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The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis

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Incidence studies · Parkinson's disease/parkinsonism · Risk factors in epidemiology

Abstract
Background: Parkinson's disease (PD) is a common neurodegenerative disorder. Epidemiological studies on the incidence of PD are important to better understand the risk factors for PD and determine the condition's natural history. ***Objective:*** This systematic review and meta-analysis examine the incidence of PD and its variation by age and gender. ***Methods:*** We searched MEDLINE and EMBASE for epidemiologic studies of PD from 2001 to 2014, as a previously published systematic review included studies published until 2001. Data were analyzed separately for age group and gender, and meta-regression was used to determine whether a significant difference was present between groups. ***Results:*** Twenty-seven studies were included in the analysis. Meta-analysis of international studies showed rising incidence with age in both men and women. Significant heterogeneity was observed in the 80+ group, which may be explained by methodological differences between studies. While males had a higher incidence of PD in all age groups, this difference was only statistically significant for those in the age range 60–69 and 70–79 ($p < 0.05$). ***Conclusion:*** PD incidence generally increases with age, although it may stabilize in those who are 80+.

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that becomes increasingly prevalent with age. Epidemiological studies on the incidence of PD are important to better understand both the risk factors for PD and determine the condition's natural history. As PD predominantly affects older adults, worldwide aging populations, especially in economically developed countries, will increasingly need to develop strategies to meet the health care needs of individuals with PD. Information on the variation in the incidence of PD between age groups and genders can be used to effectively direct these strategies to appropriate populations. Therefore, the synthesis of epidemiological data on PD incidence can help guide effective planning of medical services.

A systematic review of studies of PD incidence was last published in 2003 and included studies published up to 2001 [1]. It included 25 studies on the incidence of

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PD. Study quality was not directly reported, though methodological issues within individual studies were assessed. Studies with the highest quality found an overall incidence rate of 17 per 100,000 person-years. All studies included examined age-specific PD incidence rates, and peak PD incidence rates were found in those between 70 and 79 years in most of the studies. Only 9 studies examined age-standardized gender ratios; 5 of the 9 studies found significantly ($p < 0.05$) greater incidence in males. This systematic review provides an up-to-date synthesis of incidence studies of PD performed between 2001 and 2014, and builds on previous results by including an analysis of study quality and a meta-regression to compare gender differences across age groups.

Methods

Selection of Studies

Search strategies for studies on the incidence of PD were developed in consultation with an academic research librarian with expertise in systematic review. Studies on the prevalence of PD are discussed in a separate manuscript [2].

Both MEDLINE and EMBASE databases were searched for PD incidence studies published from January 1, 2001 to December 31, 2011 using terms specific to PD and restricted to studies of incidence and epidemiology (see online suppl. material 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000445751) for search strategy). The search was subsequently updated to include new studies published until June 2014. All studies published in English or French were included. Two independent reviewers then screened the included abstracts to determine if a full text review should be performed. Review articles or those containing non-original data were excluded; however, the reviewers examined these papers' bibliographies to check for potential additional articles. In cases where multiple papers reported the same data, the most up-to-date and complete data set was included. Every included article was also hand searched to make sure no additional studies were missed during the period of interest.

Data Extraction

Two reviewers performed the data extraction using a standardized assessment form that included the following domains: region, target study population, definition of condition, data sources, diagnostic criteria, overall incidence, and stratified (e.g. age, gender) incidence. Crude incidence rates were reported as cases per 100,000 person-years for each study; incidence proportions were reported as cases per 100,000 persons. Breakdown of incidence by socio-demographic categories (e.g. age, gender, location) was recorded when provided. All data were then independently assessed by 2 reviewers and entered into evidence tables. If the results of the data extraction differed between the 2 reviewers, a third reviewer would reassess the relevant study. Any differences among results were then discussed among reviewers until a consensus was achieved.

Quality Assessment

A quality assessment was performed for each study based on criteria developed from guidelines on the evaluation of incidence studies [3, 4]. Studies were given a score of 0–8 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 (online suppl. material 2 for quality criteria).

Data Synthesis

In order to be included in the meta-analysis, studies had to report either an estimate of the incidence rate or proportion and corresponding 95% CIs, or the raw data that could be used to calculate the estimate. Only studies that provided age- and gender-based group-specific data on PD incidence were included in the meta-analyses. In order to determine if results from the individual studies are consistent, the Cochrane Q statistic was calculated and I^2 used to quantify the amount of between-study heterogeneity. A random-effects model was used to calculate the pooled incidence per 100,000 person-years or 100,000 persons and 95% CIs. Meta-regression was then used to determine if age-specific estimates varied significantly by gender for incidence rates. For studies where the period of time over which new cases developed was not reported, incidence estimates were compiled separately as annual incidence proportions rather than incidence rates.

Results

The initial search in EMBASE and MEDLINE conducted in 2011 yielded 4,219 abstracts (online suppl. material 3 for flow diagrams). After abstract review, 219 full text articles were assessed for eligibility; 21 studies on the incidence of PD were included.

The updated EMBASE and MEDLINE searches were conducted in June 2014 and returned 2,663 abstracts (online suppl. material 3 for flow diagrams). After abstract review, 57 full text articles were assessed for eligibility. We identified 6 new studies on the incidence of PD, and 1 study that updated results on a study included in the 2011 search. In total, 27 studies on the incidence of PD published from 2001 onward were included in our systematic review (online suppl. material 3).

In all, from both searches, 14 studies [5–18] provided data that could be included in the meta-analyses. Three studies [5, 9, 15] provided information on incidence proportions as the unit of time over which new cases developed was not specified. The remainder of studies provided information on incidence rates. A Cochrane Q subgroup analysis was performed to assess for differences in PD incidence based on gender in different age groups for both the incidence rates. The number of studies reporting an incidence proportion was too small to assess gender-based differences using the Cochrane Q subgroup analysis.

Of all the studies, 16 were performed in Europe [5, 7, 8, 10, 12, 14, 18–27], 5 in Asia [9, 15, 16, 28, 29], 4 in North America [11, 13, 17, 30], 1 in Australia [31], and 1 in South America [6] (online suppl. material 3 for table of included studies). Studies used a variety of methods to identify patients with PD. Administrative data, hospital records, and chart review were used by 15 studies but were usually combined with another method such as physician referral. Mailed or door-to-door surveys were used by 5 studies, and 3 were drawn from cohort studies. Prescription drug databases were used only by 3 studies. The final study used physician referral exclusively. Diagnostic criteria used to establish PD diagnosis also varied considerably between studies. The most commonly used criteria were the UK brain bank (9 studies) and 2 or more cardinal motor signs of PD (rest tremor, bradykinesia, rigidity, impaired postural reflexes; 6 studies). One study each used the Gleb criteria, Hughes diagnostic criteria, and the Japanese Research Committee on Neurodegenerative disease criteria. In addition, one study used self-reported diagnosis only and another 7 did not report on the diagnostic criteria used to diagnose PD.

Quality scores for the included study ranged from 2 to 7 out of a possible 8 points. The mean score was 4.9, and the median score was 5 (online suppl. material 3 for table of included studies with quality scores).

Age

The overall incidence rate of PD in females 40 years and older was 37.55 per 100,000 person-years (95% CI 26.20–53.83), and 61.21 (95% CI 43.57–85.99) in males 40 years and older. Meta-analysis of the data showed an increase in incidence for both males and females with age. In females, incidence rates increased steadily over time, from 3.26 per 100,000 person-years at age 40–49 to 103.48 at age 80+ and peaked between the ages 70 and 79 in a majority of studies (fig. 1). In males, incidence rates rose from 3.57 per 100,000 person-years at age 40–49 to 258.47 at age 80+ (fig. 2). In contrast to females, incidence continued to rise after age 80 according to approximately half the number of studies.

The separate meta-analysis of the annual incidence proportions showed similar trends. In females, incidence proportions generally increased with age, from 2.94 per 100,000 persons at age 40–49, peaking at 104.99 between the ages 70 and 79 before dropping off to 66.02 at age 80+ (table 1). In males, incidence proportions also generally increased with age, from 3.59 per 100,000 persons at age 40–49, peaking at 132.72 between the ages 70 and 79 before dropping to 110.48 at age 80+ (table 1; fig. 2).

Gender

Gender-specific incidence rates of PD were analyzed stratified by age. Between the ages of 60 and 69, males had significantly higher incidence rates of 58.22 per 100,000 person-years than females with 30.32 per 100,000 person-years ($p = 0.0012$). Males also had significantly higher incidence rates than females between 70 and 79 years, with 162.58 per 100,000 person-years compared to 93.32 per 100,000 person-years ($p = 0.023$). In all other age groups, males had small, nonsignificantly higher incidence rates than females (table 2).

Other Studies of Interest

Three high-quality papers (score >5) were found but not included in the meta-analysis as they did not report age- and gender-specific incidence rates or proportions. These studies provided information on Asian and Eastern European populations that were not well represented in the meta-analysis.

Das et al. [29] was the only study that examined PD in a south Asian Indian population, reporting average annual incidence rates (AAIRs) for males and females in different age categories. AAIRs peaked earlier for males, than females. Male AAIRs peaked at 60–69 years; female AAIRs continued to rise in 70–79 years before dropping off in the 80+ age group. Hristova et al. [21] and Kyrozis et al. [22] both provided incidence rates not stratified by gender and age and therefore could not be included in the meta-analysis. Both represented unique European populations (Bulgaria and Greece, respectively) and found peak incidence between 70 and 80 years.

Discussion

General Comments on Methodology

This analysis identified many potentially important differences in the incidence of PD, which could possibly be attributed to environmental or genetic factors. However, as this meta-analysis contains studies with a range of methodological strategies, the differences between age- and gender-specific incidence may also be due to methodological differences or potential population confounders. Ideally, only studies using the same methods of case ascertainment would be combined in the meta-analysis. However, only 27 studies of PD incidence were found, with only 14 providing data that could be combined in the meta-analysis. There were only a few studies that used identical methodologies for case ascertainment. As all methods of case ascertainment have drawbacks, including attrition, misclassifica-

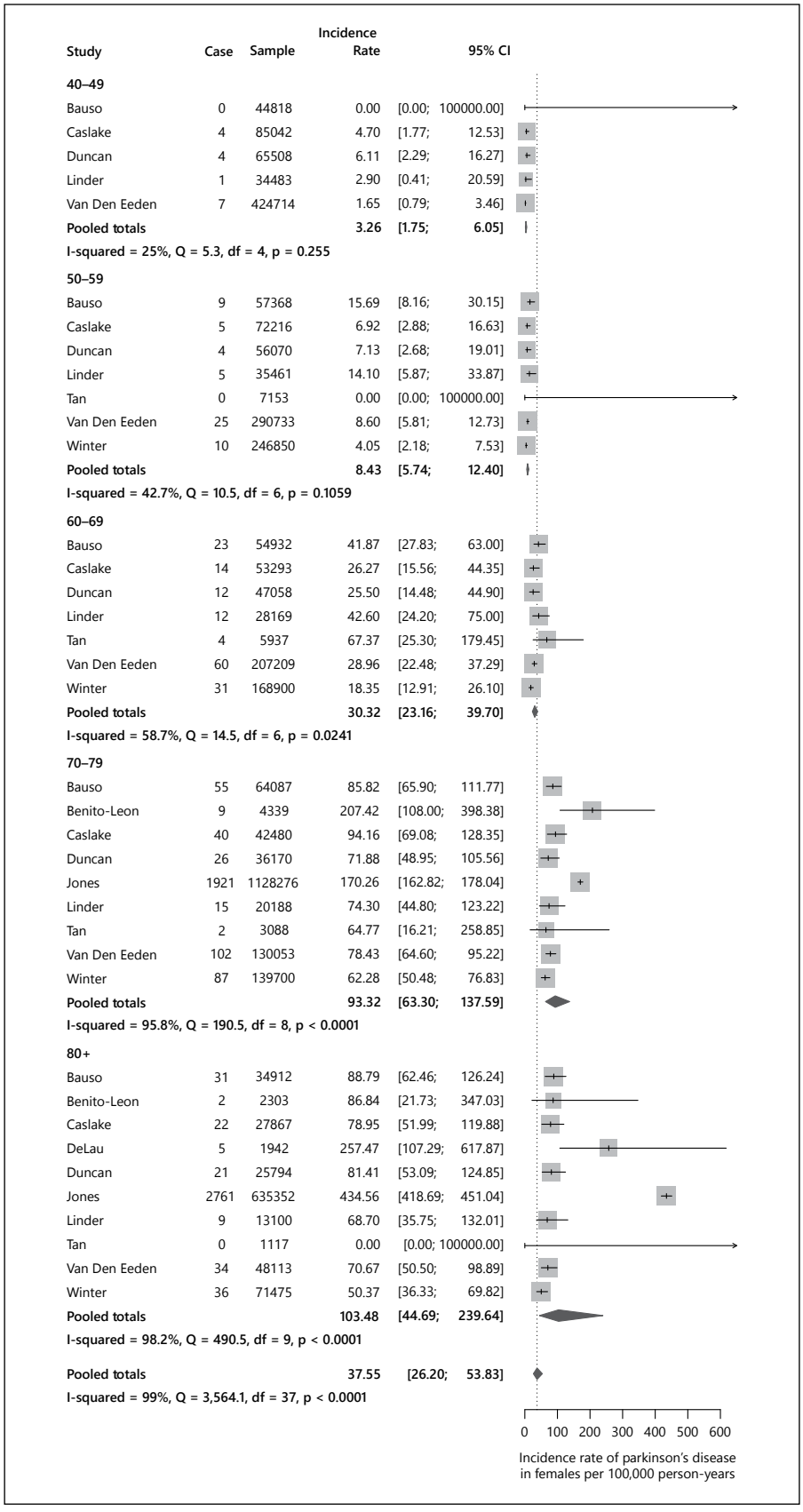

Fig. 1. Female incidence rate.

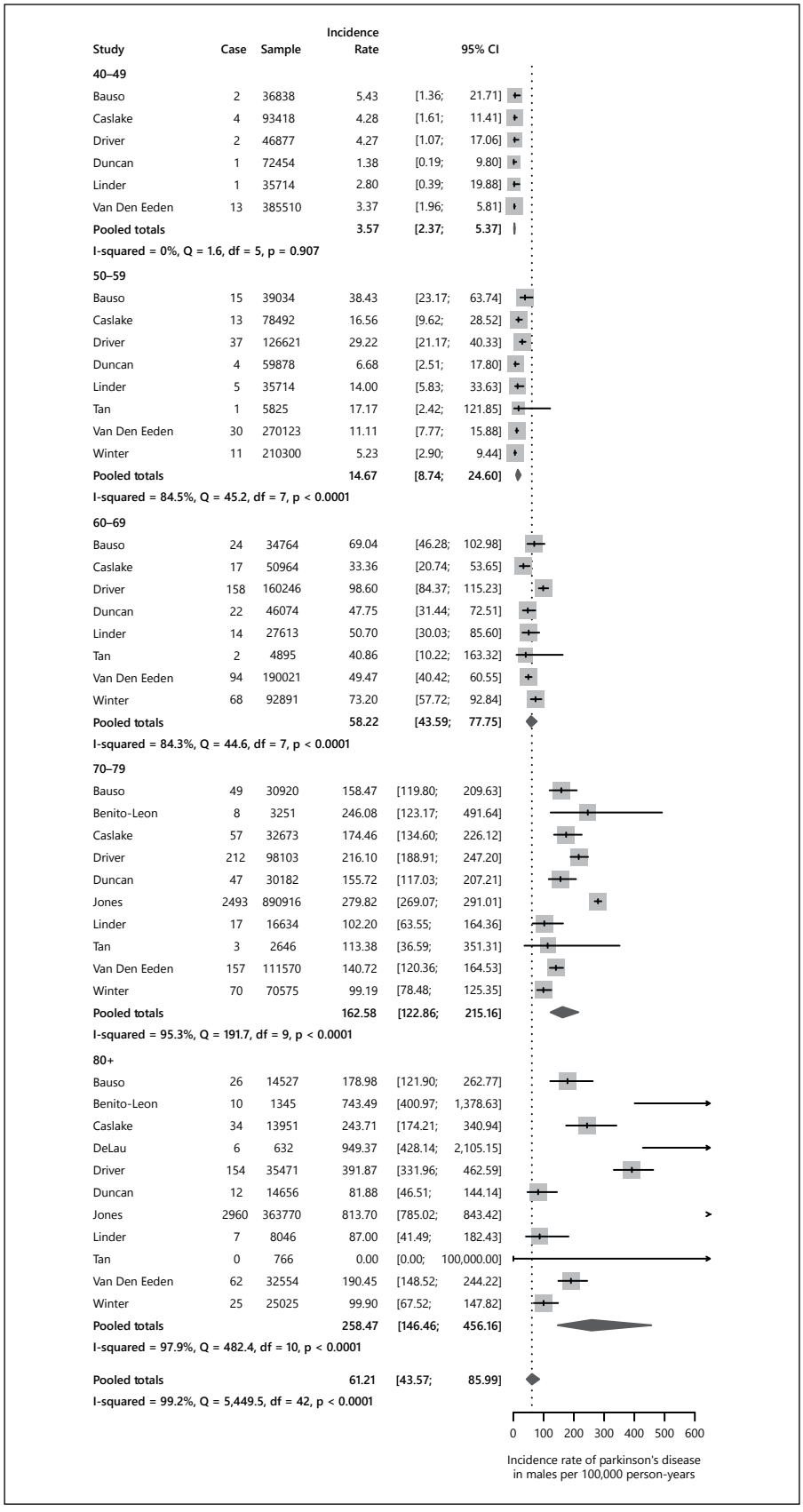

Fig. 2. Male incidence rate.

Table 1. Meta-analysis of gender-specific PD incidence

Age group	Gender-specific incidence proportions					
	female			male		
	pooled total	95% CI	I^2, %	pooled total	95% CI	I^2, %
40–49	2.94	0.95–9.09	16.8	3.59	0.70–18.39	59.9
50–59	13.40	6.77–26.51	51.7	19.68	7.31–52.97	78.3
60–69	58.53	37.05–92.45	64.2	55.10	15.88–191.22	94.3
70–79	104.99	81.15–135.84	25.4	132.72	81.99–214.86	72.7
80+	66.02	48.43–90.00	0	110.48	78.56–155.38	0
Total	37.16	23.24–59.41	90.4	44.21	25.82–75.73	93.1

Table 2. Meta-regression for gender differences in PD incidence between males and females

Age group	Cochrane Q subgroup analysis; pooled incidence rate (95% CI)		p value
	female	male	
40–49	3.26 (1.75–6.05)	3.57 (2.37–5.37)	0.7259
50–59	8.43 (5.74–12.40)	14.67 (8.74–24.60)	0.0893
60–69	30.32 (23.16–39.70)	58.22 (43.59–77.75)	0.0012*
70–79	93.32 (63.30–137.59)	162.58 (122.86–215.16)	0.023*
80+	103.48 (44.69–239.64)	258.47 (146.46–456.16)	0.0642

* Denotes significant value.

tion, and nonresponse, the quality of individual studies may be equally as important as the method of case ascertainment in determining PD incidence. Therefore, we chose to combine studies using different methodologies and examine closely for heterogeneity using the I^2 statistic calculated from the Cochrane Q chi-square test for heterogeneity. I^2 values showed low to moderate heterogeneity in the female age groups from 40 to 70, with considerable heterogeneity in those 70–79 and 80+. Similarly, heterogeneity increased with age in males, though considerable heterogeneity was found in all age groups over 50.

The reported incidence rates in the 80+ age category for both genders were the most heterogeneous, leading one to question if methodological differences could account for this variation. In the 80+ age group, 4 of the 5 studies that reported the lowest incidence rates for males and females used administrative data or hospital records to obtain incidence data, whereas 4 of the 5 studies that reported the highest incidence rates for males and females used surveys, either mailed or door-to-door, or were cohort studies.

Low incidence rate estimates in the studies that used administrative data may have occurred, as studies that rely on medical records exclude those patients who do not seek medical care and patients in whom PD may not have been diagnosed by a physician [32]. Furthermore, prescription drug data may be confounded by extrinsic factors such as culturally determined treatment practices or access to reimbursement for medication [33]. The 4 studies with lower incidence rates in the 80+ group also had lower estimates in other age categories, but were more consistent with other studies. Therefore, it may be that the issues causing an under-reporting of incident PD cases from administrative data are exacerbated in the very elderly population. For example, elderly people may be less likely to seek medical treatment, or they may have one or more competing diseases that precede a PD diagnosis [32].

Higher incidence rates were most common in studies that had several follow-up visits with prospective cases or used multiple sources of ascertainment. Prospective studies are preferable to retrospective studies where medical

records or administrative data are used, as PD is not easily diagnosed and symptoms that appear over time may change the diagnosis [1]. Furthermore, validity of administrative data has been shown to vary significantly based on the types of databases, number of codes used, and nature of the conditions of interest [34]. For this reason, studies that included information from follow-up visits with clinicians or medical experts built in to their methodology may have higher reported incidence rates, as it is possible to identify more number of cases.

Age

This meta-analysis of PD incidence rates and proportions showed an increasing incidence in males and females with age across all regions identified in this systematic review. The overall incidence rates and proportions were found to be higher than in the last published systematic review, which reported an overall incidence rate of 17 per 100,000 person-years [1]. The increase seen in this systematic review may be attributed to changes in methodology or to an aging population, as incident PD increased with age.

For females, the peak incidence of PD between 70 and 79 in most studies was consistent with data from the previous review, while few studies showed a continued increase in incidence as was found for the male population [1]. However, the underlying population in the most elderly age group was by far the smallest, as mortality in old age competes with disease incidence. Therefore, even a small number of cases had a large impact on the incidence rates and proportions in the 80+ group, which may have led to the increased incidence after 80+ group in males. Conversely, the incident rates for females over 80 may be underestimated due to the methodological challenges explored earlier in this study. While a majority of studies found decreasing rates of PD in the 80+ group in females, the overall incidence rate and proportion from the meta-analysis increased in this age range.

Gender

Lastly, this study showed a significant gender-based difference in incident rates of PD between ages 60–69 and 70–79. However, a systematic review of PD prevalence studies found significant differences between the genders only between 50 and 59 years of age, and no significant differences in prevalence when stratified by geographic location [35]. One potential explanation for the increased incidence in males not causing a parallel increase in prevalence is the more benign course of the disease in females, speculated to be caused by higher estrogen activity, which leads to higher dopamine levels in the striatum [36]. This finding is supported by a meta-analysis on PD mortality performed by Xu et al. [37], who found that male patients had slightly increased premature mortality risk over female patients. Furthermore, PD has increasing mortality with disease duration, and as males have been shown to have earlier onset than women, mortality from the disease would occur earlier, which could also offset the increased incidence in males [1]. This evidence is supported despite the fact that males have a higher mortality than females in this age group regardless of PD diagnosis, as Diem-Zangerl et al. [38] observed a significantly higher standardized mortality rate (1.3, 95% CI 1.1–1.6) for males with PD vs. the general population, but not for females (1.1, 95% CI 0.9–1.4).

This systematic review has brought to light many interesting points on international incidence rates and proportions of PD in relation to age and gender, as well as highlighted some potential issues with comparing studies which use varying epidemiological methods. These potential problems were especially underscored in the 80+ elderly population, which may not access medical services and treatment in a traditional or well-documented manner. Comparing incidence across studies that have such different methods of ascertainment must be done with caution, and ideally studies that use similar, validated protocols should be used. These criteria should further extend to the included population, where cases of PD are clearly defined, as some studies use PD as an all-inclusive term, while others refer exclusively to idiopathic PD. In order to reduce variability, standardized minimum standards for measuring incidence should be established in order to produce more accurate estimates [39].

The results of this study showed a statistically significant difference in incidence rates and proportions between males and females in certain age groups. Further epidemiological analysis into this finding, with more sensitive diagnostic tools and high-quality methodology should be undertaken to validate these results and also explore potential variation in other demographic factors, such as geographic location and income. These results will become increasingly important as worldwide populations are aging. PD represents a common neurodegenerative disease that has only a moderate increase in premature mortality over the age-matched general population. Accurate estimates of the burden of disease must be obtained so that steps can be taken to prepare for and mitigate the impacts from an increasing number of individuals living with this disease [38].

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Authors Roles

L. Hirsch was involved in the analysis and interpretation of data, the drafting and revising of the manuscript. T. Pringsheim was involved in the design and conceptualization of the study, analysis and interpretation of data, the drafting and revising of the manuscript, and obtaining study funding. N. Jette was involved in the design and conceptualization of the study, analysis and interpretation of data, revising of the manuscript, and obtaining study funding. A. Frolkis was involved in the analysis and interpretation of data. T. Steeves was involved in the design and conceptualization of the study, interpretation of data, and the drafting and revising the manuscript.

Financial Disclosure Statement

The authors have no financial conflicts of interest to declare.

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