Sasco [433]	Nested case-control	Harvard College and University of Pennsylvania Alumni Study	76 cases, 317 controls among total population of 50,002	Self-report, information from treating physician	Current versus never smokers: OR 0.51 (0.26–1.0)
					Past versus never smokers: OR 0.77 (0.40–1.50)
Grandinetti [432]	Cohort	Honolulu Asia-Aging study, USA	58 cases among 8,006 men	Hospital records, death certificates, neurologist practice records, medical record review	Ever versus never smokers: RR 0.44 (0.26–0.75)
Hernan [428]	Cohort	Nurses Health Study, USA	153 cases among 121,700 women	Self-report, medical records or information from treating physician	Current versus never smokers: RR 0.4 (0.2–0.7)
					Past versus never smokers: RR 0.7 (0.5–1.0)
Hernan [428]	Cohort	Health Professionals Follow-up Study, USA	146 cases among 51,529 men	Self-report, medical records or information from treating physician	Current versus never smokers: RR 0.3 (0.1–0.8)
					Past versus never smokers: RR 0.5 (0.4–0.7)
Paganini-Hill [434]	Nested case-control	Leizure World Study, California, USA	395 cases, 2,320 controls among population of 13,979	Death certificates, hospital records, questionnaire	Current versus never smokers: RR 0.42 (0.25–0.69)
					Past versus never smokers: RR 0.92 (0.73–1.16)
Wirdefeldt [435]	Nested case-control	Swedish Twin Registry, Sweden	476 cases, 2,380 controls among population of 52,149	Hospital records, death certificates	Current versus never smokers: RR 0.56 (0.40–0.79)
					Past versus never smokers: RR 1.15 (0.74–1.79)
Thacker [429]	Cohort	Cancer Prevention Study II Nutrition Cohort, USA	413 cases among 79,977 women and 63,348 men	Self-report, medical records or information from treating physician	Current versus never smokers: RR 0.27 (0.13–0.56)
					Past versus never smokers: RR 0.78 (0.64–0.95)
Tan [431]	Cohort	Singapore Chinese Health Study	157 cases among population of 63,257	Hospital and outpatient records, self-report, medical records	Current versus never smokers: RR 0.29 (0.16–0.52)
					Past versus never smokers: RR 0.77 (0.48–1.23)
Chen [430]	Cohort	National Institutes of Health American Association of Retired Persons Diet and Health Cohort	1,662 cases among population of 305,468	Self-report, medical records or information from treating physician	Current versus never smokers: OR 0.56 (0.45–0.70)
					Past versus never smokers: OR 0.78 (0.70–0.86)

risk. Very little risk reduction was reported for less than 10 years of smoking, suggesting that longer duration of smoking is needed for a risk reduction [430].

Suggested systemic biases in studies of smoking and PD

Although a large number of studies have shown that cigarette smoking is inversely associated with PD, it has been argued that the association may be explained by various biases [402, 403, 441–443]. First, as mentioned above, there may be lack of information regarding PD diagnoses in the death certificates and medical records of smokers (information bias). Second, there may be selective mortality of smokers from causes other than PD (competing risks, a form of selection bias). If smokers die earlier than non-smokers from causes unrelated to PD, smokers may be under-represented among prevalent PD patients. Third, individuals with PD may be less prone to smoke or more prone to quit (reverse causation). Last, smoking and PD may share common covariates (confounding) not accounted for in the studies. For example, genetic factors may be associated with both an increased risk of PD and a higher likelihood of abstaining from smoking.

Several studies have tried to address the issue of confounding by a factor that increases the risk of PD and also is related to abstaining from smoking. For example, it has been suggested that PD patients tend to be more introverted, more nervous, more self-controlled, and less likely to take risks; personality traits possibly associated with abstaining from smoking [425, 444–446]. Confounding by genetic factors has been addressed in twin studies, in which co-twins of cases are used as controls, a design that controls for genetic as well as shared early environmental factors. As mentioned above, the two largest such studies confirmed the inverse association and also reported a dose-response relationship, indicating that confounding by genetic factors is unlikely [427, 435]. Similarly, a case-control study that used siblings as controls reported a significant inverse association between smoking and PD with a dose-response relationship [447], a result that was confirmed in an expanded dataset [448].

To investigate the presence of a non-genetic unknown confounder that increases the risk of PD and is related to abstaining from smoking, a study analyzed parental smoking in relation to PD [449]. The authors reasoned that children of smoking parents are exposed to smoke and are more likely to become smokers themselves, and if smoking is protective, their risk of PD would be lower compared to children of non-smokers. In the presence of a confounder (such as an infectious agent or a toxin), no association would be expected between parental smoking and risk of PD. Using data from the Nurses Health Study and the Health Professionals Follow-up Study, the pooled RR of PD was 0.73 (95% CI 0.53–1.00) for individuals whose parents both smoked compared to individuals whose parents were both non-smokers, thus suggesting a causal relationship [449].

Another approach to study the relationship between smoking and PD was taken in an ecologic study [450] that examined the male to female ratio in PD incidence in different countries and compared these ratios with the corresponding male to female ratios of smoking. When no individual-level data are available, this study design is less informative compared to a case-control or a cohort study. Nevertheless, the authors reported that with increasing proportion of women who smoke in a country, the incidence of PD in women relative to that in men declined, an expected finding in the presence of a causal relationship [450].

There is some evidence that smoking may also delay onset of PD. Two retrospective case series studies reported that PD patients who smoked had later onset of disease compared to never smokers [451, 452]. However, in this study design, reverse causation is an obvious concern; no prospective data are available. Case series studies have reported no effect of smoking on disease progression [442, 453, 454].

Few studies examined the association between smokeless tobacco specifically and PD risk. A case-control study reported a strong inverse association (OR 0.18, 95% CI 0.04–0.82, in ever users vs. never users of smokeless tobacco) [423]. A prospective study that assessed PD mortality as the outcome reported a RR of 0.22 (95% CI 0.07–0.67) for current users of smokeless tobacco at enrollment versus never users [455]. The meta-analysis of 11 US studies mentioned above [440] reported a non-significant inverse association for chewing tobacco after adjustment for other types of smoking (OR 0.66, 95% CI 0.43–1.02) [440].

Molecular mechanism

Several mechanisms for the protective effect of smoking on risk of PD have been suggested [403, 456]. Cigarette smoke contains numerous different compounds, but nicotine has attracted most interest, as it stimulates dopaminergic neurons, relieves PD symptoms, and also possesses a neuroprotective effect [456]. A recent study investigated the effect of five different compounds of cigarette smoke (anabasine, cotinine, hydroquinone, nicotine, and nomicotine) on the fibrillation of the α-Synuclein protein (that among other proteins aggregates in Lewy bodies in PD). Nicotine and hydroquinone did inhibit formation of α-Synuclein fibrils, with nicotine being more effective, indicating that these compounds stabilize soluble oligomeric forms of α-Synuclein [457]. That smokeless tobacco, resulting in nicotine exposure of equivalent amount to cigarette smoking, also is inversely associated with PD

lends some support to the notion that nicotine is the protective agent.

In sum, a large body of evidence shows that smoking decreases the risk of PD by about 50%. Although causality of the relationship has been debated, prospective studies suggest that the relationship is indeed true. Different forms of information and selection bias as well as reverse causation are all unlikely in a prospective design. A clear inverse dose-response relationship has been demonstrated. Confounding by genetic factors has been adequately addressed in family-based designs. Experimental studies have indicated a link between primarily nicotine and the α-Synuclein protein, although the exact molecular mechanism for the protective effect of smoking in PD remains to be clarified.

Alcohol

Case-control studies

Several case-control studies have investigated the association between alcohol intake and PD. The methods for assessing alcohol intake and analyzing the data varied across studies. Many studies estimated amount of alcohol consumed, while others simply studied alcohol intake as a dichotomous variable (ever vs. never or regular use vs. non-regular use), precluding analyses of dose-response effects. Most studies controlled for age and sex and several, though not all, adjusted for additional co-variates, such as smoking, coffee, and education. Only a few studies examined the associations between different types of alcoholic beverages and PD.

Although many of the case-control studies reported ORs below unity, the association was non-significant in most studies [142, 143, 293, 298, 303, 309, 310, 380, 407, 408, 410, 413, 415, 423]. A Swedish study that investigated the relationship of PD with beer, wine, and liquor reported inverse associations for each of these types of alcoholic beverages in univariate analyses. Following adjustment for several dietary factors as well as smoking, however, the associations did not remain significant [295]. An Italian study found a reduction of PD risk for ever versus never alcohol drinkers, adjusting for smoking, coffee, and education (OR 0.61, 95% CI 0.39–0.97) [424]. However, for drinking alcohol during more than 30 years versus never and for number of drinks per day, the associations were non-significant. These authors suggested that light to moderate drinkers may have lower risk of PD, while heavy drinkers may be more similar to non-drinkers regarding risk of PD [424].

A Spanish study reported an inverse association with PD for moderate-to-heavy drinkers versus moderate or light drinkers (*P* value 0.001), but this study did not adjust for confounders [421]. A study conducted in Singapore reported an inverse association between alcohol intake as a continuous variable and PD (*P* value 0.001) [358]. Two studies reported decreasing risk of PD with increasing amount of alcohol intake, although comparisons between categories of alcohol intake were generally non-significant [417, 458]. One relatively large (342 cases) German study observed risk estimates below unity for beer and spirits, but not for wine [458]. A Chinese study reported lower PD risk associated with regular liquor drinking (OR 0.28, 95% CI 0.12–0.65) [146]. In a small co-twin controlled study of 31 monozygotic twin pairs, the unaffected twin drank more alcohol than the affected twin, corresponding to a RR of 0.5 [426].

Prospective studies

Similar to smoking, prospective data regarding alcohol and PD are limited. The Nurses Health Study and the Health Professionals Follow-up Study both reported RR estimates around unity for total alcohol intake, adjusted for age, smoking, and coffee [459]. The results were similar when the analyses were restricted to never smokers. In pooled results, there was an inverse relationship between beer and PD (OR 0.6; 95% CI 0.5–0.9, for more than or equal to one beer per week vs. less than one beer per month), but no associations between wine or liquor and PD [459]. The Honolulu Asia-Aging study reported a RR of 0.76 (95% CI 0.45–1.28) for ever alcohol use versus never, adjusted for age, smoking, and coffee [432]. Similarly, the Singapore Chinese Health study reported a non-significantly decreased risk for at least weekly drinkers versus non- or less-than-weekly drinkers, controlling for smoking, caffeine, and tea (RR 0.60, 95% CI 0.31–1.16) [431], although alcohol drinking was uncommon in this population.

Two of the case-control studies nested in cohorts that examined smoking [434, 435] also reported results for alcohol intake. The Leisure World cohort study found an inverse relationship of PD with alcohol intake (number of drinks per day) in univariate analyses for all types of beverages (beer, wine, and liquor), although it was more evident for beer. However, when controlling for co-variates (among others, smoking and coffee), the relationship was no longer significant [434]. The Swedish co-twin controlled study reported non-significant ORs below unity for different categories of total alcohol intake after controlling for smoking, coffee, and education; in analyses restricted to never smokers, there was also an inverse association (OR 0.56, 95% CI 0.39–0.80 for ever drinkers vs. never drinkers) [435].

In sum, although several studies reported relative risk estimates below unity, few estimates were statistically significant. It is possible that a weak inverse association between alcohol and PD exists. Only a few studies examined the effects of different types of beverages, but some

results indicate that the effect may be stronger for beer than for wine or liquor. An alternative explanation for the observed inverse association may be residual confounding, possibly by smoking or coffee.

Physical activity

Case-control studies

Relatively few case-control studies examined the relationship between physical activity and PD. One study reported that engaging in competitive sports or having regular exercise was not associated with PD [315]. Higher level of exercise increased risk in some age groups, but the pattern was inconsistent with no adjustment for possible confounders, notably smoking [315]. One smaller case-control study (32 cases) reported similar level of physical activity in cases and controls [460], another including a subset of cases with early onset PD reported a decreased risk associated with regular exercise, confined to younger age groups [355]. A case-control study nested within the Harvard College Alumni cohort reported non-significant ORs below unity for engaging in varsity athletics and exercise at the time of college, for usual physical activity such as stair climbing and walking, as well as for practice of sports in adulthood before PD onset [461].

Prospective studies

Three prospective cohort studies investigated the effect of physical activity on PD risk. In the Nurses Health Study and the Health Professionals Follow-up Study, recreational physical activity was assessed in categories of metabolic equivalent task (MET) hours per week, controlling for all possible confounders [462]. No association between physical activity and PD was observed in women. In men, an inverse association was observed (RR 0.7, 95% CI 0.5–1.1 for the highest quintile of MET hours per week compared to the lowest, *P* for trend 0.007). The association was entirely due to vigorous rather than moderate physical activity [462]. Based on 101 male PD cases, the Harvard Alumni Health Study reported a non-significantly decreased risk of PD associated with recreational physical activity, such as stair climbing or walking and sports of different intensity, controlling for smoking, tea, and coffee [463]. The largest cohort study (413 PD cases) was based on data from the Cancer Prevention Study II Nutrition cohort [464]. Controlling for a large number of possible confounders, this study reported a non-significantly decreased risk of PD in the highest category of recreational physical activity (in MET hours per week) (RR for the highest quintile vs. no activity 0.8, 95% CI 0.6–1.2, *P* for

trend 0.07). The association was due to moderate to vigorous rather than light activity with similar results in men and women [464].

In sum, although relatively few studies have investigated physical activity in relation to PD, several suggest that vigorous physical activity may lower the risk. However, the association is probably weak.

Body mass index (BMI)

Few studies have examined the relationship between adiposity and PD. A large Italian case-control study (318 cases) reported a non-significantly decreased risk of PD with increasing BMI preceding onset of PD, controlling for smoking, coffee, education, and diabetes, among other variables [465]. Similarly, a Chinese case-control study nested within a nutrition intervention trial cohort observed declining risk of PD with increasing BMI at baseline (RR 0.43, 95% CI 0.20–0.93 for the highest BMI category vs. the lowest) in univariate analyses. When controlling for smoking (among other variables), the association persisted [466]. The Honolulu-Heart Study that followed a cohort of men in Hawaii measured BMI, subscapular skinfold thickness, and triceps skinfold thickness at baseline, and detected 137 incident PD cases [467]. No association between BMI or subscapular skinfold thickness and PD was found. However, higher triceps skinfold thickness was associated with increased risk of PD (*P* for trend < 0.001), controlling for smoking, coffee, and physical activity (among other variables) [467]. Likewise, a large Finnish cohort study (272 male and 254 female PD cases) [468], reported increased risk of PD with increasing BMI, controlling for a large number of possible confounders (RR 2.03, 95% CI 1.44–2.85 comparing the highest BMI category vs. the lowest). The authors noted that the dose-response relationship was less apparent in women than in men [468].

The Nurses Health Study and Health Professionals Follow-up Study examined self-measured BMI, waist circumference, and waist to hip ratio in relation to PD, controlling for smoking, coffee, and alcohol [469]. Based on 249 male and 202 female patients, no associations were detected overall, but when analyses were restricted to never smokers, higher waist circumference and waist to hip ratio were associated with increased risk (RR 1.9 for the highest vs. the lowest waist circumference category, *P* for trend 0.03) [469]. The Harvard Alumni Health Study observed (based on 106 male cases) no association between BMI at college entry and later development of PD [470].

Thus, studies of adiposity and PD are few and the results conflicting. Epidemiologic evidence does not support a strong relationship between adiposity and PD risk.

Diet

Specific food items

Nutritional epidemiological studies in PD have focused on groups of food items, macronutrients (such as protein, fat, and carbohydrates), or other specific nutrients. Some case-control studies assessed risk of PD in relation to a large number of different food items. An early US study reported lower preference for nuts, plums, and salad oil or dressing and higher preference for spicy foods among cases than controls [289, 471]. Another study reported higher preference for almonds and plums among cases [472]. One small study reported lower risk associated with intake of meat products, milk, and fruit [473] whilst another small study reported a positive association with intake of nuts and seeds [153]. A Spanish study that assessed a large range of different food items found that intake of peas lowered risk of PD (OR 0.60, 95% CI 0.40–0.89), with no association for any other food item [474]. Similarly, a Chinese study and a study conducted in Texas, USA, found no associations between PD and intake of vegetables or fruit [144, 301], although the latter study reported an inverse relationship between intake of fish and PD (OR 0.5, 95% CI 0.3–0.9 for fish intake more than once a month vs. less often) [301].

In an Indian study, vegetarian diet was unrelated to risk of PD [143]. A large German study (342 cases) reported an association of PD with high intake of sweets, cookies, and cakes, as well as low intake of potatoes and PD [458], but these associations were stronger among cases with longer (more than 3 years) duration of disease, suggesting reverse causality due to a disease-related change in dietary habits. A Swedish case-control study reported inverse associations of PD with intake of meat and ham, eggs, and wheat bread [295]. An inverse association between intake of meat and PD was also found in a Chinese case-control study nested within a nutrition intervention trial [466], but this study reported no associations of PD with intake of eggs, fruits, or vegetables and PD.

Coffee and tea

Intake of coffee and tea in relation to PD has been studied extensively. Caffeine acts as an adenosine receptor antagonist and experimental evidence suggests that it may exert a neuroprotective effect [475, 476]. Several case-control studies reported an inverse association of PD with coffee or total amount of caffeine intake [295, 358, 404, 416, 423, 424, 448, 458]; a few also reported a dose-response relationship [358, 424], although others found no such association [136, 142, 301, 303, 407, 415, 417, 421]. Some of these studies did not adjust for smoking and other co-variates, but

most of them did. A case-control study nested within the Leisure World Cohort Study, California, reported lower risk of PD associated with higher coffee intake (OR 0.64, 95% CI 0.48–0.84 for two or more cups per day vs. none)[434]. However, another case-control study nested within the Swedish Twin cohort found no association [435].

Based on 58 incident cases, an early report from the prospective Honolulu-Asia Aging study of Hawaiian men found no association between coffee and PD [432]. However, with longer follow-up and more incident cases detected, an inverse association was seen following adjustment for age and smoking (RR for coffee non-drinkers vs. drinkers 2.2, 95% CI 1.4–3.3) [477]. Risk estimates were similar for total amount of caffeine [477]. Similarly, a strong inverse relationship of PD with coffee and total caffeine intake was reported in the Health Professionals Follow-up Study, a cohort of men (RR 0.42, 95% CI 0.23–0.78 for highest vs. lowest quintile, P for trend < 0.001) [478]. In the Nurses Health Study, a cohort of women, there was no significant association between total caffeine intake and PD overall (P for trend 0.6), but an apparent U-shaped relationship, with lowest risk among women with moderate caffeine intake (1–3 cups of coffee per day) [478].

The suggested impact of gender on the association between caffeine and PD was also studied prospectively in the Cancer Prevention Study II Cohort among both men and women [479]. The inverse association in men was confirmed as well as the lack of association in women overall. However, when stratifying by estrogen replacement therapy, the authors observed an inverse association between caffeine and PD mortality in women who never used estrogens (RR 0.53, 95% CI 0.36–0.79 for more than 3 cups of coffee per day vs. none), but no association in women who used estrogens. The authors suggested that the protective effect of caffeine may be abrogated by postmenopausal estrogens [479], a theory supported by some experimental evidence [480].

In contrast to these findings, two Finnish prospective studies found inverse associations between coffee and PD of similar magnitude in men and women. One study based on residents in five geographic areas of Finland reported a hazard ratio (HR) of 0.40 (95% CI 0.23–0.71) for five cups of coffee per day or more versus none (P for trend 0.005) [481]. The Finnish Mobile Clinic study reported a RR of 0.26 (95% CI 0.07–0.99) for 4–9 cups of coffee per day versus none (P for trend 0.18) [482]. An inverse association was also reported from the Singapore Chinese Health Study for total caffeine intake (RR 0.64, 95% CI 0.40–1.03 for highest vs. lowest quartile, P for trend 0.016, men and women combined) although the association was not significant for coffee intake [431].

In a meta-analysis of 8 case-control studies and five cohort studies the pooled RR was 0.69 (95% CI 0.59–0.80)

for coffee drinkers versus non-coffee drinkers and 0.75 (95% CI 0.64–0.86) per three additional cups of coffee per day [436], although there was moderate heterogeneity. The estimates were similar in case-control and cohort studies and in analyses restricted to studies that adjusted for smoking. The authors concluded that the epidemiologic evidence of an inverse association between coffee drinking and PD is strong and that confounding is unlikely, although reverse causation cannot be completely ruled out [436].

Of the 7 case-control studies that investigated tea intake for a possible association with PD, three reported an inverse association [295, 310, 358], three found no association [142, 144, 415], and one reported an increased risk [136]. The Leisure World cohort study and a Finnish cohort study reported no associations [434, 481]. In the Health Professionals Follow-up Study [478], there was an inverse association between tea intake and PD in men who did not drink coffee (RR 0.4, 95% CI 0.2–1.2 for more than one cup per day vs. none, P for trend 0.02), but no association in women. The results were similar for other caffeinated beverages [478]. Only the Singapore Chinese Health Study [431] examined the effects of black and green tea separately; there was no association with PD for green tea, but intake of black tea was inversely associated with PD (RR 0.28, 95% CI 0.12–0.64 for highest vs. lowest tertile, P for trend 0.0004). The association persisted after adjusting for caffeine intake, leading the authors to hypothesize that compounds in black tea other than caffeine may be responsible for the apparent protective effect [431].

Dairy products

Among different groups of food items investigated in the prospective Nurses Health Study and the Health Professionals Follow-up Study, an association with dairy products was found in men, but not in women (RR 1.8, 95% CI 1.2–2.8 for highest vs. lowest quintile, P for trend 0.004 in men; RR 1.1, 95% CI 0.7–1.7, P for trend 0.9 in women) [483]. No other food items were related to PD risk. Calcium and vitamin D intake were associated with PD risk when the source was dairy products, but not when the source was non-dairy products [483], suggesting that a compound in dairy products other than calcium or vitamin D was responsible for the association. In line with these results, the Honolulu-Asia Aging study [484] (men only) reported increased risk of PD associated with intake of milk (RR 2.3, 95% CI 1.3–4.1 for more than 16 oz of milk per day vs. none, P for trend 0.007), although intake of other dairy products was unrelated to PD. The increased risk for milk was independent of calcium intake also in this study [484].

In the Cancer Prevention Study II Nutrition cohort, which includes both men and women, intake of dairy products increased risk of PD (RR 1.6, 95% CI 1.1–2.2 for highest vs. lowest quintile, P for trend 0.05) [485]. The relationship was linear in men (P for trend 0.04), but in women, the highest risk was observed for the second quintile and the trend was non-significant (P for trend 0.5). The association was mostly explained by milk consumption. Similar associations were observed for calcium, vitamin D, and protein intake, but these were stronger from dairy sources than from non-dairy sources [485].

A meta-analysis of all prospective studies on dairy products yielded a pooled RR of 1.6 (95% CI 1.3–2.0) for highest versus lowest quintile of milk or dairy products intake overall; RR 1.8 (95% CI 1.4–2.4) in men, and RR 1.3 (95% CI 0.8–2.1) in women [485]. Thus, although the underlying mechanism is unknown, available evidence supports a role for dairy products in PD, especially in men.

Macronutrients

Among case-control studies that assessed the role of macronutrients in PD (total energy intake, intake of fat, protein, and carbohydrates), two reported higher energy intake among cases than among controls [486, 487] and two found no such association [488, 489]. One case-control study reported lower risk with increasing glycemic index, but no associations for glycemic load or total intake of carbohydrates [490]. In the prospective Nurses Health Study and the Health Professionals Follow-up Study, there was increased caloric intake around the time of diagnosis [483], but not preceding the diagnosis [491], suggesting that this may be a consequence of the disease itself. Intake of protein or carbohydrates has not been associated with PD [431, 485–487, 489, 491]. A few case-control studies reported increased risk for intake of animal fat or saturated fat [487–489]. However, in an extended sample of one of these studies [488], the association was no longer observed [492]. Instead, lower risk of PD was observed for higher intake of cholesterol in men (OR 0.53, 95% CI 0.33–0.86 for highest vs. lowest quartile, P for trend 0.007) [493], a variable that was not analyzed in the initial study.

The Nurses Health Study and the Health Professionals Follow-up Study [491] reported no overall effect of fat intake on PD risk. Replacement of polyunsaturated fat with saturated fat in the statistical models increased risk of PD in men (RR 1.83, 95% CI 1.10–3.03 for 5% energy replacement), but not in women [491]. The prospective Rotterdam study found an inverse association between intake of total fat as well as unsaturated fat and PD (HR per standard deviation of total fat intake 0.69, 95% CI 0.52–0.91; HR per standard deviation of polyunsaturated fatty acids 0.66, 95% CI 0.46–0.96) [494]. The prospective Singapore Chinese Health Study reported lower risk of PD associated with intake of monounsaturated fat (RR 0.75,

95% CI 0.47–1.19 for highest vs. lowest quartile, *P* for trend 0.05), with no association for polyunsaturated fat [431]. Thus, findings regarding the role of macronutrients in PD, in particular fat, are conflicting.

Antioxidants

The role of antioxidants in PD has been studied based on the hypothesis that oxidative stress is involved in the pathogenesis of the disease. Results have been conflicting. One study reported lower serum levels of vitamins E and A in PD cases than in controls [495], but most early case-control studies that examined serum levels of vitamin C, vitamin E, beta-carotene, or vitamin A found no associations [496–500]. A German hospital-based case-control study [486] reported an inverse relationship between vitamin C intake and PD (*P* for trend 0.04; OR for highest quartile compared to lowest 0.60, 95% CI 0.33–1.09), but no association with vitamin E or beta-carotene intake. In three US case-control studies [487, 489, 501], no associations of PD with vitamin C, E, A (or carotenoid) intake were reported. Similarly, retrospective data from the Rotterdam study showed no associations of PD with vitamin C or beta-carotene intake, although an inverse association with vitamin E intake was reported (OR 0.3, 95% CI 0.1–0.9 for the highest vs. the lowest tertile, *P* for trend 0.03) [502]. A population-based case-control study conducted in Washington found no associations for vitamin C, E, A, or beta-carotene intake in the initial study [488] nor in an extended dataset [492].

Antioxidants also have been examined in the context of a few prospective studies. A case-control study nested within the Honolulu-Asia Aging Study found no association between intake of vitamin E and PD [503]. Another nested case-control study (the Leisure World Cohort Study, California) reported increased risk of PD associated with dietary vitamin C and A in univariate analysis, but the associations did not remain significant in multivariate analysis [434]. In the Nurses Health Study and the Health Professionals Follow-up Study, total vitamin E intake and use of vitamin E supplements were not associated with PD. However, when vitamin E from foods only was considered, there was an inverse association (RR 0.68, 95% CI 0.49–0.93 for highest vs. lowest quintile of dietary vitamin E intake) [504]. Intake of vitamin C or beta-carotenoids was not related to PD risk. The authors concluded that other nutrients in foods rich in vitamin E may be protective, or, that moderate, but not high, intake of vitamin E may be protective [504]. The Singapore Chinese Health Study reported an inverse relationship between total vitamin E intake and PD risk (RR 0.64, 95% CI 0.39–1.05 for highest vs. lowest quartile, *P* for trend 0.03), but no association with intake of vitamins C or A [431].

A meta-analysis of 7 case-control and one cohort study that assessed intake of antioxidants in relation to PD risk reported an inverse association with moderately high vitamin E intake (defined as second and third quartile or second to fourth quintile of intake) and PD (pooled RR 0.81, 95% CI 0.67–0.98), whereas high intake of vitamin E (defined as fourth quartile or fifth quintile of intake) was not associated with further reduction in PD risk (pooled RR 0.78, 95% CI 0.57–1.06) [505]. For vitamin C and beta-carotene, the meta-analyses showed no associations with PD. In a clinical trial of early PD, treatment with vitamin E did not delay progression of PD symptoms [506].

Vitamin D intake was not related to PD risk in a population-based case-control study [488]. The prospective Cancer Prevention Study II Cohort, USA, reported higher risk of PD associated with vitamin D intake from dairy products (RR 1.8, 95% CI 1.3–2.7 for highest quintile vs. lowest), but total vitamin D intake and vitamin D intake from non-dairy products were unrelated to PD [485]. In contrast, a case-control study found lower plasma levels of vitamin D in cases than in controls (*P* = 0.01) [507]. Similarly, the only prospective study reported lower risk of PD associated with higher plasma levels of vitamin D at baseline (RR 0.33, 95% CI 0.14–0.80 for highest vs. lowest quartile) [508]. Calcium supplements were not related to PD risk in the Nurses Health Study and the Health Professionals Follow-up Study [483]. Similarly, no association between dietary calcium and PD risk was found in two case-control studies [489, 492].

Vitamins B6, B12, and folate that are thought to reduce levels of homocysteine, have been investigated because of the hypothesized neurotoxic effect of homocysteine. In a German case-control study, intake of folic acid equivalents was related to lower risk of PD (OR 0.51, 95% CI 0.26–0.99 for highest quartile vs. lowest), although the corresponding trend test was non-significant (*P* for trend 0.08) [486]. A US case-control study found no associations with folate or vitamin B6 intake [489]. Similarly, total and dietary vitamin B6, B12 intake as well as folate intake were unrelated to PD in the Nurses Health Study and the Health Professionals Follow-up Study [509]. In the Rotterdam study [510], vitamin B12 and folate intake were unrelated to PD, but intake of vitamin B6 showed an inverse association (HR 0.46, 95% CI 0.22–0.96 for highest tertile vs. lowest, *P* for trend 0.05). The authors concluded that intake of vitamin B6 may lower the risk of PD through mechanisms unrelated to homocysteine metabolism [510].

Minerals

Dietary iron has been investigated for a possible role in PD primarily because of its role in oxidative stress. Three case-control studies found no association between dietary iron

intake and PD [488, 489, 511]. Another study [492] reported increased risk of PD with intake of iron (OR 1.7, 95% CI 1.0–2.7 for highest vs. lowest quartile, *P* for trend 0.016), as well as evidence of an interaction between iron and manganese. With low intake of both iron and manganese as the reference group, OR for high intake of both iron and manganese was 1.9 (95% CI 1.2–2.9) [492]. In an extended sample of the same study, the association between iron intake and PD was observed only in men (OR 1.82, 95% CI 1.11–2.99 for highest vs. lowest quartile, *P* for trend 0.013 in men; OR 1.12, 95% CI 0.59–2.12 for highest vs. lowest quartile, *P* for trend 0.31 in women). The association was stronger among men with low intake of cholesterol [493]. The only prospective study on dietary iron and PD risk (based on the Nurses Health Study and the Health Professionals Follow-up Study) reported no association for total iron intake (dietary iron and supplements), but dietary iron was associated with a moderately increased risk (RR 1.30, 95% CI 0.94–1.80, *P* for trend 0.02), largely explained by intake of nonheme rather than heme iron [512]. The association was stronger among individuals with low vitamin C intake (*P* for interaction 0.02).

Data are scarce regarding dietary intake of minerals other than iron in relation to PD. One case-control study observed no associations for intake of zinc, manganese, or copper [492]. A small case-control study (54 cases) reported higher blood levels of mercury in cases than controls [380], a finding not confirmed in another case-control study [313].

In sum, most studies on dietary factors in relation to PD were of case-control design, with potential for recall and selection bias. In particular some early studies lacked validated exposure assessment instruments and adjustment for possible confounders, notably smoking. Overall, dietary factors do not seem to play a major role in PD. There is strong evidence, however, for caffeine as a protective agent in PD. Intake of dairy products, in particular milk, may be a risk factor, but underlying mechanisms are unknown. There is finally some evidence that intake of vitamin E may be protective in PD, but results are not consistent.

Pre-existing medical conditions

Olfactory dysfunction

Olfactory dysfunction is common in PD patients [513] and there is a neuropathological correlate with Lewy bodies in the olfactory bulb [514]. A few prospective studies have examined the risk of PD following olfactory dysfunction. In a study of first-degree relatives of PD patients, four of 25 relatives with hyposmia had abnormal striatal dopamine transporter binding by single photon emission computed tomography (SPECT) versus none of 23 relatives without

hyposmia [515]. At 2 years of follow-up, four of 40 relatives with hyposmia had PD, versus none of 38 relatives without hyposmia [516]. At 5 years of follow-up, one additional relative with hyposmia had PD [517]. All relatives with hyposmia who developed PD had abnormal dopamine transporter binding at baseline [517]. In the Honolulu-Asia Aging study, individuals were tested for olfactory dysfunction at baseline and followed for incident PD [518]. Olfactory dysfunction was associated with increased risk of PD at 4 years of follow-up (OR 5.2, 95% CI 1.5–25.6 for lowest quartile vs. top two quartiles), whereas at 8 years of follow-up, there was no association [518]. In a study of twin pairs discordant for PD, two of 19 unaffected twins developed PD after about 7 years, both of whom with normal olfactory function at baseline, but faster decline [519].

Thus, although prospective studies are small, olfactory dysfunction appears to be associated with increased risk of PD, preceding PD symptoms with about 2–7 years.

REM sleep behavior disorder

REM (rapid eye movement) sleep behavior disorder (RBD) is a parasomnia characterized by abnormal behavior during REM sleep representing enactment of dreams, most common in men, and often reported by PD as well as MSA and DLB patients. Imaging and autopsy studies suggest an association with neuropathological changes in the brainstem, such as neuronal loss and Lewy bodies in the locus coeruleus and the substantia nigra [520]. In a case series of 29 patients with RBD, 11 (38%) were diagnosed with PD about 13 years after the onset of RBD symptoms [521]. Another study reported that of 44 RBD patients followed prospectively, 9 (20%) developed PD, 6 (14%) developed LBD, one (2%) developed MSA, and four (9%) developed mild cognitive impairment on average 11.5 years after onset of RBD [522]. The largest prospective study (93 RBD patients) used a survival design and reported a 5-year risk of neurodegenerative disease at 17.7%, 10-year risk at 40.6%, and 12-year risk at 52.4%. Neurodegenerative diagnoses included PD, LBD, Alzheimer's disease, and MSA [523]. A retrospective case series study that focused on cases with RBD preceding PD, LBD, or MSA with more than 15 years reported a median interval between onset of RBD and neurodegenerative disease of 25 years [524]. Thus, these results suggest that RBD is associated with not only PD, but also LBD and MSA, and that the time interval between onset of RBD and onset of neurodegenerative disease may be very long.

Infections

A possible infectious cause of PD has been suggested because patients suffering from encephalitis lethargica in

the 1920s sometimes developed parkinsonism. The encephalitis lethargica pandemic was preceded by the influenza pandemic starting in 1918, and viral experiments indicated that the influenza virus could be the common etiologic agent [525, 526]. In the 1960s (when specific diagnostic criteria for PD were not yet developed), there was debate over whether PD and postencephalitic parkinsonism belonged to the same disease category. Based on cases with the diagnosis "Parkinson's syndrome" with onset in 1920–1924 compared to cases with onset in 1955–1959, Poskanzer and Schwab [527] observed that mean age at onset of parkinsonian symptoms increased from about 32 years to about 59 years. Therefore, they hypothesized that most cases with "Parkinson's syndrome" were survivors of the encephalitis letargica pandemic and that the underlying etiology was a subclinical influenza infection resulting in onset of parkinsonian symptoms several decades later [527]. However, Duvoisin et al. [528] pointed out that mean age at onset for parkinsonism prior to the encephalitis letargica pandemic and after in the 1940s was similar. They argued, based on clinical evidence, that postencephalitic parkinsonism and true paralysis agitans, as described by James Parkinson, were different entities [528]. Subsequent studies failed to identify the influenza virus in brains of PD patients [529, 530].

Because influenza A virus may affect brain regions implicated in PD (including the substantia nigra) [531], it has been hypothesized to play a role in PD [532]. Parkinsonism, however, is also observed (either in the acute phase or as a long-term complication) in viral encephalitis due to viruses other than influenza [533]. Overall, however, there is no clear evidence for involvement of an infectious agent in PD. Case-control studies have analyzed antibody titres in serum or cerebrospinal fluid for a large number of viruses (including influenza), as well as Bordetella pertussis [146, 534–539]. Whilst most studies found similar antibody levels in cases and controls, one study observed higher antibody levels for herpes simplex [538], while another study found lower antibody levels for herpes simplex, rubella and measles [539]. Similarly, studies that examined self-reported history of influenza [132, 292, 344] or other viral infections [142, 411, 540] generally reported no association with PD. A case-control study nested within the Harvard Alumni cohort, USA [541] found reduced PD risk associated with measles infection (OR 0.53, 95% CI 0.31–0.93) and another case-control study [411] found increased PD risk associated with diphtheria (OR 2.3, 95% CI 1.2–4.7) and croup (OR 4.1, 95% CI 1.1–16.1).

Based on the observation that individuals born around the years of the influenza pandemic had an increased risk of PD, the authors of a British study hypothesized that PD may be caused by intrauterine influenza infection [542]. These results, however, were not confirmed in a later study [543].

It has been suggested that an intrauterine infection affected development of dopaminergic neurons resulting in lower reserves, which might be associated with increased vulnerability to PD in adulthood [544]. Season and place of birth can be used as proxy variables for some intrauterine or early life exposures. A Japanese study of parkinsonism patients reported excess births in winter and spring [545]. Mattock et al. [542] observed that PD patients were more commonly born between March and June, but Ebmeier et al. [543] found no season of birth effect. A US study investigated PD-related mortality by state of birth and found a relative increase in western versus eastern states [546]. Another US study using mortality data for the state in which PD cases lived at the time of death found a north to south gradient [547]. Thus, conclusive evidence regarding the possible relation between viral infections and PD is lacking.

Inflammation

The hypothesis that inflammation may be related to the pathogenesis of PD has been derived from postmortem studies showing the presence of activated microglia cells and increased levels of inflammatory cytokines in substantia nigra and striatum [548–551]. A few studies also reported altered levels of serum inflammatory markers in PD patients [552–554]. In rats, chronic infusion of bacterial endotoxin lipopolysaccharide (LPS) into substantia nigra resulted in activation of microglia followed by degeneration of dopaminergic neurons [555], suggesting that inflammation may precede neurodegeneration. In cell culture, the toxin MPTP also induced an inflammatory response [556]. However, based on postmortem data it is impossible to sort out whether the inflammatory response is a consequence or a cause of neurodegeneration. Microglial activation may be initiated by either environmental toxins or infectious agents, and neuronal injury may lead to neurodegeneration resulting in reactive activation of microglia in a self-perpetuating cycle [548]. Non-steroidal anti-inflammatory drugs (NSAIDs) protected against neuronal loss caused by MPTP in animals [551]. Based on this evidence, epidemiological studies have investigated the possible role of NSAIDs in PD.

The prospective Nurses Health Study and the Health Professionals Follow-up Study initially reported lower risk of PD associated with regular use of non-aspirin NSAIDs (pooled RR 0.55, 95% CI 0.32–0.96) [557]. For aspirin and acetaminophen, no associations were observed. There was no dose-response relationship, however, between non-aspirin NSAIDs and PD [557]. When the same authors followed up their finding in the Cancer Prevention Study II Nutrition cohort, with more detailed information on type of NSAIDs, they found lower PD risk associated with ibuprofen (P for trend 0.03), but not with other NSAIDs, aspirin or acetaminophen [558]. A meta-analysis of results

from all three cohorts gave a RR estimate of 0.74 (95% CI 0.58–0.93) for ever versus never use of non-aspirin NSAID [558]. In contrast, the Rotterdam prospective study reported no association between NSAIDs and PD [559].

Two population-based case-control studies [560, 561] and a family-based case-control study [448] found no association between NSAIDs or aspirin and PD. A hospital-based study, in which most controls were spouses or relatives of PD cases, reported lower PD risk associated with use of over the counter NSAIDs (OR 0.81, 95% CI 0.67–0.98 for ever vs. never use), with no dose-response relationship [416]. A large case-control study (1,258 cases) nested within the General Practice Research Database in the UK [562] used register-based prescriptions as source of information regarding NSAID use. Although no information about over the counter drug use was available, this design controls for recall bias, as prescription information was recorded before onset of PD. Overall, there was no significant relation between non-aspirin NSAIDs and PD (OR 0.93, 95% CI 0.80–1.08 for ever vs. never use), but in men, use of non-aspirin NSAIDs was associated with lower PD risk (OR 0.79, 95% CI 0.65–0.96). In contrast to other studies, this study reported increased PD risk associated with aspirin and acetaminophen (OR 1.29, 95% CI 1.05–1.28 for ever vs. never aspirin use; OR 1.16, 95% CI 1.00–1.35 for ever vs. never acetaminophen use). However, there were no dose-response relationships [562].

In a meta-analysis of two cohort and five case-control studies the pooled RR for non-aspirin NSAID use was 0.85 (95% CI 0.77–0.94), with a similar association for ibuprofen (pooled RR 0.75, 95% CI 0.64–0.89), but no association for aspirin [563]. Risk reduction was greater for regular use of non-aspirin NSAIDs and long duration of use [563], indicating a possible dose-response relationship.

In sum, although evidence is limited, there is a suggestive protective effect of NSAIDs in PD.

Mental illness

Examining the associations between different diseases may provide clues to etiology, as diseases may share genetic or environmental risk factors. A shared etiologic component in PD and psychiatric diseases has been hypothesized because psychiatric symptoms and diseases, primarily depression and anxiety disorders, are common in PD patients. Three hospital-based case-control studies reported increased PD risk related to previous depression with ORs between 1.54 and 3.01 [131, 143, 291]. Another hospital-based study [141] and a population-based study [409] found no association. Obvious limitations of these studies are potential recall bias and reverse causation.

A case-control study nested within a general practitioner database [564] also reported increased risk related to history of depression (OR 2.4, 95% CI 2.1–2.7). Average duration between first depressive episode and diagnosis of PD was 10 years, but with large variation. No analyses focusing on time between onset of depression and PD were performed, but the authors noted that depression seemed to be more common shortly before PD diagnosis [564], questioning whether depression was an early manifestation of PD. Following individuals with and without depression for subsequent PD diagnosis using the same database also showed increased PD risk (HR 3.13, 95% CI 1.95–5.01, for depressed vs. non-depressed individuals) [565]. A population-based case-control study including 196 incident PD cases within the Rochester Epidemiology project, USA, reported increased PD risk related to previous depression overall (OR 1.9, 95% CI 1.1–3.2), but when depressive episodes occurring within 5 years prior to PD onset were excluded, the association was not significant [566]. This study also reported increased PD risk related to previous anxiety disorder (OR 2.2, 95% CI 1.4–3.4) that persisted when restricting to diagnoses that occurred 5, 10, and 20 years before PD onset [566].

A Danish prospective study based on national hospital discharge diagnoses [567] reported increased PD risk among patients with affective disorder (depression or mania) (HR 2.20, 95% CI 1.70–2.84), as well as among patients with depression alone (HR 2.24, 95% CI 1.72–2.93) compared to patients with osteoarthritis. Using patients with diabetes as the control group, even higher risk estimates were obtained [567]. A Swedish study using similar methodology [568] reported increased PD risk related to previous psychiatric disease overall (standardized incidence ratio, SIR, 3.11, 95% CI 2.97–3.25), as well as related to subcategories of psychiatric disease such as mood disorders (SIR 3.20, 95% CI 2.99–3.41), neurotic or personality disorders (SIR 2.99, 95% CI 2.72–3.27) and schizophrenic disorders (SIR 3.07, 95% CI 2.81–3.35). PD risk related to psychiatric disease increased with earlier age at PD diagnosis and was higher in women than in men [568]. None of these studies performed analyses by time between onset of depression and PD. There is no epidemiologic evidence that drugs used to treat psychiatric diseases are associated with PD.

A few studies evaluated familial aggregation of PD and psychiatric disorders. An early study [569] reported that among relatives of 7 PD cases, 12% had a history of depression; all of them were women. No control group was included [569]. The population-based Rotterdam study found no association between PD in first-degree relatives and depression [570]. The Rochester Epidemiology project, USA, in which relatives were evaluated individually, reported increased risk of depressive disorders (HR 1.45, 95% CI 1.11–1.89) as well as anxiety disorders (HR 1.55, 95% CI 1.05–2.28) in first-degree relatives of PD cases compared to first-degree relatives of controls [571].

In sum, epidemiologic evidence indicates an association between depression and PD that may be explained by shared etiological factors; alternatively, depression may be an early manifestation of PD. Anxiety disorders also seem to be related to PD, but such studies are few.

Dementia

A possible etiologic link between PD and dementia has been suggested based on overlapping clinical and neuro-pathological features as well as co-occurrence in families. Epidemiology studies have focused on familial aggregation. A population-based case-control study reported higher frequency of first-degree relatives with PD among Alzheimer's patients than among controls, corresponding to a RR of 2.9 [572]. Re-analysis of these data pooled with data from another study [573] gave similar results (RR 2.4, 95% CI 1.0–5.8) [574]. Other studies, however, reported no increased risk of PD in relatives of patients with Alzheimer's disease [575–578], although two of these were small, including only 70 [576] and 98 [577] Alzheimer cases.

A hospital-based study including both PD and Alzheimer cases, that collected information about relatives through spouses (who also were used as controls), reported no significant associations between family history of PD and Alzheimer's disease nor family history of Alzheimer's disease and PD [130]. Similarly, a population-based study reported no association overall between family history of Alzheimer's disease and PD with and without dementia; there was, however, increased risk of Alzheimer's disease in siblings (RR 3.2, 95% CI 1.1–9.4), though not in parents, of PD cases with dementia versus controls [579]. Another hospital-based study found no increased risk of Alzheimer's disease in relatives of PD cases without dementia compared to controls [580]. Yet another hospital-based study reported higher frequency of family history of PD in PD cases with family history of Alzheimer's disease compared to PD cases without family history of Alzheimer's disease, corresponding to an OR of 1.7 (95% CI 1.1–2.6) [581]. The population-based Rochester study, in which relatives were evaluated individually, reported increased risk of cognitive impairment or dementia in relatives of PD cases compared to controls (HR 1.37, 95% CI 1.03–1.81); the association was stronger among early onset PD cases [582]. Another population-based study reported increased risk of Alzheimer's disease in relatives of young-onset PD cases versus controls (HR 2.86, 95% CI 1.44–5.71), but no association overall [583].

Thus, epidemiologic evidence for a shared etiologic component (genetic or environmental) in PD and dementia at the population level is conflicting. Some studies indicate an association between the diseases, but other studies could not confirm this. Beside the methodological difficulties of familial aggregation studies discussed in a previous section, comparison between studies is hampered by differences in diagnostic criteria.

Essential tremor

Similar to mental diseases and dementia, an association between PD and essential tremor has been suggested based on common clinical features and families in which both PD and essential tremor occur. Although the clinical presentation of tremor differs in PD (primarily resting tremor) and essential tremor (primarily action or postural tremor), onset of PD may be preceded by postural tremor in the hands [584]. A few case series studies of essential tremor patients reported higher than expected prevalence of PD [585, 586] but others did not [587, 588]. One early familial aggregation study reported that the observed frequency of essential tremor among relatives of 32 PD cases was higher than expected [127], but another early study reported no increased frequency of essential tremor among relatives of 52 PD cases [129]. Similarly, a larger (100 PD cases) hospital-based study found no increased frequency of family history of essential tremor in PD cases versus controls [589]. Further, frequency of family history of PD was similar in essential tremor cases and controls [589]. A larger (487 PD cases) hospital-based study reported increased risk of action tremor in relatives of patients with tremor-dominant PD versus relatives of controls (RR 2.14, 95% CI 1.53–2.98) but not in patients with PD dominated by postural instability and gait difficulties (RR 1.81, 95% CI 0.66–5.02) [590]. The authors raised the question whether action tremor in the relatives of PD patients was a manifestation of PD rather than a distinct condition [590].

The Rochester study [591] evaluated relatives individually instead of obtaining all information through the proband. In this population-based sample, risk of essential tremor was increased in relatives of PD patients with young (before 66 years) onset versus relatives of controls (HR 2.24, 95% CI 1.26–3.98), but not in relatives of PD patients with onset after 66 years. In a hospital-based sample, relative risk of essential tremor was higher in relatives of patients with tremor-dominant or mixed form of PD compared to patients with akinetic-rigid form of PD [591]. Another population-based study reported increased risk of essential tremor in male relatives of PD cases, but no increased risk overall [583].

Only one study [592] assessed the risk of PD among patients with essential tremor in a longitudinal design. This population-based study reported increased risk of PD (RR 4.27, 95% CI 1.72–10.61) as well as increased risk of parkinsonism (RR 3.47, 95% CI 1.82–6.59) in patients with essential tremor compared to controls [592].

As discussed above, the familial aggregation of PD and essential tremor may be explained by tremor occurring as a manifestation of PD. Although evidence is scarce, an etiologic link between the diseases may also exist.

Cancer

Based on death records, an early study [593] reported a higher than expected frequency of cancer among persons with parkinsonism, whilst another [4] found lower frequency of cancer in death records of parkinsonism patients. Using hospital-based PD cases and controls and cancer diagnoses from death records, two subsequent studies also reported contradictory findings; one [594] reported higher whereas another [595] reported lower frequency of cancer in PD cases. The use of death records as the source of cancer information resulted in a restriction to fatal cancers that mostly occurred after the onset of PD (although onset of cancer in relation to PD was unknown). Comparison of observed versus expected cancer incidence is problematic if cases are not representative of the population from which the expected frequencies were derived. Confounding by smoking is another concern; a lower incidence of smoking-related cancers may be attributed to a lower prevalence of smoking among PD patients.

Two studies from the 1980s used medical records to obtain cancer diagnoses and provided results separately for cancer occurring before and after onset of PD [409, 596]. The first study found a lower than expected prevalence of cancer both before and after PD onset (RR 0.43, $P < 0.00005$) [596]. PD cases who smoked had a slightly higher observed versus expected cancer frequency than non-smoking PD cases, but the inverse association with PD remained (RR 0.64, $P = 0.16$), suggesting that reduced smoking did not completely explain the lower cancer risk among PD cases. The other smaller study [409] (118 cases) found no differences in cancer prevalence between PD cases and controls.

Another study [111] used death certificates to obtain both cancer and PD diagnoses on 8,629 cases and more than 200,000 controls. Overall, this study reported lower cancer risk among PD cases than controls (proportionate mortality ratio, PMR, 0.29, 95% CI 0.20–0.37). When cancers were separated into groups according to strong, moderate, and weak association with smoking, the association remained (PMR 0.09, 0.16, and 0.41, respectively) [111], confirming that smoking as a shared risk factor (although with opposite effects on PD and cancer risk) did not fully explain the inverse association between PD and cancer. However, use of death certificates as the source for both cancer and PD diagnoses may result in a bias; a PD diagnosis may have been omitted more often from a death certificate when cancer was listed as the cause of death.

Lower cancer risk in PD cases was also reported in a Danish study based on hospital discharge PD diagnoses and register-based cancer cases (RR for cancer overall 0.9, 95% CI 0.8–1.0) [597].The inverse association was even stronger for smoking-related cancers (RR 0.5, 95% CI 0.4–0.6). Similar results were observed in a case-control study with cancer information from death records (RR for overall cancer 0.7, 95% CI 0.3–1.5; RR for smoking-related cancer 0.4, 95% CI 0.1–0.5) [105] and another study based on 10,322 patients treated with anti-parkinson medications without validated PD diagnoses (SMR 0.56, 95% CI 0.51–0.61 for overall cancer [598]; SMR 0.51, 95% CI 0.42–0.60 for smoking-related cancer) [599]. Two substantially smaller studies [540, 600] (228 and 352 cases, respectively) based on hospital-ascertained PD cases and register-based as well as self-reported cancer diagnoses found no associations between PD and cancer. Another case-control study [601] used self-reported cancer diagnoses and adjusted for smoking in the analyses. This study reported lower risk of cancer occurring before PD onset (OR 0.5, 95% CI 0.3–1.0) that was actually strengthened after adjusting for smoking (OR 0.4, 95% CI 0.2–0.7) [601].

More recent studies reported cancer occurring before and after PD onset separately (cancer before PD analyzed with a case-control design, cancer after PD analyzed with a cohort design). A population-based case-control study including 196 incident PD cases within the Rochester Epidemiology project, USA, reported no significant association for cancer preceding PD onset (OR 0.79, 95% CI 0.49–1.27 for overall cancer) [602], but higher risk of cancer after onset of PD (RR 1.64, 95% CI 1.15–2.35 for overall cancer) [603]. This association largely was due to an increased risk of non-melanoma skin cancer, suggesting that more intensive surveillance may have played a role [603]. A Danish study based on national hospital discharge and cancer registers (including more than 14,000 PD cases) reported lower risk of cancer after onset of PD (SIR 0.9, 95% CI 0.8–0.9 for overall cancer; SIR 0.6, 95% CI 0.5–0.6 for smoking-related cancer), an association that was largely restricted to men [604]. For cancer occurring before PD onset, there was no association overall (OR 1.04, 95% CI 0.96–1.12) but for smoking-related cancers, there was an inverse association (OR 0.68, 95% CI 0.58–0.81) [605].

A study based on the General Practice Research Database in the UK reported lower risk of overall cancer after onset of PD (IRR 0.77, 95% CI 0.64–0.92); the inverse association was stronger for smoking-related cancers [606]. The prospective Physicians Health Study, USA [607] identified 487 incident PD cases by a combination of self-report and medical records and obtained additional cancer diagnoses from pathology reports. This study found no significant association before (OR 0.83, 95% CI 0.57–1.21) [607] nor after onset of PD (RR 0.85, 95% CI 0.59–1.22)

[608]. However, PD cases who smoked had a lower risk of smoking-related cancer, whereas non-smoking PD cases had an increased risk [607, 608], an observation made also in the Rochester study [602]. Driver et al. suggested that this result may be explained, in part, by gene-environment interaction [607, 608].

Although overall cancer risk among PD cases was lower in several studies, a relatively consistent finding was increased risk of melanoma [596, 597, 604, 605, 608]. In some studies, higher frequency of non-melanoma skin cancer [603, 604] and breast cancer [600, 604, 605] was also reported. Based on experimental evidence, a potential link between PD and melanin was suggested in the 1980s [609]. The Nurses Health Study and the Health Professionals Follow-up Study reported increased PD risk with lighter hair color [610]. Since the 1970s, a number of case-reports suggested that l-dopa therapy may increase risk of melanoma, but critical reviews of these studies concluded that there is no solid evidence for a causal role of l-dopa in increasing risk or progression of melanoma [611, 612]. It has been suggested that an increased melanoma risk in PD cases could arise due to shared genetic factors or by confounding by social class. However, the same authors acknowledged that, as the association between PD and melanoma was observed in the Physicians Health Study [608], a cohort homogeneous with regard to social class, confounding by social class is unlikely [613]. Further, family history of melanoma was associated with increased risk of PD in the Nurses Health Study and the Health Professionals Follow-up Study (pooled RR 1.85, 95% CI 1.22–2.79) [614], cohorts that are also homogeneous with regard to social class. Potentially related to both PD and melanoma are genes regulating the synthesis of l-dopa, which is involved both in the synthesis of dopamine in nigral neurons and melanin in melanocytes [615].

A meta-analysis of 29 studies reported a pooled RR of cancer in PD cases versus controls of 0.73 (95% CI 0.63–0.83) [616]. When skin cancers were excluded, there was a somewhat stronger association (RR 0.69, 95% CI 0.62–0.78). Further, the association was stronger for smoking-related cancers than non-smoking-related cancers. The results did not vary substantially by study design, study quality, or length of follow-up [616].

In sum, several studies of cancer and PD had important methodological limitations, such as potential information bias, lack of appropriate control group, confounding, poor cancer onset information, and sample size too small to examine specific cancer types. Further, the variation in methodology makes comparisons among studies difficult. Still, considering more recent studies, in particular cohort studies, evidence for a lower cancer risk among PD patients is fairly consistent. Underlying mechanisms are unclear, although several authors suggested shared genetic factors,

pointing out that several of the genes involved in familial PD also are implicated in cancer [617–619].

Head trauma

In boxers, brain damage due to repeated head trauma leading to progressive cognitive dysfunction, psychiatric, as well as parkinsonian symptoms, has been recognized since the 1960s [620]. This syndrome is distinct from PD but a role of head trauma in PD still has been investigated chiefly in hospital-based case-control studies, in which recall bias is an obvious concern. Further, head injury was most commonly assessed by self-report. Only a minority of studies adjusted for possible confounders such as smoking, and different definitions of head trauma make comparisons between studies difficult. Of 22 case-control studies, 9 reported increased risk of PD following head trauma [131, 132, 300, 310, 312, 355, 621–623] with ORs ranging between 1.4 and 11.7. The remaining 13 studies found no association [140–142, 145, 147, 154, 156, 296, 309, 315, 358, 411, 420]. One of the "positive" studies [623] was population-based, included incident PD cases, and obtained information on head injuries from medical records. Although estimates were unstable, this study reported no risk increase of PD following mild head trauma, but an increased risk for more severe trauma (OR 11.0, 95% CI 1.4–85.2) and for trauma requiring hospitalization (OR 8.0, 95% CI 1.0–64.0) [623]. The delay between trauma and onset of PD symptoms was on average 21 years [623].

A co-twin controlled study based on 93 male twin pairs discordant for PD from the NAS-NRC World War II Veteran Twins cohort [624] reported increased risk of PD associated with head trauma (OR 3.8, 95% CI 1.3–11 for any head trauma). Although estimates were unstable, there was a trend of increasing risk with number of head injuries (OR 4.3, 95% CI 0.46–41 for two head traumas, P for trend 0.02). Head trauma was relatively common in this population (probably due to male gender and veteran status). When restricting the analyses to head trauma that occurred 10 years or more before the diagnosis of PD, the association remained [624]. A study of sibling pairs in which both had a PD diagnosis reported that the sibling with a previous head trauma had earlier age at onset ($P = 0.03$) than the sibling without head trauma [625].

Few prospective studies have examined the role of head trauma in PD. A small population-based prospective study observed no association [626]. Two studies used Danish national hospital discharge data but took different approaches [627, 628]. One of them [628] followed a national cohort of individuals above 20 years in 1981, identified head trauma that caused hospitalization between 1981 and 1993, and hospital discharge PD diagnoses after 1995 (8,769 cases). No association was observed between head

trauma and PD [628]. The other Danish study [627] included 13,695 PD cases with a hospital discharge diagnosis after 1986 and 68,445 population-based controls matched by age and sex. Head trauma that required hospitalization between 1977 and date of first hospitalization due to PD were considered in the analyses. This study reported increased risk of PD following head trauma (OR 1.5, 95% CI 1.4–1.7), but the increase was almost entirely due to trauma that occurred during the 3 months before first hospital contact due to PD (OR 8.0, 95% CI 5.6–11.6). Head trauma that occurred between 4 months and 9 years before first hospital contact due to PD only slightly increased risk of PD (OR 1.5, 95% CI 1.3–1.7), and for traumas that occurred 10 years or more before, there was no association (OR 1.1, 95% CI 0.9–1.3) [627]. The authors interpreted these results as being due to reverse causation [627].

In sum, although some retrospective studies reported an association between head trauma and PD, these studies are prone to recall bias. Because the association was not confirmed in prospective studies, there is no compelling evidence for a role of head trauma in PD.

Diabetes

The role of diabetes in PD has been investigated primarily because of its role in other neurodegenerative diseases, such as Alzheimer's disease. An early case-control study [127] reported higher prevalence of self- reported diabetes in PD cases versus controls, but no measure of association or P values were provided. Three other case-control studies based on self-reported diabetes [142, 303, 358] and one small (58 cases) prospective study [432] observed no association between diabetes and PD. A study based on a cohort of elderly and diagnoses from insurance claims reported increased risk of parkinsonism associated with diabetes (OR 1.5, 95% CI 1.2–1.9 in men, OR 1.7, 95% CI 1.4–2.0 in women) [629]. Although this study was large (791 parkinsonism cases), diagnoses were not validated. A hospital-based case-control study [540] with self-reported information on diabetes validated by medical records reported lower risk of PD associated with diabetes in men (OR 0.52, 95% CI 0.28–0.97) but a weaker association in women (OR 0.80, 95% CI 0.35–1.83); the inverse association was stronger in non-smoking men (OR 0.09, 95% CI 0.02–0.44, P for interaction 0.01) [540]. Two other hospital-based case-control studies [137, 630] reported lower risk of PD associated with self-reported diabetes (OR 0.35, 95% CI 0.15–0.75 [137]; OR 0.4, 95% CI 0.2–0.8 [630]). A study with diabetes information solely from medical records observed no association when smoking and other cardiovascular risk factors were included in the statistical model [631].

Several recent prospective studies examined the relation between diabetes and PD. Based on residents in five geographic areas in Finland, one large study reported higher risk of PD associated with diabetes assessed through a combination of self-report, hospital discharge information and prescription data (HR 1.85, 95% CI 1.22–2.79) [632]. Similarly, the Physicians Health Study observed increased risk of PD associated with self-reported diabetes (RR 1.34, 95% CI 1.01–1.77) [633].The association between diabetes and PD was modified by BMI (P for interaction 0.04); PD risk was decreased among individuals with both diabetes and high BMI. PD risk was highest for short duration of diabetes and lack of diabetic complications, findings indicating that diabetes may not be a genuine risk factor for PD. This study also observed that diabetes and PD occurred close in time, questioning whether surveillance bias could play a role [633].

The prospective Nurses Health Study and Health Professionals Follow-up Study found no associations between self-reported diabetes and subsequent diagnosis of PD [634]. Within the General Practice Research Database in the UK, 3,637 PD cases and an equal number of subjects without PD were followed for incident diabetes [635]. A lower incidence of diabetes was observed among PD cases than among non-PD subjects (RR 0.55, 95% CI 0.38–0.81). To a large extent the association was driven by l-dopa use. When a retrospective case-control design was applied to study the association between history of diabetes and PD, no association was observed [635].

In sum, one study with insurance record PD diagnoses without validation [629] and one small case-control study [127] reported increased PD risk among patients with diabetes, but this association was not confirmed in five other well designed case-control studies [142, 358, 540, 631, 635]. Two large prospective studies reported increased PD risk associated with diabetes [632, 633], one prospective study reported no association [634], whereas another reported lower risk of diabetes among PD cases [635]. Surveillance bias may cause a spurious positive association, an issue that may be of particular importance for a disease such as diabetes that can remain undetected during a long period of time. Thus, evidence regarding a possible relationship between diabetes and PD is inconclusive.

Vascular diseases

Similar to diabetes, vascular diseases have been investigated in PD as these play a role in Alzheimer's disease. An early case-control study [127] reported higher frequency of hypertension among PD cases compared to controls, although no P value was provided. Six other case-control studies [132, 142, 303, 358, 409, 466] found no association between self-reported hypertension and PD, one study

found lower risk of PD associated with hypertension in univariate analyses, but when adjusting for smoking and other variables, the association did not persist [631]. Another case-control study reported increased PD risk associated with hypertension in women (OR 1.62, 95% CI 1.00–2.62) but not in men [540].

Three case-control studies [137, 141, 434], one with prospective data nested within the Leisure World Cohort, California [434], reported lower risk of PD in relation to hypertension (OR 0.3, 95% CI 0.2–0.4 [141]; OR 0.48, 95% CI 0.26–0.88 [137]; OR 0.71, 95% CI 0.56–0.89 [434]). The prospective Honolulu-Asia Aging study found no association between hypertension at baseline and PD based on 58 PD cases [432]. Similarly, no association between hypertension and PD was observed in the larger (in total 530 cases) prospective Nurses Health Study and the Health Professionals Follow-up Study [634]. These authors observed a decline in systolic blood pressure following diagnosis of PD [634].

Few studies have investigated heart disease or stroke in relation to PD. One case-control study reported no association for stroke, but increased PD risk associated with heart disease, although the estimate was unstable (OR 5.5, 95% CI 1.4–22.1) [358]. Another study reported decreased risk associated with ischaemic heart disease (OR 0.36, 95% CI 0.19–0.69) [137]. Yet another study reported lower risk of PD associated with previous stroke (OR 0.2, 95% CI 0.1–0.5) [141]. These studies were hospital-based, questioning whether the controls were representative of the population that gave rise to the PD cases. Three other case-control studies found no relationships between heart disease or stroke and PD [540], between coronary artery disease and PD [142] or between stroke and PD [466]. A large (3,637 cases) population-based study nested within the General Practice Research Database in the UK reported increased risk of PD associated with history of stroke or transient ischaemic attack (TIA) (OR 1.65, 95% CI 1.41–1.94) as well as increased risk of stroke (IRR 1.46, 95% CI 1.03–2.07) and TIA (IRR 1.86, 95% CI 1.40–2.47) after onset of PD [636].

Serum cholesterol, implicated in Alzheimer's disease, is involved in the same molecular pathway as coenzyme Q10, which has antioxidant properties [637], suggesting a possible role in PD. Among the few studies that examined this relationship, one study found no association between self-reported hyperlipidemia and PD [142]. Another found lower risk of PD associated with total serum cholesterol and total serum lipids in univariate but not in multivariate analyses [631]. However, for high serum triglycerides, the multivariate analyses showed lower PD risk (OR 0.49, 95% CI 0.27–0.89) [631]. A hospital-based case-control study, in which spouses of patients from a movement disorder clinic were used as controls, reported increased PD risk

with lower serum low-density lipoprotein (LDL) cholesterol (OR for lowest category vs. highest 2.6, 95% CI 1.1–6.0), but no significant association for total and high-density lipoprotein (HDL) cholesterol [638].

A small (58 cases) prospective study based on the Honolulu-Asia Aging study observed initially no relationship between serum cholesterol at baseline and PD [432] whilst extended follow-up revealed lower PD risk with increasing levels of serum LDL cholesterol at baseline (RR 0.6, 95% CI 0.4–1.1 for highest quintile vs. lowest, *P* for trend 0.04) [639]. The Rotterdam study also found that high serum total cholesterol was associated with lower PD risk; the association was, however, observed only in women (RR per mmol increase in cholesterol 0.59, 95% CI 0.45–0.78 in women; 1.01, 95% CI 0.78–1.30 in men) [640]. No association was observed for HDL cholesterol [640]. The larger Nurses Health Study and Health Professionals Follow-up Study (in total 530 incident PD cases) found no association between self-reported high cholesterol and PD [634]. However, similar to the Rotterdam study [640], a trend of decreasing PD risk with increasing levels of self-reported total serum cholesterol was observed that was significant in women (*P* for trend 0.04) but not in men (*P* for trend 0.19) [634]. In contrast, a Finnish prospective study reported increased PD risk associated with high serum levels of total cholesterol at baseline (RR 1.86, 95% CI 1.31–2.63 for highest vs. lowest category, *P* for trend 0.02) [641].

Statins, the most commonly used therapy for hyperlipidemia, have been hypothesized to play a role in neurodegenerative diseases because they protect against oxygen radical damage and inhibit inflammatory response [642]. A study nested within the General Practice Research Database in the UK reported no association between statin use and PD [643].

In sum, there is no compelling epidemiologic evidence that hypertension, heart disease, or stroke plays a role in the etiology of PD. A few studies found a modest protective effect of high serum cholesterol in PD, especially in women, but the results are not consistent.

Estrogen

A protective role of estrogen in PD has been hypothesized mainly based on the lower incidence and prevalence of PD in women than in men, but also on experimental evidence that estrogen has neuroprotective and antioxidant effects on dopaminergic neurons [644]. Additionally, postmenopausal estrogen treatment has been reported to retard PD progression [645, 646]. A small case-control study reported increased risk of PD associated with hysterectomy (OR 3.36, 95% CI 1.05–10.77), but no associations for age at menopause or use of postmenopausal estrogens [647]. Increased PD risk was also reported in another study in

relation to duration of reproductive life (age at menopause minus age at menarche) less than 36 years (OR 2.07, 95% CI 1.00–4.30) and total pregnancy time more than 30 months (OR 2.19, 95% CI 1.22–3.91) [648]. Similar to the first indicated study [647], no associations were observed for age at menopause, postmenopausal estrogen use, and age at menarche [648]. In contrast, however, this study reported lower PD risk associated with surgical menopause (OR 0.30, 95% CI 0.13–0.77) [648]. A hospital-based study using spouses of male PD cases or friends of cases as controls also observed no association between postmenopausal estrogen use and PD [649]. Further, no relation between parity and PD was observed in a case-control study nested within the Leisure World cohort in California [434].

The prospective Nurses Health Study [650] and Cancer Prevention Study II Nutrition cohort [479] assessed estrogen-related factors using self-reported baseline information. In the Nurses Health Study, 154 incident PD cases were detected, and in the Cancer Prevention Study II Nutrition cohort, 340 deaths due to PD were identified. Neither study observed a relationship between age at menopause, type of menopause (surgical vs. natural), or parity and PD [479, 650]. Oral contraceptive use for more than 5 years was related to increased PD risk in the Nurses Health Study (RR 1.63, 95% CI 1.03–2.58) [650], but not in the Cancer Prevention Study II Nutrition cohort [479]. In contrast, postmenopausal estrogen use was related to increased PD mortality in the Cancer Prevention Study II Nutrition cohort (RR 1.33, 95% CI 1.07–1.67) [479], but not in the Nurses Health Study [650]. In the latter, an interaction was observed between postmenopausal estrogen use and coffee in relation to PD; among women with low coffee consumption, PD risk in relation to estrogen use was lower (OR 0.66, 95% CI 0.35–1.24) and among women with high coffee consumption, PD risk in relation to estrogen was higher (OR 1.55, 95% CI 0.76–3.18, P for interaction 0.02). Inhibition of caffeine metabolism by hormonal factors was suggested as a mechanism for this interaction [650]. In an extended follow-up of the Nurses Health Study, there was no relation with PD for postmenopausal estrogen use, parity, age at menopause, oral contraceptive use, number of reproductive years or type of menopause [651].

A prospective population-based study reported increased risk of parkinsonism associated with previous oophorectomy (HR 1.75, 95% CI 1.04–2.95), but the association was not significant for PD alone [652]. The prospective Rotterdam study reported higher PD risk with increasing number of children in men but not in women, an association that did not remain significant after adjusting for confounders [653].

In sum, few epidemiological studies investigated reproductive factors and risk of PD. Except from a suggestion that postmenopausal estrogen treatment modifies the association between coffee and PD, there is no clear evidence that reproductive factors play an important role in PD etiology.

Uric acid and gout

A protective role of uric acid, a powerful antioxidant and oxygen radical scavenger, in aging was hypothesized in the 1980s [654]. A postmortem study of 4 PD cases showed decreased levels of uric acid in substantia nigra compared to controls [655]. Another study of 11 PD cases found no differences in cerebrospinal fluid levels of uric acid between cases and controls [656]. Similarly, another small (43 PD cases) study [657] observed no differences in serum uric acid levels between PD cases, Alzheimer cases, and controls. However, a recent study found lower levels of serum uric acid in PD cases than controls (P value 0.03) [658].

Four prospective studies have assessed the relationship between serum uric acid levels and PD .In the Honolulu-Asia Aging study of men, higher serum uric acid at baseline was associated with lower PD risk (RR 0.6, 95% CI 0.4–1.0 for serum uric acid above the median vs. below the median) [659]. The inverse association was stronger in non-smokers than smokers [659].The Rotterdam study also found lower PD risk with increasing baseline serum uric acid (P for trend 0.04), but no interaction by smoking status or gender [660]. Similarly, a case-control study nested within the Health Professionals Follow-up Study of men reported an inverse association between baseline serum uric acid and PD (RR 0.43, 95% CI 0.18–1.02 for highest vs. lowest quartile of serum uric acid, P for trend 0.017) [661]. The association was stronger when cases with serum uric acid measurement within 4 years prior to PD diagnosis were excluded (RR 0.17, 95% CI 0.04–0.69 for highest vs. lowest quartile of serum uric acid). This study observed no interaction between serum uric acid levels and smoking [661]. A meta-analysis of these three prospective studies yielded a RR of 0.80 (95% CI 0.71–0.90) per 1.32 mg/dl increase in serum uric acid concentration (corresponding to 1 standard deviation in the Health Professionals Follow-up Study) [661]. Another prospective study based on the Atherosclerosis Risk in Communities Cohort, including men and women, and Black Americans as well as Caucasians, also reported an inverse association between baseline serum uric acid and PD (OR 0.4, 95% CI 0.2–0.8 for highest vs. lowest quartile) [662].

Two studies investigated gout, as a marker for high serum uric acid concentration, in relation to PD. A large case-control study was performed within the General Practice Research Database, UK [663]. Previous gout was associated with lower risk of PD (OR 0.69, 95% CI 0.48–0.99), with the strongest associations among men, non-smokers and individuals above 60 years [663]. A prospective study based on

health insurance records in British Columbia, USA, also reported lower PD risk among individuals with gout (RR 0.70, 95% CI 0.59–0.83) [664]. Thus, these results are in line with the findings on serum uric acid and PD.

Although studies of the relationship between uric acid or gout and PD are few and based on limited number of PD cases, the prospective design and relatively consistent results indicate a possible protective effect. Higher serum uric acid concentration has been linked also to slower clinical progression of PD [665, 666].

Comments and perspectives

PD is a common neurodegenerative disease, especially among the elderly. Estimates of incidence and prevalence vary considerably among studies, at least partly due to differences in case ascertainment, diagnostic criteria, demographics of underlying populations, and reporting, but are consistently higher in men than in women. PD is associated with about a two-fold increased relative mortality. Familial aggregation studies consistently show a familial component and a number of genes have been identified that cause familial as well as sporadic PD.

Increasing knowledge about the genetics of PD has resulted in valuable insights regarding PD pathogenesis. However, the known PD genes are still estimated to account for only a small proportion of all PD at the population level. Further, these genes explain only a small proportion of familial PD, indicating that more PD genes and loci remain to be identified. Genetic heterogeneity probably increases difficulties to find new genes. Strategies that may facilitate gene discovery in the future include large-scale studies, high-density genotyping, accounting for known mutations, and use of techniques to detect gene dosage effects and genomic rearrangements. Genetic findings may lead to development of new therapies; for example, therapies targeting α-Synuclein expression.

The degree of epidemiologic evidence for some lifestyle and environmental factors are summarized in Table 6, using the first three categories of the Institute of Medicine (IOM) classification of strength of evidence, also applied in a recent consensus statement regarding environmental risk factors in PD [667]. There is substantial evidence that smoking is protective and coffee could be protective against PD, but the physiologic mechanisms for these relations are poorly understood. Other lifestyle factors do not seem to be major determinants of PD risk, but there may be weak protective effects of alcohol and, perhaps, physical activity. Diet does not seem to play a major role in PD, although there is tentative evidence that dairy products or milk increases and dietary vitamin E lowers the risk of the disease. Many lifestyle and dietary factors, important

Table 6 Degree of epidemiologic evidence for associations between environmental and lifestyle exposures and PD

Exposure	Epidemiologic evidence	Direction of association
Pesticides	Limited	Positive
Metals	Inadequate	
Organic solvents	Inadequate	
Magnetic fields	Inadequate	
Smoking	Sufficient	Negative
Alcohol	Limited	Negative
Physical activity	Limited	Negative
Adiposity	Inadequate	
Coffee	Sufficient	Negative
Intake of dairy products	Limited	Positive
Intake of macronutrients	Inadequate	
Dietary intake of antioxidants	Limited	Negative
Dietary intake of minerals	Inadequate	

Degree of epidemiologic evidence was categorized according to the first three categories of the Institute of Medicine (IOM) classification, used in a consensus statement on environmental risk factors in PD [667]. The categories are described as follows: (1) Sufficient evidence of an association. In this category, a consistent association has been observed between an exposure and a health outcome in human studies, in which chance and bias, including confounding, could be ruled out with reasonable confidence. (2) Limited suggestive evidence of an association. In this category, evidence suggests an association, but chance, bias, and confounding could not be ruled out with confidence. (3) Inadequate or insufficient evidence to determine whether an association exists. In this category, evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding an association between an exposure and a health outcome

from a public health perspective, have been assessed mostly by retrospective studies, leaving room for possible recall bias. Thus, there is a need for more prospective studies in these areas. For example, the possible detrimental effect of dairy products and protective effect of dietary vitamin E need further investigation.

Despite a large number of studies on occupational exposures, causal relationships have not been established. Evidence is limited on the role of metals, chemicals and magnetic fields, but there is suggestive evidence for pesticides increasing PD risk. Although many studies were negative, an association seems to be stronger and more consistent for pesticides in general and particularly for insecticides, than for any specific compound. Methodological limitations, such as misclassification of exposure, low frequency and intensity of exposure, inadequate sample size in many studies and retrospective designs, have been major obstacles. Regarding pesticides, the prevailing ambiguities, notwithstanding a large number of studies, are indeed of concern. Progress is unlikely unless larger studies are designed with more precise quantifications of exposure, and proper adjustments for confounding. Retrospective cohort

studies represent a realistic study design for this purpose; prospective studies would be unpractical due to the long latency time between exposure and disease onset.

Although both genetic and environmental risk factors in PD have been documented, there is very limited information on gene-environment interactions. Future studies may be improved by collecting information on both environmental exposures and genetic polymorphisms in relevant genes in samples sufficiently large to enable detection of interactions. Genes of interest include, for example, those involved in the metabolism of toxins, such as the CYP genes.

As exemplified by RBD, there is growing evidence for a long pre-clinical period before the motor manifestations in PD. History of mental illness is associated with increased PD risk; however, similar to essential tremor, studies cannot completely rule out that psychiatric symptoms or tremor are early manifestations of PD. Epidemiologic evidence for a shared etiological component between PD and dementia is not consistent. Despite several methodological concerns, there is evidence that PD patients have a lower cancer risk. The lower smoking prevalence among PD patients than in the general population is an obvious contributor to this finding, whilst a lower diagnostic intensity among PD patients also may play a role. Findings regarding history of head trauma are inconsistent. For vascular diseases, diabetes, or hormonal factors and PD, epidemiologic evidence is limited and inconclusive. Finally, based on limited but high quality evidence, uric acid seems to be associated with lower PD risk. The association between PD and other diseases can offer clues to the study of pathogenic mechanisms. Shared genetic factors have been hypothesized, for example, some PD genes are also implicated in cancer, but environmental factors, over and beyond tobacco smoking, need also to be considered.

Based on the apparent protective effect of smoking, the therapeutic effect of nicotine has been tested in a few clinical trials, but no improvement of motor symptoms with transdermal nicotine treatment has been documented [668, 669]. Moreover, on the basis of the apparent protective effect of coffee in PD, adenosine receptor (A_{2A}) antagonists have also been tested and there is evidence that they improve parkinsonian symptoms in animal models [670] and clinical trials [671–674]. Lastly, the more recently indicated protective effect of uric acid, together with its ability to slow disease progression, has led to the initiation of a clinical trial of inosine, a precursor that increases uric acid levels. Such an intervention is obviously complicated by the trade-off between possible beneficial effects on PD and adverse effects in terms of risk of gout.

Etiologic studies of PD take place at the border of what can be accomplished through observational research. Reasons for this include the insidious onset and the long pre-clinical period, which makes it challenging to identify incident cases in a standardized fashion, thereby introducing problems such as selection bias, reverse causation, and others; the heterogeneity of phenotype without generally accepted criteria that allow classification into clinically distinct categories; and the fact that many of the potential chemical causes are extraordinarily difficult to ascertain and are often mutually confounded. Hence, our hopes to control PD through primary intervention in the foreseeable future are not high.

References

1. Marsden CD. Movement disorders. In: Weatherall DJ, Ledingham JGG, Warrell DA, editors. Oxford textbook of medicine, vol. 3. New York: Oxford University Press Inc.; 1996. p. 3998–4022.

2. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988;51:745–52.

3. McNaught KS, Olanow CW. Proteolytic stress: a unifying concept for the etiopathogenesis of Parkinson's disease. Ann Neurol. 2003;53:S73–84.

4. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967;17:427–42.

5. Marttila RJ, Rinne UK. Epidemiology of Parkinson's disease in Finland. Acta Neurol Scand. 1976;53:81–102.

6. Schoenberg BS, Anderson DW, Haerer AF. Prevalence of Parkinson's disease in the biracial population of Copiah County, Mississippi. Neurology. 1985;35:841–5.

7. Calne DB, Snow BJ, Lee C. Criteria for diagnosing Parkinson's disease. Ann Neurol. 1992;32(Suppl):S125–7.

8. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol. 1999;56:33–9.

9. Ward CD, Gibb WR. Research diagnostic criteria for Parkinson's disease. Adv Neurol. 1990;53:245–9.

10. Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism–a prospective study. Can J Neurol Sci. 1991;18:275–8.

11. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-

pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55:
181–4.

12. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology. 1992;42:1142–6.

13. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology. 2001;57:1497–9.

14. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain. 2002;125:861–70.

15. Litvan I, MacIntyre A, Goetz CG, Wenning GK, Jellinger K, Verny M, et al. Accuracy of the clinical diagnoses of Lewy body disease, Parkinson disease, and dementia with Lewy bodies: a clinicopathologic study. Arch Neurol. 1998;55:969–78.

16. 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.

17. de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, Baldereschi M, et al. Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54:S21–3.

18. de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, 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;62:10–5.

19. Claveria LE, Duarte J, Sevillano MD, Perez-Sempere A, Cabezas C, Rodriguez F, et al. Prevalence of Parkinson's disease in Cantalejo, Spain: a door-to-door survey. Mov Disord. 2002;17:242–9.

20. Morgante L, Rocca WA, Di Rosa AE, De Domenico P, Grigoletto F, Meneghini F, et al. Prevalence of Parkinson's disease and other types of parkinsonism: a door-to-door survey in three Sicilian municipalities. The Sicilian Neuro-Epidemiologic Study (SNES) Group. Neurology. 1992;42:1901–7.

21. Schoenberg BS, Osuntokun BO, Adeuja AO, Bademosi O, Nottidge V, Anderson DW, 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;38:645–6.

22. 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; 90:111–5.

23. Zhang ZX, Roman GC, Hong Z, Wu CB, Qu QM, Huang JB, et al. Parkinson's disease in China: prevalence in Beijing, Xian, and Shanghai. Lancet. 2005;365:595–7.

24. Bermejo F, Gabriel R, Vega S, Morales JM, Rocca WA, Anderson DW. Problems and issues with door-to-door, two-phase surveys: an illustration from central Spain. Neuroepidemiology. 2001;20:225–31.

25. 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.

26. Anderson DW, Rocca WA, de Rijk MC, Grigoletto F, Melcon MO, Breteler MM, et al. Case ascertainment uncertainties in prevalence surveys of Parkinson's disease. Mov Disord. 1998;13:626–32.

27. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Influence of strict, intermediate, and broad diagnostic criteria on the age- and sex-specific incidence of Parkinson's disease. Mov Disord. 2000;15:819–25.

28. Baldereschi M, Di Carlo A, Rocca WA, Vanni P, Maggi S, Perissinotto E, et al. Parkinson's disease and Parkinsonism in a longitudinal study: two-fold higher incidence in men. ILSA Working Group. Italian Longitudinal Study on Aging. Neurology. 2000;55:1358–63.

29. Benito-Leon J, Bermejo-Pareja F, Morales-Gonzalez JM, Porta-Etessam J, Trincado R, Vega S, et al. Incidence of Parkinson disease and parkinsonism in three elderly populations of central Spain. Neurology. 2004;62:734–41.

30. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. Neurology. 1999;52:1214–20.

31. Brewis M, Poskanzer DC, Rolland C, Miller H. Neurological disease in an English city. Acta Neurol Scand. 1966;42(Suppl 24): 1–89.

32. Chen RC, Chang SF, Su CL, Chen TH, Yen MF, Wu HM, et al. Prevalence, incidence, and mortality of PD: a door-to-door survey in Ilan county, Taiwan. Neurology. 2001;57:1679–86.

33. 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: 1240–4.

34. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology. 2009;72:432–8.

35. Fall PA, Axelson O, Fredriksson M, Hansson G, Lindvall B, Olsson JE, et al. Age-standardized incidence and prevalence of Parkinson's disease in a Swedish community. J Clin Epidemiol. 1996;49:637–41.

36. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain. 2004;127:550–60.

37. Granieri E, Carreras M, Casetta I, Govoni V, Tola MR, Paolino E, et al. Parkinson's disease in Ferrara, Italy, 1967 through 1987. Arch Neurol. 1991;48:854–7.

38. Leentjens AF, Van den Akker M, Metsemakers JF, Troost J. The incidence of Parkinson's disease in the Netherlands: results from a longitudinal general practice-based registration. Neuroepidemiology. 2003;22:311–2.

39. 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(Pt 4): 665–76.

40. Mayeux R, Marder K, Cote LJ, Denaro J, Hemenegildo N, Mejia H, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988–1993. Am J Epidemiol. 1995;142:820–7.

41. 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.

42. Morioka S, Sakata K, Yoshida S, Nakai E, Shiba M, Yoshimura N, et al. Incidence of Parkinson disease in Wakayama, Japan. J Epidemiol. 2002;12:403–7.

43. Tan LC, Venketasubramanian N, Jamora RD, Heng D. Incidence of Parkinson's disease in Singapore. Parkinsonism Relat Disord. 2007;13:40–3.

44. Taylor KS, Counsell CE, Harris CE, Gordon JC, Smith WC. Pilot study of the incidence and prognosis of degenerative Parkinsonian disorders in Aberdeen, United Kingdom: methods and preliminary results. Mov Disord. 2006;21:976–82.

45. Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, Bloch DA, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol. 2003;157:1015–22.

46. 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;104:960–4.

47. Linder J, Stenlund H, Forsgren L. Incidence of Parkinson's disease and parkinsonism in northern Sweden: a population-based study. Mov Disord. 2010;25:341–8.

48. Winter Y, Bezdolnyy Y, Katunina E, Avakjan G, Reese JP, Klotsche J, et al. Incidence of Parkinson's disease and atypical parkinsonism: Russian population-based study. Mov Disord. 2010;25:349–56.

49. Hristova D, Zachariev Z, Mateva N, Grozdev I. Incidence of Parkinson's disease in Bulgaria. Neuroepidemiology. 2010;34:76–82.

50. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. Mov Disord. 2003;18:19–31.

51. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology. 2007;68:326–37.

52. Taba P, Asser T. Incidence of Parkinson's disease in estonia. Neuroepidemiology. 2003;22:41–5.

53. Wermuth L, Bech S, Petersen MS, Joensen P, Weihe P, Grandjean P. Prevalence and incidence of Parkinson's disease in The Faroe Islands. Acta Neurol Scand. 2008;118:126–31.

54. Elbaz A, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Risk tables for parkinsonism and Parkinson's disease. J Clin Epidemiol. 2002;55:25–31.

55. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry. 2004;75:637–9.

56. Taylor KS, Cook JA, Counsell CE. Heterogeneity in male to female risk for Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007;78:905–6.

57. Barbosa MT, Caramelli P, Maia DP, Cunningham MC, Guerra HL, Lima-Costa MF, et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambui study). Mov Disord. 2006;21:800–8.

58. Bergareche A, De La Puente E, Lopez de Munain A, Sarasqueta C, de Arce A, Poza JJ, et al. Prevalence of Parkinson's disease and other types of Parkinsonism. A door-to-door survey in Bidasoa, Spain. J Neurol. 2004;251:340–5.

59. Chan DK, Cordato D, Karr M, Ong B, Lei H, Liu J, et al. Prevalence of Parkinson's disease in Sydney. Acta Neurol Scand. 2005;111:7–11.

60. de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meche FG, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology. 1995;45:2143–6.

61. Kis B, Schrag A, Ben-Shlomo Y, Klein C, Gasperi A, Spoegler F, et al. Novel three-stage ascertainment method: prevalence of PD and parkinsonism in South Tyrol, Italy. Neurology. 2002;58:1820–5.

62. Li SC, Schoenberg BS, Wang CC, Cheng XM, Rui DY, Bolis CL, et al. A prevalence survey of Parkinson's disease and other movement disorders in the People's Republic of China. Arch Neurol. 1985;42:655–7.

63. Melcon MO, Anderson DW, Vergara RH, Rocca WA. Prevalence of Parkinson's disease in Junin, Buenos Aires Province, Argentina. Mov Disord. 1997;12:197–205.

64. Nicoletti A, Sofia V, Bartoloni A, Bartalesi F, Gamboa Barahon H, Giuffrida S, et al. Prevalence of Parkinson's disease: a door-to-door survey in rural Bolivia. Parkinsonism Relat Disord. 2003;10:19–21.

65. Okada K, Kobayashi S, Tsunematsu T. Prevalence of Parkinson's disease in Izumo City, Japan. Gerontology. 1990;36:340–4.

66. Tan LC, Venketasubramanian N, Hong CY, Sahadevan S, Chin JJ, Krishnamoorthy ES, et al. Prevalence of Parkinson disease in Singapore: Chinese vs Malays vs Indians. Neurology. 2004;62:1999–2004.

67. Wang SJ, Fuh JL, Teng EL, Liu CY, Lin KP, Chen HM, et al. A door-to-door survey of Parkinson's disease in a Chinese population in Kinmen. Arch Neurol. 1996;53:66–71.

68. Wirdefeldt K, Gatz M, Bakaysa SL, Fiske A, Flensburg M, Petzinger GM, et al. Complete ascertainment of Parkinson disease in the Swedish Twin Registry. Neurobiol Aging. 2008;29:1765–73.

69. Racette BA, Good LM, Kissel AM, Criswell SR, Perlmutter JS. A population-based study of parkinsonism in an Amish community. Neuroepidemiology. 2009;33:225–30.

70. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology. 2007;68:384–6.

71. Kessler II. Epidemiologic studies of Parkinson's disease. II. A hospital-based survey. Am J Epidemiol. 1972;95:308–18.

72. Paddison RM, Griffith RP. Occurrence of Parkinson's disease in black patients at Charity Hospital in New Orleans. Neurology. 1974;24:688–90.

73. Lombard A, Gelfand M. Parkinson's disease in the African. Cent Afr J Med. 1978;24:5–8.

74. Woo J, Lau E, Ziea E, Chan DK. Prevalence of Parkinson's disease in a Chinese population. Acta Neurol Scand. 2004;109:228–31.

75. Trenkwalder C, Schwarz J, Gebhard J, Ruland D, Trenkwalder P, Hense HW, et al. Starnberg trial on epidemiology of Parkinsonism and hypertension in the elderly. Prevalence of Parkinson's disease and related disorders assessed by a door-to-door survey of inhabitants older than 65 years. Arch Neurol. 1995;52:1017–22.

76. Zhang ZX, Roman GC. Worldwide occurrence of Parkinson's disease: an updated review. Neuroepidemiology. 1993;12:195–208.

77. McInerney-Leo A, Gwinn-Hardy K, Nussbaum RL. Prevalence of Parkinson's disease in populations of African ancestry: a review. J Natl Med Assoc. 2004;96:974–9.

78. Attia Romdhane N, Ben Hamida M, Mrabet A, Larnaout A, Samoud S, Ben Hamda A, et al. Prevalence study of neurologic disorders in Kelibia (Tunisia). Neuroepidemiology. 1993;12:285–99.

79. Ashok PP, Radhakrishnan K, Sridharan R, Mousa ME. Epidemiology of Parkinson's disease in Benghazi, North-East Libya. Clin Neurol Neurosurg. 1986;88:109–13.

80. Okubadejo NU, Bower JH, Rocca WA, Maraganore DM. Parkinson's disease in Africa: a systematic review of epidemiologic and genetic studies. Mov Disord. 2006;21:2150–6.

81. D'Alessandro R, Gamberini G, Granieri E, Benassi G, Naccarato S, Manzaroli D. Prevalence of Parkinson's disease in the Republic of San Marino. Neurology. 1987;37:1679–82.

82. Rosati G, Granieri E, Pinna L, Aiello I, De Bastiani P, Tola R, et al. Parkinson's disease. Prevalence and incidence in the Province of Sassari, North Sardinia. Acta Neurol (Napoli). 1978;33:201–7.

83. Rosati G, Granieri E, Pinna L, Aiello I, Tola R, De Bastiani P, et al. The risk of Parkinson disease in Mediterranean people. Neurology. 1980;30:250–5.

84. Rosati G, Granieri E, Pinna L, Devoto MC. The frequency of Parkinson's disease in the Province of Nuoro (Sardinia). Acta Neurol (Napoli). 1979;1:303–8.

85. 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.

86. Sutcliffe RL, Meara JR. Parkinson's disease epidemiology in the Northampton District, England, 1992. Acta Neurol Scand. 1995;92:443–50.

87. Berger K, Breteler MM, Helmer C, Inzitari D, Fratiglioni L, Trenkwalder C, et al. Prognosis with Parkinson's disease in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54:S24–7.

88. Chen H, Zhang SM, Schwarzschild MA, Hernan MA, Ascherio A. Survival of Parkinson's disease patients in a large prospective cohort of male health professionals. Mov Disord. 2006;21:1002–7.

89. D'Amelio M, Ragonese P, Morgante L, Reggio A, Callari G, Salemi G, et al. Long-term survival of Parkinson's disease: a population-based study. J Neurol. 2006;253:33–7.

90. de Lau LM, Schipper CM, Hofman A, Koudstaal PJ, Breteler MM. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. Arch Neurol. 2005;62:1265–9.

91. Driver JA, Kurth T, Buring JE, Gaziano JM, Logroscino G. Parkinson disease and risk of mortality: a prospective comorbidity-matched cohort study. Neurology. 2008;70:1423–30.

92. Ebmeier KP, Calder SA, Crawford JR, Stewart L, Besson JA, Mutch WJ. Mortality and causes of death in idiopathic Parkinson's disease: results from the Aberdeen whole population study. Scott Med J. 1990;35:173–5.

93. Elbaz A, Bower JH, Peterson BJ, Maraganore DM, McDonnell SK, Ahlskog JE, et al. Survival study of Parkinson disease in Olmsted County, Minnesota. Arch Neurol. 2003;60:91–6.

94. 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;18:1312–6.

95. 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;67:300–7.

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

97. 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.

98. Louis ED, Marder K, Cote L, Tang M, Mayeux R. Mortality from Parkinson disease. Arch Neurol. 1997;54:260–4.

99. Marttila RJ, Rinne UK, Siirtola T, Sonninen V. Mortality of patients with Parkinson's disease treated with levodopa. J Neurol. 1977;216:147–53.

100. Morgante L, Salemi G, Meneghini F, Di Rosa AE, Epifanio A, Grigoletto F, et al. Parkinson disease survival: a population-based study. Arch Neurol. 2000;57:507–12.

101. Vanacore N, Bonifati V, Bellatreccia A, Edito F, Meco G. Mortality rates for Parkinson's disease and parkinsonism in Italy (1969–1987). Neuroepidemiology. 1992;11:65–73.

102. Diem-Zangerl A, Seppi K, Oberaigner W, Poewe W. Mortality in Parkinson's disease, a 20-year follow-up study. Mov Disord. 2010;25:661–2.

103. 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.

104. Ishihara LS, Cheesbrough A, Brayne C, Schrag A. Estimated life expectancy of Parkinson's patients compared with the UK population. J Neurol Neurosurg Psychiatry. 2007;78:1304–9.

105. Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology? J Neurol Neurosurg Psychiatry. 1995;58:293–9.

106. Uitti RJ, Ahlskog JE, Maraganore DM, Muenter MD, Atkinson EJ, Cha RH, et al. Levodopa therapy and survival in idiopathic Parkinson's disease: Olmsted County project. Neurology. 1993;43:1918–26.

107. Roos RA, Jongen JC, van der Velde EA. Clinical course of patients with idiopathic Parkinson's disease. Mov Disord. 1996;11:236–42.

108. Levy G, Tang MX, Louis ED, Cote LJ, Alfaro B, Mejia H, et al. The association of incident dementia with mortality in PD. Neurology. 2002;59:1708–13.

109. Fahn S, Elton RL, the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, editors. Recent developments in Parkinson's disease, vol. 2. Florham Park, NJ: Macmillan Healthcare Information; 1987. p. 153–63.

110. Wermuth L, Stenager EN, Stenager E, Boldsen J. Mortality in patients with Parkinson's disease. Acta Neurol Scand. 1995;92:55–8.

111. Gorell JM, Johnson CC, Rybicki BA. Parkinson's disease and its comorbid disorders: an analysis of Michigan mortality data, 1970 to 1990. Neurology. 1994;44:1865–8.

112. Paulson GW, Gill WM. Are death certificates reliable to estimate the incidence of Parkinson's disease? Mov Disord. 1995;10:678.

113. Marsden CD. Parkinson's disease in twins. J Neurol Neurosurg Psychiatry. 1987;50:105–6.

114. Marttila RJ, Kaprio J, Koskenvuo M, Rinne UK. Parkinson's disease in a nationwide twin cohort. Neurology. 1988;38:1217–9.

115. Ward CD, Duvoisin RC, Ince SE, Nutt JD, Eldridge R, Calne DB. Parkinson's disease in 65 pairs of twins and in a set of quadruplets. Neurology. 1983;33:815–24.

116. Vieregge P, Schiffke KA, Friedrich HJ, Muller B, Ludin HP. Parkinson's disease in twins. Neurology. 1992;42:1453–61.

117. Vieregge P, Hagenah J, Heberlein I, Klein C, Ludin HP. Parkinson's disease in twins: a follow-up study. Neurology. 1999;53:566–72.

118. Johnson WG, Hodge SE, Duvoisin R. Twin studies and the genetics of Parkinson's disease–a reappraisal. Mov Disord. 1990;5:187–94.

119. Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, et al. Parkinson disease in twins: an etiologic study. Jama. 1999;281:341–6.

120. Wirdefeldt K, Gatz M, Schalling M, Pedersen NL. No evidence for heritability of Parkinson disease in Swedish twins. Neurology. 2004;63:305–11.

121. Morrish PK, Rakshi JS, Bailey DL, Sawle GV, Brooks DJ. Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [18F]dopa PET. J Neurol Neurosurg Psychiatry. 1998;64:314–9.

122. Burn DJ, Mark MH, Playford ED, Maraganore DM, Zimmerman TR Jr, Duvoisin RC, et al. Parkinson's disease in twins studied with 18F-dopa and positron emission tomography. Neurology. 1992;42:1894–900.

123. Piccini P, Burn DJ, Ceravolo R, Maraganore D, Brooks DJ. The role of inheritance in sporadic Parkinson's disease: evidence from a longitudinal study of dopaminergic function in twins. Ann Neurol. 1999;45:577–82.

124. Holthoff VA, Vieregge P, Kessler J, Pietrzyk U, Herholz K, Bonner J, et al. Discordant twins with Parkinson's disease: positron emission tomography and early signs of impaired cognitive circuits. Ann Neurol. 1994;36:176–82.

125. Laihinen A, Ruottinen H, Rinne JO, Haaparanta M, Bergman J, Solin O, et al. Risk for Parkinson's disease: twin studies for the detection of asymptomatic subjects using [18F]6-fluorodopa PET. J Neurol. 2000;247(Suppl 2):110–3.

126. Martin WE, Young WI, Anderson VE. Parkinson's disease. A genetic study. Brain. 1973;96:495–506.

127. Barbeau A, Pourcher E. New data on the genetics of Parkinson's disease. Can J Neurol Sci. 1982;9:53–60.

128. Alonso ME, Otero E, D'Regules R, Figueroa HH. Parkinson's disease: a genetic study. Can J Neurol Sci. 1986;13:248–51.

129. Marttila RJ, Rinne UK. Parkinson's disease and essential tremor in families of patients with early-onset Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988;51:429–31.

130. Mickel SF, Broste SK, Hiner BC. Lack of overlap in genetic risks for Alzheimer's disease and Parkinson's disease. Neurology. 1997;48:942–9.

131. Taylor CA, Saint-Hilaire MH, Cupples LA, Thomas CA, Burchard AE, Feldman RG, et al. Environmental, medical, and family history risk factors for Parkinson's disease: a New England-based case control study. Am J Med Genet. 1999;88:742–9.

132. Semchuk KM, Love EJ, Lee RG. Parkinson's disease: a test of the multifactorial etiologic hypothesis. Neurology. 1993;43:1173–80.

133. Payami H, Larsen K, Bernard S, Nutt J. Increased risk of Parkinson's disease in parents and siblings of patients. Ann Neurol. 1994;36:659–61.

134. Payami H, Zareparsi S, James D, Nutt J. Familial aggregation of Parkinson disease: a comparative study of early-onset and late-onset disease. Arch Neurol. 2002;59:848–50.

135. de la Fuente-Fernandez R. Maternal effect on Parkinson's disease. Ann Neurol. 2000;48:782–7.

136. Preux PM, Condet A, Anglade C, Druet-Cabanac M, Debrock C, Macharia W, et al. Parkinson's disease and environmental factors. Matched case-control study in the Limousin region, France. Neuroepidemiology. 2000;19:333–7.

137. Herishanu YO, Medvedovski M, Goldsmith JR, Kordysh E. A case-control study of Parkinson's disease in urban population of southern Israel. Can J Neurol Sci. 2001;28:144–7.

138. Marder K, Levy G, Louis ED, Mejia-Santana H, Cote L, Andrews H, et al. Familial aggregation of early- and late-onset Parkinson's disease. Ann Neurol. 2003;54:507–13.

139. Bonifati V, Fabrizio E, Vanacore N, De Mari M, Meco G. Familial Parkinson's disease: a clinical genetic analysis. Can J Neurol Sci. 1995;22:272–9.

140. De Michele G, Filla A, Volpe G, De Marco V, Gogliettino A, Ambrosio G, et al. Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy. Mov Disord. 1996;11:17–23.

141. McCann SJ, LeCouteur DG, Green AC, Brayne C, Johnson AG, Chan D, et al. The epidemiology of Parkinson's disease in an Australian population. Neuroepidemiology. 1998;17:310–7.

142. Morano A, Jimenez-Jimenez FJ, Molina JA, Antolin MA. Risk-factors for Parkinson's disease: case-control study in the province of Caceres, Spain. Acta Neurol Scand. 1994;89:164–70.

143. Behari M, Srivastava AK, Das RR, Pandey RM. Risk factors of Parkinson's disease in Indian patients. J Neurol Sci. 2001;190:49–55.

144. Chan DK, Woo J, Ho SC, Pang CP, Law LK, Ng PW, et al. Genetic and environmental risk factors for Parkinson's disease in a Chinese population. J Neurol Neurosurg Psychiatry. 1998;65:781–4.

145. Werneck AL, Alvarenga H. Genetics, drugs and environmental factors in Parkinson's disease. A case-control study. Arq Neuropsiquiatr. 1999;57:347–55.

146. Wang WZ, Fang XH, Cheng XM, Jiang DH, Lin ZJ. A case-control study on the environmental risk factors of Parkinson's disease in Tianjin, China. Neuroepidemiology. 1993;12:209–18.

147. Zorzon M, Capus L, Pellegrino A, Cazzato G, Zivadinov R. Familial and environmental risk factors in Parkinson's disease: a case-control study in north-east Italy. Acta Neurol Scand. 2002;105:77–82.

148. Rybicki BA, Johnson CC, Peterson EL, Kortsha GX, Gorell JM. A family history of Parkinson's disease and its effect on other PD risk factors. Neuroepidemiology. 1999;18:270–8.

149. Korchounov A, Schipper HI, Preobrazhenskaya IS, Kessler KR, Yakhno NN. Differences in age at onset and familial aggregation between clinical types of idiopathic Parkinson's disease. Mov Disord. 2004;19:1059–64.

150. Spanaki C, Plaitakis A. Bilineal transmission of Parkinson disease on Crete suggests a complex inheritance. Neurology. 2004;62:815–7.

151. Marttila RJ, Rinne UK. Arteriosclerosis, heredity, and some previous infections in the etiology of Parkinson's disease. A case-control study. Clin Neurol Neurosurg. 1976;79:46–56.

152. Rossi P, Albanese A, Moro E, Genvardi M, Tonali P. Clinical genetic study of familial Parkinson's disease in Italy. Adv Neurol. 1999;80:181–6.

153. Butterfield PG, Valanis BG, Spencer PS, Lindeman CA, Nutt JG. Environmental antecedents of young-onset Parkinson's disease. Neurology. 1993;43:1150–8.

154. Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, et al. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology. 1996;46:1275–84.

155. Autere JM, Moilanen JS, Myllyla VV, Majamaa K. Familial aggregation of Parkinson's disease in a Finnish population. J Neurol Neurosurg Psychiatry. 2000;69:107–9.

156. Duzcan F, Zencir M, Ozdemir F, Cetin GO, Bagci H, Heutink P, et al. Familial influence on parkinsonism in a rural area of Turkey (Kizilcaboluk-Denizli): a community-based case-control study. Mov Disord. 2003;18:799–804.

157. Elbaz A, Grigoletto F, Baldereschi M, Breteler MM, Manubens-Bertran JM, Lopez-Pousa S, et al. Familial aggregation of Parkinson's disease: a population-based case-control study in Europe. EUROPARKINSON Study Group. Neurology. 1999;52:1876–82.

158. Kuopio A, Marttila RJ, Helenius H, Rinne UK. Familial occurrence of Parkinson's disease in a community-based case-control study. Parkinsonism Relat Disord. 2001;7:297–303.

159. Kurz M, Alves G, Aarsland D, Larsen JP. Familial Parkinson's disease: a community-based study. Eur J Neurol. 2003;10:159–63.

160. Marder K, Tang MX, Mejia H, Alfaro B, Cote L, Louis E, et al. Risk of Parkinson's disease among first-degree relatives: a community-based study. Neurology. 1996;47:155–60.

161. Rocca WA, McDonnell SK, Strain KJ, Bower JH, Ahlskog JE, Elbaz A, et al. Familial aggregation of Parkinson's disease: the Mayo Clinic family study. Ann Neurol. 2004;56:495–502.

162. Sundquist K, Li X, Hemminki K. Familial risks of hospitalization for Parkinson's disease in first-degree relatives: a nationwide follow-up study from Sweden. Neurogenetics. 2006;7:231–7.

163. Sveinbjornsdottir S, Hicks AA, Jonsson T, Petursson H, Gugmundsson G, Frigge ML, et al. Familial aggregation of Parkinson's disease in Iceland. N Engl J Med. 2000;343:1765–70.

164. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, et al. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology. 1999;20:239–47.

165. Khoury MJ, Beaty TH, Cohen BH. Fundamentals of genetic epidemiology. New York: Oxford University Press; 1993.

166. Elbaz A, McDonnell SK, Maraganore DM, Strain KJ, Schaid DJ, Bower JH, et al. Validity of family history data on PD: evidence for a family information bias. Neurology. 2003;61:11–7.

167. Thacker EL, Ascherio A. Familial aggregation of Parkinson's disease: a meta-analysis. Mov Disord. 2008;23:1174–83.

168. Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science. 2003;299:256–9.

169. Gasser T, Muller-Myhsok B, Wszolek ZK, Oehlmann R, Calne DB, Bonifati V, et al. A susceptibility locus for Parkinson's disease maps to chromosome 2p13. Nat Genet. 1998;18:262–5.

170. Hicks AA, Petursson H, Jonsson T, Stefansson H, Johannsdottir HS, Sainz J, et al. A susceptibility gene for late-onset idiopathic Parkinson's disease. Ann Neurol. 2002;52:549–55.

171. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature. 1998;392:605–8.

172. Lautier C, Goldwurm S, Durr A, Giovannone B, Tsiaras WG, Pezzoli G, et al. Mutations in the GIGYF2 (TNRC15) gene at the PARK11 locus in familial Parkinson disease. Am J Hum Genet. 2008;82:822–33.

173. Leroy E, Boyer R, Auburger G, Leube B, Ulm G, Mezey E, et al. The ubiquitin pathway in Parkinson's disease. Nature. 1998;395:451–2.

174. Paisan-Ruiz C, Bhatia KP, Li A, Hernandez D, Davis M, Wood NW, et al. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann Neurol. 2009;65:19–23.

175. Paisan-Ruiz C, Jain S, Evans EW, Gilks WP, Simon J, van der Brug M, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron. 2004;44:595–600.

176. Pankratz N, Nichols WC, Uniacke SK, Halter C, Rudolph A, Shults C, et al. Genome screen to identify susceptibility genes for Parkinson disease in a sample without parkin mutations. Am J Hum Genet. 2002;71:124–35.

177. Pankratz N, Nichols WC, Uniacke SK, Halter C, Murrell J, Rudolph A, et al. Genome-wide linkage analysis and evidence of gene-by-gene interactions in a sample of 362 multiplex Parkinson disease families. Hum Mol Genet. 2003;12:2599–608.

178. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997;276:2045–7.

179. Ramirez A, Heimbach A, Grundemann J, Stiller B, Hampshire D, Cid LP, et al. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet. 2006;38:1184–91.

180. Shojaee S, Sina F, Banihosseini SS, Kazemi MH, Kalhor R, Shahidi GA, et al. Genome-wide linkage analysis of a Parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays. Am J Hum Genet. 2008;82:1375–84.

181. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, et al. Alpha-Synuclein locus triplication causes Parkinson's disease. Science. 2003;302:841.

182. Strauss KM, Martins LM, Plun-Favreau H, Marx FP, Kautzmann S, Berg D, et al. Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. Hum Mol Genet. 2005;14:2099–111.

183. Valente EM, Abou-Sleiman PM, Caputo V, Muqit MM, Harvey K, Gispert S, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science. 2004;304:1158–60.

184. Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron. 2004;44:601–7.

185. Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med. 2004;351:1972–7.

186. Payami H, Nutt J, Gancher S, Bird T, McNeal MG, Seltzer WK, et al. SCA2 may present as levodopa-responsive parkinsonism. Mov Disord. 2003;18:425–9.

187. Berg D, Niwar M, Maass S, Zimprich A, Moller JC, Wuellner U, et al. Alpha-synuclein and Parkinson's disease: implications from the screening of more than 1, 900 patients. Mov Disord. 2005;20:1191–4.

188. Kruger R, Kuhn W, Muller T, Woitalla D, Graeber M, Kosel S, et al. Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nat Genet. 1998;18:106–8.

189. Zarranz JJ, Alegre J, Gomez-Esteban JC, Lezcano E, Ros R, Ampuero I, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol. 2004;55:164–73.

190. Golbe LI, Di Iorio G, Bonavita V, Miller DC, Duvoisin RC. A large kindred with autosomal dominant Parkinson's disease. Ann Neurol. 1990;27:276–82.

191. Spira PJ, Sharpe DM, Halliday G, Cavanagh J, Nicholson GA. Clinical and pathological features of a Parkinsonian syndrome in a family with an Ala53Thr alpha-synuclein mutation. Ann Neurol. 2001;49:313–9.

192. Chartier-Harlin MC, Kachergus J, Roumier C, Mouroux V, Douay X, Lincoln S, et al. Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. Lancet. 2004;364:1167–9.

193. Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson EM, Schule B, et al. Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. Neurology. 2007;68:916–22.

194. Ibanez P, Bonnet AM, Debarges B, Lohmann E, Tison F, Pollak P, et al. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet. 2004;364:1169–71.

195. Nishioka K, Hayashi S, Farrer MJ, Singleton AB, Yoshino H, Imai H, et al. Clinical heterogeneity of alpha-synuclein gene duplication in Parkinson's disease. Ann Neurol. 2006;59:298–309.

196. Ross OA, Braithwaite AT, Skipper LM, Kachergus J, Hulihan MM, Middleton FA, et al. Genomic investigation of alpha-synuclein multiplication and parkinsonism. Ann Neurol. 2008;63:743–50.

197. Ahn TB, Kim SY, Kim JY, Park SS, Lee DS, Min HJ, et al. Alpha-Synuclein gene duplication is present in sporadic Parkinson disease. Neurology. 2008;70:43–9.

198. Brueggemann N, Odin P, Gruenewald A, Tadic V, Hagenah J, Seidel G, et al. Re: Alpha-synuclein gene duplication is present in sporadic Parkinson disease. Neurology. 2008;71:1294.

199. Troiano AR, Cazeneuve C, Le Ber I, Bonnet AM, Lesage S, Brice A. Re: Alpha-synuclein gene duplication is present in sporadic Parkinson disease. Neurology. 2008;71:1295.

200. Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M. Alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. Proc Natl Acad Sci USA. 1998;95:6469–73.

201. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Nature. 1997;388:839–40.

202. West AB, Zimprich A, Lockhart PJ, Farrer M, Singleton A, Holtom B, et al. Refinement of the PARK3 locus on chromosome 2p13 and the analysis of 14 candidate genes. Eur J Hum Genet. 2001;9:659–66.

203. DeStefano AL, Lew MF, Golbe LI, Mark MH, Lazzarini AM, Guttman M, et al. PARK3 influences age at onset in Parkinson disease: a genome scan in the GenePD study. Am J Hum Genet. 2002;70:1089–95.

204. Pankratz N, Uniacke SK, Halter CA, Rudolph A, Shults CW, Conneally PM, et al. Genes influencing Parkinson disease onset: replication of PARK3 and identification of novel loci. Neurology. 2004;62:1616–8.

205. Martinez M, Brice A, Vaughan JR, Zimprich A, Breteler MM, Meco G, et al. Genome-wide scan linkage analysis for Parkinson's disease: the European genetic study of Parkinson's disease. J Med Genet. 2004;41:900–7.

206. Karamohamed S, DeStefano AL, Wilk JB, Shoemaker CM, Golbe LI, Mark MH, et al. A haplotype at the PARK3 locus influences onset age for Parkinson's disease: the GenePD study. Neurology. 2003;61:1557–61.

207. Sharma M, Mueller JC, Zimprich A, Lichtner P, Hofer A, Leitner P, et al. The sepiapterin reductase gene region reveals association in the PARK3 locus: analysis of familial and

sporadic Parkinson's disease in European populations. J Med Genet. 2006;43:557–62.

208. Funayama M, Hasegawa K, Kowa H, Saito M, Tsuji S, Obata F. A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2–q13.1. Ann Neurol. 2002;51:296–301.

209. Farrer M, Stone J, Mata IF, Lincoln S, Kachergus J, Hulihan M, et al. LRRK2 mutations in Parkinson disease. Neurology. 2005;65:738–40.

210. Lesage S, Durr A, Tazir M, Lohmann E, Leutenegger AL, Janin S, et al. LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. N Engl J Med. 2006;354:422–3.

211. Paisan-Ruiz C, Nath P, Washecka N, Gibbs JR, Singleton AB. Comprehensive analysis of LRRK2 in publicly available Parkinson's disease cases and neurologically normal controls. Hum Mutat. 2008;29:485–90.

212. Lesage S, Brice A. Parkinson's disease: from monogenic forms to genetic susceptibility factors. Hum Mol Genet. 2009;18: R48–59.

213. Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M, et al. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. N Engl J Med. 2006; 354:424–5.

214. Lu CS, Simons EJ, Wu-Chou YH, Fonzo AD, Chang HC, Chen RS, et al. The LRRK2 I2012T, G2019S, and I2020T mutations are rare in Taiwanese patients with sporadic Parkinson's disease. Parkinsonism Relat Disord. 2005;11:521–2.

215. Tan EK, Shen H, Tan LC, Farrer M, Yew K, Chua E, et al. The G2019S LRRK2 mutation is uncommon in an Asian cohort of Parkinson's disease patients. Neurosci Lett. 2005;384:327–9.

216. Okubadejo N, Britton A, Crews C, Akinyemi R, Hardy J, Singleton A, et al. Analysis of Nigerians with apparently sporadic Parkinson disease for mutations in LRRK2, PRKN and ATXN3. PLoS One. 2008;3:e3421.

217. Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol. 2008;7:583–90.

218. Ishikawa A, Tsuji S. Clinical analysis of 17 patients in 12 Japanese families with autosomal-recessive type juvenile parkinsonism. Neurology. 1996;47:160–6.

219. Takahashi H, Ohama E, Suzuki S, Horikawa Y, Ishikawa A, Morita T, et al. Familial juvenile parkinsonism: clinical and pathologic study in a family. Neurology. 1994;44:437–41.

220. Farrer M, Chan P, Chen R, Tan L, Lincoln S, Hernandez D, et al. Lewy bodies and parkinsonism in families with parkin mutations. Ann Neurol. 2001;50:293–300.

221. Pramstaller PP, Schlossmacher MG, Jacques TS, Scaravilli F, Eskelson C, Pepivani I, et al. Lewy body Parkinson's disease in a large pedigree with 77 Parkin mutation carriers. Ann Neurol. 2005;58:411–22.

222. West AB, Maidment NT. Genetics of parkin-linked disease. Hum Genet. 2004;114:327–36.

223. Foroud T, Uniacke SK, Liu L, Pankratz N, Rudolph A, Halter C, et al. Heterozygosity for a mutation in the parkin gene leads to later onset Parkinson disease. Neurology. 2003;60:796–801.

224. Dekker MC, Bonifati V, van Duijn CM. Parkinson's disease: piecing together a genetic jigsaw. Brain. 2003;126:1722–33.

225. Clark LN, Afridi S, Karlins E, Wang Y, Mejia-Santana H, Harris J, et al. Case-control study of the parkin gene in early-onset Parkinson disease. Arch Neurol. 2006;63:548–52.

226. Klein C, Lohmann-Hedrich K, Rogaeva E, Schlossmacher MG, Lang AE. Deciphering the role of heterozygous mutations in genes associated with parkinsonism. Lancet Neurol. 2007;6: 652–62.

227. Sun M, Latourelle JC, Wooten GF, Lew MF, Klein C, Shill HA, et al. Influence of heterozygosity for parkin mutation on onset

age in familial Parkinson disease: the GenePD study. Arch Neurol. 2006;63:826–32.

228. Lesage S, Lohmann E, Tison F, Durif F, Durr A, Brice A. Rare heterozygous parkin variants in French early-onset Parkinson disease patients and controls. J Med Genet. 2008;45:43–6.

229. Shimura H, Schlossmacher MG, Hattori N, Frosch MP, Trockenbacher A, Schneider R, et al. Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease. Science. 2001;293:263–9.

230. Valente EM, Bentivoglio AR, Dixon PH, Ferraris A, Ialongo T, Frontali M, et al. Localization of a novel locus for autosomal recessive early-onset parkinsonism, PARK6, on human chromosome 1p35–p36. Am J Hum Genet. 2001;68:895–900.

231. Valente EM, Salvi S, Ialongo T, Marongiu R, Elia AE, Caputo V, et al. PINK1 mutations are associated with sporadic early-onset parkinsonism. Ann Neurol. 2004;56:336–41.

232. Bonifati V, Rohe CF, Breedveld GJ, Fabrizio E, De Mari M, Tassorelli C, et al. Early-onset parkinsonism associated with PINK1 mutations: frequency, genotypes, and phenotypes. Neurology. 2005;65:87–95.

233. Healy DG, Abou-Sleiman PM, Gibson JM, Ross OA, Jain S, Gandhi S, et al. PINK1 (PARK6) associated Parkinson disease in Ireland. Neurology. 2004;63:1486–8.

234. Li Y, Tomiyama H, Sato K, Hatano Y, Yoshino H, Atsumi M, et al. Clinicogenetic study of PINK1 mutations in autosomal recessive early-onset parkinsonism. Neurology. 2005;64:1955–7.

235. Rogaeva E, Johnson J, Lang AE, Gulick C, Gwinn-Hardy K, Kawarai T, et al. Analysis of the PINK1 gene in a large cohort of cases with Parkinson disease. Arch Neurol. 2004;61:1898–904.

236. Tan EK, Yew K, Chua E, Puvan K, Shen H, Lee E, et al. PINK1 mutations in sporadic early-onset Parkinson's disease. Mov Disord. 2006;21:789–93.

237. Clark LN, Afridi S, Mejia-Santana H, Harris J, Louis ED, Cote LJ, et al. Analysis of an early-onset Parkinson's disease cohort for DJ-1 mutations. Mov Disord. 2004;19:796–800.

238. Hedrich K, Djarmati A, Schafer N, Hering R, Wellenbrock C, Weiss PH, et al. DJ-1 (PARK7) mutations are less frequent than Parkin (PARK2) mutations in early-onset Parkinson disease. Neurology. 2004;62:389–94.

239. Hering R, Strauss KM, Tao X, Bauer A, Woitalla D, Mietz EM, et al. Novel homozygous p.E64D mutation in DJ1 in early onset Parkinson disease (PARK7). Hum Mutat. 2004;24:321–9.

240. Lockhart PJ, Lincoln S, Hulihan M, Kachergus J, Wilkes K, Bisceglio G, et al. DJ-1 mutations are a rare cause of recessively inherited early onset parkinsonism mediated by loss of protein function. J Med Genet. 2004;41:e22.

241. Tan EK, Tan C, Zhao Y, Yew K, Shen H, Chandran VR, et al. Genetic analysis of DJ-1 in a cohort Parkinson's disease patients of different ethnicity. Neurosci Lett. 2004;367:109–12.

242. Mitsumoto A, Nakagawa Y. DJ-1 is an indicator for endogenous reactive oxygen species elicited by endotoxin. Free Radic Res. 2001;35:885–93.

243. Taira T, Saito Y, Niki T, Iguchi-Ariga SM, Takahashi K, Ariga H. DJ-1 has a role in antioxidative stress to prevent cell death. EMBO Rep. 2004;5:213–8.

244. Najim al-Din AS, Wriekat A, Mubaidin A, Dasouki M, Hiari M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor–Rakeb syndrome. Acta Neurol Scand. 1994;89:347–52.

245. Ning YP, Kanai K, Tomiyama H, Li Y, Funayama M, Yoshino H, et al. PARK9-linked parkinsonism in eastern Asia: mutation detection in ATP13A2 and clinical phenotype. Neurology. 2008;70:1491–3.

246. Di Fonzo A, Chien HF, Socal M, Giraudo S, Tassorelli C, Iliceto G, et al. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology. 2007;68:1557–62.

247. Lin CH, Tan EK, Chen ML, Tan LC, Lim HQ, Chen GS, et al. Novel ATP13A2 variant associated with Parkinson disease in Taiwan and Singapore. Neurology. 2008;71:1727–32.

248. Li YJ, Scott WK, Hedges DJ, Zhang F, Gaskell PC, Nance MA, et al. Age at onset in two common neurodegenerative diseases is genetically controlled. Am J Hum Genet. 2002;70:985–93.

249. DeStefano AL, Latourelle J, Lew MF, Suchowersky O, Klein C, Golbe LI, et al. Replication of association between ELAVL4 and Parkinson disease: the GenePD study. Hum Genet. 2008;124:95–9.

250. Haugarvoll K, Toft M, Ross OA, Stone JT, Heckman MG, White LR, et al. ELAVL4, PARK10, and the Celts. Mov Disord. 2007;22:585–7.

251. Noureddine MA, Qin XJ, Oliveira SA, Skelly TJ, van der Walt J, Hauser MA, et al. Association between the neuron-specific RNA-binding protein ELAVL4 and Parkinson disease. Hum Genet. 2005;117:27–33.

252. Maraganore DM, de Andrade M, Lesnick TG, Strain KJ, Farrer MJ, Rocca WA, et al. High-resolution whole-genome association study of Parkinson disease. Am J Hum Genet. 2005;77:685–93.

253. Prestel J, Sharma M, Leitner P, Zimprich A, Vaughan JR, Durr A, et al. PARK11 is not linked with Parkinson's disease in European families. Eur J Hum Genet. 2005;13:193–7.

254. Nichols WC, Kissell DK, Pankratz N, Pauciulo MW, Elsaesser VE, Clark KA, et al. Variation in GIGYF2 is not associated with Parkinson disease. Neurology. 2009;72:1886–92.

255. Meeus B, Nuytemans K, Crosiers D, Engelborghs S, Pals P, Pickut B, et al. GIGYF2 has no major role in Parkinson genetic etiology in a Belgian population. Neurobiol Aging. 2011;32:308–12.

256. Bras J, Simon-Sanchez J, Federoff M, Morgadinho A, Januario C, Ribeiro M, et al. Lack of replication of association between GIGYF2 variants and Parkinson disease. Hum Mol Genet. 2009;18:341–6.

257. Di Fonzo A, Fabrizio E, Thomas A, Fincati E, Marconi R, Tinazzi M, et al. GIGYF2 mutations are not a frequent cause of familial Parkinson's disease. Parkinsonism Relat Disord. 2009;15:703–5.

258. Vilarino-Guell C, Ross OA, Soto AI, Farrer MJ, Haugarvoll K, Aasly JO, et al. Reported mutations in GIGYF2 are not a common cause of Parkinson's disease. Mov Disord. 2009;24:619–20.

259. Scott WK, Nance MA, Watts RL, Hubble JP, Koller WC, Lyons K, et al. Complete genomic screen in Parkinson disease: evidence for multiple genes. Jama. 2001;286:2239–44.

260. Morgan NV, Westaway SK, Morton JE, Gregory A, Gissen P, Sonek S, et al. PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. Nat Genet. 2006;38:752–4.

261. Di Fonzo A, Dekker MC, Montagna P, Baruzzi A, Yonova EH, Correia Guedes L, et al. FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. Neurology. 2009;72:240–5.

262. Satake W, Nakabayashi Y, Mizuta I, Hirota Y, Ito C, Kubo M, et al. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. Nat Genet. 2009;41:1303–7.

263. Simon-Sanchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet. 2009;41:1308–12.

264. Tan EK, Kwok HK, Tan LC, Zhao WT, Prakash KM, Au WL, et al. Analysis of GWAS-linked loci in Parkinson disease reaffirms PARK16 as a susceptibility locus. Neurology. 2010;75:508–12.

265. Lill CM, Bagade S, McQueen MB, Roehr JT, Kavvoura F, Schjeide BMM, et al. The PDGene Database. Alzheimer Research Forum. 2010. http://www.pdgene.org/. Accessed 23 Sept 2010.

266. Grabowski GA. Gaucher disease. Enzymology, genetics, and treatment. Adv Hum Genet. 1993;21:377–441.

267. Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009;361:1651–61.

268. Goker-Alpan O, Giasson BI, Eblan MJ, Nguyen J, Hurtig HI, Lee VM, et al. Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. Neurology. 2006;67:908–10.

269. Goker-Alpan O, Lopez G, Vithayathil J, Davis J, Hallett M, Sidransky E. The spectrum of parkinsonian manifestations associated with glucocerebrosidase mutations. Arch Neurol. 2008;65:1353–7.

270. McCulloch CC, Kay DM, Factor SA, Samii A, Nutt JG, Higgins DS, et al. Exploring gene-environment interactions in Parkinson's disease. Hum Genet. 2008;123:257–65.

271. Gatto NM, Rhodes SL, Manthripragada AD, Bronstein J, Cockburn M, Farrer M, et al. Alpha-Synuclein gene may interact with environmental factors in increasing risk of Parkinson's disease. Neuroepidemiology. 2010;35:191–5.

272. Brighina L, Frigerio R, Schneider NK, Lesnick TG, de Andrade M, Cunningham JM, et al. Alpha-synuclein, pesticides, and Parkinson disease: a case-control study. Neurology. 2008;70:1461–9.

273. Brighina L, Schneider NK, Lesnick TG, de Andrade M, Cunningham JM, Mrazek D, et al. Alpha-Synuclein, alcohol use disorders, and Parkinson disease: a case-control study. Parkinsonism Relat Disord. 2009;15:430–4.

274. Elbaz A, Levecque C, Clavel J, Vidal JS, Richard F, Amouyel P, et al. CYP2D6 polymorphism, pesticide exposure, and Parkinson's disease. Ann Neurol. 2004;55:430–4.

275. Deng Y, Newman B, Dunne MP, Silburn PA, Mellick GD. Further evidence that interactions between CYP2D6 and pesticide exposure increase risk for Parkinson's disease. Ann Neurol. 2004;55:897.

276. Dick FD, De Palma G, Ahmadi A, Osborne A, Scott NW, Prescott GJ, et al. Gene-environment interactions in parkinsonism and Parkinson's disease: the Geoparkinson study. Occup Environ Med. 2007;64:673–80.

277. Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, et al. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998;393: 702–5.

278. Checkoway H, Franklin GM, Costa-Mallen P, Smith-Weller T, Dilley J, Swanson PD, et al. A genetic polymorphism of MAO-B modifies the association of cigarette smoking and Parkinson's disease. Neurology. 1998;50:1458–61.

279. Mellick GD, McCann SJ, Le Couter DG. Parkinson's disease, MAOB, and smoking. Neurology. 1999;53:658.

280. Hernan MA, Checkoway H, O'Brien R, Costa-Mallen P, De Vivo I, Colditz GA, et al. MAOB intron 13 and COMT codon 158 polymorphisms, cigarette smoking, and the risk of PD. Neurology. 2002;58:1381–7.

281. 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.

282. Barbeau A, Roy M, Bernier G, Campanella G, Paris S. Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. Can J Neurol Sci. 1987;14:36–41.

283. Bhatt MH, Elias MA, Mankodi AK. Acute and reversible parkinsonism due to organophosphate pesticide intoxication: five cases. Neurology. 1999;52:1467–71.

284. Meco G, Bonifati V, Vanacore N, Fabrizio E. Parkinsonism after chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). Scand J Work Environ Health. 1994;20: 301–5.

285. Sechi GP, Agnetti V, Piredda M, Canu M, Deserra F, Omar HA, et al. Acute and persistent parkinsonism after use of diquat. Neurology. 1992;42:261–3.

286. Muller-Vahl KR, Kolbe H, Dengler R. Transient severe parkinsonism after acute organophosphate poisoning. J Neurol Neurosurg Psychiatry. 1999;66:253–4.

287. Bocchetta A, Corsini GU. Parkinson's disease and pesticides. Lancet. 1986;2:1163.

288. Sanchez-Ramos JR, Hefti F, Weiner WJ. Paraquat and Parkinson's disease. Neurology. 1987;37:728.

289. 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.

290. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology. 1992;42:1328–35.

291. Hubble JP, Cao T, Hassanein RE, Neuberger JS, Koller WC. Risk factors for Parkinson's disease. Neurology. 1993;43:1693–7.

292. Hertzman C, Wiens M, Snow B, Kelly S, Calne D. A case-control study of Parkinson's disease in a horticultural region of British Columbia. Mov Disord. 1994;9:69–75.

293. Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, et al. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. Neurology. 1997;48:1583–8.

294. Menegon A, Board PG, Blackburn AC, Mellick GD, Le Couteur DG. Parkinson's disease, pesticides, and glutathione transferase polymorphisms. Lancet. 1998;352:1344–6.

295. 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.

296. Baldereschi M, Di Carlo A, Vanni P, Ghetti A, Carbonin P, Amaducci L, et al. Lifestyle-related risk factors for Parkinson's disease: a population-based study. Acta Neurol Scand. 2003;108:239–44.

297. Baldi I, Cantagrel A, Lebailly P, Tison F, Dubroca B, Chrysostome V, et al. Association between Parkinson's disease and exposure to pesticides in southwestern France. Neuroepidemiology. 2003;22:305–10.

298. Galanaud JP, Elbaz A, Clavel J, Vidal JS, Correze JR, Alperovitch A, et al. Cigarette smoking and Parkinson's disease: a case-control study in a population characterized by a high prevalence of pesticide exposure. Mov Disord. 2005;20:181–9.

299. Frigerio R, Sanft KR, Grossardt BR, Peterson BJ, Elbaz A, Bower JH, et al. Chemical exposures and Parkinson's disease: a population-based case-control study. Mov Disord. 2006;21:1688–92.

300. Dick FD, De Palma G, Ahmadi A, Scott NW, Prescott GJ, Bennett J, et al. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. Occup Environ Med. 2007;64:666–72.

301. Dhillon AS, Tarbutton GL, Levin JL, Plotkin GM, Lowry LK, Nalbone JT, et al. Pesticide/environmental exposures and Parkinson's disease in East Texas. J Agromed. 2008;13:37–48.

302. Hancock DB, Martin ER, Mayhew GM, Stajich JM, Jewett R, Stacy MA, et al. Pesticide exposure and risk of Parkinson's disease: a family-based case-control study. BMC Neurol. 2008;8:6.

303. Ho SC, Woo J, Lee CM. Epidemiologic study of Parkinson's disease in Hong Kong. Neurology. 1989;39:1314–8.

304. Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, et al. Occupation and risk of parkinsonism: a multicenter case-control study. Arch Neurol. 2009;66:1106–13.

305. Koller W, Vetere-Overfield B, Gray C, Alexander C, Chin T, Dolezal J, et al. Environmental risk factors in Parkinson's disease. Neurology. 1990;40:1218–21.

306. Wechsler LS, Checkoway H, Franklin GM, Costa LG. A pilot study of occupational and environmental risk factors for Parkinson's disease. Neurotoxicology. 1991;12:387–92.

307. Jimenez-Jimenez FJ, Mateo D, Gimenez-Roldan S. Exposure to well water and pesticides in Parkinson's disease: a case-control study in the Madrid area. Mov Disord. 1992;7:149–52.

308. Chaturvedi S, Ostbye T, Stoessl AJ, Merskey H, Hachinski V. Environmental exposures in elderly Canadians with Parkinson's disease. Can J Neurol Sci. 1995;22:232–4.

309. Smargiassi A, Mutti A, De Rosa A, De Palma G, Negrotti A, Calzetti S. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy. Neurotoxicology. 1998;19:709–12.

310. Dong JQ, Zhang ZX, Zhang KL. Parkinson's disease and smoking: an integral part of PD's etiological study. Biomed Environ Sci. 2003;16:173–9.

311. Nuti A, Ceravolo R, Dell'Agnello G, Gambaccini G, Bellini G, Kiferle L, et al. Environmental factors and Parkinson's disease: a case-control study in the Tuscany region of Italy. Parkinsonism Relat Disord. 2004;10:481–5.

312. Wright JM, Keller-Byrne J. Environmental determinants of Parkinson's disease. Arch Environ Occup Health. 2005;60:32–8.

313. Petersen MS, Halling J, Bech S, Wermuth L, Weihe P, Nielsen F, et al. Impact of dietary exposure to food contaminants on the risk of Parkinson's disease. Neurotoxicology. 2008;29:584–90.

314. Wong GF, Gray CS, Hassanein RS, Koller WC. Environmental risk factors in siblings with Parkinson's disease. Arch Neurol. 1991;48:287–9.

315. Kuopio AM, Marttila RJ, Helenius H, Rinne UK. Environmental risk factors in Parkinson's disease. Mov Disord. 1999;14:928–39.

316. 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;62:91–5.

317. Firestone JA, Lundin JI, Powers KM, Smith-Weller T, Franklin GM, Swanson PD, et al. Occupational factors and risk of Parkinson's disease: a population-based case-control study. Am J Ind Med. 2010;53:217–23.

318. Polder A, Skaare JU, Skjerve E, Loken KB, Eggesbo M. Levels of chlorinated pesticides and polychlorinated biphenyls in Norwegian breast milk (2002–2006), and factors that may predict the level of contamination. Sci Total Environ. 2009;407:4584–90.

319. Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues JF, Brochard P. Neurodegenerative diseases and exposure to pesticides in the elderly. Am J Epidemiol. 2003;157:409–14.

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

321. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology. 1998;50:1346–50.

322. Gorell JM, Peterson EL, Rybicki BA, Johnson CC. Multiple risk factors for Parkinson's disease. J Neurol Sci. 2004;217:169–74.

323. Costello S, Cockburn M, Bronstein J, Zhang X, Ritz B. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. Am J Epidemiol. 2009;169:919–26.

324. Elbaz A, Clavel J, Rathouz PJ, Moisan F, Galanaud JP, Delemotte B, et al. Professional exposure to pesticides and Parkinson disease. Ann Neurol. 2009;66:494–504.

325. Stern M, Dulaney E, Gruber SB, Golbe L, Bergen M, Hurtig H, et al. The epidemiology of Parkinson's disease. A case-control study of young-onset and old-onset patients. Arch Neurol. 1991;48:903–7.

326. Fleming L, Mann JB, Bean J, Briggle T, Sanchez-Ramos JR. Parkinson's disease and brain levels of organochlorine pesticides. Ann Neurol. 1994;36:100–3.

327. Corrigan FM, Wienburg CL, Shore RF, Daniel SE, Mann D. Organochlorine insecticides in substantia nigra in Parkinson's disease. J Toxicol Environ Health A. 2000;59:229–34.

328. Koldkjaer OG, Wermuth L, Bjerregaard P. Parkinson's disease among Inuit in Greenland: organochlorines as risk factors. Int J Circumpolar Health. 2004;63(Suppl 2):366–8.

329. Weisskopf MG, Knekt P, O'Reilly EJ, Lyytinen J, Reunanen A, Laden F, et al. Persistent organochlorine pesticides in serum and risk of Parkinson disease. Neurology. 2010;74:1055–61.

330. Ascherio A, Chen H, Weisskopf MG, O'Reilly E, McCullough ML, Calle EE, et al. Pesticide exposure and risk for Parkinson's disease. Ann Neurol. 2006;60:197–203.

331. Petrovitch H, Ross GW, Abbott RD, Sanderson WT, Sharp DS, Tanner CM, et al. Plantation work and risk of Parkinson disease in a population-based longitudinal study. Arch Neurol. 2002;59: 1787–92.

332. Kamel F, Tanner C, Umbach D, Hoppin J, Alavanja M, Blair A, et al. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am J Epidemiol. 2007;165:364–74.

333. Dosemeci M, Alavanja MC, Rowland AS, Mage D, Zahm SH, Rothman N, et al. A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. Ann Occup Hyg. 2002;46:245–60.

334. Acquavella JF, Alexander BH, Mandel JS, Burns CJ, Gustin C. Exposure misclassification in studies of agricultural pesticides: insights from biomonitoring. Epidemiology. 2006;17:69–74.

335. Wang SJ, Fuh JL, Liu CY, Lin KP, Chang R, Yih JS, et al. Parkinson's disease in Kin-Hu, Kinmen: a community survey by neurologists. Neuroepidemiology. 1994;13:69–74.

336. Svenson LW, Platt GH, Woodhead SE. Geographic variations in the prevalence rates of Parkinson's disease in Alberta. Can J Neurol Sci. 1993;20:307–11.

337. Tandberg E, Larsen JP, Nessler EG, Riise T, Aarli JA. The epidemiology of Parkinson's disease in the county of Rogaland, Norway. Mov Disord. 1995;10:541–9.

338. Kuopio AM, Marttila RJ, Helenius H, Rinne UK. Changing epidemiology of Parkinson's disease in southwestern Finland. Neurology. 1999;52:302–8.

339. Yesalis CE 3rd, Lemke JH, Wallace RB, Kohout FJ, Morris MC. Health status of the rural elderly according to farm work history: the Iowa 65+ rural health study. Arch Environ Health. 1985;40:245–53.

340. Imaizumi Y. Geographical variations in mortality from Parkinson's disease in Japan, 1977–1985. Acta Neurol Scand. 1995;91:311–6.

341. Sethi KD, Meador KJ, Loring D, Meador MP. Neuroepidemiology of Parkinson's disease: analysis of mortality data for the USA and Georgia. Int J Neurosci. 1989;46:87–92.

342. Strickland D, Bertoni JM, Pfeiffer RF. Descriptive epidemiology of Parkinson's disease through proxy measures. Can J Neurol Sci. 1996;23:279–84.

343. Ritz B, Yu F. Parkinson's disease mortality and pesticide exposure in California 1984–1994. Int J Epidemiol. 2000;29:323–9.

344. Hertzman C, Wiens M, Bowering D, Snow B, Calne D. Parkinson's disease: a case-control study of occupational and environmental risk factors. Am J Ind Med. 1990;17:349–55.

345. Frigerio R, Elbaz A, Sanft KR, Peterson BJ, Bower JH, Ahlskog JE, et al. Education and occupations preceding Parkinson disease: a population-based case-control study. Neurology. 2005;65:1575–83.

346. Park J, Yoo CI, Sim CS, Kim HK, Kim JW, Jeon BS, et al. Occupations and Parkinson's disease: a multi-center case-control study in South Korea. Neurotoxicology. 2005;26:99–105.

347. Kirkey KL, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Gorell JM. Occupational categories at risk for Parkinson's disease. Am J Ind Med. 2001;39:564–71.

348. Tsui JK, Calne DB, Wang Y, Schulzer M, Marion SA. Occupational risk factors in Parkinson's disease. Can J Public Health. 1999;90:334–7.

349. Rocca WA, Anderson DW, Meneghini F, Grigoletto F, Morgante L, Reggio A, et al. Occupation, education, and Parkinson's disease: a case-control study in an Italian population. Mov Disord. 1996;11:201–6.

350. Tanner CM, Chen B, Wang W, Peng M, Liu Z, Liang X, et al. Environmental factors and Parkinson's disease: a case-control study in China. Neurology. 1989;39:660–4.

351. Park J, Yoo CI, Sim CS, Kim JW, Yi Y, Jung KY, et al. Occupations and Parkinson's disease: a case-control study in South Korea. Ind Health. 2004;42:352–8.

352. Goldman SM, Tanner CM, Olanow CW, Watts RL, Field RD, Langston JW. Occupation and parkinsonism in three movement disorders clinics. Neurology. 2005;65:1430–5.

353. Lee E, Burnett CA, Lalich N, Cameron LL, Sestito JP. Proportionate mortality of crop and livestock farmers in the United States, 1984–1993. Am J Ind Med. 2002;42:410–20.

354. Tuchsen F, Jensen AA. Agricultural work and the risk of Parkinson's disease in Denmark, 1981–1993. Scand J Work Environ Health. 2000;26:359–62.

355. Tsai CH, Lo SK, See LC, Chen HZ, Chen RS, Weng YH, et al. Environmental risk factors of young onset Parkinson's disease: a case-control study. Clin Neurol Neurosurg. 2002;104:328–33.

356. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to rural environmental factors: a population based case-control study. Can J Neurol Sci. 1991;18:279–86.

357. Marder K, Logroscino G, Alfaro B, Mejia H, Halim A, Louis E, et al. Environmental risk factors for Parkinson's disease in an urban multiethnic community. Neurology. 1998;50:279–81.

358. Tan EK, Tan C, Fook-Chong SM, Lum SY, Chai A, Chung H, et al. Dose-dependent protective effect of coffee, tea, and smoking in Parkinson's disease: a study in ethnic Chinese. J Neurol Sci. 2003;216:163–7.

359. Gatto NM, Cockburn M, Bronstein J, Manthripragada AD, Ritz B. Well-water consumption and Parkinson's disease in rural California. Environ Health Persp. 2009;117:1912–8.

360. Rybicki BA, Johnson CC, Uman J, Gorell JM. Parkinson's disease mortality and the industrial use of heavy metals in Michigan. Mov Disord. 1993;8:87–92.

361. Hatcher JM, Pennell KD, Miller GW. Parkinson's disease and pesticides: a toxicological perspective. Trends Pharmacol Sci. 2008;29:322–9.

362. Dick FD. Parkinson's disease and pesticide exposures. Br Med Bull. 2006;79–80:219–31.

363. Brown TP, Rumsby PC, Capleton AC, Rushton L, Levy LS. Pesticides and Parkinson's disease—is there a link? Environ Health Persp. 2006;114:156–64.

364. Li AA, Mink PJ, McIntosh LJ, Teta MJ, Finley B. Evaluation of epidemiologic and animal data associating pesticides with Parkinson's disease. J Occup Environ Med. 2005;47:1059–87.

365. Di Monte DA. The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? Lancet Neurol. 2003;2:531–8.

366. Sherer TB, Betarbet R, Greenamyre JT. Environment, mitochondria, and Parkinson's disease. Neuroscientist. 2002;8: 192–7.

367. 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;3:1301–6.

368. McCormack AL, Thiruchelvam M, Manning-Bog AB, Thiffault C, Langston JW, Cory-Slechta DA, et al. Environmental risk factors and Parkinson's disease: selective degeneration of nigral

dopaminergic neurons caused by the herbicide paraquat. Neurobiol Dis. 2002;10:119–27.

369. Thiruchelvam M, Richfield EK, Baggs RB, Tank AW, Cory-Slechta DA. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: implications for Parkinson's disease. J Neurosci. 2000;20:9207–14.

370. Uversky VN, Li J, Fink AL. Pesticides directly accelerate the rate of alpha-synuclein fibril formation: a possible factor in Parkinson's disease. FEBS Lett. 2001;500:105–8.

371. Hatcher JM, Richardson JR, Guillot TS, McCormack AL, Di Monte DA, Jones DP, et al. Dieldrin exposure induces oxidative damage in the mouse nigrostriatal dopamine system. Exp Neurol. 2007;204:619–30.

372. Le Couteur DG, McLean AJ, Taylor MC, Woodham BL, Board PG. Pesticides and Parkinson's disease. Biomed Pharmacother. 1999;53:122–30.

373. Di Monte DA, Lavasani M, Manning-Bog AB. Environmental factors in Parkinson's disease. Neurotoxicology. 2002;23:487–502.

374. Elbaz A, Tranchant C. Epidemiologic studies of environmental exposures in Parkinson's disease. J Neurol Sci. 2007;262:37–44.

375. Jankovic J. Searching for a relationship between manganese and welding and Parkinson's disease. Neurology. 2005;64:2021–8.

376. Kuhn W, Winkel R, Woitalla D, Meves S, Przuntek H, Muller T. High prevalence of parkinsonism after occupational exposure to lead-sulfate batteries. Neurology. 1998;50:1885–6.

377. Dexter DT, Wells FR, Agid F, Agid Y, Lees AJ, Jenner P, et al. Increased nigral iron content in postmortem parkinsonian brain. Lancet. 1987;2:1219–20.

378. Dexter DT, Carayon A, Javoy-Agid F, Agid Y, Wells FR, Daniel SE, et al. Alterations in the levels of iron, ferritin and other trace metals in Parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. Brain. 1991;114(Pt 4):1953–75.

379. Riederer P, Sofic E, Rausch WD, Schmidt B, Reynolds GP, Jellinger K, et al. Transition metals, ferritin, glutathione, and ascorbic acid in parkinsonian brains. J Neurochem. 1989;52:515–20.

380. Ngim CH, Devathasan G. Epidemiologic study on the association between body burden mercury level and idiopathic Parkinson's disease. Neuroepidemiology. 1989;8:128–41.

381. McDonnell L, Maginnis C, Lewis S, Pickering N, Antoniak M, Hubbard R, et al. Occupational exposure to solvents and metals and Parkinson's disease. Neurology. 2003;61:716–7.

382. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, et al. Occupational exposures to metals as risk factors for Parkinson's disease. Neurology. 1997;48:650–8.

383. Coon S, Stark A, Peterson E, Gloi A, Kortsha G, Pounds J, et al. Whole-body lifetime occupational lead exposure and risk of Parkinson's disease. Environ Health Persp. 2006;114:1872–6.

384. Jimenez-Jimenez FJ, Molina JA, Aguilar MV, Arrieta FJ, Jorge-Santamaria A, Cabrera-Valdivia F, et al. Serum and urinary manganese levels in patients with Parkinson's disease. Acta Neurol Scand. 1995;91:317–20.

385. Park J, Yoo CI, Sim CS, Kim JW, Yi Y, Shin YC, et al. A retrospective cohort study of Parkinson's disease in Korean shipbuilders. Neurotoxicology. 2006;27:445–9.

386. Finkelstein MM, Jerrett M. A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. Environ Res. 2007;104:420–32.

387. Fryzek JP, Hansen J, Cohen S, Bonde JP, Llambias MT, Kolstad HA, et al. A cohort study of Parkinson's disease and other neurodegenerative disorders in Danish welders. J Occup Environ Med. 2005;47:466–72.

388. Fored CM, Fryzek JP, Brandt L, Nise G, Sjogren B, McLaughlin JK, et al. Parkinson's disease and other basal ganglia or movement disorders in a large nationwide cohort of Swedish welders. Occup Environ Med. 2006;63:135–40.

389. Stampfer MJ. Welding occupations and mortality from Parkinson's disease and other neurodegenerative diseases among United States men, 1985–1999. J Occup Environ Hyg. 2009;6:267–72.

390. Marsh GM, Gula MJ. Employment as a welder and Parkinson disease among heavy equipment manufacturing workers. J Occup Environ Med. 2006;48:1031–46.

391. Logroscino G, Chen H, Wing A, Ascherio A. Blood donations, iron stores, and risk of Parkinson's disease. Mov Disord. 2006;21:835–8.

392. Marder K, Logroscino G, Tang MX, Graziano J, Cote L, Louis E, et al. Systemic iron metabolism and mortality from Parkinson's disease. Neurology. 1998;50:1138–40.

393. Ohlson CG, Hogstedt C. Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury—a case-referent study. Scand J Work Environ Health. 1981;7:252–6.

394. Savitz DA, Checkoway H, Loomis DP. Magnetic field exposure and neurodegenerative disease mortality among electric utility workers. Epidemiology. 1998;9:398–404.

395. Johansen C. Exposure to electromagnetic fields and risk of central nervous system disease in utility workers. Epidemiology. 2000;11:539–43.

396. Noonan CW, Reif JS, Yost M, Touchstone J. Occupational exposure to magnetic fields in case-referent studies of neurodegenerative diseases. Scand J Work Environ Health. 2002;28:42–8.

397. Li X, Sundquist J, Sundquist K. Socioeconomic and occupational groups and Parkinson's disease: a nationwide study based on hospitalizations in Sweden. Int Arch Occup Environ Health. 2009;82:235–41.

398. Dorn HF. Tobacco consumption and mortality from cancer and other diseases. Public Health Rep. 1959;74:581–93.

399. Kahn HA. The Dorn study of smoking and mortality among U.S. veterans: report on eight and one-half years of observation. Natl Cancer Inst Monogr. 1966;19:1–125.

400. Hammond EC. Smoking in relation to the death rates of one million men and women. Natl Cancer Inst Monogr. 1966;19:127–204.

401. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J. 1976;2:1525–36.

402. Shahi GS, Moochhala SM. Smoking and Parkinson's disease—a new perspective. Rev Environ Health. 1991;9:123–36.

403. Morens DM, Grandinetti A, Reed D, White LR, Ross GW. Cigarette smoking and protection from Parkinson's disease: false association or etiologic clue? Neurology. 1995;45:1041–51.

404. Nefzger MD, Quadfasel FA, Karl VC. A retrospective study of smoking in Parkinson's disease. Am J Epidemiol. 1968;88:149–58.

405. Kessler II, Diamond EL. Epidemiologic studies of Parkinson's disease. I. Smoking and Parkinson's disease: a survey and explanatory hypothesis. Am J Epidemiol. 1971;94:16–25.

406. Marttila RJ, Rinne UK. Smoking and Parkinson's disease. Acta Neurol Scand. 1980;62:322–5.

407. Haack DG, Baumann RJ, McKean HE, Jameson HD, Turbek JA. Nicotine exposure and Parkinson disease. Am J Epidemiol. 1981;114:191–200.

408. Godwin-Austen RB, Lee PN, Marmot MG, Stern GM. Smoking and Parkinson's disease. J Neurol Neurosurg Psychiatry. 1982;45:577–81.

409. Rajput AH, Offord KP, Beard CM, Kurland LT. A case-control study of smoking habits, dementia, and other illnesses in idiopathic Parkinson's disease. Neurology. 1987;37:226–32.

410. Mayeux R, Tang MX, Marder K, Cote LJ, Stern Y. Smoking and Parkinson's disease. Mov Disord. 1994;9:207–12.

411. Martyn CN, Osmond C. Parkinson's disease and the environment in early life. J Neurol Sci. 1995;132:201–6.

412. Hellenbrand W, Seidler A, Robra BP, Vieregge P, Oertel WH, Joerg J, et al. Smoking and Parkinson's disease: a case-control study in Germany. Int J Epidemiol. 1997;26:328–39.

413. Gorell JM, Rybicki BA, Johnson CC, Peterson EL. Smoking and Parkinson's disease: a dose-response relationship. Neurology. 1999;52:115–9.

414. Vanacore N, Bonifati V, Fabbrini G, Colosimo C, Marconi R, Nicholl D, et al. Smoking habits in multiple system atrophy and progressive supranuclear palsy. European Study Group on Atypical Parkinsonisms. Neurology. 2000;54:114–9.

415. 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;155:732–8.

416. Powers KM, Kay DM, Factor SA, Zabetian CP, Higgins DS, Samii A, et al. Combined effects of smoking, coffee, and NSAIDs on Parkinson's disease risk. Mov Disord. 2008;23:88–95.

417. Evans AH, Lawrence AD, Potts J, MacGregor L, Katzenschlager R, Shaw K, et al. Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006;77:317–21.

418. Elbaz A, Manubens-Bertran JM, Baldereschi M, Breteler MM, Grigoletto F, Lopez-Pousa S, et al. Parkinson's disease, smoking, and family history. EUROPARKINSON Study Group. J Neurol. 2000;247:793–8.

419. Tanner CM, Chen B, Wang WZ, Peng ML, Liu ZL, Liang XL, et al. Environmental factors in the etiology of Parkinson's disease. Can J Neurol Sci. 1987;14:419–23.

420. Hofman A, Collette HJ, Bartelds AI. Incidence and risk factors of Parkinson's disease in The Netherlands. Neuroepidemiology. 1989;8:296–9.

421. 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.

422. Tzourio C, Rocca WA, Breteler MM, Baldereschi M, Dartigues JF, Lopez-Pousa S, et al. Smoking and Parkinson's disease. An age-dependent risk effect? The EUROPARKINSON Study Group. Neurology. 1997;49:1267–72.

423. Benedetti MD, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study. Neurology. 2000;55:1350–8.

424. Ragonese P, Salemi G, Morgante L, Aridon P, Epifanio A, Buffa D, et al. A case-control study on cigarette, alcohol, and coffee consumption preceding Parkinson's disease. Neuroepidemiology. 2003;22:297–304.

425. Duvoisin RC, Eldridge R, Williams A, Nutt J, Calne D. Twin study of Parkinson disease. Neurology. 1981;31:77–80.

426. Bharucha NE, Stokes L, Schoenberg BS, Ward C, Ince S, Nutt JG, et al. A case-control study of twin pairs discordant for Parkinson's disease: a search for environmental risk factors. Neurology. 1986;36:284–8.

427. Tanner CM, Goldman SM, Aston DA, Ottman R, Ellenberg J, Mayeux R, et al. Smoking and Parkinson's disease in twins. Neurology. 2002;58:581–8.

428. 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;50:780–6.

429. Thacker EL, O'Reilly EJ, Weisskopf MG, Chen H, Schwarzschild MA, McCullough ML, et al. Temporal relationship between cigarette smoking and risk of Parkinson disease. Neurology. 2007;68:764–8.

430. Chen H, Huang X, Guo X, Mailman RB, Park Y, Kamel F, et al. Smoking duration, intensity, and risk of Parkinson disease. Neurology. 2010;74:878–84.

431. Tan LC, Koh WP, Yuan JM, Wang R, Au WL, Tan JH, et al. Differential effects of black versus green tea on risk of Parkinson's disease in the Singapore Chinese Health Study. Am J Epidemiol. 2008;167:553–60.

432. 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.

433. Sasco AJ, Paffenbarger RS Jr. Smoking and Parkinson's disease. Epidemiology. 1990;1:460–5.

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

435. Wirdefeldt K, Gatz M, Pawitan Y, Pedersen NL. Risk and protective factors for Parkinson's disease: a study in Swedish twins. Ann Neurol. 2005;57:27–33.

436. 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.

437. Sugita M, Izuno T, Tatemichi M, Otahara Y. Meta-analysis for epidemiologic studies on the relationship between smoking and Parkinson's disease. J Epidemiol. 2001;11:87–94.

438. Allam MF, Campbell MJ, Hofman A, Del Castillo AS, Fernandez-Crehuet Navajas R. Smoking and Parkinson's disease: systematic review of prospective studies. Mov Disord. 2004;19:614–21.

439. Allam MF, Del Castillo AS, Navajas RF. Parkinson's disease, smoking and family history: meta-analysis. Eur J Neurol. 2003;10:59–62.

440. Ritz B, Ascherio A, Checkoway H, Marder KS, Nelson LM, Rocca WA, et al. Pooled analysis of tobacco use and risk of Parkinson disease. Arch Neurol. 2007;64:990–7.

441. Fratiglioni L, Wang HX. Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. Behav Brain Res. 2000;113:117–20.

442. Golbe LI, Cody RA, Duvoisin RC. Smoking and Parkinson's disease. Search for a dose-response relationship. Arch Neurol. 1986;43:774–8.

443. Riggs JE. Cigarette smoking and Parkinson disease: the illusion of a neuroprotective effect. Clin Neuropharmacol. 1992;15:88–99.

444. Ward CD, Duvoisin RC, Ince SE, Nutt JD, Eldridge R, Calne DB, et al. Parkinson's disease in twins. Adv Neurol. 1984;40:341–4.

445. Ogawa T. Personality characteristics of Parkinson's disease. Percept Mot Skills. 1981;52:375–8.

446. Poewe W, Gerstenbrand F, Ransmayr G, Plorer S. Premorbid personality of Parkinson patients. J Neural Transm Suppl. 1983;19:215–24.

447. Scott WK, Zhang F, Stajich JM, Scott BL, Stacy MA, Vance JM. Family-based case-control study of cigarette smoking and Parkinson disease. Neurology. 2005;64:442–7.

448. Hancock DB, Martin ER, Stajich JM, Jewett R, Stacy MA, Scott BL, et al. Smoking, caffeine, and nonsteroidal anti-inflammatory drugs in families with Parkinson disease. Arch Neurol. 2007;64:576–80.

449. O'Reilly EJ, Chen H, Gardener H, Gao X, Schwarzschild MA, Ascherio A. Smoking and Parkinson's disease: using parental smoking as a proxy to explore causality. Am J Epidemiol. 2009;169:678–82.

450. Morozova N, O'Reilly EJ, Ascherio A. Variations in gender ratios support the connection between smoking and Parkinson's disease. Mov Disord. 2008;23:1414–9.

451. Kandinov B, Giladi N, Korczyn AD. Smoking and tea consumption delay onset of Parkinson's disease. Parkinsonism Relat Disord. 2009;15:41–6.

452. De Reuck J, De Weweire M, Van Maele G, Santens P. Comparison of age of onset and development of motor complications between smokers and non-smokers in Parkinson's disease. J Neurol Sci. 2005;231:35–9.

453. Alves G, Kurz M, Lie SA, Larsen JP. Cigarette smoking in Parkinson's disease: influence on disease progression. Mov Disord. 2004;19:1087–92.

454. Kandinov B, Giladi N, Korczyn AD. The effect of cigarette smoking, tea, and coffee consumption on the progression of Parkinson's disease. Parkinsonism Relat Disord. 2007;13:243–5.

455. O'Reilly EJ, McCullough ML, Chao A, Henley SJ, Calle EE, Thun MJ, et al. Smokeless tobacco use and the risk of Parkinson's disease mortality. Mov Disord. 2005;20:1383–4.

456. Quik M. Smoking, nicotine and Parkinson's disease. Trends Neurosci. 2004;27:561–8.

457. Hong DP, Fink AL, Uversky VN. Smoking and Parkinson's disease: does nicotine affect alpha-synuclein fibrillation? Biochim Biophys Acta. 2009;1794:282–90.

458. Hellenbrand W, Seidler A, Boeing H, Robra BP, Vieregge P, Nischan P, et al. Diet and Parkinson's disease. I: a possible role for the past intake of specific foods and food groups. Results from a self-administered food-frequency questionnaire in a case-control study. Neurology. 1996;47:636–43.

459. Hernan MA, Chen H, Schwarzschild MA, Ascherio A. Alcohol consumption and the incidence of Parkinson's disease. Ann Neurol. 2003;54:170–5.

460. Fertl E, Doppelbauer A, Auff E. Physical activity and sports in patients suffering from Parkinson's disease in comparison with healthy seniors. J Neural Transm Park Dis Dement Sect. 1993;5:157–61.

461. Sasco AJ, Paffenbarger RS Jr, Gendre I, Wing AL. The role of physical exercise in the occurrence of Parkinson's disease. Arch Neurol. 1992;49:360–5.

462. Chen H, Zhang SM, Schwarzschild MA, Hernan MA, Ascherio A. Physical activity and the risk of Parkinson disease. Neurology. 2005;64:664–9.

463. Logroscino G, Sesso HD, Paffenbarger RS Jr, Lee IM. Physical activity and risk of Parkinson's disease: a prospective cohort study. J Neurol Neurosurg Psychiatry. 2006;77:1318–22.

464. Thacker EL, Chen H, Patel AV, McCullough ML, Calle EE, Thun MJ, et al. Recreational physical activity and risk of Parkinson's disease. Mov Disord. 2008;23:69–74.

465. Ragonese P, D'Amelio M, Callari G, Di Benedetto N, Palmeri B, Mazzola MA, et al. Body mass index does not change before Parkinson's disease onset. Eur J Neurol. 2008;15:965–8.

466. Ma L, Zhang L, Gao XH, Chen W, Wu YP, Wang Y, et al. Dietary factors and smoking as risk factors for PD in a rural population in China: a nested case-control study. Acta Neurol Scand. 2006;113:278–81.

467. Abbott RD, Ross GW, White LR, Nelson JS, Masaki KH, Tanner CM, et al. Midlife adiposity and the future risk of Parkinson's disease. Neurology. 2002;59:1051–7.

468. Hu G, Jousilahti P, Nissinen A, Antikainen R, Kivipelto M, Tuomilehto J. Body mass index and the risk of Parkinson disease. Neurology. 2006;67:1955–9.

469. Chen H, Zhang SM, Schwarzschild MA, Hernan MA, Willett WC, Ascherio A. Obesity and the risk of Parkinson's disease. Am J Epidemiol. 2004;159:547–55.

470. Logroscino G, Sesso HD, Paffenbarger RS Jr, Lee IM. Body mass index and risk of Parkinson's disease: a prospective cohort study. Am J Epidemiol. 2007;166:1186–90.

471. Golbe LI, Farrell TM, Davis PH. Case-control study of early life dietary factors in Parkinson's disease. Arch Neurol. 1988;45:1350–3.

472. Vieregge P, von Maravic C, Friedrich HJ. Life-style and dietary factors early and late in Parkinson's disease. Can J Neurol Sci. 1992;19:170–3.

473. Kondo K, Watanabe K. Lifestyles, risk factors, and inherited predispositions in Parkinson's disease. Preliminary report of a case-control study. Adv Neurol. 1993;60:346–51.

474. Ayuso-Peralta L, Jimenez-Jimenez FJ, Cabrera-Valdivia F, Molina J, Javier MR, Almazan J, et al. Premorbid dietetic habits and risk for Parkinson's disease. Parkinsonism Relat Disord. 1997;3:55–61.

475. Ross GW, Petrovitch H. Current evidence for neuroprotective effects of nicotine and caffeine against Parkinson's disease. Drugs Aging. 2001;18:797–806.

476. Schwarzschild MA, Agnati L, Fuxe K, Chen JF, Morelli M. Targeting adenosine A2A receptors in Parkinson's disease. Trends Neurosci. 2006;29:647–54.

477. Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH, et al. Association of coffee and caffeine intake with the risk of Parkinson disease. Jama. 2000;283:2674–9.

478. Ascherio A, Zhang SM, Hernan MA, Kawachi I, Colditz GA, Speizer FE, et al. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Ann Neurol. 2001;50:56–63.

479. Ascherio A, Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Rodriguez C, 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.

480. Xu K, Xu Y, Brown-Jermyn D, Chen JF, Ascherio A, Dluzen DE, 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.

481. Hu G, Bidel S, Jousilahti P, Antikainen R, Tuomilehto J. Coffee and tea consumption and the risk of Parkinson's disease. Mov Disord. 2007;22:2242–8.

482. Saaksjarvi K, Knekt P, Rissanen H, Laaksonen MA, Reunanen A, Mannisto S. Prospective study of coffee consumption and risk of Parkinson's disease. Eur J Clin Nutr. 2008;62:908–15.

483. 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.

484. Park M, Ross GW, Petrovitch H, White LR, Masaki KH, Nelson JS, et al. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. Neurology. 2005;64:1047–51.

485. Chen H, O'Reilly E, McCullough ML, Rodriguez C, Schwarzschild MA, Calle EE, et al. Consumption of dairy products and risk of Parkinson's disease. Am J Epidemiol. 2007;165:998–1006.

486. Hellenbrand W, Boeing H, Robra BP, Seidler A, Vieregge P, Nischan P, 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.

487. 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.

488. 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;14:21–7.

489. 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;28:1102–9.

490. Murakami K, Miyake Y, Sasaki S, Tanaka K, Fukushima W, Kiyohara C, et al. Dietary glycemic index is inversely associated with the risk of Parkinson's disease: a case-control study in Japan. Nutrition. 2010;26:515–21.

491. 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.

492. 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;60:1761–6.

493. Powers KM, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD, Checkoway H. Dietary fats, cholesterol and iron as risk factors for Parkinson's disease. Parkinsonism Relat Disord. 2009;15:47–52.

494. 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;64:2040–5.

495. Abbott RA, Cox M, Markus H, Tomkins A. Diet, body size and micronutrient status in Parkinson's disease. Eur J Clin Nutr. 1992;46:879–84.

496. King D, Playfer JR, Roberts NB. Concentrations of vitamins A, C and E in elderly patients with Parkinson's disease. Postgrad Med J. 1992;68:634–7.

497. Fernandez-Calle P, Jimenez-Jimenez FJ, Molina JA, Cabrera-Valdivia F, Vazquez A, Garcia Urra D, et al. Serum levels of ascorbic acid (vitamin C) in patients with Parkinson's disease. J Neurol Sci. 1993;118:25–8.

498. Jimenez-Jimenez FJ, Molina JA, Fernandez-Calle P, Vazquez A, Cabrera-Valdivia F, Catalan MJ, et al. Serum levels of beta-carotene and other carotenoids in Parkinson's disease. Neurosci Lett. 1993;157:103–6.

499. Fernandez-Calle P, Molina JA, Jimenez-Jimenez FJ, Vazquez A, Pondal M, Garcia-Ruiz PJ, et al. Serum levels of alpha-tocopherol (vitamin E) in Parkinson's disease. Neurology. 1992;42:1064–6.

500. Jimenez-Jimenez FJ, Molina JA, Fernandez-Calle P, Vazquez A, Pondal M, del Ser T, et al. Serum levels of vitamin A in Parkinson's disease. J Neurol Sci. 1992;111:73–6.

501. 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;12:190–6.

502. de Rijk MC, Breteler MM, den Breeijen JH, Launer LJ, Grobbee DE, van der Meche FG, et al. Dietary antioxidants and Parkinson disease. The Rotterdam Study. Arch Neurol. 1997;54:762–5.

503. 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;46:1270–4.

504. 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;59:1161–9.

505. Etminan M, Gill SS, Samii A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. Lancet Neurol. 2005;4:362–5.

506. The Parkinson Study Group N. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med. 1993;328:176–83.

507. Evatt ML, Delong MR, Khazai N, Rosen A, Triche S, Tangpricha V. Prevalence of vitamin d insufficiency in patients with Parkinson disease and Alzheimer disease. Arch Neurol. 2008;65:1348–52.

508. Knekt P, Kilkkinen A, Rissanen H, Marniemi J, Saaksjarvi K, Heliovaara M. Serum vitamin D and the risk of Parkinson disease. Arch Neurol. 2010;67:808–11.

509. Chen H, Zhang SM, Schwarzschild MA, Hernan MA, Logroscino G, Willett WC, et al. Folate intake and risk of Parkinson's disease. Am J Epidemiol. 2004;160:368–75.

510. de Lau LM, Koudstaal PJ, Witteman JC, Hofman A, Breteler MM. Dietary folate, vitamin B12, and vitamin B6 and the risk of Parkinson disease. Neurology. 2006;67:315–8.

511. Logroscino G, Marder K, Graziano J, Freyer G, Slavkovich V, Lojacono N, et al. Dietary iron, animal fats, and risk of Parkinson's disease. Mov Disord. 1998;13(Suppl 1):13–6.

512. Logroscino G, Gao X, Chen H, Wing A, Ascherio A. Dietary iron intake and risk of Parkinson's disease. Am J Epidemiol. 2008;168:1381–8.

513. Doty RL, Deems DA, Stellar S. Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology. 1988;38:1237–44.

514. Hawkes CH, Shephard BC, Daniel SE. Olfactory dysfunction in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1997;62:436–46.

515. Berendse HW, Booij J, Francot CM, Bergmans PL, Hijman R, Stoof JC, et al. Subclinical dopaminergic dysfunction in asymptomatic Parkinson's disease patients' relatives with a decreased sense of smell. Ann Neurol. 2001;50:34–41.

516. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BL, Wolters E, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol. 2004;56:173–81.

517. Ponsen MM, Stoffers D, Wolters E, Booij J, Berendse HW. Olfactory testing combined with dopamine transporter imaging as a method to detect prodromal Parkinson's disease. J Neurol Neurosurg Psychiatry. 2010;81:396–9.

518. Ross GW, Petrovitch H, Abbott RD, Tanner CM, Popper J, Masaki K, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol. 2008;63:167–73.

519. Marras C, Goldman S, Smith A, Barney P, Aston D, Comyns K, et al. Smell identification ability in twin pairs discordant for Parkinson's disease. Mov Disord. 2005;20:687–93.

520. Gagnon JF, Postuma RB, Mazza S, Doyon J, Montplaisir J. Rapid-eye-movement sleep behaviour disorder and neurodegenerative diseases. Lancet Neurol. 2006;5:424–32.

521. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology. 1996;46:388–93.

522. Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Marti MJ, Valldeoriola F, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol. 2006;5:572–7.

523. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology. 2009;72:1296–300.

524. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology. 2010;75:494–9.

525. Gamboa ET, Wolf A, Yahr MD, Harter DH, Duffy PE, Barden H, et al. Influenza virus antigen in postencephalitic parkinsonism brain. Detection by immunofluorescence. Arch Neurol. 1974;31:228–32.

526. Ravenholt RT, Foege WH. 1918 influenza, encephalitis lethargica, parkinsonism. Lancet. 1982;2:860–4.

527. Poskanzer DC, Schwab RS. Cohort analysis of Parkinson's syndrome: evidence for a single etiology related to subclinical infection about 1920. J Chronic Dis. 1963;16:961–73.

528. Duvoisin RC, Yahr MD, Schweitzer MD, Merritt HH. Parkinsonism before and since the Epidemic of Encephalitis Lethargica. Arch Neurol. 1963;9:232–6.

529. Schwartz J, Elizan TS. Search for viral particles and virus-specific products in idiopathic Parkinson disease brain material. Ann Neurol. 1979;6:261–3.

530. Wetmur JG, Schwartz J, Elizan TS. Nucleic acid homology studies of viral nucleic acids in idiopathic Parkinson's disease. Arch Neurol. 1979;36:462–4.

531. Takahashi M, Yamada T, Nakajima S, Nakajima K, Yamamoto T, Okada H. The substantia nigra is a major target for neurovirulent influenza A virus. J Exp Med. 1995;181:2161–9.

532. Takahashi M, Yamada T. A possible role of influenza A virus infection for Parkinson's disease. Adv Neurol. 2001;86:91–104.

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

534. Fazzini E, Fleming J, Fahn S. Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. Mov Disord. 1992;7:153–8.

535. Fiszer U, Tomik B, Grzesiowski P, Krygowska-Wajs A, Walory J, Michalowska M, et al. The antibodies against Bordetella pertussis in sera of patients with Parkinson's disease and other non-neurological diseases. Acta Neurol Scand. 2004;110: 113–7.

536. Hubble JP, Cao T, Kjelstrom JA, Koller WC, Beaman BL. Nocardia species as an etiologic agent in Parkinson's disease: serological testing in a case-control study. J Clin Microbiol. 1995;33:2768–9.

537. Marttila RJ, Halonen P, Rinne UK. Influenza virus antibodies in Parkinsonism. Comparison of postencephalic and idiopathic Parkinson patients and matched controls. Arch Neurol. 1977;34:99–100.

538. Marttila RJ, Arstila P, Nikoskelainen J, Halonen PE, Rinne UK. Viral antibodies in the sera from patients with Parkinson disease. Eur Neurol. 1977;15:25–33.

539. Elizan TS, Madden DL, Noble GR, Herrmann KL, Gardner J, Schwartz J, et al. Viral antibodies in serum and CSF of Parkinsonian patients and controls. Arch Neurol. 1979;36:529–34.

540. Powers KM, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD, Checkoway H. Diabetes, smoking, and other medical conditions in relation to Parkinson's disease risk. Parkinsonism Relat Disord. 2006;12:185–9.

541. Sasco AJ, Paffenbarger RS Jr. Measles infection and Parkinson's disease. Am J Epidemiol. 1985;122:1017–31.

542. Mattock C, Marmot M, Stern G. Could Parkinson's disease follow intra-uterine influenza?: a speculative hypothesis. J Neurol Neurosurg Psychiatry. 1988;51:753–6.

543. Ebmeier KP, Mutch WJ, Calder SA, Crawford JR, Stewart L, Besson JO. Does idiopathic parkinsonism in Aberdeen follow intrauterine influenza? J Neurol Neurosurg Psychiatry. 1989;52: 911–3.

544. Logroscino G. The role of early life environmental risk factors in Parkinson disease: what is the evidence? Environ Health Persp. 2005;113:1234–8.

545. Miura T, Shimura M, Kimura T. Season of birth in parkinsonism. Prog Biometeorol. 1987;6:157–62.

546. Betemps EJ, Buncher CR. Birthplace as a risk factor in motor neurone disease and Parkinson's disease. Int J Epidemiol. 1993;22:898–904.

547. Kurtzke JF, Goldberg ID. Parkinsonism death rates by race, sex, and geography. Neurology. 1988;38:1558–61.

548. Liu B, Gao HM, Hong JS. Parkinson's disease and exposure to infectious agents and pesticides and the occurrence of brain injuries: role of neuroinflammation. Environ Health Persp. 2003;111:1065–73.

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

550. McGeer PL, Yasojima K, McGeer EG. Inflammation in Parkinson's disease. Adv Neurol. 2001;86:83–9.

551. Esposito E, Di Matteo V, Benigno A, Pierucci M, Crescimanno G, Di Giovanni G. Non-steroidal anti-inflammatory drugs in Parkinson's disease. Exp Neurol. 2007;205:295–312.

552. Stypula G, Kunert-Radek J, Stepien H, Zylinska K, Pawlikowski M. Evaluation of interleukins, ACTH, cortisol and prolactin concentrations in the blood of patients with parkinson's disease. Neuroimmunomodulation. 1996;3:131–4.

553. Dobbs RJ, Charlett A, Purkiss AG, Dobbs SM, Weller C, Peterson DW. Association of circulating TNF-alpha and IL-6 with ageing and parkinsonism. Acta Neurol Scand. 1999;100:34–41.

554. Chen H, O'Reilly EJ, Schwarzschild MA, Ascherio A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. Am J Epidemiol. 2008;167:90–5.

555. Gao HM, Jiang J, Wilson B, Zhang W, Hong JS, Liu B. Microglial activation-mediated delayed and progressive degeneration of rat nigral dopaminergic neurons: relevance to Parkinson's disease. J Neurochem. 2002;81:1285–97.

556. Wang T, Pei Z, Zhang W, Liu B, Langenbach R, Lee C, et al. MPP+-induced COX-2 activation and subsequent dopaminergic neurodegeneration. FASEB J. 2005;19:1134–6.

557. Chen H, Zhang SM, Hernan MA, Schwarzschild MA, Willett WC, Colditz GA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol. 2003;60:1059–64.

558. Chen H, Jacobs E, Schwarzschild MA, McCullough ML, Calle EE, Thun MJ, et al. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. Ann Neurol. 2005;58:963–7.

559. Bornebroek M, de Lau LM, Haag MD, Koudstaal PJ, Hofman A, Stricker BH, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Neuroepidemiology. 2007;28:193–6.

560. Bower JH, Maraganore DM, Peterson BJ, Ahlskog JE, Rocca WA. Immunologic diseases, anti-inflammatory drugs, and Parkinson disease: a case-control study. Neurology. 2006;67:494–6.

561. Ton TG, Heckbert SR, Longstreth WT Jr, Rossing MA, Kukull WA, Franklin GM, et al. Nonsteroidal anti-inflammatory drugs and risk of Parkinson's disease. Mov Disord. 2006;21:964–9.

562. Hernan MA, Logroscino G, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and the incidence of Parkinson disease. Neurology. 2006;66:1097–9.

563. Gagne JJ, Power MC. Anti-inflammatory drugs and risk of Parkinson disease: a meta-analysis. Neurology. 2010;74:995–1002.

564. Leentjens AF, Van den Akker M, Metsemakers JF, Lousberg R, Verhey FR. Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord. 2003;18:414–8.

565. Schuurman AG, van den Akker M, Ensinck KT, Metsemakers JF, Knottnerus JA, Leentjens AF, et al. Increased risk of Parkinson's disease after depression: a retrospective cohort study. Neurology. 2002;58:1501–4.

566. Shiba M, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Mov Disord. 2000;15:669–77.

567. Nilsson FM, Kessing LV, Bolwig TG. Increased risk of developing Parkinson's disease for patients with major affective disorder: a register study. Acta Psychiatr Scand. 2001;104:380–6.

568. Li X, Sundquist J, Hwang H, Sundquist K. Impact of psychiatric disorders on Parkinson's disease: a nationwide follow-up study from Sweden. J Neurol. 2008;255:31–6.

569. Stern SL, Hurtig HI, Mendels J, Balaban D. Psychiatric illness in relatives of patients with Parkinson's disease: a preliminary report. Am J Psychiatry. 1977;134:443–4.

570. Fahim S, van Duijn CM, Baker FM, Launer L, Breteler MM, Schudel WJ, et al. A study of familial aggregation of depression, dementia and Parkinson's disease. Eur J Epidemiol. 1998;14:233–8.

571. Arabia G, Grossardt BR, Geda YE, Carlin JM, Bower JH, Ahlskog JE, et al. Increased risk of depressive and anxiety

disorders in relatives of patients with Parkinson disease. Arch Gen Psychiatry. 2007;64:1385–92.

572. Hofman A, Schulte W, Tanja TA, van Duijn CM, Haaxma R, Lameris AJ, et al. History of dementia and Parkinson's disease in 1st-degree relatives of patients with Alzheimer's disease. Neurology. 1989;39:1589–92.

573. Amaducci LA, Fratiglioni L, Rocca WA, Fieschi C, Livrea P, Pedone D, et al. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. Neurology. 1986;36:922–31.

574. van Duijn CM, Clayton D, Chandra V, Fratiglioni L, Graves AB, Heyman A, et al. Familial aggregation of Alzheimer's disease and related disorders: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. Int J Epidemiol. 1991;20(Suppl 2):S13–20.

575. Huff FJ, Auerbach J, Chakravarti A, Boller F. Risk of dementia in relatives of patients with Alzheimer's disease. Neurology. 1988;38:786–90.

576. Li G, Shen YC, Li YT, Chen CH, Zhau YW, Silverman JM. A case-control study of Alzheimer's disease in China. Neurology. 1992;42:1481–8.

577. Fratiglioni L, Ahlbom A, Viitanen M, Winblad B. Risk factors for late-onset Alzheimer's disease: a population-based, case-control study. Ann Neurol. 1993;33:258–66.

578. Silverman JM, Raiford K, Edland S, Fillenbaum G, Morris JC, Clark CM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part VI. Family history assessment: a multicenter study of first-degree relatives of Alzheimer's disease probands and nondemented spouse controls. Neurology. 1994;44:1253–9.

579. Marder K, Tang MX, Alfaro B, Mejia H, Cote L, Louis E, et al. Risk of Alzheimer's disease in relatives of Parkinson's disease patients with and without dementia. Neurology. 1999;52:719–24.

580. Levy G, Louis ED, Mejia-Santana H, Cote L, Andrews H, Harris J, et al. Lack of familial aggregation of Parkinson disease and Alzheimer disease. Arch Neurol. 2004;61:1033–9.

581. Rosen AR, Steenland NK, Hanfelt J, Factor SA, Lah JJ, Levey AI. Evidence of shared risk for Alzheimer's disease and Parkinson's disease using family history. Neurogenetics. 2007;8:263–70.

582. Rocca WA, Bower JH, Ahlskog JE, Elbaz A, Grossardt BR, McDonnell SK, et al. Risk of cognitive impairment or dementia in relatives of patients with Parkinson disease. Arch Neurol. 2007;64:1458–64.

583. Costello S, Bordelon Y, Bronstein J, Ritz B. Familial associations of Alzheimer disease and essential tremor with Parkinson disease. Eur J Neurol. 2010;17:871–8.

584. Shahed J, Jankovic J. Exploring the relationship between essential tremor and Parkinson's disease. Parkinsonism Relat Disord. 2007;13:67–76.

585. Geraghty JJ, Jankovic J, Zetusky WJ. Association between essential tremor and Parkinson's disease. Ann Neurol. 1985;17:329–33.

586. Hornabrook RW, Nagurney JT. Essential tremor in Papua, New Guinea. Brain. 1976;99:659–72.

587. Rajput AH, Offord KP, Beard CM, Kurland LT. Essential tremor in Rochester, Minnesota: a 45-year study. J Neurol Neurosurg Psychiatry. 1984;47:466–70.

588. Larsson T, Sjogren T. Essential tremor: a clinical and genetic population study. Acta Psychiatr Scand Suppl. 1960;36:1–176.

589. Cleeves L, Findley LJ, Koller W. Lack of association between essential tremor and Parkinson's disease. Ann Neurol. 1988;24:23–6.

590. Louis ED, Levy G, Mejia-Santana H, Cote L, Andrews H, Harris J, et al. Risk of action tremor in relatives of tremor-dominant and postural instability gait disorder PD. Neurology. 2003;61:931–6.

591. Rocca WA, Bower JH, Ahlskog JE, Elbaz A, Grossardt BR, McDonnell SK, et al. Increased risk of essential tremor in first-degree relatives of patients with Parkinson's disease. Mov Disord. 2007;22:1607–14.

592. Benito-Leon J, Louis ED, Bermejo-Pareja F. Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study. J Neurol Neurosurg Psychiatry. 2009;80:423–5.

593. Westlund K, Hougen A. Cancer as a cause of death among patients with other cronic diseases. JAMA. 1956;162:1003.

594. Pritchard PB III, Netsky MG. Prevalence of neoplasms and causes of death in paralysis agitans. A necropsy study. Neurology. 1973;23:215–22.

595. Harada H, Nishikawa S, Takahashi K. Epidemiology of Parkinson's disease in a Japanese city. Arch Neurol. 1983;40:151–4.

596. Jansson B, Jankovic J. Low cancer rates among patients with Parkinson's disease. Ann Neurol. 1985;17:505–9.

597. Moller H, Mellemkjaer L, McLaughlin JK, Olsen JH. Occurrence of different cancers in patients with Parkinson's disease. BMJ. 1995;310:1500–1.

598. Raschetti R, Spila-Alegiani S, Vanacore N, Ancona C, Meco G. Mortality in a population-based cohort of patients treated with antiparkinsonian drugs. Acta Neurol Scand. 1998;97:20–6.

599. Vanacore N, Spila-Alegiani S, Raschetti R, Meco G. Mortality cancer risk in parkinsonian patients: a population-based study. Neurology. 1999;52:395–8.

600. Minami Y, Yamamoto R, Nishikouri M, Fukao A, Hisamichi S. Mortality and cancer incidence in patients with Parkinson's disease. J Neurol. 2000;247:429–34.

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

602. Elbaz A, Peterson BJ, Yang P, Van Gerpen JA, Bower JH, Maraganore DM, et al. Nonfatal cancer preceding Parkinson's disease: a case-control study. Epidemiology. 2002;13:157–64.

603. Elbaz A, Peterson BJ, Bower JH, Yang P, Maraganore DM, McDonnell SK, et al. Risk of cancer after the diagnosis of Parkinson's disease: a historical cohort study. Mov Disord. 2005;20:719–25.

604. Olsen JH, Friis S, Frederiksen K, McLaughlin JK, Mellemkjaer L, Moller H. Atypical cancer pattern in patients with Parkinson's disease. Br J Cancer. 2005;92:201–5.

605. Olsen JH, Friis S, Frederiksen K. Malignant melanoma and other types of cancer preceding Parkinson disease. Epidemiology. 2006;17:582–7.

606. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Cancer risk in association with Parkinson disease: a population-based study. Parkinsonism Relat Disord. 2010;16:186–90.

607. Driver JA, Kurth T, Buring JE, Gaziano JM, Logroscino G. Prospective case-control study of nonfatal cancer preceding the diagnosis of Parkinson's disease. Cancer Causes Control. 2007;18:705–11.

608. Driver JA, Logroscino G, Buring JE, Gaziano JM, Kurth T. A prospective cohort study of cancer incidence following the diagnosis of Parkinson's disease. Cancer Epidemiol Biomarkers Prev. 2007;16:1260–5.

609. Lerner MR, Goldman RS. Skin colour, MPTP, and Parkinson's disease. Lancet. 1987;2:212.

610. Gao X, Simon KC, Han J, Schwarzschild MA, Ascherio A. Genetic determinants of hair color and Parkinson's disease risk. Ann Neurol. 2009;65:76–82.

611. Zanetti R, Loria D, Rosso S. Melanoma, Parkinson's disease and levodopa: causal or spurious link? A review of the literature. Melanoma Res. 2006;16:201–6.

612. Vermeij JD, Winogrodzka A, Trip J, Weber WE. Parkinson's disease, levodopa-use and the risk of melanoma. Parkinsonism Relat Disord. 2009;15:551–3.

613. Zanetti R, Rosso S, Loria DI. Parkinson's disease and cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:1081.

614. Gao X, Simon KC, Han J, Schwarzschild MA, Ascherio A. Family history of melanoma and Parkinson disease risk. Neurology. 2009;73:1286–91.

615. Herrero Hernandez E. Pigmentation genes link Parkinson's disease to melanoma, opening a window on both etiologies. Med Hypotheses. 2009;72:280–4.

616. Bajaj A, Driver JA, Schernhammer ES. Parkinson's disease and cancer risk: a systematic review and meta-analysis. Cancer Causes Control. 2010;21:697–707.

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

618. Inzelberg R, Jankovic J. Are Parkinson disease patients protected from some but not all cancers? Neurology. 2007;69:1542–50.

619. D'Amelio M, Ragonese P, Sconzo G, Aridon P, Savettieri G. Parkinson's disease and cancer: insights for pathogenesis from epidemiology. Ann N Y Acad Sci. 2009;1155:324–34.

620. Lacava G. Boxer's Encephalopathy. J Sports Med Phys Fitness. 1963;168:87–92.

621. Factor SA, Weiner WJ. Prior history of head trauma in Parkinson's disease. Mov Disord. 1991;6:225–9.

622. Stern MB. Head trauma as a risk factor for Parkinson's disease. Mov Disord. 1991;6:95–7.

623. Bower JH, Maraganore DM, Peterson BJ, McDonnell SK, Ahlskog JE, Rocca WA. Head trauma preceding PD: a case-control study. Neurology. 2003;60:1610–5.

624. Goldman SM, Tanner CM, Oakes D, Bhudhikanok GS, Gupta A, Langston JW. Head injury and Parkinson's disease risk in twins. Ann Neurol. 2006;60:65–72.

625. Maher NE, Golbe LI, Lazzarini AM, Mark MH, Currie LJ, Wooten GF, et al. Epidemiologic study of 203 sibling pairs with Parkinson's disease: the GenePD study. Neurology. 2002;58:79–84.

626. Williams DB, Annegers JF, Kokmen E, O'Brien PC, Kurland LT. Brain injury and neurologic sequelae: a cohort study of dementia, parkinsonism, and amyotrophic lateral sclerosis. Neurology. 1991;41:1554–7.

627. Rugbjerg K, Ritz B, Korbo L, Martinussen N, Olsen JH. Risk of Parkinson's disease after hospital contact for head injury: population based case-control study. BMJ. 2008;337:a2494.

628. Spangenberg S, Hannerz H, Tuchsen F, Mikkelsen KL. A nationwide population study of severe head injury and Parkinson's disease. Parkinsonism Relat Disord. 2009;15:12–4.

629. Pressley JC, Louis ED, Tang MX, Cote L, Cohen PD, Glied S, et al. The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism. Neurology. 2003;60:87–93.

630. D'Amelio M, Ragonese P, Callari G, Di Benedetto N, Palmeri B, Terruso V, et al. Diabetes preceding Parkinson's disease onset. A case-control study. Parkinsonism Relat Disord. 2009;15:660–4.

631. Scigliano G, Musicco M, Soliveri P, Piccolo I, Ronchetti G, Girotti F. Reduced risk factors for vascular disorders in Parkinson disease patients: a case-control study. Stroke. 2006;37:1184–8.

632. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. Diabetes Care. 2007;30:842–7.

633. Driver JA, Smith A, Buring JE, Gaziano JM, Kurth T, Logroscino G. Prospective cohort study of type 2 diabetes and the risk of Parkinson's disease. Diabetes Care. 2008;31:2003–5.

634. Simon KC, Chen H, Schwarzschild M, Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. Neurology. 2007;69:1688–95.

635. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Diabetes in patients with idiopathic Parkinson's disease. Diabetes Care. 2008;31:1808–12.

636. Becker C, Jick SS, Meier CR. Risk of stroke in patients with idiopathic Parkinson disease. Parkinsonism Relat Disord. 2009;16:31–5.

637. Okello E, Jiang X, Mohamed S, Zhao Q, Wang T. Combined statin/coenzyme Q10 as adjunctive treatment of chronic heart failure. Med Hypotheses. 2009;73:306–8.

638. Huang X, Chen H, Miller WC, Mailman RB, Woodard JL, Chen PC, et al. Lower low-density lipoprotein cholesterol levels are associated with Parkinson's disease. Mov Disord. 2007;22:377–81.

639. Huang X, Abbott RD, Petrovitch H, Mailman RB, Ross GW. Low LDL cholesterol and increased risk of Parkinson's disease: prospective results from Honolulu-Asia Aging Study. Mov Disord. 2008;23:1013–8.

640. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum cholesterol levels and the risk of Parkinson's disease. Am J Epidemiol. 2006;164:998–1002.

641. Hu G, Antikainen R, Jousilahti P, Kivipelto M, Tuomilehto J. Total cholesterol and the risk of Parkinson disease. Neurology. 2008;70:1972–9.

642. Becker C, Meier CR. Statins and the risk of Parkinson disease: an update on the controversy. Expert Opin Drug Saf. 2009;8:261–71.

643. Becker C, Jick SS, Meier CR. Use of statins and the risk of Parkinson's disease: a retrospective case-control study in the UK. Drug Saf. 2008;31:399–407.

644. Shulman LM. Is there a connection between estrogen and Parkinson's disease? Parkinsonism Relat Disord. 2002;8:289–95.

645. Marder K, Tang MX, Alfaro B, Mejia H, Cote L, Jacobs D, et al. Postmenopausal estrogen use and Parkinson's disease with and without dementia. Neurology. 1998;50:1141–3.

646. Saunders-Pullman R, Gordon-Elliott J, Parides M, Fahn S, Saunders HR, Bressman S. The effect of estrogen replacement on early Parkinson's disease. Neurology. 1999;52:1417–21.

647. Benedetti MD, Maraganore DM, Bower JH, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Hysterectomy, menopause, and estrogen use preceding Parkinson's disease: an exploratory case-control study. Mov Disord. 2001;16:830–7.

648. Ragonese P, D'Amelio M, Salemi G, Aridon P, Gammino M, Epifanio A, et al. Risk of Parkinson disease in women: effect of reproductive characteristics. Neurology. 2004;62:2010–4.

649. Currie LJ, Harrison MB, Trugman JM, Bennett JP, Wooten GF. Postmenopausal estrogen use affects risk for Parkinson disease. Arch Neurol. 2004;61:886–8.

650. Ascherio A, Chen H, Schwarzschild MA, Zhang SM, Colditz GA, Speizer FE. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. Neurology. 2003;60:790–5.

651. Simon KC, Chen H, Gao X, Schwarzschild MA, Ascherio A. Reproductive factors, exogenous estrogen use, and risk of Parkinson's disease. Mov Disord. 2009;24:1359–65.

652. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology. 2008;70:200–9.

653. Frigerio R, Breteler MM, de Lau LM, Sanft KR, Bower JH, Ahlskog JE, et al. Number of children and risk of Parkinson's disease. Mov Disord. 2007;22:632–9.

654. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA. 1981;78:6858–62.

655. Church WH, Ward VL. Uric acid is reduced in the substantia nigra in Parkinson's disease: effect on dopamine oxidation. Brain Res Bull. 1994;33:419–25.

656. Tohgi H, Abe T, Takahashi S, Kikuchi T. The urate and xanthine concentrations in the cerebrospinal fluid in patients with vascular dementia of the Binswanger type, Alzheimer type dementia, and Parkinson's disease. J Neural Transm Park Dis Dement Sect. 1993;6:119–26.

657. Ahlskog JE, Uitti RJ, Low PA, Tyce GM, Nickander KK, Petersen RC, et al. No evidence for systemic oxidant stress in Parkinson's or Alzheimer's disease. Mov Disord. 1995;10:566–73.

658. Annanmaki T, Muuronen A, Murros K. Low plasma uric acid level in Parkinson's disease. Mov Disord. 2007;22:1133–7.

659. Davis JW, Grandinetti A, Waslien CI, Ross GW, White LR, Morens DM. Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. Am J Epidemiol. 1996;144: 480–4.

660. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum uric acid levels and the risk of Parkinson disease. Ann Neurol. 2005;58:797–800.

661. Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA, Ascherio A. Plasma urate and risk of Parkinson's disease. Am J Epidemiol. 2007;166:561–7.

662. Chen H, Mosley TH, Alonso A, Huang X. Plasma urate and Parkinson's disease in the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol. 2009;169:1064–9.

663. Alonso A, Rodriguez LA, Logroscino G, Hernan MA. Gout and risk of Parkinson disease: a prospective study. Neurology. 2007;69:1696–700.

664. De Vera M, Rahman MM, Rankin J, Kopec J, Gao X, Choi H. Gout and the risk of Parkinson's disease: a cohort study. Arthritis Rheum. 2008;59:1549–54.

665. Schwarzschild MA, Schwid SR, Marek K, Watts A, Lang AE, Oakes D, et al. Serum urate as a predictor of clinical and radiographic progression in Parkinson disease. Arch Neurol. 2008;65:716–23.

666. Ascherio A, LeWitt PA, Xu K, Eberly S, Watts A, Matson WR, et al. Urate as a predictor of the rate of clinical decline in Parkinson disease. Arch Neurol. 2009;66:1460–8.

667. Bronstein J, Carvey P, Chen H, Cory-Slechta D, DiMonte D, Duda J, et al. Meeting report: Consensus statement–Parkinson's disease and the environment: Collaborative on Health and the Environment and Parkinson's Action Network (CHE PAN) Conference 26–28 June 2007. Environ Health Persp. 2009;117: 117–21.

668. Vieregge A, Sieberer M, Jacobs H, Hagenah JM, Vieregge P. Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. Neurology. 2001;57:1032–5.

669. Lemay S, Chouinard S, Blanchet P, Masson H, Soland V, Beuter A, et al. Lack of efficacy of a nicotine transdermal treatment on motor and cognitive deficits in Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28:31–9.

670. Xu K, Bastia E, Schwarzschild M. Therapeutic potential of adenosine A(2A) receptor antagonists in Parkinson's disease. Pharmacol Ther. 2005;105:267–310.

671. Hauser RA, Hubble JP, Truong DD. Randomized trial of the adenosine A(2A) receptor antagonist istradefylline in advanced PD. Neurology. 2003;61:297–303.

672. Hauser RA, Shulman LM, Trugman JM, Roberts JW, Mori A, Ballerini R, et al. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. Mov Disord. 2008;23:2177–85.

673. LeWitt PA, Guttman M, Tetrud JW, Tuite PJ, Mori A, Chaikin P, et al. Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). Ann Neurol. 2008;63:295–302.

674. Stacy M, Silver D, Mendis T, Sutton J, Mori A, Chaikin P, et al. A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. Neurology. 2008;70:2233–40.

675. Pankratz N, Nichols WC, Uniacke SK, Halter C, Rudolph A, Shults C, et al. Significant linkage of Parkinson disease to chromosome 2q36-37. Am J Hum Genet. 2003;72:1053–7.