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REVIEW

Risk of Dementia in Parkinson's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT: Estimates of the risk of dementia in Parkinson's disease (PDD) vary widely. We aimed to review the incidence of PDD and in a meta-analysis estimate the pooled annual incidence and relative risk of PDD while also exploring factors that may contribute to heterogeneity between studies. Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines were followed and MEDLINE and EMBASE were searched for articles reporting the number of cases of dementia in a population, followed longitudinally, with a minimum of 100 dementia-free Parkinson's disease (PD) patients at baseline. Meta-analyses and meta-regressions were used to estimate the pooled incidence rate of PDD and the relative risk of PDD versus healthy controls (HC). A total of 32 studies were identified, 25 reporting the incidence of PDD and 10 reporting the relative risk of PDD versus HC. The pooled incidence rate of PDD was 4.45 (95% confidence interval [CI], 3.91–4.99) per 100 person-years at risk, equating to a 4.5% annual risk of dementia in a PD prevalent population. The relative risk of PDD was estimated to be 3.25 (95% CI, 2.62–4.03) times greater than HC. Factors contributing to study heterogeneity and disparities in the estimated risk of PDD include the age of patients, year of recruitment, and study location. Significant gaps remain with no studies identified in several geographical regions. Future studies should stratify by age and standardize reporting to reduce overall heterogeneity. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: dementia; epidemiology meta-analysis; Parkinson's disease

Dementia and cognitive impairment more broadly are common in Parkinson's disease (PD) and of particular concern for patients and care partners.[1,2] Cognitive changes can occur throughout the course of PD, and although the prevalence and severity of dementia in PD (PDD) increases over time,[3-5] inherent neuropathological heterogeneity and differences in neurotransmitter deficits contribute to marked variation in the onset and speed of progression of cognitive impairment.[6-8]

However, the epidemiology characterizing the risk of PDD remains unclear and estimates of the prevalence and incidence of PDD differ.[9,10] Although in one

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systematic review, the cross-sectional prevalence of PDD was estimated to be between 24% and 31%,[11] it is the future risk of developing dementia that is of particular importance to patients with PD. These estimates of the incidence of PDD require longitudinal studies, but relatively few with adequate follow up have explored this, and there is wide variation across studies.[12] Early estimates indicated the risk of PDD was up to 10 per 100 patient years, equivalent to a 10% annual risk of developing dementia in a PD prevalent population, relative to a global annual incidence of dementia ranging from 0.4% in individuals 65–69 years old to 6.5% in 85+ year olds.[10,12-14] However, more recently studies with a range of different designs and recruitment criteria (including selected cohorts,[15] national databases[16] and regional-based population studies)[17,18] have pointed to a lower incidence of PDD, suggesting the current incidence of PDD may be lower than the earlier estimates. Furthermore, although the increased risk of PDD relative to similarly aged individuals without PD is well established, estimates quantifying the relative magnitude of the increased risk range between 2.5 to 6 and are mostly derived from small cohort studies.[6,10]

A variety of methodological and clinical factors likely underlie the difference in estimates of the incidence of PDD between studies. The age of patients, duration and stage of disease, severity of clinical phenotype, and presence of baseline mild cognitive impairment or neuropsychiatric symptoms are all recognized as factors, which influence the time to develop PDD. Differences in case selection and characteristics of recruited patients likely contribute to disparities in estimates of incidence.[19-26] There may also be racial and ethnic differences in the risk of PDD,[27,28] whereas, to date, the included populations in cohort studies published in Europe and North America have been predominantly white, differences in the incidence of PDD between these studies and a number of large studies in Asia have not been explored.[15,16,29] Methodological differences such as the assessment of cognition and determination of dementia, the attrition rate, and differences in the recruitment of patients from a population-based sample versus a more selected clinic-based sample also likely contribute. The age of study may also be important and changes to management and diagnostic procedures may underlie recent decreases in the estimates of incidence of PDD. Furthermore, studies have used different estimates of risk, which contributes to the difficulty comparing respective rates of PDD across different longitudinal cohorts.

It is often reported that up to 50% of patients with PD develop dementia after 10 years, rising to 80% after 20 years.[6,10,30] However, these estimates are based on a number of individual studies with relatively small sample sizes, several of which were conducted over 15 years ago.[5,9,21] In addition, more recent studies suggest the long-term risk of dementia may be lower than these estimates, possibly reflecting the general decline reported in the incidence of dementia overall, although this decline may have reversed more recently.[14,31] We aimed to address these differences by conducting a systematic review and meta-analysis examining the incidence of PDD, and separately the relative risk of PDD compared to individuals without PD, in cohorts with adequate (ie, at least 4 years) longitudinal data. We also explore potential sources of heterogeneity between estimates, assessing a number of clinical and methodological factors, which may contribute to differences in the incidence rate.

Methods

This systematic review was registered on PROSPERO and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[32] and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[33]

Search and Selection Strategy

Longitudinal studies were included that identified new cases of PDD over a mean follow up ≥4 years with >100 dementia-free patients with PD at baseline.

Searches were conducted on Ovid accessing Embase and Medline databases from inception to July 20, 2023, later updated on February 14, 2024 using a pre-defined search strategy (Supplementary Table S2). References of relevant reviews were also searched to identify additional studies meeting the inclusion criteria, and experts in the field were also consulted. Deduplication was initially performed in Ovid and any remaining duplicates were then removed manually.

Included studies fulfilled the following inclusion criteria (1) longitudinal studies with at least 4 years follow up; (2) reported data on individuals with PD; (3) included a minimum of 100 participants with PD who were dementia free at baseline; and (4) new cases of dementia were identified during the course of the study. The exclusion criteria were (1) articles not written in English; (2) case reports, reviews, and conference abstracts; (3) duplicate cohorts with overlapping cases; (4) restricted to specific PD subpopulations (eg, those receiving deep brain stimulation); and (5) outcomes were not related to cognitive functioning or dementia. Only studies that either reported the incidence rate of PDD or included available data to allow reviewers to calculate this were included in the meta-analysis.

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Data Extraction

One author (L.L.G.) assessed the titles and abstracts of all references to identify publications for full text review. The full texts were assessed and any publication not clearly meeting exclusion criteria (n = 54) was selected for independent review by a second author (D.W.) Both authors (L.L.G. and D.W.) independently identified studies meeting the inclusion criteria and any disagreement over the eligibility of studies was resolved with consensus discussion with other authors (P.S. and D.A.) Where more than one study reported data from the same cohort, the study with the longest longitudinal follow up was included, followed by the largest sample size.

Two authors (L.L.G. and R.L.) independently extracted data in duplicate using a standardized data collection form. Consensus discussion and arbitration by a third author resolved disagreements. Information was extracted categorically relating to study design, location, recruitment (single clinic, multi-center, population-based region-wide, national dataset), duration of follow up, recruitment date, the PDD diagnostic criteria used, and patient characteristics at study entry including mean age, sex, duration of PD, proportion with mild cognitive impairment (MCI), years of education, and Hoehn and Yahr (H&Y) stage. The outcome extracted was cases of dementia with a clinical diagnosis. In one study, scores on a standardized measure were used to define "cognitive impairment" and, because of the difference in methodology, this study was included in the systematic review, but not in the meta-analysis.[34]

For each study, the number of incident cases of dementia, the total person-time at risk, the incidence rate and 95% confidence intervals (CIs) were extracted. Where the total person-time at risk was not reported, this was calculated from number of individuals with PD multiplied by the mean duration of follow up or information provided in CONSORT flow diagrams. In one study,[15] additional information was obtained from the authors. If not reported, the incidence rate of PDD per 100 person-years was calculated from (number of dementia cases/time-person years)*100.

Where possible, hazard or risk ratios (collectively described as the relative risk [RR]) were extracted comparing incidence of PDD to healthy controls (HC). Where available, adjusted RR estimates were chosen to minimize the influence of potential confounding factors. In three studies,[15,35,36] the RR was not reported and hazard ratios were calculated from published Kaplan–Meier curves.[37,38]

The quality of included studies and risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS), which assesses selection, comparability, exposure, and outcome in cohort studies that we adapted for use (presented in Supplementary Table S2).[39] Two authors (L.L.G. and R.L.) gave each study a score of poor, fair, or good as per criteria listed in Supplementary Table S2. A third author (D.W.) arbitrated where there was a difference in the ratings between reviewers.

Data Analysis

Studies were included in the primary meta-analysis if they reported the incidence rate with CIs or the necessary information to calculate this.[40] The overall median incidence rate was calculated with accompanying first and third quartiles (p25–p75), and the presence of outliers was assessed (any estimate 1.5 times the interquartile range beyond the first or third quartile). High heterogeneity between studies was anticipated and, therefore, a priori, we planned to report the pooled, weighted estimate generated by random effects models using the DerSimonian and Laird method. Sources of heterogeneity were explored in subgroup analyses of study and patient characteristics, and the magnitude of between-study heterogeneity was quantified by the I^2 in addition to the Cochran Q statistic to calculate the significance.[41] Additionally, univariate meta-regression was conducted to explore the influence of a number of variables (mean age, H&Y score, year of recruitment and study quality) on the incidence of PDD. Subgroup meta-analysis was also conducted for studies (n = 4) stratifying incidence rates by age categorized into three groups (<70 years, 70–79 years, and 80+ years).

Random-effects meta-analysis was also applied in a secondary meta-analysis to quantify a pooled estimate of the RR of PDD versus HC. There were insufficient studies to allow subgroup analyses. However, sensitivity analysis was performed to assess the robustness of the pooled RR excluding studies where the hazard ratio was calculated from published Kaplan–Meier curves.

Publication bias for the measures of RR was assessed visually with funnel plots and statistically using Egger test. However, the effects of publication bias are not well established for epidemiological studies exploring incidence rates, and therefore, these tests were not performed for the primary analysis.[42] Stata version 16.1 or 18.0 was used for all meta-analyses and meta-regressions. The metan package was used to generate the forest plots, pooled estimates, and to assess for publication bias.

Results

Identification and Description of Studies

The search strategy identified 8568 studies supplemented by four additional studies identified from

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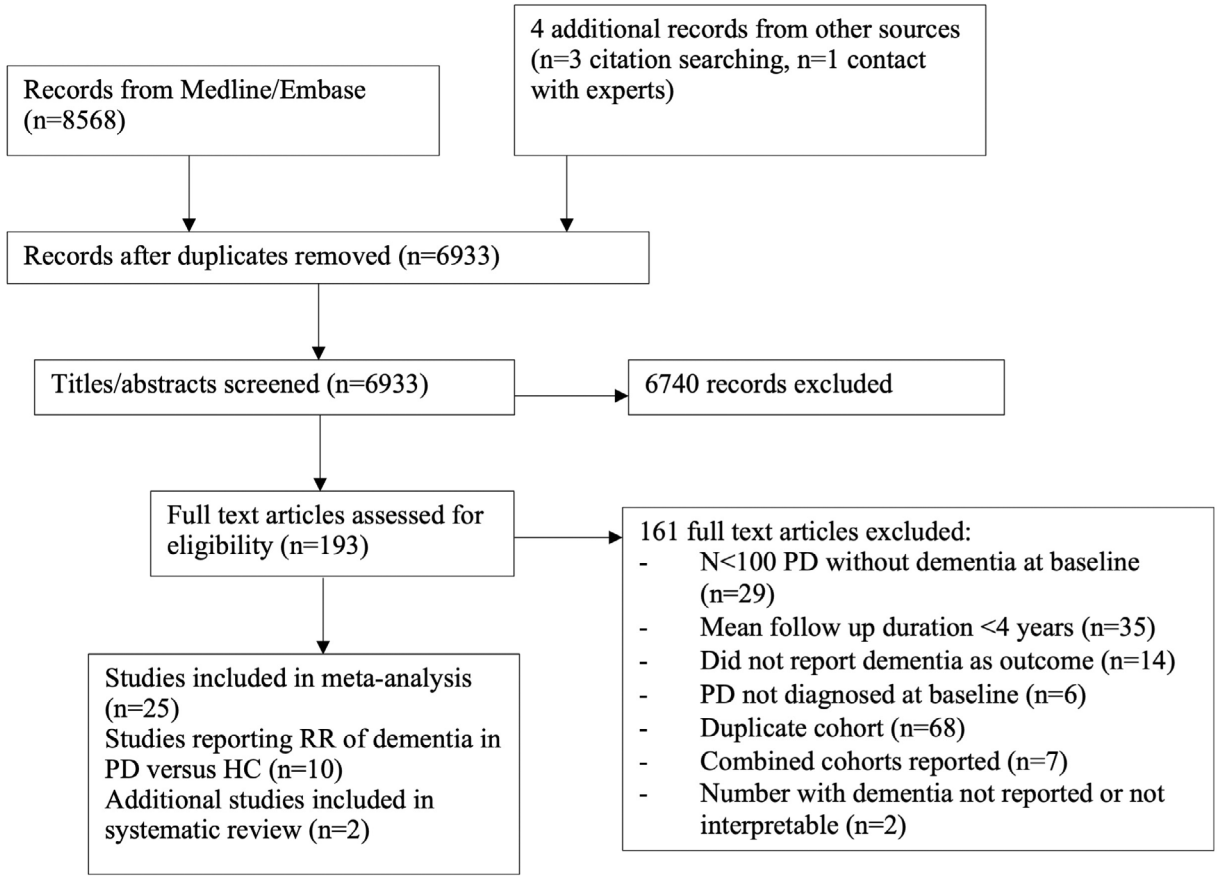

FIG. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 flow diagram which included searches of databases, registers, and other sources. RR, relative risk; PD, Parkinson's disease; HC, healthy controls.

other sources, and then reduced to 6933 after duplicates were removed (Fig. 1). Following screening of titles and abstracts, 193 articles met the criteria for full-text review, of which 161 were excluded. In total, 32 articles met the inclusion criteria, 25 were included in the primary meta-analysis,[9,16-18,21,29,35,43-58] 10 studies were included in a secondary meta-analysis,[15-17,35,36,47,59-62] and two studies were included only in the systematic review[5,34] (see Supplementary Table S3 for the complete list). One article has been included as a duplicate because it reports separately on the incidence of PDD in two distinct cohorts.[15]

The characteristics of the included studies are shown in Tables 1 and 2, and the full details of all included studies are reported in Supplementary Table S3. The secondary meta-analysis estimating the relative risk of PDD versus HC included five studies that did not report an incidence rate of PDD,[36,59-62] in addition to five studies included in both analyses.[15-17,35,47] Two studies included in the systematic review were not included in either meta-analysis (n = 1 reported the cumulative incidence of PDD over 20 years,[5] n = 1 Mini-Mental State Examination [MMSE] scores were used to diagnose "cognitive impairment," which is not comparable to the clinical diagnoses of dementia made in other studies).[34]

Incidence of PDD

Thirty-two studies reported on the incidence of PDD, of which 25 were included in the primary meta-analysis, with a total of 95,388 patients with PD across 720,653 time person years at risk (although one study[29] contributed the majority with 79,622 patients over 602,862 time person years). The pooled incidence rate of PDD was 4.45 (3.91–4.99) per 100 person-years, equating to a 4.45% annual risk of PDD in a dementia-free PD prevalent population. Heterogeneity between estimates was high $I^2 = 97.9\%$, $P < 0.001$. The overall results are shown in Fig. 2. The median incidence rate of PDD was 4.23 (p25–p75, 2.71–6.34), and there were no outliers.

Sources of Heterogeneity

Estimates of the incidence of PDD by clinical and study characteristics are also presented in Tables 1 and 2.

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TABLE 1 *Pooled estimates for the incidence rate of dementia in PD grouped by study characteristics*

Study characteristic	Subgroup	Number of studies	Patients with PD	Time person years	Pooled incidence rate per 100 person years (95% CI)
Study design	Prospective	17	4096	25,985.5	5.02 [3.95–6.09]
	Retrospective	8	91,292	6994667.5	3.75 [2.90–4.60]
Study recruitment	Single clinic	8	2938	16,257	4.06 [2.52–5.61]
	Multi-site clinic	6	2283	14845.6	5.29 [3.34–7.24]
	Population based study region-wide	7	2418	19,000	4.65 [2.92–6.38]
	National healthcare dataset	3	87,749	670,550	4.76 [3.32–6.19]
Study location	Asia	6	87,205	671,369	3.04 [2.63–3.45]
	Europe	13	6634	38021.6	4.85 [3.40–6.30]
	North America	5	1347	10454.3	5.70 [3.03–8.37]
	New Zealand	1	202	808	-
First year of recruitment	>2007	11	5689	38574.1	3.10 [2.30–3.90]
	≤2007	14	89,699	682078.7	5.72 [4.87–6.56]
Duration of follow up (mean)	<5 years	10	4715	19781.5	5.51 [3.76–7.27]
	5–10 years	11	10,385	90472.6	4.18 [3.24–5.11]
	>10 years	4	80,288	610399.0	3.17 [2.17–4.16]
Dementia diagnosis	MDS PDD	10	3150	19543.3	3.83 [2.78–4.88]
	DSM/ICD	10	90,154	690559.5	4.79 [3.99–5.59]
	Other	5	2084	10550.3	5.67 [2.12–9.22]

Abbreviations: PD, Parkinson's disease; CI, confidence interval; MDS PDD, Movement Disorder Society dementia in PD; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases.

Study Characteristics

Year of Recruitment

The pooled incidence rate of PDD was higher in studies that recruited their first patient before 2007 than those who recruited after 2007, and the heterogeneity between these groups was significant (Cochran's $Q = 19.4$, $P < 0.001$) (see Table 1 and Supplementary Appendix S1e6). Meta-regression found significant association between the year of first recruitment and the incidence rate (adjusted $R^2 = 18.8\%$, $P = 0.016$).

Study Design

The incidence rate of PDD was similar irrespective of the recruitment cohort; the heterogeneity across studies grouped by single clinic, multi-site clinics, population-based samples and national healthcare datasets was not significant (see Table 1 and Supplementary Appendix S1e1). The incidence rate of PDD was higher in prospective studies relative to retrospective studies, but the heterogeneity between these groups did not meet significance (Cochran's $Q = 3.32$, $P = 0.07$). The incidence rate of PDD was lower in studies with more than 10 years follow up and highest in studies with less than 5 years follow up, however, the heterogeneity between these groups was not significant (Cochran's $Q = 5.65$, $P = 0.06$) (see Table 1 and Supplementary Appendices S1 and S1, S3).

Study Location

The pooled incidence rate of PDD was lowest in studies conducted in Asia and highest in studies conducted in North America, with significant heterogeneity across estimates grouped by continent (Cochran's $Q = 8.91$, $P = 0.012$) (see Table 1 and Supplementary Appendix S1e4). One study conducted in New Zealand was not included in this subgroup analysis. No studies conducted in Africa or South America were identified in this review.

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TABLE 2 *Pooled estimate for incidence rate of PDD grouped by baseline characteristics of people with PD across different studies*

	Patient characteristics	Number of studies	Pooled incidence rate per 100 person years (95% CI)
Overall		**25**	4.45 [3.91–4.99]
Age of patients at baseline (mean), years	<65	5	2.70 [1.49–3.91]
	66–70	13	4.36 [3.61–5.12]
	70+	7	6.23 [4.58–7.89]
Years of education (mean)[a]	<12 years	7	4.50 [3.14–5.85]
	>12 years	8	5.45 [3.51–7.40]
Duration of disease at baseline[b]	<2 years post diagnosis	14	4.66 [3.48–5.85]
	>2 years post diagnosis	9	4.68 [3.52–5.83]
Hoehn and Yahr stage at baseline (mean)[c]	<2	5	3.54 [1.64–5.45]
	≥2	8	5.78 [3.90–7.66]
Mild cognitive impairment at baseline[d]	<25%	5	4.50 [1.44–7.56]
	>25%	6	5.07 [4.37–5.78]
Quality assessment rating	Good	9	3.78 [3.17–4.39]
	Fair	8	4.13 [2.69–5.58]
	Poor	8	5.65 [3.06–8.23]

[a]Reported in n = 15 studies.
[b]Reported in n = 23 studies.
[c]Reported in n = 13 studies.
[d]Reported in n = 11 studies.
Abbreviations: PDD, dementia in Parkinson's disease; PD, Parkinson's disease, PD; CI, confidence interval.

Dementia Diagnosis

The incidence rate of PDD was lower in studies applying Movement Disorder Society (MDS) PDD criteria to diagnose dementia, but the heterogeneity across groups based on the dementia diagnostic criteria applied was not significant. The CI for the incidence rate of PDD was particularly wide for the pooled estimate of the incidence rate for studies using "other" criteria to diagnose dementia (see Table 1 and Supplementary Appendix S1e5).

Study Population Characteristics

Age

The incidence rate of PDD was higher in studies with participants with a mean age over 70 years and lower in studies with a mean age of 65 and under (see Table 2 and Fig. 3). There was significant heterogeneity between the age groups ($Q = 11.85$, $P = 0.003$) and meta-regression found significant association between the mean age of patients with PD and the incidence rate of PDD (adjusted $R^2 = 24.0\%$, $P = 0.005$). The two studies with the lowest incidence of PDD included participants with a mean age <62 (see Supplementary Table S1e3),[15,57] whereas the highest incidence rate of PDD (at least double the pooled incidence rate in PD) was reported in two studies with a mean age of 78[55] and 79.4 years,[45] respectively. Sub meta-analysis of studies stratifying incidence rates of PDD by age (n = 4) found an 8.13% annual risk of PDD for patients over 80 and 2.65% annual risk in patients with PD under 70 (see Table 3 and forest plots in Supplementary Appendix S1e12).

Other Patient Characteristics

Meta-regression showed significant association between the incidence rate of PDD and the mean H&Y score (adjusted $R^2 = 27.90\%$, $P = 0.02$), and the incidence of PDD tended to be higher in studies with a H&Y score ≥2, although heterogeneity between studies with mean H&Y score greater or less than 2 was not significant (see Table 2 and Supplementary Appendix S1e10). Heterogeneity was not found between studies grouped by mean duration of PD at baseline (de novo PD [duration <2 years] versus prevalent PD [duration >2 years]), mean years of education (fewer than vs. more than 12 years) or proportion with MCI at baseline (<25% vs. >25%) (see Supplementary Appendices S1e7–9). There were six included studies with >25% MCI at baseline and the pooled incidence rate among these studies was 5.07

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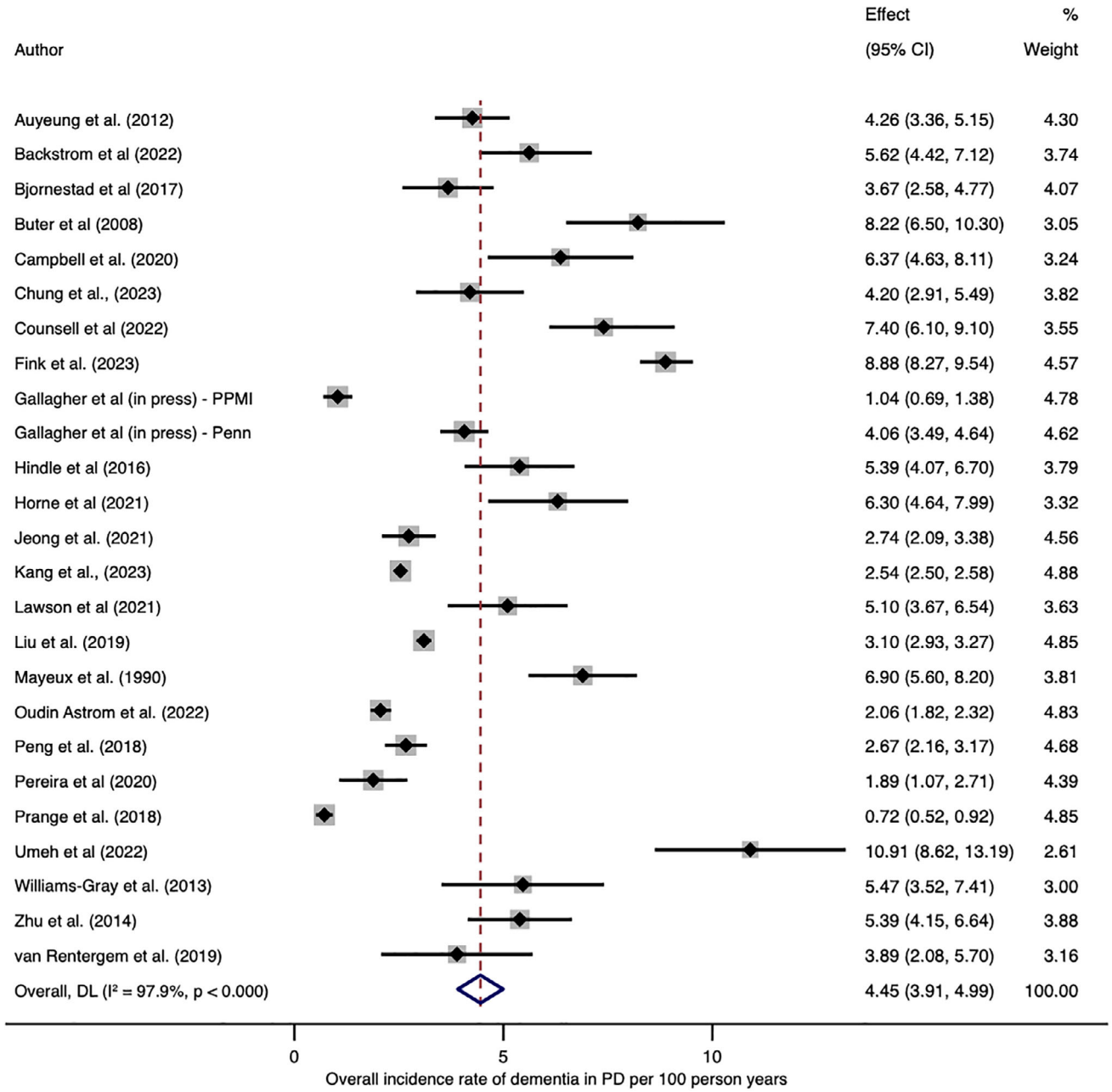

FIG. 2. Forest plot of the overall incidence rate of dementia in Parkinson's disease per 100 person years for 25 included studies sequenced by publication date. [Color figure can be viewed at wileyonlinelibrary.com]

(4.37–5.78) per 100 person years without significant heterogeneity between these studies ($I^2 = 19.9\%$, $P = 0.28$) (see Supplementary Appendix S1e9). However, MCI was not categorized in early studies and the earliest study included in this meta-analysis, which reported the number of patients with MCI at baseline was published in 2013.[9]

Quality Assessment

Quality was variable across the studies, nine of 25 studies were rated as good, eight as fair and eight as poor quality. The incidence rate of PDD was lowest in good quality studies and highest in poor quality studies (see Table 2 and Supplementary Appendix S1e11), but meta-regression found no effect of study quality on the estimate of the incidence rate ($P = 0.23$), and the heterogeneity between groups by quality score was not significant ($Q = 2.0$, $P = 0.37$). Differences in attrition rates and the characteristics of participants lost to follow up in prospective studies are reported in Supplementary Table S4.

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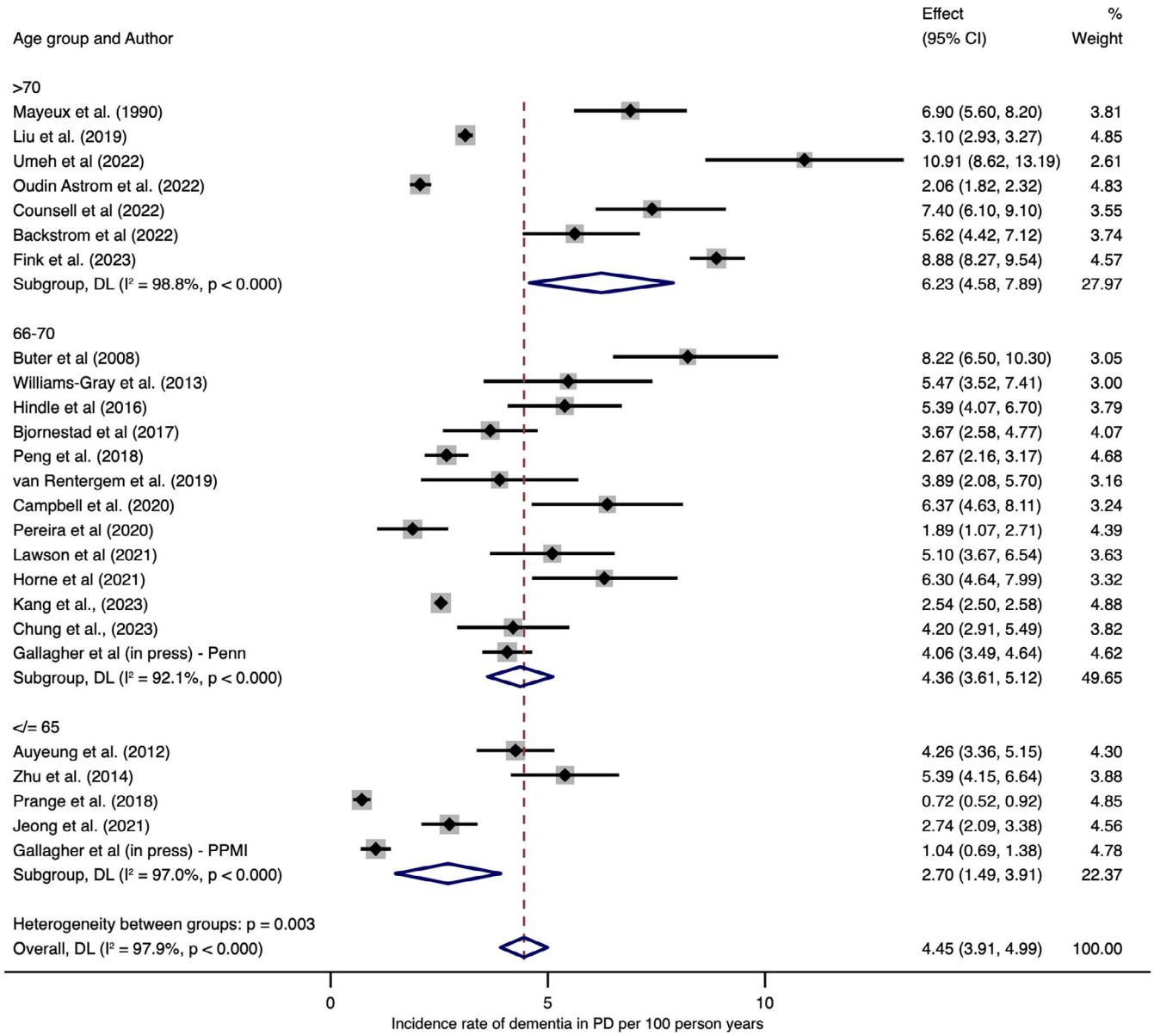

FIG. 3. Forest plot of the incidence rate of dementia in Parkinson's disease (PDD) per 100 person years in studies grouped by the mean age of participants at baseline. [Color figure can be viewed at wileyonlinelibrary.com]

Risk of PDD Versus HC

Ten studies reported on the relative risk of PDD versus HC, in three studies the hazard ratio was calculated from the published Kaplan–Meier curves. The pooled estimate was 3.25 (95% CI, 2.61–4.03) indicating the risk of PDD is three times the risk of dementia in HC (Fig. 4). The overall heterogeneity across studies was high ($I^2 = 98.4\%$, $P < 0.001$). There was minimal difference in the RR in sensitivity analysis excluding the three studies where the hazard ratio was calculated from published Kaplan–Meier curves (RR, 3.33 [95% CI, 2.64–4.21]). The quality of studies included in this meta-analysis was variable (good n = 5, poor n = 5), but quality of study did not contribute to differences in the pooled estimate of RR (Q = 0.02, $P = 0.88$).

TABLE 3 *Pooled incidence rate of PDD per 100 person years in studies with age-stratified incidence rates (n = 4)*

Age group	Pooled incidence rate per 100 person years	95% CI	I^2 %
Under 70	2.65	1.81–3.50	93.6
70–79	5.72	3.87–7.56	97.7
80+	8.13	5.14–11.13	98.2

Abbreviations: PDD, dementia in Parkinson's disease; CI, confidence interval.

Publication Bias

There was no evidence of publication bias for RR measures from visual inspection of funnel plots

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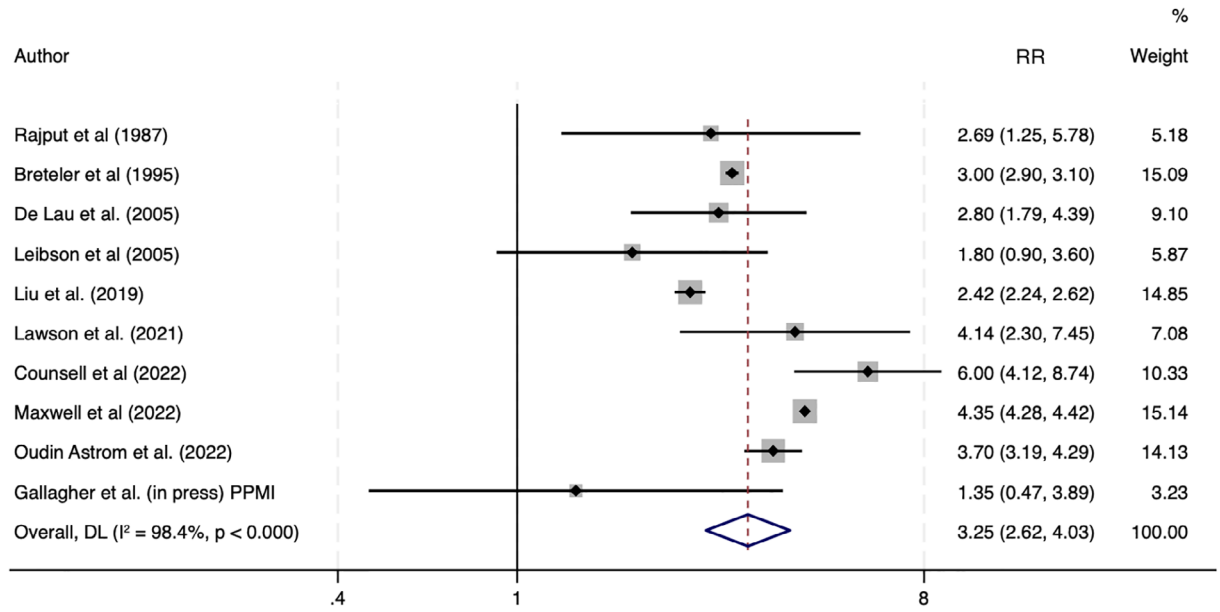

FIG. 4. Forest plot of secondary meta-analysis of the pooled relative risk of dementia in Parkinson's disease versus healthy controls. RR, relative risk. [Color figure can be viewed at wileyonlinelibrary.com]

(Supplementary Fig. S1e13) and Egger's test was non-significant ($P = 0.27$).

Discussion

In this systematic review and meta-analysis, we estimate the incidence of PDD and examine the influence of study and patient-associated factors on the risk of PDD. The pooled incidence rate of PDD was 4.45 (3.91–4.99) per 100 person years, equivalent to a 4.5% annual risk of dementia in a dementia-free PD prevalent population. However, this should be interpreted with caution because of the degree of heterogeneity in the estimates between studies ($I^2 = 97.9\%$, $P < 0.001$). Because of this heterogeneity, we also report the median incidence rate that indicated a similar risk of PDD with an incidence rate of 4.23 per 100 person years. Additionally, the risk of dementia was estimated to be 3.25 times greater in PD than in HC.

The location of the study, the year of recruitment, and the mean age of included participants were identified as significant sources of heterogeneity between studies estimating the incidence rate of PDD. In individuals over 80 with PD, the estimated annual risk of developing dementia was 8.1% versus 2.7% annual risk of dementia for patients under 70 with PD. Consistent with these findings, increased age has previously been established as a risk factor for developing PDD.[23,63,64] Indeed, several of the included studies found the incidence rate of dementia increased progressively with age.[16,29,47,55] Furthermore, although age and duration of disease are often interrelated factors, previous studies have suggested, in line with our findings, that it is age that is most associated with an increased risk of developing dementia.[23,64,65] This is also highlighted by the low conversion to dementia over 20 years reported in individuals with early onset PD.[66] The increased risk of PDD with advancing age likely occurs secondary to the age-associated increase in the burden of α-synuclein, vascular, and Alzheimer's disease neuropathological change, which independently predict cognitive decline and dementia.[67-69] H&Y stage was another factor associated with the incidence of PDD, suggesting it is the stage of disease, rather than duration that contributes to an elevated risk of PDD.[17,70]

The incidence rate of PDD was higher in older studies where the first patient was recruited before the end of 2007. This recent decline in the incidence rate of PDD corresponds with the longitudinal decline in the incidence of all-cause dementia reported in population studies in North America and Europe, although this decline may now be in reverse.[14,31,71] Although the cause of this is not fully established, recent changes in management and health interventions targeting key risk factors may contribute to reductions in the incidence of both PDD and other causes of dementia.[6,72] However, a number of study factors including the study quality, changes in the ascertainment of dementia diagnosis and overrepresentation of older patients in earlier studies may also contribute to the higher incidence rate of PDD in older studies. The MDS PDD criteria were introduced in 2007 to provide consensus guidelines to improve consistency in the diagnosis of PDD.[73] Despite this, we found significant heterogeneity across studies using the MDS PDD criteria ($I^2 = 94.4\%$, $P < 0.001$) and we did not find heterogeneity between groups

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dependent on the diagnostic criteria applied. However, the wide CI where "other" diagnostic criteria are used suggests that use of other global measures of cognition such as Clinical Dementia Rating (CDR), Scale for Outcomes in Parkinson's Disease-Cognition (SCOPA-COG) or Unified Parkinson's Disease Rating Scale (UPDRS) to support dementia diagnoses leads to significant variability in reported incidence rates of PDD.

The pooled incidence rate of PDD was lowest in studies conducted in Asia and highest in studies conducted in North America. This suggests that the risk of dementia is not uniform across all populations and may reflect ethnic or other differences across the respective study populations. However, considerable geographical gaps remain with no studies found reporting the incidence rate of PDD in South America or Africa.

Other patient characteristics such as education and presence of MCI that have previously been established as risk factors for the conversion to dementia[15,17,26,64,74,75] were not identified as significant sources of heterogeneity in our study. However, these factors were not reported by all studies included in the meta-analysis, so the pooled incidence rate was taken from a smaller sample. They may also have been confounded by other factors contributing to differences in the incidence rate; for example, in one study the older age of patients may have disproportionately increased the PDD incidence rate despite a low % of MCI at baseline,[55] contributing to a higher overall estimate of the incidence of PDD in studies with <25% of patients with MCI at study entry (see Supplementary Appendix S1e9). Unfortunately, there were insufficient studies available to facilitate use of multivariable meta-regression to adjust for the confounding effects of variables and the low power for meta-regression analyses is a limitation of this study. Nevertheless, it is likely that multiple factors including age, education, MCI, and study design all contribute differentially to the risk of dementia across each study, and therefore, it is important to consider the individual risk factors pertinent to each patient when discussing future risk of dementia.

In addition, although other sources of heterogeneity, such attrition rates, were identified in the assessment of quality, this was highly variable across studies (see Supplementary Table S4). There was a high attrition rate in most of the prospective studies included that increased with longer durations of follow up.[9,15,21,35] Studies comparing the attributes of individuals who dropped out invariably reported they were older with lower cognitive ability and more advanced disease suggesting cases of dementia may have been overrepresented in those lost to follow up.[10,21,48,76,77] Although some degree of attrition is inevitable in prospective studies with prolonged follow up, this may have led to underestimates in the incidence rate of dementia and contributed to differences across studies. Furthermore, the greater attrition rate in studies with longer follow up may contribute to the lower pooled estimated incidence rate in studies with >10 years follow up relative to <5 years (Table 1). There was also heterogeneity in the reporting of attrition rate across studies; studies excluding non-responders from baseline analysis potentially introduce additional bias,[43] whereas in others there was no description of the patients lost to follow up.[45] The lower incidence rate in retrospective studies relative to prospective studies may in part reflect ascertainment bias; patients included in large retrospective studies often rely on routine clinical care, whereas participants in prospective studies are assessed frequently with rigorous implementation of clinical guidelines. However, the testing interval was also variable across studies (range, 0.5–4 years) and longer intervals likely missed cases of PDD because of increased attrition from death in the interval (particularly given PDD is associated with increased mortality).[12,61]

The current study pooled 95,388 persons with PD over 7.55 years of follow up to estimate the incidence of PDD and used Cochran's Q and meta-regression to identify possible sources of heterogeneity across studies. However, there are several limitations that need to be addressed. Heterogeneity across studies was high and although we have discussed a number of potential factors, not all sources have been identified. For example, genetic differences in apolipoprotein E (APOE) or β-glucocerebrosidase (GBA) are known to influence the progression of cognitive decline in PD, but were not explored in this meta-analysis.[78] Furthermore, we have estimated the incidence rate of PDD, but the rate of dementia is not continuous throughout the course of the disease, likely rising as age and neuropathological co-morbidity increases. This is best illustrated in the Campaign cohort where the incidence rate of PDD increased from 3.87 per 100 person years at 5 years to 5.47 at 10 years.[9,22] Nonlinear cognitive decline was also described in a second cohort with an inflection point reported at 13 years post diagnosis.[79] Further studies are needed to explore differences in the incidence of dementia as PD progresses. Additionally, to maximize the number of studies included in the meta-analysis, inclusion of a control group was not a requirement in our primary analysis. We conducted a secondary meta-analysis to estimate the risk of PDD versus HC, but the reduced number of studies limited the possible subgroup analyses.

The pooled incidence rate of PDD in this meta-analysis equates to an annual risk of 4.5%, which suggests the cumulative incidence of dementia at 10 years is close to the 50% often cited,[5,6,9,15,46,47] and we find the risk of PDD is 3.2 times greater than in similarly aged HC. However, in studies that recruited patients with PD after 2007, the pooled incidence rate is 3.10 per 100 person years, which indicates the current cumulative incidence of dementia at 10 years may only

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be 30%. Moreover, it is crucial to acknowledge the heterogeneity and differences associated with estimates to highlight the importance of considering a wide range of demographic and clinical factors when communicating the risk of dementia to individuals with PD. Future studies should aim to reduce heterogeneity by stratifying estimates by age and applying more homologous study methods across a range of diverse populations.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article and the full data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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