INPLASY PROTOCOL

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None declared.

Features of plasma homocysteine, vitamin B12, and folate in Parkinson's disease: An updated meta-analysis

Liu, YT[1]; Gou, MY[2]; Gou, XY[3].

Review question / Objective: **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.**
Eligibility 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.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 April 2023 and was last updated on 27 April 2023 (registration number INPLASY202340099).

INTRODUCTION

Review question / Objective: **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.**

Condition being studied: **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). 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. 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. In parallel, Hcy may play a role in PD onset or progression through gene defects and apoptosis. FA and Vit B12 are necessary cofactors in Hcy metabolism, 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. Furthermore, deficiencies in FA and Vit B12 are associated with neuronal degeneration. At the same time, dopaminergic drugs may affect serum Hcy levels. Increased Hcy level is a modifiable risk factor for CI and dementia.

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). However, other studies have reported inconsistent results. 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.

METHODS

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.

Participant or population: 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.

Intervention: We reviewed the original text again and regrouped it. For all the three parameters, we compared "PD vs HCs", "untreated PD vs HCs", "LDA-treated PD vs untreated PD", "COMTI treated PD vs HCs", "Non-COMTI-treated PD vs HCs", "COMTI treated PD vs Non-COMTI treated PD".

Comparator: Summary of differences in blood homocysteine, vitamin B12, and folate levels between PD groups,we compared "PD vs HCs", "untreated PD vs HCs", "LDA-treated PD vs untreated PD", "COMTI treated PD vs HCs", "Non-COMTI-treated PD vs HCs", "COMTI treated PD vs Non-COMTI treated PD", "PD-CI vs PD-NCI", "PD-NP vs PD-NNP", "Male vs Female".

Study designs to be included: We reviewed the original text again and regrouped it. For all the three parameters, we compared "PD vs HCs", "untreated PD vs HCs", "LDA-treated PD vs untreated PD", "COMTI treated PD vs HCs", "Non-COMTI-treated PD vs HCs", "COMTI treated PD vs Non-COMTI treated PD", "PD-CI vs PD-NCI", "PD-NP vs PD-NNP", "Male vs Female".

Eligibility 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.

Information sources: 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.

Main outcome(s): (1) PD patients had significantly increased Hcy level, and decreased Vit B12 and FA levels compared to healthy controls. (2) Higher Hcy level was found in Dopaminergic medications treated PD patients than in untreated patients. (3) PD patients with cognitive impairment had higher Hcy level, lower Vit B12 and FA levels than those with no cognitive impairment. (4) PD patients with neuropathy had significantly increased Hcy level and decreased Vit B12 level compared to PD patients with no neuropathy. 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.

Quality assessment / Risk of bias analysis: 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. Engauge Digitizer 4.1 was used to collect data from statistical charts. The quality of the original studies was evaluated by the Newcastle-Ottawa Scale. Egger's test was used to assess the publication bias when at least 10 studies were included in the meta-analysis. 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.

Strategy of data synthesis: All data were analyzed using Stata 15.0 statistical software. 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. The fixed-effects model was used when $I^2 < 50\%$; otherwise, the random-effects model was used.

Subgroup analysis: 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. For all the three parameters, we compared "PD vs HCs", "untreated PD vs HCs", "LDA-treated PD vs untreated PD", "COMTI treated PD vs HCs", "Non-COMTI-treated PD vs HCs", "COMTI treated PD vs Non-COMTI treated PD", "PD-CI vs PD-NCI", "PD-NP vs PD-NNP", "Male vs Female".

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.

Language restriction: Papers published in English.

Country(ies) involved: China.

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

Contributions of each author:

Author 1 - Yiti Liu - YL participated in the study design. YL independently screened the literature. YL was involved in collecting and analyzing the data. YL drafted the manuscript.
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