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Review article

Conversion to MCI and dementia in Parkinson's disease: a systematic review and meta-analysis

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ABSTRACT

Objective: To systematically review and meta-analyse conversion rates from normal cognition to Mild Cognitive Impairment (MCI) and dementia in Parkinson's disease (PD) patients. Reversion rates in patients with MCI (i.e. PD-MCI) were also investigated.

Methods: Electronic searches of PsycINFO, Medline and EBSCOhost were conducted in January 2018, with 1833 articles identified after duplicate removal. Articles were included if they assessed conversion/reversion in PD patients between normal cognition, PD-MCI and PD dementia (PD-D).

Results: In total, 39 articles met the inclusion criteria, representing 4011 patients (mean age range 58–75; 61% male). Within three years, in those with PD and normal cognition, 25% (95%CI 20–30%) converted to PD-MCI and 2% (95%CI 1–7%) converted to dementia. Of those with PD-MCI, 20% (95%CI 13–30%) converted to dementia while 28% (95%CI 20–37%) reverted back to a state of normal cognitive function. The conversion rates to MCI and dementia were higher, and reversion rates lower, when follow-up was ≥3 years. When International Parkinson and Movement Disorder Society (MDS) criteria were used to diagnose MCI, Level I criteria were associated with a greater reversion estimate from PD-MCI to normal cognitive function.

Conclusions: These findings summarise the trajectory of cognitive impairment in PD and highlight that MCI is common in this patient group. Understanding cognitive trajectories in PD patients is important for patient care in terms of prognosis, as well as for identifying windows for intervention for cognitive symptoms. As the number of PD patients increases with an ageing population, this information can inform future policy and planning.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder clinically defined by motor dysfunction [1]. A key non-motor comorbid symptom is cognitive impairment [2], which can have a greater effect than motor symptoms on the quality of life of the patient and carer [3], as well as being a risk factor for early mortality [4]. Mild Cognitive Impairment (MCI) is an intermediate cognitive stage on the continuum between normal cognitive functioning and dementia, and is associated with an increased risk of dementia [5]. Fifteen to forty percent of PD patients meet MCI (PD-MCI) criteria at the time of diagnosis [6,7], and this increases to 20–57% at three to five years [8,9]. PD-MCI is therefore a critical state to consider as it develops early in PD [10], and as the disease progresses, patients with PD are up to six times more likely to develop dementia (PD-D) than the general population [11] and the risk is greatest in those presenting with PD-MCI [12].

It is estimated that 19–38% of patients with PD have PD-MCI [13], and 17–31% have PD-D [14]. The prevalence and severity of cognitive impairment increases with age and time since diagnosis, with over 80% of individuals developing PD-D within 20 years of diagnosis [15]. Many different diagnostic criteria for MCI exist [16], of which the most commonly applied in clinical and research settings are the Petersen [5] and the International Working Group MCI Criteria [17]. However, in PD patients, the most frequently applied criteria are those developed by the Movement Disorder Society (MDS) [18]. In addition to a diagnosis of PD based on UK PD Brain Bank Criteria [18], these criteria require assessment of cognitive function using either an abbreviated Level I (LI) or a more comprehensive Level II (LII) assessment [18]. Each level

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includes suggested tests and cut-off scores, between one to two standard deviations below norms, for defining impairment specific in PD patients [18]. LI criteria require either impairment on a global cognitive test validated for use in PD or impairment on two tests within any cognitive domain (e.g. memory, attention, language etc.) [18]. Contrastingly, LII criteria require two tests in each of five cognitive domains (attention and working memory, executive function, language, memory and visuospatial function), with impairment on at least two tests in one cognitive domain or on two tests in different cognitive domains [18]. Compared to LI criteria, LII criteria are a more conservative classification of PD-MCI and capture more severely impaired individuals.

While patients with PD-MCI are at increased risk of converting to PD-D [18] it is also common for patients to revert back to a state of normal cognitive function (i.e. PD-N) [19], similar to findings in non-PD groups [20]. Although reverting back to normal cognition from MCI may be due to factors during assessment, such as tiredness, being nervous about taking a test, stress [21] or, in the case of those with PD, dopaminergic replacement medication [22]; MCI is also known as a transient and (slowly) fluctuating state [23], increasing the difficulty of assessment. However, MCI is now considered a clinically meaningful state and is being increasingly diagnosed in the community [24]. It is therefore important and timely to synthesise and evaluate findings relative to MCI trajectories.

Cognitive decline in PD can occur relatively quickly, with 50% of patients showing significant decline within three years [25]. Previous reviews have focused on the prevalence of PD-MCI or PD-D; that is, percentages of patients classified at one point in time. Although useful for policy and planning [14,26], these are not as useful in providing information on prognosis (in terms of longitudinal change).

Therefore, the primary aim of this systematic review is to summarise conversion rates from PD-N to PD-MCI or PD-D, and from PD-MCI to PD-D, as well as reversion rates back to PD-N from PD-MCI. The secondary aim is to investigate how MCI classification criteria influence conversion rates. While MCI is an important intermediary cognitive state that is difficult to classify, it is also an ideal time to implement interventions to reduce risk of more severe cognitive decline and dementia.

2. Method

2.1. Search strategy

This review adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [27]. An electronic literature search was performed on the 14th January 2018, using PsycINFO and Medline through Ovid, and EBSCOhost. The search terms included: Parkin* AND mci OR mild cognitive impairment OR mild neurocognitive disorder.

Articles were included if they assessed conversion to or from MCI/mild neurocognitive disorder, from or to PD-N, or to PD-D. Studies were included if they were longitudinal; had operationalised definitions of normal cognitive functioning, MCI and dementia; examined one or more of the conversion stages; were peer reviewed; and, published in English. Articles were excluded if participants did not have a clinical diagnosis of PD, and had parkinsonism symptoms due to other causes [28], or if PD-MCI was not captured (i.e. study only assessed conversion from PD-N to PD-D without assessing PD-MCI).

Titles and abstracts were screened to identify articles that were eligible for inclusion. If the article was not rejected in this preliminary assessment, the full text article was obtained to evaluate against the inclusion/exclusion criteria. Eligibility of articles was assessed by two independent reviewers (DS and DG). Fig. 1 shows the results of the electronic search and article selection as per PRISMA guidelines [29]. Data extracted included: author and date, sample type, sample size with sex breakdown, age, diagnostic criteria used for PD-MCI and PD-D, follow-up time, sample size at baseline for PD-N and PD-MCI where applicable, and conversion rates for each stage. Diagnostic criteria for MCI using MDS criteria [18] of LI or LII with standard deviation cut-offs were also extracted when provided. In studies that included more than one follow-up period, data were extracted from the previous follow-up, not the baseline. For example, if baseline and two follow-up periods were included, first, data between baseline to first follow-up were extracted, then data between first follow-up and final follow-up were extracted.

2.2. Quality assessment

Quality of studies was based on the combination of two existing checklists used for cohort studies [30,31]. This was performed by two reviewers (DS and DG), with higher scores indicating higher quality study design, with scores ranging from 0 to 14.

2.3. Statistical approach

Comprehensive Meta-Analysis V3 (CMA) was used for meta-analyses. For studies with multiple classification criteria for MCI (e.g. MDS LI and LII), all data were entered, i.e. relative to each classification. For studies with multiple follow-ups (e.g. cohort assessed at 2, 3 and 6 years), conversion data were entered relative to each follow-up. However, due to the way frequencies and percentages were presented across the included studies, the follow-up period was relative to the last assessment, not study baseline. For example, if a cohort was assessed at 2, 3 and 6 years, they had 2 (baseline to 2 years), 1 (2–3 years) and 3 (3–6 years) year follow-ups.

For studies with multiple outcome classifications (i.e. MCI or dementia) and/or follow-up periods, event-rates were averaged across outcome definitions and follow-up periods within studies (i.e. individual studies were entered only once into the pooled statistic); this was done within the CMA package. A random effects model was used. Pooled conversion rates of normal cognition to PD-MCI and PD-D; from PD-MCI to PD-D; and, reversion from PD-MCI to PD-N were calculated separately. Conversion and reversion rates relative to MCI classification criteria (any MDS, MDS LI and MDS LII), and follow-up period (any, under 3 years, and 3 years and over) were also calculated separately.

3. Results

A total of 3099 articles were identified for initial screening. After removal of 1266 duplicates, 1833 articles remained. After screening titles and abstracts, 142 articles met inclusion criteria and were selected for review. One-hundred and three articles were excluded with reasons provided in Fig. 1. In total, 39 articles were included in this systematic review and meta-analysis and are listed in Table 1. A critical appraisal assessment found all the studies to be of good quality. The average score was 8.7 (ranging from 7 to 11), out of a possible score of 14 (see Table 1) with no studies excluded due to poor quality.

3.1. Description of studies

All 39 studies measured conversion rates that either included one or more of the following; PD-N to PD-MCI, PD-N to PD-D, PD-MCI to PD-D, or PD-MCI reverting back to PD-N. The earliest study was published in 2006 [50], with the remaining 38 studies published between 2010 and 2018. Sample sizes ranged from 24 to 390, with 62% of studies with a sample size below 100. Follow-up times varied from one to sixteen years. The most common follow-up period was two years (n = 10 studies; see Table 1). Seven studies measured follow-up at multiple time points [10,11,19,38,41,47,53].

There were studies included in this review where there may-be some overlap of samples. Attempts were made to confirm this with authors, however we were not always able to get a response, or when we did, the extent of overlap was not confirmed. As the sample

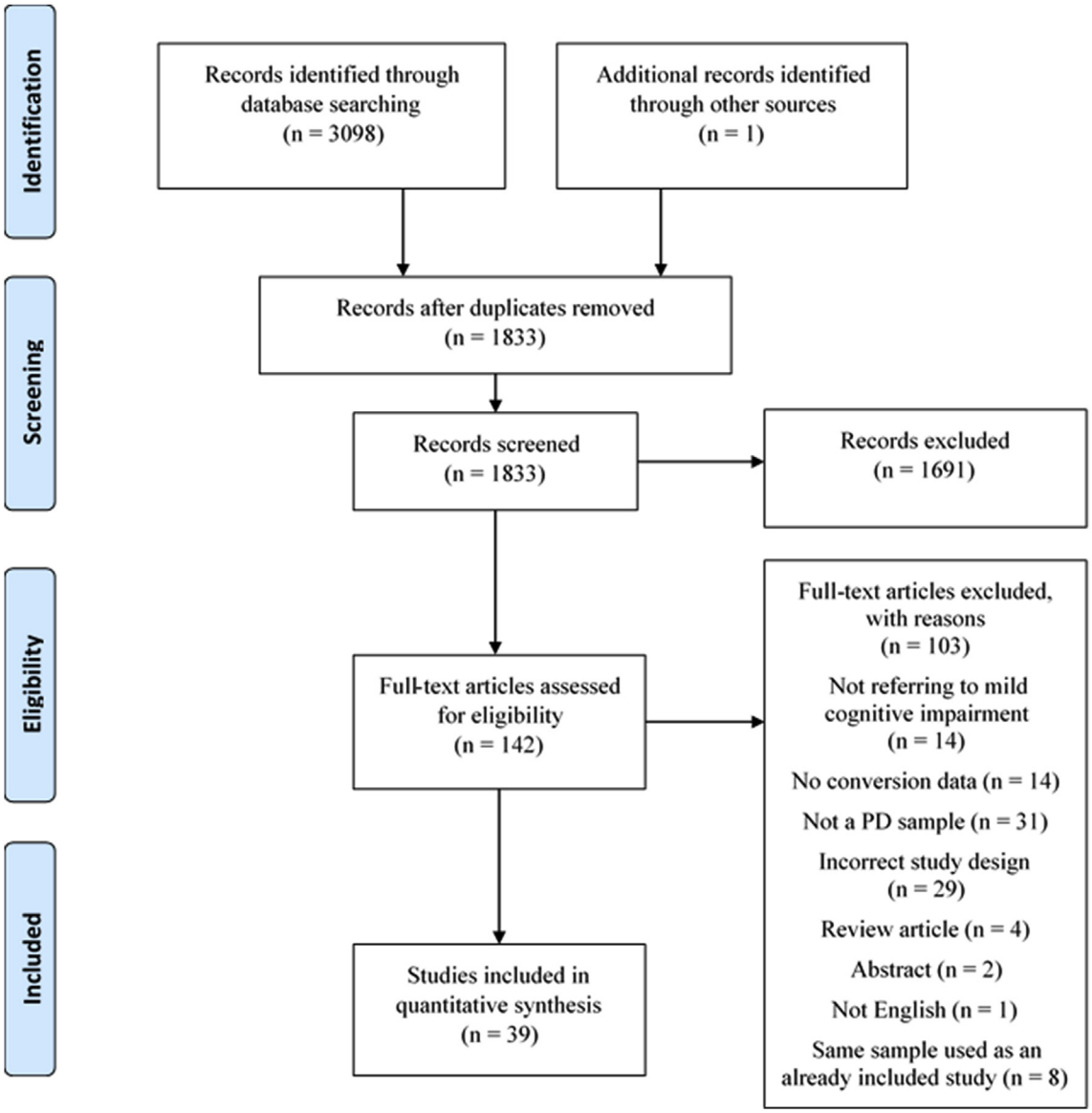

Fig. 1. The article selection and screening process using the PRISMA flow diagram [29]. Databases searched included PsycINFO and Medline through Ovid, and EBSCOhost.

characteristics differed, the studies were included. This consisted of three studies conducted in Italy [10,42,58], five Korean studies [39,48,54,63,67], and three Singapore studies [43,52,64]. Although the PPMI (Parkinson's Progression Markers Initiative) sample was used for two studies [51,62], they were both included as they had different baseline characteristics (including sample size and diagnostic distribution); further, one study was a one-year follow-up and the second study was a two-year follow-up.

Studies came from: Norway (n = 2), Canada (n = 4), Japan (n = 1), Sweden (n = 1), Italy (n = 4), USA (n = 5), Netherlands (n = 1), Singapore (n = 3), Spain (n = 3), China (n = 1), UK (n = 3), Korea (n = 5), Australia (n = 1), India (n = 1), Germany (n = 1), New Zealand (n = 1) and the PPMI sample that included sites in USA, Europe and Israel (n = 2). Thirty-four samples were clinical based (see Table 1). They included patients from hospitals or specialist PD centres and university clinics. The largest clinical study, consisting of 390 participants, was the PPMI, which includes newly diagnosed PD participants from over 30 different sites [62]. In contrast, only three were population based and two were community based (see Table 1).

The pooled mean age of participants was 66 years, with the youngest sample having a mean age of 58 [61] and the oldest having a mean age of 75 years [11]. Thirty-eight studies included both female and male participants and one study did not report sex distributions [10]. The total 39 studies represented 4011 PD patients; out of the 38 studies that included sex distributions, 39% were female, consistent with literature reporting a higher prevalence of PD in males [68].

3.2. PD-MCI diagnostic criteria

Most studies (n = 27) used the MDS criteria for classifying PD-MCI [18]. Of the studies that used MDS criteria, nine studies used LI criteria and 14 studies used LII criteria (see Table 1). Four studies used both LI and LII criteria [12,53,57,63]. The PPMI protocol, which follows MDS criteria, was used in one study [62]. Of the remaining eleven studies, three studies used Petersen criteria [35,47,50]; the reasons given for this, were that one was not able to adhere to MDS criteria, due to limited testing used in a retrospective sample [35]; another was due to cultural reasons [47]; and the final study was conducted before MDS diagnostic criteria were established [50]. One study [46] used a combination of the International Working Group and Petersen criteria for a

Table 1
Summary of included articles.

Authors	Sample Type	Total sample size (*n*)	Age *M* (*SD*)	PD-MCI diagnostic criteria (*SD*)	PD-D diagnostic criteria	Follow-up	PD-N sample size at base-line	PD-N to PD-MCI %	PD-N to PD-D %	PD-MCI sample size at base-line	PD-MCI to PD-N %	PD-MCI to PD-D %	CA (/14)
Anang, Gagnon, Bertrand, Romenets, Latreille, Panisset, Montplaisir and Postuma [32]	Patients recruited from Movement Disorders Clinics of McGill University Health Centre, Canada, clinical sample	80 (29 Female, 51 Male)	66.2 (10.9)	MDS Level I (1-2)	MDS Level I and II	4.4 years (mean)	38	n/a	n/a	42	n/a	52	10
Baba, Hosokai, Nishio, Kikuchi, Hirayama, Suzuki, Hasegawa, Aoki, Takeda and Mori [33]	Tohoku University Hospital, Japan, clinical sample	46 (26 Female, 20 Male)	65.6 (6.4) (PD-N) 64.9 (6.5) (PD-MCI)	MDS Level I (1)	MDS Criteria Level I	3 years	29	31	10	17	65	18	7
Battista, Rubino, Valente, Giustini, Vanacore and Meco [34]	Outpatient service, Parkinson's disease centre, Rome, clinical sample	54 (21 Female, 30 Male)	69.7 (8.1)	MDS Level II (*SD* n/a)	MDS Criteria	4.7 years (mean)	32	34	6	22	n/a	36	8
Besser, Litvan, Monsell, Mock, Weintraub, Zhou and Kukull [35]	USA, mainly clinical sample	41 (16 Female, 25 Male)	70.2 (8.5)	Petersen criteria [36] (*SD* n/a)	Clinical Dementia Rating	1 year	n/a	n/a	n/a	41	n/a	5	11
Blume, Lange, Rothenfusser, Doenitz, Bogdahn, Brawanski and Schlaier [37]	Germany, clinical sample	40 (10 Female, 30 Male)	61.8 (6.7)	MDS Level II (2.0)	MDS Criteria	3 years	14	n/a	14	26	n/a	31	8
Broeders, de Bie, Velseboer, Speelman, Muslimovic and Schmand [38]	Referred by neurology outpatient clinics,	123 (57 Female, 66 Male)	65.1 (10.6) (PD-N)	MDS Level II (1.5)	MDS Criteria	3 years	62	37	5	35	11	17	10
	Amsterdam, clinical sample		68.2 (8.1) (PD-MCI)			3 - 5 years	31	19	0	33	9	24	
#Chung, Shin, Cho, Lee, Sohn, Seong and Lee [39]	Patients from university hospital, Korea, clinical sample	182 (89 Female, 93 Male)	71.4 (6.8) MCI converters 69.2 (6.5) MCI non-converters	Seoul Neuropsychological Screening Battery	Seoul Neuropsychological Screening Battery	3 years (mean)	n/a	n/a	n/a	182	n/a	41	8
Claassen, Josephs, Ahlskog, Silber, Tippmann-Peikert and Boeve [40]	USA, Mayo clinical sample with RBD	27 (3 Female, 24 Male)	72 (median)	Clinical diagnosis	MDS Criteria	6.2 years (mean)	9	11	44	3	n/a	33	9
Domellof, Lundin, Edstrom and Forsgren [41]	Sweden, population sample	125 (50 Female, 75 Male)	71.1 (median)	MDS Level II modified, language not assessed) (*SD* n/a)	MDS Criteria	1 year	72	15	0	53	21	9	11
						1-3 years	72	21	0	43	2	26	
						3-5 years	57	30	0	40	10	38	
						5-8 years	33	27	0	28	4	50	
*Erro, Santangelo, Barone, Picillo, Amboni, Longo, Giordano, Moccia, Allocca, Pellecchia and Vitale [42]	Patients from Parkinson's disease Centre in Naples, Italy, clinical sample	76 (29 Female, 47 Male)	60.5 (8.3)	MDS Level I (*SD* n/a)	n/a	2 years	38	42	n/a	27	n/a	n/a	8
+Foo, Mak, Yong, Wen, Chander, Au, Sitoh, Tan and Kandiah [43]	Tertiary neurology centre, Singapore, clinical sample	54 (13 Female, 41 Male)	63.39 (6.86)	MDS Level II (1.5)	n/a	1.5 years	54	22	n/a	n/a	n/a	n/a	10
Galtier, Nieto, Lorenzo and Barroso [12]	Patients with idiopathic PD recruited from Candelaria University Hospital, Spain, clinical sample	43 (19 Female, 24 Male)	59.19 (9.64)	MDS Level I and Level II (1.5)	MDS Criteria	6 – 8 years	15	n/a	27	24	54	46	8
				MDS Level I (1.5	MDS Criteria	6 – 8 years	29	n/a	34	10	50	50	
Garcia-Diaz, Segura, Baggio, Uribe, Campabadal, Abos, Marti, Valldeoriola, Compta, Bargallo and Junque [44]	Patients from outpatient movement disorders unit, Spain, clinical sample	44 (14 Female, 30 Male)	61.68 (9.93)	MDS Level II (1.5)	MDS Criteria	4 years	28	39	0	16	31	1	9

(*continued on next page*)

Table 1 (*continued*)

Authors	Sample Type	Total sample size (*n*)	Age *M* (*SD*)	PD-MCI diagnostic criteria (*SD*)	PD-D diagnostic criteria	Follow-up	PD-N sample size at base-line	PD-N to PD-MCI %	PD-N to PD-D %	PD-MCI sample size at base-line	PD-MCI to PD-N %	PD-MCI to PD-D %	CA (/14)
Gasca-Salas, Estanga, Clavero, Aguilar-Palacio, Gonzalez-Redondo, Obeso and Rodriguez-Oroz [45]	Patients recruited from Movement Disorder Unit of the University Clinic of Navarra, Spain, clinical sample	49 (15 Female, 34 Male)	69.2 (median)	MDS Level II (1.5)	MDS Criteria	31 months	23	22	4	26	n/a	42	10
Gomperts, Locascio, Rentz, Santarlasci, Marquie, Johnson and Growdon [46]	Prospective cohort study, USA, clinical sample	46 (13 Female, 33 Male)	68.5 (6.2)	Winblad criteria (1)	MDS Criteria	5 years (maximum)	35	23	3	11	9	45	8
Gu, Chen, Lu and Pan [47]	Department of neurology of the Southern Medical University, Guangzhou, China, clinical sample	26 (7 Female, 19 Male)	61.72 (PD-MCI) 64.48 (PD-D)	Petersen criteria (1.5)	MMSE	1 year 2 years	n/a n/a	n/a n/a	n/a n/a	17 14	n/a n/a	18 21	8
Hobson and Meara [11]	PD cohort in North Wales, UK, clinical sample	166 (75 Female, 91 Male)	71.3 (PD-N) 74.8 (PD-MCI) 77.6 (PD-D)	MDS Level I (1.5)	MDS Criteria Level I	4 years 4 - 6 years 16-year survivors	37 14 2	41 71 100	16 14 0	14 14 2	0 7 0	86 64 100	9
#Hong, Sunwoo, Chung, Ham, Lee, Sohn and Lee [48]	Patients from university hospital, Korea, clinical sample	46 (31 Female, 15 Male)	66.2	MDS Level I (1)	n/a	2.4 years (mean)	46	28	n/a	n/a	n/a	n/a	10
Hu, Szewczyk-Krolikowski, Tomlinson, Nithi, Rolinski, Murray, Talbot, Ebmeier, Mackay and Ben-Shlomo [49]	Oxford discovery cohort, UK, population sample	155 (66 Female, 89 Male)	67.3 (8.7)	MDS Level I with MoCA (*SD* n/a) MDS Level I with MMSE (*SD* n/a)	MDS Criteria MDS Criteria	1.5 years 1.5 years	84 70	39 26	0 16	64 43	33 49	11 19	9
Janvin, Larsen, Aarsland and Hugdahl [50]	Community based study, Norway, community sample	72 (40 Female, 32 Male)	71 (8.1)	Petersen criteria modified (1.5)	DSM-III-R criteria	4 years	30	n/a	20	29	n/a	62	10
Jones, Kuhn and Szymkowicz [51]	Parkinson's Progression Markers Initiative cohort, 33 sites in USA, Europe, Israel and Australia, clinical sample	364 160 Female, 204 Male)	60.1 (9.80)	MoCA (*SD* n/a)	MoCA (*SD* n/a)	1 year	257	28	n/a	107	39	n/a	8
+Kandiah, Zhang, Cenina, Au, Nadkarni and Tan [52]	Tertiary neurology centre, Singapore, clinical sample	64 (16 Female, 48 Male)	66.37 (7.86)	MDS Level II (1.5)	MDS Criteria	2 years	42	31	n/a	22	n/a	41	9
Lawson, Yarnall, Duncan, Breen, Khoo, Williams-Gray, Barker, Burn and group [53]	Community and clinical samle, UK	212 (78 Female, 134 Male)	61.2 (10.1) (PD-N) 67.3 (8.4) (PD-MCI *SD* 1.0) 69.1 (8.8) (PD-MCI *SD* 1.5) 68.7 (9.0) (PD-MCI *SD* 2.0)	MDS Level II modified (1, 1.5 and 2.0) MDS Level I	n/a n/a	1.5 years 3 years 1.5 years 3 years	73 60 111 103	22 30 15 14	0 0 0 0	139 130 77 60	12 14 25 17	5 8 8 13	9
#Lee, Cho, Song, Kim, Lee, Sohn and Lee [54]	Patients from university hospital, Korea, clinical sample	51 (17 Female, 34 Male)	70.6 (6.8) (PD-MCI non-converters) 73.2 (5.6) (PD-MCI converters)	Seoul Neuropsychological Screening Battery (1.0)	Seoul Neuropsychological Screening Battery	2 years	n/a	n/a	n/a	51	n/a	29	7

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Table 1 (*continued*)

Authors	Sample Type	Total sample size (*n*)	Age *M* (*SD*)	PD-MCI diagnostic criteria (*SD*)	PD-D diagnostic criteria	Follow-up	PD-N sample size at base-line	PD-N to PD-MCI %	PD-N to PD-D %	PD-MCI sample size at base-line	PD-MCI to PD-N %	PD-MCI to PD-D %	CA (/14)
Loftus, Bucks, Thomas, Kane, Timms, Barker and Gasson [55]	Ongoing ParkC study in Western Australia, community sample	104 (36 Female, 68 Male)	62.34 (8.93) (PD-N) 70.63 (6.03) (PD-MCI single domain) 68.53 (8.4) (PD-MCI multiple domain)	MDS Level II (1.5)	MDS Criteria	2 years	65	31	n/a	39	23	n/a	8
McDermott, Fisher, Bradford and Camicioli [56]	Canadian community and clinical sample	51 (21 Female, 30 Male)	71.49 (4.65)	MDS Level II (1.5) MDS Level II (2.0) Clinical Dementia Rating Scale Dementia Rating Scale	MDS Criteria MDS Criteria Clinical Dementia Rating Scale Dementia Rating Scale	3 years 3 years 3 years 3 years	26 34 41 28	12 6 37 21	0 3 17 4	20 12 7 20	15 0 0 25	50 75 43 35	8
Nagano-Saito, Al-Azzawi, Hanganu, Degroot, Mejia-Constain, Bedetti, Lafontaine, Soland, Chouinard and Monchi [57]	Canadian clinical sample	24 (13 Female, 11 Male)	60.33 (5.8)	MDS Level I and Level II (1.5)	n/a	20 months	12	25	n/a	12	n/a	n/a	8
Pedersen, Larsen, Tysnes and Alves [19]	Norwegian ParkWest study, population sample	178 (64 Female, 114 Male)	63.5 (9.1) (PD-N) 71.3 (7.5) (Prevalent PD-MCI) 71.7 (8) (Incident PD-MCI)	MDS Level I (1.5)	MDS Criteria	1 year 1–3 years 3–5 years	139 132 108	10 18 8	0 1 3	36 32 36	39 16 25	0 31 42	10
*Pellecchia, Savastano, Moccia, Picillo, Siano, Erro, Vallelunga, Amboni, Vitale, Santangelo and Barone [58]	Patients from Parkinson's disease Centre in Naples, Italy, clinical sample	42 (17 Female, 25 Male)	59.3 (8)	MDS Criteria Level II (*SD* n/a)	n/a	4 years	42	55	n/a	n/a	n/a	n/a	7
Pigott, Rick, Xie, Hurtig, Chen-Plotkin, Duda, Morley, Chahine, Dahodwala, Akhtar, Siderowf, Trojanowski and Weintraub [59]	Prospective cohort with normal baseline cognition, Pennsylvania, USA, clinical sample	141 (52 Female, 89 Male)	68.6 (7)	MDS Level I (1.5)	MDS Criteria	6 years	141	43	n/a	n/a	n/a	n/a	10
Postuma, Bertrand, Montplaisir, Desjardins, Vendette, Romenets, Panisset and Gagnon [60]	Patients with PD from sleep disorders laboratory, Canada, clinical sample	42 (8 Female, 34 Male)	67.5 (10.6) (No RBD), 70.5 (7.4) (RBD)	MoCA	MDS Criteria	3.9 years (mean)	19	n/a	0	23	n/a	57	9
*Santangelo, Vitale, Picillo, Moccia, Cuoco, Longo, Pezzella, di Grazia, Erro, Pellecchia, Amboni, Trojano and Barone [10]	Patients from Parkinson's disease Centre in Naples, Italy, clinical sample	76 (Female, Male, n/a)	59.2 (8.7)	MDS Level II (1.5)	MDS Criteria	2 years 2 – 4 years	41 27	29 26	0 0	21 23	10 35	0 13	10
Sanyal, Banerjee and Rao [61]	Hospital based prospective case, India, clinical sample	250 (88 Female, 162 Male)	57.89 (12.065)	MMSE	DSM III-R criteria	7 years	92	n/a	10	90	n/a	13	10

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Table 1 (*continued*)

Authors	Sample Type	Total sample size (*n*)	Age *M* (*SD*)	PD-MCI diagnostic criteria (*SD*)	PD-D diagnostic criteria	Follow-up	PD-N sample size at base-line	PD-N to PD-MCI %	PD-N to PD-D %	PD-MCI sample size at base-line	PD-MCI to PD-N %	PD-MCI to PD-D %	CA (/14)
Schrag, Siddiqui, Anastasiou, Weintraub and Schott [62]	Parkinson's Progression Markers Initiative cohort, 33 sites in USA, Europe, Israel and Australia, clinical sample	390 (136 Female, 254 Male)	61.2 (9.8)	PPMI protocol (1.5)	PPMI protocol	2 years	314	16	1	n/a	n/a	n/a	7
#Sunwoo, Jeon, Ham, Hong, Lee, Lee, Sohn and Lee [63]	Patients from university hospital, Korea, clinical sample	111 (62 Female, 49 Male)	67.7 (7.1) (PD-N) 74.3 (7) (PD-MCI)	MDS Level I and Level II (*SD* n/a)	MDS Criteria	2 years	46	39	n/a	65	n/a	34	8
+Wen, Ng, Chander, Au, Tan and Kandiah [64]	Tertiary neurology centre, Singapore, clinical sample	42 (9 Female, 33 Male	62.5 (8.19) (PD-N) 65.32 (6.34) (PD-MCI)	MDS Level II (1.5)	n/a	1.5 years	42	29	n/a	n/a	n/a	n/a	8
Williams, Arzola, Strutt, Simpson, Jankovic and York [65]	Baylor College of Medicine, USA, clinical sample	37 (12 Female, 25 Male)	66.6 (9.0)(non-DBS) 62.10 (10.3) (STN-DBS)	MDS Criteria (2.0)	Criteria by Caviness and colleagues	2 years	29	21	n/a	8	n/a	75	9
Wood, Myall, Livingston, Melzer, Pitcher, MacAskill, Geurtsen, Anderson and Dalrymple-Alford [66]	Convenience sample of PD patients recruited from research institute and movement disorders clinic, New Zealand, clinical sample	121 (44 Female, 77 Male)	66 (8) (PD-N) 70.2 (5.7) (PD-MCI)	MDS Level II – Three primary criteria (2)	MDS Criteria	4 years	n/a	n/a	n/a	46	20	39	7
				MDS Level II - Three primary criteria (1.5)	MDS Criteria	4 years	n/a	n/a	n/a	56	18	38	
				MDS Level II - Three primary criteria (1)	MDS Criteria	4 years	n/a	n/a	n/a	96	19	25	
				MDS Level II – Two in one domain (1.5)	MDS Criteria	4 yearss	n/a	n/a	n/a	37	3	51	
				MDS Level II – one in each of 2 domains (1.5)	MDS Criteria	4 year	n/a	n/a	n/a	56	7	38	
#Ye, Jeon, Ham, Lee, Lee, Lee, Lee and Sohn [67]	Patients from university hospital, Korea, clinical sample	216 (111 Female, 105 Male)	68.9 (7.1)	MDS Level I (*SD* n/a)	MDS Criteria	2.7 years (mean)	71	n/a	14	145	n/a	28	7

Note. DBS = Deep brain stimulation; DSM III-R = Diagnostic and Statistics Manual of Mental Disorders, Third Edition, Revised; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MDS = Movement Disorder Society; PD-D = Parkinson's disease dementia; PD-MCI = Parkinson's disease Mild Cognitive Impairment; PD-N = Parkinson's disease normal cognition; PPMI = Parkinson's Progression Markers Initiative; RBD = Rapid eye movement (REM) sleep behaviour disorder; *Possible overlap of samples from Italy; #Possible overlap of samples from Korea; +Possible overlap of samples from Singapore; CA = Critical appraisal.

MCI diagnosis [17]. The Seoul Neuropsychological Screening Battery [69], was used for two Korean samples [39,54]. Two studies [51,60] used the MoCA [70]. Criteria by Caviness and colleagues [71] were used for one study [65]. The Mini-Mental State Examination was used for a study administered by a neurologist without reference to MDS criteria [61]. Finally, one study did not state PD-MCI criteria [40].

For defining cognitive impairment four studies used a 1.0 standard deviation cut-off [33,46,48,54], fifteen studies used a 1.5 standard deviation cut-off (see Table 1) and two studies used a 2.0 standard deviation cut-off [37,65]. One study used a 1.0–2.0 standard deviation cut-off [32], and another used 1.5 and 2.0 standard deviation cut-offs [56]. Two studies used three cut-off points (1, 1.5 and 2 SDs) [53,66]. Fourteen studies did not specify what cut-offs were used (see Table 1).

3.3. PD-D diagnostic criteria

MDS diagnostic criteria [2] were used for dementia in 24 studies (see Table 1). Two studies [50,61] used DSM III criteria [72]. One study [47] used the Mini Mental State Examination [73], two studies [39,54] used the Seoul Neuropsychological Screening Battery [69], one study [35] used the Clinical Dementia Rating Scale [74], one study [51] used the MoCA and a final study [62] used PPMI protocol [75]. Six studies [42,43,48,57,58,64] did not specify PD-D criteria, as conversion to PD-D was not part of the study. One final study recording conversion to PD-D did not specify diagnostic criteria [53]. Dementia in this review is considered to be a permanent state, and therefore there are no reversion rates provided from dementia. One paper did report reversal to PD-MCI and PD-N from PD-D [49], however this was found when using MMSE screening cut-off scores, and the same pattern of results were not found using MoCA screening cut-off scores.

3.4. Conversion rates: PD-N to PD-MCI

Twenty-seven studies included conversion rates from PD-N to PD-MCI over follow-up times ranging from one to 16 years (see Table 1). The pooled conversion rate, averaged across all definitions and follow-ups, was 28% (95%CI 24–33%). When follow-up was restricted to within three years, the rate was 25% (95%CI 20–30%) and this increased to 29% (95%CI 22–37%) for follow-up ≥3 years. See Table S1 in the Supplementary Material for full results, including those relating to MCI classification. Heterogeneity for these overall estimates was relatively high (I^2 68–73). Heterogeneity was lower when only including studies using MDS LII criteria. The type of classification system did not appear to affect conversion rates from PD-N to PD-MCI, with all 95%CIs overlapping.

3.5. Conversion rates: PD-N to PD-D

Twenty-one studies included conversions rates from PD-N to PD-D with follow-up times ranging from one to eight years (see Table 1). The averaged conversion rate, across all definitions and follow-ups, was 6% (95%CI 4–11%). For follow-ups under three years, this rate was 2% (95%CI 1–7%), and for follow-ups ≥3 years, this was 8% (95%CI 4–13%). See Table S2 in the Supplementary Material for full results, including those relating to MCI classification. Again, the type of classification system did not appear to affect conversion rates from PD-N to PD-D, with all 95%CIs overlapping; and heterogeneity was generally high, except when only assessing studies using MDS LII criteria.

3.6. Reversion rates: PD-MCI to PD-N

Fifteen studies included results for reverting back to PD-N from PD-MCI (see Table 1). Follow up times ranged from one to six years. The averaged conversion rate, across all definitions and follow-up periods, was 24% (95%CI 17–34%). For studies with follow-up periods under three years, the rate was 28% (95%CI 20–37%), and 21% (95%CI 13–33%) in those studies with follow-up periods ≥3 years. See Table S3 in the Supplementary Material for full results, including those relating to MCI classification. Heterogeneity was the lowest for studies using the MDS LII criteria. The MDS Levels did appear to affect estimates for the overall (i.e. all follow-ups) and < 3 years reversion rates. Across all follow-ups, using LI criteria, 35% (95%CI 22–51%) reverted to PD-N from PD-MCI, as compared to 15% (95%CI 11–21%) for LII criteria. For follow-ups under three years, using LI criteria, 34% (95%CI 24–45%) reverted to PD-N from PD-MCI, compared to 16% (95%CI 11–24%) using LII criteria. Although rates also varied between Levels for follow-ups three years and greater, confidence intervals overlapped: LI 31% (95%CI 14–54%) and LII 16% (95%CI 9–25%).

3.7. Conversion rates: PD-MCI to PD-D

Twenty-nine studies reported conversion rates from PD-MCI to PD-D (See Table 1). Follow-up times ranged from one to seven years. On average, across all definitions and follow-up periods, 31% (95%CI 25–38%) of those with PD-MCI converted to PD-D. The rate was 20% (95%CI 13–30%) for studies with follow-ups less than three years, and 34% (95%CI 27–43%) for those with follow-ups ≥3 years. See Table S4 in the Supplementary material for full results, including those relating to MCI classification; however, MCI classification type did not appear to affect conversion rates (with all confidence intervals overlapping). Heterogeneity was consistently high, even when looking at studies employing MDS LII criteria, which showed lower heterogeneity in other conversion calculations.

All conversion and reversion rates are summarised in Fig. 2.

4. Discussion

This review and meta-analysis is the first to systematically pool conversion and reversion rates from normal cognitive function to MCI and dementia in PD patients. It was found that, within three years, in those with PD and normal cognition, 25% convert to PD-MCI while only 2% progress to PD-D. Further, 20% with PD-MCI progress to PD-D over the same time period. These results support findings of what is seen in non-PD groups, where the risk of converting to MCI is higher than converting to dementia in those with no cognitive impairment [76–78]. Of those diagnosed with MCI, the reversion rate to normal cognitive function was high: 28% within three years. Lower rates of reversion (18%) have been found in non-PD groups [79].

Differences in conversion rates between the two Levels of the MDS criteria for PD-N to PD-MCI, along with PD-N to PD-D, were unremarkable. For example, when assessing conversion between a state of normal cognitive function and PD-MCI, the MDS-LII criteria produced slightly higher (2–4%) estimates than the LI criteria (25% versus 23% for < 3 years; 31% versus 27% for ≥3 years); all confidence intervals overlapped.

With regard to the MCI group, the results show relatively high conversion rates to dementia (31% in all studies combined) and that MDS criteria type – LI or LII – appeared not to dramatically affect conversion rates from PD-MCI to PD-D (all confidence intervals overlapped). This supports findings found in the general population (i.e. not specific to PD) that any cognitive impairment is a risk factor for dementia [80,81]. For conversion from PD-MCI to PD-D, rates were higher for LII than LI criteria for follow-ups less than three years (15% v 13%); while rates were lower for LII criteria than LI for follow-ups three years and greater (27% v 36%). This pattern reflects the LII criteria selecting more severely impaired individuals, who convert to dementia more quickly. However, again, all confidence intervals around pooled conversion estimates overlapped, so the differences between the Levels are not of clinical importance.

Reversion rates from PD-MCI to normal cognitive function were also high (24% overall) and in contrast to the dementia conversion results, there were large differences between estimates using the two Levels of

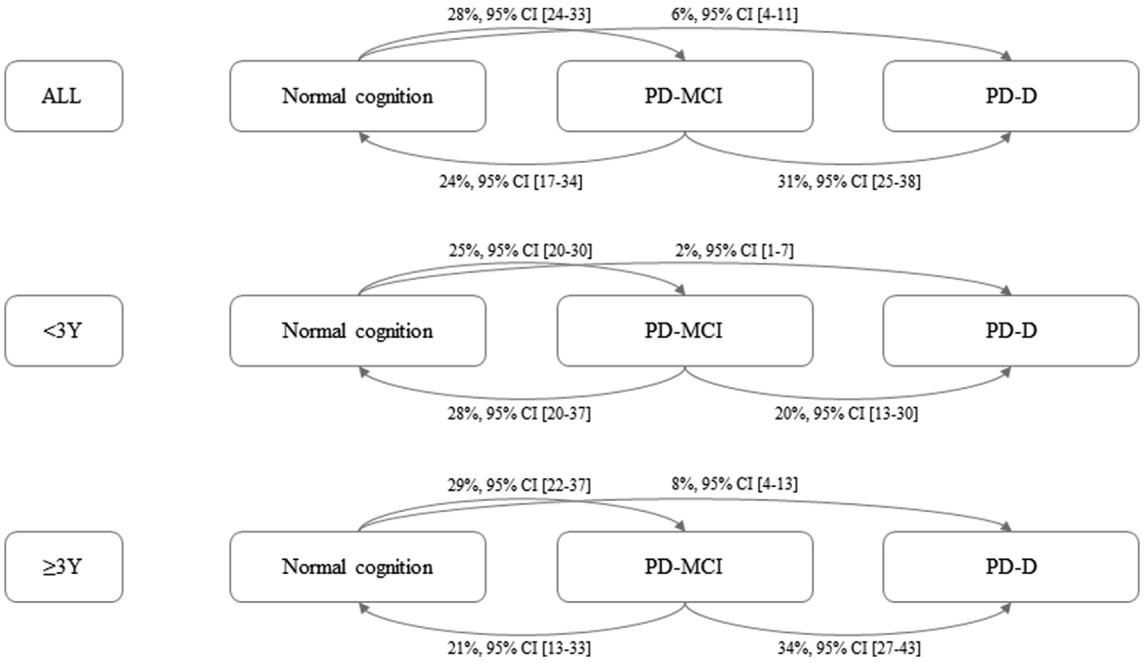

Fig. 2. Graphical summary of meta-analysis of conversion and reversion rates. These rates are averaged over all Parkinson's disease Mild Cognitive Impairment classifications and follow-ups. PD-MCI = Parkinson's disease Mild Cognitive Impairment; PD-D = Parkinson's disease dementia.

criteria (confidence intervals did not overlap for overall estimates regardless of follow-up period, and for < 3 years). Specifically, LII criteria produced much lower reversion estimates: 16% v 34% for < 3 years and 16% v 31% for ≥3 years. These results could be reflecting the fact that LII criteria, by definition, select more severely cognitively impaired individuals, who are less likely to revert back to normal cognitive functioning. This provides a strong justification for using LII criteria; however, it needs to be considered that, in a clinical setting, LII criteria may not be practical due to the additional administration time.

The instability of MCI presents a major challenge to intervention studies focused on dementia prevention. One of the reasons for limited progress in developing interventions for PD-MCI is a lack of robust diagnostic criteria [82], highlighting the need for more uniform criteria in PD-MCI research [83]. This will assist with the design and development of non-pharmacological interventions such as cognitive training, as well as improving the measuring of efficacy of (pharmacological and non-pharmacological) clinical trials. Other challenges include non-cognitive predictors of conversion between cognitive states may have clinical utility. For example, akinetic-dominant sub-type of PD is associated with a higher prevalence of conversion to PD-D than tremor-dominant subtype [61]. Biological predictors of conversion to a more impaired state, reported across included studies, were atrophy in brain regions of frontostriatal [54] and subcortical areas [43]; along with amyloid burden [46] and low serum uric acid [58]. In addition to biological predictors, the influence of depression also needs to be considered as a predictor for dementia [32,61]. Screening for these biomarkers in conjunction with cognitive testing and/or imaging markers including Fluorodeoxyglucose Positron Emission Tomography (FDG PET) [84] may assist with improving diagnostic criteria.

Adding to the challenge of intervention studies are factors that contribute to heterogeneity, which includes sub-types of MCI in PD. Multiple sub-types of MCI in PD have been proposed, including, non-amnestic single domain, non-amnesic multi domain, and amnestic single domain [85,86]. In a large cohort of PD-MCI patients, 39% presented with non-amnestic single domain, 31% with amnestic multiple domain, 23% with non-amnestic multiple domain and 7% amnestic single domain [86]. This illustrates the heterogeneity in MCI classification systems.

As expected, the conversion rate to dementia was higher, and reversion rate to normal cognitive function lower, in PD-MCI cases when looking at follow-up times ≥3 years.

These results are important in demonstrating that cognitive decline is relatively quick in PD, and that we need to take this into account in the design and timing of interventions. Another factor that needs to be considered is that conversion rates may differ in patients with dementia with Lewy bodies, this can contribute to an earlier and faster rate of cognitive decline [7]. Intervention in a state of normal cognitive function, or in the earliest stages of PD-MCI, will likely have the greatest benefit in terms of reducing risk of cognitive decline and incidence of PD-MCI/PD-D. Particularly with findings demonstrating that reversion from PD-MCI to normal cognitive function was lower when follow-ups were greater than three years, as compared to less than three years. Two studies in this review [42,48] demonstrated that those with subjective memory complaints were more likely to convert to PD-MCI from PD-N than those without, further highlighting the importance of early diagnosis and intervention. Examples of interventions include cognitive training and exercise. Cognitive training has been found to be effective in PD, with combined effect sizes ranging from small for overall cognitive outcomes, to large effects for working memory [87]. Exercise has also demonstrated significant results in improving attention and working memory in patients with PD [88]. Intervening before a dementia diagnosis has the most pronounced effect [89].

The variability in prevalence rates of PD-MCI and PD-D are likely due to age, subtype of PD, sampling strategy, and diagnostic criteria [18,90,91]. Distinguishing cognitive impairment due to the ageing process from cognitive impairment due to an early dementia in PD requires accurate diagnostic methods [18], which requires further work in the field. The prevalence of classified cognitive impairments in PD are also complicated by the cognitive domains that can be affected, and those that are measured within studies, which can differ between PD-MCI and PD-D [92]. For example, executive function is a common early impairment [93], but is not a requirement in MDS LI testing [18]. Differences were also observed between studies with population versus clinical samples. A clinical sample is more likely to consist of patients that have a higher degree of severity in their condition, giving a biased impression of condition at a population-level [94], although their

estimates can be well applied within similar clinic settings.

Interestingly, the risk of eventually converting to dementia has been found to be higher in those that have reverted back to a normal cognitive state from MCI [95]. We were unable to assess this using our group-level meta-analytical approach. Using individual-level data would enable this and would be a good avenue for future research.

Although the MDS criteria were commonly used by most of the studies (n = 27), there was a lack of consistency with regards to which level of criteria were used and the cut-off scores. The MDS has a list of recommended cognitive tests; however, there is little conformity with the type of tests used. The Montreal Cognitive Assessment (MoCA) has demonstrated higher sensitivity to executive and visuospatial function impairments associated with PD than the Mini-Mental State Examination (MMSE) [96], and is a recommended test by the MDS [97]. Despite this, the MMSE is commonly used in PD research [98] and was used in many studies included in this review [11,12,19,32,33,35,38,39,41,43–50,52–56,58,60,61,63,65,]. Although most of the studies did use MDS criteria, 11 studies didn't, and this may have contributed to the heterogeneity of results (for overall pooled estimates). For example, conversion rates in studies that used either MDS LI or LII criteria were generally lower compared with those that used any classification. Differences between follow-up up periods and a small number of studies for some analyses are other contributing factors to heterogeneity. Although studies were grouped as less than three years or greater than three years, follow-up times varied considerably. Shorter follow-up periods are more likely to have lower conversion rates, with longer follow-up times not only having higher conversion rates, but also making it difficult to distinguish between changes due to ageing or the disease process.

A limitation of this review/meta-analysis is that there are no matched groups of healthy controls, however this was not the aim of the review (nor studies included in this meta-analysis). Secondly, in assessing conversion rates to PD-MCI or PD-D, age is an important factor that needs to be taken into account, as conversion rates are likely to increase as the age of a person with PD increases [13]. A meaningful age analysis was not possible in this review primarily because of the similar mean ages of selected samples. A critical appraisal found all studies to be of good quality. The most common reasons for papers not scoring maximally were; no procedures in place to minimise attrition; and information on qualifications of assessors.

With the increasing rates of PD [99], prognosis and the implementation of preventative measures become of great importance. We report conversion and reversion rates, a meta-analysis carried out following a systematic search of the literature, between normal cognitive function, MCI and dementia for the first time. Given the high rates of MCI and increased risk of dementia in MCI-PD patients, these results highlight the importance of screening and management (including treatment and prevention) of cognitive impairment in this patient group. The high reversion rates (PD-MCI to PD-N), particularly within three years, highlight the need for more refined criteria and better methods of cognitive assessment particularly in early disease stages. This will have important implications for treatment and prevention of further cognitive impairment and dementia in PD.

Authors Contribution

Dimitrios Saredakis, BPsych (Hons): University of South Australia, Australia, Conceptualisation of study. Electronic search and article selection. Data extraction and drafting the manuscript for intellectual content.

Lyndsey E Collins-Praino, PhD: The University of Adelaide, Australia, Interpreted the data; contributed to and revised the manuscript for intellectual content.

Daria S Gutteridge, BPsych (Hons): University of South Australia, Australia, Independently assessed eligibility of articles and data extraction. Contributed to and revised the manuscript for intellectual content.

Blossom CM Stephan, PhD: Newcastle University, United Kingdom, Interpreted the data; contributed to and revised the manuscript for intellectual content.

Associate Professor Hannah AD Keage, PhD: University of South Australia, Australia, Conceptualisation of study. Statistical analysis. Interpreted the data; contributed to and revised the manuscript for intellectual content.

Disclosures

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Appendix A. Supplementary data

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