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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.

**Keywords** Parkinson disease · Epidemiology · Risk factor

**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 |

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

**Table 1** conitnued

| Study [reference] | Population | Ascertainment | No. of incident cases | Age group (years) Incidence/100,000 person-years | | | | | | Diagnostic criteria |
|---|---|---|---|---|---|---|---|---|---|---|
| Van den Eeden [45] | California, USA | Medical care program records, drug prescriptions and practice referrals | 588 | <30 | 40–49 | 50–59 | 60–69 | 70–79 | 80–89 | CAPIT/UK Brain Bank |
| | | | | 0 | 3 | 10 | 39 | 107 | 119 | |
| | | | | 30–39 | | | | | | |
| | | | | 0 | | | | | | |
| | | | | 5 | | | | | | |
| Benito-Leon [29] | Spain | Screening and clinical exam | 30 | 65–69 | 70–74 | 75–79 | 80–84 | 85+ | | UK Brain Bank |
| | | | | 0 | 113 | 159 | 100 | 305 | | |
| De Lau [33] | Rotterdam, the Netherlands | Screening and clinical exam | 132 | 55–65 | 65–75 | 75–85 | 85+ | | | 2 of 4[a] without antiparkinson medications, or 1 sign if on medications |
| | | | | 30 | 140 | 330 | 430 | | | |
| Foltynie [36] | Cambridgshare, UK | General practitioners, neurology or geriatrician practice records, hospital records, clinical exam | 201 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 80+ | UK Brain Bank |
| | | | | 0.9 | 2.0 | 9.6 | 41.2 | 75.5 | 86.2 | |
| Taylor [44] | Aberdeen, UK | General practitioners and hospital records, referral letters | 50 | 0–39 | 40–49 | 50–59 | 60–69 | 70–79 | 80–89 | 2 of 4[a] |
| | | | | 0 | 3.1 | 19.6 | 5.3 | 147.3 | 317.2 | |
| | | | | | | | | | 90–99 | |
| | | | | | | | | | 108.0 | |
| Tan [43] | Singapore | Phone screening, medical and hospital records | 12 | 50–59 | 60–69 | 70–79 | 80+ | | | Gelb [8] |
| | | | | 10 | 54 | 56 | 0 | | | |
| Driver [34] | Physician's Health Study, USA | Self-report and medical records | 563 | 40–44 | 45–49 | 50–54 | 55–59 | 60–64 | 65–69 | 2 of 4[a] |
| | | | | 0 | 6 | 17 | 39 | 67 | 134 | |
| | | | | | 70–74 | 75–79 | 80–84 | 85–89 | 90–99 | |
| | | | | | 190 | 255 | 355 | 615 | 446 | |
| Hristova [49] | Plovdiv, Bulgaria | Questionnaires to general practicioners and neurologists, hospital, outpatient and nursing home records; clinical exam | 244 | 0–39 | 40–44 | 45–49 | 50–54 | 55–59 | 60–64 | UK Brain Bank |
| | | | | 0 | 0.7 | 2.0 | 3.3 | 9.9 | 27.7 | |
| | | | | | 65–69 | 70–74 | 75–79 | 80–84 | 85+ | |
| | | | | | 36.5 | 57.1 | 76.3 | 52.9 | 6.0 | |
| Linder [47] | Umeå, Sweden | Review of referral letters to neurological department, letter asking for referral of suspected cases to practitioners in catchment area; clinical exam | 60 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 80–89 | UK Brain Bank |
| | | | | 2.5 | 2.8 | 27.9 | 54.3 | 138.3 | 124.3 | |
| | | | | | | | | | 90+ | |
| | | | | | | | | | 0 | |
| Winter [48] | Moscow, Russia | Referral to neurology department, primary care and hospital records; clinical exam | 308 | 0–44 | 45–49 | 50–54 | 55–59 | 60–64 | 65–69 | UK Brain Bank |
| | | | | 0 | 2.1 | 3.7 | 5.6 | 18.0 | 25.6 | |
| | | | | | | | 70–74 | 75–79 | 80+ | |
| | | | | | | | 80.4 | 70.0 | 61.6 | |

[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 | 60–69 | 70+ | | | | Progressive rest tremor plus 1 or more of rigidity and bradykinesia |
| | | | | 92 | 145 | 615 | | | | |
| Schoenberg [6] | Copiah County, Mississippi | Screening and clinical exam | 31 | 40–64 | 65–74 | 75+ | | | | 2 of rest tremor, bradykinesia, rigidity, parkinsonian gait or posture, retropulsion, masked facies, micrographia |
| | | | | 128 | 550 | 958 | | | | |
| Okada [65] | Izumo, Japan | Screening, public financial assistance register and clinical exam in a subset of cases | 66 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 80–89 | 2 of 4[a] |
| | | | | 23 | 20 | 64 | 339 | 479 | 336 | |
| Wang [46] | 29 provinces, China | Screening and clinical exam | 566 | <50 | 50–59 | 60–69 | 70–79 | 80+ | | 3 of 3[b] |
| | | | | 0.7 | 23 | 89 | 158 | 132 | | |
| Morgante [20] | Sicily, Italy | Screening and clinical exam | 63 | 0–49 | 50–59 | 60–69 | 70–79 | 80–89 | 90–99 0 | 2 of 4[a] |
| | | | | 0 | 116 | 621 | 1,978 | 3,055 | | |
| Tison [22] | Gironde, France | Screening and clinical exam | 60 | 65–69 | 70–74 | 75–79 | 80–84 | 85–89 | 90+ | 2 of 4[a] |
| | | | | 500 | 200 | 1,800 | 2,200 | 2,200 | 6,100 | |
| De Rijk [60] | Rotterdam | Screening and clinical exam | 97 | 55–64 | 65–74 | 75–84 | 85–94 | | | 2 of 4[a] without antiparkinson medications, or 1 sign if on medications |
| | | | | 300 | 1,000 | 3,100 | 4,300 | | | |
| Wang [67] | Kinmen, China | Screening and clinical exam | 23 | 50–59 | 60–69 | 70–79 | 80+ | | | 2 of 4[a], or 1 sign if on medications |
| | | | | 273 | 535 | 565 | 1,839 | | | |
| Melcon [63] | Junin, Argentina | Screening and clinical exam | 51 | 40–49 | 50–59 | 60–69 | 70–79 | 80+ | | 2 of 4[a] |
| | | | | 0 | 153 | 637 | 1,727 | 657 | | |
| Chen [32] | Ilan County, Taiwan | Screening and clinical exam | 37 | 40–49 | 50–59 | 60–69 | 70–79 | 80+ | | 2 of 4[a] |
| | | | | 38 | 123 | 547 | 820 | 2,198 | | |
| Kis [61] | South Tyrol, Italy | Screening and clinical exam | 12 | 60–64 | 65–69 | 70–74 | 75–79 | 80–85 | | 2 of 4[a], or 1 sign if on medications |
| | | | | 510 | 976 | 649 | 6,542 | 1,136 | | |
| Benito-Leon [16] | Spain | Screening and clinical exam | 81 | 65–69 | 70–74 | 75–79 | 80–84 | 85+ | | 2 of 4[a] without antiparkinson medications, or 1 sign if on medications |
| | | | | 500 | 1,600 | 1,900 | 3,200 | 1,500 | | |
| Nicoletti [64] | Cordillera Province, Bolivia | Screening and clinical exam | 5 | 40–49 | 50–59 | 60+ | | | | 2 of 4[a], at least one resting tremor or bradykinesia |
| | | | | 133 | 371 | 443 | | | | |
| Bergareche [58] | Bidasoa, Spain | Screening and clinical exam | 18 | | 65–74 | 75–84 | >84 | | | 2 of 4[a], or 1 of 4 + improvement with antiparkinson treatment |
| | | | | | 328 | 2,537 | 2,069 | | | |
| Tan [66] | Singapore | Screening and clinical exam | 46 | 50–59 | 60–69 | 70–79 | 80+ | | | Gelb [8] |
| | | | | 50 | 280 | 510 | 1,250 | | | |

**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 | 60–69 | 70–79 | 80+ | 2 of 3[b] |
| | | | | 1639 | 1159 | 3,951 | 9,191 | |
| Zhang [23] | Bejing, Xian Shanghai, China | Screening and clinical exam | 277 | 55–64 | 65–74 | 75–84 | 85+ | Calne [7] |
| | | | | 210 | 939 | 2,420 | 2,721 | |
| Barbosa [57] | Bambui, Brazil | Screening and clinical exam | 39 | 64–69 | 70–74 | 75–79 | 80–84 | 85+ Bradykinesia + 1 of rest tremor, rigidity or postural instability |
| | | | | 800 | 2,900 | 2,800 | 8,500 | 14,300 |
| Wirdefeldt [68] | Sweden | Screening and clinical exam | 132 | 50–59 | 60–69 | 70–79 | 80–89 | Gelb [8] |
| | | | | 99 | 506 | 1,063 | 1,508 | |
| Racette [69] | USA (Amish community) | Screening and clinical exam | 15 | 60–69 | 70–79 | 80–89 | 90+ | 3 of 4[a], or 2 of 4[a] with 1 displaying asymmetry |
| | | | | 1,515 | 8,235 | 1,2820 | 16,666 | |

[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]<br>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)<br>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, trifluralin, 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)<br>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)<br>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)<br>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)<br>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)<br>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)<br>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)<br>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)<br>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 lipopolysacharide (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 neuropathological 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 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.

**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

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.

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