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The influence of white matter hyperintensity on cognitive impairment in Parkinson's disease

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Abstract

The aim of this meta-analysis was to review systematically and to identify the relationship between the severity and location of white matter hyperintensities (WMHs) and the degree of cognitive decline in patients with Parkinson's disease (PD). We searched the PubMed, EMBASE, Web of Science, Ovid, and Cochrane Library databases for clinical trials of the severity and location of WMHs on the degree of cognitive impairment in PD through October 2020. We conducted the survey to compare the association of WMH burden in patients with PD with mild cognitive impairment (PD-MCI) versus those with normal cognition (PD-NC) and in patients with PD with dementia (PDD) versus those with PD without dementia (PD-ND). Nine studies with PD-MCI versus PD-NC and 10 studies with PDD versus PD-ND comparisons were included. The WMH burden in PD-MCI patients was significantly different compared to that in PD-NC patients (standard mean difference, SMD = 0.39, 95% CI: 0.12 to 0.66, $p = 0.005$), while there was no correlation shown in the age-matched subgroup of the comparison. In addition, PDD patients had a significantly higher burden of WMHs (SMD = 0.8, 95% CI: 0.44 to 1.71, $p < 0.0001$), especially deep white matter hyperintensities (SMD = 0.54, 95% CI: 0.36 to 0.73, $p < 0.00001$) and periventricular hyperintensities (SMD = 0.70, 95% CI: 0.36 to 1.04, $p < 0.0001$), than PD-NC patients, regardless of the adjustment of age. WMHs might be imaging markers for cognitive impairment in PDD but not in PD-MCI, regardless of age, vascular risk factors, or race. Further prospective studies are needed to validate the conclusions.

Introduction

Cognitive impairment, including impairment in attention, executive function, memory, speech, and visual perception, is a common and salient manifestation of Parkinson's disease (PD) and interferes with the ability to perform activities of daily living and patient outcomes.[1–6] Our recent studies have demonstrated various neuroimaging markers and their relative neuropathogenesis in PD and PD Syndromes (PDS), which appear to contribute to motor/non-motor dysfunctions and discriminative aspects.[7–12] According to the degree of cognitive

impairment,[13,14] PD patients can be classified into those with PD with normal cognition (PD-NC), PD with mild cognitive impairment (PD-MCI), and PD with dementia (PDD). Approximately 30% of PD patients have mild cognitive impairment.[15,16] Moreover, it has been reported that over 80% of PD patients could deteriorate into dementia in the terminal stage of PD,[5,6,17–19] and PD-MCI patients have an increased risk of dementia.[20,21] Multiple longitudinal studies have shown that PD-MCI is a prodromal stage of PDD.[22–26] Therefore, early identification and intervention may delay the progression of MCI to dementia in PD. Currently, significant advances have been made in neuroimaging modalities in neurodegenerative disease.[12,27–29] Neuroimaging on cognitive impairment has become a research hotspot in PD, providing in vivo insights into examining the structural and biochemical changes in PD.[23,30–39] However, no reliable predictors of cognitive impairment exist in PD so far. Therefore, there is an urgent need for reliable neuroimaging biomarkers for the early identification and monitoring of the progression of PD.

White matter hyperintensities (WMHs) are neuroimaging biomarkers characterized by the signal enhancement of the T2-weighted sequence in magnetic resonance imaging.[40] The location of WMHs commonly includes the periventricular, deep, basal ganglia, and infratentorial areas. Regional WMHs are believed to have different pathological origins, and the etiology of WMHs is unclear. Previous research[41,42] found that axonal loss, demyelination, and mild gliosis may be involved in WMHs. The possible pathogenetic mechanisms include blood–brain barrier impairment; chronic ischemia, which is due to damage to the microvascular structure; and brain hypoperfusion, resulting from the dysfunction of cerebrovascular autoregulation.[43–45] WMHs have been confirmed to be related to cognitive impairment and dementia, especially Alzheimer's disease (AD).[46,47] In the spectrum of neurodegenerative diseases, the incidence of PD is second only to AD.[48–50] Whether WMHs are correlated with cognitive impairment in PD remains controversial. Sunwoo et al.,[51] reported that WMH burden could be a significant neuroimaging marker for PD-MCI conversion to PDD. In addition, one study[52] independently demonstrated that WMHs but not vascular risk factors are a risk factor for PD-MCI. However, other studies[53,54] did not find a significant difference in total WMH burden between PD and age-matched individuals. The impact of WMHs on cognitive impairment in PD patients remains unclear.

Previous studies demonstrated that different locations of lesions may result in distinct cognitive subdomain impairments in older individuals.[55–61] WMHs are commonly located in the frontal and parietal subcortical white matter.[62] It has been reported that WMHs in the parietal lobe are related to orienting efficiency, while WMHs in the frontal and temporal lobes are involved in attention and executive dysfunction.[63] Global WMH burdens are crucial to memory and executive function in PD patients.[56] The mechanisms underlying WMHs in different regions may be diverse, but the detailed pathogenies of WMHs remain elusive.

In our study, we pooled WMH data of PD patients with different degrees of cognitive impairment by meta-analysis, such as the PD-NC group, PD-MCI group, or PDD group. The aim of our study was to investigate the relationship between the severity and location of WMHs and the degree of cognitive decline in patients with PD and to explore whether WMHs can be effective biomarkers for PD patients with cognitive impairment (PD-MCI or PDD).

Methods

Literature search

We systematically searched the PubMed, Web of Science, and EMBASE databases, combined with Ovid and Cochrane Library, for articles published in full up to February 1, 2021. Three sets of keywords were combined to find articles. The detailed search strategy is shown in Table S1. The included articles were searched for publications that met the study criteria. We searched the following base terms as follows.

#1 White matter lesion OR WML OR white matter hyperintensity* OR WMH OR Leukoaraiosis OR small vessel disease OR RS-fMRI OR resting-state functional MRI.

#2 cognitive impairment OR cognitive dysfunction OR cognitive dysfunctions OR dysfunction, cognitive OR dysfunctions, cognitive OR cognitive impairments OR cognitive impairment OR impairment, cognitive OR impairments, cognitive OR mild cognitive impairment OR cognitive impairment, mild OR cognitive impairments, mild OR impairment, mild cognitive OR impairments, mild cognitive OR mild cognitive impairments OR mild neurocognitive disorder OR disorder, mild neurocognitive OR disorders, mild neurocognitive OR mild neurocognitive disorders OR neurocognitive disorder, mild OR neurocognitive disorders, mild OR cognitive decline OR cognitive declines OR decline, cognitive OR declines, cognitive OR mental deterioration OR deterioration, mental OR deteriorations, mental OR mental deteriorations OR dementia.

#3 Parkinson Disease OR Parkinson's Disease OR Parkinsonism.

#1 AND #2 AND #3

Study selection

For the present meta-analysis, we compared WMH studies comparing one group of PD-MCI patients to PD-NC patients or comparing another group of PDD patients to PD patients without dementia (PD-ND, including PD-NC). The inclusion criteria of the studies were as follows: (1) the type of study was case–control or longitudinal; (2) the study population contained PD-NC versus PD-MCI comparisons or PDD versus PD-ND comparisons, and WMHs in the studies were measured by quantitative methods. The measurement of WMHs contained visual and volumetric methods, while the former method included the Scheltens' visual rating scale, Fazekas score, Erkinjuntti scale or the age-related white matter change (ARWMC) rating scale; and (3) papers were published in English. The exclusion criteria were as follows: (1) in the comparison group, cognitively normal subjects as the control group were not extracted; (2) the PD group without cognitive categorization (PD-MCI or PDD) was also removed; (3) secondary or hereditary forms of Parkinsonism were excluded; and (4) the expression of grade data to WMH scale was removed. Moreover, we excluded duplicate studies, reviews, case reports, conference papers, or animal experimental studies. Two authors (Hailing Liu and Bin Deng) selected relevant studies independently. Any disagreements regarding article selection or data extraction were resolved through discussion or negotiation with the third author (Fen Xie).

Data abstraction

According to the inclusion criteria, two reviewers independently screened the abstracts and papers to find eligible studies. The demographic information extraction included the first author's name, country, ethnicity, publication year, number of cases and controls, age, and disease duration. Hoehn and Yahr staging (HY) combined with the Unified Parkinson's Disease Rating Scale part III (UPDRS III) was used to evaluate the severity and advancement of Parkinsonism. The Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) was included to evaluate global cognitive function. The optimal cutoff scores for cognitive dysfunction were determined according to the organization of the Movement Disorder Society Task Force,[64–66] and the degree of cognitive dysfunction in PD was classified as normal cognition, mild cognitive impairment, and dementia. Moreover, WMH information (detailed data, location, and method of measurement) was extracted. The location of WMHs included periventricular, deep, basal ganglia, and infratentorial areas, the sum of which was the total WMH. However, the classification of WMH location measured by visual and volumetric methods is not consistent, and there were not enough unified data on WMH location to extract in the comparison group of MCI and PPD. Therefore, we divided all the trials into eight comparison groups: WMH by the volumetric method in PD-MCI versus PD-NC, WMH by the visual method in PD-MCI versus PD-NC, WMH by the volumetric method in PDD versus PD-ND, and total WMH, deep white matter hyperintensity (DWMH), periventricular hyperintensity (PVH), basal ganglia hyperintensity (BGH), and WMH of infratentorial areas in PDD versus PD-ND by the visual method. Information on the adjustment for vascular risk factors was extracted if available. If the information was missing, we contacted the relevant authors via email for related information about the studies.

Assessment of methodological quality

The Newcastle-Ottawa Scale (NOS),[67] with scores ranging from zero to nine stars, was utilized to assess the quality of the included articles, which was judged on three broad viewpoints, including selection, comparability, and outcome. More than seven stars were considered high quality on the basis of the NOS.

Statistical analysis

Using Review Manager 5.3, our meta-analysis was conducted to identify whether there was a significant difference between the two groups, including PD-MCI versus PD-NC and PDD versus PD-ND. We used a standardized mean difference (SMD) method to pool the individual markers with a random-effects model for included trials used different methods to measure WMHs (including various visual scores). We calculated Std. (Standard) Mean Difference (SMD) with a 95% confidence interval (CI) for each outcome measure.[68] The χ^2 and the I^2 tests were used to calculate the heterogeneity of pooled studies. Then, a random-effects model was used if $I^2 > 50\%$; otherwise, a fixed-effects model was used. A result with a value of $p < 0.05$ was considered indicative of a significant difference.

Second, we conducted sensitivity analysis[69] to verify the robustness of the review conclusions by omitting each individual study and identifying the reason for heterogeneity. In addition, subgroup analyses[70] were conducted to assess the impact of heterogeneity based on age matching and race. In addition, we used Stata 16 to assess publication bias via Begg's funnel plot and Egger's linear regression. $p < 0.05$ was considered statistically significant.

Results

Study identification and selection

A total of 758 potentially relevant articles were obtained through the search of databases. Full-text articles of 42 of these articles remained to assess eligibility after removing duplicates, conference reports, reviews, case reports, and unrelated studies by screening the titles and abstracts. After screening the full articles, an additional 27 articles were excluded because of a lack of relevant comparisons and appropriate data for WMHs. Finally, 15 studies were included. Four studies included PD-MCI versus PD-NC, and PDD versus PD-ND population comparisons. Five studies contained a group of PD-MCI versus PD-NC, while six studies only included a comparison of PDD versus PD-ND. According to different measurements, seven studies with the volumetric method and two with visual methods included PD-MCI versus PD-NC group, while two studies with the volumetric method and eight with visual methods were included in PDD versus PD-ND comparison. A flow diagram of the article selection is displayed in Figure 1. Fourteen case–control studies and one longitudinal study were assessed. The study by Seung-Jae Lee 2010 obtained seven stars because of the small samples and confusing pattern of grouping, which contained comparisons of PD-ND, PD-MCI, and PDD. The evaluation results of the methodological quality of all included articles are summarized in Tables 1 and 2.

Characteristics of the involved studies

In our meta-analysis, 15 studies, including 1733 participants, met the inclusion criteria. Nine studies contained PD-MCI (408 patients) versus PD-NC (471 patients) comparisons, and 10 articles included PDD (301 patients) versus PD-ND (553 patients) comparisons. The basic participant demographics and characteristics of the two groups are presented in Tables 1 and 2. As expected, we found higher age, disease duration, HY stage, UPDRS III, and MMSE (MoCA) scores for PD-MCI than for the PD-NC population. Similar results were shown for PDD compared to PD without dementia. The meta-analysis of WMH severity in different stages of PD is illustrated as follows. However, information on WMH location was unavailable in the PD-MCI and PD-NC groups because of limited information. In the PDD versus PD-ND comparison, we obtained WMH data for different locations, including total WMH, deep white matter hyperintensity, periventricular hyperintensity, basal ganglia hyperintensity, and the WMH of infratentorial areas. Vascular factors included hypertension, diabetes, and stroke.

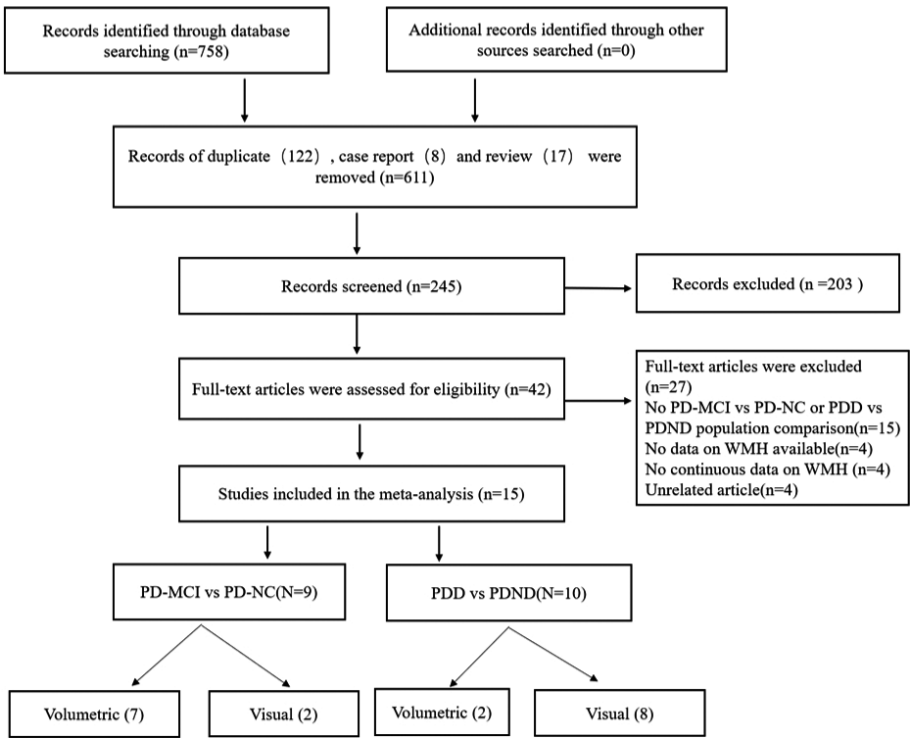


Figure 1. A flow diagram of the literature selection.

Table 1. Demographic characteristics of nine included studies of this meta-analysis for PD-MCI and PD-NC comparison.

Study	Country/ ethnicity	Sample size		Age[a]		Disease duration (year)		H-Y stage[a]		UPDRS-III[a]		MMSE/MOCA [a]		WMH severity [b]		WMH method	Adjusted vascular risk	NOS score
		PD-MCI	PD-NC	PD-MCI	PD-NC	PD-MCI	PD-NC	PD-MCI	PD-NC	PD-MCI	PD-NC	PD-MCI	PD-NC	PD-MCI	PD-NC			
Amboni (2015)[73]	Italy/ Caucasian	21	21	65.2 (8.7)	65.8 (6.5)	6.6 (3.7)	5.9 (2.6)	1.5 (0.6)	1.5 (0.4)	14.3 (8.5)	13.1 (5.3)	26.68 (1.79)/Na	28.66 (1.43)/Na	0.42 (0.43)	0.40 (0.46)	Volumetric	Na	8
Baggio (2015)[74]	Spain/ Caucasian	22	43	66.1 (12.2)	64.0 (9.8)	8.8 (4.0)	10.8 (5.1)	Na	Na	18.2 (8.7)	14.1 (7.5)	28.50 (1.22)/ Na	29.35 (0.90)/Na	0.97 (1.03)	0.79 (1.27)	Volumetric	Na	8
Huang (2020)[77]	Singapore/ Asian	94	81	65.4 (7.8)	61.3 (9.5)*	Na	Na	1.8 (0.4)	1.7 (0.4)	25.1 (11.1)	17.3 (7.5)	Na/23.20 (3.74)	Na/27.07 (2.21)	1.24 (2.86)	1.0 (3.41)	Volumetric	Diabetes	8
Kandiah (2013)[71]	Singapore/ Asian	24	67	68.9 (6.1)	63.3 (7.5)*	4.9 (2.6)	5.3 (4.2)	1.8 (0.8)	1.9 (0.3)	Na	Na	26.92 (2.47)/ 24.5 (2.43)	28.31 (1.66)/ 26.99 (2.84)	8.20 (6.87)	4.09 (6.11)	Volumetric	Hypertension	8
Mak (2015)[75]	USA/ Caucasian	25	65	69.4 (6.4)	63.4 (7.6)*	5.0 (2.7)	5.4 (4.3)	1.8 (0.4)	1.9 (0.4)	20.0 (8.4)	17.5 (7.0)	26.70 (2.60)/ 24.50 (2.40)	28.4 (1.60)/ 27.0 (2.90)	12.30 (10.30)	4.20 (5.80)	Volumetric	Hypertension	8
Melzer (2013)[72]	New Zealand/ Caucasian	28	63	71.0 (7.3)	64.0 (9.2)*	5.8 (5.1)	3.7 (3.2)	2 (1.2)	2 (1.0)	30.6 (12.3)	25.3 (13.7)	27.40 (1.50)/ 23.0 (2.30)	29.00 (1.10)/ 26.70 (2.30)	6.40 (14.50)	1.00 (19.60)	Volumetric	Na	8
Stojkovic (2018)[76]	Italy/ Caucasian	61	46	65.6 (7.9)	61.5 (8.1)*	8.9 (5.3)	7.2 (5.4)	2.4 (0.8)	2.1 (0.9)	44.5 (11.9)	36.5 (13.6)	26.98 (1.58)/ 24.54 (3.28)	28.39 (1.42)/ 27.43 (2.29)	1.15 (2.03)	0.43 (0.61)	Volumetric	Na	8
Ham (2014)[79]	Korea/ Asian	46	41	70.3 (8.1)	69.0 (6.1)	Na	Na	Na	Na	29.4 (10.9)	22.9 (9.4)	25.70 (3.50)/Na	28.10 (1.90)/Na	1.39 (1.90)	1.41 (1.80)	Visual	Hypertension, diabetes	8
Shin (2012)[78]	Korea/ Asian	87	44	69.5 (6.9)	66.6 (6.4)	3.1 (3.06)	2.2 (2.03)	Na	Na	19.0 (9.3)	17.9 (9.9)	25.70 (2.70)/Na	28.00 (1.50)/Na	2.40 (1.40)	2.30 (1.60)	Visual	Hypertension, diabetes, stroke	8
Means of total		408	471	67.7	63.8	6.16	5.7	1.9	1.8	25.1	20.5	26.51/23.7	28.50/26.9	3.23	2.33			

Abbreviations: H–Y stage, Hoehn and Yahr scale stage; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; Na, no available. The value of [a] is mean (standard deviation). [b]WMH severity present as mean (standard deviation) for volume in milliliters and visual rating; NOS, Newcastle-Ottawa Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.
*All included studies were not age-matched.

Table 2. Characteristics of 10 studies including WMH severity in PDD and PD-ND comparison.

Study	Country/ ethnicity	Sample size		Age [a]		Disease duration [a]		H-Y stage [a]		UPDRS-III [a]		MMSE/MOCA [a]		WMH severity [a]		Method	Adjusted vascular risk	NOS score
		PDD	PD-ND	PDD	PD-ND	PDD	PD-ND	PDD	PD-ND	PDD	PD-ND	PDD	PD-ND	PDD	PD-ND			
Beyer (2006)[80]	Norway/ Caucasian	16	19	73.9	71.3	12.5 (7.4)	12.7 (6.4)	3.1 (0.6)	2.3 (0.6)	42.3 (12.4)	27.2 (13.1)	18.8 (4.5)/Na	28.5 (1.9)/Na	T 11.00 (5.55) D 7.10 (5.00) P 3.90 (1.40) B 1.20 (1.80) In 0.50 (1.20)	T 6.30 (2.84) D 3.30 (2.50) P 3.00 (1.00) B 0.90 (2.00) In 0.30 (1.10)	Scheltens scale	Hypertension, diabetes, stroke	8
Daidaa (2018)[84]	Japan/ Asian	21	103	70.7 (9.0)*	62.2 (10.3)	9.5 (6.3)	11.1 (6.2)	3.6 (0.9)	2.8 (0.8)	Na	Na	19.6 (6.7)/Na	28.2 (1.8)/Na	T 2.57 (1.03) D 1.14 (0.91) P 1.43 (0.68)	T 1.32 (0.61) D 0.72 (0.66) P 0.6 (0.70)	Scheltens scale	Hypertension, diabetes, stroke	8
Lee (2010)[81]	Korea/ Asian	35	11	70.2 (7.0)	65.5 (6.5)	1.9 (1.7)	1.4 (1.06)	2.2 (0.9)	1.5 (0.7)	22.5 (12.7)	8.5 (7.1)	19.7 (4.8)/Na	28.7 (1.1)/Na	T 12.50 (10.10) D 6.30 (5.00) P 3.40 (1.80) B 2.10 (3.30) In 0.60 (1.40)	T 4.60 (5.50) D 2.90 (3.80) P 1.10 (0.80) B 0.50 (1.00) In 0.20 (0.40)	Scheltens scale	Hypertension, diabetes, stroke	7
Gonza´lez-Redondo (2012)[82]	Spain/ Caucasian	26	39	74.0 (6.0)*	68.0 (8.0)	14.0 (4.9)	13.3 (3.6)	3.6 (0.7)	2.8 (0.8)	44.6 (11.1)	32.2 (9.3)	Na	Na	T 6.70 (6.20) D 6.16 (5.68) P 0.75 (1.56) B 0.44 (0.98) In 0.08 (0.19)	T 5.70 (7.60) D 4.06 (5.38) P 0.35 (0.76) B 0.71 (1.53) In 0	Scheltens scale	Hypertension, diabetes, stroke	8
Jokia (2018)[85]	Japan/ Asian	50	50	75.7 (6.2)	74.5 (5.5)	Na	Na	Na	Na	Na	Na	Na	Na	T 3.32 (1.01)	T 2.27 (0.65)	Faceca	Hypertension, diabetes	8

(*Continued*)

Table 2 Continued.

Study	Country/ ethnicity	Sample size		Age [a]		Disease duration [a]		H-Y stage [a]		UPDRS-III [a]		MMSE/MOCA [a]		WMH severity [a]		Method	Adjusted vascular risk	NOS score
		PDD	PD-ND	PDD	PD-ND	PDD	PD-ND	PDD	PD-ND	PDD	PD-ND	PDD	PD-ND	PDD	PD-ND			
														D 1.54 (0.58) P 1.78 (0.74)	D 1.38 (0.60) P 1.40 (0.53)			
Sławek (2013)[83]	Poland/ Caucasian	57	135	67.9 (8.7)*	61.9 (9.1)	8.7 (6.3)	5.9 (4.6)	2.4 (0.7)	2.0 (0.7)	42.9 (18.9)	29.6 (15.3)	25.0 (3.2)/Na	28.2 (1.6)/Na	T 2.84 (2.30) D 1.62 (1.30) P 1.24 (1.25)	T 1.78 (2.05) D 0.88 (1.06) P 0.88 (1.20)	Erkinjuntti scale	Hypertension, diabetes	8
Shin (2012)[78]	Korea/ Asian	44	40	71.6 (6.0)*	66.6 (6.4)	4.4 (2.6)	2.2 (2.03)	Na	Na	28.5 (10.8)	17.9 (9.9)	18.6 (4.9)/Na	28.0 (1.5)/Na	T 3.10 (1.90)	T 2.30 (1.60)	Scheltens scale	Hypertension, diabetes, stroke	8
Ham (2014)[79]	Korea/ Asian	36	41	69.8 (5.9)	69.0 (6.1)	Na	Na	Na	Na	34.2 (13.6)	22.9 (9.4)	18.7 (3.5)/Na	28.1 (1.9)/Na	T 2.80 (3.40)	T 1.41 (1.80)	ARWMC	Hypertension, diabetes	8
Melzer (2013)[72]	New Zealand/ Caucasian	18	63	73.7 (6.5)	64.0 (9.2)	12.3 (8.6)	3.7 (3.2)	4 (2–4)	2 (1–3)	52.9 (16.3)	25.3 (13.7)	24.1 (3.0)/ 16.4 (3.7)	29.0 (1.1)/ 26.7 (2.3)	10.5 (17.9)	1.0 (19.6)	Volumetric	Na	8
Stojkovic (2018)[76]	Italy/ Caucasian	23	46	70.6 (5.8)	61.5 (8.1)	11.9 (5.9)	7.2 (5.4)	3.7 (1.1)	2.1 (0.9)	61.0 (10.0)	36.5 (13.6)	14.0 (6.3)/ 11.3 (6.5)	28.3 (1.4)/ 27.4 (2.2)	2.01 (2.41)	0.43 (0.61)	Volumetric	Na	8
Means of total		301	553	71.7	66.4	8.8	7.9	2.8	2.2	39.6	24.1	22.5/13.5	27.9/26.9					

Abbreviations: ARWMC, age-related white matter changes. The value of [a] is mean (standard deviation); B, Basal ganglia hyperintensity; D, Deep white matter hyperintensity; H–Y stage, Hoehn and Yahr scale stage; In, Infratentorial areas hyperintensity; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; Na, no available; NOS, Newcastle-Ottawa Scale; P, Periventricular hyperintensity; T, Total white matter hyperintensity; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.

*All included studies were not age-matched.

Data analysis

WMH in PD-MCI versus PD-NC

Nine studies,[71–79] seven with the volumetric method and two with visual method included WMH data for PD-MCI versus PD-NC comparisons. According to different WMH quantification methods, we performed meta-analysis to identify WMH data in volumetric and visual measurements separately. In the volumetric data analysis, a random-effects model was used as a result of heterogeneity ($p = 0.02$, $I^2 = 62\%$). The meta-analysis showed that the WMH burden was higher in PD-MCI than in PD-NC (SMD = 0.39, 95% CI: 0.12 to 0.66, $p = 0.005$) (Fig. 2A). Then, we performed the sensitivity analysis to identify the reason for heterogeneity and confirmed that Elijah Mak 2015[75] was the reason for heterogeneity. After removing the study, we found that the WMH burden in the PD-MCI group was inferior to that in PD-NC (SMD = 0.27, 95% CI: 0.08 to 0.45, $p = 0.005$), with a heterogeneity of 11% ($p = 0.35$). In addition, considering age as a confounder, we conducted subgroup analysis according to the matched age. In the age-matched subgroup, we found no significant difference between comparisons (SMD = 0.1, 95% CI: −0.29 to 0.5, $p = 0.60$; $I^2 = 0\%$, $p = 0.80$), while a significant difference was observed in the subgroup without adjustment for age (SMD = 0.48, 95% CI: 0.15 to 0.82, $p = 0.005$; $I^2 = 71\%$, $p = 0.008$) (Fig. 2B). When the study by Elijah Mak 2015 was removed, the heterogeneity decreased ($p = 0.19$, $I^2 = 37\%$) and a significant difference remained ($p = 0.01$). Furthermore, considering race might be a confounding variable, we performed subgroup analysis according to different ethnicities (Asian vs. Caucasian). In the Asian subgroup, we found no significant difference between comparisons (SMD = 0.33, 95% CI: −0.22 to 0.88, $p = 0.24$; $I^2 = 75\%$, $p = 0.05$), while a significant difference was observed in the Caucasian subgroup (SMD = 0.42, 95% CI: 0.08–0.77, $p = 0.02$; $I^2 = 61\%$, $p = 0.04$) (Fig. 2C). However, in the Caucasian with adjustment for age group, no significant difference was observed ($p = 0.6$) without heterogeneity ($I^2 = 0\%$) (Fig. 2D).

In the visual data of WMH from two studies, Asians with adjustment for age, we found no significant difference in WMH burden between PD-MCI and PD-NC comparison (SMD = 0.03, 95% CI: −0.25 to 0.30, $p = 0.86$) (Fig. 2E) with fixed-effects model ($I^2 = 0\%$).

Total WMH in PDD versus PD-ND

A total of 854 participants in 10 studies[72,76,78–85] were pooled to assess the effects of total WMH in PDD versus PD-ND population comparisons, eight of which were measured with the visual rating scale, incidentally, such as Fazekas, Scheltens' scale, Erkinjuntti scale or the ARWMC rating scale, and another two were measured with the volumetric method. In visual studies, a significant difference existed (SMD = 0.8, 95% CI: 0.44 to 1.71, $p < 0.0001$; $I^2 = 77\%$, $p < 0.0001$) (Fig. 3A), suggesting that WMH severity in PDD patients was higher than that in PD-ND patients. Then, we found that a significant difference remained during the sensitivity analysis conducted by removing every article one by one, suggesting that the result was stable. Considering age as a confounder, we also conducted subgroup analysis according to matched age in PDD versus PD-ND. Interestingly, we found significant difference between comparisons not only in the age-matched subgroup (SMD = 0.91, 95% CI: 0.54 to 1.27, $p < 0.00001$; $I^2 = 42\%$, $p = 0.16$), but also in the age-unmatched subgroup (SMD = 0.71, 95% CI: 0.07 to 1.36, $p = 0.03$; $I^2 = 87\%$, $p < 0.0001$) (Fig. 3B). Furthermore, considering race might be a confounding variable, we also performed subgroup analysis between Asian versus Caucasian. Still, a significant difference between PDD and PD-ND comparisons was found not only in the Asian subgroup (SMD = 0.84, 95% CI: 0.37 to 1.32, $p = 0.0005$; $I^2 = 77\%$, $p = 0.002$), but also in the Caucasian subgroup (SMD = 0.5, 95% CI: 0.09 to 0.92, $p = 0.02$; $I^2 = 55\%$, $p = 0.11$) (Fig. 3C). In volumetric studies, the meta-analysis showed that the WMH burden was higher in PDD than in PD-ND (SMD = 0.78, 95% CI: 0.21 to 1.34, $p = 0.007$) (Fig. 3D).

Deep white matter hyperintensity (DWMH) in PDD versus PD-ND

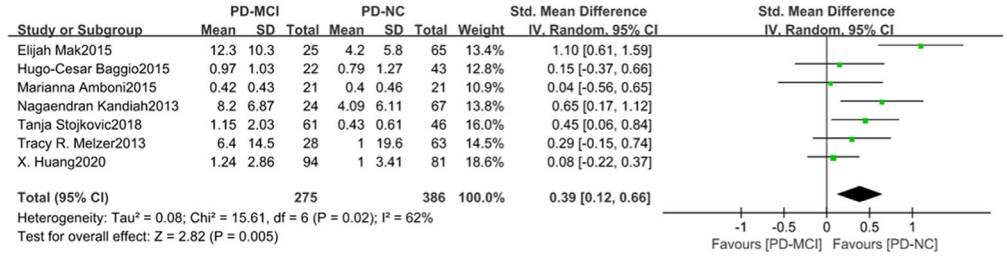
Six studies,[80–85] including 564 participants, were pooled to evaluate DWMH severity in the PDD versus PD-ND comparison. DWMH severity in PDD patients was higher than that in PD-ND patients (SMD = 0.54, 95% CI: 0.36 to 0.73, $p < 0.00001$; $I^2 = 0\%$, $p = 0.50$) (Fig. 4A).

Periventricular hyperintensity (PVH) in PDD versus PD-ND

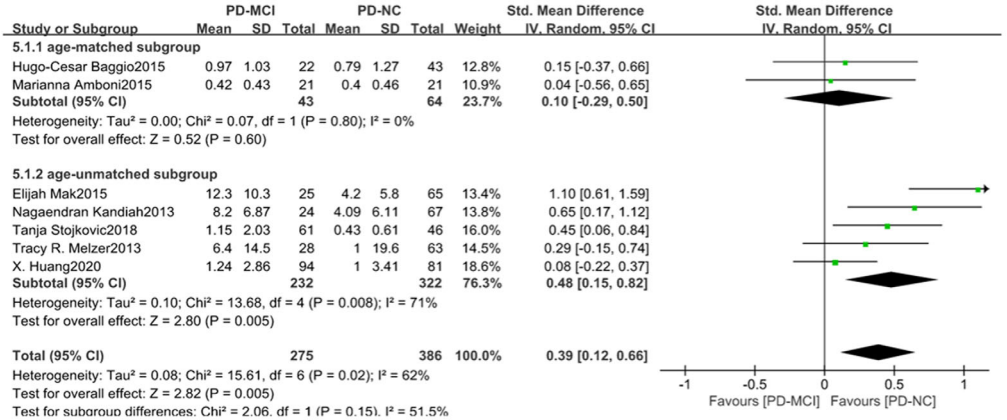
PVH was evaluated in six studies[80–85] (564 participants). Compared with patients with PD without dementia, the

Figure 2. Forest plot showing the Std. mean difference and 95% confidence intervals of differences in WMHs between the PD-MCI and PD-NC patients. (A) WMH severity with the volumetric method in patients with PD-MCI compared to PD-NC; (B) Subgroup analysis of WMH according to whether age-matched or not between comparisons; (C) Subgroup analysis of WMH in Asians and Caucasians; (D) WMHs in Caucasians with age-matched group; (E) WMHs with visual methods in patients with PD-MCI compared to PD-NC.

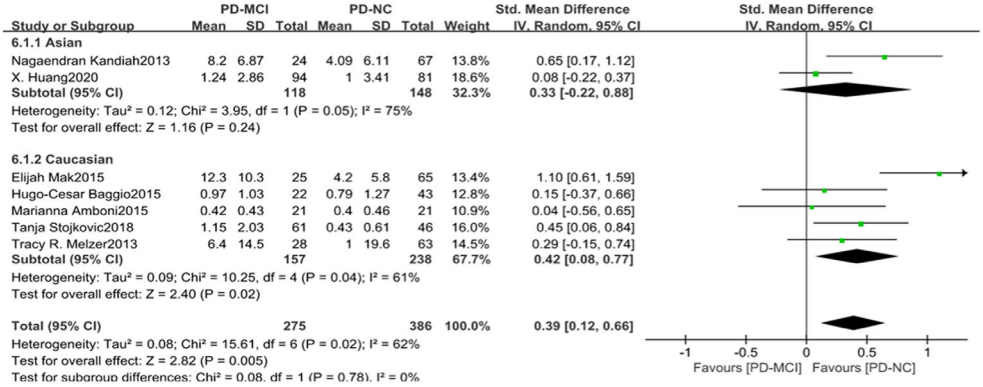
(A) WMH with volumetric method



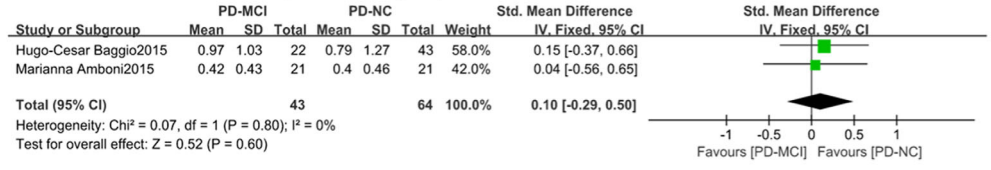
(B) WMH in age-matched subgroup



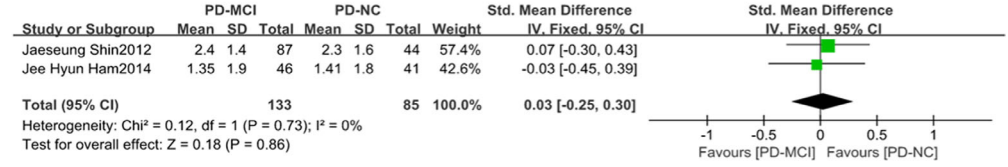
(C) WMH in ethnicity subgroup



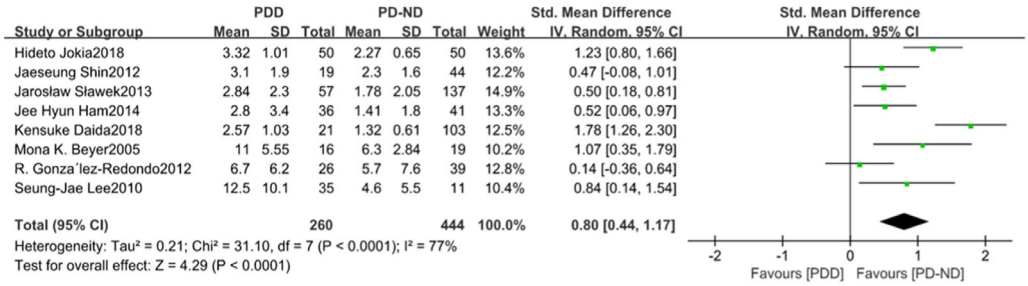
(D) WMH in Caucasians with age-matched group



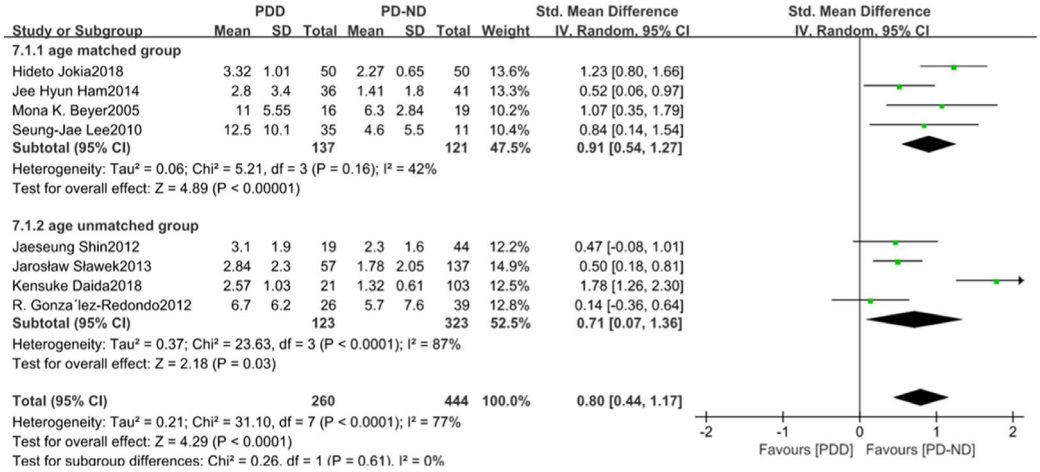
(E) WMH with visual methods



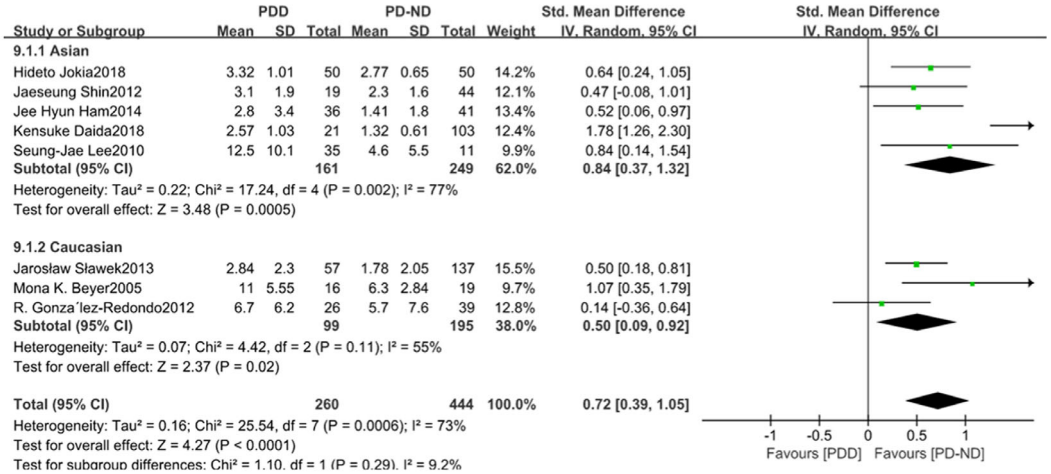
(A) Total WMH with visual methods



(B) Total WMH in age-matched subgroup



(C) Total WMH in ethnicity subgroup



(D) Total WMH with volumetric method

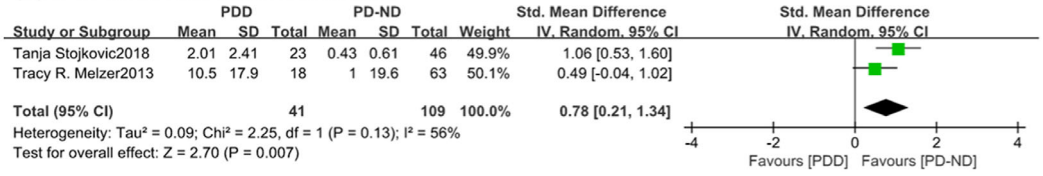


Figure 3. Forest plot showing the Std. mean difference and 95% confidence intervals of differences in WMHs between the PDD and PD-ND patients. (A) Total WMH with the visual measurement between the PDD and PD-ND groups; (B) Subgroup analysis of total WMH according to whether age-matched or not; (C) Subgroup analysis of total WMH in Asians and Caucasians; (D) Total WMH with volumetric method between the PDD and PD-ND groups.

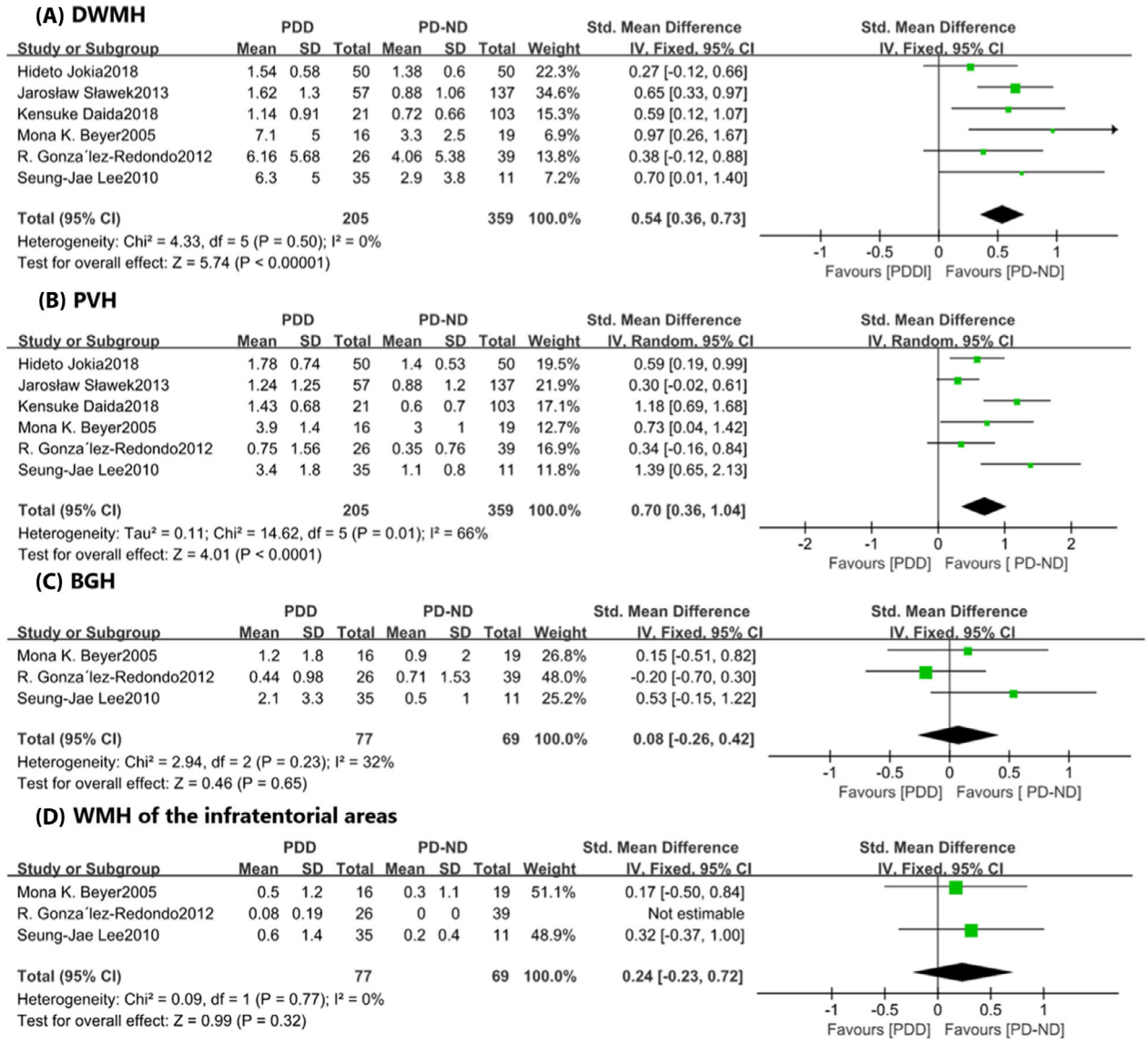


Figure 4. Forest plot showing the Std. mean difference and 95% confidence interval of differences in different locations of WMHs between PDD and PD-ND patients. (A) DWMH between-group comparisons; (B) PVH in PDD versus PD-ND patients; (C) Basal ganglia hyperintensity (BGH) in PDD versus PD-ND patients; (D) WMH in the infratentorial areas in PDD versus PD-ND patients.

severity of PVH in PDD patients was significantly higher (SMD = 0.70, 95% CI: 0.36 to 1.04, $p < 0.0001$), with a heterogeneity of 66% ($p = 0.01$) (Fig. 4B). A sensitivity analysis was conducted by removing every article one by one, and the heterogeneity still existed. We also found that a significant difference remained during the sensitivity analysis, suggesting that the result was stable.

Basal ganglia hyperintensity (BGH) in PDD versus PD-ND

Three studies[80–82] presented data related to WMHs in the basal ganglia region. However, there were no significant results for the PDD versus PD-ND comparisons ($p = 0.65$) (Fig. 4C). After removing one trial by Seung-

Jae 2010, an identical result was demonstrated between the two groups without heterogeneity. (SMD = −0.07, 95% CI: −0.47 to 0.33, $p = 0.72$; $I^2 = 0\%$, $p = 0.41$).

WMH of the infratentorial areas in PDD versus PD-ND

Three studies[80–82] were pooled to evaluate the effects of the WMH of infratentorial areas, with no significant differences between the PDD and PD-ND groups (SMD = 0.24, 95% CI: −0.23 to 0.72, $p = 0.32$; $I^2 = 0\%$, $p = 0.77$) (Fig. 4D).

Publication bias

To assess publication bias in meta-analyses of recruited studies, Begg's funnel plot and egger's test were conducted. In the volumetric studies of PD-MCI and PD-NC comparison, the Begg's funnel plot did not show significant asymmetry ($p = 0.881$) (Fig. 5A), and no small-study effects existed ($t = -0.84$, $p = 0.438$) (Fig. 5B) through egger's test. In the visual studies between PDD and PD-ND comparison, the distribution of each study was basically symmetrical in Begg's funnel plot ($p = 0.386$) (Fig. 5C). In addition, egger's tests did not reveal evidence for bias in the homogeneous studies. ($t = 0.73$, $p = 0.494$) (Fig. 5D).

Discussion

It is well known that cognitive impairment and even dementia may occur in PD patients, which would aggravate the condition and reduce the quality of life.[86] WMHs are associated with cognitive impairment in the general population.[11,30] Moreover, previous reports[53,87]demonstrated that WMHs might exacerbate some motor symptoms or cognitive deficits in PD patients. Accumulating evidence suggests that WMHs independently contribute to postural and gait disturbances. However, the relationship between WMHs and the severity of cognition impairment in PD is still inconclusive.

In the PD-MCI and PD-NC groups with the volumetric method, WMH severity was significantly different. However, subgroup analysis indicated the opposite results when studies were separated by whether they were age-matched. In the matched-age subgroup analysis, compared to PD-NC, a correlation was not observed in the

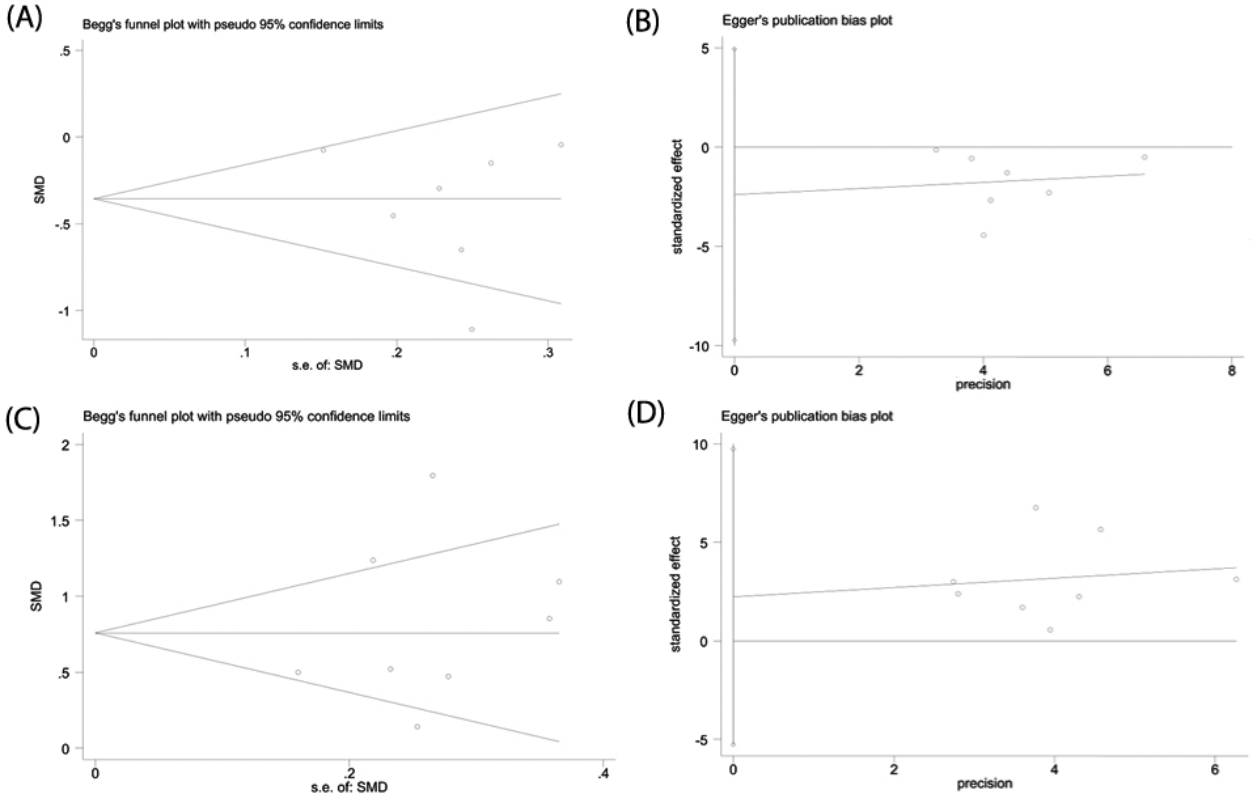


Figure 5. Begg's funnel plot and egger's test of publication bias in the selection of studies. (A) In the volumetric studies of PD-MCI and PD-NC comparison, the Begg's funnel plot is basically symmetrical; (B) Egger's method showed that the publication bias was small; (C) and (D) In the visual studies of PDD and PD-ND comparison, Begg's funnel plot (C), and egger's method (D) did not reveal publication bias.

PD-MCI. In the two matched-age studies with visual methods, the difference was not observed as well. In a previous study,[40] WMHs were inherently age-related and age was prone to generate false positives. In addition, a study reported that WMH-related cognitive and affective functions decreased with age in PD patients.[88] Consequently, no significant difference in WMHs was observed between the PD-MCI and PD-NC groups after adjusting for age, suggesting that the effect of WMHs may be inconspicuous in the early stage of PD. Similar to our results, a study[54] found that WMHs are not involved in cognitive impairment in the early stage of PD. Furthermore, another study[53] found that the WMH burden was not significantly different between PD patients and age-matched individuals in the cross-sectional stage; however, the progression of WMHs still aggravated cognitive dysfunction in PD patients. Therefore, the above-mentioned results indicated that the influence of WMHs on cognition might be apparent in the later stage of PD, such as in PDD but not in PD-MCI. This finding needs further confirmation in larger prospective studies. Several following-up studies[89,90] revealed that WMH on longitudinal changes may increase the risks for cognitive decline in PD. The greater baseline WMH burden showed, the more significantly cognitive decline in Parkinson's patients, suggesting baseline WMH burden could be the risk for future cognitive decline.

In our present meta-analysis, we confirmed that WMHs might be correlated with cognitive impairment in patients with PDD, the severe cognitive status of PD. A significant difference was confirmed in the total WMH scores by visual methods (SMD = 0.8, 95% CI: 0.44 to 1.71, $p < 0.0001$), and by volumetric method as well (SMD = 0.78, 95% CI: 0.21 to 1.34, $p = 0.007$). Only one longitudinal study by R. Gonza´lez-Redondo[82] in the pooled studies showed no difference in the total WMH between the two groups of patients. However, the authors found that the progression of WMHs may have a mild impact on cognition in follow-up. We performed an age-matched subgroup analysis of visual studies in PDD and PD-ND comparison, and we not only found significant differences in age-matched subgroups (SMD = 0.91, $p < 0.00001$), but also in age-unmatched subgroups between comparisons (SMD = 0.71, $p = 0.03$). The outcome may indicate that WMH burden in PDD patients is more severe than that in PD-ND, regardless of age. Moreover, in the PDD versus PD without dementia comparison, cerebrovascular risk factors (hypertension and diabetes mellitus) did not differ across groups, suggesting that vascular risk factors might not be related to WMH development. After controlling for vascular risk factors, WMHs were significantly related to cognitive impairment in PD patients,[80,85] suggesting that WMHs might be a reliable and independent risk factor for PDD. A previous study[91] illustrated that WMHs were associated with PDD, independent of age and vascular risk factors, which is consistent with our pooled results.

Visual and volumetric methods are the main approaches to evaluate the severity of WMH. Each method has pros and cons. The visual rating methods are more convenient, while the volumetric method is more sensitive.[92] In our study, the visual rating method was usually used in the comparative researches between PDD and PD-ND due to wide application in the studies with large differences between groups. In contrast, the volumetric method was time-consuming, but sensitive and reliable; and it was more suitable for studies with small differences between groups, such as comparisons between PD-NC and PD-MCI. Our results are consistent in the comparisons regardless of different methods.

To our knowledge, small vessel disease is more common among Asians. Considering race might be a confounding variable, we performed subgroup analysis according to different ethnicities, Asian versus Caucasian. In the PD-MCI versus PD-NC comparison by two measurements, no significant difference was observed both in the Caucasian and Asian after adjustment for age. Meanwhile, WMH severity was significantly different between Asian and Caucasian in the PDD and PD-ND groups, regardless of age-matched or not. The severity of WMH in different degrees of PD might be similar in Asians and Caucasians.

The localization of WMHs presented specific effects on cognitive impairment.[93] In our study, the PDD group presented significant differences in DWMHs and PVHs but not in WMHs in the basal ganglia and infratentorial areas. In the pooled analysis of PVHs in comparison groups, five of six studies showed a significant difference, while another study (R. Gonza´lez-Redondo 2012) showed that the progression of PVH had a mild impact on cognition. Four of six studies had significantly more severe DWMHs than those in the PD-ND group. Few data have suggested that WMHs in the basal ganglia and infratentorial areas are associated with cognition in PDD. The present study confirmed that PVHs and DWMHs negatively influence cognitive impairment in PDD. WMH locations are correlated with domain-specific cognitive dysfunction in people with PD, including executive, attention, memory, speed learning, and visuospatial function. Previous studies[93,94] reported that PVHs might have a significantly more negative effect on cognitive impairment than DWMHs, especially on executive function and processing speed. Moreover, a meta-analysis[95] concluded that PVHs, DWMHs, and the progression of WMHs may be involved in the impairment of domain-specific cognition, including attention and executive function. Diverse locations of

WMHs disrupt the connection of cortical and subcortical structures, resulting in cognitive function damage. Several theories[61] propose that DWMHs may destroy arcuate u-fibers of short cortex-cortical connections, while the PVHs have a stronger effect on the long-term high-density area connecting the distant cortical regions[96] and appear to have a larger effect on cognition than DWMHs. WMHs may damage nerve transmission and connections between neurons, leading to exacerbated speed and executive dysfunction.

WMHs, as typical signs of cerebral small vessel disease, may exacerbate cognitive impairment in PD through a variety of hypothetical mechanisms. Blood–brain barrier leakage and endothelial dysfunction are the predominant pathophysiological mechanisms.[97] Recent studies[10] demonstrated that inflammatory, metabolic, and vascular factors are involved in PDD patients with diabetes and may be biomarkers for PD diagnosis. In addition, genetic variation may influence the immediate tissues surrounding microvessels or the risk of microvasculature injury, leading to the deterioration of PVHs or DWMHs.[98] It has been reported that WMHs, as markers of cerebral small vessel disease, could be alleviated through the treatment of modifiable vascular risk factors and lifestyle modification.[99] Moreover, previous longitudinal studies[90] demonstrated that baseline WMH burden was a significant predictor of future cognitive decline in PD, especially for the conversion from PD-MCI to PDD.

The results of our meta-analysis show that WMHs associated with cognitive dysfunction in PDD might offer opportunities for treatment and prevention. WMHs and the cerebrovascular structure can benefit from managing vascular risk factors in young patients (<50 years).[100] Vascular risk elements might be correlated with WMHs in early PD patients with cognitive decline.[99] WMHs might accelerate brain atrophy throughout adulthood in the general population, which is due to vascular risk factors but also exists independently.[101] A previous study reported that high blood pressure was independently associated with the progression of WMHs.[102] The literature has demonstrated that cerebrovascular risk factors, especially hypertension, may be related to WMHs in adulthood[103] or early-stage of the PD but not PDD.[90] This result is consistent with our finding that vascular risk factors did not show an important role in the deterioration of WMHs in PDD independently, suggesting that vascular factors may result in the disease progression in young patients or those with PD-MCI and that the other nonvascular factors might contribute to the progression of PDD. Therefore, it is beneficial to decrease WMHs at an early stage by treating cerebrovascular disease. In addition, orthostatic hypotension (OH) is correlated to both WMHs and cognitive decline in PD patients. One hypothesis is that OH may contribute to cognitive decline through cerebral hypoperfusion, resulting in WMH; another hypothesis indicated that OH and cognitive decline in PD may share the underlying identical a-synuclein-related pathology.[104]

Several limitations and advantages should be acknowledged in our study. First, WMH quantification methods (visual and volumetric measurements) vary, which might contribute to the variability in our results and induce heterogeneity. Therefore, we performed meta-analysis in volumetric and visual measurements to identify WMH data separately and got identical results. Second, data in different studies vary, and data conversion might induce errors. Third, an inherent limitation and statistical bias might exist because of the limited number of studies and small samples. However, Begg's funnel plot and egger's test showed that the publication bias was small, suggesting that the results were reliable. Fourth, the relation between WMH location and specific cognitive domains in PD (particularly in PD-MCI) has not been perfectly demonstrated as a result of the scarce data available. Fifth, the relationship between the progression of WMHs and the cognitive deterioration in long-term follow-up is more reliable. Consequently, further longitudinal studies are needed. The confirmation of the possible role of WMHs in cognitive impairment in PD may be crucial for physicians not only for understanding the underlying mechanism but also for the formulation of treatment strategies.

Conclusion

WMH severity might play a crucial role in cognition in patients with PDD, regardless of age race, and vascular risk factors, especially DWMHs and PVHs, which might be imaging markers for PDD. Further prospective studies in large populations are warranted to validate the conclusions.

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Author Contributions

Conceived and designed the study: H.L.L, B.D., Y.H.C, Z.C.X, S.Z.Z, and Q.W. Performed the study: H.L.L, B.D., Y.H.C, Z.C.X, F.X, Z.Y., and Q.W. Revised the paper for intellectual content: X.H.Y, X.Y.H, S.Z.Z, and B.D. Data statistics and analysis: H.L.L, B.D., Y.H.C, and Q.W. Wrote the paper: H.L.L, B.D., S.Z.Z, and Q.W. All authors read and approved the final manuscript.

Conflict of Interest

These authors declare no conflict of interest.

Consent Statement

As this is a systematic review and did not include original patient data, the informed consent was not required.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search strategy in PubMed, Web of Science, EMBASE databases, Ovid, and Cochrane Library.

