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Systematic Review

Features of Plasma Homocysteine, Vitamin B12, and Folate in Parkinson's Disease: An Updated Meta-Analysis

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Abstract

Background: Many studies have shown that the levels of homocysteine (Hcy), vitamin B12 (Vit B12), and folate (FA) are abnormal in patients with Parkinson's disease (PD), but the results have not been consistent. Therefore, we conducted this meta-analysis to summarize the features of Hcy, Vit B12, and FA in PD patients. **Methods**: A systematic literature search was conducted on PubMed, Cochrane Library, Web of Science, and Embase databases. **Results**: A total of 71 studies were included. The analysis showed the following. (1) PD patients had significantly increased Hcy level (standardized mean difference [SMD] 0.80, 95% confidence interval [CI] [0.61, 0.99]; $p < 0.001$), and decreased Vit B12 (SMD –0.33, 95% CI [–0.43, –0.22]; $p < 0.001$) and FA levels (SMD –0.13, 95% CI [–0.19, –0.06]; $p < 0.001$) compared to healthy controls. (2) Higher Hcy level (SMD 0.48, 95% CI [0.30, 0.67]; $p < 0.001$) was found in Dopaminergic medications treated PD patients than in untreated patients. (3) PD patients with cognitive impairment had higher Hcy level (SMD 0.71, 95% CI [0.50, 0.92]; $p < 0.001$) and lower Vit B12 (SMD –0.22, 95% CI [–0.34, –0.09]; $p = 0.001$) and FA levels (SMD –0.17, 95% CI [–0.29, –0.04]; $p = 0.009$) than those with no cognitive impairment. (4) PD patients with neuropathy had significantly increased Hcy level (SMD 0.87, 95% CI [0.43, 1.31]; $p < 0.001$) and decreased Vit B12 level (SMD –0.40, 95% CI [–0.81, –0.00]; $p = 0.049$) compared to PD patients with no neuropathy. **Conclusions**: In conclusion, PD patients may have higher Hcy levels and lower Vit B12 and FA levels than the healthy population. Thus, Hcy, Vit B12, and FA may play a role in cognitive impairment and neuropathy in PD patients.

Keywords: Parkinson's disease; PD; homocysteine; Hcy; vitamin B12; folate

1. Introduction

Parkinson's disease (PD) has become the fastest-growing neurological disorder. Its clinical manifestations include motor symptoms (e.g., tremor, bradykinesia, rigidity, and abnormal posture) and nonmotor symptoms (e.g., cognitive impairment [CI], sleep dysfunction, olfactory loss, and autonomic dysfunction) [1]. The pathological change in PD is dopaminergic neuron degeneration. However, the exact pathophysiological mechanisms of PD remain poorly defined. Increasing evidence has demonstrated that oxidative stress may play a critical role in the onset and progression of PD [2]. Neurons are more vulnerable to damage in folate (FA) and vitamin B12 (Vit B12) deficiency, as well as increased homocysteine (Hcy); the underlying mechanisms may be increased oxidative stress and decreased methylation [3]. In parallel, Hcy may play a role in PD onset or progression through gene defects and apoptosis [4]. FA and Vit B12 are necessary cofactors in Hcy metabolism [5], and may have an underlying association with PD onset or progression. Hcy, Vit B12, and FA levels are associated with each other. The major causes of hyperhomocysteinemia are deficiencies in FA and Vit B12, which are necessary for Hcy metabolism [6]. Furthermore, deficiencies in FA and Vit B12 are associated with neuronal degeneration [7]. At the same time, dopaminergic drugs may affect serum Hcy levels [8,9]. Increased Hcy level is a modifiable risk factor for CI and dementia [10].

In recent years, a large number of studies have investigated the associations between Hcy, Vit B12, FA and PD. Some studies have shown that PD patients have increased levels of Hcy and decreased levels of Vit B12 and FA compared with age-matched healthy controls (HCs) [8,11–14]. However, other studies have reported inconsistent results [15–17]. Therefore, we conducted this meta-analysis to comprehensively assess the precise differences in Hcy, Vit B12, and FA levels between PD patients and healthy populations and summarize the conclusions.

2. Methods

We using the Meta-Analyses (PRISMA) extension for this meta- analysis, a detailed PRISMA checklist was provided (see **Supplementary Materials**). The protocol for this study was registered with PROS-PERO, registration number: CRD42023401379.

2.1 Search Strategy

A systematic literature search was conducted on PubMed, Cochrane Library, Web of Science, and Embase databases. The search terms "homocysteine", "Hcy", "folate", "folic acid", "vitamin B12", "cobalamin", "Parkinson", "Parkinson's disease", and "PD" were used. Two independent authors screened all articles, and reference lists of full review articles were also included in the meta-analysis.

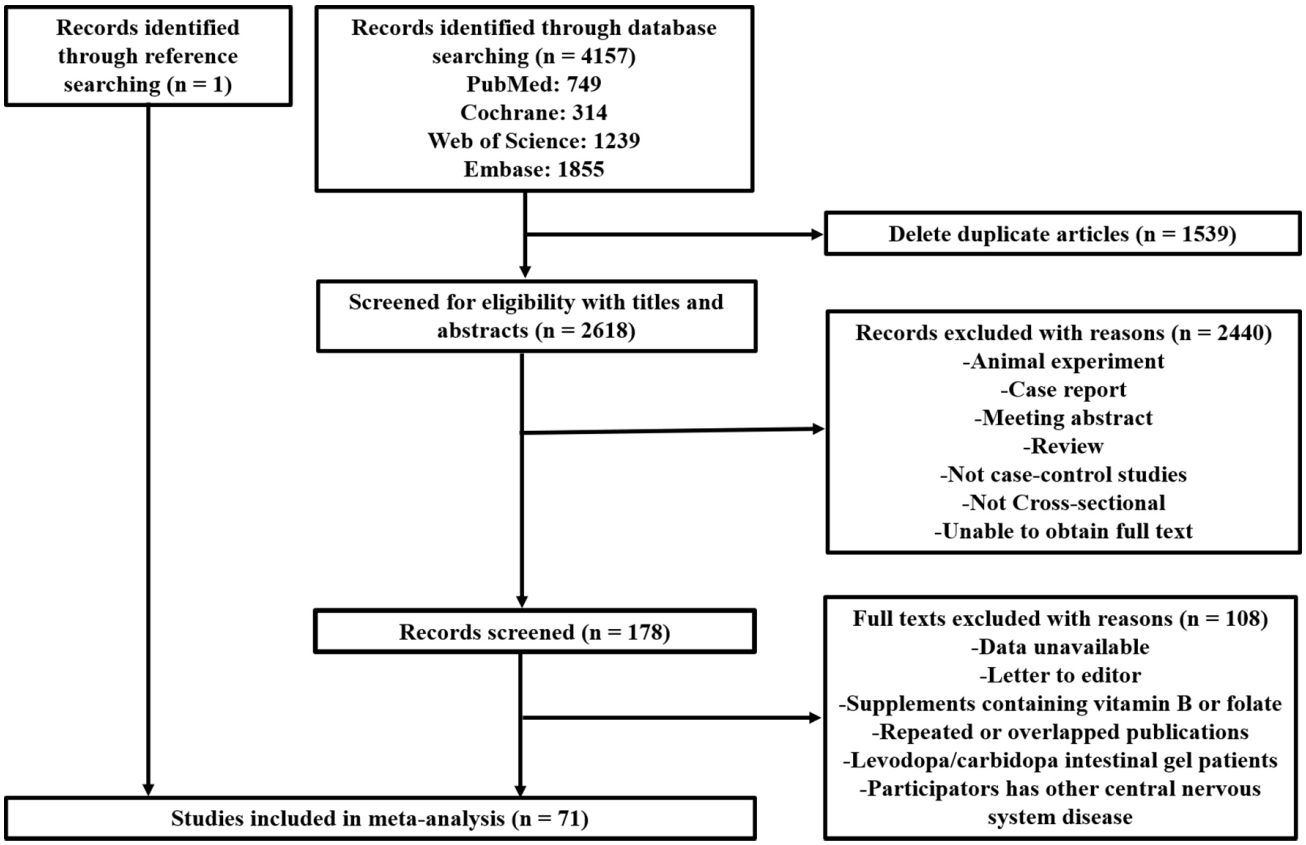

Fig. 1. Overview of the literature search and selection.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria were: PD patients with no psychopathology and HCs with no history of central nervous system (CNS) disease; papers published in English; case–control or cross-sectional studies describing the associations among serum levels of Hcy, Vit B12, FA, and PD; data expressed as the mean and standard deviation or calculable.

The exclusion criteria were: animal experiments; case reports; meeting abstracts; reviews; letters to the editor; inability to access the full text, repeated or overlapping publications, supplements containing Vit B12 or FA, levodopa/carbidopa intestinal gel patients; and participants with other CNS diseases.

2.3 Data Collection and Quality Assessment

Two independent reviewers extracted the following data for each study: first author; year of publication; country; sample size; age; sex; use of anti-parkinsonian drugs; plasma Hcy, Vit B12, and FA levels; and PD diagnostic criteria, etc. (**Supplementary Tables 1,2**). Engauge Digitizer 4.1 (Markmitch, Goteborg, Sweden) was used to collect data from statistical charts. The quality of the original studies was evaluated by the Newcastle-Ottawa Scale [18]. Egger's test was used to assess the publication bias when at least 10 studies were included in the meta-analysis [19]. Publication bias was also assessed by funnel plots when there were at least 10 studies. To evaluate the influence of each individual study on the pooled estimate, sensitivity analysis was conducted by omitting each study one by one when there were at least 10 studies. Two independent reviewers completed the data extraction to reduce bias. Any disagreements were resolved through discussion.

Patients with untreated PD were newly diagnosed PD patients who have never received dopaminergic drugs; and PD patients who have been receiving dopaminergic drug (LDA) treatment (such as levodopa, amantadine, pramipexole, biperiden, and entacapone, etc.) were identified as LDA-treated PD patients. Patients with catechol-O-methyltransferase inhibitor (COMTI)-treated PD were those receiving entacapone, tolcapone, or opicapone treatment; and patients with non-COMTI-treated PD were patients not receiving entacapone, tolcapone, or opicapone treatment, and being treated with other dopaminergic drugs. Patients with PD-CI were PD patients with CI; PD patients with no CI (NCI) were identified as PD-NCI patients (clinical data and assessment scales for cognition in the included studies are listed in **Supplementary Table 3**). PD patients with evidence of peripheral neuropathy (NP) without a defined cause were identified as PD-NP patients; and PD patients with no neuropathy (NNP) were identified as PD-NNP (clinical data of the included studies are shown in **Supplementary Table 4**).

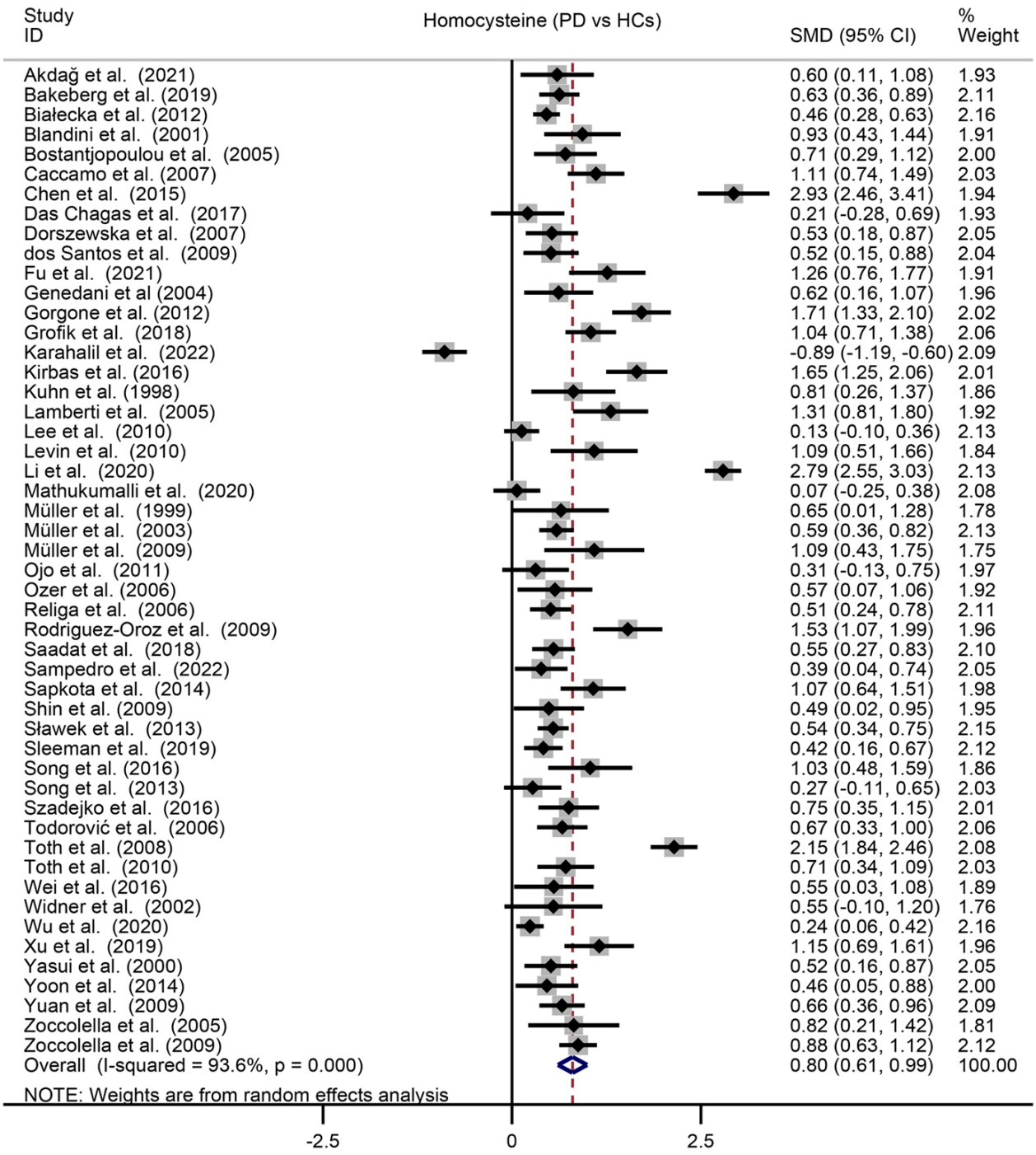

Fig. 2. Forest plot for comparison of plasma Hcy levels between PD patients and HCs. CI, Confidence interval; HCs, Healthy controls; Hcy, Homocysteine; PD, Parkinson's disease; SMD, Standardized mean difference.

2.4 Statistical Analysis

All data were analyzed using Stata 15.0 statistical software (StataCorp LP, College Station, TX, USA). The standardized mean difference (SMD) and 95% confidence interval (CI) were used to evaluate the differences in plasma levels of Hcy, Vit B12, and FA between groups. The weighted mean difference and 95% CI were used to evaluate the differences in age. Statistical heterogeneity between the studies was assessed by I^2; $I^2 \geq 50\%$ indicates significant heterogeneity [20]. The fixed-effects model was used when $I^2 < 50\%$; otherwise, the random-effects model was used.

3. Results

3.1 Study Selection, Characteristics, and Quality Assessment

The selection of studies is indicated in Fig. 1. A total of 4157 potentially relevant studies from the PubMed, Embase, Web of Science, and Cochrane Library databases, and

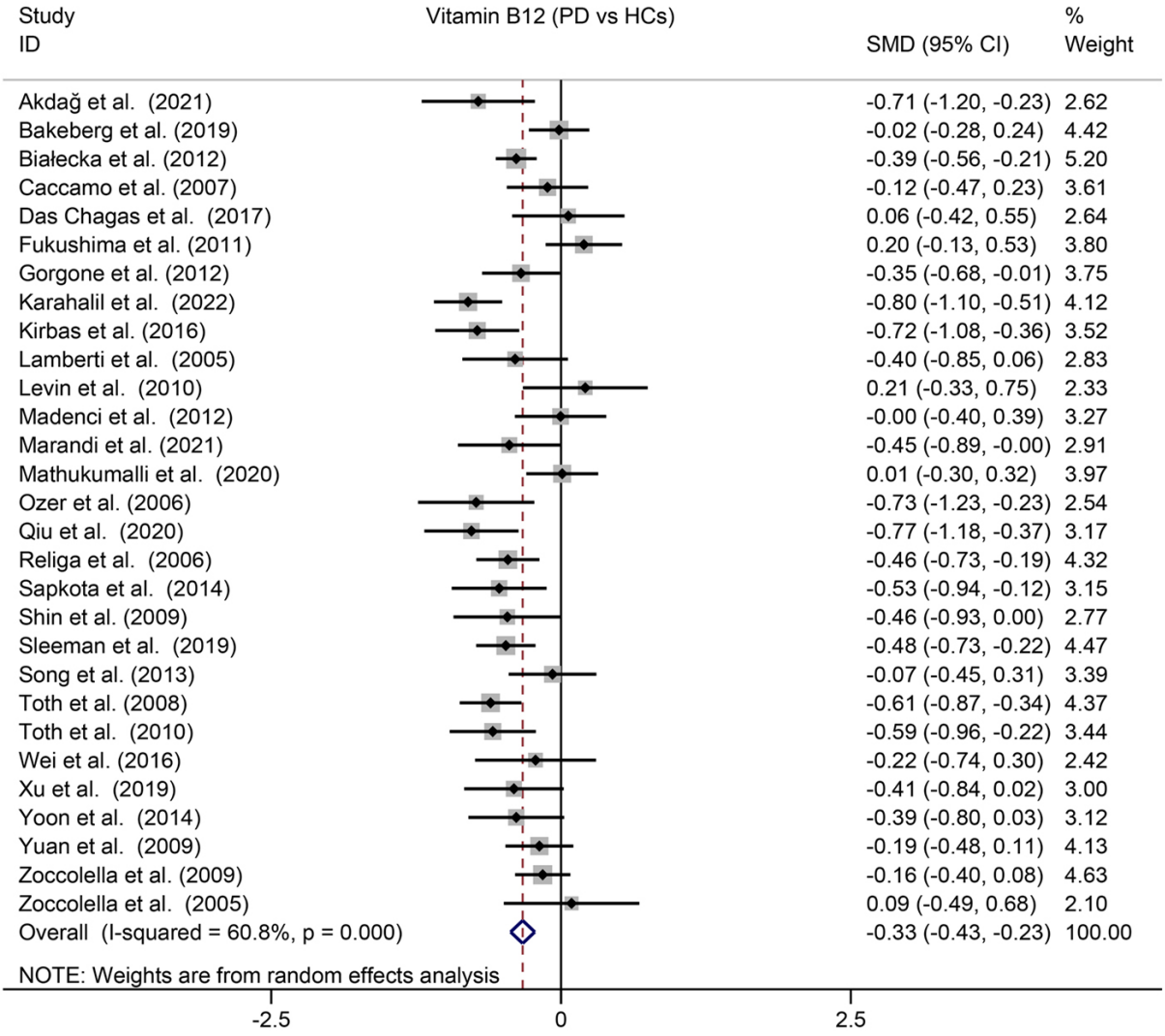

Fig. 3. Forest plot for comparison of plasma Vit B12 levels between PD patients and HCs. CI, Confidence interval; HCs, Healthy controls; PD, Parkinson's disease; SMD, Standardized mean difference; Vit B12, Vitamin B12.

1 study from reference lists were searched. In the end, 71 articles (54 case–control studies [8,9,11–17,21–65] and 17 cross-sectional studies [66–82] were included in the current analysis. All of the included original studies scored ≥5 (4 studies scored 9, 23 studies scored 8, 32 studies scored 7, 10 studies scored 6, and 2 studies scored 5), which showed high-quality or moderate results (**Supplementary Table 2**).

3.2 Analysis of Serum Hcy Levels between Groups

The meta-analysis of 50 articles (4455 PD patients and 3792 HCs) showed that the PD group had significantly higher plasma Hcy level than the HCs (SMD 0.80, 95% CI [0.61, 0.99]; $p < 0.001$), with substantial heterogeneity ($I^2 = 93.6\%$, $p < 0.001$) (Table 1, Fig. 2). Untreated PD patients had higher plasma Hcy level than HCs (SMD 0.29, 95% CI [0.17, 0.41]; $p < 0.001$), with no significant heterogeneity ($I^2 = 16.1\%$, $p = 0.295$) (Table 1, **Supplementary Fig. 1**). LDA-treated PD patients had higher plasma Hcy level than untreated PD patients (SMD 0.48, 95% CI [0.30, 0.67]; $p < 0.001$), with no significant heterogeneity ($I^2 = 43.4\%$, $p = 0.089$) (Table 1, **Supplementary Fig. 2**). Lower plasma Hcy level in COMTI-treated PD patients than in non-COMTI-treated PD patients (SMD –0.49, 95% CI [–0.64, –0.33]; $p < 0.001$) was observed, with no significant heterogeneity ($I^2 = 31.8\%$, $p = 0.163$) (Table 1, **Supplementary Fig. 3**. PD-CI patients had higher plasma Hcy level (SMD 0.71, 95% CI [0.50, 0.92]; $p < 0.001$) than PD-NCI patients, with significant heterogeneity ($I^2 = 65.6\%$, $p = 0.001$) (Table 1, **Supplementary Fig. 4**). Higher plasma Hcy level in PD-NP patients than in PD-NNP patients (SMD 0.87, 95% CI [0.43, 1.31], $p < 0.001$) was observed, with significant heterogeneity ($I^2 = 80.3\%$, $p < 0.001$) (Table 1, **Supplementary Fig. 5**). Male PD patients had higher plasma Hcy level (SMD 0.30, 95% CI [0.10, 0.50]; $p = 0.003$) than female patients, with significant heterogeneity ($I^2 = 54.1\%$, $p = 0.026$) (Table 1, **Supplementary Fig. 6**).

Table 1. Summary of meta-analysis of differences in blood homocysteine, vitamin B12, and folate levels between groups.

Blood indices	Studies	Participants	Effect estimates		Heterogeneity estimates			Egger's test	
			SMD [95% CI]	*p*-value	I^2	*p*-value	Model	t	*p*-value
Hcy (PD vs HCs)	50	4455/3792	0.80 (0.61, 0.99)	<0.001*	93.6%	<0.001*	Random	1.38	0.174
Hcy (Untreated PD vs HCs)	10	505/1093	0.29 (0.17, 0.41)	<0.001*	16.1%	0.295	Fixed	0.11	0.914
Hcy (LDA-treated PD vs Untreated PD)	8	609/155	0.48 (0.30, 0.67)	<0.001*	43.4%	0.089	Fixed	-	-
Hcy (COMTI treated PD vs HCs)	6	165/173	0.74 (0.26, 1.22)	0.002*	76.5%	0.001*	Random	-	-
Hcy (Non-COMTI treated PD vs HCs)	20	1271/1242	0.94 (0.74, 1.14)	<0.001*	80.0%	<0.001*	Random	2.89	0.010*
Hcy (COMTI treated PD vs Non-COMTI treated PD)	9	269/468	–0.49 (–0.64, –0.33)	<0.001*	31.8%	0.163	Fixed	-	-
Hcy (PD-CI vs PD-NCI)	12	480/1120	0.71 (0.50, 0.92)	<0.001*	65.6%	0.001*	Random	1.33	0.214
Hcy (PD-NP vs PD-NNP)	8	193/608	0.87 (0.43, 1.31)	<0.001*	80.3%	<0.001*	Random	-	-
Hcy (Male vs Female)	9	596/479	0.30 (0.10, 0.50)	0.003*	54.1%	0.026*	Random	-	-
VitB12 (PD vs HCs)	29	2232/2133	–0.33 (–0.43, –0.23)	<0.001*	60.8%	<0.001*	Random	0.22	0.831
VitB12 (Untreated PD vs HCs)	6	194/405	–0.47 (–0.67, –0.28)	<0.001*	<0.1%	0.451	Fixed	-	-
VitB12 (LDA-treated PD vs Untreated PD)	4	257/85	0.07 (–0.18, 0.32)	0.590	43.0%	0.153	Fixed	-	-
VitB12 (COMTI treated PD vs HCs)	5	112/118	–0.30 (–0.57, –0.04)	0.024*	37.7%	0.170	Fixed	-	-
VitB12 (Non-COMTI treated PD vs HCs)	10	611/689	–0.28 (–0.40, –0.17)	<0.001*	42.2%	0.076	Fixed	0.48	0.641
VitB12 (COMTI treated PD vs Non-COMTI treated PD)	9	250/457	0.08 (–0.25, 0.41)	0.638	76.1%	<0.001*	Random	-	-
VitB12 (PD-CI vs PD-NCI)	10	399/812	–0.22 (–0.34, –0.09)	0.001*	<0.1%	0.908	Fixed	1.36	0.212
VitB12 (PD-NP vs PD-NNP)	7	182/495	–0.40 (–0.81, –0.00)	0.049*	72.6%	0.001*	Random	-	-
VitB12 (Male vs Female)	3	213/155	–0.23 (–0.64, 0.17)	0.257	68.0%	0.044*	Random	-	-
FA (PD vs HCs)	24	1861/1818	–0.13 (–0.19, –0.06)	<0.001*	49.2%	0.004	Fixed	–1.79	0.087
FA (Untreated PD vs HCs)	5	164/375	–0.19 (–0.39, 0.01)	0.069	<0.1%	0.429	Fixed	-	-
FA (LDA-treated PD vs Untreated PD)	4	257/85	0.12 (–0.13, 0.37)	0.344	30.5%	0.229	Fixed	-	-
FA (COMTI treated PD vs HCs)	5	112/118	0.11 (–0.15, 0.37)	0.402	38.7%	0.163	Fixed	-	-
FA (Non-COMTI treated PD vs HCs)	11	662/740	–0.25 (–0.36, –0.14)	<0.001*	17.5%	0.277	Fixed	–1.54	0.157
FA (COMTI treated PD vs Non-COMTI treated PD)	9	250/457	0.27 (0.01, 0.53)	0.045	61.4%	0.008*	Random	-	-
FA (PD-CI vs PD-NCI)	10	399/812	–0.17 (–0.29, –0.04)	0.009*	30.6%	0.164	Fixed	0.44	0.668
FA (PD-NP vs PD-NNP)	3	72/72	–0.25 (–0.99, 0.49)	0.510	68.7%	0.041*	Random	-	-
FA (Male vs Female)	3	213/155	–0.08 (–0.29, 0.13)	0.478	<0.1%	0.559	Fixed	-	-

CI, Confidence interval; COMTI, Catechol-O-methyltransferase inhibitor; FA, Folate; HCs, Healthy controls; Hcy, Homocysteine; LDA, Dopaminergic drugs; Non-COMTI, Dopaminergic drugs excluding COMTIs; PD, Parkinson's disease; PD-CI, PD patients with cognitive impairment; PD-NCI, PD patients with no cognitive impairment; PD-NP, PD patients with neuropathy; PD-NNP, PD patients with no neuropathy; SMD, Standardized mean difference; Vit B12, Vitamin B12; *Statistically significant differences.

Table 2. Summary of meta-analysis based on region.

Blood indices	Asian			European			Total		
	Studies	SMD [95% CI]	*p*-value	Studies	SMD [95% CI]	*p*-value	Studies	SMD [95% CI]	*p*-value
Hcy (PD vs HCs)	19	0.79 (0.34, 1.24)	<0.001*	31	0.81 (0.65, 0.98)	<0.001*	50	0.80 (0.61, 0.99)	<0.001*
Hcy (Untreated PD vs HCs)	6	0.33 (0.20, 0.46)	<0.001*	4	0.11 (–0.16, 0.38)	0.415	10	0.29 (0.17, 0.41)	<0.001*
Hcy (Non-COMTI treated PD vs HCs)	6	0.89 (0.69, 1.08)	<0.001*	14	0.97 (0.70, 1.23)	<0.001*	20	0.94 (0.74, 1.14)	<0.001*
Hcy (PD-CI vs PD-NCI)	5	1.02 (0.62, 1.42)	<0.001*	7	0.53 (0.39, 0.68)	<0.001*	12	0.71 (0.50, 0.92)	<0.001*
VitB12 (PD vs HCs)	13	–0.39 (–0.59, –0.20)	<0.001*	16	–0.32 (–0.39, –0.24)	<0.001*	29	–0.33 (–0.43, –0.22)	<0.001*
VitB12 (Non-COMTI treated PD vs HCs)	4	–0.46 (–0.82, –0.10)	0.013*	6	–0.25 (–0.38, –0.12)	<0.001*	10	–0.28 (–0.40, –0.17)	<0.001*
VitB12 (PD-CI vs PD-NCI)	2	–0.19 (–0.52, 0.14)	0.257	8	–0.22 (–0.36, –0.08)	0.001*	10	–0.22 (–0.34, –0.09)	0.001*
FA (PD vs HCs)	10	–0.28 (–0.41, –0.16)	0.001*	14	–0.07 (–0.20, 0.06)	0.259	24	–0.13 (–0.19, –0.06)	<0.001*
FA (Non-COMTI treated PD vs HCs)	4	–0.35 (–0.57, –0.13)	0.002*	7	–0.22 (–0.34, –0.10)	<0.001*	11	–0.25 (–0.36, –0.14)	<0.001*
FA (PD-CI vs PD-NCI)	2	–0.49 (–1.07, 0.08)	0.093	8	–0.11 (–0.25, 0.02)	0.105	10	–0.17 (–0.29, –0.04)	0.009*

CI, Confidence interval; COMTI, Catechol-O-methyltransferase inhibitor; FA, Folate; HCs, Healthy controls; Hcy, Homocysteine; LDA, Dopaminergic drugs; Non-COMTI, Dopaminergic drugs excluding COMTIs; PD, Parkinson's disease; PD-CI, PD patients with cognitive impairment; PD-NCI, PD patients with no cognitive impairment; SMD, Standard mean difference; Vit B12, Vitamin B12; *Statistically significant differences.

3.3 Analysis of Serum Vit B12 Levels between Groups

The meta-analysis of 29 articles (2232 PD patients and 2133 HCs) showed that PD patients had significantly lower plasma Vit B12 levels than HCs (SMD –0.33, 95% CI [–0.43, –0.23]; $p < 0.001$) with substantial heterogeneity ($I^2 = 60.8\%, p < 0.001$) (Table 1, Fig. 3). Compared to PD-NCI patients, PD-CI patients had lower plasma Vit B12 level (SMD –0.22, 95% CI [–0.34, –0.09]; $p = 0.001$), with no significant heterogeneity ($I^2 < 0.1\%$, $p = 0.908$) (Table 1, **Supplementary Fig. 7**).

3.4 Analysis of Serum FA Levels between Groups

The meta-analysis of 24 articles (1861 PD patients and 1818 HCs) indicated that PD patients had lower plasma FA level than HCs (SMD –0.13, 95% CI [–0.19, –0.06]; $p < 0.001$), with no significant heterogeneity ($I^2 = 49.2\%$, $p = 0.004$) (Table 1, Fig. 4). PD-CI patients had significantly lower plasma FA level (SMD –0.17, 95% CI [–0.29, –0.04]; $p = 0.009$) than PD-NCI patients, with no significant heterogeneity ($I^2 = 30.6\%$, $p = 0.164$) (Table 1, **Supplementary Fig. 8**).

3.5 Subgroup Analysis Based on Region

We divided the study populations into Asian and European subgroups to analyze the differences in plasma Hcy, Vit B12, and FA levels between groups. This subgroup meta-analysis was performed when there were at least 10 studies to avoid significant public bias. We found that untreated PD patients had higher plasma Hcy level than HCs in the Asian population ($p < 0.001$); however, this difference was not statistically significant ($p = 0.451$) in the European population (Table 2). Lower plasma Vit B12 level was only found in European PD-CI patients than in PD-NCI patients; this difference was not statistically significant ($p = 0.257$) in the Asian population (Table 2). Lower plasma FA level was only found in Asian PD patients; this difference was not statistically significant ($p = 0.257$) in the European population (Table 2).

3.6 Sensitivity Analysis

Sensitivity analysis demonstrated that the pooled effect indicators of the meta-analyses were stable after removing each study, which suggested that the results were reliable. However, in the analysis of Hcy level between untreated PD patients and HCs, when removing Kirbas' study [33], the total heterogeneity changed from 80.4% to 16.1%. For FA level between PD patients and HCs, when removing Karahalil's study [32], the total heterogeneity changed from 70.3% to 49.2%. Therefore, we excluded these two studies from the final statistical analyses.

3.7 Publication Bias

The funnel plots were mostly symmetrical, suggesting the potential for minor publication bias (**Supplementary Figs. 9–18**). Egger's test showed that there was no evidence of publication bias between groups, with exception of the comparison of Hcy level between non-COMTI-treated PD patients and HCs (Table 1).

4. Discussion

To the best of our knowledge, this is the most comprehensive review with the largest sample size focusing on the features of plasma Hcy, Vit B12, and FA in PD patients. The results showed that PD patients may have higher Hcy levels and lower Vit B12 levels than the healthy population. PD-CI patients had higher Hcy levels and lower Vit B12 and FA levels compared with PD-NCI patients. We speculate that this difference may involve changes in PD pathogenesis or may be a secondary change in PD. Hcy, Vit B12, and FA may play a critical role in PD onset and progression. Thus, additional studies are needed to verify whether supplementation with Vit B12 and FA to increase Vit B12 level and decrease Hcy level may decrease the risk of PD or delay PD progression.

The exact cause of higher Hcy level and lower Vit B12 level in PD patients remains unclear. We speculate that several factors may be involved. First, Vit B12 and FA act as co-enzymes of methionine and are necessary for Hcy metabolism. Vit B12 and FA deficiency can lead to higher plasma Hcy level [3], and Hcy level is negatively correlated with plasma Vit B12 and FA level in PD patients [83]. Second, hyperhomocysteinemia can increase the production of reactive oxygen species and decrease the production and bioavailability of nitric oxide, which may trigger more inflammation [84]. Inflammation is an important pathophysiological mechanism of PD [85]. Third, Hcy is an excitatory amino acid that can enhance calcium influx, leading to excitotoxicity and neuronal cell death through binding N-methyl-D-aspartate (NMDA) or directly activating group I metabotropic glutamate receptors [84]. The increased synaptic function of NMDA receptors in the substantia nigra pars reticulata was observed in a PD mouse model, and microinjection of NMDA receptors antagonist into the substantial nigra pars reticulata resulted in improvements in motor deficits [86]. Fourth, higher Hcy level can increase the permeability of the blood-brain-barrier (BBB) by directly activating the NMDA receptor on cerebrovascular endothelial cells [87]. Numerous studies have demonstrated the hyperpermeability of the BBB in PD, which may be involved in the pathophysiology of PD [88–90]. Vit B12 can improve the integrity of the BBB by upregulating the expression of the cholinergic receptor [91].

Our meta-analysis also found a lower trend in blood FA level in PD patients than in HCs. FA deficiency may increase the amounts of α-synuclein, which is the main pathological protein that accumulates in PD by inhibiting DNA methylation and then upregulating α-synuclein gene expression [3]. As the most commonly prescribed medication for PD, LDA may increase Hcy level by upregulating the expression and activities of methionine adeno-

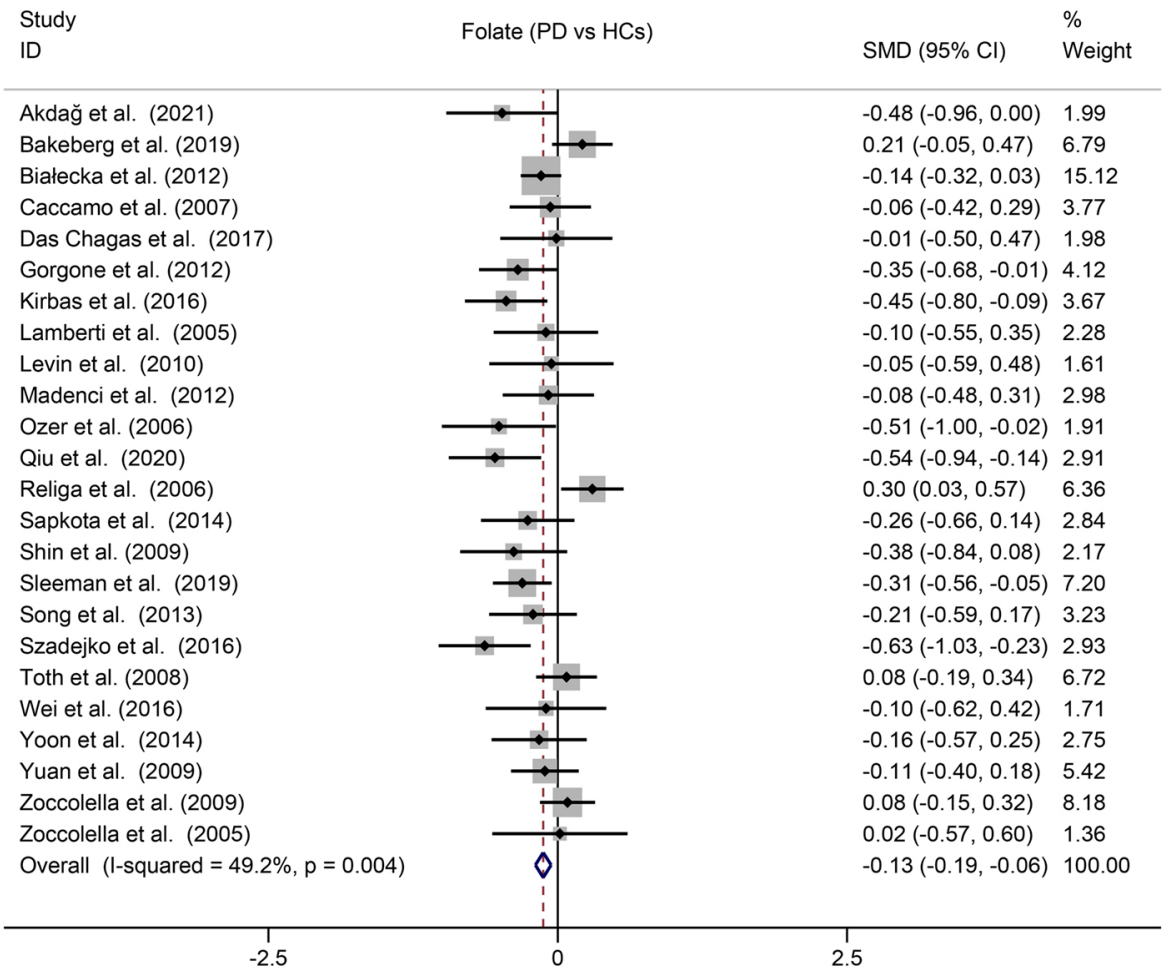

Fig. 4. Forest plot for comparison of plasma FA levels between PD patients and HCs. CI, Confidence interval; FA, Folate; HCs, Healthy controls; PD, Parkinson's disease; SMD, Standardized mean difference.

syl transferase and COMT [17,92]. This may explain our results showing that treated PD patients had significantly higher plasma Hcy level than untreated patients. COMTI treatment may decrease Hcy level [17], which is consistent with our finding that COMTI-treated PD patients had significantly lower plasma Hcy level than non-COMTI-treated patients.

Our meta-analysis found that PD-CI patients had higher Hcy level and lower Vit B12 and FA levels than PD-NCI patients. Increased Hcy level is a modifiable risk factor for CI and dementia. Treatment with Vit B can slow the rate of whole and regional brain atrophy and cognitive decline in patients with CI [93]. CI is a common non-motor symptom in PD patients. Additional studies are needed to determine whether Vit B12 and FA supplementation can help delay the occurrence and deterioration of CI in PD patients.

PD patients may have an increased prevalence of neuropathy than HCs [54,67,94]. Our meta-analysis found that PD-NP patients had higher Hcy level and lower Vit B12 level compared to PD-NNP patients (Table 1, **Supplementary Figs. 7,15**). This is consistent with the results from another study, which showed that peripheral neuropathy is associated with lower plasma Vit B12 and elevated Hcy [95]. Whether supplementation with Vit B12 or decreased Hcy level can improve neuropathy in PD patients also needs to be explored.

5. Conclusions

PD patients may have higher Hcy and lower Vit B12 levels than the healthy population. Whether Hcy increases the risk of PD or Vit B12 decreases the risk of PD needs to be further studied in the future. Hcy, Vit B12, and FA may play a role in CI and neuropathy in PD patients. More studies are needed to explore whether Vit B12 and FA supplementation can help decrease the risk of PD, delay PD progression or cognitive impairment, or improve neuropathy in PD patients.

6. Limitations

This meta-analysis had several limitations. First, the sample size of some subgroups was relatively small. Second, we only included studies published in English. Third, the age heterogeneity between studies was also a poten-

tial limitation of our meta-analysis. The included studies demonstrated significant heterogeneity in the comparison of Hcy, Vit B12, and FA levels between PD patients and HCs. In addition, other factors may have led to the different results; for example, differences in methodology, treat regimes and duration, severity of the PD, diet, exercise, and gastrointestinal conditions may have affected blood Hcy, Vit B12, and FA levels. However, in the current analysis, we did not adjust for these confounding factors.

Availability of Data and Materials

The original contributions presented in the study are included in the article/supplementary material. Inquiries can be directed to the corresponding authors.

Author Contributions

YL and XG participated in the study design. YL and MG independently screened the literature. YL and MG were involved in collecting and analyzing the data. YL and MG drafted the manuscript. YL and XG contributed to the revision of the article. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2205115.

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