REVIEW

The Prevalence of Parkinson's Disease: A Systematic Review and Meta-analysis

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ABSTRACT: Parkinson's Disease (PD) is a common neurodegenerative disorder. We sought to synthesize studies on the prevalence of PD to obtain an overall view of how the prevalence of this disease varies by age, by sex, and by geographic location. We searched MEDLINE and EMBASE for epidemiological studies of PD from 1985 to 2010. Data were analyzed by age group, geographic location, and sex. Geographic location was stratified by the following groups: 1) Asia, 2) Africa, 3) South America, and 4) Europe/North America/ Australia. Meta-regression was used to determine whether a significant difference was present between groups. Forty-seven studies were included in the analysis. Meta-analysis of the worldwide data showed a rising prevalence of PD with age (all per 100,000): 41 in 40 to 49 years; 107 in 50 to 59 years; 173 in 55 to 64 years;

428 in 60 to 69 years; 425 in 65 to 74 years; 1087 in 70 to 79 years; and 1903 in older than age 80. A significant difference was seen in prevalence by geographic location only for individuals 70 to 79 years old, with a prevalence of 1,601 in individuals from North America, Europe, and Australia, compared with 646 in individuals from Asia (P < 0.05). A significant difference in prevalence by sex was found only for individuals 50 to 59 years old, with a prevalence of 41 in females and 134 in males (P < 0.05). PD prevalence increases steadily with age. Some differences in prevalence by geographic location and sex can be detected. © 2014 International Parkinson and Movement Disorder Society

Key Words: prevalence studies; risk factors in epidemiology; Parkinson's disease/Parkinsonism

Parkinson's disease (PD) is among the most prevalent neurodegenerative conditions. Although its cause remains unknown, many investigators believe that the disease arises from an interaction between genetic and environmental factors that leads to progressive degeneration of neurons in susceptible regions of the brain. Despite decades of investigations, the identity of most

of these factors, the nature of their interaction, and the molecular pathways of neurodegeneration that they initiate remain poorly understood.

Epidemiological data regarding the prevalence of PD are of interest for their potential to identify risk factors and improve understanding of the condition's natural history. Increasingly, these data have also been used to guide effective planning of medical services. Most economically developed and many developing countries are experiencing marked demographic shifts, with progressively larger proportions of their populations entering old age. Because PD affects predominantly older persons, many countries around the world are facing a future of unsustainable demands on limited healthcare resources.

One of the great challenges in studying the epidemiology of PD is that prevalence estimates for the condition have varied widely across studies and countries. Environmental and genetic factors are routinely

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proposed to explain the observed variability, but these likely only capture a portion of the variance. The variable demographics of the populations studied and the marked differences in the methodologies of the studies have likely had a profound effect on outcomes. For example, studies that have relied on medical records to generate an estimate of prevalence exclude from their estimates individuals who have not been seen by physicians for their condition, and individuals who have been seen by physicians but were misdiagnosed as not having the condition. Those studies that have relied on the analysis of drug consumption data in a given region can be confounded by numerous other factors, including culturally determined treatment practices, and variable access to reimbursement for medications that vary by country and region.²

In theory, case ascertainment through door-to-door or population-based random sampling offers a more robust alternative. The latter approaches have the advantage of including those patients who have not sought medical attention and those who have not had adequate access to medical care, and should in theory be more suitable for international comparisons. These approaches, however, are expensive, and in some instances may be impractical because of legislative restrictions on the use of personal data.³

This systematic review examines the prevalence of PD worldwide with a meta-analysis of published, door-to-door or population-based random sampling assessments of the condition. The study took place as part of a larger effort initiated by the Public Health Agency of Canada to determine the incidence and prevalence of 15 neurological diseases.

Methods

Selection of Studies

Search strategies for studies on the prevalence of PD were developed in consultation with an academic research librarian with expertise in systematic review. Studies on the incidence of PD are discussed in a separate manuscript.

Both MEDLINE and EMBASE databases were searched using terms specific to PD, and restricted to studies of prevalence and epidemiology (see Supplemental Data Appendix e-1). The sensitivity of the electronic search was checked by comparing relevant references found in the bibliographies of the identified articles against those contained in the database. All studies published in English or French were included. Two independent reviewers screened abstracts to determine whether a full text review should be performed. All studies of door-to-door surveys or random population samples with a physical examination by a health professional to confirm or exclude a diagnosis of PD were included.

We established a date limit of 1985 for study inclusion, because before this date magnetic resonance imaging, which has revolutionized the diagnosis of many neurological disorders, was not in routine clinical use. Our study was part of a larger effort to determine the prevalence of 15 neurological disorders in which magnetic resonance imaging plays a greater diagnostic role than in PD, and our choice of date limit also ensured consistency with the broader research initiative within which we were operating. Review articles or papers using nonoriginal data were also excluded, but their bibliographies were reviewed to ensure additional articles were not missed. In cases in which studies reported duplicate data, the study reporting the most up-to-date and complete data set was included.

Data Extraction

Data extraction was performed in duplicate using a standardized assessment form that included the following domains: Study reference, screening procedure, diagnostic criteria, exclusion criteria, number of PD cases used to estimate prevalence, results, study design, screening personnel, target population. Crude prevalence was reported as cases per 100,000 persons for each study. Breakdown of prevalence by sociodemographic categories (e.g., age, sex) was recorded if given. All data were independently assessed by two reviewers, and the extracted data were entered into evidence tables. If the results of the data extraction differed between the two reviewers, a third reviewer re-assessed the relevant study. Any differences among results were then discussed among the reviewers until consensus could be achieved.

Quality Assessment

A quality assessment was performed for each study based on criteria developed from guidelines on the evaluation of prevalence studies. 4,5 Studies were given a score of 0 to 8 based on the degree to which they fulfilled 8 criteria relating to the rigor of the clinical assessment, the quality of the statistical analysis, and the extent to which the sample population represented the population at large (see Supplemental Data Appendix e-2 for quality criteria).

Data Synthesis

The Cochrane Q statistic was calculated and I² used to quantify the amount of between-study heterogeneity. When significant heterogeneity was absent, the pooled prevalence per 100,000 people and 95% confidence intervals were calculated using a fixed-effects model. When significant heterogeneity was present, a random-effects model was used. With a fixed-effect model, the studies are weighted using the inverse of the variance (larger studies receive more weight), and

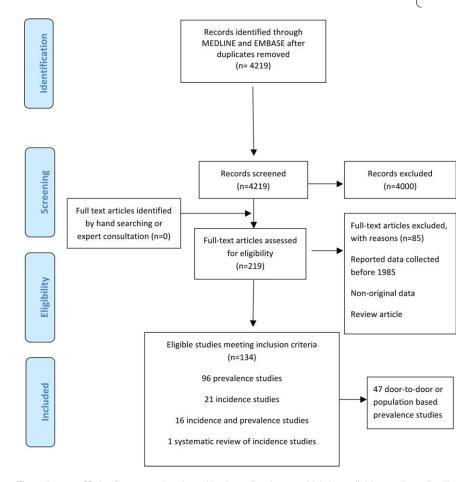


FIG. 1. Flow diagram. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

with a random-effects model the inverse variance is corrected by a measure of between-study variation (tau-squared), thus reducing the effects of sample size. Because prevalence is a proportion, study estimates were combined using a log transformation to help normalize the data. Data were analyzed by age group, geographic location, and sex. Geographic location was stratified by the following groups: 1) Asia, 2) Africa, 3) South America, and 4) Europe/North America/Australia. Studies from Europe, North America, and Australia were combined into a single geographic group because of the overall small number of studies performed in each of these locations, and the predominantly white population in each region. Metaregression was used to determine whether a significant difference was present between groups. A sensitivity analysis of the data was performed by study quality; studies receiving a quality score of 7 or higher were combined using meta-analysis and compared with studies with a quality score lower than 7 to determine whether significant differences were present based on quality.

For all tests, P < 0.05 was deemed significant. All statistical analyses were carried out in R version 2.14.⁶ The meta package was used to produce the pooled estimates and forest plots.⁷ The metafor pack-

age was used to conduct the meta-regression, using restricted maximum likelihood estimation.⁸

Results

The combined MEDLINE and EMBASE searches (conducted in December 2010) yielded 4,219 abstracts (see Fig. 1, Prisma Flow Diagram). Two hundred nineteen full-text articles were reviewed. We identified 112 studies on the prevalence of PD, with 47 of these studies using a door-to-door survey or random population sample that included a physical examination by a health professional to confirm or exclude a diagnosis of PD.

Of the 47 included studies, 21 were performed in Asia, 9-29 11 in Europe, 1,30-39 5 in Africa, 40-44 4 in Australia, 45-48 4 in South America, 49-52 and 2 in North America 53,54 (see Supplemental Data Table e-1). Most studies used a two-stage procedure to identify individuals with PD. In stage 1, screening questionnaires were administered (usually in person, and rarely by mailed questionnaire) to elicit symptoms of PD. In stage 2, individuals who screened positive in stage 1 were examined by a health care professional (usually a neurologist) to confirm or refute a diagnosis

TABLE 1. PD prevalence by study quality (per 100,000)

Age Group	All Included Studies	Studies with Quality Score 7+	Studies with Quality Score <7
40-49	41	Analysis not possible	Analysis not possible
	95%Cl 20, 81 l ² 0		
50-59	107	156	82
	95% Cl 54, 211	95% CI 71, 342	95% Cl 37, 180
	l ² 85.4	l ² 53	l ² 41.3
55-64	173	220	99
	95% CI 88, 340	95% Cl 156, 311	95% Cl 13, 785
	l^2 74	I^2 0	l ² 89.4
60-69	428	503	383
	95% CI 235, 780	95% Cl 342, 741	95% CI 180, 814
	l ² 95	l ² 40.8	l ² 95
65-74	425	572	317
	95% Cl 193, 939	95% CI 227, 1439	95%Cl 34, 2951
	l ² 89	l ² 52.3	l ² 96.5
70-79	1,087	1.277	980
	95% Cl 627, 1,883	95% CI 819, 1,993	95% CI 444, 2,161
	l ² 97.4	l ² 82	l ² 98.3
+ 08	1,903	2,498	1,607
	95% Cl 1,132, 3,198	95% CI 1,571, 3,972	95% CI 701, 3,682
	l ² 95.9	l ² 80.7	l ² 97.6
Overall	315	571	251
	95% Cl 113, 873	95% Cl 243, 1,339	95% Cl 75, 842
	l ² 94.5	l ² 91.4	l ² 91.2

of PD, and to rule out secondary causes (e.g., drug-induced parkinsonism or vascular parkinsonism) or cases of atypical parkinsonism. Between studies, diagnostic criteria for PD varied, with 2 or 3 cardinal motor signs of PD (rest tremor, bradykinesia, rigidity, impaired postural reflexes, and a 5th sign referred to in some studies) applied in 24 studies; UK brain bank criteria applied in eight studies; EUROPARKINSON diagnostic criteria applied in two studies; National Institute of Neurologic Disorders and Stroke criteria and Schoenburg criteria in one study each. Diagnostic criteria remained undefined in 10 studies. The median quality score was 6, and the mean quality score was 5.9.

Age

Meta-analysis of the worldwide data revealed a rising prevalence of PD with age: 41 per 100,000 in individuals 40 to 49 years; 107 per 100,000 in individuals 50 to 59 years; 173 per 100,000 in individuals 55 to 64 years; 428 per 100,000 in individuals 60 to 69 years; 425 per 100,000 in individuals 65 to 74 years; 1,087 per 100,000 in individuals 70 to 79 years; and 1,903 per 100,000 in individuals over age 80 (Table 1).

We performed a sensitivity analysis on the agestratified data to determine whether our meta-analysis results differed based on the study quality score (see Table 1). We performed a meta-analysis of highquality studies (quality score 7 or 8 out of 8 points), and compared this with a meta-analysis of studies with quality scores of 6 or less. Although no statistically significant difference was found by meta-regression in the age-stratified prevalence estimates grouped by quality score, prevalence estimates in all age groups were higher in the high-quality studies. With the exception of the 50 to 59 age group category, prevalence estimates from high-quality studies also had narrower 95% confidence intervals, and smaller I² values, indicating less between-study heterogeneity.

In our analysis of the prevalence of PD by age and geographic location, individuals 70 to 79 years of age in Asia had a significantly lower prevalence of PD (646 per 100,000) compared with individuals of the same age in Europe, North America, and Australia (1,602 per 100,000; P < 0.05) (Table 2). The data were insufficient to make comparisons between geographic locations for the age groups 50 to 59, 60 to 69, and over 80.

Sex

The effect of sex on the prevalence of PD was also analyzed and stratified by age group and by geographic location. Worldwide, in the 50 to 59 age group, males had a significantly increased prevalence of PD of 134 per 100,000 relative to females, with a prevalence of PD of 41 per 100,000 (P < 0.05) (Table 3). A slight, nonsignificant male preponderance of PD was present in most other age groups. Stratified by geographic location, however, no significant difference in prevalence was found between males and females in any region, although prevalence rates were more equal between males and females in Asia than in other

TABLE 2. Prevalence of PD by age and geographic location (per 100,000)

Geographic location	50-59 years	60-69 years	70-79 years	80+ years
Asia	88	376	646	1,418
	95% CI	95% CI	95% CI	95% CI
	39, 201	166, 848	320, 1,345	612, 3,285
	l ² 87.4	1^2 96.7	l ² 95.8	$1^2 95.9$
Europe/North	113	540	1,602	2,953
America/	95% CI	95% CI	95% CI	95% CI
Australia	49, 261	373, 781	1,219, 2,105	1,936, 4,503
	I^2 0	l^2 0	1^2 67.9	$I^2 80.1$
South America	228	637	2,180	6,095
	95% CI	95% CI	95% CI	95% CI
	90, 579	377, 1,074	1,335, 3,559	1,975, 18,813
	l ² 11.3	I ² N/A	I^2 55.7	l ² 91

regions (Europe/North America/Australia, Asia, or South America) (Table 4).

Discussion

General Comments on Methodology

Our analysis has identified a number of intriguing differences in prevalence rates of PD related to age, sex, and geographic distribution. Although environmental or genetic factors may be responsible for these findings, as with all meta-analyses, our findings may equally have arisen from confounders within populations or methodological differences within the studies themselves.

For example, small differences in diagnostic and inclusion criteria of the studies included in an analysis can have profound effects on reported prevalence rates. De Rijk and colleagues⁵⁵ have demonstrated in community-based studies that a change in diagnostic criteria for PD may result in a decrease of up to 36% in identified cases.⁵⁵ Differences in methods of ascertainment also may have had a significant impact on the reported rates of PD across studies. The specific content of any questionnaire used for the assessment of PD is a major source of variance. Some questionnaires may have relatively few questions relating specifically to PD, 46 and where content may indeed relate to parkinsonism, the specific questions may be highly variable. The ability of questionnaires to identify PD signs has been a matter of debate, because recent studies have highlighted their poor sensitivity and specificity for the detection of mild PD signs early in the disease.56 Others have found that the sensitivity of screening for neurological disorders may be increased with the addition of physical tasks to symptom questionnaires.⁵⁷ As screening questionnaires to identify putative cases were used in the first stage in most of the studies included in our analysis, disease prevalence may be underestimated because of failures to capture the mildest cases.

TABLE 3. Prevalence of PD by sex and age group (per 100,000)

Age Group	Female	Male
40-49 years	45	36
	95% CI 18, 113	95% Cl 15, 86
	I^2 0	I^2 0
50-59 years	41	134
	95% Cl 24, 71	95% CI 63, 285
	l^2 29.3	l ² 86
55-64 years	150	233
	95% Cl 75, 30	95% CI 120, 452
	1^2 44.8	l ² 53.2
60-69 years	392	389
	95% CI 202, 762	95% CI 211, 715
	l ² 93.2	l ² 90.7
65-74 years	610	706
	95% Cl 322, 1,157	95% Cl 389, 1,280
	l ² 78.1	l ² 78.3
70-79 years	813	932
	95% CI 433, 1,524	95% Cl 494, 1,757
	l ² 95.8	l ² 95.6
80+ years	1,517	2,101
	95% CI 840, 2,740	95% Cl 918, 4,809
	$1^2 90.3$	l^2 92.3

The level of training of the screening personnel who are performing the initial screen to identify patients with parkinsonism also may be reasonably expected to influence ascertainment. Review of the included studies indicates that the personnel screening subjects for PD had widely differing levels of training and clinical experience, although neurologists or movement disorder subspecialists typically performed physical examinations of cases screening positive. This wide range of expertise becomes especially important when one considers that up to 24% of the diagnoses of PD are incorrect when compared with pathological diagnoses.⁵⁸

Our sensitivity analysis based on study quality failed to show a significant difference in prevalence estimates based on study quality. However, prevalence estimates using higher-quality studies were higher in all age groups, with narrow confidence intervals, and less between-study heterogeneity, suggesting that the higher-quality studies may provide a more precise estimate of disease prevalence.

TABLE 4. Prevalence of PD by sex and geographic location (per 100,000)

Geographic location	Female	Male
Asia	306	371
	95% CI 184, 511	95% CI 219, 629
	l ² 98.6	l ² 98.8
Europe/North	1,267	1,535
America/Australia	95% CI 1,005, 1,595	95% CI 1,188, 1,983
South America	808	1,267
	95% CI 356, 1,832	95% Cl 583, 2,752
	l ² 88.5	1^2 89.3

Geographic Variability

Analyses of geographic variation of prevalence are easily confounded by demographic variation between populations. Our meta-analysis attempted to control for the effects of demographic differences with agespecific analyses. Comparing within age groups across regions, our study identified in the 70- to 79-year-old population a significantly lower prevalence of PD in Asia than in North America, Europe, and Australia, as well as a lower prevalence of PD (not reaching statistical significance), in all other age groups in Asia compared with other regions. Caveats relating to methodological differences aside, genetic or environmental susceptibilities to PD could reasonably explain these findings.

Age

Our meta-analysis identified a steady increase in PD prevalence with age across all regions of the world. This finding is in agreement with some studies, ^{33,59} and is in contradistinction to others that have reported a peak at approximately age 70 followed by decreasing prevalence by the age of 80 and thereafter. 34,60 One interpretation for the previously reported decline in prevalence among the oldest old is that it is caused by under-ascertainment of PD among older subjects, which occurs when patients are detected through medical records only. Regardless of the possible explanations, the interpretation of all age-related data must be undertaken with the understanding that the numbers of patients of advanced age in any given study are generally small, and a few reported cases can therefore have a significant impact on results. A systematic review of incidence studies of PD found that most studies have reported that PD incidence rises steadily with age to a peak occurring between the ages of 70 to 79. A few studies have reported that PD incidence continues to increase in those aged 80 and older.⁶¹

Sex

Finally, our study demonstrated sex differences in worldwide PD prevalence rates between males and females, with a lower prevalence of PD noted in females than in males in the 50- to 59-year age group. From a neurobiological perspective, some support for this finding may be seen in Haaxma et al.'s study⁶² reporting that women, once they acquire PD, may have a more benign phenotype with slower progression of disease than men. The authors have speculated that this phenotypic difference is attributable to higher estrogen activity, which leads in turn to higher dopamine levels in the striatum.⁶² A systematic review of incidence studies of PD reported a significantly greater incidence of PD in men than in women in most of the studies that have provided age-standardized sex ratios,

and that onset of disease in men was often slightly earlier than in women.⁶¹

Changes over time in the incidence of PD and the length of survival of individuals with PD will affect PD prevalence. Although we did not perform a time trend analysis of PD prevalence, one might expect the prevalence of PD to increase over time because of increases in incidence or improved survival. Data from England and Wales have shown decreasing PD mortality rates in both men and women from 1993 to 2006, potentially because of improvements in PD treatments and general medical care.⁶³

The results of our systematic review have brought to light intriguing differences in the prevalence of PD reported by geographic region, age, and sex; however, it has also served to emphasize the problems inherent in performing epidemiologic evaluations across widely disparate populations, cultures, and regions. Very few of the available studies included in our analysis could be said to be without methodological flaws; and the variability of methodological approaches applied across studies precludes simplistic comparisons. A consensus statement on the minimal scientific standard for prevalence studies would improve the quality and consistency of subsequent studies attempting to move beyond our own.

The results of our own study suggest the possibility of racial and geographic variation in the prevalence of PD. These findings argue for further epidemiologic surveys, specifically with high-quality screening instruments for PD and confirmation of diagnoses with sensitive, internationally accepted diagnostic criteria to ensure greater comparability. Additional, longer-term prospective studies would help establish whether the clinical progression and prognosis of the disease differs between racial groups and among different parts of the world.

Where reliable differences in prevalence can be demonstrated between populations, opportunities may arise for more refined molecular epidemiology of PD, allowing more direct attempts to identify alleles that differ in type and frequency across populations to influence disease susceptibility, progression, or treatment response.

The potential for these important scientific insights aside, an equally pressing imperative for the development of accurate prevalence estimates of PD lies in the need to prepare for the effects of the demographic shift that is currently taking place in many regions of the world. An accurate estimate of the magnitude of disease burden will be a necessary first step for efforts to mitigate a projected wave of neurodegenerative disease that threatens to overtake the already beleaguered public health infrastructures of many of the world's mature economies.

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Supporting Data

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