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Parkinson's Disease Case Ascertainment in the EPIC Cohort: The NeuroEPIC4PD Study

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Key Words

Parkinson's disease · Cohort study · Case ascertainment · Record linkage · Validation · EPIC study · Incidence

Abstract

Background/Aims: Large epidemiological prospective studies represent an important opportunity for investigating risk factors for rare diseases such as Parkinson's disease (PD). Here we describe the procedures we used for ascertaining PD cases in the EPIC (European Prospective Investigation into Cancer and Nutrition) study. ***Methods:*** The following three-phase procedure was used: (1) elaboration of a NeuroEPIC4PD template for clinical data collection, (2) identification of all potential PD cases via record linkage and (3) validation of the diagnosis through clinical record revision, in a population of 220,494 subjects recruited in 7 European countries. All cases were labelled with the NeuroEPIC4PD diagnoses of 'definite',

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'very likely', 'probable', or 'possible' PD. ***Results:*** A total of 881 PD cases were identified, with over 2,741,780 person-years of follow-up (199 definite, 275 very likely, 146 probable, and 261 possible). Of these, 734 were incident cases. The mean age at diagnosis was 67.9 years (SD 9.2) and 458 patients (52.0%) were men. Bradykinesia was the most frequent presenting motor sign (76.5%). Tremor-dominant and akinetic rigid forms of PD were the most common types of PD. A total of 289 patients (32.8%) were dead at the time of the last follow-up. ***Conclusions:*** This exercise proved that it is feasible to ascertain PD in large population-based cohort studies and offers a potential framework to be replicated in similar studies.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. PD is characterised by motor dysfunction such as bradykinesia, resting tremor, rigidity, and postural instability but also affects the autonomic nervous system, cognition and a range of other non-motor functions [1]. The incidence of the disease rises with age, peaking at 119.5 per 100,000 person-years in the seventh decade, with a lifetime risk of developing the disease of 1.5–3% [2–5]. The median age of onset is in the late 1960s [4–6] and the mean duration of the disease from diagnosis to death is 15 years [3]. Because of the ageing pattern of Western populations, an increase in incidence can be anticipated.

Large established prospective population studies offer an important opportunity for investigating the role of risk factors in rarer diseases such as PD, with relatively small additional effort for ascertaining cases. In particular, data coming from such studies can shed light on the potential mechanisms of action of factors known to be negatively associated with PD (cigarette smoking) using modern advanced epidemiological techniques (such as Mendelian randomisation). To date PD has been investigated in relatively small cohorts [7–17] (with the numbers of PD cases ranging from 41 [15] to 656 [16]) or using self-reported diagnosis only [17]. Cohort studies with large sample sizes and well-characterised and validated case definitions have a high degree of power for detecting weak associations with environmental factors.

The aim of this study was to describe the procedures used to ascertain PD cases in the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort in order to enable investigators to prospectively assess the association between prediagnostic risk factors and the incidence of the disease – the NeuroEPIC4PD study. The methods used in this study are expected to be generalisable to other cohorts.

Materials and Methods

The EPIC Study

The EPIC study is a large, well-established, multicentre cohort study ongoing in 10 Western European countries [18]. At baseline, information on lifestyle (education, occupation, lifetime tobacco and alcohol consumption, physical activity, oral contraceptive, and hormone replacement therapy), menstrual and reproductive history and past medical history was collected through a questionnaire. Anthropometric assessments and blood pressure were measured in a standardised way [18]. Dietary intake was assessed through self-administered quantitative dietary questionnaires and a 24-hour dietary recall questionnaire [19]. EPIC was originally designed to investigate the role of nutrition in cancer aetiology but it has also demonstrated its value for investigating other medical conditions such as cardiovascular diseases [20] and diabetes [21].

The NeuroEPIC4PD Population

The NeuroEPIC4PD study is based on a source population of 220,494 subjects recruited in Sweden (Umeå and Malmo), the UK (Cambridge), the Netherlands (Utrecht), Germany (Heidelberg), Spain (Navarra, San Sebastian and Murcia), Italy (Turin, Varese, Florence, and Naples), and Greece from the general population residing in defined geographical areas between 1992 and 2002 within the EPIC study [18]. An exception was the Utrecht PROSPECT cohort which was based on breast cancer screening participants [18]. The Naples and Utrecht PROSPECT cohorts were restricted to women, whereas all other cohorts included both sexes. In EPIC, follow-up for mortality and specific causes of death is carried out actively or through linkage with mortality registries at regional and national levels [18]. To date, follow-up is 98.5% complete.

Expected PD Cases

Numbers of expected PD cases were calculated in order to compare completeness of procedures used in different centres and to estimate the workload of phase III in each centre. They were estimated applying sex- and age-specific incidence rates coming from weighted averages of population-based studies investigating PD incidence [4, 22–27]. Sex- and age-specific cumulative incidence rates were calculated over the sex- and centre-specific follow-up periods in each EPIC subcohort, resulting in estimates of expected cases during the current follow-up.

Case Ascertainment Methods

Case ascertainment was organised in three phases. In phase I the NeuroEPIC4PD template for clinical data collection – including the NeuroEPIC4PD label to be attached to each diagnosis – was elaborated by a group of experienced neurologists and epidemiologists. During phase II, each centre identified *potential cases* through record linkage with one or more local sources of information. Clinical records of potential cases were then reviewed by experts in movement disorders and given a final diagnosis with a NeuroEPIC4PD label during phase III (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000381857). The three phases will be described in more detail below.

Phase I: NeuroEPIC4PD Template for Clinical Data Collection

The first NeuroEPIC meeting took place on November 29, 2010. During the meeting the strategy for PD case ascertainment was discussed in detail by a group of neurologists and epidemiologists. The final outcome was the elaboration of the template for clinical data collection (online suppl. appendix 1) and the definition of the NeuroEPIC4PD label to be given to every case ascertained in EPIC. The template included sections on general information, diagnostic criteria according to the UK Brain Bank [28], additional clinical data, medication, surgical treatment, autopsy, source of information, quality of data, and final diagnosis. Possible final diagnoses included PD, multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism, dementia with Lewy bodies, essential tremor, PD with essential tremor, unclassifiable parkinsonism (UP), and other diagnosis.

Each diagnosis was labelled with a NeuroEPIC4PD label, which was based on a matrix combining the following two variables: (1) the amount and quality of data available and (2) the degree of confidence of the neurologist expert in movement disorders reviewing the evidence (online suppl. fig. 2 and appendix 1). The amount and quality of data available could be rated as 'poor', 'good' or 'excellent', where 'excellent data' was defined as a complete set of clinical data able to give a clear picture of the case (including detailed neurological examinations) with scattered non-essential missing information, 'good data' was defined as a set of data giving a fairly complete idea of the case with scattered essential information missing and 'poor data' was defined as an incomplete set of data, with much essential information missing. The degree of confidence of the neurologist could be rated as 'high', 'medium' or 'low' on the basis of his/her final judgement of the clinical history of the single case. It was stated very clearly that this judgement was independent of the amount of information available (a neurologist could have a high degree of confidence despite very poor information or a low degree of confidence despite very detailed information). Diagnoses were defined as 'definite' only when the degree of confidence of the neurologist was high and data quality excellent, as 'very likely' when the degree of confidence of the neurologist was high but data quality was either good or poor and as 'probable' when the degree of confidence of the neurologist was medium and data quality was either excellent or good; finally, diagnoses were defined as 'possible' in all remaining cases.

Phase II: Identification of Potential PD Cases

Potential PD cases were identified by centre-specific strategies in order to optimise local sources of data. The general principle was to increase sensitivity as much as possible in order to minimise the number of false negatives, given that the subsequent clinical record review would maximise specificity. In addition, patterns of possible referral pathways for PD cases in each centre were collected in order to evaluate the adequacy of the sources of information used. Specific sources of information by centre used in phase II are shown in online supplementary figure 1; details of the procedures can be found in online supplementary appendix 2.

Phase III: Case Validation and Collection of Additional Clinical Data

For all potential cases identified in phase II, clinical records were searched for and reviewed by a neurologist expert in movement disorders. For each subject for whom at least some information was available, a clinical data form was filled in (online suppl. appendix 1). Each potential case was then attached a final diagnosis (PD, multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism, dementia with Lewy bodies, essential tremor, PD with essential tremor, unclassifiable parkinsonism, and other diagnosis) and labelled with a NeuroEPIC4PD label (online suppl. fig. 2).

Results

The source population used for the NeuroEPIC4PD study included 220,494 subjects recruited in 13 EPIC centres across 7 European countries (online suppl. table 1). The mean age of the population at recruitment was 53.1 years (SD 10.0). The recruitment framework oversampled women by design, resulting in a total of 83,320 (37.8%) men recruited, with the exception of Utrecht and Naples, which recruited women only. The entire population was followed up for a mean of 12.4 years (SD 2.8), generating a total 2,741,780 person-years. Of the entire cohort, 19,473 subjects (8.8%) died according to the updated vital status by the last follow-up visit.

Applying the sex- and age-specific incidence rates of PD derived from population-based studies, a total of 309 PD cases were expected over the current follow-up period. These were distributed according to figures shown in table 1.

Phase II: Identification of Potential PD Cases

A total of 1,723 potential PD cases were identified across all centres (online suppl. fig. 3 and table 1). Overall potential cases were about 5.6 times more than expected cases. In Utrecht and Varese potential cases were very close to expected. In Murcia and Turin potential cases were more than 10 times higher than expected, while in the remaining centres they were between about 250 and 650%, with the exception of Cambridge where they were 800%. Differences are likely to be due to differences in sources of information used by the centres.

Phase III: Case Validation and Collection of Additional Clinical Data

Additional clinical information was collected using the NeuroEPIC4PD template in 1,336 out of 1,723 potential cases (77.5%). Few centres (Umeå, Navarra, Murcia, Varese, Naples, and Greece) were able to verify all potential cases; other centres (Malmo, San Sebastian and Florence) could verify the great majority of potential cases (87.7–98.0%) and others (Utrecht, Cambridge, Heidelberg, and Turin) only a smaller proportion of potential

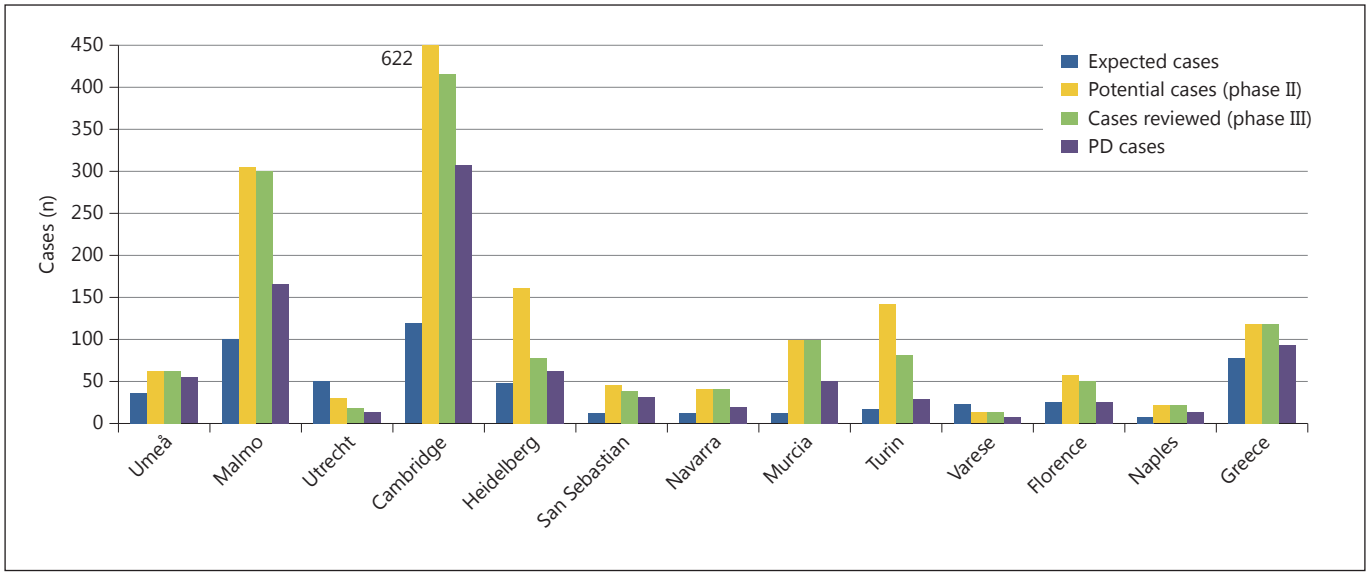

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Fig. 1. Number of expected PD cases, potential cases, cases reviewed in phase II, and ascertained PD cases by centre in the NeuroEPIC4PD study.

Table 1. Total population, expected PD cases, potential PD cases, and final diagnoses of the subjects recruited in the centres participating in the NeuroEPIC4PD study

Centre	Population	Expected PD cases	Potential cases (phase II)	Cases reviewed in phase III	Incident PD	Prevalent PD	Total PD	Parkinsonian-related disorders	Other diseases
Umeå (SE)	25,717	23	62	62 (100.0)	55	1	56	6	0
Malmo (SE)	28,097	63	305	299 (98.0)	140	17	166[a]	79	54
Utrecht (NL)	17,031	27	31	17 (54.8)	13	1	14	3	0
Cambridge (UK)	30,440	75	622	416 (66.9)	213	70	307[a]	18	91
Heidelberg (DE)	25,538	25	162	77 (47.5)	50	12	62	12	3
San Sebastian (ES)	8,417	8	46	39 (84.8)	31	1	32	6	1
Navarra (ES)	8,084	8	41	41 (100.0)	18	3	21	13	7
Murcia (ES)	8,516	7	99	99 (100.0)	52	1	53	24	22
Turin (IT)	10,587	10	143	81 (56.6)	28	1	29	44	8
Varese (IT)	11,896	11	13	13 (100.0)	3	3	7[a]	6	0
Florence (IT)	13,596	13	57	50 (87.7)	23	3	26	3	21
Naples (IT)	5,061	4	22	22 (100.0)	13	0	13	0	9
Greece (GR)	27,514	35	120	120 (100.0)	95	0	95	16	9
Total	220,494	309	1,723	1,336	734	113	881	230	225

Cases reviewed in phase III: values in parentheses indicate % of potential.
[a] Incident and prevalent PD cases do not total all PD cases, as there are missing data on date of diagnosis.

cases (47.5–66.9%; table 1; fig. 1). The variation in these proportions is mainly due to the ability of retrieving clinical records of potential cases and to the extent to which the criteria used in phase II had a high sensitivity (including a higher proportion of false-positive cases who would not have a clinical record for PD, artificially inflating the number of potential cases).

On the basis of the clinical information available, 881 PD cases (65.9%), 230 parkinsonian-related disorders (17.2%) and 225 unrelated conditions (16.8%) were identi-

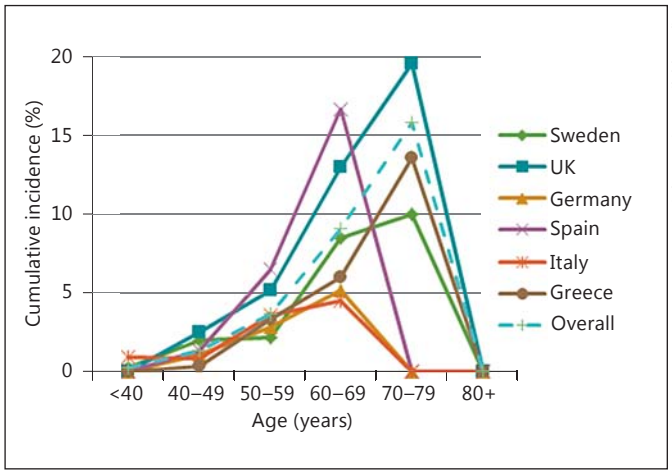

Fig. 2. Age-specific cumulative incidence of PD by country, in men.

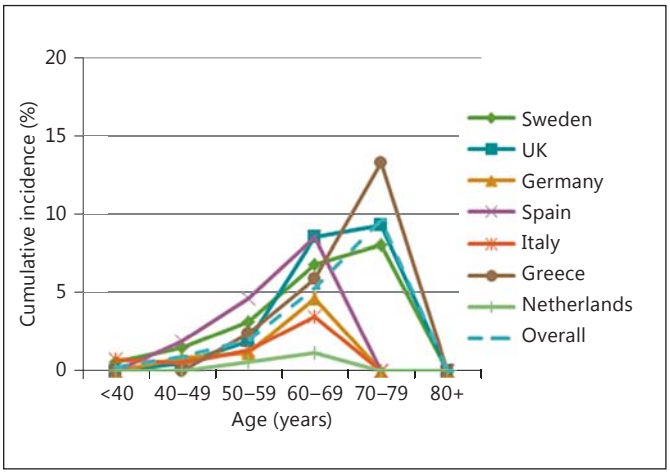

Fig. 3. Age-specific cumulative incidence of PD by country, in women (y-axis is deliberately on the same scale as in figure 2 for facilitating comparison).

fied (table 1). Cases who received a diagnosis after the date of recruitment were defined as *incident cases* (n = 734). Out of the 881 PD cases, 199 were labelled as definite PD cases (22.6%), 275 as very likely (31.2%), 146 as probable (29.6%), and 261 as possible (29.6%). Among the parkinsonian-related disorders, those identified were 26 multiple system atrophy, 22 progressive supranuclear palsy, 34 vascular parkinsonism, 34 dementia with Lewy bodies, 30 essential tremor, and 9 PD with essential tremor. Additionally, 75 cases (5.6% of the total) were defined as having unclassifiable parkinsonism (online suppl. table 2).

PD cases are more than double those originally expected. All centres ascertained more than the expected number of cases, apart from Utrecht and Varese where about half of expected cases were ascertained. For all other centres, proportions range from 200% in Florence to 757% in Murcia (table 1; fig. 1). In each country, the shape of the age- and sex-specific cumulative incidence peaks at 70–79 years, with the exception of Spain and Germany where it peaks at 60–69 years in both men and women (fig. 2, 3). Apart from the Netherlands, differences between observed and expected curves are mainly due to age truncation of the cohorts. In fact in all countries, the incidence rates at older ages are much lower than expected but this may simply reflect the age composition of the EPIC cohort (online suppl. table 1).

General and clinical characteristics of PD patients are described in table 2. Despite women outnumbering men in this study, there is a slight predominance of men among PD patients, except for the definite PD category. Individuals with PD were recruited when they were on average 61.9 years of age (SD 8.2). They noticed their first motor symptoms at a mean age of 66.8 years (SD 8.3) and were diagnosed on average 1 year later, i.e. at 67.9 years (SD 9.2). Relaxing the criteria of certainty of the diagnosis, the gap between the first motor symptom and diagnosis shortens. Bradykinesia is the most frequent cardinal sign (present in 76.5% of all PD patients). The prevalence of bradykinesia, resting tremor and rigidity increases the certainty of the diagnosis. This is not observable for postural instability, which remains roughly constant across categories and slightly more frequent among probable cases (table 2). Tremor-dominant and akinetic rigid forms are the most common types of PD across all NeuroEPIC4PD labels and their relative difference decreases, decreasing the certainty of the diagnosis (online suppl. fig. 4). Levodopa and dopamine agonists are the most common drugs taken by these PD patients and all drugs are proportionally taken more frequently by patients with a more certain diagnosis. A total of 16 PD patients had surgical treatment with deep brain stimulation. A total of 289 (32.8% of the entire sample) were dead at the time of the last follow-up within the NeuroEPIC4PD study (table 2).

Discussion

This exercise proved that it is feasible to ascertain PD cases in large population-based multicentre studies. By maximising the local expertise and sources of informa-

Table 2. General and clinical characteristics of the PD cases, using the NeuroEPIC4PD labels

	Definite PD	Very likely PD	Probable PD	Possible PD	All PD
Subjects	199	275	146	261	881
Male	77 (38.7)	164 (59.6)	73 (50.0)	144 (55.2)	458 (52.0)
Mean age at recruitment, years	59.1±8.4	61.5±8.0	61.6±6.6	64.8±8.1	61.9±8.2
Mean age at symptom onset, years	64.9±8.1	65.4±9.4	69.0±7.1	71.0±8.1	66.8±8.3
Mean age at diagnosis, years	65.7±7.8	66.2±10.2	69.3±7.5	71.0±9.2	67.9±9.2
Cardinal signs[a]					
Resting tremor	151 (75.9)	121 (63.0)	91 (62.3)	29 (24.8)	392 (59.9)
Bradykinesia	192 (96.5)	147 (76.6)	118 (80.8)	43 (36.8)	500 (76.5)
Rigidity	191 (96.0)	132 (68.8)	114 (78.1)	42 (35.9)	479 (73.2)
Postural instability	33 (16.6)	31 (16.2)	31 (21.2)	19 (16.2)	114 (17.4)
Treatment					
Dopamine receptor agonists	133 (66.8)	128 (46.5)	67 (45.9)	42 (16.1)	370 (42.0)
Levodopa	177 (88.9)	163 (59.3)	114 (78.1)	79 (30.3)	533 (60.5)
COMT inhibitors	85 (42.7)	84 (30.5)	35 (24.0)	25 (9.6)	229 (26.0)
MAO-B inhibitors	61 (30.7)	65 (23.6)	36 (24.7)	24 (9.2)	186 (21.1)
Amantadine	16 (8.0)	16 (5.8)	8 (5.5)	5 (1.9)	45 (5.1)
Antimuscarinic	2 (1.0)	5 (1.8)	0 (0.0)	5 (1.9)	12 (1.4)
DBS-STN	9 (4.5)	3 (1.1)	1 (0.9)	0 (0.0)	13 (0.3)
DBS-VIM	1 (0.5)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.2)
DBS-GP	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Death	16 (8.0)	99 (36.0)	46 (31.5)	128 (49.0)	289 (32.8)

Values in parentheses are percentages. [a] Coded as cardinal sign, i.e. symptom recorded during the first 3 years of disease. PIGD = Postural instability/gait disturbance; DBS = deep brain stimulation; STN = substantia nigra; VIM = ventral intermediate nucleus of the thalamus; GP = globus pallidus.

tion, and through involving epidemiologists and neurologists in the project, we were able to ascertain a considerable number of cases labelled with a different degree of certainty, which will allow us to exploit the invaluable resource of a prospective study in investigating risk factors for this relatively rare neurodegenerative disorder.

Using a three-phase approach, we were able to optimise our search by maximising sensitivity in phase II (thus minimising the false-negative rate) and specificity in phase III (therefore minimising the false-positive rate). The only limit to this approach remains the proportion of potential cases which could not be ascertained, thus introducing potential false negatives in our sample. However, in the present case this proportion was low and only seen in a few centres for practical reasons (Utrecht and Heidelberg). In Cambridge and Turin this is more likely due to having relaxed criteria for identifying potential cases in phase II; in fact in both centres, the number of ascertained cases is well above the number of expected cases (fig. 1). Also, it is important to note that in the context of studying a rare disease in a large cohort study it is of greater relevance to minimise false-positive diagnoses which may bias results towards the null than to minimise false negatives which will be diluted in a very large set of non-cases, making their impact negligible.

The finding of a higher number of cases than expected may be due to two reasons. Firstly, expected cases were calculated for the follow-up period for which data had been centralised in EPIC, while in each centre, case ascertainment was conducted for a longer period of follow-up, counting the follow-up time which was available locally. Secondly, we expect more cases according to the healthy cohort effect, given that cigarette smoking is inversely associated with PD [29]. If fewer smokers than in the general population enrol in epidemiological studies (as occurred in EPIC), this would lead to a lower than expected number of smoking-related diseases but to a higher number of PD cases.

Finally, the large differences between potential and ascertained cases reflect the different methods used in phase I. When more specific methods were used (Umeå, Heidelberg and Greece), it was more likely that a potential case was a true case. Overall, the plots of age-specific incident rates by country confirm that the procedures used

were appropriate for the population observed and that the quality of our case ascertainment procedures was quite high. Moreover, the NeuroEPIC4PD label is able to effectively discriminate between a high and low certainty of diagnosis. The NeuroEPIC4PD labelling was studied in order to optimise the trade-off between power and specificity. By including possible cases, the power for detecting associations with potential risk/protective factors is maximised; the presence of the label, however, allows sensitivity analyses only in those cases with a higher degree of certainty.

Clinical characteristics of PD cases using the NeuroEPIC4PD label reflect the fact that the label is also calculated on the basis of the amount and quality of data available. The crude mortality among PD cases is higher than in the rest of the population, apart from the definite PD. Age at diagnosis seems to be inversely correlated with degree of certainty of diagnosis. This may reflect reduced specificity of symptoms such as bradykinesia, rigidity and postural instability, which are more common (less sensitive) and multifactorial in origin (arthritis, cerebrovascular diseases, etc.), especially in the aged.

The results of this exercise are expected to inform case ascertainment of PD in other cohort studies. As can easily be deduced by the complexity and heterogeneity of the procedures used, maximising the local resources and sources of information is of paramount importance in this exercise. The epidemiological effort is to harmonise data coming from such different sources and to build a method which allows for the trade-off between power and specificity that studies of this nature encounter.

This type of study should coordinate closely with other population-based PD cohort studies such as the CamPaIGN study [30]. These can potentially produce complementary information for investigating the complex interactions of risk factors underlying PD. While cohort studies can shed light on the role of potential risk factors (and molecular markers) in developing PD, the patient cohorts can investigate the role of the same risk factors (and the same biological markers) in PD survival, complementing the causal inference process.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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