EPIDEMIOLOGY OF PARKINSON'S DISEASE

The Rotterdam Study

Maarten C. de Rijk

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Epidemiology of Parkinson's disease

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Voor mijn ouders

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Contents

Publications and manuscripts on which this thesis is based

Chapter 2
MC de Rijk, MMB Breteler, A Hofman. Epidemiology of Parkinson's disease. (submitted)

Chapter 3.1
JP Alonso, MC de Rijk, A Hofman, MMB Breteler. What do complaints suggestive for parkinsonism tell us? Experience from the Rotterdam Study. (submitted)

Chapter 3.2
MC de Rijk, WA Rocca, DW Anderson, MO Melcon, MMB Breteler, DM Maraganore. A population perspective on diagnostic criteria for Parkinson's disease. Neurology 1997;48:1277-81.

Chapter 4.1
MC de Rijk, MMB Breteler, GA Graveland, A Ott, DE Grobbee, FGA van der Meché, A Hofman. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology 1995;45:2143-6.

MC de Rijk, MMB Breteler, GA Graveland, A Ott, FGA van der Meché, A Hofman. De prevalentie van parkinsonisme en de ziekte van Parkinson bij ouderen; het ERGO-onderzoek. Ned Tijdschr Geneeskd 1996;140:196-200.

Chapter 4.2
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Chapter 4.3
MC de Rijk, MMB Breteler, A Ott, FGA van der Meché, A Hofman. Incidence of parkinsonism and Parkinson's disease in the Rotterdam Study. (submitted)

Chapter 5.1
MC de Rijk, MMB Breteler, A Ott, AJC Slooter, CM van Duijn, C Van Broeckhoven, FGA van der Meché, A Hofman. Apolipoprotein E genotype, Parkinson's disease, and dementia in Parkinson's disease: the Rotterdam Study. (submitted)

Chapter 5.2
MC de Rijk, MMB Breteler, JH den Breeijen, LJ Launer, DE Grobbee, FGA van der Meché, A Hofman. Dietary antioxidants and Parkinson's disease: the Rotterdam Study. Arch Neurol 1997;45:782-5.

Chapter 5.3

MC de Rijk, MMB Breteler, FGA van der Meché, A Hofman. Smoking and the risk of Parkinson's disease: the Rotterdam Study. (submitted)

Chapter 5.4

MC de Rijk, MMB Breteler, FGA van der Meché, A Hofman. Family history of Parkinson's disease and dementia, and the risk of Parkinson's disease: the Rotterdam Study. (submitted)

Chapter 1

Introduction

1 Introduction

Only few descriptions of neurologic diseases precede James Parkinson's "*Shaking Palsy*". In this monograph, published in 1817, he clearly and accurately described a constellation of signs that now bears his name.[1] The definition he proposed largely contained what now is used to designate parkinsonism clinically *(Figure 1.1)*.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

Figure 1.1 *The definition of "Shaking Palsy" as was published in James Parkinson's monograph in 1817.*

At present, Parkinson's disease (PD), after Alzheimer's disease, is generally considered to be the most frequent progressive neurodegenerative disease in the elderly. Due to the growing proportion of elderly in many populations, more and more persons will be affected by this disabling disease which constitutes a large burden to man and society. Since the publication of James Parkinson's essay, almost two centuries have elapsed and, in spite of numerous efforts to unravel the nature of the disease, the etiology of PD is still unknown. Yet, the neuropathologic and biochemical changes that cause the signs of the disease seem to be settled, based on knowledge

that was mainly accumulated in only the past three decades. Neuropathologically, PD is defined by selective degeneration of pigmented neurons of the pars compacta of the substantia nigra and other brainstem ganglia, with cytoplasmic inclusions, called Lewy bodies, in the surviving neurons as the hallmark.[2-5] These lesions lead to a deficiency of striatal dopamine. It is now considered that parkinsonian signs only become clinically overt after dopaminergic cell loss of approximately 50%,[5,6] and that at that moment the endogeneous dopamine content is depleted by 80%.[2,4-6]

Hitherto, many hypotheses on the etiology of PD and reports on the frequency of the disease have emerged, and as many have been critized. In Chapter 2 of this thesis, a brief overview of the most important items with regard to epidemiologic research on PD will be given, focusing on developments from the past decade.
In the following chapters of the thesis, various epidemiologic aspects of PD will be addressed. All studies that are described in this thesis are community-based studies in which each participant was examined in person. In Chapter 3, we discussed diagnostic issues in population studies on PD. Several aspects of screening for parkinsonism in a general elderly population are described in Chapter 3.1. In Chapter 3.2, another methodologic aspect of epidemiologic studies on PD is dealt with, namely the impact of different diagnostic criteria for PD on prevalence estimates of the disease, and the applicability of these criteria in an epidemiologic setting. In Chapter 4 data are shown on frequency of PD. Results from studies on prevalence of parkinsonism and PD in The Netherlands, comparisons of prevalence estimates derived from five similar European studies, and on incidence rates in the Rotterdam Study are presented in Chapters 4.1, 4.2, and 4.3, respectively. In Chapter 5 results are given from four etiologic studies on PD that pertain to various determinants that have been linked with PD. The cross-sectional relation between dietary antioxidant intake and PD is described in Chapter 5.1. Chapter 5.2 deals with the association of apolipoprotein E genotype with PD and dementia in PD. Chapter 5.3 is about the allegedly protective effect of smoking against PD, an issue which is still controversial. Chapter 5.4 shows the risk of PD conditional on a positive family history of PD or dementia. Finally, in Chapter 6, methodologic issues and findings of the presented studies are discussed, as well as the implications of these findings for the understanding of PD, and for future research.

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Chapter 2

Epidemiology of Parkinson's disease: a review

2 Epidemiology of Parkinson's disease: a review

In 1817, the British physician James Parkinson[1] was the first who recognized and described several neurologic symptoms as one entity which now bears his name. Parkinson's disease (PD) is one of the most frequent chronic neurodegenerative diseases in the elderly. Due to the growing proportion of elderly in many populations, more and more persons will be affected by the disease. Excessive dopaminergic cell death in the substantia nigra in the brain leads to the disease,[2-5] but the cause of this cell loss is still poorly understood. Relatively little epidemiologic reseach has been conducted on PD. We will now review developments in epidemiologic research of PD, most from the past decade, and discuss diagnosis, disease frequency, risk factors, comorbidity, and prognosis.

Diagnosis

Diagnostic criteria

For the diagnosis of PD, the postmortem neuropathologic examination of the brain is generally considered to be the gold standard. Neuropathologically, PD is defined by selective degeneration of pigmented neurons of the pars compacta of the substantia nigra and other brainstem ganglia,[2,5-9] with specific inclusions in the surviving neurons, referred to as Lewy bodies, as the pathognomonic hallmark.[6,7] Still, the neuropathologic diagnosis is not that distinct: additional Alzheimer's disease lesions frequently occur in pathologically confirmed PD;[7,10-12] in 21%[13] up to 55%[14,15] of patients with Alzheimer's disease or other neurodegenerative diseases concomitant PD lesions are reportedly found; in pathologically confirmed non-demented PD patients correlations between distinct clinical patterns and neuropathologic patterns have been observed;[7] and in a substantial proportion of non-parkinsonian subjects older than 60 years Lewy bodies are found.[6,16] For the clinical diagnosis of PD, the generally accepted prerequisite is assessment of the presence of parkinsonism, based on a combination of four typical clinical features, referred to as cardinal signs, i.e. resting tremor, bradykinesia, rigidity, and impaired postural reflexes. Various combinations of these cardinal signs have been proposed for ascertainment of the presence of parkinsonism.[8,17-20] The diagnosis of PD, sometimes referred to as idiopathic parkinsonism or idiopathic PD, requires that other causes of parkinsonism

be excluded. For the diagnosis of PD, sometimes additional requirements related to duration of symptoms, asymmetry of signs, or responsiveness to levodopa treatment are used. In a recent report, it was argued that for use in epidemiologic settings the diagnosis of PD requires the presence of at least two of resting tremor, bradykinesia, and rigidity in absence of other possible causes of parkinsonism and without additional requirements.[20] The correlation between the clinical picture and postmortem findings is relatively poor: 24% of the cases who during life had been diagnosed as PD had a neuropathologic diagnosis other than PD.[8] Application of very strict clinical criteria may improve the cliniconeuropathologic correlation,[8,21] but will lead to exclusion of more than 30% of pathologically genuine PD patients.[21]

Differential diagnosis

Besides PD, which accounts for 70%[22,23] to 85%[24] of all parkinsonian patients, many other disorders (such as dementia, Lewy Body disease, multiple system atrophy, progressive supranuclear palsy, drug-induced parkinsonism, and vascular parkinsonism) may cause parkinsonism. Most of these disorders are distinguished from PD by typical features or a specific time relation between putative cause and disease. In practice, however, the clinical distinction between PD and other parkinsonian syndromes is often difficult to make.[4,8,13,18,21,25-27] PD is clinically heterogeneous in age of onset,[28-30] predominance of motor signs,[12,18,29,31,32] responsiveness to levodopa treatment,[12,33] and clinical course,[18,33,34] and may, consequently, mimic a secondary cause of parkinsonism. In general, some misdiagnosis of PD is inevitable but can be reduced by applying strict exclusion criteria such as presence of pyramidal signs, cognitive deficits that occurred clearly before the onset of the parkinsonian syndrome, poor levodopa responsiveness, neuroleptic-induced parkinsonism, cerebellar ataxia, marked autonomic dysfunction, or abnormalities of eye movements.[4,8,21]

Frequency

Methodologic considerations

Differences in case-finding procedures, diagnostic criteria, and response rates may hamper comparison of prevalence and incidence figures across studies. Broadly, two case-finding methods have been used to study prevalence of PD. One is based on existing medical records. Patients who fail to seek medical attention for their parkinsonism, and those whose records were lost or could not be retrieved, will not be included in the prevalence estimates. The other case-finding method relies on in-

person screening of all subjects within a defined population.[22,35,36] Often, a two-stage design is used which encompasses in the first stage a brief screening of all subjects in a population and subsequently, in the second stage, a more extensive evaluation of those who screened positive.[22,35,37] This method should reduce the number of undiagnosed patients by identifying persons with parkinsonism before they have come to medical attention. It was shown that the percentage of newly diagnosed patients due to the screening can grow to considerable proportions in the range from 24%[38,39] to 35% and 42%,[22,35] and increases with age.[23] Apart from case-finding methods, different diagnostic criteria may also have their impact on frequency estimates.[20,39]

Prevalence

All studies on the prevalence of PD that were published before 1985 were based on existing medical records, as were most prevalence studies published during the last decade.[40-48] The prevalence estimates based on these studies varied widely.[49] In many register-based studies, it was found that the prevalence of PD increased with age till a certain age with a decline thereafter.[43,46-49] Since 1985, when the results of the first community-based prevalence survey on PD were published,[35] evidence has been growing that a decline in prevalence in the highest ages is artefactual. All community-based prevalence surveys with an in-person screening showed an increase in the prevalence of PD or parkinsonism with age, even in the highest age categories.[22,23,35,36,38,39,50-52] Overall, the prevalence estimates ranged from 0.6% for those aged 65 to 69 years to 3.5% for those aged 85 to 89 years, with an overall prevalence of 1.6% for subjects aged 65 years or older.[23] The prevalence estimates derived from these studies are remarkably similar *(Figure 2.1)*, suggesting no clear variation across countries if similar methodologies and diagnostic criteria are used. The discrepancy between the results of a Chinese study,[51] that showed low age-specific prevalence figures, and the other community surveys could be due to differences in survival or classification of PD patients, or in etiologic factors. The eight-fold higher prevalence estimates that were reported for East Boston, Massachusetts,[52] referred to all parkinsonism, as no distinction between PD and other parkinsonism could be made, and were probably inflated due to broad diagnostic criteria.

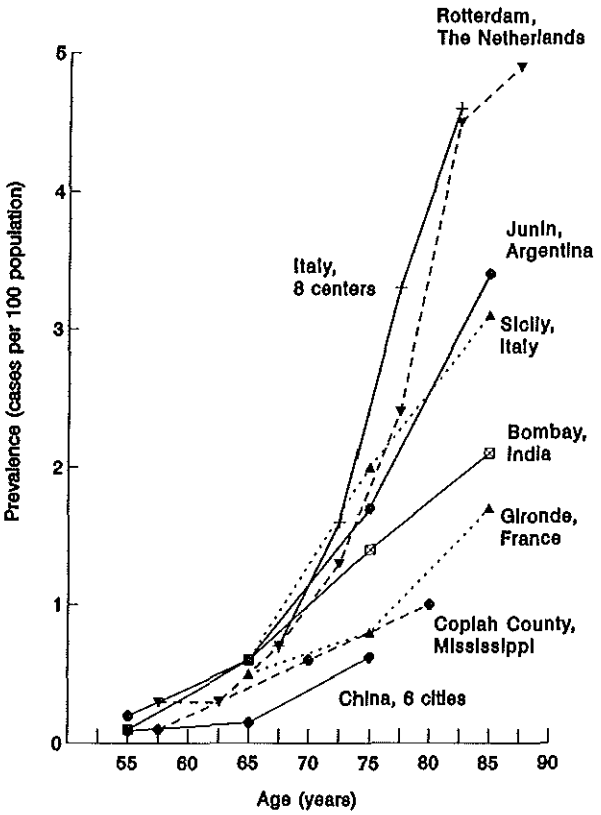

Figure 2.1 *Age-specific prevalence, for both sexes combined, of Parkinson's disease from several community-based surveys with an in-person screening to detect Parkinson's disease.*

Incidence

Incidence rates could provide better estimates of occurrence of PD, avoiding differences in survival of PD patients across countries, but studies on incidence of PD are scarce. Only few studies provide age-specific[48,53,54] or age- and sex-specific[24,45,47,55,56] incidence rates of PD. In none of these, except two,[54,56] a screening instrument to detect PD was administered to each individual. The incidence rates per

100,000 person years varied; for the age-group 75 to 84 years from 133 in New York,[47] and 132 in Honolulu, Hawaii,[54] to 254 in Rochester,[24] and 510 in Rotterdam, The Netherlands[56] with in the latter three studies a drop beyond the age of 85 years *(Figure 2.2)*. The figures from the two studies with an in-person screening varied

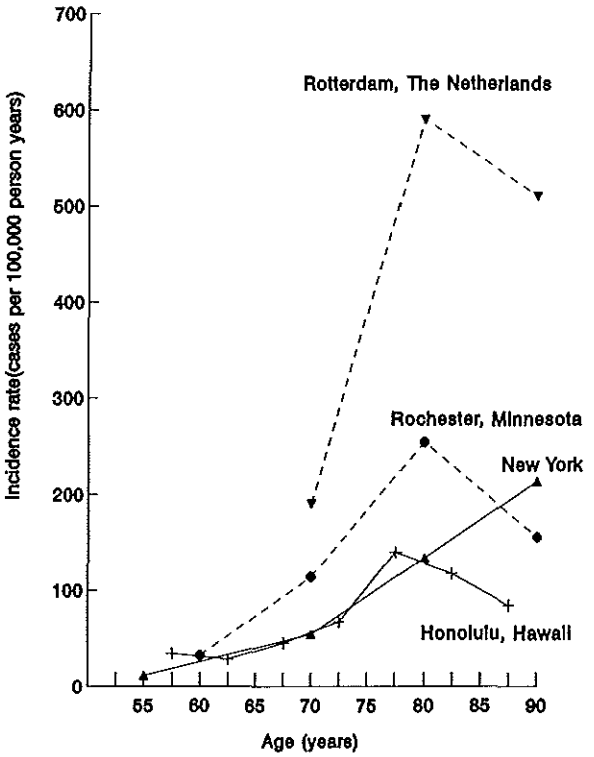

Figure 2.2 *Age-specific incidence rates of Parkinson's disease from several community-based surveys.*

considerably.[54,56] The reason for this is speculative, but, as in the Hawaiian study 20 years had elapsed between the previous, register-based, screening and the most recent in-person screening, many parkinsonian subjects who did not come to medical attention will not have been included in the incidence estimates. Also, in the Rotterdam Study the number of incident cases per age-group was small leading to more unstable estimates. More incidence estimates provided by community surveys

with an in-person screening at both baseline and follow-up have to be awaited to establish the true incidence of PD and to confirm the decline of incidence at higher ages.

Risk factors

Methodologic issues

Numerous studies on risk factors for PD have been published. Almost exclusively, these studies were based on register-based prevalent cases which have some well known methodologic drawbacks, such as information bias and selection bias.
Selection bias may have occurred if mortality in patients is selectively influenced by the determinants studied or when diagnosis of PD is dependent on, or promoted by, putative risk factors (e.g., head trauma, postive family history of PD, depression before the diagnosis of PD). Also, the selection of controls may have been biased: the use of spouses as controls will lead to overmatching if for example dietary habits are investigated, and hospital controls may not properly reflect the distribution of risk factors in the population from which the cases were derived. Information bias (e.g., recall bias) may have been introduced where healthy controls or spouses served as controls. In this section, we will mainly focus either on the few prospective studies in which the exposure was measured before the onset of the disease or on large cross-sectional studies. The associations between most putative determinants and PD still have to be confirmed in cohort studies, ideally in a community-based setting.

Gender

Higher prevalences of PD for men[46-48] or for women[43,57] have been reported in register-based studies, while in most community surveys with an in-person screening no significant differences in the prevalence of PD between men and women were found.[22,23,35,36,38,50] Even if we look at register-based incidence studies on PD with age- and sex-specific estimates, no differences between sexes seem to exist,[24,45,53,55] except in two.[47,48] These findings may indicate a similar risk of PD in men and women if putative differences in survival or in probability of diagnosis of PD patients have been avoided.

Smoking

Smoking is one of the determinants of PD that has been studied most frequently. Since Dorn first reported an inverse association between smoking and PD,[58] this finding has been confirmed in most other studies,[59-64] but not in all.[65-67] Most studies

that found an inverse association were based on prevalent cases and the inverse association was disputed with various arguments like biased results due to confounding, selective mortality, cause-effect bias, symptom suppression, or diagnostic competition.[59] To date, few prospective studies exist,[58,62,63,68-71] all suggesting an on average two- to three-fold reduction of the risk of PD among smokers. However, all but two,[62,63] focused on mortality follow-up of smokers and non-smokers. PD diagnosis was retrieved through death certificates in which smoking related diseases may overshadow PD as the listed cause of death, especially in smokers, thus erroneously implying less frequent occurrence of PD among smokers. Even in countries with excellent death certificate registration, in only 70% of diagnosed PD patients the PD diagnosis is listed on death certificates.[72] The two prospective community-based studies based on an in-person screening for PD showed a similarly reduced risk of PD among smokers.[62,63]

It is still speculative which biologic mechanism may explain the protective effect.[59,73] In the substantia nigra of smokers, monoamino oxidase B (MAO B) levels are reduced.[73] As a result, less dopamine will be oxidated, yielding a neuroprotective effect through reduced free radical production. Less dopamine oxidation will result in increased synaptic dopamine availability, thereby reducing the symptom severity or delaying the onset of clinical PD.[59] MAO B mediated oxidation of protoxins to neurotoxins may be reduced as well.[74-76] The compounds of cigarette smoke that inhibit MAO B are not known.[73,77,78] Also, smoking may induce other enzymatic processes that are involved in the metabolism of xenobiotics, thereby augmenting protection against oxidative stress or toxins.[79] Other possible mechanisms include that nicotine may directly stimulate dopamine release[75,80] or nicotine receptors,[81,82] or that smoking-associated carbon monoxide could protect against hydrogen peroxide related peroxidation of the membrane.[83] A different point of view contains that persons predestinated to get PD may exhibit a (premorbid) personality that predelicts persons to restrain from smoking[4,59,84,85] which leads to a seemingly higher risk of PD among non-smokers. However, personality differences in PD patients have only been assessed retrospectively and recall bias may have occurred.

In general, one could argue for the existence of a true inverse association of smoking with PD, because of consistent, biologically plausible, findings in epidemiologic studies that have been confirmed in prospective community-based studies.

Antioxidants

Increased free radical production and an inadequate antioxidant defence system may play a role in the etiology of PD.[86-88] Indications for such oxidative stress were found

in several neuropathological studies,[89-95] some suggesting increased lipid peroxidation in the dopaminergic cells.[96,97] It has been speculated that high intake of antioxidants, either through diet or supplements, may decrease the risk of PD or slow down its progression. The few studies on dietary antioxidant intake and the association with PD yielded equivocal results.[98-104] Two recent large case-control studies based on prevalent cases found no protective effect of dietary antioxidants on PD.[98,104] but potential biases could not be excluded.[104] A recent case-control study, nested in a prospective study, suggested a significant inverse association between PD and consumption of vitamin E containing foods (legumes) more than 25 years before (odds ratio of 0.28 per at least one serving per day).[103] Theoretically, ß-carotene[105] and vitamin C could have an antioxidative effect in the brain as well, but in studies on PD such an effect has not been found.[98,101,102,104,106-108] Considering the currently existing evidence, vitamin E may be a dietary antioxidant that protects against the development of Parkinson's disease but this needs to be confirmed in more prospective community-based studies.

Toxins

Renewed interest in neurotoxins that may cause PD was raised when it was observed that through intravenous injection, or possibly also through inhalation,[109,110] the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a parkinsonian syndrome strikingly resembling PD, both clinically and pathologically.[111] Much research was focused on the relation between PD and direct or indirect exposure to potentially toxic compounds such as MPTP (and its metabolite MPP^+) containing pesticides, especially herbicides.[112] As shown in Table 1, a positive relation with PD has been found for pesticide use, or for rural living, farming, and well water drinking (all reflecting possible exposure to compounds of pesticides). Some other studies indicated an association between exposure in industrial environments (e.g., heavy metals) and PD *(Table 2.1)*.[110] A positive link with pesticide use was also reported by Butterfield et al.[113] and Hubble et al.,[114] but in the latter study PD was not linked to rural living, farming, and well water drinking.[114] To date, it is not clear whether environmental neurotoxins are potentiated by genetic defects in detoxification systems in the brain, [115,116] but there are some indications that polymorphisms of such susceptibility genes are involved in the etiology of PD.[117-120] As all case-control studies were retrospective and register-based, the results have to be interpreted with caution. Information bias may have occurred, especially when the notion exists that inhalation of toxic compounds could cause some brain damage. Moreover, almost exclusively the associations have been established indirectly without direct measurement of the

true exposure. In the future, job exposure matrices may be a more objective tool to evaluate the relation between PD and the precise exposure, interaction between toxin exposure and susceptibility genes could be investigated, or cohorts of farmers or industrial workers could be followed to assess whether or not they are exposed to an increased risk of PD.

Head trauma

The notion that a severe head injury, as observed by James Parkinson,[1] can cause parkinsonism,[121,122] that persons, like boxers, who have experienced multiple head trauma in the past may develop parkinsonian signs, and that head trauma may (temporarily) worsen the disease severity in PD patients,[123] led to the hypothesis that PD and head trauma may be etiologically related. This could be through directly trauma-induced damage of the striatal pathway, or it could be that the stress that accompanies the head trauma induces (transient) parkinsonian signs,[123-125] possibly through depression of striatal dopamine levels.[123,125] In most recent studies on head trauma and the occurrence of PD, the relation remained controversial.[60,61,67,114,126-131] A significant positive association was observed in only three case-control studies *(Table 2.2)*,[126,127,130] but recall bias could not be excluded. A follow-up study from Rochester, Minnesota, among persons with a severe head trauma revealed no increased risk of either PD or Alzheimer's disease,[132] nor did the Rotterdam Study.[133] *(Table 2.2)*. These observations in follow-up studies make a etiologic relation between PD and head trauma unlikely.

Genetics

Until the seventies it was generally considered that hereditary factors played an important role in the etiology of Parkinson's disease. Negative findings in some twin and case-control studies, and the increasing popularity of the toxic hypothesis during the eighties, temporarily discredited the genetic hypothesis. However, the nineties have come with a revival of the belief in genetic components being involved in the development of the disease.

Familial aggregation, twin studies, and multiplex families

Earlier studies of familial aggregation of PD were methodologically flawed or imperfect,[134] in that they were based on highly selected hospital-series often without confirmation of positive family histories or including atypical or monosymptomatic family members, or based on parkinson-plus syndromes.[135] More recent, and methodologically better, studies do show family aggregation, with a relative risk of

Table 2.1 *The associations* between potentially toxic environmental factors and Parkinson's disease from selected case-control studies*

Investigator (reference)	Number of patients	Rural living	Farming	Well water drinking	Pesticides use	Industrial toxins
Ho et al.[232]	35	2.2 (1.0-5.0)†	1.7 (0.8-3.8)	-	3.6 (1.0-12.9)	-
Tanner et al.[233]	100	0.6 (0.2-1.0)	0.4 (0.2-0.8)‡	0.7 (0.4-1.3)	-	2.4 (1.3-4.3)
Koller et al.[234]	150	1.9 (1.2-3.0)§	1.3 (0.9-2.1)	1.7 (1.0-2.7)	1.1 (0.7-1.7)	-
Golbe et al.[100]	106	2.0 (1.1-3.7)§	1.3 (0.7-2.6)	1.1 (0.6-2.3)	7.0 (2.0-25.0)	-
Wong et al.[235]	38	4.3 (1.4-13.7)§	2.7 (0.7-9.5)	2.8 (0.9-8.2)	1.0	-
Stern et al.[127]	149	1.7 (0.9-3.1)	-	0.8 (0.5-1.6)	0.9 (0.6-1.5)‖	-
Semchuk et al.[126,236,237]¶	130	0.8 (0.5-1.2)	1.9 (1.1-3.3)	1.1 (0.6-2.0)	2.3 (1.3-4.0)	-#
Seidler et al.[61]**	380	1.0 (0.7-1.4)	0.8 (0.6-1.1)	0.8 (0.6-1.2)	1.6 (1.1-2.4)	1.0 (0.7-1.4)††

* Odds ratios (OR) with 95% confidence intervals (95% CI) in parentheses.
† In original paper, 95% CI was not presented. We reconstructed the 95% CI.
‡ Wheat growing.
§ In original paper, 95% CI was not presented. We reconstructed the 95% CI by using the McNemar test for matched pairs.
‖ Herbicide use, the OR for insecticide use was 0.5 (0.2-1.1).
¶ Exposure in first 45 years of life.
# No association (in article, OR was not provided).
** In original paper, exposures were categorized. The overall ORs for exposure versus no exposure were kindly provided by the investigators.
†† Exposure to anorganic compounds, assessed through job exposure matrix. Data were kindly provided by the investigators.

Table 2.2 *The associations* between risk factors and Parkinson's disease from follow-up and selected case-control studies*

Investigator (reference)	Type of study	Head trauma (any)	Head trauma (with loss of consciousness)	Family history of PD	Family history of dementia
Stern et al.[127]	Case-control	2.9 (1.5-5.8)	-	-	-
Williams et al.[132]	Retrospective follow-up	0.9 (0.4-1.9)	-	-	-
Factor et al.[130]	Case-control	2.3 (1.0-4.9)†	3.1 (1.1-8.7)†	-	-
Semchuk et al.[126]	Case-control	4.0 (1.9-8.3)		5.1 (2.2-11.9)	
Breteler et al.[67]	Case-control	0.8 (0.5-1.2)	1.3 (0.7-2.3)	2.9 (1.4-6.1)	1.0 (0.6-1.5)
De Michele et al.[60]	Case-control	2.3 (1.0-5.6)	-	14.6 (7.2-29.6)	-
Seidler et al.[60]	Case-control	1.3 (0.8-2.0)‡	-	12.6 (4.4-36.1)	8.2 (1.7-39.0)§
de Rijk et al.[133]	Prospective follow-up	0.7 (0.3-1.7)	0.6 (0.1-2.5)	2.5 (0.9-7.3)‖	1.4 (0.7-3.0)‖

* Odds ratios (OR) with 95% confidence intervals (95% CI) in parentheses.

† In original paper, 95% CI was not presented. We reconstructed the 95% CI.

‡ In original paper, exposure was categorized. The overall OR for exposure versus no exposure was kindly provided by the investigators.

§ In original paper, data were not presented. Data were kindly provided by the investigators.

‖ Unpublished data.

around 3 for subjects with first-degree relatives with Parkinson,[67,136,137] but some showed a more elevated risk *(Table 2.2)*.[60,61] Several twin studies inititally reported very low concordance rates in twins and no differences in concordance rates between monozygotic and dizygotic twins, which was interpreted as excluding an important genetic component.[138-140] Reappraisal of these studies, however, showed that they were methodologically limited and far from conclusive, and their results compatible with autosomal dominant inheritance with reduced penetrance, heterogeneity, or a multifactorial etiology.[141] A considerable number of studies have been published describing families in which several members were affected with PD,[134,142-145] of which some with a highly typical clinical picture and pathological confirmation, at least in some cases.[145] The segregation ratios in most of these families suggest autosomal dominant inheritance with reduced penetrance. Recently, in one of these families linkage was shown with chromosome 4 (4q21-23).[146] Several groups reported that on positron emission tomography of discordant twin pairs many of the clinically unaffected sibs showed a decreased ^{18}Fluoro-dopa uptake in the striatum,[147-149] and the same was found by Brooks and colleagues for some asymptomatic members of multicase families. This may suggest that genetic factors do play a role but also that, given the difference in clinical expression, environmental factors influence the expression of the disease.

Anticipation

Increasing number of trinucleotide repeats have been recognized to play a role in the etiology of a large number of neurodegenerative diseases in the latest years. Several researchers reported a younger average age at onset in the proband generation as compared to the parental generation in families with PD.[150-152] However, dectection bias could not be excluded in any of these studies and no other evidence for trinucleotide repeats involvement in PD exists to date.[153]

Mitochondrial inheritance

Among PD patients disfunction of the mitochondrial energy chain have been described.[92,93,95] Part of the enzyme complexes involved in the mitochondrial electron transport are encoded for by the mitochondrial DNA.[154] There is, however, no evidence for an increased maternal transmission of the disease.[155] Since nuclear DNA is also involved in the functioning of the mitochondrial respiration chain genetic disturbances in one of these genes remains possible.[156]

Candidate genes

Several genes that on biochemical or pathofysiological grounds might be involved in PD have been evaluated in association studies. Most of these studies showed no allelic associations with PD and candidate gene polymorphisms,[157-160] but associations with gene polymorphisms of monoamino oxidase B and A (MAO B, MAO A),[161,162] and cytochrome P450 (CYP2D6)[118,119,163,164] have been reported. As PD, and especially PD dementia, shares many neuropathologic and other features with Alzheimer's disease,[7,10,11,165-169] it has been hypothesized that the apolipoprotein E4 genotype, which is an important genetic determinant for late-onset Alzheimer's disease,[170-172] may be associated with PD dementia or PD in general.[173-180] Yet, in most studies no association was found.[174-178,180]

Gene-environment interaction

The most likely hypotheses regarding the etiology of Parkinson's disease at the moment are that the disease results from a genetically determined susceptibility for exogeneous toxins, from a genetically determined defect that leads to overproduction of endogeneous neurotoxins or a decreased clearing of toxic substances that normally appear in the brain, or an inherited mitochondrial dysfunction.[79,117,181] It seems plausible that there is at least some interaction between genetic and environmental factors and that the disease is heterogeneous. With regard to CYP2D6 polymorphisms it has been suggested that there might be interaction with smoking, and this could also be the case with MAO B.[73] However, studies exploring this hypothesis have not yet been performed.

Prognosis

Progression of the disease

In PD, extrapyramidal signs only become clinically overt after dopaminergic cell loss of approximately 50%,[4,5,182,183] and endogeneous dopamine is depleted by 80% at that moment.[4,5,184] The first question that arises is when the excessive degeneration of dopaminergic cells actually starts. Several models and time frames have been proposed.[185-189] For long, the prevailing idea has been that the duration of the preclinical phase in PD is probably more than 20 years.[3,4,116,186] New evidence, however, in part based on positron emission tomography-scanning studies correlating in vivo the proportion of functional dopaminergic neurons with the disease duration, advocates a much shorter presymptomatic period of approximately 5 years.[184,190] The rate of deterioration of nigral cells is probably most prominent and curvilinear in the

preclinical or very early phase of Parkinson's disease,[3,5,184,187,190] approaching a linear pattern later on.[187,188] The rapid decline may be associated with a higher age of onset,[29,34] (not observed by others)[28,191] with more severe symptoms at onset, especially bradykinesia and gait disturbances,[29,191] and with cognitive dysfunction.[191,192] Goetz et al. did not find external factors (e.g., chemicals, herbicides, antiparkinsonian drugs) associated with a rapid progression.[34] In some of these studies, no age adjustment was made which may have resulted in confounding of the prognostic meaning of for example cognitive decline and age. Moreover, as most studies were carried out in specialized movement disorder (outpatient) clinics and selected patient series, it is not clear whether the results can be generalized to a general PD patients population.

Depression

A large percentage of PD patients will encounter a depression during their disease, the most reliable estimates being around 45%,[193-198] which is much higher than in the general population. The nature of this mental disorder in PD is not clear. Depression has been regarded as reactive to PD, but this hypothesis has been opposed by others.[196] An endogenous origin of the depression was proposed as the depression is independent of the severity of PD[193,198-201] and appeared often to have its onset before, or just after, the symptoms of PD began [67,193,199] Reduced serotonin in the brain of PD patients has been implicated in the etiology of depression.[200,202] Low serotonin levels in PD patients could partly be attributed to concurrent neurodegeneration of serotonin pathways as a result of PD alterations in the brain.[7,196,197] Although there may be biological support for serotonergic dysfunction in PD, epidemiologic evidence for frequent episodes of depression before the onset of PD is limited as it was only found in one community-based[67] and two hospital-based case-control studies,[193,199] and could not be confirmed in the only prospective community-based study.[133]

Cognitive function

Dementia appears in a high frequency in PD patients during the course of their disease. Estimates of dementia in PD vary around 35%.[46,203,204] In non-demented PD patients, mild cognitive changes such as visuospatial deficits, impaired executive functions, and verbal fluency may occur as well,[205,206] and the latter might predict incident dementia.[206] In most studies it was shown that PD patients have a two- to three-fold increased risk of dementia when compared with non-parkinsonian persons,[129,203,207,208] with one community-based study yielding a five-fold increased

risk.[209] The dementia said to be typical for PD has been referred to as "subcortical dementia", but both term and appropiateness are debated;[205,210,211] the pathologic substrate has not unequivocally been established nor has a distinct neuropsychologic pattern.

The etiology of dementia in PD remains unsettled. PD dementia may be caused by neuropathologic lesions located in the middle part of the substantia nigra,[7,212] or cortex,[213,214] but concurrent Alzheimer's disease pathology may, in some instances, attribute to the dementia in PD as well.[7,10,11,215] In all these neuropathologic studies, the number of cases were small, and not always consecutive series were used which may lead to selection bias. Little research has been conducted on risk factors for dementia in PD. The development of dementia may be promoted by various factors, such as predominance[204] or severity[216] of parkinsonian signs, older age at onset of motor manifestation,[203,204,207,216] depression,[203,216] or rapid progression of the PD.[203,207]

Comorbidity

Concurrent diseases in PD, other than depression and dementia, have less well been established and only few recent studies exist. Mostly, information on concomitant diseases was retrieved through death certifiates or medical records which limitations we have discussed earlier in this review. In PD, low frequencies of cancer,[204,217-220] cerebrovascular diseases,[204,221,222] and ischemic heart diseases[204,221] have been reported, in contrast to a higher frequency of lung diseases.[72,204,219,222] But these findings are conflicting; for PD patients also increased risks of death with heart diseases[72,219] and cancer[72] were observed, although for cancer this was not significant. When comparisons were made between a relatively unselected PD population and population controls, Ben-Shlomo and Marmot observed among PD patients a higher adjusted risk of dying from ischemic heart disease, cerebrovascular disease, and respiratory disease (hazard ratios were 2.3, 3.6, and 3.7, respectively).[220] The use of different study populations and methodologies could account for the ambiguity. Prospective follow-up studies in which disease status is directly measured, preferably in a community-based setting, are needed to provide more evidence.

Mortality

It could be expected that the burden of concurrent diseases, like dementia and depression, will reduce the life expectancy of PD patients. Indeed, without exception a standardized mortality ratio higher than 1 was observed,[24,72,220,223-225] ranging from 1.6[24] to 3.4.[225] It was hypothesized that since the beginning of the seventies when

levodopa treatment became available, survival in PD patients may have been prolonged. Rajput et al. found a marginally favorable effect of levodopa treatment on survival but noticed that PD patients who did not receive treatment were in a poorer general health.[24] In a more recent study also from Rochester, Minnesota,[226] that showed improved survival attributed to levodopa therapy, a similar selection bias may have occurred and it is doubtful whether this bias can adequately be controlled for. Kurtzke and Murphy found some evidence of a 5 years increase in survival in PD patients since the introduction of levodopa.[227] A shift in PD mortality rates has occurred towards the older ages since,[227] or even before,[228,229] the introduction of levodopa therapy, suggesting an increase in survival of PD patients. It still remains unclear whether this is due to levodopa treatment or better general management of PD patients. On the other hand, many studies, all based on death certificates, reported an increase in age-adjusted PD mortality rate in the last decades.[227,228,230,231] These observations, however, could be readily explained by improved accuracy of death certificates or changes in certification,[229] changes in diagnostic criteria, improved diagnosis, and increased awareness of PD as a prominent neurodegenerative disease in the higher ages. Reduced survival has been associated with higher age of onset, more severe motor signs at diagnosis, and cognitive impairment,[192,224,226,229]

Conclusions and considerations for future research

PD is among the most frequent neurodegenerative disorders in the elderly and its etiology is still largely unknown. In this review, we have discussed diagnostic criteria, frequency, determinants, and prognosis of PD.

In an epidemiologic setting, a diagnosis of PD based on the presence of at least two out of three cardinal signs (i.e., bradykinesia, resting tremor, and rigidity) seemed to be most applicable but several other criteria have been proposed. The prevalence increases with age: from 0.6% for persons between the age of 65 to 69 years to 3.5% for those between the age of 85 to 89 years. The incidence has been less well established. It has been shown through population screening that register-based prevalence figures are probably underestimated.

Many determinants of PD have been investigated, almost always in a case-control design and based on prevalent cases. Women probably run the same risk as men to develop PD. There is strong evidence that smokers have an approximately two- to three-times reduced risk of PD. This has consistently been reported, also in prospective studies, and several plausible explanations based on biologic

mechanisms exist. As oxidative stress may be etiologically involved in PD, intake of antioxidants may reduce the risk of PD. Of all antioxidants that have been investigated, only vitamin E intake may exert a protective effect. The results of studies on the associations between PD and toxins, environmental risk factors, and head trauma are less unequivocal. Many case-control studies showed a positive association between PD and exposure to potentially neurotoxic products such as pesticides but these findings may have been flawed by various biases. Nor for environmental factors neither for head trauma clear patterns were discerned.

The duration of the preclinical period in PD is disputed but could be as short as five years. The progression of the disease is more rapid if the age of onset of motor symptoms is above 70 years of age, if the motor symptoms at time of diagnosis are more severe, or if cognitive impairment is present early in the disease. Concomitant diseases in PD patients are prevalent, especially dementia, depression, and respiratory diseases, but cerebrovascular and ischemic heart diseases may be frequently found as well. PD patients have an on average two-fold higher mortality rate when compared with control subjects. Pneumonia is of one of the causes of death that has been reported most consistently but vascular diseases have been implicated as well. Among PD patients, cancer may occur in a remarkably low frequency. However, most studies on comorbidity and mortality were based on death certificates, of which the reliability has been proven to be poor, and this could explain the discrepancy in findings from various studies.

To overcome biased study results, more prospective cohort studies on determinants of PD patients are needed, preferably in a community setting in which each individual is regularly screened for PD. Some of these studies are under way. This design will also allow to study prevalence and incidence, and to compare comorbidity, mortality, and causes of death between persons with and without PD. Also, cohorts with a higher than usual exposure to specific substances that have been involved in the etiology of PD, e.g., farmers, could be followed up prospectively or retrospectively.

In vitro experiments may give clues to which deficits in the cell metabolism, for example due to differences in enzyme activity, contribute to the cause of PD. Evidence exists that polymorphisms of candidate genes encoding for enzymes involved in the production or elimination of free radicals, in specific subunits of the mitochondrial respiratory chain, or in xenobiotics, and genes involved in dopamine synthesis or metabolism are linked to PD, but this is not conclusive. It seems likely that it is not only genetic factors, but the interplay between genetically determined susceptibility and specific environmental factors that lead to PD. Therefore, if the interaction between these candidate genes and environmental factors will be studied,

the results might be more promising. With regard to smoking and neurotoxins in relation to PD, the extent to which the effect of exposure is modified or potentiated by putative susceptibility genes could be investigated in populations, but this requires large numbers of patients.

Eventually, insight into the etiology of PD could give clues to neuroprotective treatment and may result in effective measures to prevent this devastating disease in the elderly.

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Chapter 3

Diagnosis of Parkinson's disease

3.1 Screening for Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disorder among the elderly and its prevalence has been investigated in many studies.[1-4] In studies in which a population is actively screened for parkinsonism, usually a stepped diagnostic approach is applied, with first a screening for all individuals (by either questions or examination, or both) followed by a complete neurological assessment for those who screened positive.[5-7] However, neither the prevalence of complaints suggestive for parkinsonian signs, nor the usefulness and test characteristics of a questionnaire as a screening instrument to detect probable parkinsonian signs and PD in a general, non-hospital-based, population are known. Therefore, we investigated the prevalence of subjective complaints and related physical signs suggestive for parkinsonism, the capability of a screening questionnaire to detect such physical signs, and the sensitivity of a screening questionnaire to detect PD in a general elderly population.

Methods

Study population

The study was part of the Rotterdam Study, a community-based prospective cohort study on the frequency and determinants of chronic diseases in the elderly.[8] The conduct of the study has been approved by the Medical Ethics Committee of Erasmus University Rotterdam. The study started in June 1990 and the baseline survey was completed in June 1993. All inhabitants aged 55 years or over of Ommoord, a suburb of Rotterdam, The Netherlands, were invited to participate. Both independently living persons and institutionalized persons were included. Of the 10,275 eligible subjects, 7,983 (78%) agreed to participate and signed informed consent statements. All participants were interviewed at home and were invited for subsequent examinations at a research center. In the present study we included those 6,568 subjects (82.3%) of whom information on subjective complaints was available, who underwent the complete neurologic screening examination at the research center, and, to guarantee adequate numbers for age-specific analyses, were between 55 and 95 years of age.

Data collection

In the home interview, trained research assistants asked the participants whether they

had any tremor, and whether they had experienced slowness and/or stiffness of movement. These questions had been reported to be most useful and feasible when screening for parkinsonism.[7,9] During the screening examination at the research center, the presence of related parkinsonian signs (i.e., resting tremor, rigidity, and bradykinesia) and essential tremor in a subject was assessed by trained study physicians who used a structured protocol and were unaware of the complaints reported by the subject.[10] The results from this examination were regarded the gold standard. The persons who were suspected of a possible PD were further evaluated for a final diagnosis of PD by a neurologist.[10]

Data analysis

We calculated age- and sex-specific prevalence estimates by 10 year age categories of self-reported tremor and slowness/stiffness of movement as well as of parkinsonian signs, postural tremor, and action tremor as assessed by the study physicians.

Regarding the use of a questionnaire as a screening tool or diagnostic test, we compared the relation between presence of subjective symptoms and corresponding physical signs by calculating sensitivity (the probability of a positive test result if the disease or sign is actually present) and specificity (the probability of a negative test result given the absence of the disease). In addition, we calculated the positive predictive values of the subjective complaints for the presence of parkinsonian signs (the probability that a person who screened positive actually has the disease or sign), and the likelihood ratio of a positive screening result (the ratio of the probability of a positive test result if the disease is present and the corresponding probability if the disease is absent). Positive predictive values inform the clinician about how good the test is at predicting the disease and depend on the prevalence of the disease,[11,12] the likelihood ratio indicates whether a test result is informative or not (a ratio greater than 1 for a specific variable indicates a raised probability of the presence of the true sign or disease whereas a ratio of 1 implies a failure to discriminate between presence or absence of the disease).

The various combinations of symptoms and signs that we used for these calculations were the following: (1) we compared tremor as a complaint with the presence of any tremor, including resting tremor, postural tremor, and action tremor; (2) we compared complaints of slowness and/or stiffness of movement with the combination of either bradykinesia and rigidity, and the combination of either bradykinesia, rigidity, or reduced fingertapping speed; (3) and we compared the presence of any of the complaints with the presence of any of the signs as assessed by the study physicians.

We also assessed the sensitivity of the screening questions to detect PD patients in a population, for all PD patients combined, and stratified according to patients who were diagnosed through the study or were already known to be affected by the disease.
Finally, we investigated the extent to which the test characteristics were dependent on age.

Results

Prevalence

Table 3.1.1 shows the age distribution of the study population, the percentages of subjective complaints as reported by the subjects, and the prevalence of related signs as assessed by the study physicians. Thirty-nine percent of the study population were men. The proportion of persons who reported to have a tremor and the proportion of persons who had experienced slowness/stiffness increased with age and was overall higher, for slowness/stiffness even more than three times higher, than estimated by the study physicians. The age-specific prevalence estimates for both men and women were virtually similar.

Screening and diagnostic test

The comparisons between self-reported symptoms and objectively assessed signs, calculated as sensitivity, specificity, likelihood ratios, and positive predictive values of these subjective complaints for the presence of signs are shown in Table 3.1.2. Since we found no differences in prevalences for men and women, we report the data for both sexes combined. Both sensitivity and positive predictive values proved to be rather low. If questions on tremor and slowness or stiffness would be used to detect subjects with either possible tremor, rigidity, or bradykinesia, approximately half of the subjects would be missed.
If the questionnaire was used to detect PD patients with true PD, the sensitivity was higher (88.9%), but the screening questionnaire still failed to detect more than 10% of the cases. This percentage of missed PD patients increases with age, from 0% in the age-group 55 to 64 years, to 25% in the age-group 85 to 94 years. In the latter group, the prevalence of PD is high, and, consequently, a substantial number of PD patients (3 out of 12) would not have been detected by the screening questionnaire. This is illustrated in Figure 3.1.1. After stratification according to patients already known to be affected by the disease and those who were detected through the screening in the study, the sensitivity was 90.0% and 81.8% *(Table 3.1.3).*

Table 3.1.1 *Age distribution of the study population and the age-specific prevalence (%) of subjective complaints and corresponding signs as assessed by the study physicians*

	Subjective complaints		Signs as assessed by physicians			Numbers of subjects
Age (years)	Tremor	Slowness/stiffness	Any tremor	Bradykinesia/rigidity	Bradykinesia/ rigidity/reduced fingertapping speed	
55-64	8.6% (218)*	18.4% (467)	4.6% (117)	2.6% (66)	3.0% (77)	2533
65-74	12.5% (295)	21.9% (519)	10.4% (245)	6.4% (151)	7.2% (171)	2367
75-84	20.5% (271)	32.4% (428)	16.5% (218)	12.2% (162)	15.1% (200)	1323
85-94	24.9% (86)	49.3% (170)	23.8% (82)	23.8% (82)	29.3% (101)	345
Total	13.2% (870)	24.1% (1584)	10.1% (662)	7.0% (461)	8.4% (549)	6568

* Number of subjects are given in parentheses.

Table 3.1.2 *Age-specific sensitivity (sens), specificity (spec), positive predictive values (PPV), and likelihood ratios of a positive screening test result (LR) of subjective complaints in screening for corresponding signs (as assessed by study physician)*

	Tremor				Slowness/stiffness*				Tremor or slowness/stiffness			
Age (years)	Sens (%)	Spec (%)	PPV (%)	LR	Sens (%)	Spec (%)	PPV (%)	LR	Sens (%)	Spec (%)	PPV (%)	LR
55-64	27.4	92.3	14.7	3.6	39.4	82.1	5.6	2.2	42.4	77.6	12.1	1.9
65-74	36.3	90.3	30.2	3.7	39.1	79.2	11.4	1.9	48.7	73.9	24.1	1.9
75-84	45.4	84.4	36.5	2.9	43.2	69.2	16.4	1.4	60.8	63.8	34.5	1.7
85-94	48.8	82.5	46.5	2.7	62.2	54.8	30.0	1.4	72.9	50.0	46.5	1.5
Total	39.3	89.7	29.9	3.8	44.7	77.4	13.0	2.0	54.8	72.7	25.6	2.0

* If reduced fingertapping speed had been included in the gold standard, then for all age categories the sensitivity would have been 58.3%, specificity 71.1%, and the positive predictive value 15.6%.

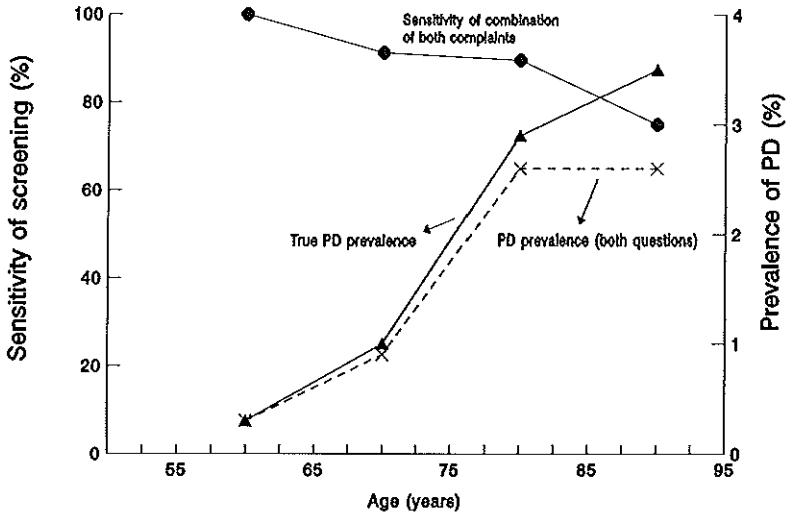

Figure 3.1.1 *Sensitivity of either tremor or slowness/stiffness of movement as a screening tool for Parkinson's disease (PD) by age (left y-axis). Also, the true age-specific prevalence of PD is shown, and the prevalence of PD as would have been estimated if a screening for PD solely relied on questions on these subjective complaints (right y-axis).*

Table 3.1.3 *Sensitivity* of any of the subjective complaints (either tremor or slowness/stiffness, or both) suggestive for Parkinson's disease (PD) as a screening tool for all PD patients, for those who were known to be affected by the disease, and for those who were detected through the screening in the study (early PD)*

	All PD patients	Known PD	Early PD
Age (yrs)			
55-64	100.0	100.0	100.0
65-74	91.3	90.5	100.0
75-84	89.7	93.8	71.4
85-94	75.0	72.7	100.0
Total	88.9	90.0	81.8

* Sensitivity in percentage.

Discussion

Prevalence

In this study we provided age-specific prevalence figures of subjective complaints that may indicate the presence of parkinsonism. To date, these figures were hardly available. Only in the study by Morgante et al. information was shown that might be indicative for the age- and sex-specific prevalence of such complaints in an elderly population.[6] The investigators reported the prevalence of persons that screened positive for possible parkinsonism, using a combination of symptom questionnaire and some physical tests. Their estimates were similar to the prevalence of a comparable combination of subjective complaints as estimated in our study. These findings suggest that a surprisingly large proportion of elderly experience slowness or stiffness of movement, or tremor, or a combination of these.

Screening and diagnostic test

In community surveys on frequency of disease complete case-ascertainment is pursued, and a sensitive screening instrument is necessary. However, in a two-phase approach, as often used in community surveys on the frequency of PD, a highly sensitive screening instrument may load neurologists with a large number of persons who have to be evaluated in the second phase but falsely screened positive. A large proportion of false positives will lead to loss of time, more costs etcetera and will thereby reduce the benefits of such stepped-screening approach. On the other hand, a very specific (and probably time and cost effective) screening instrument may lead to underestimation of the frequency of the disease.

In our study, the screening characteristics of the questionnaire proved to be poor to detect corresponding signs. Although the detection rate of PD was considerably better, this decreased with age, in particular in the highest age-group, where the prevalence of PD is high; the sensitivy of questions to detect PD was only 75%.

In the ideal study of validiting a screening instrument, all subjects should also undergo "the gold standard" test, independently of the screening instrument that is evaluated, as was done in our study. The gold standard should ideally be 100% accurate. For clinical signs of parkinsonism, especially in an epidemiological setting, this will be difficult to achieve. Especially in elderly, comorbidity may mimic signs suggestive for parkinsonism, especially slowness or stiffness of movement, and thus reducing the discriminative ability of these complaints. Also, in an early stage of the disease, some of the parkinsonian signs may be very subtle or, especially tremor, may be infrequently present and will not always be noticed during the screening examination. This may have caused us to misclassify some subjects who actually had

signs as having no signs. As a result, we may have underestimated the sensitivity of the questionnaire. Moreover, incorporation of more questions related to complaints typical for parkinsonism into the screening questionnaire may improve the sensitivity. The high prevalences of subjective complaints compared to the relatively low true prevalence of probable parkinsonian signs (and, eventually, even lower prevalence of parkinsonism)[6,10] will result in low positive predictive values for parkinsonian signs as shown in our study. The positive predictive values were higher in the higher age groups. This was expected since positive predictive values increase with increasing prevalence.[13,14]

Modification of test characteristics

The very few published studies that reported on sensitivity and specificity of screening questionnaires for parkinsonism showed higher values for sensitivity and specificity.[5,7,9] These studies were based on small samples of well diagnosed hospital-based PD patients and healthy controls. As the spectrum of disease in the people included in these validation studies probably differed from the spectrum of disease in the general population in which the test was to be used, the reported sensitivities and specificities will have overestimated the actual performance of the screening instrument. Sensitivity and specificity are partly functions of individual patient characteristics.[12,13,15,16] As clearly demonstrated in our study, age was such a characteristic that strongly modified sensitivity and specificity. Moreover, if a general population is screened for parkinsonism, both PD patients in a very early phase of the disease, with cardinal signs less prominently present, and PD patients with a clear clinical picture will emerge. Intuitively, it can be conceived that in both PD populations a screening questionnaire will perform differently as we showed with our data, being less sensitive and specific in patients in an early phase of the disease. However, in the latter population, the age-specific estimates of the sensitivity fluctuated due to the small number of newly detected PD patients.

We conclude that complaints suggestive for parkinsonism, such as tremor, slowness of movement, and stiffness, are frequent in a general elderly population. Their presence increases the likelihood that parkinsonian signs are present, but are of relatively little use when applied as the sole screening instrument to detect parkinsonian signs in a general elderly population. The validity of a screening instrument should be assessed only in the same population in which the screening instrument will be used, and preferably in subgroups.

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3.2 Diagnostic criteria for Parkinson's disease

None of the numerous diagnostic criteria for Parkinson's disease (PD) have been compared in diverse population settings. Our preliminary experience in a South American city is that the application of different criteria may significantly impact on prevalence data.[1] Differing diagnostic criteria may obscure the comparison of prevalence studies from different regions, and etiologic insights drawn from such comparisons may be flawed. In this article, we assess, for three recent community studies, the extent to which various diagnostic criteria for PD may affect prevalence estimates. We also address, in general, the usefulness and limitations of these diagnostic criteria for community studies.

Methods

We used data from three separate community studies of PD. These studies were conducted in Junín, a small city in Buenos Aires Province, Argentina;[1,2] in Ommoord, a suburb of Rotterdam, the Netherlands;[3] and in Riposto (Catania Province), Santa Teresa di Riva (Messina Province), and Terrasini (Palermo Province), three semi-rural municipalities in Sicily, Italy.[4-7] For simplicity, we refer to these investigations as "the Junín Study," "the Rotterdam Study," and "the Sicily Study." Each investigation relied on a two-phase approach to detect PD. In phase 1, specially trained personnel screened all participants for parkinsonism, and those suspected of having the syndrome were invited for a neurological examination. In phase 2, project neurologists conducted the examinations, and, when parkinsonism was present, they distinguished PD from other causes of this syndrome. Table 3.2.1 provides additional details for the populations studied and the case-finding methods used.

Diagnostic criteria

In the current research, we applied eight sets of diagnostic criteria to assess the impact of different clinical definitions of PD. The sets included variations of cardinal signs (i.e., resting tremor, bradykinesia, rigidity, and impaired postural reflexes), and of additional clinical features (i.e., duration of symptoms, asymmetry of cardinal signs, and response to drug treatment). For each set, the diagnosis of PD in a subject with parkinsonism was made only if no other cause of parkinsonism was apparent.

The eight sets of diagnostic criteria are specified in Table 3.2.2. Set 1 was used in the Rotterdam Study and the Sicily Study.[3,4] Because this set is the least restrictive, it was used as the reference for comparison with other sets. Set 2 was used in the Junín Study.[1] Set 3 was derived from the United Kingdom Parkinson's Disease Society Brain Bank criteria.[8] Set 4 was applied in a prevalence study from Bombay, India,[9] and also resembles the diagnostic criteria of Calne et al.[10] Set 5 ignores impairment of postural reflexes, and was derived from diagnostic criteria of Rajput et al.[11] Sets 6-8 require cardinal signs (same as set 1) and specify additional clinical features: duration of symptoms, asymmetry of cardinal signs, or response to anti-

Table 3.2.1 Sample or population sizes and case-finding methods for three studies of Parkinson's disease: Junín (Argentina), Rotterdam (the Netherlands), and Sicily (Italy)*

	Junín	Rotterdam	Sicily
Sample or population size, restricted to persons 50-89 years of age, except for Rotterdam where the age range is 55-89 years	5,728 inhabitants; systematic sample of blocks and dwellings throughout the city	6,833 inhabitants; complete enumeration of the suburb Ommoord	6,746 inhabitants; complete enumeration of three semi-rural municipalities
Phase 1: screening	Questions only, to one responsible adult who answers for all adult household members	Questions and brief physical examination, in each individual	Questions and brief physical test, in each individual
Questions (personnel)	Tremor, bradykinesia, rigidity, previous diagnosis of PD (interviewers)	Previous diagnosis of PD, antiparkinsonian drug use (interviewers)	Tremor, bradykinesia, rigidity, previous diagnosis of PD (physicians)
Examination (personnel)	Not applicable	Resting tremor, bradykinesia, rigidity, impaired postural reflexes (physicians)	Tandem gait, elbow tone (physicians)

***Table 3.2.1** (continuation)*

	Junín	Rotterdam	Sicily
Phase 2: neurological examination of persons screened positive (personnel)	Assessment of resting tremor, bradykinesia, rigidity, impaired postural reflexes, additional neurological items (neurologists)	Motor part of UPDRS,[15] additional neurological items (neurologists or specially trained residents in neurology)	Assessment of resting tremor, bradykinesia, rigidity, impaired postural reflexes, additional neurological items (neurologists)
Documentation of cardinal signs	Dichotomous	Five-point scale of UPDRS	Dichotomous
Documentation of duration	From history, verification in medical records	From history, verification in medical records	From history, verification in medical records
Documentation of asymmetry of cardinal signs	Not systematically assessed	Score difference of ≥2 on UPDRS for all 8 bilateral items†	Dichotomous
Documentation of treatment responsiveness	From history, verification in medical records	From history, verification in medical records	From history, verification in medical records

* Abbreviations: PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

† Resting tremor of hand or foot; rigidity of upper or lower extremity; finger tapping; grip; rapid alternating hand movements; leg agility.

parkinsonian medication. The requirement of at least one year duration of motor symptoms (set 6) was proposed by Koller,[12] and the requirement of asymmetry (set 7) was advanced by Calne et al.[10] Responsiveness to antiparkinsonian medication (set 8), where applicable, is widely accepted as an inclusion criterion.[8,12-14]

In the Junín Study and the Sicily Study,[1,4] a dichotomous scale was used to assess the presence or absence of cardinal signs, whereas in the Rotterdam Study[3] the five-point Unified Parkinson's Disease Rating Scale (UPDRS) was applied.[15] To increase methodologic comparability across the studies, we converted the data from the Rotterdam Study to a dichotomous scale by scoring any presence of resting tremor, bradykinesia, or rigidity (score 1-4 on the UPDRS) as "present."

Table 3.2.2 *Prevalence (cases per 100,000 population) of Parkinson's disease, by diagnostic criteria, age, and study*

		Junín*		Rotterdam†		Sicily‡	
Diagnostic criteria	Age (yrs)	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence
Cardinal signs only:							
Set 1 *(reference)*							
At least two cardinal signs of the following four: resting tremor, bradykinesia, rigidity, and impaired postural reflexes.	50-59	3	153	2	172	3	116
	60-69	17	773	10	367	13	621
	70-79	21	1,727	27	1,320	31	1,978
	80-89	11	3,125	28	3,111	15	3,055
	Total	52		67		62	
Set 2							
At least two cardinal signs of the following four: resting tremor, bradykinesia, rigidity, and impaired postural reflexes. One sign must be either resting tremor or bradykinesia.	50-59	3	153	2	172	3	116
	60-69	14	637	10	367	13	621
	70-79	21	1,727	27	1,320	31	1,978
	80-89	11	3,125	28	3,111	15	3,055
	Total	49		67		62	
Set 3							
At least two cardinal signs of the following four: resting tremor, bradykinesia, rigidity, and impaired postural reflexes. One sign must be bradykinesia.	50-59	1	51	2	172	3	116
	60-69	8	364	10	367	12	574
	70-79	19	1,563	27	1,320	28	1,787
	80-89	10	2,841	28	3,111	13	2,648
	Total	38		67		56	
Set 4							
At least three cardinal signs of the following four: resting tremor, bradykinesia, rigidity, and impaired postural reflexes.	50-59	1	51	2	172	3	116
	60-69	9	500	9	330	11	526
	70-79	17	1,398	18	880	26	1,659
	80-89	8	2,273	21	2,333	12	2,444
	Total	35		50		52	

Set 5							
At least two cardinal signs of the following	50-59	3	153	2	172	3	116
three: resting tremor, bradykinesia, and	60-69	14	637	10	367	13	621
rigidity.	70-79	21	1,727	26	1,271	31	1,978
	80-89	11	3,125	26	2,889	15	3,055
	Total	49		64		62	
Cardinal signs with additional clinical features:							
Set 6							
At least two cardinal signs of the following	50-59	3	153			3	116
four: resting tremor, bradykinesia, rigidity,	60-69	12	546			13	621
and impaired postural reflexes.	70-79	20	1,645			28	1,787
There must be at least one year duration of	80-89	8	2,273			15	3,055
symptoms.	Total	43				59	
Set 7							
At least two cardinal signs of the following	50-59			1	86	1	39
four: resting tremor, bradykinesia, rigidity,	60-69			5	183	4	191
and impaired postural reflexes.	70-79			17	831	10	638
One or more of the first three signs must	80-89			14	1,556	7	1,426
display asymmetry.	Total			37		22	
Set 8							
At least two cardinal signs of the following	50-59	2	102	2	172	2	77
four: resting tremor, bradykinesia, rigidity,	60-69	8	364	7	257	9	430
and impaired postural reflexes.	70-79	13	1,069	17	831	21	1,340
If treated, there must be a therapeutic	80-89	7	1,989	25	2,778	8	1,629
response to anti-parkinsonian medication.	Total	30		51		40	

* Denominators were: 50-59 = 1,962; 60-69 = 2,198; 70-79 = 1,216; 80-89 = 352.

† Denominators were: 50-59 = 1,161; 60-69 = 2,726; 70-79 = 2,046; 80-89 = 900.

‡ Denominators were: 50-59 = 2,596; 60-69 = 2,092; 70-79 = 1,567; 80-89 = 491.

Data analysis

We examined the data in terms of the different sets of diagnostic criteria, both within and across the three studies. For each study separately, we present the number of subjects with PD, by age, according to the various sets of diagnostic criteria. We also present age-specific prevalences. Our analyses pertained to subjects younger than 90 years of age because the Junín Study and the Sicily Study included only a few individuals who were 90 years of age or older. We decided not to present data separately by sex because recent prevalence data have an inconsistent sex pattern.

Results

Table 3.2.2 shows the impact of various sets of diagnostic criteria on numbers of cases of PD. Set 1 was the reference for comparison, and it yielded the highest numbers of cases. Sets 1-5 pertain only to cardinal signs. Among these sets, set 4 led to the greatest loss of cases: Junín, 33%; Rotterdam, 25%; Sicily, 16%. That set required three or four cardinal signs. The least loss of cases (Junín, 6%; Rotterdam, 0%; Sicily, 0%) came with set 2 which required two, three, or four cardinal signs with one being either resting tremor or bradykinesia. For set 5, which ignored impaired postural reflexes, the loss of cases was also minor: Junín, 6%; Rotterdam, 5%; Sicily, 0%.

Sets 6-8 required at least two of the four cardinal signs, together with additional clinical features. For set 6, which required at least one year duration of symptoms, the loss of cases was greater in the Junín Study than in the Sicily Study, 17% versus 5% (again using set 1 as reference). The Rotterdam Study was excluded from this comparison because data on duration of symptoms were lacking for several subjects with PD. For set 7, which required any of resting tremor, bradykinesia, or rigidity to display asymmetry between left and right limbs, the loss of cases was severe: 45%, Rotterdam; 65%, Sicily. Data on asymmetry were not systematically obtained in the Junín Study. For set 8, which required a therapeutic response for those subjects treated with anti-parkinsonian medication, the loss of cases was also substantial: 42%, Junín; 24%, Rotterdam; 36%, Sicily.

Table 3.2.2 shows also the impact of the above-mentioned sets of diagnostic criteria on the age-specific prevalence of PD. The patterns seen here are consonant with the results presented above. For example, the most restrictive requirement is that one or more of resting tremor, bradykinesia, or rigidity display asymmetry (set 7). This finding holds true across the spectrum of age, for both the Rotterdam and Sicily studies.

Discussion

In prevalence studies of PD in geographically defined communities, there is a need for diagnostic criteria that are credible yet practical to apply, even outside of clinics. Postmortem neuropathologic examination of the brain is generally considered to be the gold standard for the diagnosis of PD[8] but during life, the diagnosis can only be based on the clinical picture. Although many recent prevalence studies of PD have followed similar case-finding approaches (involving door-to-door screening and physical examination),[1,3,4,9,16-18] there has been little agreement on what diagnostic criteria to use and it has remained unclear to which extent different diagnostic criteria may affect prevalence estimates of PD.

Our study clearly demonstrates the differential impact of alternative sets of diagnostic criteria on the prevalence of PD. Some combinations of at least two cardinal signs (i.e., sets 1-2 versus set 5, *Table 3.2.2*) did not appreciably change the prevalence. By contrast, the use of at least two cardinal signs together with additional clinical requirements (viz., set 1 versus sets 7-8, *Table 3.2.2*) led to more pronounced drops in prevalence. We will consider some issues related to the diagnosis of PD, and finally endorse a set of diagnostic criteria for use in community studies.

Resting tremor or bradykinesia, or both

The requirement that one cardinal sign must be either resting tremor or bradykinesia had almost no effect on prevalence (set 1 versus set 2, *Table 3.2.2*). We see no reason to recommend this requirement for community studies of PD.

Bradykinesia

The requirement that one cardinal sign must be bradykinesia had mixed effects on prevalence (set 1 versus set 3, *Table 3.2.2*). We do not know whether this requirement has value for community studies of PD; the possibility remains that it may cause the prevalence to be somewhat understated.

Three of four cardinal signs

The requirement of at least three cardinal signs from resting tremor, bradykinesia, rigidity, and impaired postural reflexes reduced the prevalence noticeably (set 1 versus set 4, *Table 3.2.2*). We cannot recommend this requirement for community studies of PD because it would exclude less severe forms of the condition.

Impaired postural reflexes

Disregarding impaired postural reflexes as a cardinal sign appears to alter prevalence only slightly (sets 1-2 versus set 5, *Table 3.2.2*). This finding calls into question the need to consider impaired postural reflexes in the diagnostic criteria of PD, especially since 1) impaired postural reflexes in the elderly is not specific for PD, and 2) the sign

usually occurs late in the course of the disease.[19]

Duration of symptoms

The requirement of at least one year duration of symptoms had noticeably more impact on prevalence for the Junín Study than for the Sicily Study (set 1 versus set 6, *Table 3.2.2*). Thus, at least in some populations, a duration requirement would likely exclude several subjects with recent onset of PD. For this reason, we do not endorse incorporating a duration requirement into diagnostic criteria for community studies of PD.

Asymmetry of cardinal signs

The requirement that at least one of resting tremor, bradykinesia, or rigidity displays asymmetry had a dramatic impact on prevalence (set 1 versus set 7, *Table 3.2.2*). A rigorous assessment of asymmetry may require expertise in PD that is not always available in the field setting of a community study. Treatment of PD may obscure the asymmetry, and, in the more advanced stages of the condition, asymmetry of symptoms may be inapparent. Moreover, asymmetry of cardinal signs of parkinsonism is not unique to PD; it is reported in some cases of progressive supranuclear palsy and multiple system atrophy.[20,21] These considerations suggest the impracticality of requiring asymmetry of cardinal signs in the diagnostic criteria for community studies of PD.

Response to anti-parkinsonian medication

The requirement of treatment response (set 1 versus set 8, *Table 3.2.2*) had a lesser, but still sizable, impact on prevalence than did the requirement of asymmetry of cardinal signs (set 1 versus set 7). Treatment response is of questionable value in the field setting of a community study. First, treatment response presupposes that a treatment was administered. Some community studies have identified many persons with PD who had never been diagnosed previously and, therefore, had never been treated.[1,4,16] Such persons would be judged differently than established, treated PD patients. A bias may be introduced if there are important differences, clinical or sociodemographic, between treated and untreated persons with PD. Second, treatment response relates to the choice of medication (levodopa versus other drugs), the timing of starting treatment (earlier versus later in the course of the disease), and the adequacy of the dosing. Third, there is no completely satisfactory approach to measuring treatment response. Objective scales such as the UPDRS are not routinely used in medical practice. Subjective assessment is hampered in patients with long disease duration who no longer recall the initial effect of a treatment that over time has provided diminishing benefit. Medical records documenting the initial treatment response may not always be available. Because of these limitations, we would not

include treatment response as a requirement in the diagnosis of PD when conducting community studies.

Final recommendation

For community studies of PD, we favor diagnostic criteria that are more easily applied in the field context and that tend to be more inclusive than exclusive. We recommend the following: at least two of resting tremor, bradykinesia, or rigidity, in the absence of other apparent causes of parkinsonism.

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Chapter 4

Frequency of Parkinson's disease

4.1 Prevalence of Parkinson's disease in the Rotterdam Study

Parkinson's disease (PD) is among the most frequent chronic neurodegenerative diseases in the elderly. However, prevalence estimates of PD vary widely, ranging from 10 to 405 per 100,000 population.[1] This variation may be due to differences in case-finding procedures, in diagnostic criteria, and in the age distribution of populations. We present the results of a population-based PD prevalence survey among 6,969 subjects living in Rotterdam, the Netherlands, in which we examined each individual neurologically.

Methods

Study population

This study forms part of the Rotterdam Study, a population-based cohort study on prevalence, incidence and determinants of diseases in the elderly.[2] The four main areas of interest of the Rotterdam Study are neurologic diseases, ophthalmologic diseases, locomotor diseases, and cardiovascular diseases. The cross-sectional survey started in 1990 and was completed in June 1993. All inhabitants of Ommoord, a suburb of Rotterdam, the Netherlands, who were 55 years of age or older, either living independently or institutionalized, were invited to participate in the study by mail and were contacted by telephone 2 weeks later. Names and addresses were drawn from the municipal register, which is reliable, complete and updated weekly. Of the 10,275 eligible subjects, 7,983 (78%) agreed to participate and signed informed consent statement. All participants were interviewed at home and most were subsequently examined at a research center. The number who visited the research center decreased slightly, to 7,129 (69%), due to refusal, disease, or death. In this prevalence study we included the 6,969 (68%) subjects who had a neurologic screening examination or who were using antiparkinsonian medication or reported that they had PD.

Case-finding and diagnostic procedures

To assess the prevalence of PD we used a two-phase design. In the first phase, all participants were asked about previous diagnosis of PD, and any drug use was coded

according to the Anatomical Therapeutic Chemical (ATC) classification index.[3] In addition, every participant was neurologically examined by one of the study physicians. All subjects who either used antiparkinsonian drugs (ATC-code N04), reported that they had PD, or had at least one possible cardinal sign of parkinsonism (i.e., resting tremor, rigidity, bradykinesia, or impaired postural reflexes) at the neurologic screening examination were invited for further evaluation in a second phase.

In the second phase, those who screened positive were examined by a neurologist or a neurologist-in-training. A structured clinical work-up, comprising the motor examination of the Unified Parkinson's Disease Rating Scale (UPDRS),[4] a neurologic examination, and standardized history taking, was used to establish the diagnosis parkinsonism and to classify this parkinsonism. We used diagnostic criteria agreed upon in EUROPARKINSON (European Community Concerted Action on the Epidemiology of Parkinson's disease).[5] Parkinsonism was diagnosed as 'definite' if at least two of the cardinal signs were present in a subject not taking antiparkinsonian drugs, or if in a subject treated with antiparkinsonian medication one or more signs, documented by medical history, had improved by treatment. Parkinsonism was classified as 'possible' if only one sign was present in an untreated subject or if a specifically treated patient did not report benefit from treatment and had only one cardinal sign. Possible parkinsonism is not included in the prevalence figures. All newly diagnosed patients with definite parkinsonism were reevaluated by a second neurologist.

PD was defined in a person with definite parkinsonism by exclusion of all other possible causes of parkinsonism. Parkinsonism associated with other causes included (1) drug-induced (i.e., following use of neuroleptics or other anti-dopaminergic drugs in the 6 months before onset of symptoms and with no history of parkinsonism); (2) parkinsonism related to cerebrovascular disease (i.e., with a clear time relationship between cerebrovascular event and onset of atypical parkinsonism, preferably supported by neuroimaging, usually without tremor); (3) parkinsonism associated with dementia; (4) parkinsonism in multiple system atrophy or progressive supranuclear palsy; and (5) other parkinsonism. Included in this last category were subjects with more than one possible cause or with no clear time relationship between the possible cause and the parkinsonism, as well as those subjects in whom all other possible causes of parkinsonism could be excluded but who had not shown any progression over more than 15 years in the course of the disease and who did not respond to antiparkinsonian drugs.

Some screened positive subjects could not be evaluated in the second phase for a

variety of reasons, such as refusal, disease, or death. For these subjects we obtained additional information from medical records of neurologists and general practitioners. They had to meet the same inclusion and exclusion criteria for parkinsonism and PD as those who could be examined.

In demented patients the neurologic screening examination was often difficult to conduct or to interpret. Therefore, irrespective of the results of the screening, we reviewed the medical records of demented institutionalized participants to check for a previous diagnosis of PD or secondary parkinsonism.

Data analysis

We calculated age- and sex-specific prevalence figures of parkinsonism and PD for the study population that underwent a complete first-phase screening. The prevalence figures are presented in 10-years age groups and are presented separately for men and women. To determine whether overall age-adjusted prevalences for men and women differed significantly, we performed a logistic regression analysis in which gender and age were entered as determinants in the model.

Results

Of the 6,969 participants, 653 (9.4%) screened positive and were invited for evaluation in the second phase. Table 4.1.1 shows the age and sex distributions of the study population and the percentages of subjects who screened positive.

Table 4.1.1 Age and sex distribution of the study population and percentages of subjects screening screenpositive*

	Men		Women		Total	
Age (years)	Total	Screen-positive	Total	Screen-positive	Total	Screen-positive
55-64	1098	4.4 (48)	1471	3.1 (45)	2569	3.6 (93)
65-74	1090	9.1 (99)	1389	7.3 (102)	2479	8.1 (201)
75-84	521	18.2 (95)	940	14.8 (139)	1461	16.0 (234)
85-94	101	25.7 (26)	336	27.7 (93)	437	27.2 (119)
95+	3	(0)	20	30.0 (6)	23	26.1 (6)
Total	2813	9.5 (268)	4156	9.3 (385)	6969	9.4 (653)

* Numbers of subjects who screened positive are given in parentheses.

In the second phase, 499 subjects who screened positive (76%) were clinically examined. Of the subjects evaluated, we found 89 subjects to have parkinsonism, and in 69 of these this parkinsonism was attributed to PD. In 128 of the 154 subjects who screened positive who could not be further examined, we obtained a sufficient amount of other medical information on which to base the diagnosis. This revealed another 40 subjects with parkinsonism, of whom 28 met the diagnostic criteria for PD. Therefore, we identified a total of 129 subjects with parkinsonism of whom 97 subjects were suffering from PD. The other diagnoses included parkinsonism associated with dementia (9/129); drug-induced parkinsonism (3/129); parkinsonism related to vascular disease (1/129); multiple system atrophy (2/129), or progressive supranuclear palsy (1/129); and other parkinsonism (16/129). Table 4.1.2 presents the age- and sex-specific prevalence figures of parkinsonism and PD in the total study population.

Table 4.1.2 Prevalence* (%) of any parkinsonism (PS) and Parkinson's disease (PD) in the Rotterdam Study

	Men		Women		Total	
Age (yrs)	PS	PD	PS	PD	PS	PD
55-64	0.4 (4)	0.4 (4)	0.3 (5)	0.2 (3)	0.4 (9)	0.3 (7)
65-74	1.4 (15)	1.2 (13)	1.1 (15)	0.8 (11)	1.2 (30)	1.0 (24)
75-84	3.8 (20)	2.7 (14)	4.5 (42)	3.4 (32)	4.2 (62)	3.1 (46)
85-94	5.0 (5)	3.0 (3)	6.3 (21)	4.8 (16)	5.9 (26)	4.3 (19)
95+	(0)	(0)	10.0 (2)	5.0 (1)	(2)	(1)
Total	1.6 (44)	1.2 (34)	2.0 (85)	1.5 (63)	1.9 (129)	1.4 (97)

* Numbers of patients are given in parentheses.

The prevalence increased with age, even in the highest age categories. The prevalence of PD did not differ significantly between men and women.
Twelve subjects with PD (12%) were newly diagnosed through the study protocol; 11 of them were 70 years of age or older. Of the 75 subjects who reported that they had PD, 12 (16%) turned out to be not affected by the disease. Seven of those participants

had never been diagnosed with PD, and five subjects with a previous diagnosis of PD were excluded since they did not fulfill the inclusion criteria for PD used in this study; one of these patients had a nonprogressive hemiparkinsonism; two patients did not have parkinsonism according to the UPDRS, and the two other patients had more than one possible cause for their parkinsonism. In addition, we classified one subject with a previous diagnosis of multiple system atrophy and two subjects with a previous diagnosis of progressive supranuclear palsy as having PD since no other neurologic symptoms were present to justify the previous diagnoses. Of all patients with PD, 73 (75%) used antiparkinsonian medication.

Discussion

We found a consistent and rapid increase in the prevalence of both parkinsonism and PD with age, with no leveling off in the highest age categories and no significant gender difference.

The overall response in our study was good but nonresponse may have led to a certain underestimation of the prevalence. Indeed, in the Rotterdam Study, the prevalence of PD was higher among those who screened positive who could not be examined in the second phase than among those who could. Furthermore, we classified parkinsonian participants with atypical parkinsonism or with no clear time relationship between the possible cause and the parkinsonism as having 'other parkinsonism'. This may also have resulted in some underestimation of the prevalence of PD in our study.

Prevalences of PD, reported in various studies, show wide variation.[1] Many of these studies were based on existing medical records.[6-12] Differences in case-finding procedures, in diagnostic criteria, and in accessibility and level of medical services may hamper comparison. Some of these studies dated from before levodopa treatment was available, and the advent of this treatment may have influenced survival of parkinsonian patients,[13,14] and thus the prevalence. Moreover, patients who failed to seek medical attention for their parkinsonism were not systematically included in these studies. PD is a neurodegenerative disease with an insidious onset, and parkinsonian symptoms are likely to remain unrecognized or to be misclassified or accepted as part of a normal aging process. This also leads to underestimation of the prevalence and might explain the lower prevalence estimates[6-12] than that reported in our study, as well as the decrease in prevalence of PD in the higher age categories reported in some studies.[9-11]

Not until 1985 were there published results of population-based prevalence studies on PD. All population-based studies showed an increase in the prevalence with age, even

in the highest age category.[15-21] Although the methodology used in these studies should limit the underestimation of prevalence mentioned before, the age-specific prevalence estimates for the age category 70 to 80 years varied from 0.6% in China[15] to 1.3% in France,[21] 1.8% in our study, and 2.0% in Sicily.[16] The prevalence estimates of parkinsonism and PD in our study are among the highest reported thus far and are in concordance with the results of the Sicilian and French studies, which, together with the Chinese study, were the only ones to administer a direct screening instrument to each individual, including a brief neurologic examination by a physician. The discrepancy between the results of the Chinese study and those of the studies conducted in Rotterdam, Sicily, and France could be due to differences in survival of PD patients, in classification, and in etiologic factors.

Although some prevalence studies indicated higher prevalences for men[7,8,15,20] or for women,[9,10] we, like some other investigators,[11,12,17,21] found no significant gender differences in the prevalence.

The screening instrument used in this study enabled us to detect 12 subjects with PD (12%) who had not been diagnosed before. Remarkably, overall prevalence figures in our study were similar to those in the Sicilian and French studies, in spite of a lower percentage of newly diagnosed subjects in the Rotterdam Study (12% versus 35% and 27%), which may be due to differences in referral habits and in accessibility of medical services.

In conclusion, we found an increase in the prevalence of parkinsonism and PD with age, even in the highest age categories. A substantial proportion of patients with PD were previously undetected, especially among the oldest.

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4.2 Prevalence of Parkinson's disease in Europe

Parkinson's disease is one of the most common chronic neurodegenerative diseases in the elderly. Prevalence estimates of Parkinson's disease vary widely across studies and countries[1] but the interpretation of this geographical variation is hampered by differences in methodology and diagnostic criteria. Consequently, it remains unclear whether a true variation exists. As part of a European Community Concerted Action on the Epidemiology of Parkinson's disease (EUROPARKINSON),[2] we conducted a collaborative comparison of five European prevalence surveys of all types of parkinsonism, including Parkinson's disease.

Methods

EUROPARKINSON is a collaborative effort to study the prevalence, incidence, and determinants of Parkinson's disease in Europe including five studies, one each from France,[3] Italy,[4] and the Netherlands,[5] and two from Spain. All five studies are community surveys of both independently living and institutionalised elderly subjects 55 years of age or older, with a sample size of at least 1,000 subjects. The characteristics of the five study populations are summarised in Table 4.2.1.

Case finding procedures

All studies used a two-phase design to assess the prevalence of parkinsonism and Parkinson's disease. In phase 1, participants were screened in person using a symptom questionnaire and a brief physical examination. Those who screened positive were extensively evaluated by neurologists in phase 2. The only exception was the study in France in which the physical examination was not used to screen independently living subjects, while all institutionalised participants were examined by a neurologist without any screening. Details of the screening procedures used in each study are presented in Table 4.2.2.

Diagnostic criteria

With two exceptions, the five studies adhered to common diagnostic criteria for parkinsonism and Parkinson's disease. Parkinsonism was diagnosed when at least two of four cardinal signs (i.e., resting tremor, rigidity, bradykinesia, and impaired

Table 4.2.1 *Characteristics of the study populations*

Population	Investigators	Geographic location	Urban or rural	Size of study population	Response rate	Age (yr)	Type of sample	Years of study
France *(Gironde)*	Dartigues et al.[3]	Gironde region	Urban and rural	3,149	71%	65+	Stratified random sample	1988-1989
Italy *(8 centers)*	Amaducci et al.[4]	8 provinces across Italy	Urban and rural	4,510	80%	65+	Stratified random sample	1992-1994
The Netherlands *(Rotterdam)*	Breteler et al.[5]	City of Rotterdam, Ommoord district	Urban	6,969*	68%	55+	Complete enumeration	1990-1993
Spain *(Girona)*	Lopez-Pousa et al.	Group of villages in Girona province	Rural	1,450	84%	70+	Complete enumeration	1990-1991
Spain *(Pamplona)*	Manubens-Bertran et al.	City of Pamplona	Urban	1,127	82%	70+	Stratified random sample	1991

* In the present comparison, persons aged 55 years to 64 years (n = 2569) who particpated in the Rotterdam Study, were excluded.

postural reflexes) were present in a subject not receiving antiparkinsonian medication, or if one or more cardinal signs, documented by medical history, had improved by antiparkinsonian treatment. However, in the study from France, untreated subjects with an isolated typical resting tremor were also included. In the study from Girona, Spain, only untreated subjects with at least three cardinal signs or treated subjects with at least two cardinal signs were included. Parkinson's disease was defined among those affected by parkinsonism by exclusion of all other possible causes. Parkinsonism associated with other causes included: (1) parkinsonism in dementia

***Table 4.2.2** Case-finding procedures*

Population	Phase 1		Phase 2	
	Screening procedure*	Personnel	Diagnostic protocol	Personnel
France *(Gironde)**	*Questions:* Tremor plus rigidity or bradykinesia, anti-parkinsonian drugs	Psychologists	Structured clinical work-up (UPDRS,† neurological examination)	Neurologists
Italy *(8 centers)**	*Questions:* Tremor, previous diagnosis, anti-parkinsonian drugs *Neurological examination:* Walking on heels, elbow tone	Trained interviewers Physicians	Structured clinical work-up (UPDRS,† neurological examination)	Neurologists
The Netherlands *(Rotterdam)**	*Questions:* Previous diagnosis, anti-parkinsonian drugs *Neurological examination:* Resting tremor, rigidity or cogwheeling, bradykinesia, impaired postural reflexes	Trained interviewers Physicians	Structured clinical work-up (UPDRS,† neurological examination)	Neurologists
Spain *(Girona)**	*Questions:* Tremor, previous diagnosis, anti-parkinsonian drugs *Neurological examination:* Tremor, rigidity, bradykinesia	Physicians Physicians	Structured clinical work-up (UPDRS,† neurological examination)	Neurologists
Spain *(Pamplona)*‡	*Questions:* Previous diagnosis, anti-parkinsonian drugs *Neurological examination:* Tremor, gait disturbances, clinical impression	Physicians Physicians	Structured clinical work-up (UPDRS,† neurological examination)	Neurologists

* Screening was positive if at least one of the screening items was positive. In the institutionalized subjects from the French study, the phase-2 procedures were directly applied without any screening.

† UPDRS = Unified Parkinson's Disease Rating Scale.[23]

‡ Screening was positive if at least one question was answered positively or two signs were present at the screening examination.

(i.e., onset of dementia clearly before the occurrence of parkinsonism); (2) parkinsonism with associated features (e.g., multiple system atrophy, or progressive supranuclear palsy); (3) drug-induced parkinsonism (i.e., parkinsonism following the use of neuroleptics or other anti-dopaminergic drugs in the six months preceding onset of symptoms and with no history of parkinsonism); (4) vascular parkinsonism (i.e., clear time-relationship between a cerebrovascular event and onset of atypical parkinsonism, preferably supported by neuroimaging, usually without tremor); and (5) unspecified parkinsonism. Included in this last category were patients with no clear time-relationship between the possible cause (e.g., dementia, antidopaminergic drugs) and parkinsonism, or with more than one possible cause. Patients otherwise fulfilling the criteria for Parkinson's disease who showed no progression of the disease over 15 years or were not responsive to antiparkinsonian drugs were considered "unspecified". To increase reliability across studies, the medical records of most parkinsonian subjects were reviewed by an adjudication panel composed of neurologists from each of the participating centers.

Data analysis

We calculated age- and sex-specific prevalence figures of parkinsonism and Parkinson's disease for each survey separately, and for all studies combined. The overall prevalence was directly age-standardised using the 1991 European population as the standard. The prevalence estimates are presented by 5-year age groups. To obtain stable prevalence estimates, age groups with less than 10 subjects in the denominator were discarded. Since the study from France oversampled institutionalised subjects, prevalence estimates in this study were weighted for the sampling fraction. The prevalence estimates for the age range from 65 to 90 years (70 to 90 years for the two studies from Spain) were also displayed in graphical form, plotted in the middle of the corresponding age group. For the three smallest studies (the French and the two Spanish studies), we presented the data graphically by 10-year age groups to obtain a monotonous curve, not influenced by unstable estimates due to small numbers. The likelihood ratio test was performed to test for heterogeneity across centers. To investigate whether age- and sex-adjusted prevalence figures of Parkinson's disease differed across studies, we calculated prevalence ratios and the corresponding 95% confidence intervals (95%CI) using Poisson regression analyses with the Rotterdam study (the largest) as reference for comparison. We also used Poisson regression analysis to determine whether the overall age-adjusted prevalence was significantly different in men and women.

Results

The overall study population comprised 17,205 elderly individuals, of whom 14,636 were 65 years of age and older *(Table 4.2.1)*. The response rates ranged from 68% in the survey from the Netherlands to 84% for the survey from Girona, Spain *(Table 4.2.1)*. Prevalence figures and the prevalence ratios of parkinsonism and Parkinson's disease for the individual studies and overall are shown in Tables 4.2.3 and 4.2.4, and in Figures 4.2.1 and 4.2.2. The overall age-standardised prevalence (%) in

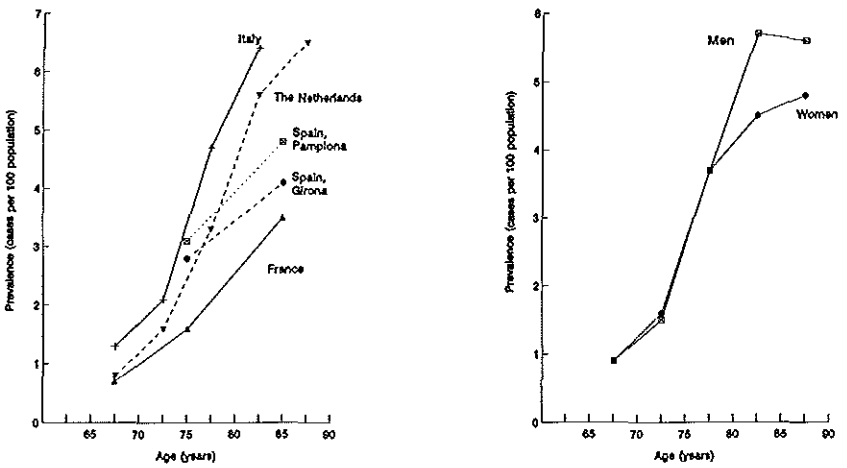

Figure 4.2.1 *Age-specific prevalence, for both sexes combined, of parkinsonism in five European surveys. The prevalence estimates are plotted in the middle of the corresponding age groups: for the studies from Italy and the Netherlands by 5 year age groups, for the studies from France and Spain by 10 year age groups. Overall age-specific prevalence for women and men is shown in the right figure.*

subjects 55 years of age or older was 2.3 for parkinsonism and 1.6 for Parkinson's disease. Prevalence figures of parkinsonism increased from 0.9 for those aged 65 to 69 years to 5.1 for those 85 to 89 years. The prevalence figures for Parkinson's disease increased from 0.6 for those aged 65 to 69 years to 3.5 for those 85 to 89

Table 4.2.3 *Age- and sex-specific prevalence (%) of parkinsonism* and overall age- and sex-adjusted prevalence ratios*

Population		Age group (year)†							Prevalence ratio (95% CI)
		65-69	70-74	75-79	80-84	85-89	90-94	95-99	
France	Women	0.6	1.2	2.8	3.2	3.8	5.3	28.6	
(Gironde)‡		(4/667)	(8/656)	(14/507)	(16/496)	(13/340)	(6/113)	(8/28)	0.7 (0.5-0.9)
	Men	0.8	0.6	2.1	3.2	3.9	4.5	-	
		(5/641)	(3/473)	(6/285)	(6/190)	(5/129)	(1/22)	-	
Italy	Women	1.4	2.4	4.1	5.7	-	-	-	
(8 centers)		(8/568)	(13/538)	(22/541)	(31/542)				
	Men	1.2	1.8	5.3	7.0	-	-	-	1.3 (1.0-1.7)
		(7/585)	(11/602)	(30/571)	(39/555)				
The Netherlands	Women	0.9	1.3	3.7	5.6	6.9	4.4	10.0	
(Rotterdam)		(6/705)	(9/684)	(20/544)	(22/396)	(17/245)	(4/91)	(2/20)	
	Men	0.8	2.1	2.9	5.6	5.1	4.5	-	Reference
		(5/613)	(10/477)	(10/341)	(10/180)	(4/79)	(1/22)	-	
Spain	Women	-†	1.5	5.0	4.1	4.4	5.0	-	
(Girona)			(5/328)	(13/256)	(7/170)	(4/90)	(1/20)	-	
	Men	-	0.4	4.0	2.6	6.7	-	-	1.0 (0.7-1.3)
			(1/262)	(6/150)	(3/114)	(3/45)	-	-	

Spain	Women	-	1.3	3.8	2.0	3.6	6.8	-	
(Pamplona)			(1/75)	(6/159)	(3/150)	(5/137)	(3/44)		
	Men	-	4.2	2.6	6.6	7.0	8.9	-	0.9 (0.6-1.3)
			(3/71)	(4/152)	(10/152)	(10/142)	(4/45)		
Total	Women	0.9	1.6	3.7	4.5	4.8	5.2	20.8	
		(18/1940)	(36/2281)	(75/2007)	(79/1754)	(39/812)	(14/268)	(10/48)	
	Men	0.9	1.5	3.7	5.7	5.6	6.7	-	
		(17/1839)	(28/1885)	(56/1499)	(68/1191)	(22/395)	(6/89)	-	

* Numbers in parentheses indicate the actual numerator and denominator.

† Dashes indicate age groups that were not included in the survey or for which prevalence estimates were not computed because of small numbers.

‡ Prevalence estimates of the French study were weighted according to the sampling procedure; the denominators reported in the table were artificially computed dividing the observed number of cases by the weighted prevalence.

Table 4.2.4 *Age- and sex-specific prevalence (%) of Parkinson's disease* and overall age- and sex-adjusted prevalence ratios*

Population		Age group (year)†							Prevalence ratio (95% CI)
		65-69	70-74	75-79	80-84	85-89	90-94	95-99	
France	Women	0.2	0.2	1.8	1.0	2.2	1.9	7.1	
(Gironde)‡		(1/500)	(2/974)	(9/487)	(5/493)	(7/324)	(2/113)	(2/28)	
	Men	0.7	0.5	1.3	2.9	1.6	4.5	-	0.4 (0.3-0.6)
		(4/556)	(2/399)	(4/308)	(5/173)	(2/125)	(1/22)	-	
Italy	Women	0.9	2.2	3.0	4.1	-	-	-	
(8 centers)		(5/568)	(12/538)	(16/541)	(22/542)				
	Men	0.5	1.0	3.7	5.0	-	-	-	1.2 (0.9-1.6)
		(3/585)	(6/602)	(21/571)	(28/555)				
The Netherlands	Women	0.6	1.0	2.4	4.8	5.3	3.3	5.0	
(Rotterdam)		(4/705)	(7/684)	(13/544)	(19/396)	(13/245)	(3/91)	(1/20)	
	Men	0.8	1.7	2.3	3.9	3.8	-	-	Reference
		(5/613)	(8/477)	(8/341)	(7/180)	(3/79)	(0/22)	-	
Spain	Women	-†	1.5	4.7	3.5	4.4	5.0		
(Girona)			(5/328)	(12/256)	(6/170)	(4/90)	(1/20)	-	
	Men	-	0.4	4.0	2.6	6.7	-	-	0.7 (0.5-1.1)
			(1/262)	(6/150)	(3/114)	(3/45)	-	-	

Spain *(Pamplona)*	Women	-	(0/75)	3.1 (5/159)	1.3 (2/150)	2.2 (3/137)	2.2 (1/44)	-	1.1 (0.8-1.6)
	Men	-	1.4 (1/71)	1.3 (2/152)	4.6 (7/152)	4.9 (7/142)	2.2 (1/45)	-	
Total	Women	0.6 (10/1773)	1.0 (26/2599)	2.8 (55/1987)	3.1 (54/1751)	3.4 (27/796)	2.6 (7/268)	6.3 (3/48)	
	Men	0.7 (12/1754)	1.0 (18/1811)	2.7 (41/1522)	4.3 (50/1174)	3.8 (15/391)	2.2 (2/89)	-	

* Numbers in parentheses indicate the actual numerator and denominator.

† Dashes indicate age groups that were not included in the survey or for which prevalence estimates were not computed because of small numbers.

‡ Prevalence estimates of the French study were weighted according to the sampling procedure; the denominators reported in the table were artificially computed dividing the observed number of cases by the weighted prevalence.

years. The prevalence of both parkinsonism and Parkinson's disease increased with age, following a similar pattern in all studies, with no decrease in extreme ages. After adjustment for age and sex, there were no statistically significant differences across surveys, except for the French study in which prevalences were consistently lower. The likelihood ratio test showed heterogeneity across centers when the survey form France was included ($p<0.001$). When the survey from France was excluded, there were no statistically significant differences across centers ($p = 0.21$). The overall age- and sex-specific prevalences of parkinsonism and Parkinson's disease are graphically presented in Figures 4.2.1 and 4.2.2. The prevalences for men and women were not significantly different; for parkinsonism the women-men ratio was 0.96 (95%CI: 0.80-1.16), and for Parkinson's disease 0.94 (95%CI: 0.75-1.18).

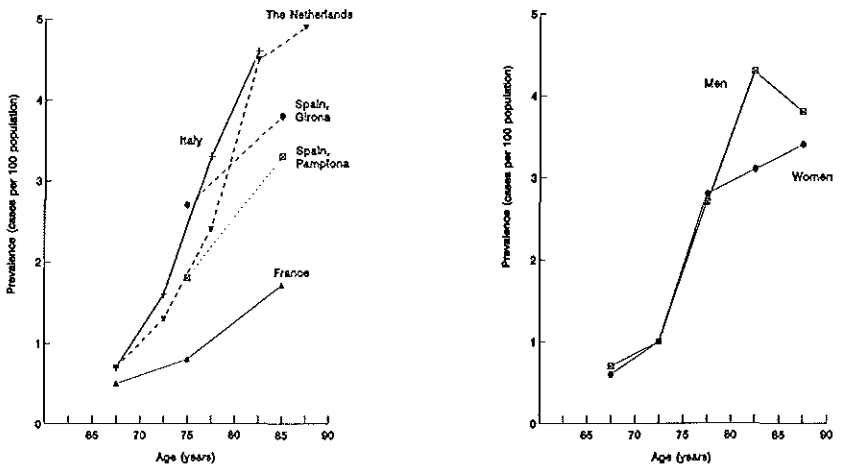

Figure 4.2.2 *Age-specific prevalence, for both sexes combined, of Parkinson's disease in five European surveys. The prevalence estimates are plotted in the middle of the corresponding age groups: for the studies from Italy and the Netherlands by 5 year age groups, for the studies from France and Spain by 10 year age groups. Overall age-specific prevalence for women and men is presented in the right figure.*

The frequency distribution by type of parkinsonism for all studies combined was as follows: Parkinson's disease 68%, parkinsonism in dementia 9%, drug-induced parkinsonism 5%, parkinsonism with associated features 1%, vascular parkinsonism 3%, and unspecified parkinsonism 14%. The proportion of subjects with Parkinson's disease who were newly diagnosed through the surveys varied from 11% in France and 13% in the Netherlands, to 26% in Girona, Spain, 31% in Italy, and 52% in Pamplona, Spain. In all surveys, the percentage of newly diagnosed patients with Parkinson's disease increased with age. For all studies combined, this percentage increased from 18% for those aged 65 to 70 years to 36% for those 80 to 85 years.

Discussion

Methodological considerations

The striking variation in prevalence estimates of Parkinson's disease reported from various studies and different populations, ranging from 10 to 405 cases per 100,000 population,[1] may be caused, partly or completely, by variation in the methods used. The three most important methodological elements are the case finding strategy,[6] the diagnostic criteria for parkinsonism and Parkinson's disease, and the degree of coverage of the target population (response rate).

As for case finding strategies, studies that rely on existing medical records exclude from the prevalence estimate those patients who failed to seek medical attention for their symptoms, those who were incorrectly diagnosed, and those whose records were not retrieved. The alternative case finding approach involves the direct or indirect contact of all subjects in the study population to assess their disease status. This approach should eliminate the underestimation of prevalence and should be more suitable for international comparisons since it reduces the variation due to differences in access to and quality of medical care in various populations.

Our study is the first comparison of results from several prevalence surveys of Parkinson's disease which used similar case finding strategy and diagnostic criteria. Although the five EUROPARKINSON surveys were not designed as a multicenter study, the investigators met and exchanged their methods and data collection instruments early in the planning of the surveys. Therefore, we have reached an unprecedented level of methodological homogeneity. To increase comparability across centers, the medical documentation of a majority of parkinsonian patients underwent a centralised review by an adjudication panel.

Despite this effort to homogenize our methodology, the five surveys still present some

variation. The screening procedures were somewhat different in number of items tested and personnel involved. In the French study, no physical examination was performed as part of the screening, while in the four remaining studies it was. Also the use of diagnostic criteria for parkinsonism varied somewhat with a broadening of the criteria in the French study and a restriction of the criteria in the Girona study. There were variations in the differential diagnosis of parkinsonism by specific aetiology. Parkinson's disease represented 70% to 96% of all parkinsonisms in Italy, the Netherlands, and Girona, Spain, whereas Parkinson's disease was only 59% of all parkinsonisms in Pamplona, Spain, and 48% in France. A large percentage of parkinsonian subjects in the French study had concurrent dementia with no clear time-relationship between onset of dementia and onset of extrapyramidal signs. These subjects were classified as "unspecified parkinsonism". In addition, a high percentage of subjects in France were receiving antidopaminergic agents, and were classified as "drug-induced parkinsonism". It was again difficult in these subjects to isolate the role of antidopaminergic drugs from the independent occurrence of Parkinson's disease.

In a two-phase survey, failure to study a large segment of the target population (non-response) due to refusal or other obstacles may cause an underestimation or an overestimation of prevalence.[7] Unfortunately, the five surveys had different response rates, and the impact of this variation on our findings is unknown.

Age

The prevalence of parkinsonism and Parkinson's disease increased with age in all five surveys for both men and women, with no decrease at higher ages. This suggests that the prevalence, and probably also the incidence, of Parkinson's disease continues to increase beyond age 85 or 90 years. Various other surveys based on a design of direct[6,8] or indirect[9,10] contact of all subjects in the population also showed a continuing increase in the prevalence of Parkinson's disease with age. By contrast, other prevalence studies based on existing medical records showed a peak in prevalence and a decline among the oldest old.[11-14] We speculate that these contrasting patterns are due to the underascertainment of Parkinson's disease among older subjects which occurs when patients are detected through medical records only. Our five surveys showed indeed that the percentage of subjects with Parkinson's disease who had not been previously diagnosed increases with advancing age in the general population.

Sex

Most prevalence studies that indicated higher prevalences of Parkinson's disease in men[8,12,15-17] or in women,[11,14] were based on medical records, whereas most surveys with an in-person screening for parkinsonism, like our study, found no significant gender differences.[6,9,10,18] These findings suggest that the risk of Parkinson's disease is equal in men and women, but the referral to medical services varies by gender across populations.

Geographical comparison

It has been postulated that geographic differences in the prevalence of Parkinson's disease may yield etiological clues.[19-21] After adjusting for the effect of age and sex using Poisson regression models, our data did not suggest significant differences in prevalence across European countries, with the exception of the French survey. Morgante *et al.* showed that a substantial proportion of parkinsonian subjects go undetected when only a questionnaire screening, as in the French survey, is used.[6] We think that the differences in methodology and in diagnostic criteria discussed above may partly account for the lower prevalence estimates of Parkinson's disease in the French survey. Therefore, our overall impression is that there is no evidence for the prevalence of Parkinson's disease being different across European countries.

Although the overall prevalences were similar in our five surveys, there was a wide variation in the percentage of newly diagnosed patients with Parkinson's disease who were detected through the screening. This may be due to differences in referral pattern and in access to medical services across the four countries. These findings emphasize the importance using a direct screening when assessing Parkinson's disease prevalence.

Comparing our findings with those from other recent surveys based on a similar case finding approach, we found striking similarities with the Sicilian study.[6] This comparison strengthens our overall impression of limited geographic variation in prevalence when methods are homogeneous.

Some authors reported that persons living in a rural environment have a higher risk of developing Parkinson's disease than persons living in towns, and suggested an environmental cause for Parkinson's disease.[18,22] In our study, the more rural population (Girona) or mixed populations (France, Italy) did not have a higher prevalence of Parkinson's disease than the more urban populations (Pamplona, Rotterdam).

Conclusions

To allow comparisons across countries, an effort was made in EUROPARKINSON to increase homogeneity of case finding strategy and diagnostic criteria in five European surveys on the prevalence of Parkinson's disease. Accounting for the French study which deviated somewhat from the common methods, our findings suggest that the prevalence of Parkinson's disease is similar across European countries. The prevalence of both parkinsonism and Parkinson's disease increases steeply with age, and is similar in men and women.

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4.3 Incidence of Parkinson's disease in the Rotterdam Study

The prevalence of parkinsonism and Parkinson's disease (PD) is high and strongly increases with age, even in the oldest old.[1-4] Incidence rates yield an estimate of the absolute risk of PD, but studies on incidence of PD are scarse. Only few studies have provided age-specific,[5-7] or age- and sex-specific[8-11] incidence estimates of PD, but all but one[7] were register-based. One of the limitations of register-based studies is that these will fail to include patients who have not come to medical attention for their parkinsonian signs, thereby underestimating the risk of the disease.[1,3,12] A recent comparative study of European community-based prevalence surveys on PD showed that underestimation of the prevalence by medical records may vary from 11% to 52% and increases with age.[3] Register-based incidence rates may be even more severely underestimated. We present the results of a study in Rotterdam, the Netherlands, on the incidence of parkinsonism and PD in a general elderly population, in which participants underwent a neurologic screening examination at baseline and follow-up.

Methods

Study population

This study was part of the Rotterdam Study, a community-based cohort study on the frequency, etiology, and prognosis of chronic disabling diseases in the elderly.[13] The study focusses on four groups of diseases: neurologic, cardiovascular, locomotor, and ophthalmologic disorders. All residents of Ommoord, a suburb of Rotterdam, the Netherlands, who were 55 years of age or older, either living independently or institutionalized, were invited to the study. The study has been approved by the Medical Ethics Committee of Erasmus University. The baseline survey started in 1990 and was completed in June 1993. Of the 10,275 eligible subjects, 7,983 (78%) agreed to participate and signed informed consent statements. Follow-up examinations took place from September 1993 until the end of 1994. At baseline, all participants were interviewed at home and thereafter 7,129 were examined at a research center. The number who underwent the complete screening examination for parkinsonism was somewhat lower (6,969) due to refusal, disease, death, or logistic reasons. At baseline, 129 subjects were identified with parkinsonism,[14] and for two subjects the

disease status was uncertain. This resulted in a cohort of 6,838 persons who had a neurologic screening examination at baseline and were at risk to develop a parkinsonian syndrome during follow-up. For the cohort at risk for PD we further excluded 272 subjects who were demented at baseline as a diagnosis of dementia before the onset of parkinsonism precludes a diagnosis of PD,[14] leaving 6,566 subjects at risk for PD *(Table 4.3.1)*.

Table 4.3.1 *Age and sex distribution of the study population at risk for any incident parkinsonism* (including Parkinson's disease), and for incident Parkinson's disease† separately*

	Persons at risk for any parkinsonism*			Persons at risk for Parkinson's disease†		
Age-group (years)	Men	Women	Total	Men	Women	Total
55-64	849	1,135	1,984	847	1,131	1,978
65-74	1,144	1,413	2,557	1,134	1,406	2,540
75-84	614	1,026	1,640	579	966	1,545
85-94	153	456	609	126	345	471
95+	9	39	48	5	27	32
Total	2,769	4,069	6,838	2,691	3,875	6,566

* Persons with parkinsonism at baseline (n =129) have been excluded.

† Persons with either parkinsonism or dementia at baseline (n = 401) have been excluded.

Case-finding and diagnostic procedures

Both at baseline and at follow-up, we used a two-phase design to identify subjects with PD.[14] In the first phase, each participant was briefly neurologically examined by one of the study physicians. All subjects who had at least one possible cardinal sign of parkinsonism (i.e., resting tremor, rigidity, bradykinesia, or impaired postural reflexes) at the neurologic screening examination or those persons with incident parkinsonism who were reported by their general practitioner or neurologist during follow-up, were invited for further evaluation in a second phase by a neurologist or a neurologist-in-training. In the second phase, a structured clinical work-up comprising

the motor examination of the Unified Parkinson's Disease Rating Scale (UPDRS),[15] a neurologic examination, and standardized history taking, was used to establish the diagnosis parkinsonism and to classify this parkinsonism. Most incident PD patients were reevaluated by a second neurologist. For the subjects who could not be reexamined for parkinsonism at follow-up (due to death, migration, disease, logistic reasons, or refusal) we obtained information through a surveillance system that continuously monitors the total cohort for interval cases of parkinsonism. Through this surveillance system that consists of computer linkages with the general practitioners' and pharmacies's automated medical record systems, we were notified of incident patients with parkinsonism, including PD, and had access to their medical records. Parkinsonism was diagnosed if at least two of the cardinal signs were present in a subject, irrespective of antiparkinsonian medication, or if in a subject treated with antiparkinsonian medication (levodopa) one or more signs, documented by medical history, had improved by the treatment. PD was defined in a person with parkinsonism if other possible causes of parkinsonism were absent. The diagnostic criteria for the several subtypes of parkinsonism have been reported previously.[14] In short: parkinsonism due to other causes included (1) parkinsonism associated with baseline dementia as assessed by a three-phase approach;[16] (2) drug-induced parkinsonism (i.e., following use of neuroleptics or other anti-dopaminergic drugs in the 6 months before onset of symptoms and with no history of parkinsonism); (3) parkinsonism related to cerebrovascular disease (i.e., with a clear time relationship between cerebrovascular event and onset of atypical parkinsonism, preferably supported by neuroimaging, usually without tremor); (4) parkinsonism in multiple system atrophy or progressive supranuclear palsy; and (5) other parkinsonism. Included in this last category were subjects with more than one possible cause or with no clear time relationship between the possible cause and the parkinsonism, as well as those subjects in whom all other possible causes of parkinsonism could be excluded but who did not respond to antiparkinsonian drugs. As the age of onset of parkinsonism and PD, we took the midpoint between the age at baseline and the age at diagnosis.

Data analysis

We calculated age- and sex-specific incidence rates per 10 year age-groups by dividing the number of incident patients by the number of person-years (the sum of each participant's contribution of follow-up time per age-group), and Poisson standard errors and 95% confidence intervals (95% CI) of the incidence estimates. The follow-up period ended at follow-up screening, age of onset of parkinsonism or PD, or death.

For those participants who were not rescreened, were not reported with incident parkinsonism through the surveillance system, and did not die, follow-up time was counted till the end of December 1994. We determined whether overall age-adjusted incidence rates for men and women differed significantly through Cox regression analysis, with age at baseline and sex as covariates (expressed as relative risk; RR).

Results

Table 4.3.1 shows the age- and sex-distributions of the 6,838 subjects who were at risk to develop any parkinsonism, and of the 6,566 persons at risk for PD. For those at risk for parkinsonism, 5,313 (77.7%) were completely reexamined in person at follow-up screening. Of those who could not be reexamined, 449 had died, 558 refused screening examinations, 62 could not be reached, and in 456 the screening examination was incomplete or not conducted due to logistic reasons. Of the subjects at risk for PD, 5,236 (79.7%) underwent the complete in-person screening at follow-up, 339 had died, 497 refused screening examinations, 55 could not be reached, and in 439 the screening examination was not complete. All who did not undergo the screening at follow-up could be followed by the surveillance system.

After a mean follow-up period of 2.14 years (SD ± 0.86), 62 subjects with incident parkinsonism were identified of whom 35 (56%) had incident PD. In Table 4.3.2, the follow-up time, and the incidence rates are shown for the parkinsonism cohort. For the subjects at risk for PD, similar information is presented in Table 4.3.3. Incidence rates of both parkinsonism and PD increased with age, except for the higest age-group in women where the incidence rate of PD seemed to decrease. The incidence estimates in the highest age-groups, however, were based on small numbers and, as a consequence, the 95% CI were relatively wide. The differences between men and women were statistically non-significant; for women compared with men the age-adjusted RR of parkinsonism was 1.18 (95% CI 0.68-2.04), and of PD 1.16 (95% CI 0.66-2.04). Although between the age of 75 to 94 years the age-specific incidence rates of PD for men seemed higher, this was again statistically statistically not significant. Besides PD (35/62), the other diagnoses were parkinsonism associated with dementia (8/62); drug-induced parkinsonism (1/62); multiple system atrophy (2/62); progressive supranuclear palsy (1/62); and other parkinsonism (15/62).

Table 4.3.2 *Age- and sex-specific follow-up time in person years (pyrs) of the cohort at risk for parkinsonism*, number of incident cases with parkinsonism (PS), and incidence rates (cases per 1,000 pyrs, with 95% confidence interval) of any parkinsonism in the Rotterdam Study, 1990-1994*

	Men				Women				Total			
Age-group (years)	Pyrs	PS	Rate	95% CI	Pyrs	PS	Rate	95% CI	Pyrs	PS	Rate	95% CI
55-64	1,796	1	0.6	0.1-3.9	2,569	1	0.4	0.1-2.8	4,366	2	0.5	0.1-1.8
65-74	2,317	4	1.7	0.7-4.6	3,112	17	5.5	3.4-8.8	5,430	21	3.9	2.5-5.9
75-84	1,244	11	8.8	4.9-16.0	2,326	12	5.2	2.9-9.1	3,572	23	6.4	4.3-9.7
85-94	279	3	10.7	3.5-33.2	934	12	12.8	7.3-22.6	1,214	15	12.4	7.4-20.5
95+	15	0	-	-	55	1	18.3	2.6-129.0	70	1	14.3	2.0-101.2
Total	5,651	19	3.4	2.1-5.3	8,997	43	4.8	3.5-6.4	14,652	62	4.2	3.3-5.4

* Persons with parkinsonism at baseline (n =129) have been excluded.

Table 4.3.3 *Age- and sex-specific follow-up time in person years (pyrs) of the cohort at risk for Parkinson's disease*, number of incident cases with Parkinson's disease (PD), and incidence rates (cases per 1,000 pyrs, with 95% confidence interval) of PD in the Rotterdam Study, 1990-1994*

	Men				Women				Total			
Age-group (years)	Pyrs	PD	Rate	95% CI	Pyrs	PD	Rate	95% CI	Pyrs	PD	Rate	95% CI
55-64	1,792	0	-	-	2,560	1	0.4	0.1-2.8	4,352	1	0.2	0.0-1.6
65-74	2,290	2	0.9	0.2-3.5	3,085	11	3.6	2.0-6.4	5,376	13	2.4	1.4-4.2
75-84	1,172	8	6.8	3.4-13.6	2,163	9	4.2	2.2-8.0	3,335	17	5.1	3.2-8.2
85-94	234	2	8.6	2.1-34.2	719	2	2.8	0.7-11.1	952	4	4.2	1.6-11.2
95+	8	0	-	-	39	0	-	-	47	0	-	-
Total	5,496	12	2.2	1.2-3.8	8,566	23	2.7	1.8-4.0	14,062	35	2.5	1.8-3.5

* Persons with either parkinsonism or dementia at baseline (n = 401) have been excluded.

Discussion

We found a strong and consistent increase in the incidence of both parkinsonism and PD with age, at leasts till the age of 84 years, and no significant gender differences. Our study had several strengths. Both at baseline and follow-up, participants were screened in person by the use of a similar examination and similar diagnostic work-up. Only a small proportion who screened positive in the screening phase did not undergo the second, diagnostic, phase. For those, and for the persons who were screened at baseline but could not be examined at follow-up, we were able to achieve a complete follow-up and to obtain information through a population surveillance system. In the latter group, however, we may have missed some subjects with very mild signs and those who had not sought medical attention yet. Our follow-up period was relatively short. This reduced the proportion of subjects who could not be rescreened in person due to death, disease, or migration, and ensured a more complete case-ascertainment. It also allowed us to take the midpoint between the age at baseline and the age at diagnosis as the age of onset of parkinsonism and PD, an approach we had chosen because in a parkinsonian syndrome it may be hard to indicate objectively when the first symptom has started. However, due to the short follow-up period, the numbers of both person-years of follow-up time and incident cases were comparatively low, resulting in less stable incidence estimates as reflected by the wide 95% CI *(Table 4.3.3)*.

The expected pattern of age-specific incidence rates will follow depends on the underlying process or event that causes PD. Several patterns pertaining to the rate of excessive degeneration of dopaminergic cells in PD have been proposed.[17,18] Fearnley and Lees in their neuropathologic study of non-parkinsonian subjects reported a linear decrease in the number of dopaminergic neurons with advancing age in the substantia nigra.[19] Also, in healthy persons the number of Lewy bodies, that may indicate presymptomatic PD, increases with age.[20] In line with these observations, PD may be caused by an accelerated normal aging process and an increase in the incidence of PD with age would be expected, even in the highests age-groups. If, on the contrary, the degenerative process in PD is induced by, for example, accumulated toxic exposures in genetically susceptible individuals, then at a certain age people may have outlived their risk of PD and a decrease in incidence rates in the highest age-groups will be a possibility as well. Our data on the incidence pattern in the oldest old are inconclusive; for both sexes the incidence rates of parkinsonism continued to rise until the highest age, but the rate of PD in women decreased after the age of 85 years.

In all published population-based studies on incidence of PD, age-specific incidence estimates were lower compared with ours, as is shown in Figure 4.3.1. All but one[7] were based on existing medical records or case-finding strategies that not systematically included incident PD patients who had not recognized their parkinsonian symptoms yet or had not come to medical attention for their parkinsonism.[9,11] The number of PD patients that go undetected in a population can grow to considerable proportions;[1,3] e.g., in a study in Copiah County, Mississippi, 40% of the PD patients were newly detected through the in-person screening,[12] and thus register-based incidence rates will be underestimated. The only published community-based study, thusfar, on the incidence of PD in which each participant was screened at follow-up showed also lower incidence estimates than our study.[7] This study, however, is not completely comparable with ours because no baseline in-person screening was conducted and it was restricted to Hawaiian men of Japanese and Okinawan ancestry. Also, as in the Hawaiian study 20 years had elapsed between the previous, register-based, screening and the screening for PD, many parkinsonian subjects who did not come to medical attention, or were lost in the interval, will not have been included in the incidence estimates.

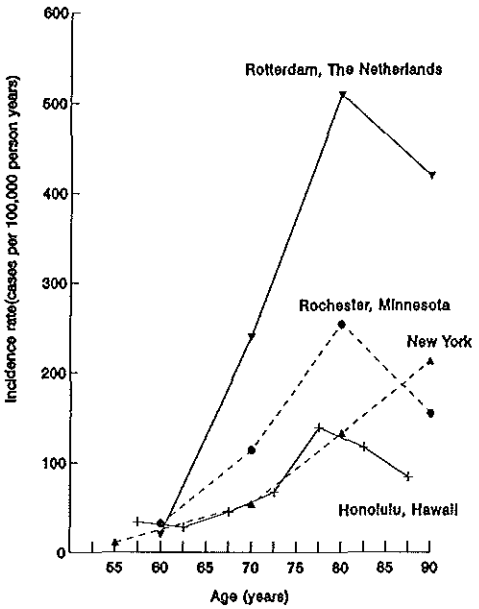

Figure 4.3.1 *Age-specific incidence rates of Parkinson's disease from the Rotterdam Study compared with three large population-based surveys; one from Rochester, Minnesota,[9] one from New York,[11] and one from Honolulu, Hawaii.[7]*

In many, if not most, studies the prevalence of PD has been reported to be higher in men than women.[21] In contrast to these, in most incidence studies with age- and sex-specific estimates no sex differences were found.[5,8-11] These findings are in line with our findings and may indicate a similar age-specific risk of PD in men and women.

If the survival of persons with different causes of parkinsonism were similar, one

would expect that among incident parkinsonian patients the proportion of PD patients would be the same as among the parkinsonians subject that had been identified in the prevalence survey. In the present incidence study, however, 56% of the incident parkinsonian syndrome was caused by PD whereas in the prevalence survey of the Rotterdam Study this proportion was 75%.[14] This reflects the less favorable survival of patients with a secondary parkinsonism, compared with PD patients. Indeed, strongly reduced survival has been implicated in parkinsonism associated with dementia,[22,23] multiple system atrophy,[24,25] and progressive supranuclear palsy.[26, 27]

We conclude that the incidence of parkinsonism and PD is higher than expected, that the incidence continues to rise with age at least till the age of 85 years, and that men and women run the same age-specific risk in developing PD. Longer follow-up and more prospective cohort studies are awaited to confirm these findings and to provide more precise estimates, especially in the oldest old.

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Chapter 5

Determinants of Parkinson's disease

5.1 Apolipoprotein genotype and Parkinson's disease

The etiology of Parkinson's disease (PD) and dementia in PD is still largely unknown. Links between PD and Alzheimer's disease (AD) have been suggested,[1,2] and clinicopathological studies have implicated AD pathology, especially ß-amyloid plaques, as a possible contributing factor to dementia in PD.[3,4] The apolipoprotein E 4 allele (APOE*4) has been associated with both AD[5] and Lewy Body disease (LBD),[6] and may mediate ß-amyloid plaques formation in the brain.[5-7] Reports on the APOE*4 in PD with and without dementia, however, are contradictory; few suggesting an association between APOE*4 and PD dementia, and most no association.[8] Gearing and colleagues showed an association between the APOE*4 and PD-related changes in AD.[9] We investigated the association of APOE genotypes with PD and dementia in PD in a large sample of the Rotterdam Study.

Methods

This study formed part of the Rotterdam Study, a community-based cohort study among 7,983 independently living and institutionalized inhabitants, 55 years of age or older, from a suburb of Rotterdam, the Netherlands.[10] Informed consent was obtained from the participants and the study was approved by the Medical Ethics Committee of Erasmus University Rotterdam.

Diagnosis of Parkinson's disease and dementia

We identified subjects with PD through a two-phase design with an in-person screening of all participants, followed by a diagnostic work-up of those who were suspected of parkinsonism.[11] The diagnostic criteria for PD have been described previously.[11] Participants were also screened for dementia.[12] For the diagnosis "PD dementia", onset of PD had to have clearly preceded the onset of the cognitive changes and the DSM-III-R criteria for dementia had to be fulfilled.

Study population

Blood samples of 80 of the 97 prevalent PD patients in the Rotterdam Study were available for APOE genotyping. Of those 80 PD patients, 19 were demented. In three

(16%) of these, the pattern of cognitive deficits was compatible with possible concurrent AD. APOE genotype was also assessed in 1,008 randomly selected subjects who were not necessarily healthy but had neither signs of parkinsonism nor dementia.

ApoE genotyping

APOE genotyping was performed on coded blood samples without knowledge of the clinical diagnosis.[13]

Data analysis.

We used logistic regression analysis to calculate odds ratios (OR) with 95% confidence intervals (95%CI) to assess whether the APOE*4 and APOE*2 alleles were associated with PD. The most frequent APOE genotype (APOE3E3) was used as the reference. In addition, we assessed the associations of APOE*4 and APOE*2 with dementia within the PD patient group. In subanalyses, we excluded subjects with APOE2E4 since this genotype may obscure differences between APOE*4 and APOE*2 carriers; and the three demented PD patients with possible concurrent AD. In all analyses, we adjusted for age and sex.

Results

The characteristics of the study population and the distribution of the APOE genotypes are summarized in Table 1. PD patients, especially the demented, were on average older and the proportion of women among them was higher than in the rest of the population. The distribution of genotypes in the control population was in Hardy-Weinberg equilibrium. We found no association of APOE*4 and APOE*2 with total PD; for carriers of APOE*4 the OR of PD was 0.9 (0.5-1.5), and 1.2 (0.7-2.3) for APOE*2 carriers. Within the PD patients group, both carriers of APOE*4 and APOE*2 were more often demented as compared with PD patients with the APOE3E3; the OR of dementia for APOE*4 carriers was 4.8 (1.3-17.9), which was statistically significant, and for APOE*2 carriers 3.3 (0.8-14.5). Exclusion of subjects with APOE2E4 did not substantially alter the results (within the PD patient group, the OR of dementia became 5.3 (1.3-21.1) for APOE*4 carriers, and 3.0 (0.7-14.0) for APOE*2 carriers). Also in the PD group, the association between APOE*4 and dementia appeared to be robust if the demented PD patients with possible concurrent AD were excluded (OR 3.7 (1.0-14.6)).

Table 5.1.1 *The characteristics of the study population and the distribution of the APOE genotypes and alleles (PD is Parkinson's disease, PDD- is PD without dementia, PDD+ is PD dementia)*

	All PD (n=80)	PDD- (n=61)	PDD+ (n=19)	Controls (n=1,008)
Age (±SD)	78 (8)	77 (8)	82 (8)	69 (8)
Proportion men (%)	33.8	37.7	21.1	39.9
APOE genotype frequency				
APOE3E3 (%)	57.5 (46)*	65.5 (40)	31.6 (6)	56.2 (566)
APOE2E2 (%)	1.3 (1)	0.0 (0)	5.3 (1)	1.0 (10)
APOE2E3 (%)	17.5 (14)	16.4 (10)	21.1 (4)	14.8 (149)
APOE2E4 (%)	3.8 (3)	3.3 (2)	5.3 (1)	1.9 (19)
APOE3E4 (%)	17.5 (14)	13.1 (8)	31.6 (6)	24.2 (244)
APOE4E4 (%)	2.5 (2)	1.6 (1)	5.3 (1)	2.0 (20)
APOE allele frequency				
APOE*2 (%)	11.9 (19)†	9.8 (12)	18.4 (7)	9.3 (188)
APOE*3 (%)	75.0 (120)	80.4 (98)	57.9 (22)	75.7 (1525)
APOE*4 (%)	13.1 (21)	9.8 (12)	23.7 (9)	15.0 (303)

* Numbers of subjects are given in parentheses.

† Numbers of alleles are given in parentheses.

Discussion

We found that among PD patients APOE*4 was significantly associated with an almost five-fold increased risk of dementia, and that the risk for APOE*2 carriers was increased as well, though this failed to reach significance. These associations are unlikely to result from misclassification of AD or LBD patients as PD dementia patients because we carefully restricted the diagnosis of PD to those in whom the onset of parkinsonian signs had clearly preceded the cognitive changes in absence of other clinical features. However, as AD and PD may have shared determinants, concurrent AD in a proportion of the PD patients might have occurred in a higher frequency than would be expected in a non-PD population. It could be conjectured that this could, in part, account for the associations we found. However, the majority of the demented PD patients in our study sample displayed clinical features atypical

for AD and exclusion of those with possible concurrent AD did not affect the associations.

In most previous studies on the APOE genotype and PD, neither the comparison within the PD patient group has been made, nor age-adjustment was used. In contrast to other studies, our control population was both derived from the same source population as the PD patients and based on a general, not necessarily healthy, elderly population, including institutionalized persons. This methodology may explain why we were able to find an effect of APOE*4 on dementia in PD, whereas others did not.[8]

Our findings might indicate that APOE*2 is associated with PD dementia as well. However, this association was statistically non-significant, possibly because APOE*2 is a rare allele and, as a consequence, we had too little power in our study to evaluate this. APOE*2 has been related to a larger ß-amyloid plaque burden in LBD,[7] and may increase the risk of early-onset AD.[13] In reports on APOE genotype and PD or PD dementia, hardly any attention was paid to the APOE*2 allele frequency. In most of these reports, however, but not all,[14] the APOE*2 allele frequency was higher in PD patients,[8,15-17] or in PD dementia[18,19] than in controls, but larger studies may be needed to confirm a putative association.

We conclude that among elderly PD patients, carriers of the APOE*4 allele appear to have a strongly increased risk of dementia.

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5.2 Dietary antioxidants and Parkinson's disease

The cause of dopaminergic cell loss in patients with Parkinson's disease (PD) is still unknown but increased free radical production and an inadequate antioxidant defence system may play a role.[1-3] Therefore, it has been postulated that high intake of antioxidants may reduce the risk of PD or may decrease the progression of the disease.[4-6] We investigated the association between dietary antioxidant intake and PD in non-demented independently living participants from the community-based Rotterdam Study in which each person was individually screened for PD.

Methods

This study formed part of the Rotterdam Study, a community-based cohort study on prevalence, incidence and determinants of diseases in the elderly as extensively described elsewhere.[7] The study started in 1990 and the cross-sectional survey was completed in June 1993. All inhabitants of Ommoord, a suburb of Rotterdam, the Netherlands, who were 55 years of age or older, either living independently or institutionalized, were invited to participate. Of 10,275 eligible subjects, 7,983 accepted (78%) and signed informed consent statements. All participants were interviewed at home and most were subsequently examined at a research center. The study was approved by the Medical Ethics Committee of Erasmus University.

Information on dietary intake

Information on daily dietary intake in the last year was obtained from a modified version of a previously validated 170 item semi-quantitative food frequency questionnaire.[8] In order to elicite reliable dietary information, dietary data were obtained from those subjects who were aged 55 to 95 years, showed no cognitive impairment at baseline (*Mini Mental State Examination* score > 25 and a *Geriatric Mental State Schedule* score equal to 0),[9] and were non-institutionalized (n = 5,646). The food questionnaire was administered during the home interview as part of the standard study protocol. Each questionnaire was reviewed by a dietician during the subject's visit to the research center before the diagnosis of PD was established. Respondents also indicated the number of years without a change in the dietary habit and were asked whether they consumed vitamin supplements and if so which brand

names and what quantity. Average daily dietary nutrient intake was calculated by multiplying the frequency and amount consumed for each food item by its nutrient content listed in an automated version of the Dutch Food Composition Table.[10]

Diagnosis of Parkinson's disease

We used a two-phase design to identify subjects with PD in the total study population.[11] The screening consisted of questions regarding a previous diagnosis of PD, registration of any drug use, and a brief neurological examination by one of the study physicians. Those who screened positive were evaluated in a second phase by a neurologist or a neurologist in training. A structured clinical work-up, that comprised the motor examination of the Unified Parkinson's Disease Rating Scale (UPDRS),[12] a neurological examination and standardized history taking, was used to establish the diagnosis parkinsonism and to classify this parkinsonism. PD was diagnosed if at least two of four cardinal signs (i.e., resting tremor, rigidity, bradykinesia, or impaired postural reflexes) were present in a subject not taking antiparkinsonian drugs or when in a subject treated with antiparkinsonian medication one or more signs, documented by medical history, had improved by treatment. In addition, all other causes of parkinsonism had to be absent.

Study population

The study population consisted of all non-demented independently living participants of the Rotterdam Study. For the current analyses, persons whose reported dietary intake contained inconsistencies (n = 211), persons who had one or more parkinsonian signs but did not have PD (n = 44), persons who were demented but were erroneously administered the food frequency questionnaire (n = 19), and persons who had missing information on confounding variables (n = 30) were excluded. Among the 5,342 subjects who could be included in the analyses, 31 had PD. Eight of these PD patients were detected through the screening for PD and had not been diagnosed previously. The Hoehn & Yahr stage[13] of the 31 PD patients ranged from 1 to 3 (median 1.9), and the median disease duration was 2.8 years.

Data analysis

We investigated the association between PD and the following dietary antioxidants: vitamin E, ß-carotene, vitamin C, and flavonoids. Because patients with PD may specifically seek a beneficial effect from the use of vitamin supplements we also performed the analyses with exclusion of the supplement users. We used analysis of variance to compare average daily caloric and antioxidant intake, adjusted for

differences in age and sex, between subjects with and without PD. We used multiple logistic regression analysis to calculate the odds ratios (OR) with corresponding 95% confidence intervals (95%CI) to assess the relation between daily dietary antioxidant intake and PD. We analyzed dietary antioxidant intake as a continous variable as well as categorized by tertiles with the lowest level of intake as the reference. In all analyses, we adjusted for the potential confounding factors age, sex, current smoking, and energy intake.[14] For the water-soluble vitamin C and flavonoids the adjustment was made for caloric intake, and for the fat-soluble vitamin E and ß-carotene the adjustment was made for the percentage energy from fat intake. Food-patterns may change as a result of advanced PD. Therefore, to assess whether the associations were affected by patients with more advanced disease, we performed an analysis restricted to PD patients with a Hoehn & Yahr stage 1 to 2.

Results

Characteristics of the PD patients and the control subjects and their mean age- and sex-adjusted daily energy and dietary antioxidants intake are shown in Table 5.2.1.

Table 5.2.1 *Characteristics of the study population, and the age- and sex-adjusted mean daily dietary energy and antioxidant intake* (± SD) in the Parkinson's disease (PD) patients and the control population*

	PD patients (n = 31)	Control subjects (n = 5311)
Age (years)	71.0 (6.6)†	67.7 (7.8)
Proportion women (%)	48	59
Vitamin supplement users (%)	16	12
Caloric intake (Kcal/day)	1834 (436)	1976 (504)
Percentage energy from fat	37.3 (7.1)	36.3 (6.2)
Vitamin E (mg/day)*	11.7 (5.6)‡	13.9 (6.2)
ß-carotene (mg/day)*	1.37 (0.59)	1.53 (0.76)
Vitamin C (mg/day)*	118 (42)	120 (54)
Flavonoids (mg/day)*	27.5 (9.5)	28.5 (12.2)

* Additionally adjusted for energy intake.
† ± SD.
‡ p = 0.013

Table 5.2.2 *The association between daily dietary antioxidant intake and Parkinson's disease (PD), calculated as crude and adjusted* odds ratios (OR) with corresponding 95% confidence intervals (95% CI), with and without PD patients with a Hoehn & Yahr stage (H&Y) over 2*

	All PD patients (n=31) Crude OR*	*All PD patients (n=31)* Adjusted OR†‡	*PD patients with H&Y stage ≤2 (n=23)* Adjusted OR†‡
Vitamin E *(per 10 mg/day)*	0.6 (0.3-1.2)	0.5 (0.2-0.9)	0.6 (0.3-1.4)
ß-carotene *(per 1 mg/day)*	0.6 (0.3-1.1)	0.6 (0.3-1.2)	0.8 (0.4-1.6)
Vitamin C *(per 100 mg/day)*	0.8 (0.4-1.6)	0.9 (0.4-1.8)	0.8 (0.3-1.9)
Flavonoids *(per 10 mg/day)*	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.1 (0.7-1.5)

* Adjusted for age, gender, current smoking, and energy intake.

None of the differences in mean intake were statistically significant, except for vitamin E which intake was lower in the PD patients group. The number of years without a change in dietary habits did not differ significantly between the PD patients and the control population (4.4 versus 4.7 years). Table 5.2.2 shows the relations between daily dietary vitamin intake and PD. Subjects with higher vitamin E intakes had PD significantly less often than those with lower vitamin E intakes (adjusted OR of 0.5 (95%CI; 0.2-0.9) per 10 mg daily vitamin E intake). ß-carotene intake was also inversely related to PD but this association was not significant. Dietary vitamin C and dietary flavonoids intake were not associated with PD. When we confined the analyses to PD patients with a Hoehn & Yahr stage 1 to 2 (n = 23), the association for vitamin E was similar, but no longer significant, probably due to the smaller numbers *(Table 5.2.2)*. Exclusion of vitamin supplement users yielded exactly the same estimates.

When analyzed in tertiles, the association between dietary intake of vitamin E and PD appeared to be dose-dependent: compared with the lowest tertile, the OR of PD for the middle tertile was 0.8 (95%CI; 0.4-1.8), and for the upper tertile 0.3 (95%CI; 0.1-

0.9); p-trend is 0.03. For ß-carotene, Vitamin C, and flavonoids intake, no clear patterns were discerned *(Figure 5.2.1)*.

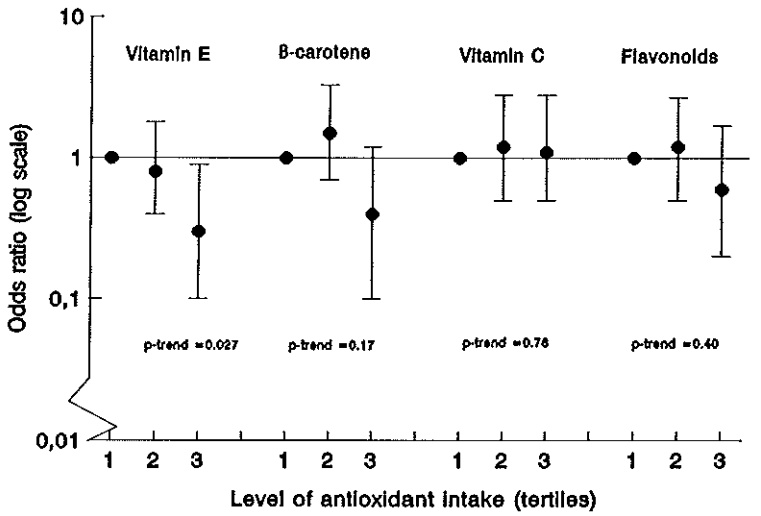

Figure 5.2.1 *The association of level of daily dietary vitamin intake, categorized by tertiles, with Parkinson's disease expressed as adjusted odds ratios (dots) with the corresponding 95% confidence intervals (bars). Level 1, low antioxidant intake, is reference level.*

Discussion

In this study we found a significant inverse relation between dietary vitamin E intake and PD among non-demented independently living persons. The magnitude of this relation seemed to be dose-dependent. We first have to consider whether the limitations that were inherent in our study may invalidate our results.

This is a cross-sectional study and a possible explanation for the observed relationship could be that the lower dietary intake of vitamin E in PD patients is a consequence rather than a cause of the disease. However, our data do not suggest that different dietary habits in PD patients resulted from the disease. When we excluded PD patients with more advanced disease, or those who used vitamin supplements, the associations did not change. Moreover, the study sample included

31 relatively mild PD patients of whom eight were detected through the screening and had not been diagnosed previously. Finally, the PD patients did not report changing their dietary habits more often than the controls. These observations, and evidence that the food frequency questionnaire properly reflects dietary habits over the past five years,[15] suggests that we have measured dietary habits in PD patients prior to the onset of their disease which started on average less than three years ago.

It is unlikely that the dietary data collection was biased as there is no specific hypothesis that relates a specific food item to PD. Also, dietary vitamin intake was indirectly calculated using a food composition table. Importantly, the food frequency questionnaire was administered as part of the larger base-line data collection in the Rotterdam Study and the dieticians were not informed of any of the diseases in the participants. Furthermore, one quarter of the PD patients included in this current study were not aware of their disease.

Findings in several neuropathological studies have implicated oxidative stress in the pathogenesis of PD,[16-22] some suggesting increased lipid peroxidation in the dopaminergic cells.[23,24] A high intake level of fat-soluble antioxidants like vitamin E and ß-carotene might reduce lipid peroxidation in the substantia nigra. Only few studies on dietary antioxidant intake and the association with PD exist.[5,6,25-28] Two retrospective case-control studies suggested an inverse association between PD and intake of food items high in vitamin E.[25,26] In these studies, however, dietary intake was not quantitated and the PD patients had to rate their food consumption compared with that of their spouses. Two case-control studies found no protective effect of dietary antioxidants on PD.[5,28] In the first one a large fraction of the PD patients were demented (36%) whereas the controls were non-demented[5] while the latter was hospital-based and found that the associations between PD and food items were influenced by disease duration, suggesting potential biases.[28] In a recent nested case-control study among Hawaiian men of Japanese and Okinawan ancestry, an inverse association was found between PD and consumption of vitamin E containing foods (legumes) more than 25 years before.[6] The large DATATOP study, that investigated whether in PD patients treatment with the antioxidant tocopherol (a component of vitamin E) slowed down the progression of the disease, could not detect such a protective effect.[29] As extrapyramidal signs only become clinically overt after dopaminergic cell loss of approximately 50%,[30,31] and the rate of deterioration of nigral cells is probably most prominent in the preclinical or very early phase of PD,[32-35] a putative beneficial effect of treatment with tocopherol in PD patients may be harder to detect than a protective effect of cumulative dietary intake of vitamin E over an extended period in the past. The richest sources of vitamin E are vegetable

oils, nuts, wheat germs, and cod liver oil.

Theoretically, ß-carotene may also inhibit lipid peroxidation in the brain[36] and vitamin C and flavonoids could have their antioxidative effect in the brain as well. In the few published studies, however, in which the associations between PD and ß-carotene and vitamin C were investigated no effect could be found.[5,27,28,37-39] Flavonoids are antioxidants naturally occurring in vegetables, fruit, tea, and wine,[40] and have recently gained much attention regarding a protective effect in coronary heart disaese.[40,41] To date, the association between PD and flavonoids has never been investigated. Although in vitro flavonoids inhibit lipid peroxidation,[40,42] we found no protective effect by flavonoids intake at all.

In conclusion, we found a dose-dependent inverse association between dietary intake of vitamin E and PD. This is compatible with a protective effect of high dietary antioxidant intake against the development of PD. These findings need to be confirmed in prospective studies, in which dietary habits have been measured before the onset of PD.

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5.3 Smoking and the risk of Parkinson's disease

Since the late fifties, when an apparent protective effect of smoking on Parkinson's disease (PD) was first reported in studies on mortality follow-up of smokers,[1] many investigators have focused on the relation between cigarette smoking and PD.[2] Although in most studies an inverse association of smoking with PD was found,[2-4] a reduced risk of PD among smokers remains controversial.[2,5,6] Most studies that reported an inverse association were based on prevalent cases and it was suggested that the apparent inverse association could be artefactual due to confounding, selective mortality, cause-effect bias, symptom suppression, or diagnostic competition.[2] The few prospective studies that paid attention to the association between smoking and PD also reported a two- to three-fold reduction of the risk of PD among smokers.[1,3,7-9] However, all but one,[3] investigated follow-up of smokers and non-smokers through death certificates in which smoking-related diseases may overshadow PD as the recorded, underlying, cause of death, especially in smokers. This possible underreporting of PD might erroneously suggest a less frequent occurrence of PD among smokers.

Considering these limitations in previous studies and new biologically plausible evidence for a neuroprotective mechanism mediated by smoking that could protect against PD,[10] we prospectively investigated the risk of PD in non-smokers compared with smokers in a general elderly population. In our community-based cohort study, subjects were examined neurologically at baseline and at follow-up.

Methods

Study population

This study was part of the Rotterdam Study, a community-based cohort study on prevalence, incidence and determinants of chronic disabling diseases in elderly persons.[11] The conduct of the study was approved by the Medical Ethics Committee of Erasmus University. The baseline survey started in 1990 and was completed in June 1993. All inhabitants of Ommoord, a suburb of Rotterdam, the Netherlands, who were 55 years of age or older, were invited to participate in the study. Both independently living and institutionalized subjects were included. Of the 10,275 eligible subjects, 7,983 (78%) agreed to participate and signed informed consent

statements. In the cross-sectional survey, all participants were interviewed at home and 6,969 underwent the complete baseline neurologic screening examination for parkinsonism. Follow-up examinations took place from September 1993 till the end of 1994. Persons who had a neurologic screening examination at base-line and were free of parkinsonism and dementia at that time, and thus at risk for incident PD, were followed up for incident PD (n = 6,566). Subjects of whom baseline smoking history data were incomplete (n = 124) were excluded from the present study, resulting in a study population of 6,442 subjects.

Case-finding and diagnostic procedures

Both at baseline and at follow-up, we used a two-phase design to identify subjects with PD.[12] In the first phase of the screening for parkinsonism, participants were briefly examined neurologically by one of the study physicians. Those who screened positive or those with incident parkinsonism who were reported by their general practitioner or neurologist during the follow-up interval, were invited for further evaluation in a second phase by a neurologist or a neurologist in training. A structured clinical work-up was used to establish the diagnosis parkinsonism and to classify this parkinsonism. PD was diagnosed if at least two of four cardinal signs (i.e., resting tremor, rigidity, bradykinesia, or impaired postural reflexes) were present in a subject not taking antiparkinsonian drugs or when in a subject treated with antiparkinsonian medication one or more signs, documented by medical history, had improved by treatment. For the diagnosis of incident PD, all causes of secondary parkinsonism, and dementia before the onset of incident parkinsonism, had to be absent as well.

For all 1,282 subjects who could not be reexamined at follow-up (320 had died, 51 could not be reached, 480 refused, and 431 random subjects did not undergo the complete neurologic screening examination due to logistic reasons) we obtained information through a surveillance system by computer linkage with the general practitioners' automated medical record systems. Through this surveillance system we were notified of incident patients with parkinsonism and had access to their medical records. We took the midpoint between age at baseline and age at diagnosis as the age at onset of PD. As PD has an insidious onset, an objective indication of when the first symptom of the disease had actually started is hard to achieve for all patients in an equally adequate way. Given the relatively short follow-up period, the age at midpoint of follow-up was considered a good approximation of the age at onset.

Data collection on smoking

At baseline, smoking status was assessed in all subjects. Subjects were categorized into a group who at baseline had never smoked (non-smokers), a group who had smoked but had quit smoking before baseline examinations (ex-smokers), and a group of persons who were still smokers at baseline (baseline-smokers). The combination of the latter two groups, ex-smokers and baseline-smokers, formed the group ever-smokers. In smokers, we also asked the average number of cigarettes smoked, the age at which a subject had started smoking, and the number of years that a subject had smoked. In ex-smokers, the age at which subjects quit smoking was assessed.

Data analysis

We calculated the cumulative incidences of PD for non-smokers, ever-smokers, and for ex-smokers and baseline-smokers separately. Using Cox proportional hazard analyses, we estimated the age- and sex-adjusted relative risk (RR) with corresponding 95% confidence interval (95% CI) of PD among non-smokers as compared with smokers, both ex- and baseline-smokers combined and separately. In a separate analysis, we stratified by sex to assess whether the effect of smoking was modified by sex. A dose-effect relation was analyzed by defining smoking exposure according to pack years, calculated as the average number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked.

In all analyses, we adjusted for age at entry in the study and sex, and took each participant's contributed follow-up time into account. To assess whether selective mortality had biased the associations,[13-15] we also stratified by age by categorizing the cohort into two groups; one consisting of subjects younger than 75 years of age, and of 75 years of age and over. To determine whether the inverse effect of smoking resulted from persons quitting smoking in a very early phase of the disease as a result of the disease,[5] we additionally excluded incident PD patients who had an estimated onset of PD within one year after baseline screening, and we compared the time that had elapsed since quitting smoking between ex-smokers who did and who did not develop PD. To investigate whether the proportion of ex-smokers in PD patients differed significantly from the proportion of ex-smokers in non-parkinsonian subjects, we used a logistic regression model in which we adjusted for sex and age at baseline. To assess whether smoking delays the age at onset of PD,[2] we also compared the age at onset of non-smoking incident PD patients with that of smoking PD patients, controlling for sex and follow-up time by analysis of covariance.

Results

Table 5.3.1 shows the baseline characteristics of the study population at risk to develop incident PD. The cohort was followed for a median period of 2.12 years (SD ± 0.84). The proportion of baseline-smokers and ex-smokers among those who could not be reexamined in person at follow-up was similar to those who had been reexamined.

Table 5.3.1 *Baseline characteristics of the study population at risk for incident Parkinson's disease*[*]

Median age in years (± SD)	68.7 (8.6)
Numbers of men (%) / women (%)	2,657 (41.2%) / 3,785 (58.8%)
Number of non-smokers (%)	2,240 (34.8%)
Number of ever-smokers (%)	4,202 (65.2%)
Baseline-smokers (%)	1,487 (23.1%)
Ex-smokers (%)	2,715 (42.1%)
Mean number of pack years[†] among smokers (±SD)	27.4 (23.1)
Mean number of pack years among baseline-smokers	31.2 (20.0)
Mean number of pack years among ex-smokers	25.3 (24.1)

SD = standard deviation.

* Persons with either parkinsonism or dementia at baseline (n = 401) have been excluded.

† Average number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked.

Among the 6,442 participants who were at risk for PD, we identified 34 subjects who developed PD during a total of 13,673 person years. Of ever-smokers 0.3% developed PD whereas 0.9% of the non-smokers became affected by PD *(Table 5.3.2)*. Ever-smokers had a statistically significant almost three-fold decreased risk of PD *(Table 5.3.3)*. Also, when we stratified by actual baseline smoking status (smokers; ex-smokers), or by sex, the risk was decreased though for baseline-smokers, and for women, this was statistically non-significant. Crude and adjusted RRs of PD for the various subgroups are presented in Table 5.3.3. When smoking exposure was analyzed as pack years, we found a statistically significant decrease in the risk of PD (RR per pack year smoked: 0.98 (95%CI: 0.95-1.00)). Ever-smokers

Table 5.3.2 *The incidence of Parkinson's disease (PD) in non-smokers and smokers, overall and for various subgroups, in the Rotterdam Study*

Baseline exposure	Persons at risk for PD	incident PD cases	Cumulative incidence	Incidence rate (per 1,000 pyrs*)
Non-smokers (reference)				
Total	2,240	21	0.94%	4.39
Men	220	3	1.36%	6.98
Women	2,020	18	0.89%	4.13
Smokers				
Ever-smokers	4,202	13	0.31%	1.46
Baseline-smokers	1,487	7	0.47%	2.18
Ex-smokers	2,715	6	0.22%	1.06
Men (ever-smokers)	2,437	8	0.33%	1.61
Women (ever-smokers)	1,765	5	0.28%	1.27

* persons years.

who developed incident PD, had smoked on average less pack years than smokers who stayed free of the disease: in incident PD patients the mean number of pack years was 27.4 for baseline-smokers, 14.7 for ex-smokers, and 21.5 for both groups combined (ever-smokers); the corresponding figures for smokers without the disease were, 31.2, 25.4, and 27.4, respectively. However, none of these differences were statistically significant.Stratification by age led to similar results in both age-groups; for ever-smokers younger than 75 years of age the RR of PD was 0.36 (95%CI: 0.10-1.22), and for ever-smokers aged 75 years and over the RR was 0.35 (95%CI: 0.11-1.09). Exclusion of incident PD patients with an estimated onset of PD within one year after baseline screening (n = 16) did not alter the results, the RR was 0.38 (95%CI: 0.11-1.27). The proportion ex-smokers was lower among ever-smokers who developed PD (46%) than among ever-smokers without incident PD (65%), but this difference was statistically non-significant. Moreover, ex-smokers with incident PD had not quit more recently than ex-smokers without PD (mean time since quitting was 25.5 (± 14.7) versus 19.6 (± 12.6)).

The median age at onset among PD patients who smoked was higher than the age at onset among incident PD patients who had never smoked: 80.7 versus 76.5 years of age, but this was statistically non-significant (p = 0.6).

Table 5.3.3 *The relative risk (RR) of Parkinson's disease (crude and age- and sex adjusted) with 95% confidence interval (95% CI) for smokers compared with non-smokers*

Baseline exposure	Crude RR	95% CI	Adjusted RR	95% CI
Non-smokers	1.00	Reference	1.00	Reference
Ever-smokers *(baseline- and ex-smokers combined)*	0.33	0.17-0.66	0.37	0.15-0.89
Baseline-smokers *(Ex-smokers excluded)*	0.50	0.21-1.17	0.50	0.18-1.43
Ex-smokers *(Baseline-smokers excluded)*	0.24	0.10-0.59	0.26	0.09-0.78
Men *(ever-smokers)*	0.24	0.06-0.89	0.26	0.07-0.99
Women *(ever-smokers)*	0.31	0.12-0.84	0.39	0.14-1.08
Ever-smokers *(those with an onset of PD 1 year after baseline screening excluded)*	0.31	0.15-0.64	0.41	0.17-1.03

Discussion

We found that smokers had a significantly decreased risk of PD, which was not modified by age. The findings could not be explained by artefactual associations due to quitting smoking in the early phase of disease, as was suggested previously.[5]

The strengths and limitations of our study are several. At the time of the baseline collection of information on smoking history, all participants were free of PD. As a result neither the participants nor the interviewers were aware of the participants' future disease status. Both at baseline and follow-up, participants were screened in person for PD by the use of a similar examination and similar diagnostic work-up. For those who were screened at baseline but could not be examined at follow-up, we achieved complete follow-up through a computer surveillance system, by which interval cases were reported at time of diagnosis. Among the individuals who could not be reexamined at follow-up, however, we may have missed some very early PD patients with mild signs and those who had not sought medical attention yet. Our

follow-up period was relatively short. This may have reduced the proportion of subjects who could not be rescreened in person, and ensured a more complete case-ascertainment, but led to smaller numbers of incident PD patients. Though these numbers were small, the statistical power was large enough to detect strong differences in risk.

The methodological limitations of cross-sectional and retrospective studies on smoking and PD have been extensively discussed previously by Morens *et al.*.[2] The few prospective studies that were based on follow-up of mortality of smokers had limitations as well. In these studies, smoking related diseases may predominate the diagnosis of PD as the listed primary cause of death, especially in smokers. This may lead to an underestimation of the PD frequency among smokers and to a seemingly protective effect of smoking on PD. Even in countries with excellent death certificate registration, in only 70% of diagnosed PD patients the PD diagnosis is listed on death certificates.[16] The only published prospective community-based study on smoking and PD to date showed a reduced risk of PD for smokers similar to what we found.[3] This study is not completely comparable with ours, however, because no in-person screening for PD was conducted at baseline and it was restricted to men of Japanese and Okinawan ancestry.[3]

Despite the robust finding of an inverse association between smoking and PD in most studies, it is still speculative which biologic mechanism is involved in the protective effect.[2,10] Recently, Fowler *et al.*, using Positron Emission Tomography scanning technique, found that in the substantia nigra of smokers monoamine oxidase B (MAO B) levels are reduced by 40%.[10] As a result, MAO B-mediated dopamine oxidation will be less, yielding a neuroprotective effect through reduced free radical production. In contrast to studies in which neuroprotective treatment in symptomatic PD patients did not reveal convincing results,[17] neuroprotection over decades and in the preclinical phase of the disease may be more effective.[18] In smokers, who may have been smoking for years and presumably long before the accelerated deterioration of dopaminergic cells in the substantia nigra, the continuous inhibition of MAO B could have exerted an effective neuroprotection. Another beneficial effect of MAO B reduction regards the increased synaptic dopamine availability, thereby reducing the symptom severity or delaying the onset of clinical PD.[2] Our finding that incident PD patients who are smokers may have a later age at onset compared with non-smokers, endorses this latter possibility. Reduced MAO B levels may also implicate less MAO B mediated oxidation of protoxins to neurotoxins.[19-21] The compounds of cigarette smoke that inhibit MAO B are not known.[10,22,23]

Besides the MAO B related processes, smoking may induce other enzymatic

processes that are involved in the metabolism of xenobiotics, thereby augmenting protection against oxidative stress or toxins.[24] Other possible mechanisms pertain to direct stimulation of dopamine release[20,25] or nicotine receptors[26,27] by nicotine, or to protection through smoking-associated carbon monoxide against peroxidation of the membrane.[28]

A different point of view contains the key role in reward mechanisms and addiction that has been ascribed to dopamine.[29,30] Higher dopamine levels may be linked to novelty-seeking behavior,[31] and could facilitate addiction to cigarettes. Reduced dopamine levels in the brains of preclinical PD patients[32] may keep these subjects from smoking long before the signs become clinically overt. Also, regardless whether or not dopamine related, a less novelty-seeking behavior in persons who later develop PD has been suggested[33] and this may, with other premorbid personality features, predelict these persons to restrain from smoking,[2,34] resulting in a comparatively high frequency of PD among non-smokers. To date, good evidence to support this premorbid personality hypothesis is lacking as it was only investigated in case-control studies based on prevalent cases, and thus cause and effect bias and recall bias may have occurred.

In conclusion, smokers have an almost three-fold decreased risk of PD. This inverse association is dose-dependent and this supports a causal explanation. The association cannot be explained by PD patients who quit smoking in the preclinical phase of the disease, and is independent of age. Although the benefits of smoking regarding protection against PD will not outweigh the disadvantages of smoking, better insight into the smoking-related neuroprotection may help to understand the etiology of PD and eventually to prevent PD.

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5.4 Family history and the risk of Parkinson's disease

Although numerous potential risk factors for Parkinson's disease (PD) have been studied, the cause of this neurodegenerative disease still remains unknown. Since the end of the nineteenth century, when Gowers reported 15% familial occurrence of PD,[1] a genetic component in the etiology of PD has been suspected. In twin studies performed in the seventies and eighties, however, low concordance rates of PD were found and it was concluded that hereditary factors had no major role in PD.[2-4]
Recent reports on PD candidate genes,[5-8] and familial aggregation of PD[9-16] as well as hypotheses regarding enhanced susceptibility to PD through genetically determined deficient enzymes that are involved in detoxicification of neurotoxins in the brain[17-19] illustrate the renewed interest in a genetic contribution to the pathogenesis of PD. However, the studies on familial aggregation that have been published thusfar have various methodologic limitations as most were case-control studies in which the information had been collected retrospectively, were hospital- or register-based, and pertained to a relatively young study population.
Prospective community-based familial aggregation studies in elderly could overcome these limitations, but to date no such studies exist. Therefore, we prospectively assessed the risk of PD among persons with a family history of either PD or dementia as compared with those without in a general elderly population. In our community-based cohort study, subjects were neurologically screened at baseline and at follow-up.

Methods

Study population

This study was part of the Rotterdam Study, a prospective community-based cohort study that focuses on prevalence, incidence, and determinants of cardiovascular, locomotor, ophthalmologic, and neurodegenerative diseases.[20] For this cohort study, all inhabitants aged 55 years or older from the suburb of Ommoord in Rotterdam, the Netherlands, were invited to participate. Both independently living and institutionalized residents were included in the cohort. The baseline survey started in 1990 and was completed in June 1993. Of the 10,275 eligible subjects, 7,983 (78%) agreed to

participate and signed informed consent statements. At baseline, all participants were interviewed at home and 6,969 subsequently underwent the complete in-person baseline screening for parkinsonism at a research center. Follow-up examinations took place from September 1993 till the end of 1994. Persons who had a neurologic screening examination at base-line, were free of parkinsonism and dementia at the time, and of whom the baseline data on family history of Parkinson's disease and dementia were complete, were followed up for incident PD (n = 6,341).

Case-finding and diagnostic procedures

Both at baseline and follow-up, we used a two-phase design to identify subjects with PD.[21] In the first phase of the screening for parkinsonism, every participant was briefly neurologically examined by one of the study physicians, and those who screened positive were invited for further evaluation in a second phase by a neurologist or a neurologist in training. A structured clinical work-up was used to establish the diagnosis parkinsonism and to classify this parkinsonism. PD was diagnosed if at least two of four cardinal signs (i.e., resting tremor, rigidity, bradykinesia, or impaired postural reflexes) were present in a subject not taking antiparkinsonian drugs or when in a subject treated with antiparkinsonian medication one or more signs, documented by medical history, had improved by treatment. In addition, all other causes of parkinsonism had to be excluded.[21]

For the 1,238 subjects who were not reexamined at follow-up (295 had died, 44 could not be reached, 468 refused, and 431 random subjects did not undergo the complete neurologic screening examination due to logistic reasons), we obtained information through a surveillance system by computer linkage with the Ommoord general practitioners' and pharmacies' automated medical record systems. Through this surveillance system we were notified of incident patients with parkinsonism and were allowed access to their medical records.

Data collection on family history

As part of the baseline data collection in the Rotterdam Study, information was obtained on family history for various diseases among first degree relatives. Formal pedigrees were constructed by asking the participants the year of birth of their parents, sibs, and children and, if applicable, the age of death of these relatives. Next, using a comprehensive list of diseases including PD and dementia, each participant was asked to indicate for each family member separately whether that family member was affected by a specific disease.

Data analysis

We calculated the cumulative incidences of PD among subjects with a family history of PD, dementia, and either PD or dementia, and among subjects without such family history. We used Cox proportional hazard analyses to estimate the crude and the age- and sex-adjusted relative risk (RR) of PD, with corresponding 95% confidence interval (95% CI), for the various groups with a positive family histories compared with those without such a family history. For PD and dementia separately, we calculated the RRs for persons with at least one affected relative, persons with one affected relative, and persons with at least two affected relatives. Also the RR of PD among persons with an affected relative with either PD or dementia was estimated. In all analyses, each participant's contributed follow-up time was taken into account, and for the adjusted RRs, we controlled for age at entry in study and sex.

Results

Table 5.4.1 presents the age- and sex-distribution of the study population at risk to develop PD and the distribution of those with a family history of PD or dementia, or both.

Table 5.4.1 *Baseline characteristics of the study population at risk for incident Parkinson's disease*[*]

Baseline characteristics	
Number of persons at risk for PD	6,341
Median age in years (± SD)	68.7 (8.6)
Number of women (%)	3,730 (58.8%)
Persons without a relative with either PD or dementia (%)	4,655 (73.4%)
Persons with relatives with PD (%)	313 (4.9%)
Persons with at least two relatives with PD (%)	24 (0.4%)
Persons with relatives with dementia (%)	1,498 (23.6%)
Persons with at least two relatives with dementia (%)	158 (2.5%)
Persons with at least one relative with either PD or dementia (%)	1,686 (26.6%)

SD = standard deviation.

[*] Persons with either parkinsonism or dementia at baseline (n = 401) have been excluded.

From the cohort at risk to develop PD, 32 incident PD patients emerged after a total follow-up time of 13,201 person years. The 2.1 year cumulative incidence of PD for those with a family history of PD was higher than for those without; 0.96% versus 0.43% *(Table 5.4.2)*.

Table 5.4.2 *The incidence of Parkinson's disease (PD) in persons with a family history of PD, dementia, or both, and in those without a positive family history*

Baseline information	Persons at risk for PD*	incident PD cases*	Cumulative incidence	Incidence rate†
No family history of PD or dementia	4,655	20	0.43%	2.1
Persons with at least one relative with PD	313	3	0.96%	4.8
Persons with at least two relatives with PD	24	1	4.17%	24.0
Persons with at least one relative with dementia	1,498	11	0.73%	3.5
Persons with at least two relatives with dementia	158	2	1.27%	6.1
Persons with a family history of PD or dementia	1,686	12	0.71%	3.4

* Numbers

† Incidence rate in cases per 1,000 persons years.

Of the 24 persons who had at least two relatives affected by PD, one developed incident PD. For persons with a positive family history of PD the adjusted RR risk of PD was 2.5, but this did not reach statistical significance (95% CI 0.8-8.4)(Table 3). Having at least two affected relatives with PD increased the risk of PD more than 9-fold *(Figure 5.4.1)*, and this was significant (RR 9.3 (1.3-68.2)). Subjects with a family history of dementia had a borderline significantly increased risk, RR 1.7 (0.9-3.7), which seems a little bit higher for those with at least two demented relatives, RR of 2.4 (0.6-10.2). In Figure 5.4.1 the adjusted RRs for those with one, respectively at least two affected family members is graphically displayed. For the various subgroups, the cumulative incidences, and the crude and the age- and sex-adjusted RRs of PD are presented in Tables 5.4.2 and 5.4.3.

Table 5.4.3 *The relative risk (RR) of Parkinson's disease (crude, and the age- and sex adjusted) for persons with a family history of Parkinson's disease (PD), dementia, or both. Persons without a positive family history have a relative risk of 1.0 (reference)*

Baseline information	Crude RR	Adjusted RR
Persons with at least 1 relative with PD	2.6 (0.8-8.4)*	2.5 (0.8-8.4)
Persons with at least 1 relative with dementia	1.8 (0.9-3.7)	1.8 (0.9-3.7)
Persons with at least 1 relative with either PD or dementia	1.7 (0.8-3.4)	1.7 (0.8-3.4)

* 95% confidence interval.

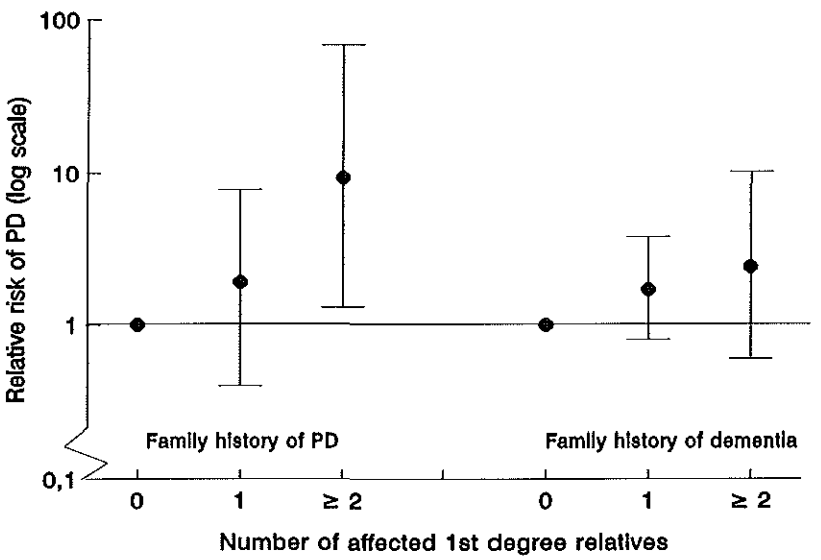

Figure 5.4.1 *The adjusted relative risk of Parkinson's disease (PD) among persons with 1, respectively ≥ 2 affected relatives with PD or dementia. The error bars denote the 95% confidence intervals.*

Discussion

This is the first prospective community-based study in which the risk of incident PD was investigated among non-parkinsonian subjects with a family history in first degree relatives of either PD or dementia compared with those without. Our preliminary results showed that both persons with family members with PD and persons with demented relatives run a higher risk to develop PD as compared with persons without such history, although this increased risk reached statistical significance only for those with at least two relatives affected by PD.

To interpret our findings, we first have to consider the limitations and strengths of our study. Although the present prospective cohort study is the largest in its kind and included more than 6,000 participants who were screened and interviewed at baseline, only a small number of persons have a family history of PD among first degree relatives, and the number of incident PD patients was small due the low incidence of PD.

Concerning the reliability of the collected information on family history, some remarks have to be made. Due to the size of the cohort and the age distribution of the members of this cohort (the oldest participant was 106 years of age), it was not feasible to verify the family history in each reported affected relative. Therefore, we chose to rely on self-reported family history. Though this may have introduced some misclassification of diagnosis of PD or dementia in relatives, this will probably have been similar in those who developed PD and in those who stayed free of the disease as the data were collected in non-parkinsonian persons at baseline. The approximately five times higher percentage of persons with a family history of dementia than the percentage of persons with a family history of PD in our study is in agreement with the overall prevalences of dementia and PD in the Rotterdam Study; 6.3% and 1.4%.[21,22] Erroneously classifying essential tremor in relatives as PD may, to some extent, have occurred, but this unlikely explains our findings: a much higher proportion of persons with a positive family history of PD would have been expected because essential tremor is highly prevalent in an elderly population.

Unique features of our study are that the study is prospective, community-based and not register-based or hospital-based, and that participants were examined in person at baseline and at follow-up. Regarding the first, through the prospective design many potential sources of biases, that might have flawed all previous studies on family history of PD, will have been reduced. All participants were at the time of the baseline interview free of both PD and dementia, and were, like the interviewers, not aware of their future disease status. Consequently, information bias with regard to collected data on family history (observer and recall bias) is a very unlikely explanation for our

findings. As the study is community-based, the incident PD patients will reflect a general PD population, thereby minimizing selection bias. Also, compared with retrospective or cross-sectional studies the role of selective mortality will be less in prospective studies. Prospective studies, however, that solely rely on incident PD patients retrieved through medical records may still potentially bear some form of selection bias such as detection bias, e.g., it is easy to conceive that new PD patients arising from families with familial PD are to be recognized and referred earlier for their signs than sporadic cases. In an earlier report, we have shown that in a general population a substantial proportion of PD patients go undetected [23]. In our study, this type of bias was circumvented by the use of similar in-person screening examinations for PD at both baseline and follow-up.

Among the many efforts to disclose a genetic contribution to the etiology of PD are studies on familial aggregation or association of PD that have been recently reported,[10-12,14-16] all showing familial aggregation, sometimes up to 22% in first degree relatives.[11,16] However, these studies have to be interpreted with some caution. All were hospital- or register-based, through which selection bias of the cases may have been occurred. Especially in the studies that were conducted in specialized movement disorder clinics, PD patients referred to these clinics may be different with respect to family history than PD patients who have been recruted in a general population. The latter is, in part, reflected by the relatively young age in those cases. Also, the studies that compared the frequency of family history of PD between PD patiens and controls, selection of controls may have been biased as well as they were spouses of friends and not population-based controls.[12,14,16] In all, the information on family history was collected retrospectively which also may have introduced bias, such as information bias, as mentioned earlier. Still, these findings suggest that PD is very prevalent in many families. This is confirmed by the accumulating number of reports on multicase families.[9,11,24-28] In most reports on multicase families, the sole atypical feature of the PD is the young age of onset.[24] The segregation ratios in most of these families suggest autosomal dominant inheritance with reduced penetrance. The genetic association studies, however, that have been conducted in an effort to identify polymorphisms of genes that may play a role in the pathogenesis of PD have led to conflicting results.[5-7,29-35]

Evidence is growing that PD is a multifactorial disease in which environmental factors and genetic factors interplay, e.g., neurotoxins may only exert their potentially toxic effect if the exposure occurs in a genetically susceptible subject.[19] Hence, a more fruitful approach may be to include putative risk factors in the analyses of association or linkage of candidate genes.

An alternative explanation for familial aggregation of PD alone, or of both PD and dementia,[13,36,37] may be that family members share the environment, and thus the environmental risk factors.[38] The finding in our study that persons with more affected family members faced a higher risk of PD does not preclude this alternative explanation.

In conclusion, our prospective study suggests that hereditary factors do contribute to the pathogenesis of PD. Longer follow-up of the cohort will be needed to confirm these preliminary findings. The findings may warrant a further search for candidate genes involved in the pathogenesis of PD.

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Chapter 6

General discussion

6 General discussion

In this thesis, studies on various epidemiologic aspects of Parkinson's disease (PD), such as diagnosis, frequency, and determinants of the disease, have been described. In order to interpret and appreciate the findings from these studies, some remarks related to the general study design and methodology, diagnosis, and implications of the findings have to be made. As for each study the more specific methodologic items have been dicussed in the corresponding chapter, this final chapter will mainly deal with advantages and limitations of community-based studies as the Rotterdam Study.[1] Also, the contribution of the findings to current knowledge of PD will be discussed. Finally, some research topics on PD will be sketched that may be explored as an extension to the studies in this thesis.

Methodologic considerations

The setting of the studies

The core of this thesis consists of studies that were conducted as part of the Rotterdam Study, except for Chapters 3.2 and 4.2 in which comparisons were made with other community-based studies. The unique feature of these community-based studies regarding PD is that all individuals were screened in person. In a defined population, such approach should allow us, if the screening instrument is adequate, to identify virtually all subjects with one or more symptoms of the parkinsonian syndrome. This is in particular relevant for PD as many persons with this disease go undetected in the population.[2,3] As a consequence, PD patients who have not been diagnosed before due to various reasons will be included in the study, yielding better prevalence and incidence estimates of the disease. Yet, in large community-based studies, it is impractical to administer a full neurologic examination by neurologists to each participant. Therefore, often a stepped approach is followed through which subjects most likely to be affected by parkinsonism will be further evaluated in a diagnostic phase. We decided to rely on an in-person screening examination rather than on a screening questionnaire. As shown in Chapter 3.1, the sensitivity of a questionnaire based on important clinical features of parkinsonism is low and may not enable researchers to detect all parkinsonian subjects in a population. Interestingly, a French community survey that based its screening mainly on a symptom

questionnaire yielded lower prevalence estimates than other European prevalence surveys with an otherwise similar methodology.[4] We feel that the application of a more objective tool such as a screening examination conducted by a physician may improve the detection rate of the disease.

Etiologic and prognostic studies that are embedded in community-based studies with an in-person screening for PD have an advantage as well, conditional on several assumptions such as random participation non-response. Such studies will yield an aselective PD patient population, in contrast to patient populations derived from specialized movement disorder clinics. Also, persons from the same study population who have not been identified with parkinsonism are suitable subjects to serve as controls because they have emerged from the same population and have been subjected to the same screening. Therefore, such a design enhances both internal and external validity.

Non-response

In all studies, non-response bears some potential for selection bias. A common assumption is that the higher the non-response is, the higher the risk of bias will be that might influence the validity of the study. This is, however, only true if the non-response is selective: if non-response is related to the determinant or outcome of interest, the findings will be flawed. The overall response rate in the Rotterdam Study was good (78%), considering the average age of the study population, and the extensiveness of the investigations. As for the PD survey it was decided not to rely on the screening questionnaire but on a complete screening examination *(Chapter 4.1)*, the response was somewhat lower, 68%.

Direct assessment of selective non-response is difficult to achieve, but an indirect approach can be used if some characteristics of the total target population are known like age and sex.[5] Regarding the PD survey that was part of the Rotterdam Study, the prevalence figures were strikingly similar to those derived from various European prevalence surveys with a variation of response rates *(Chapters 4.1 and 4.2)*, both in rural and urban settings, using similar diagnostic criteria. Screening procedures, however, differed slightly across studies. Although we cannot exclude that actually existing differences have been obscured by differences in participation rates or sensitivities of the screening instruments, the very similar estimates for all studies using similar methodology and diagnostic criteria suggest that the higher non-response in the Rotterdam Study compared with some other community-based studies has not led to serious selection bias.

Diagnosis

In epidemiologic studies, the sole approach for diagnosing parkinsonism is the use of an ante-mortem diagnosis of PD, and thus a clinical diagnosis. It was shown previously that a substantial proportion of the cases, who during life had been diagnosed as PD, had a neuropathologic diagnosis (gold standard) other than PD.[6] Preliminary data now show that refinement of clinical diagnostic criteria for PD had improved diagnostic accuracy.[7] However, although application of very strict clinical criteria may improve the clinico-neuropathologic correlation,[6,8] it will lead to exclusion of more than 30% of pathologically genuine PD patients.[8] Moreover, it can be debated whether the neuropathologic diagnosis should indeed be regarded the gold standard because the neuropathologic diagnosis of PD is not unequivocal and diagnostic errors in the neuropathologic examination may occur as well. In addition, one has to bear in mind that many of the clinico-neuropathologic correlation studies have been conducted in specialized movement disorder clinics that may attract the more atypical PD cases. Also, especially the more atypical cases will come to autopsy, thereby possibly underestimating the accuracy of a clinical diagnosis.

The different clinical diagnostic criteria for PD have been extensively discussed in Chapter 3.2. In some of the sets of the criteria, levodopa response is a prerequisite for the diagnosis PD in a parkinsonian subject.[8,9] In an epidemiologic study with an in-person screening for parkinsonism, by the virtue of its design, many thusfar unrecognized patients with PD may emerge[4] in whom administration of levodopa for diagnostic purposes is unethical and impracticle. Taken these considerations into account, a diagnosis of PD based on neurological symptoms without additional requirements is adequate and feasible for epidemiologic studies. For studies on effectiveness of new antiparkinsonian drugs or genetic linkage studies of PD, more stringent diagnostic criteria may be preferred.

Cross-sectional studies

Two studies on etiology of PD described in this thesis *(Chapters 5.1 and 5.2)* are cross-sectional. In general, cross-sectional studies have a larger potential of bias than longitudinal studies. In particular, selection bias due to selective mortality, information bias, and cause-effect bias have to be considered when interpreting the associations. In Chapter 5.2, in which the relation between dietary antioxidant intake and PD is described, extensive attention has been paid to information bias and cause-effect bias (the observed relationship may be a consequence rather than a cause of the disease). Selection bias due to selective mortality unlikely explains the inverse association between dietary vitamin E intake and PD: either PD patients with a high

dietary vitamin E intake should have been selectively removed from the population or relatively more persons, except those who have PD, with low intake of vitamin E should have died. Both possibilities are not easy to conceive.

In cross-sectional association studies on disease and polymorphisms of a gene, information bias and cause-effect bias are unlikely to play a major role. Information bias could only occur if the genotyping depends on the diagnosis of the disease, or vice-versa. In our study on the association between apolipoprotein E genotype (APOE) and dementia in PD *(Chapter 5.1)*, both diagnosis and genotyping were done independently. As PD does not affect the APOE genotype, cause-effect bias is not a matter of concern. However, selection bias could have occurred and the associations within the PD patient group may, to some extent, also be the result of an increased or decreased survival related to the APOE genotypes 2 and 4 if compared with those who are homozygous for APOE 3 genotype. For example, an increased risk of dementia in PD associated with the APOE 2 allele (APOE*2) may be found if demented PD patients who carry this allele live longer than non-demented PD patients carrying APOE*2. To rule out a possible effect of selective mortality, the findings of our study, presented in Chapter 5.1, will have to be confirmed in follow-up studies.

Longitudinal studies

The etiologic studies described in Chapters 5.3 and 5.4 are longitudinal which should limit sources of biases that may exist in cross-sectional studies. A possible bias that still remains is selection bias. Selection bias due to selective mortality has been in part addressed in the previous section. In Chapter 5.3 we described the decreased risk of PD among smokers. Smoking is a risk factor that typically influences mortality. However, our findings of a protective effect of smoking for PD would only be the result of selective mortality if smokers who were to develop PD later during follow-up had selectively died before the diagnosis of PD could be established. This unlikely explains our findings because the short follow-up period will not have allowed such a strong effect by selective mortality.

The various pros and cons regarding the findings on family history of PD or dementia and the risk of PD presented in Chapter 5.4 have been extensively discussed before. These are preliminary findings which were based on small numbers. Of the 313 persons with a positive family history of PD in first degree relatives, 4 developed PD and of 1,498 persons who reported a family history of dementia, 11 became affected by PD. As a consequence, the 95% confidence intervals were wide. Nevertheless, the findings were in agreement with the hypothesis, and it may be expected that after a

longer follow-up with more statistical power, due to more incident cases, the associations will be confirmed.

Implications of the findings

In the following section, the impact of some the findings from this thesis, and what perspective they put on current knowledge, will be addressed.

Screening

Not until now did studies exist that provide data on prevalence of subjective complaints suggestive for parkinsonian signs in a general population. We showed that this prevalence is high, and that this lowers positive predictive values of these complaints for the true presence of related parkinsonian signs. Also, our study makes clear that, in a general elderly population, a questionnaire based on two questions related to subjective complaints is probably not an adequate tool for screening for parkinsonism because of the low sensitivity, especially in the highest age-groups. Furthermore, we made clear that age strongly modifies the screening properties of a screening instrument. Besides age, other factors may be modifiers as well. This knowledge can be used in future studies that pursue complete case-ascertainment of parkinsonism and PD in a general population.

Diagnosis

It has been suggested that environmental factors play a role in the etiology of PD, solely based on comparisons of existing prevalence studies that yielded wide variations in prevalence estimates. We have shown that, besides case-finding strategies, differences in diagnostic criteria can change prevalence figures dramatically. For studies on frequency of the disease, we therefore argue to use similar diagnostic criteria, or, if prevalence estimates are being compared, to recalculate the prevalences applying similar diagnostic criteria. To allow such an approach, the sensitivity of the screening instruments used in the studies under comparison has to be similar.

Frequency

Prevalence

The first community-based studies with an in-person screening on the prevalence of PD that were published, showed a high prevalence of the disease that continued to rise with age. Later, studies with a similar design, like ours, confirmed these findings and the current opinion is that in the Western world prevalence of PD is virtually

similar across countries and regions. The latter is nicely illustrated in the EUROPARKINSON prevalence study on PD, a study with a large methodological homogeneity.

Incidence

The study on the incidence of parkinsonism and PD *(Chapter 4.3)* indicates that the incidence rates are higher than has previously been reported by others based on registers or medical records. However, based on the prevalence estimates by community-based surveys with an in-person screening and on the age-specific life expectancy of PD patients, incidence rates of PD should be that high.

Apart from the incidence rates of PD itself, the pattern that the incidence follows across the various age-groups, may reveal important information on the etiology of PD. The hypothetical pattern that age-specific incidence rates will follow depends on the underlying process or event that causes PD. In Figure 6.1 some of the patterns

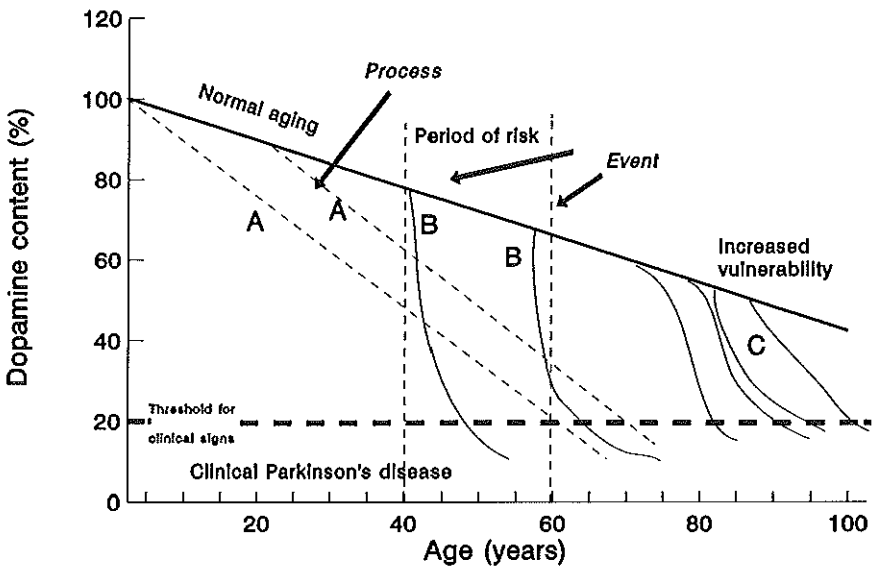

Figure 6.1 *Several patterns that the dopaminergic cell loss in the substantia nigra of Parkinson's disease (PD) patients may follow, based on age-specific incidence estimates of the disease. If PD is caused by an event in persons susceptible at a certain moment (B), then a peak in the incidence rate would be found. If PD is caused by an accelerated aging process (A) or by a vulnerability to degeneration increasing with age (C), incidence rates would increase with age without a leveling off (C).*

pertaining to the rate of excessive degeneration of dopaminergic cells in PD that have been proposed,[10, 11] are visualized. If PD is caused by an accelerated normal aging process (A) or if the vulnerability of the dopaminergic cells to degeneration increases with age (C), an increase in the incidence of PD with age would be expected, even in the highest age-groups. If, on the contrary, the degenerative process in PD is induced by an event in persons around a specific age (B), possibly on the basis of some genetic susceptibility, then a decrease in incidence rates in the highest age-groups could be expected as well. In our study, longer follow-up is needed to disclose the pattern of incidence rates in the oldest old.

Determinants

Apolipoprotein genotype

The associations we found between APOE*2, APOE*4, and PD need confirmation in longitudinal studies. Some lines of evidence, including neuropathologic, suggest that APOE*4, and maybe also APOE*2, may be involved in dementia in PD. It still has to be elucidated through which mechanism APOE genotypes may exert their effect in the pathogenesis of dementia in PD.

Vitamin E

In 1989 the large DATATOP trial started to investigate the putative protective effective of treatment with the antioxidant tocopherol (a component of vitamin E) in PD patients in an early phase of the disease,[12] although the biological availability of dietary vitamin E in the human brain, and the relation between dietary intake and PD had not been assessed before. This study showed no effect of vitamin E supplementation in PD patients.[13] The relation between vitamin E intake and its availability in the human brain has to be explored further. A recent study, that was published after we had submitted our study for publication, did not show a correlation between supplemental vitamin E and ventricular cerebrospinal fluid concentrations of vitamin E.[14] However, this study was based on only 5 relatively young PD patients with a median disease duration of almost 20 years, and the vitamin E uptake mechanisms in the brains of these PD patients may have been altered compared with healthy persons. The findings from that study need to be confirmed in a larger series of healthy subjects. Our finding that high dietary vitamin E intake, presumably during a considerable long period, is inversely associated with PD also needs confirmation in the follow-up phase of the Rotterdam Study, but it supports the hypothesis of involvement of oxidative stress in the etiology of PD.

Smoking

The convincing result that smoking is strongly related to a decreased risk of PD, when potential biases have been avoided as much as possible, confirms most earlier reports on smoking and PD. It still may not be compounds of cigarette smoke that protect against PD, but low endogenous dopamine levels in the brain that keep persons who are to get PD from starting to smoke. Another, yet unidentified, factor (confounder) may also be related to smoking. This needs further investigation.

Family history

Our prospective study on family history of PD and of dementia suggests that also in a general population of elderly persons hereditary factors do contribute to the pathogenesis of PD. Before our study, none of the studies that investigated these associations were prospective nor community-based and the results from those studies could be critized on methodologic grounds as discussed in Chapter 5.4. Our findings may warrant a further search for candidate genes involved in the pathogenesis of PD.

Recommendations for future research

In this final section, suggestions for research on issues related to the etiology and prognosis of PD, and that are within the scope of this thesis, will be dicussed. In general, to overcome biased study results, prospective cohort studies on determinants of PD patients are needed, preferably in community settings in which each individual is regularly screened for PD. This approach will allow inferences on etiology that held for general PD patient populations. Similarly, prognostic research in PD populations derived from community-based studies will have an advantage over studies on prognosis of PD that are hospital-based as in the latter studies selection bias may have occurred.

Etiologic research

Genetic factors

Despite many efforts to elucidate a major role of genetic factors in the pathogenesis of PD, it is still unknown which genes are involved, and to which extent. Evidence exists that polymorphisms of genes encoding for enzymes involved in the production or elimination of free radicals, in specific subunits of the mitochondrial respiratory chain (such as cytochrome P450 (CYP2D6)), or in xenobiotics, and genes involved in dopamine synthesis or metabolism (such as monoaomino oxidase B (MAO B)) are

linked to PD. It has been hypothesized that persons with an altered function of such enzymes are more susceptible to PD. Thusfar, results from association studies on allelic associations with PD and candidate gene polymorphisms were inconclusive[15-24] possibly due to heterogeneous patient groups. The limited knowledge on the pathogenesis of PD, and, as a consequence, the lack of promising candidate genes, further reduce the chance of a positive association. Better insight into the biochemical or pathophysiological mechanisms linked to the onset of PD may result in new candidate genes that can be tested in association studies using homogeneous patient groups. Also, larger, collaborative, linkage studies in multiple case families are needed to identify genes that are linked to the expression of PD. At the moment, a large European multi-center study is conducted to map and identify genes that confer genetic susceptibility to PD by using affected sib-pairs. Once such genes are identified, understanding of their function may yield new clues to prevention and treatment of PD. A different approach is genomic search in PD patients derived from a genetic isolate in order to enhance the probability of finding a gene associated with PD. If in one common ancestor a mutation causing PD has occurred, then the PD patients descending from this ancestor will not only share the mutation but also larger parts of the chromsome around the gene. Such larger parts are easier to search for. In a genetic isolate, the chance of having a common ancestor is considerably high. In the Netherlands, such study among PD patients from a genetic isolate is currently underway (Dr Van Duijn, Dr Oostra, Prof. van Ommen).

Gene-environment interaction

It seems likely that it is not only genetic factors, but the interplay between genetically determined susceptibility and specific environmental factors that lead to PD. Therefore, if the interaction between genes and environmental factors were studied, the results might be more promising. Several mechanisms of gene-environment interaction have been proposed.[25] In one of the hypothetical models, both the risk factor and the gene are required to increase the risk of the disease. If such a model would apply in the pathogenesis of PD, associations with genes and PD have to be investigated in relation to exposure of related factors. With regard to smoking and neurotoxins in relation to PD, the extent to which the effect of exposure is modified or potentiated by putative susceptibility genes could be investigated in populations, but this requires large numbers of patients. CYP2D6 polymorphisms have been suggested to interact with smoking,[26] and this could also be the case with other enzymes. However, studies exploring this hypothesis have not been performed yet, except for the MAO B polymorphism,[27] and are hampered by the lack of suitable

candidate genes.

In an attempt to probe the hypothesis of gene-environment interaction in the etiology of PD, family history of PD can be used as a proxy for genetic susceptibility. Preliminary results from the Rotterdam Study suggest that interaction between a positive family history and smoking may modify the risk of PD.[28]

Toxins

Toxins, like pesticides, have been implicated in the etiology of PD. Still, the extent to which toxins are responsible for the widely and uniformally distributed PD is debated. Differences in frequency estimates of PD, derived from prevalence and incidence studies with an in-person screening and similar methodology and diagnostic criteria, in urban and rural populations may hint at an environmetal factor to play a role in PD. The best approach, however, is direct measurement of the exposure in individuals and to follow these persons up till the disease becomes overt. In a setting as the Rotterdam Study, such an approach is not feasible because PD and the exposures are relatively rare. An alternative for research on the role of toxins in the pathogenesis of PD is either prospectively or retrospectively follow-up of cohorts with a higher than usual exposure to specific substances that have been implicated in the etiology of PD, e.g., farmers or industrial workers, using job exposure matrices to indicate objectively the compounds that carry the risk.

Antioxidants

Our finding that vitamin E is inversely associated with PD needs to be confirmed, and will prospectively be investigated in the Rotterdam study if more incident PD patients have been collected. Other prospective community-based studies which have originally not been designed to study PD but in which dietary vitamin intake in the participants was assessed, may also be suitable to investigate the risk of PD in relation to antioxidant intake. In some of these studies, large numbers of incident PD cases are to be expected as the follow-up period is long and a large number of participants have been incorporated at baseline. In the follow-up phases of these studies, however, a screening instrument for PD has to be implemented. Also, studies on the correlation between intake of (supplemental) vitamin E and cerebrospinal fluid concentrations of vitamin E should be extended to larger number of healthy subjects.

Prognostic research

When does Parkinson's disease start?

Clarification of the pattern of the preclinical period in PD might help to gain insight

into the pathogenesis of PD. It is still a question whether PD develops insidiously and gradually over time (and if so, over what time), or results from an acute event. A sudden start of the degeneration of the dopaminergic cells could point towards an environmental insult or to a sudden failure of the dopaminergic system to counterbalance oxidative stress because of an accumulation of toxic compounds above a certain threshold (in genetically susceptible individuals). On the other hand, a slow process could indicate, for example, a failure of the defence system against repeated oxidative stress thereby, after years, exceeding the threshold at which the parkinsonian signs become clinically overt (depletion of endogenous dopamine content by approximately 80%).

Several models and time frames regarding the pattern of start and progression of the deterioration of the dopaminergic system in PD have been proposed, as is illustrated in Figure 6.1. Recent reports, based on positron emission tomography (PET)-scanning studies correlating in vivo the proportion of functional dopaminergic neurons with the disease duration, suggested a short 5 year period of progressive decline of

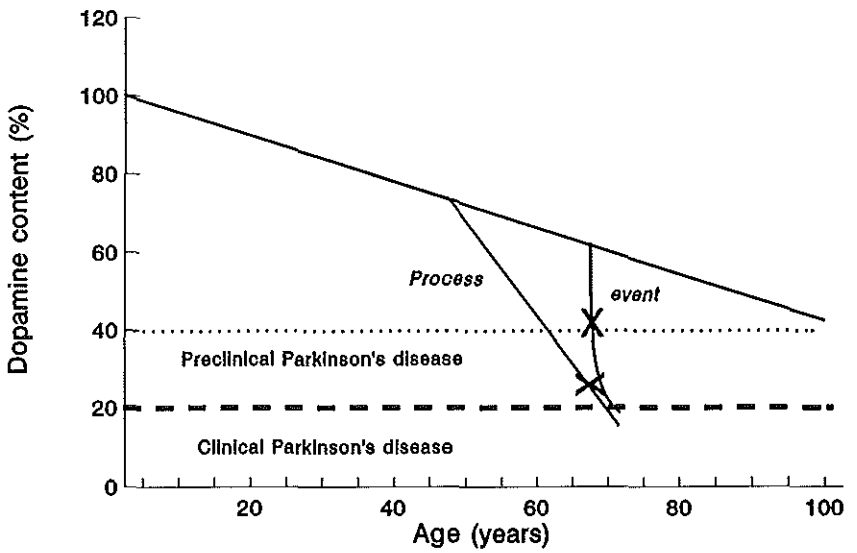

Figure 6.2 *Two hypothetical patterns of dopaminergic cell loss in the substantia nigra of Parkinson's disease (PD) patients based on possible findings from positron emission tomography (PET)-scanning in ultra-early Parkinson's disease patients. X denotes the striatal F-dopa uptake. If the uptake is low (eg 25%), then PD may be caused by a process, with a long preclinical period. If, in contrast, the uptake is higher (40%), PD may be caused by an acute event, with a short preclinical period.*

the dopaminergic system before clinical symptoms become overt.[29, 30] This time frame was assessed through exponential extrapolation of PET-scanning data in function of disease duration. It is however unclear whether this kind of extrapolation is warranted. Thusfar no PET-scanning studies in subjects with ultra-early PD have been carried out, except in twins and in sib pairs discordant for PD. In collaboration with the Paul Scherrer Institut, Villigen, Switzerland (Head: Prof. K.L. Leenders), we are currently conducting a ^{18}F-dopa PET-scanning in possibly ultra-early PD patients, detected through the active screening in the Rotterdam Study. The amount of F-dopa uptake in the striatum of these persons may enable us to estimate the curve of degeneration in preclinical PD *(see Figure 6.2)*. Whilst PET-scanning has a great potential for scientific research, its use in a general clinical setting will be limited. The PET-scanning technique is elaborative, expensive, and requires, besides a cyclotron unit, a very skillful team. Single Photon Emission Computed Tomography (SPECT)[31,32] may be an useful alternative tool to visualize in vivo dopaminergic dysfunction in the PD patient's brain. This technique is more widely avaible, easier to use, and new radioligands will make the SPECT-scanning technique even more accessible for persons at high risk for PD.

Progression

Identification of factors that contribute to a rapid progression of the clinical picture in PD patients is necessary. Only few factors such as age at onset, cognitive function at onset of the disease, depression, and severity of symptoms at onset have been investigated and have been associated with a more rapid progression of PD. However, these factors cannot be influenced, in contrast to lifestyle factors, co-medication, and blood pressure that, among others, are factors that may be also related to a different prognosis of the disease. Future prognostic research should focus on such preventable and modifiable factors.

Comorbidity and mortality

A clinical important issue is comorbidity. Comorbidity, such as osteoporosis and fracture risk, cardiovascular disease, cerebrovascular disease, and cognitive dysfunction, will impose an even larger burden to the PD patient. Remarkably, for many of these diseases little is known about the occurrence in PD patients. The Rotterdam Study provides an unique opportunity to study comorbidity in a general PD population.[1]

Ultimately, insight into the etiology of PD, and into the preclinical phase of the disease, could give clues to neuroprotective treatment. If PD were indeed preceded by a short preclinical period, this could have important implications for prevention and treatment of the disease. Also, more knowledge on concurrent diseases in PD and on preventable factors associated with a poor prognosis of PD may reduce the disease burden in a PD patient. Identification of groups at a high risk of developing clinically overt PD by either risk profile assessment or SPECT may result in measures to prevent this devastating disease in the elderly.

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Chapter 7

Summary

7.1 Summary

As in Western societies the proportion of elderly persons is growing, more and more persons will be affected by neurodegenerative diseases. Among the most frequent is Parkinson's disease (PD), a disease that is neuropathologically characterized by selective loss of dopaminergic neurons in the substantia nigra and other brainstem ganglia, leading to depletion of endogenous dopamine. The cause of this degeneration is still unknown. In this thesis, studies on various epidemiologic aspects of PD, such as diagnosis, frequency, and etiology, are described. All studies in this thesis are community-based with an active screening for PD in each individual, and most are part of the Rotterdam Study, a prospective community-based cohort study on prevalence, incidence and determinants of diseases among elderly persons. All inhabitants of Ommoord, a suburb of Rotterdam, the Netherlands, who were 55 years of age or older, either living independently or institutionalized, were invited to the study of whom 7,983 (78%) agreed to participate. For the studies decribed in this thesis, we included the 6,969 participants who underwent the complete neurologic screening examination at baseline. The Rotterdam Study started in 1990 and the baseline survey was completed in June 1993. The first follow-up phase run from September 1993 till the end of 1994.

In **Chapter 2** an overview is given of recent developments in epidemiologic research, most from the past decade, with the emphasis on large cross-sectional population-based studies and prospective studies.

Various aspects of screening for parkinsonism and PD, and diagnostic criteria of PD are discussed in **Chapter 3**.
Little is known about the prevalence and predictive value of subjective complaints suggestive for the presence of parkinsonism. For screening purposes and in clinical practice there is need for such information. In **Chapter 3.1** we investigated the prevalence of subjective complaints and related parkinsonian signs, and the sensitivity, specificity, positive predictive values (PPV), and likelihood ratios of subjective complaints for parkinsonian signs in a general elderly population. The proportion of persons that reported to have a tremor or slowness and/or stiffness increased with age, and was higher than estimated by the study physicians. For self-

reported tremor, the sensitivity, specificity, PPV, and likelihood ratio were 39.3%, 89.7%, 29.9%, and 3.8, respectively. For self-reported slowness and/or stiffness these figures were 44.7% for sensitivity, 77.4% for specificity, 13.0% for PPV, and 2.0 for the likelihood ratio. These results suggest that subjective complaints are very prevalent in a general elderly population and attribute little to the detection of true parkinsonian signs.

In **Chapter 3.2** examples are given how the choice of diagnostic criteria affects research results. Using data on PD from three community studies (from Argentina, the Netherlands, Italy), we compared the impact on prevalence of several sets of diagnostic criteria. Each set was based on cardinal signs—resting tremor, bradykinesia, rigidity, impaired postural reflexes—and required that other parkinsonism be excluded. Some sets had additional requirements related to duration of symptoms, asymmetry of signs, or response to medication. In terms of prevalence, much lower estimates were associated with the requirements of asymmetry of signs and response to medication. The assessment of these clinical features may not be practical in community studies. Impaired postural reflexes, as a cardinal sign, seemed superfluous. For community studies of PD, we recommend the following diagnostic criteria: at least two of resting tremor, bradykinesia, or rigidity, in the absence of other apparent causes of parkinsonism.

The frequency (prevalence and incidence of parkinsonism and PD) is handled in **Chapter 4**. The first part of this chapter (**Chapter 4.1**) deals with the prevalence of PD in the Rotterdam Study. All participants were examined, and those who either had at least one possible cardinal sign of parkinsonism at the neurologic screening, reported that they had PD, or were taking antiparkinsonian drugs were invited for further evaluation. The prevalence of PD in this population was 1.4% (1.2% for men, 1.5% for women). Prevalence increased with age, and prevalence figures were 0.3% for those aged 55 to 64 years, 1.0% for those 65 to 74, 3.1% for those 75 to 84 , and 4.3% for those 85 to 94 years. The corresponding age-specific figures for men were 0.4%, 1.2%, 2.7% and 3.0%, and for women 0.2%, 0.8%, 3.4% and 4.8%. Among 95- to 99-year old women the prevalence was 5.0%. Twelve percent of the subjects with PD were detected through the screening and had not been diagnosed previously. These findings are in line with the few other studies that followed a similar methodology.

In **Chapter 4.2** a comparison is made of the prevalence of parkinsonism and PD in five European populations that were surveyed with similar methodology and

diagnostic criteria. The five community surveys are Gironde (France), 8 centres in Italy, Rotterdam (the Netherlands), Girona (Spain), and Pamplona (Spain). The individuals were screened in person for parkinsonism. Overall, these surveys included 14,636 participants aged 65 years or older. The overall prevalence (per 100 population), age-adjusted to the 1991 European standard population, was 2.3 for parkinsonism and 1.6 for PD. The overall prevalence of parkinsonism increased from 0.9 for the age groups 65 to 69 years, to 5.1 for the age group 85 to 89 years. The corresponding age-specific figures for PD were 0.6 and 3.5. When adjusting for age and sex, the prevalence figures did not differ significantly across studies, except for the French study in which prevalence was lower. Prevalence was similar in men and women. Overall, 24% of the subjects with PD were newly detected through the surveys, and this percentage increased with age. The findings from this study suggest that the drop in the prevalence of PD as reported in many studies is probably artefactual due underdiagnosis of PD in the oldest old and stress the importance to screening actively for PD in a population.

In **Chapter 4.3** data on incidence of parkinsonism and PD in the Rotterdam Study are presented. Incidence data on parkinsonism and PD are sparse. Most incidence studies on parkinsonism and PD have been register-based and this presents serious methodologic limitations. The cohort, in which all participants were screened to detect PD, included 6,566 non-parkinsonian non-demented people. Between 1993-1994, 5,236 participants were reexamined, and the remainder was followed up through a surveillance system. The mean follow-up time was 2.14 years. The incidence rate per 1,000 person years (pyrs) of any parkinsonism was 4.3 (3.4 for men; 4.8 for women), and of PD 2.5 (2.2 for men; 2.7 for women). Incidence rates of parkinsonism increased from 0.5/1,000 pyrs for those aged 55 to 64 years to 14.3/1,000 pyrs for those aged 85 to 94 years. The corresponding rates of PD were 0.2/1,000 pyrs and 4.2/1,000 pyrs. The differences between men and women were statistically non-significant. Our findings suggest that incidence of parkinsonism and PD strongly increases with age and are higher than previously reported. However, the results were not conclusive on the pattern that the incidence figures would follow in the highest ages. For this, a longer follow-up will be needed.

Chapter 5 is about studies, all from the Rotterdam Study, that focus on the etiology of PD.

In **Chapter 5.1** the cross-sectional relation of apolipoprotein E genotype (APOE) with PD and PD dementia is decribed. APOE was genotyped in 80 PD patients (19 with dementia) and in 1,008 randomly selected non-demented, non-parkinsonian control

subjects. Overall, we found no association of APOE*4 or APOE*2 alleles with PD. Within the PD patients group however, carriers of APOE*4 (odds ratio 4.8, 95%CI 1.3-17.9) or APOE*2 (odds ratio 3.3, 95%CI 0.8-14.5) were more often demented as compared with PD patients with APOE3E3, suggesting that APOE contributes to the dementia pathogenesis in PD.

Oxidative stress has been implicated in the etiology of PD. From this may be inferred that high antioxidant intake might protect against degeneration of dopaminergic cells. A cross-sectional study that investigated whether high dietary intake of antioxidants might decrease the risk of PD is presented in **Chapter 5.2**. Besides the individual screening for parkinsonism, the participants were administered a semi-quantitative food frequency questionnaire. The study population comprised 5,342 non-demented independently living persons, including 31 patients with PD (Hoehn & Yahr stages 1 to 3). We calculated odds ratios as an estimate of the relative risk of PD. The odds ratio of PD was 0.5 (95% confidence interval: 0.2-0.9) per 10 mg daily dietary vitamin E intake; 0.6 (0.3-1.3) per 1 mg ß-carotene intake; 0.9 (0.4-1.9) per 100 mg vitamin C intake, and 0.9 (0.7-1.2) per 10 mg flavonoids intake, all adjusted for age, sex, current smoking, and energy intake. The association with vitamin E intake was dose-dependent (p-trend 0.03). To assess whether the association was different in patients with more advanced disease, we excluded PD patients with Hoehn & Yahr stage 2.5 or 3. This did not fundamentally alter the results. Several other issues are addressed that preclude low antioxidant intake as a result of the disease. These data suggest that a high intake of dietary vitamin E may protect against the occurrence of PD.

In **Chapter 5.3** results are presented from the study in which we prospectively assessed the risk of PD in smokers compared with non-smokers. Most studies on smoking and PD were either retrospective or cross-sectional and therefore susceptible to bias. To date no community-based prospective studies on smoking and the risk of PD in a general elderly population have been published. The cohort comprised all subjects who were screened in person for parkinsonism at the baseline survey (1990-1993) and were free of parkinsonism and dementia at the time, and of whom information on smoking history was collected at baseline (n= 6,442). After a mean follow-up period of 2.12 years, participants were reexamined for incident PD. We calculated the age- and sex-adjusted relative risk of PD, including 95% confidence intervals (95%CI), in smokers compared with non-smokers. We identified 34 incident patients with PD. Ever-smokers at baseline (ex-smokers included) had a strongly decreased risk of PD; the adjusted relavtive risk was 0.37 (0.15-0.89). For baseline-smokers the relative risk of PD was 0.50 (0.18-1.43), and for ex-smokers 0.26 (0.09-0.78). The inverse association of smoking and PD was dose-dependent.

This study strongly confirms the inverse association of smoking with PD. Smokers have an almost three-fold decreased risk of PD. The inverse association with smoking may give clues to the etiology of PD, and several mechanisms through which smoking-related protection may act are discussed.

In **Chapter 5.4** we address the genetics in PD. Since long, it has been suspected that genetic factors may contribute to the pathogenesis of PD. All studies that investigated the association between a positive family history of PD and the occurrence of PD were either retrospective or cross-sectional. We prospectively assessed the risk of PD among persons with a positive family history of PD or dementia as compared to persons without (first degree relatives). Persons with a positive family history of PD had a more than two-fold increased risk of PD although this was non-significant (RR 2.5, 95%CI 0.8-8.4). Persons with at least two relatives with PD had a 9-fold significantly increased risk of PD (9.3, 95%CI 1.3-68.2). For those with a positive family history of dementia the RR of PD was 1.8 (0.9-3.7), and for those with at least two demented relatives RR 2.4 (0.6-10.2). This finding supports genetic involvement in the etiology of PD and may warrant a further search for genes that are linked to PD.

Chapter 6 deals with various aspects of this thesis, such as study design and methodology, diagnosis of PD, and implications of the findings. An important feature of the studies decribed in this thesis is that they all are community-based and rely on an in-person screening for PD. Through this approach, persons with PD who had not been diagnosed before will be included. As a result, an unselected PD patient population will be obtained. The Rotterdam Study provides an excelent opportunity to follow up this group of patients for several types of prognostic factors and outcomes. Finally, recommendations are made for reseach topics that are an extent to the studies in this thesis.

7.2 Summary in Dutch (samenvatting)

Met de vergrijzing van de bevolking in Westerse landen zullen steeds grotere aantallen mensen getroffen worden door neurodegeneratieve aandoeningen. Eén van de neurodegeneratieve aandoeningen die het meest frequent vóórkomt is de ziekte van Parkinson. De ziekte van Parkinson wordt neuropathologisch gekenmerkt door selectief verlies van dopaminerge cellen in de substantia nigra met typische inclusielichaampjes in de overlevende neuronen ("Lewy bodies") waardoor een te kort ontstaat aan endogeen

In dit proefschrift worden onderzoeken naar verschillende epidemiologische aspecten van de ziekte van Parkinson, zoals diagnose, etiologie en frequentie van de ziekte, beschreven. Alle onderzoeken die in dit proefschrift beschreven worden, zijn bevolkingsonderzoeken waarin elke deelnemer werd gescreend op de aanwezigheid van de ziekte van Parkinson. Het leeuwedeel van de onderzoeken in dit proefschrift vormt een onderdeel van het ERGO-onderzoek, in het Engels "the Rotterdam Study" genoemd. Het ERGO-(Erasmus Rotterdam, Gezondheid en Ouderen) onderzoek is een prospectief bevolkingsonderzoek onder alle zelfstandig wonende of in een verzorgingshuis verblijvende inwoners van 55 jaar en ouder van de wijk Ommoord in Rotterdam. Van de 10275 potentiële deelnemers namen er 7983 (78%) deel aan het onderzoek. Alle deelnemers werden thuis uitgebreid geinterviewd en het merendeel van hen (7129) bezocht het onderzoekscentrum voor aanvullend onderzoek en metingen. In de onderzoeken welke beschreven zijn deze dissertatie werden de 6969 deelnemers ingesloten die allen een compleet neurologisch screeningsonderzoek hadden ondergaan tijdens het dwarsdoorsnede-onderzoek. Het ERGO-onderzoek nam een aanvang in 1990 en het dwarsdoorsnede-onderzoek werd medio 1993 afgerond. Het eerste vervolgonderzoek begon in de tweede helft van 1993 en eindigde eind 1994.

In **hoofdstuk 2** wordt een overzicht gegeven van recente epidemiologische ontwikkelingen op het gebied van de ziekte van Parkinson, waarbij de nadruk wordt gelegd op grote bevolkingsonderzoeken of prospectieve onderzoeken.

Verschillende aspecten wat betreft screening naar en diagnose van de ziekte van Parkinson worden besproken in **hoofdstuk 3**. Zo werd in **hoofdstuk 3.1** de

prevalentie van subjectieve klachten en overeenkomstige symptomen onderzocht die zouden kunnen wijzen op een parkinsonisme. Bovendien werden de sensitiviteit, specificiteit, positief voorspellende waarde en likelihood ratio van de subjectieve klachten onderzocht in relatie tot de aanwezigheid van symptomen passende bij parkinsonisme. De proportie mensen dat last had van een tremor of van traagheid en/of stijfheid nam toe met de leeftijd en was hoger dan dat de arten vaststelden. De sensitiviteit, specificiteit, positief voorspellende waarde en likelihood ratio van tremor als subjectieve klacht waren respectievelijk 39%, 90%, 30% en 3.8; voor klachten van traagheid c.q. stijfheid waren deze waarden 45%, 77%, 13% en 2.0. Het lijkt dat subjectieve klachten van beven en traagheid/stijfheid veel voorkomen bij ouderen en dat deze klachten van weinig waarde zijn bij het screenen naar symptomen van parkinsonisme.

In **hoofdstuk 3.2** laten we zien hoe het gebruik van verschillende diagnostische criteria voor de ziekte van Parkinson onderzoeksresultaten kunnen beïnvloeden. Hiertoe werden data vergeleken van 3 bevolkingsonderzoeken (uit Argentinië, Italië en Nederland). Gekeken werd hoe verschillende diagnostische criteria, allen gebaseerd op combinaties van hoodfsymptomen van parkinsonisme - rusttremor, bradykinesie, rigiditeit en gestoorde houdingsreflexen- en met uitsluiting van alle secundaire oorzaken van parkinsonisme, de prevalentieschattingen van de ziekte van Parkinson kunnen veranderen. Bij sommige criteria moest aan aanvullende voorwaarden worden voldaan zoals een asymmetrisch begin van de symptomen en goede reactie op levodopamedicatie. De prevalentie bleek het laagst te zijn indien een asymmetrisch begin of een goede medicatiereactie vereist werden maar aan deze voorwaarden is in een bevolkingsonderzoek vaak moeilijk te voldoen. Gestoorde houdingsreflexen als één van de vier hoofdsymptomen lijken niet bij te dragen tot de diagnose parkinsonsime. Voor het gebruik in bevolkingsonderzoeken bevelen we dan ook de volgende diagnostische criteria voor de ziekte van Parkinson aan: van rusttremor, rigiditeit en bradykinesie dienen ten minste twee aanwezig te zijn en alle andere mogelijke oorzaken van parkinsonisme moeten zijn uitgesloten.

De frequentie (prevalentie en incidentie) van parkinsonisme en de ziekte van Parkinson wordt behandeld in **hoofdstuk 4**. Het eerste deel van dit hoofstuk (**hoofdstuk 4.1**) gaat over de prevalentie van de ziekte van Parkinson in het ERGO-onderzoek. Alle deelnemers werden onderzocht en diegenenen die verdacht werden van een mogelijk parkinsonisme nij de screening, zeiden dat ze de ziekte van Parkinson hadden of antiparkinsonmedicatie gebruikten, werden verder geëvalueerd in een tweede, diagnostische fase. De prevalentie van de ziekte van Parkinson was

in deze populatie 1.4% (1.2% voor mannen, 1.5% voor vrouwen). De prevalentie steeg met de leeftijd van 0.3% voor de leeftijdsgroep 55-65 jaar tot 4.3% voor de groep van 85 tot 95 jaar. De overeenkomstige cijfers voor mannen waren 0.4% en 3.0%, en voor vrouwen 0.2% tot 4.8%. De prevalentie onder vrouwen tussen de leeftijd van 95 en 100 jaar was 5.0%. Twaalf procent van de personen met de ziekte van Parkinson werd ontdekt dankzij de screening en was voordien niet bekend wegens de ziekte van Parkinson. Deze bevindingen stemmen overeen met de weinige onderzoeken die de zelfde methoden toepasten.

In **hoofdstuk 4.2** worden de prevalentieschattingen van parkinsonisme en de ziekte van Parkinson in vijf Europese populaties vergeleken. Deze schattingen waren verkregen uit wat methodologie betreft vergelijkbare onderzoeken. Deze 5 bevolkingsonderzoeken zijn: Gironde (Frankrijk), Rotterdam, Girona (Spanje), Pamplona (Spanje) en 8 centra in Italië. In al deze onderzoeken werd een individuele screening naar parkinsonisme verricht. In het totaal werden 14,636 deelnemers van 65 jaar en ouder gescreend. De prevalentie van parkinsonsime in deze groep was 2.3% (leeftijdsgecorrigeerd naar de Europese standaard populatie 1991) en 1.6% voor de ziekte van Parkinson. De prevalentie van parkinsonisme nam toe van 0.9% voor de personen tussen de 65 en 70 jaar tot 5.1% voor de leeftijdsgroep 85-90 jaar. Voor de ziekte van Parkinson waren deze getallen 0.6% en 3.5%. Deze schattingen waren tussen de verschillende landen statistisch niet significant verschillend wanneer werd gecorrigeerd voor leeftijd en geslacht, behalve het Franse onderzoek dat wat afweek met lagere schattingen. De prevalentie was tussen mannen en vrouwen niet verschillend. Van alle Parkinsonpatiënten was 24% nooit eerder gediagnostiseerd met de ziekte en werd dankzij de actieve screennig ontdekt. Dit percentage steeg met de leeftijd en suggereert dat de afname van de prevalentie in de hoogste leeftijdscategorieën, welke in vele eerdere onderzoeken gevonden werd, waarschijnlijk een artefakt was ten gevolge van een onderdiagnose van de ziekte in de hoogste leeftijdscategorieën. Dit maakt duidelijk dat een screening voor de ziekte van Parkinson belangrijk is, wil men tot een zo correct mogelijke prevalentieschatting komen.

In **hoofdstuk 4.3** worden gegevens uit het ERGO-onderzoek over de incidentie van parkinsonisme en de ziekte van Parkinson getoond. Incidentiecijfers van de ziekte van Parkinson zijn nauwelijks voorhanden, en de cijfers die voorhanden zijn, zijn gebaseerd op bestaande medische gegevens. Dit heeft beperkingen zoals onderschatting van de frequentie. We onderzochten het aantal incidente Parkinsonpatiënten onder de ERGO-deelnemers die tijdens het dwarsdoorsnede-onderzoek vrij bleken te zijn van parkinsonisme en/of dementie (n = 6566). Tijdens

het vervolgonderzoek van 1993 en 1994 konden 5236 deelnemers wederom gescreend worden op parkinsonisme. Van het overige deel konden we informatie via een geautomatiseerd huisartseninformatiesysteem verkrijgen. Het incidentiecijfer per 1000 persoonsjaren (pj) van parkinsonisme was 4.3 (3.4 voor mannen; 4.8 voor vrouwen) en voor de ziekte van Parkinson 2.5 (2.2 voor mannen; 2.7 voor vrouwen). De incidentiecijfers van parkinsonisme namen toe met de leeftijd, 0.5/1000 pj voor 55 tot 65 jarigen tot 14.3/1000 pj voor personen uit de leeftijdgroep 85 tot 95 jaar. Voor de ziekte van Parkinson waren deze cijfers 0.2/1000 pj en 4.2/1000 pj. Er waren geen statistisch significante verschillen tussen mannen en vrouwen. Uit ons onderzoek blijkt dat de incidentie van parkinsonisme en de ziekte van Parkinson sterk toeneemt met de leeftijd. Het patroon van de incidentie in de allerhoogste leeftijdsgroepen staat echter nog niet vast. Hiervoor zal een langere vervolg in de tijd nodig zijn.

Hoofdstuk 5 gaat over onderzoeken die alle deel uitmaakten van het ERGO-onderzoek en zich richtten op de etiologie van de ziekte van Parkinson.
In **hoofdstuk 5.1** wordt de associatie beschreven tussen het apolipoproteïne E genotype (APOE) en de ziekte van Parkinson met en zonder dementie. APOE genotypen werden bepaald in 80 parkinsonpatiënten (19 met dementie) en in 1008 willekeurig geselecteerde controlepersonen die vrij waren van dementie en parkinsonisme. Over de hele groep genomen vonden we geen associatie van APOE*4 of APOE*2 allelen met de ziekte van Parkinson. Onder de parkinsonpatiënten bleek echter dat dragers van APOE*4 (odds ratio 4.8, 95%BI 1.3-17.9) of APOE*2 (odds ratio 3.3, 95%BI 0.8-14.5) vaker dement waren dan patiënten met APOE3E3. Hieruit kan worden afgeleid dat APOE een rol speelt in de pathogenese van de dementie bij de ziekte van Parkinson.
Er is geopperd dat oxidatieve stress verband houdt met het onstaan van de ziekte van Parkinson. Hieruit kan worden afgeleid dat een hoge inname van antioxidanten de dopaminerge cellen zou kunnen beschermen tegen degeneratie. We onderzochten of personen met een hoge inname van antioxidanten via de gewone voeding minder vaak de ziekte van Parkinson hadden (**hoofdstuk 5.2**). Bij een grote groep niet-demente, zelfstandig wonende personen, inclusief 31 parkinsonpatiënten (1 tot 3 op de Hoehn & Yahr-schaal) werd een semi-quantitatieve voedingsvragenlijst afgenomen. We berekenden de odds ratios als een schatting van het relatieve risico op de ziekte van Parkinson. De odds ratio op de ziekte van Parkinson was 0.5 (95%BI 0.2-0.9) per 10 mg dagelijkse vitamine E inname; 0.6 (95%BI: 0.3-1.3) per 1 mg ß-caroteen inname; 0.9 ((95%BI: 0.4-1.9) per 100 mg vitamine C inname, en 0.9

(95%BI: 0.7-1.2) per 10 mg flavonoiden inname, alle gecorrigeerd voor leeftijd, geslacht, roken en energieinname. De associatie van vitamine E inname met de ziekte van Parkinson was dosis gerelateerd (p-trend 0.03). Nagegaan werd of deze associatie anders zou zijn bij parkinsonpatiënten met een verder gevorderd stadium van de ziekte (2.5 en 3 op Hoehn & Yahr-schaal). Na uitsluiting van deze personen waren deze associaties ongewijzigd. Deze resultaten sluiten goed aan bij de hypothese dat een hoge vitamine E inname via de voeding zou kunnen beschermen tegen het ontstaan van de ziekte van Parkinson.

In **hoofdstuk 5.3** worden de resultaten getoond van een prospectief onderzoek naar het risico op de ziekte van Parkinson onder niet-rokers in vergelijking met rokers. De meeste onderzoeken die deze associatie onderzochten waren retrospectieve of dwarsdoorsnede-onderzoeken en daardoor gevoelig voor meedere vormen van bias. Tot nu toe bestaan er geen prospectieve onderzoeken naar roken en het risico op de ziekte van Parkinson welke in een algemene oudere bevolking werden uitgevoerd. Het cohort bestond uit alle ERGO-deelnemers die tijdens het dwarssnede-onderzoek geen dementie en parkinsonisme hadden en van wie informatie over de rookgewoonten aanwezig was (n= 6442). Na een periode van gemiddeld 2.12 jaar werden de deelnemers nogmaals gescreend op de ziekte van Parkinson. De leeftijd- en geslacht-gecorrigeerde relative risico's (RR) op de ziekte van Parkinson werden berekend voor rokers in vergelijking met niet-rokers. Vierendertig personen bleken incident de ziekte van Parkinson te hebben. Het risico op de ziekte was onder rokers sterk verminderd, een RR van 0.37 (95%BI: 0.15-0.89). De inverse associatie van roken met de ziekte van Parkinson was dosis-afhankelijk. Dit onderzoek bevestigt de inverse associatie van roken met de ziekte van Parkinson en zou tot nieuwe inzichten kunnen leiden wat betreft de etiologie van de ziekte van Parkinson. Vervolgens wordt in dit hoofdstuk geschetst via welke mogelijke mechanismen de protectieve werking van roken zou kunnen verlopen.

In **hoofdstuk 5.4** richtten we ons op de genetica en de ziekte van Parkinson. Sinds lange tijd bestaat het vermoeden dat genetische factoren een belangrijke rol spelen in het ontstaan van de ziekte van Parkinson. Alle onderzoeken die de associatie onderzochten tussen de ziekte van Parkinson en een positieve familiegeschiedenis hiervoor waren retrospectief en gebaseerd op ziekenhuispopulaties. Wij vergeleken het RR op de ziekte van Parkinson onder personen met en zonder een positieve familiegeschiedenis voor de ziekte van Parkinson en/of dementie (1ste graads familieleden). Personen met een tenminste een familielid met de ziekte van Parkinson hadden een meer dan tweevoudig toegenomen risico op de ziekte maar dit was statistisch niet significant (RR 2.5, 95%BI: 0.8-8.4). Personen met tenminste twee

familieleden aangedaan door de ziekte van Parkinson hadden een 9-keer verhoogde kans op de ziekte (9.3, 95%BI: 1.3-68.2). Het risico op de ziekte was ietwat hoger voor hen met tenminste één familielid met dementie (RR 1.8, 95%BI: 0.9-3.7), en het RR voor hen met tenminste twee demente familieleden was 2.4 (95%BI: 0.6-10.2). Deze resultaten suggereren dat genetische factoren inderdaad betrokken kunnen zijn bij het ontstaan van de ziekte van Parkinson en dat een verdere zoektocht naar kandidatgenen haar vruchten zou kunnen afwerpen.

In **Hoofdstuk 6** worden de verschillende aspecten van dit proefschrift besproken, zoals onderzoeksopzet en methodologie, diagnosis, en de implicaties van de resultaten die in dit proefschrift gepresenteerd worden. Een belangrijk kenmerk van alle onderzoeken in dit proefschrift is dat ze alle bevokingsonderzoeken zijn die gebruik maakten van een individuele screening voor de ziekte van Parkinson. Hierdoor konden nieuwe patiënten, die nog niet waren gediagnostiseerd, worden geïdentificeerd en kon een ongeselecteerde patiëntenpopulatie worden verkregen. Het Rotterdamse ERGO-onderzoek bied een uniek kans om zo'n patiëntengroep gedurende meerdere jaren te volgen voor prognostische factoren en eindpunten. Tenslotte worden aanbevelingen gedaan voor onderzoeken die een uitbreiding zouden kunnen zijn op het werk dat in dit proefschrift is beschreven.

Epilogue

Nawoord

About the author

Epilogue

Na ontelbare uren knoppenbonken, na honderden brieven verstuurd te hebben, na enkele bomen door de printer te hebben gedraaid (gewoon superwit papier), na in afstand meer dan 4 maal de aarde zijn rond getreind, na heel wat liters cafeïnehoudende dranken te hebben genuttigd is het zover: het "boekje" is af! En dat het gebeurd is, is een verdienste van velen die ik niet allemaal persoonlijk zal noemen.

Professor Hofman echter, mijn eerste promotor, mag natuurlijk niet onvermeld blijven. Zonder Bert geen ERGO, en zonder ERGO niet dit boekje. Beste Bert, zo simpel ligt het gelukkig niet en dat weet je. Ik heb het erg op prijs gesteld dat je me de ruimte liet af en toe een eigen richting aan het onderzoek te geven maar me ook op tijd bijstuurde.
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Beste Monique, het doet me een genoegen jou als co-promotor in de promotiecommissie te hebben. Je concrete en goede methodologische aanpak en je vindingrijkheid op o.a. tekstueel gebied hebben voor een aanzienlijk deel de vorm van de artikelen bepaald die we gezamelijk hebben geschreven. Dat we niet altijd op dezelfde lijn zaten, heeft het er alleen maar op verbeterd en ik hoop dan ook dat de samenwerking zal worden voortgezet.

De velen in het eerste uur (o.a. René Vermeeren, Michael Koenders, Ada Hooghart, Coby van den Heuvel, Anneke Korving), het complete ERGO-team, het Lab (Ton de Bruijn c.s.), Secretariaat (Paula, Nicky, Margaret, Andrea), Yolanda, Peter (waar is toch die goede oude "boerlageer"tijd?), de Jongens van de Automatisering en de Ommoordse huisartsen ben ik veel dank verschuldigd. Gerda Graveland heeft mij met veel enthousiasme de klinische beginselen van de ziekte van Parkinson bijgebracht en was altijd bereid af te reizen naar Ommood voor een second opinion.

I also want to express my gratitude to my colleagues from abroad. Dear EUROPARKINSON-collaborators, dear Annick and Christophe, I will remember the colloboration and the joint meetings as very usefull and pleasant. For this I am very grateful. I highly appreciate the collaboration with Walter Rocca. Dear Walter, thank you very much for the hospitality of you and your family during my stay at Mayo Clinic. I am very glad that you accepted to be a member of my PhD-committee. Through Walter I was so fortunate to got to know Dallas Anderson and Jim Maraganore. Dallas, thank you for your great help in writing our joint paper, together with Jim and Walter, and for being a walking encyclopedia. Dear Juan Pablo Alonso, finally the joint paper is finished, time to discuss other things.

Ik zal mijn collega-ERGO-onderzoekers, het theeklessebesse met Dorothée en Sandra, de verhandelingen over het steenketsen met Carl en Paul en de rust en hulp van Alewijn missen. Bedankt voor alle dingen die jullie voor mij gedaan hebben.
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About the author

Maarten de Rijk was born March 3, 1965, in Helmond, and grew up in Aarle-Rixtel. After he graduated from secondary school in 1983 *(Atheneum B, Dr Knippenbergcollege, Helmond)*, he started his medical studies at Gent University, Belgium. In 1986 he obtained his candidate degree in Medicine and he continued his study at the Medical School of Erasmus University Rotterdam. During his studies in Rotterdam, he did research electives in the laboratory of Dr M. Godschalk (Dept. of Anatomy) and at the department of Neurology (Dr C.A. van Donselaar), and internships at the University Hospitals of Gent, Belgium, and of Oulo, Finland. He was a student member of the Internationalizing Working group of Erasmus University Medical School. In 1991 he spent 4 months in the U.S. as an exchange student to work at the Maryland Psychiatric Research Center (Dr R.C. Roberts), University of Maryland Medical School, Baltimore on a neuropathologic study on schizophrenia. After he came back, he graduated from Medical School and had to fulfill his military service. During this period, that lasted till the beginning of 1993, he was a naval medical officer of the operational units of the Royal Netherlands Marines Corps. Immediately afterwards, the work on this thesis was initiated at the Department of Epidemiology & Biostatistics (Head: Prof. A. Hofman). He received his Master of Science of Clinical Epidemiology degree in 1996. April 1, 1997, he started his residency in Neurology at University Hospital Rotterdam (Head: Prof van der Meché). He is currently working at Merwede Hospital Dordrecht (Head: Dr R.P. Kleyweg).