

On the correlation between serum Cystatin C and Parkinson's disease in the Chinese population: a promising biomarker?

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As there is no clear biomarker to diagnose Parkinson's disease, this meta-analysis aims to comprehensively evaluate the correlation between serum Cystatin C levels and Parkinson's disease in the Chinese population by the meta-analysis method. PubMed, Web of Science, Embase, Cochrane Library, China national knowledge infrastructure, and China WanFang databases were systematically searched on the correlation between serum Cystatin C and Parkinson's disease. The results showed that Cystatin C level in Parkinson's disease patients compared with the control group, the standardized mean difference = 1.78 (95% CI: 1.33–2.24, $P < 0.05$). The level of Cystatin C in the late Parkinson's disease stage compared with that in the mid-term of Parkinson's disease, the standardized mean difference was = 0.78 (95% CI: 0.08–1.49, $P < 0.05$). The Cystatin C level in the mid-term of Parkinson's disease compared with that in the early Parkinson's disease stage, the standardized mean difference was 1.24 (95% CI: 0.35–2.12, $P < 0.05$). The level of Cystatin C in Parkinson's disease with mild cognitive impairment compared with Parkinson's disease without mild cognitive impairment, the standardized mean difference was 1.29 (95% CI: 0.47–2.10, $P < 0.05$). The differences were all statistically significant. In conclusion, a high level of serum Cystatin C may be involved in the occurrence and development of Parkinson's disease, whose level is higher in Parkinson's disease patients with mild cognitive impairment than that in Parkinson's disease without mild cognitive impairment. Therefore, Cystatin C in serum is a promising biomarker for diagnosing Parkinson's disease.

Keywords

Cystatin C; Parkinson's disease; Meta-analysis; Mild cognitive impairment

1. Introduction

Parkinson's disease (PD) is a common neurological disease. Patients with PD have apparent motor dysfunction and have various non-motor dysfunctions such as depression, which seriously affects the quality of patients' lives. Approximately 15 out of every 100,000 people worldwide suffer from PD [1]. At present, the diagnosis of PD mainly relies on clinical criteria, such as the clinical characteristics of patients and the clinical experience of doctors, which is still flawed. It is expected that more than 70% of substantia nigra dopaminergic neurons have been lost when a patient is diagnosed [2, 3]. The heterogeneity of the clinical features of Parkinson's dis-

ease has urged people to try to find reliable biomarkers for earlier diagnosis of PD, which is essential for doctors to optimize early intervention and monitor disease progression and patient's response to treatment.

As the understanding of the pathophysiological mechanism of PD deepens, many biological markers for the diagnosis of PD have emerged, including imaging biomarkers and biochemical characteristics. In addition, the biomarkers obtained by screening can be linked with the clinical parameters of patients, enabling us to determine the development and prognosis of the disease more accurately. Among numerous candidate biomarkers, serum Cystatin C (Cys C) has attracted a great deal of attention from researchers and clinicians.

Cys C is a protease inhibitor with 120 amino acid residues and a molecular weight of 13,000. Its primary biological effect is to inhibit the extracellular proteolytic enzyme, which belongs to the papain-like cysteine proteolytic enzyme family [4]. Almost all of the nucleated cells in human tissue can produce Cys C [5], which is produced from the nucleated cells at a practically constant rate, free filtered from the glomerulus, and entirely absorbed by the proximal renal tubules without secretion, thus becoming a sensitive biological indicator of renal function [6]. Studies have found that Cys C, preventing unwanted proteolysis, is associated with a variety of neurological diseases, such as Alzheimer's disease [7], multiple sclerosis [8], epilepsy [9], etc. A meta-analysis by Nair *et al.* [10] showed that Cys C levels in the mild cognitive impairment group with Alzheimer's disease were significantly higher than those in the control group. Wang *et al.* [11] revealed that Cys C levels were significantly associated with ischemic stroke and predict ischemic stroke risk in the meta-analysis.

Xu *et al.* [12] found that the expression of Cys C in dopaminergic neurons of the striatum is up-regulated after 6-OHDA is injected into substantia nigra striatum cells, astrocytes, and microglia cells of rats. Nagai *et al.* [13] also found that Cys C expression of dopaminergic neurons is up-regulated in the MPTP-induced PD rat model. It has been reported that elevated Cys C expression in serum of

PD patients is also associated with mild cognitive impairment (MCI) [14, 15]. Moreover, the increase of Cys C expression in PD patients's serum will aggravate the process of PD patients [14]. Li *et al.* [16] believed that the expression level of Cys C in the serum of PD patients is not related to the process of PD patients.

At present, there is no clear conclusion about the correlation between serum Cys C and PD. Therefore, this article intends to conduct a meta-analysis by collecting research literature on the correlation between serum Cystatin C expression level and PD in various databases, to comprehensively evaluate the relationship between the two.

2. Methods

2.1 Literature retrieval

We conducted this meta-analysis in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) [17]. Various databases were searched, such as PubMed, Web of Science, Embase, Cochrane Library, China national knowledge infrastructure (CNKI), and China WanFang databases, to collect researches on the correlation between serum Cystatin C levels and PD. The retrieval keywords were as follows: ("Parkinson's disease" OR "Parkinson" OR "PD" OR "parkinsonism") AND ("Cystatin C" OR "Cys C"). The retrieval time was from the establishment of each database to November 2020. There were no language restrictions. All literature retrieval and screening were carried out independently by two researchers and finally cross-checked. When the two researchers encountered a disagreement, they resolved it through discussion or turned to a third researcher for help.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

(1) It was a clinical diagnosis of PD based on accepted criteria [18]. (2) The meta-analysis was a cross-sectional study to evaluate the relationship between serum Cys C levels in PD patients and healthy or neurological controls (i.e., people with no Parkinson's syndrome). (3) The original data provided sample size, mean and standard deviation. (4) The sample was from the serum of PD patients. (5) The subjects were the Chinese population.

2.2.2 Exclusion criteria

(1) The data were just meetings, abstracts, literature reviews, etc. (2) The meta-analysis used an animal sample. (3) There was a lack of related research on numerical data. (4) The Newcastle-Ottawa scale (NOS) score was lower than 6.

2.3 Literature quality evaluation

The quality of the included studies was evaluated according to NOS [19], which was conducted independently by two researchers, and finally cross-checked. When the two researchers encountered a disagreement, they resolved it through discussion. Otherwise, a third should be involved to make judgments on the debate. The scale adopted a star system, consisting of three aspects: the selection of research

objects (including four items), the comparability of the research group (including two items), and the determination of exposure or results (including three items). Each question was created as a multiple-choice question with three answers: "yes", "no", or "unclear". "Yes" represented the low risk of bias, with a score of 1; "unclear" represented the medium risk of bias, with a score of 0; "No" represented the high risk of bias, with a score of -1. The highest score was 9 stars. When the NOS score was lower than 6, it was considered a low-quality; when the NOS was higher than or equal to 6 stars, it was considered high-quality. Only studies with NOS scores higher than or equal to 6 stars were included.

2.4 Data extraction

The data were extracted independently by two researchers and finally cross-checked. The following information was extracted from the included studies: first author, year of publication, country, detection method, age, sample size, mean and standard deviation between the PD group and the control group. Besides, we collected the odds ratio (OR) value and its 95% confidence interval (CI) of the effect of Cys C on PD in multiple logistic regression.

2.5 Statistical analysis

Data processing was performed by Stata 15.0 statistical software. The standardized mean difference (SMD) was set as effect size in the combined quantitative data analysis. The OR was used as the effective index in the pooled risk of cystatin C on PD. Cochran's Q test and I^2 test were used to analyze the heterogeneity across the included studies. If the P -value of Cochran's Q test was ≤ 0.05 , or $I^2 \geq 50\%$, indicating that there was heterogeneity, a random-effects model (REM) was adopted. Otherwise, a fixed-effects model (FEM) was used. Publication bias was assessed by the Funnel plot and Egger's test. The filling and trimming method made the funnel plot.. Finally, a sensitivity analysis was carried out to evaluate the robustness of the conclusions.

3. Results

3.1 Literature retrieval results

Screened as per strict inclusion criteria [14–16, 20–32], a total of 16 articles were included, containing 1764 patients with PD. The detailed literature screening process was shown in Fig. 1. In addition, the primary characteristics and NOS scores of the included studies were displayed in Table 1 (Ref. [14–16, 20–32]). From the above, the NOS scores of the literature included were higher than 6.

3.2 Meta-analysis results

3.2.1 Change of cystatin C level in PD group compared with the control group

All studies included comparing serum Cys C levels between PD patients and controls (Table 2). The heterogeneity was significant ($I^2 = 97\%$), so a REM was used for data analysis. The results showed that (Fig. 2), compared with the control group, serum Cys C in the PD group was significantly higher than that in the control group, SMD = 1.78 (95% CI:

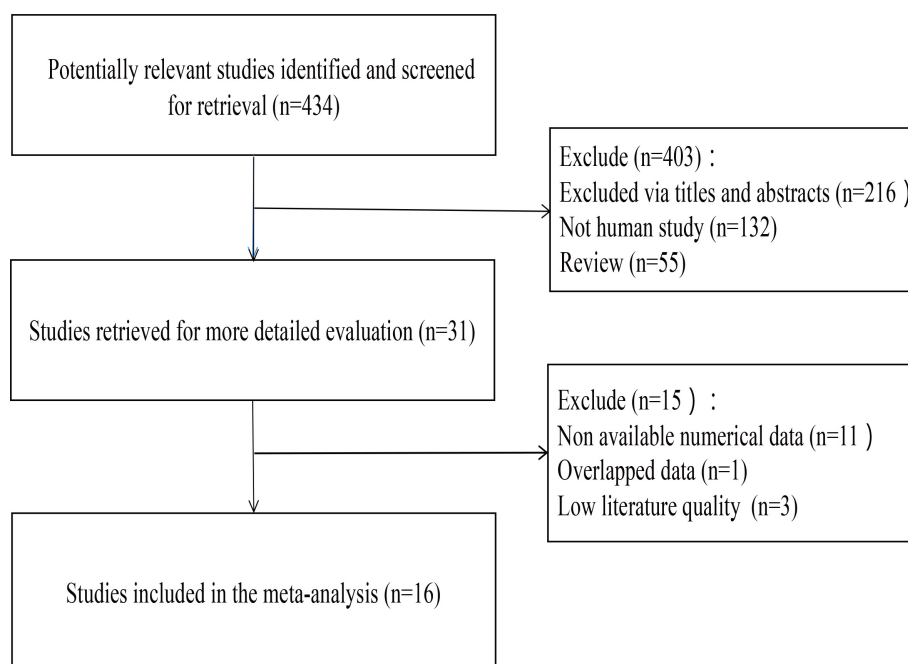


Fig. 1. Flow diagram of literature screening.

1.33~2.24, $P < 0.05$). After subgroup analysis according to the published languages, the heterogeneity did not decrease significantly. The funnel plot was symmetrical (Fig. 3), while the Egger's Test showed $P < 0.05$, indicating a particular publication bias.

3.2.2 Change of cystatin C level in the late and middle stage of PD group

There were 5 studies [14, 16, 25, 27, 29] on serum Cys C levels between late and middle stage PD patients. The heterogeneity was significant ($I^2 = 97\%$), so a REM was adopted. The results showed that (Fig. 4A), the level of serum cystatin C in patients with advanced PD was significantly higher than that in patients with intermediate PD, $SMD = 0.78$ (95% CI: 0.08~1.49, $P < 0.05$). Egger's test showed $P > 0.05$, indicating that the publication bias was low.

3.2.3 Change of cystatin C level in middle and early stage of PD group

There were 5 studies [14, 16, 25, 27, 29] on the comparison of serum Cys C levels between middle and early-stage PD patients. The heterogeneity was significant ($I^2 = 94\%$), so a REM was applied to merge the data. The results showed that (Fig. 4B), the level of serum Cys C in patients in the middle stage of PD was significantly higher than that in patients in the early-stage of PD. Egger's test showed $P < 0.05$, suggesting that there was a particular publication bias.

3.2.4 Change of cystatin C levels in PD with MCI compared with PD without MCI

There were 4 studies [14, 15, 28, 31] comparing serum Cys C levels between PD with MCI and PD without MCI. The heterogeneity was significant ($I^2 = 88.4\%$), so a REM was

adopted to analyze the data. The results showed that (Fig. 5), the level of serum Cys C in PD patients with MCI was significantly higher than that in PD patients without MCI, $SMD = 1.29$ (95% CI: 0.47~2.10, $P < 0.05$). In addition, Egger's test showed $P > 0.05$, indicating that the publication bias was low.

3.2.5 Risk of serum cystatin C on PD

Two studies [15, 22] reported multivariate logistic regression analysis of Cys C in the risk of PD. Hu *et al.* [15] included variables such as age, sex, creatinine, urea, uric acid, etc. The research of Dong *et al.* [22] contained variables such as duration of disease, Unified Parkinson's Disease Rating Scale II (UPDRS II), etc. The combined analysis results showed that, compared with the low level of serum Cys C, the high level significantly increased the risk of PD (OR = 18.87, 95% CI: 5.92~60.18, $P < 0.001$).

3.3 Sensitivity analysis

Our meta-analysis showed that serum Cys C in patients with PD was significantly higher than in the control group. This sensitivity analysis was conducted to explore the robustness. After excluding any of the studies separately, we conducted a meta-analysis again. The results showed that the original conclusion was robust (Fig. 6).

4. Discussion

Parkinson's disease (PD) is a common neurodegenerative disease, of which the main pathological changes are progressive degeneration and loss of dopaminergic neurons in substantia nigra and the formation of Lewy bodies in the cytoplasm, and the main clinical manifestations are static tremor, bradykinesia, and abnormal posture and gait. It has been confirmed that the determination of α -Synuclein (α -syn) [33],

Table 1. The primary characteristics of the included studies.

First Author	Year	Method	Age		Sample size		Serum cystatin C content (mean \pm standard)		NOS
			PD	Control	PD	Control	PD (mg/L)	Control (mg/L)	
Liu JZ [23]	2011	Hitachi 7170 ABA	71.34 \pm 11.06	67.73 \pm 10.38	53	33	1.18 \pm 0.37	0.79 \pm 0.15	7
Xu JM [24]	2014	Olympus au5400 ABA	66 \pm 9	66 \pm 9	115	110	1.06 \pm 0.2	0.96 \pm 0.16	7
Chen WW [14]	2015	Hitachi 7600 ABA	61.4 \pm 5.1	62.3 \pm 6.5	69	74	1.82 \pm 0.22	0.66 \pm 0.17	8
Cao XB [25]	2015	Olympus au5400 ABA	61–82	60–79	68	42	1.18 \pm 0.17	0.96 \pm 0.09	7
Hu WD [15]	2016	IA	66.67 \pm 9.02	65.71 \pm 8.43	162	146	1.06 \pm 0.19	0.96 \pm 0.15	8
Feng ZH [26]	2016	NR	60–80	NR	51	40	0.98 \pm 0.1	0.86 \pm 0.18	6
Lei J [20]	2017	Beckman CX4 ABA	64.79 \pm 9.51	64.1 \pm 8.45	108	108	0.98 \pm 0.22	0.88 \pm 0.16	8
Xiong KP [21]	2018	IA	65.5 \pm 9.6	65.7 \pm 8.4	106	146	1.03 \pm 0.19	0.96 \pm 0.15	8
Chang QQ [27]	2018	Beckman 5831 ABA	60.52 \pm 9.18	58.01 \pm 9.43	165	103	1.13 \pm 0.22	0.89 \pm 0.19	7
Dong XY [22]	2019	APTI	68.54 \pm 10.74	67.62 \pm 9.48	120	156	1.13 \pm 0.26	1.02 \pm 0.19	8
Li J [16]	2019	Cobas® 8000 ABA	64.47 \pm 8.54	63.84 \pm 9.32	322	214	0.97 \pm 0.22	0.89 \pm 0.17	8
Chen WW [28]	2019	ELISA	a: 63.3 \pm 10.9; b: 62.9 \pm 11.8; c: 63.1 \pm 10.6	62.2 \pm 11.2	120	50	a: 2.7 \pm 0.55; b: 3.22 \pm 0.61; c: 3.84 \pm 0.64	1.35 \pm 0.16	7
Xing XR [29]	2020	ICChem-320 ABA	Early: 57.23 \pm 10.98; middle: 56.29 \pm 10.48; late: 57.98 \pm 10.24	55.21 \pm 10.23	97	50	1.91 \pm 0.49	1.18 \pm 0.29	7
Xu JM [30]	2020	Olympus au5400 ABA	a: 64.03 \pm 10.16; b: 67.58 \pm 9.97	62.00 \pm 5.55	56	18	a: 0.96 \pm 0.12; b: 1.05 \pm 0.17	0.84 \pm 0.2	7
Ye M [31]	2020	LEIT	45–82	42–79	60	30	1.13 \pm 0.41	0.91 \pm 0.13	7
Zou Y [32]	2020	ELISA	56.37 \pm 21.44	57.35 \pm 19.87	92	87	a: 1.28 \pm 0.21; b: 1.49 \pm 0.19	0.89 \pm 0.16	7

ABA, automatic biochemical analyzer; APTI, automated particle-enhanced turbidimetric immunoassay; CSS, Cross-sectional survey; IA, immunoturbidimetry assay; LEIT, Latex enhanced immune turbidimetry; NOS, Newcastle-Ottawa Scale; NR, not report; PD, Parkinson's disease

DJ-1 [34], and other proteins in cerebrospinal fluid and the ratio of homovanillic acid to xanthine are helpful for the diagnosis of PD [3]. However, they are not effective in the diagnosis of PD in serum [35]. Recent studies have found that Cys C is associated with various nervous system diseases, of which the mechanism under neuropathological conditions is still controversial. Some studies suggest that Cys C plays a protective role in nervous system diseases. For instance, in Alzheimer's disease, Cys C and amyloid protein co-express in the brain amyloid vascular wall and senile plaque [36]. Through this co-expression, Cys C inhibits the formation of amyloid protein [37]. Liu *et al.* [38] found that exogenous Cys C can alleviate brain injury and cognitive impairment caused by subarachnoid hemorrhage by activating autophagy. However, some scholars believe that Cys C may damage neurons by activating an inflammatory response [13]. Zou *et al.* [39] reported that Cys C could enhance neuronal autophagy through VEGF-induced angiogenesis, enabling it to become a potential mediator for treating Parkinson's disease. The role of serum Cys C levels in the pathogenesis of patients with PD has not been exact yet. Therefore, this meta-analysis was conducted to explore the correlation between serum Cys C level and patients with PD.

Screened via strict inclusion and exclusion criteria, 16 available articles were included in this meta-analysis. The results showed that serum Cys C in patients with PD was significantly higher than in the control group; it was also noticed

that there was considerable heterogeneity across the included studies. Subsequently, a subgroup analysis of the published language was conducted to explore the source of heterogeneity. However, after a subgroup analysis of the studies, the heterogeneity did not decrease significantly. The symmetry of the funnel plot was good, while the result of Egger's test was statistically significant, which showed there was a particular publication bias. In the sensitivity analysis, we found that no exclusion of a study had a substantial impact on the original conclusion, indicating that the conclusion was robust. In other words, the high serum level of Cys C was involved in the development of PD.

The changes of serum Cys C level in early, middle, and late PD patients were compared to verify whether changes of serum Cys C affect the progression of PD. The results showed that serum Cys C level in middle stage patients was significantly higher than in early-stage patients with PD. In addition, compared with the middle stage of PD, Cys C level in advanced patients notably increased. Thus, it suggested that a high level of serum Cys C was associated with PD development.

In addition, we also compared the serum Cys C levels in PD patients with MCI and without MCI. The results showed that serum Cys C level in PD patients with MCI was significantly higher than in PD patients without MCI. This suggested that a high level of serum Cys C was involved cognitive impairment in patients with PD.

Table 2. Main results of the meta-analysis.

Comparison between groups	n	SMD	OR	95% CI	P for SMD	I ² (%)	P for heterogeneity	Model	P for publication bias (Egger)
PD vs. Con	16	1.78	NA	1.33~2.24	0.000	97	0.000	REM	0.000
English	6	1.25	NA	0.60~1.90	0.000	97.4	0.000	REM	0.011
Chinese	10	2.01	NA	1.42~2.60	0.000	95.8	0.000	REM	0.004
PD stage									
Late vs. Middle	5	0.78	NA	0.08~1.49	0.029	92.4	0.000	REM	0.07
Middle vs. Early	5	1.24	NA	0.35~2.12	0.006	94	0.000	REM	0.012
PD-MCI vs. PD without MCI	4	1.29	NA	0.47~2.10	0.002	88.4	0.000	REM	0.13
Cys C in MRA	2	NA	18.87	5.92~60.18	0.000	0.0	0.639	FEM	NA

CI, confidence interval; Cys C, Cystatin C; FEM, fix-effects model; MCI, mild cognitive impairment; MRA, Multiple regression analysis; OR, odds ratio; PD, Parkinson's disease; REM, random effect model; SMD, standard mean difference; NA, not applicable.

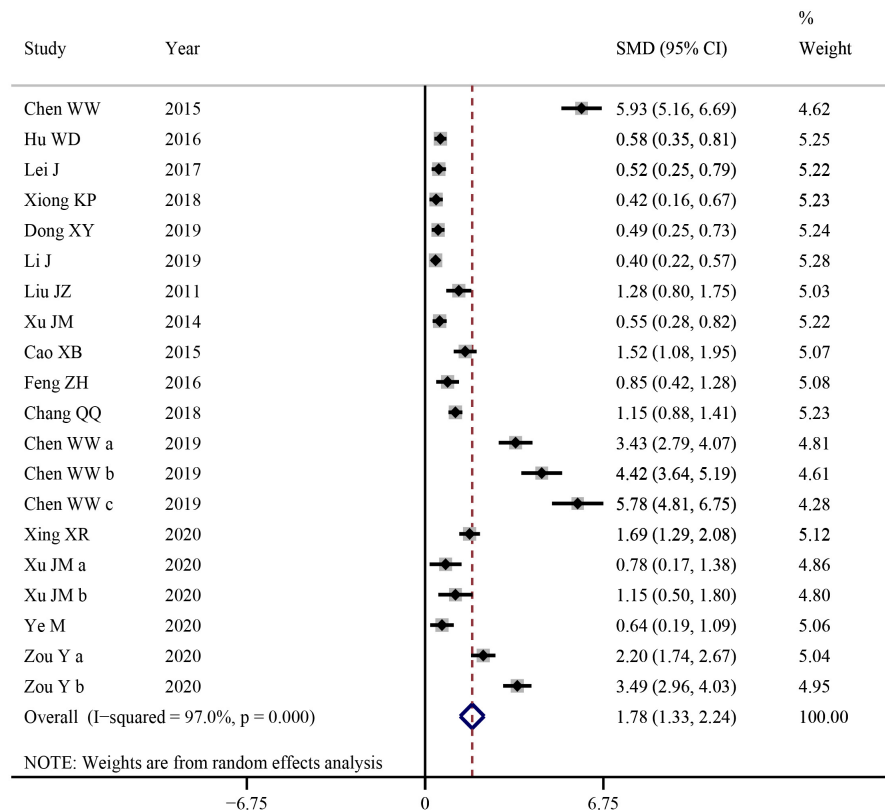


Fig. 2. Changes of cystatin levels in patients with PD. The red dotted line represents the pooled SMD. Both sides of the prism represent the 95% confidence interval of SMD. The left side favors the PD group, while the right side favors for control group. PD, Parkinson's disease; SMD, Standardized mean difference.

Considering the influence of confounding factors, we analyzed the pooled OR value of serum Cys C levels on PD's risk in multivariate logistic regression analysis. The results showed that high levels of serum Cys C significantly increased the risk of PD. However, only two studies were included in the results of multivariate analysis, and more verification is still needed for this conclusion.

Admittedly, in practical work, it is impractical to choose a single biomarker to diagnose PD. It is essential to combine other auxiliary tests (imaging, biochemical and genetic testing, etc.) or combined with behavior and dyskinesia symptoms in the progress of PD for early diagnosis. The use of high-throughput sequencing technology and public databases

provides more possibilities for discovering of more biomarkers of PD [40, 41].

Several studies showed that Cys C is a target for intervention in neurological diseases, as its expression increased with animal models of human neurological disorders [9, 42]. However, in future research, whether targeted therapy can be conducted and the mechanisms of Cys C on PD are challenging research topics.

Inevitably, this meta-analysis also has some limitations. First, all published, excluding high-quality studies that have not been published, would lead to potential publication bias to a certain extent. Second, the studies included were from based on the Chinese population and did not cover studies

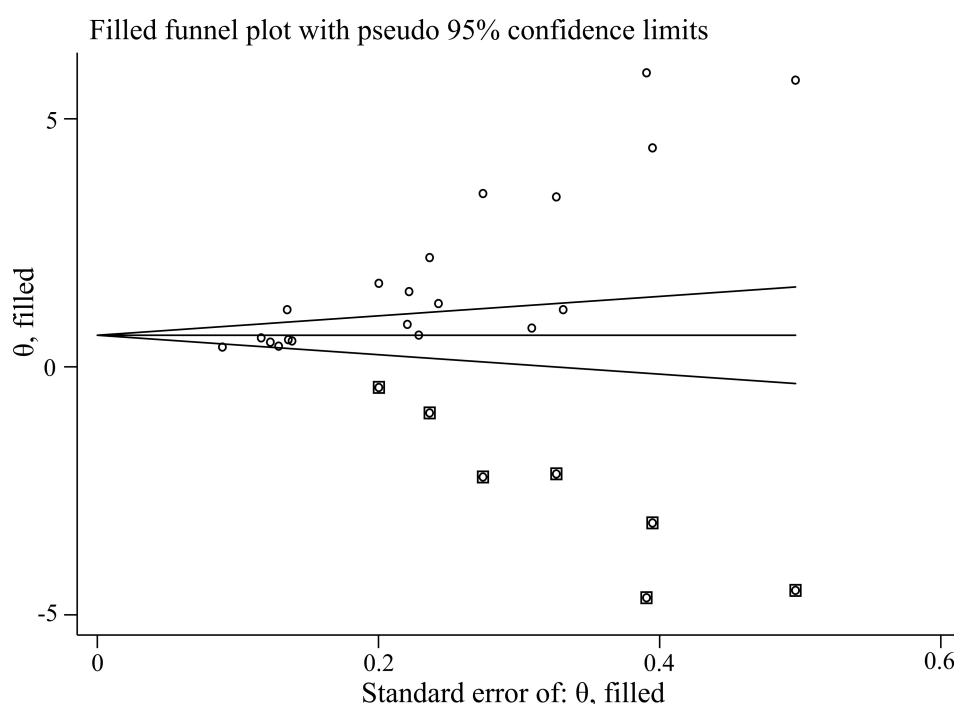


Fig. 3. Funnel plot for analyzing publication bias.

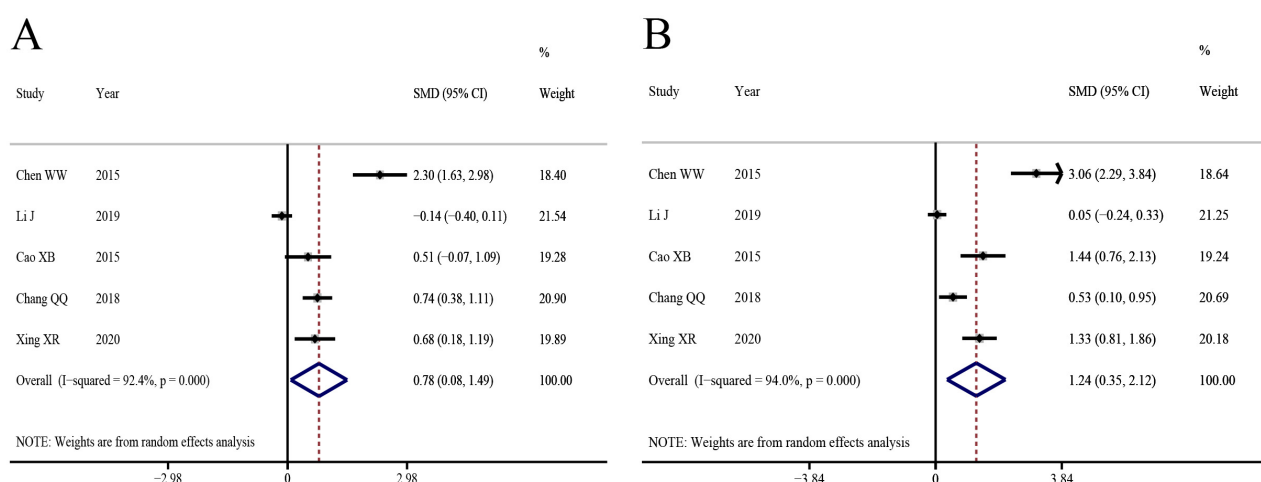


Fig. 4. Forest plot of changes of cystatin C levels in different stages of PD. (A) Late PD vs. Middle PD; The left side favors the late stage of the PD group, while the right side favors the middle stage of the PD group. (B) Middle PD vs. Early PD; The left side favors the middle stage of the PD group, while the right side favors an early stage of the PD group. The red dotted line represents the pooled SMD. Both sides of the prism represent the 95% confidence interval of SMD. PD, Parkinson's disease; SMD, Standardized mean difference.

from other populations, which might affect the conclusions' adaptability to other populations. Third, there was high heterogeneity across the studies. Even after the subgroup analysis of the language, the heterogeneity did not decrease, indicating other factors that affect the heterogeneity among the studies. Fourth, there was a particular publication bias. Although there were some limitations, this study was the first to systematically analyze the correlation between serum Cys C level and PD. Moreover, sensitivity analysis also confirmed the robustness of this correlation.

In summary, serum Cystatin C level is closely related to

PD in the Chinese population. Therefore, a high level of Cys C may be involved in the occurrence and development of Parkinson's disease. Furthermore, the expression level of Cystatin C is even higher in PD patients with mild cognitive impairment. Therefore, serum Cystatin C is a promising marker for the diagnosis of Parkinson's disease. However, it is also noted that some limitations remain, such as heterogeneity and publication bias, etc. Therefore, further in-depth studies still need to be done to explore the correlation between serum Cystatin C and Parkinson's disease.

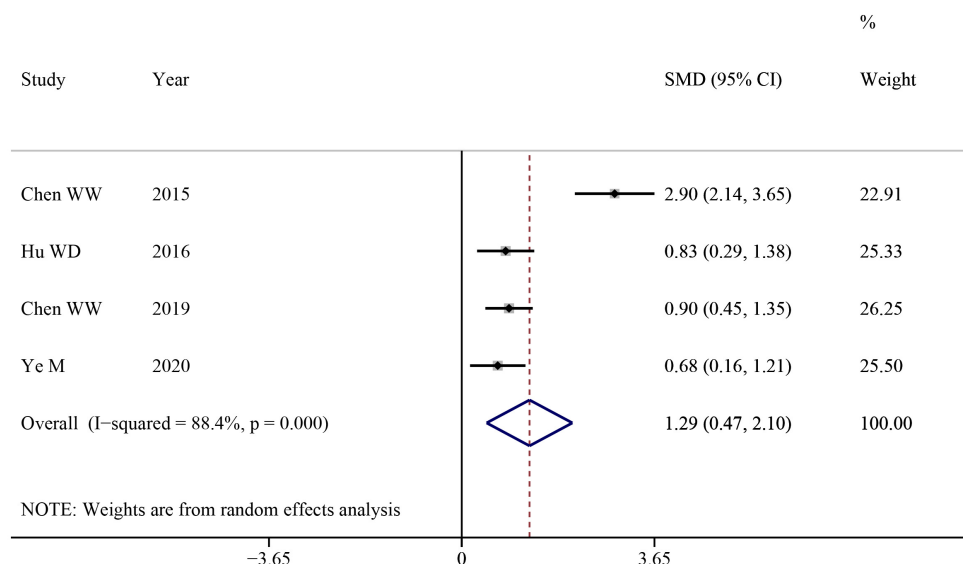


Fig. 5. Forest plot of changes of serum cystatin C in PD with MCI. The red dotted line represents the pooled SMD. Both sides of the prism represent the 95% confidence interval of SMD. The left side favors the PD group with MCI, while the right side favors the PD group without MCI. SMD: Standardized mean difference. MCI, mild cognitive impairment; PD, Parkinson's disease.

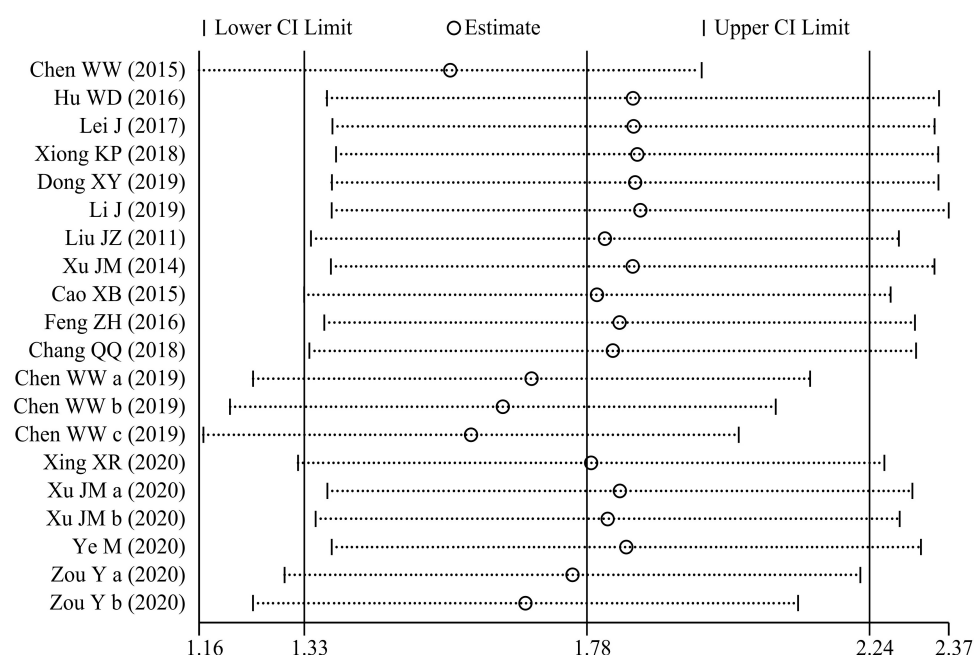


Fig. 6. Sensitivity analysis. SE, Standardized error; SMD, Standardized mean difference.

Abbreviations

Cys C, Cystatin C; FEM, fixed-effects model; MCI, mild cognitive impairment; NOS, The Newcastle-Ottawa scale; PD, Parkinson's disease; PRISMA, preferred reporting items for systematic reviews and meta-analyses; REM, random-effects model; SMD, standardized mean difference.

Author contributions

YCG, CC: Critical revision of the manuscript; YCG, CSM, CC: Substantial contribution to the conception and design

of the work, manuscript drafting; YCG, CSM, LCY: Acquisition, analysis, and interpretation of the data; YCG, CSM, LCY, CC: Revising the manuscript critically, final approval of the version to be published. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval was not needed because this is a meta-analysis.

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Conflict of interest

The authors declare no conflict of interest.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

- [1] Tysnes O, Storstein A. Epidemiology of Parkinson's disease. *Journal of Neural Transmission*. 2017; 124: 901–905.
- [2] Dutta D, Kundu M, Mondal S, Roy A, Ruehl S, Hall DA, *et al*. RANTES-induced invasion of Th17 cells into substantia nigra potentiates dopaminergic cell loss in MPTP mouse model of Parkinson's disease. *Neurobiology of Disease*. 2019; 132: 104575.
- [3] Zhang W, Sun C, Shao Y, Zhou Z, Hou Y, Li A. Partial depletion of dopaminergic neurons in the substantia nigra impairs olfaction and alters neural activity in the olfactory bulb. *Scientific Reports*. 2019; 9: 254.
- [4] Nandy SK, Bhuyan R, Seal A. Modelling family 2 cystatins and their interaction with papain. *Journal of Biomolecular Structure and Dynamics*. 2013; 31: 649–664.
- [5] Turk V, Bode W. The cystatins: protein inhibitors of cysteine proteinases. *FEBS Letters*. 1991; 285: 213–219.
- [6] Rothenbacher D, Rehm M, Iacoviello L, Costanzo S, Tunstall-Pedoe H, Belch JFF, *et al*. Contribution of cystatin C- and creatinine-based definitions of chronic kidney disease to cardiovascular risk assessment in 20 population-based and 3 disease cohorts: the BiomarCaRE project. *BMC Medicine*. 2020; 18: 300.
- [7] Hirao K, Yamashita F, Tsugawa A, Haime R, Fukasawa R, Sato T, *et al*. Association of serum cystatin C with white matter abnormalities in patients with amnesic mild cognitive impairment. *Geriatrics & Gerontology International*. 2019; 19: 1036–1040.
- [8] Nakane S, Fujita K, Azuma S, Urushihara R, Kamada M, Harada M, *et al*. CSF cystatin C and diffusion tensor imaging parameters as biomarkers of upper motor neuron degeneration in amyotrophic lateral sclerosis. *Clinical Neurology and Neurosurgery*. 2018; 172: 162–168.
- [9] Kaur G, Mohan P, Pawlik M, DeRosa S, Fajiculy J, Che S, *et al*. Cystatin C rescues degenerating neurons in a cystatin B-knockout mouse model of progressive myoclonus epilepsy. *The American Journal of Pathology*. 2010; 177: 2256–2267.
- [10] Nair P, Misra S, Nath M, Vibha D, Srivastava AK, Prasad K, *et al*. Cystatin C and risk of mild cognitive impairment: a systematic review and meta-analysis. *Dementia and Geriatric Cognitive Disorders*. 2020; 49: 1–12.
- [11] Wang Y, Li W, Yang J, Zhang M, Tian C, Ma M, *et al*. Association between Cystatin C and the risk of ischemic stroke: a systematic review and meta-analysis. *Journal of Molecular Neuroscience*. 2019; 69: 444–449.
- [12] Xu L, Sheng J, Tang Z, Wu X, Yu Y, Guo H, *et al*. Cystatin C prevents degeneration of rat nigral dopaminergic neurons: in vitro and in vivo studies. *Neurobiology of Disease*. 2005; 18: 152–165.
- [13] Nagai A, Terashima M, Sheikh AM, Notsu Y, Shimode K, Yamaguchi S, *et al*. Involvement of cystatin C in pathophysiology of CNS diseases. *Frontiers in Bioscience*. 2008; 13: 3470–3479.
- [14] Chen W, Cheng X, Zhang X, Zhang Q, Sun H, Huang W, *et al*. The expression features of serum Cystatin C and homocysteine of Parkinson's disease with mild cognitive dysfunction. *European Review for Medical and Pharmacological Sciences*. 2015; 19: 2957–2963.
- [15] Hu W, Chen J, Mao C, Feng P, Yang Y, Luo W, *et al*. Elevated cystatin C levels are associated with cognitive impairment and progression of Parkinson's disease. *Cognitive and Behavioral Neurology*. 2016; 29: 144–149.
- [16] Li J, Gu C, Zhu M, Li D, Chen L, Zhu X. Correlations between blood lipid, serum cystatin C, and homocysteine levels in patients with Parkinson's disease. *Psychogeriatrics*. 2019; 20: 180–188.
- [17] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology*. 2009; 151: 264–269.
- [18] Litvan I, Bhatia KP, Burn DJ, Goetz CG, Lang AE, McKeith I, *et al*. Movement disorders society scientific issues committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Movement Disorders*. 2003; 18: 467–486.
- [19] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*. 2010; 25: 603–605.
- [20] Lei J, Ma JH, Liang RB, Zhang XN. Association of serum $\alpha\beta 1-42$, cystatin C and UA with Parkinson's disease. *Biomedical Research*. 2017; 28: 6823–6828.
- [21] Xiong K, Dai Y, Chen J, Xu J, Wang Y, Feng P, *et al*. Increased serum cystatin C in early Parkinson's disease with objective sleep disturbances. *Chinese Medical Journal*. 2018; 131: 907–911.
- [22] Dong X, Zheng D, Nao J. Measurement of serum cystatin C: a valuable tool for evaluating dyskinesia in Parkinson's disease. *Neuroscience Letters*. 2019; 705: 172–176.
- [23] Liu JZ, Shi YL, Li LH, *et al*. Clinical value of serum cystatin C on Parkinson's disease. *Letters in Biotechnology*. 2011; 23: 115–119.
- [24] Xu J, Chen J, Mao C, Yang Y, Liu C. Preliminary relationship between serum cystatin C level and Parkinson's disease. *National Medical Journal of China*. 2015; 94: 804–807. (In Chinese)
- [25] Cao XB, Gong L, Dai J. Expression of serum IL-17, cystatin C, homocysteine in patients of Parkinson's disease and their clinical significance. *Hainan Medical Journal*. 2015; 26: 1894–1896.
- [26] Feng ZH, Nie XH, Huang Y, Wang CM, Wang T. The expression meaning of serum Cysc in Parkinson's patients with obstructive sleep apnea-hypopnea syndrome. *Chinese Medical Record*. 2016; 17: 90–93. (In Chinese)
- [27] Chang QQ, Li HY. Analysis of serum lipids, cystatin C and homocysteine levels in patients with Parkinson's disease. *Journal of Clinical Neuroscience*. 2018; 26: 495–501.
- [28] Chen WW, Wang M. The correlations between ApoA-1, MDA, Cys-C and hemodynamic parameters and cognitive function of Parkinson's disease. *Labeled Immunoassays*. 2019; 26: 620–624.
- [29] Xing XR, Hao YN, Sun Z, Zhao XC, Yuan FL. Clinical significance of serum cystatin C and β -amyloid protein 1-42 in patients with Parkinson's disease. *Progress in Modern Biomedicine*. 2020; 20: 1561–1568.
- [30] Xu JM, Chen J, Xu R, Feng P, Mao CJ, Yang YP, *et al*. The change of cystatine C in Parkinson's disease patients with obstructive sleep apnea syndrome. *Chinese Journal of Neurology*. 2014; 47: 365–369. (In Chinese)
- [31] Ye M, Xu JJ, Xie J, Shi P, Zhang L, Liu X. Correlation analysis of the serum levels of cystatin C and uric acid with cognitive impairment in Parkinson's disease. *Journal of Bengbu Medical College*. 2020; 45: 185–187. (In Chinese)
- [32] Zou Y, Zhong CZ, Guo CX, Wang YL. Serum expression of cystatin C and homocysteine in early Parkinson's disease and its relationship with sleep disorders. *Journal of Brain and Nervous Diseases*. 2020; 28: 96–100.

- [33] Eusebi P, Giannandrea D, Biscetti L, Abraha I, Chiasserini D, Orso M, *et al.* Diagnostic utility of cerebrospinal fluid α -synuclein in Parkinson's disease: a systematic review and meta-analysis. *Movement disorders*. 2017; 32: 1389–1400.
- [34] Dos Santos MCT, Scheller D, Schulte C, Mesa IR, Colman P, Bujac SR, *et al.* Evaluation of cerebrospinal fluid proteins as potential biomarkers for early stage Parkinson's disease diagnosis. *PLoS ONE*. 2018; 13: e206536.
- [35] An C, Pu X, Xiao W, Zhang H. Expression of the DJ-1 protein in the serum of Chinese patients with Parkinson's disease. *Neuroscience Letters*. 2018; 665: 236–239.
- [36] Haan J, Maat-Schieman ML, van Duinen SG, Jansson O, Thorsteinsson L, Roos RA. Co-localization of β /A4 and cystatin C in cortical blood vessels in Dutch, but not in Icelandic hereditary cerebral hemorrhage with amyloidosis. *Acta Neurologica Scandinavica*. 2010; 89: 367–371.
- [37] Belen T, Ribe EM, Weiqian M, Troy CM, Efrat L. Cystatin C protects neuronal cells from amyloid-beta-induced toxicity. *Journal of Alzheimer's Disease*. 2010; 19: 885–894.
- [38] Liu Y, Li J, Wang Z, Yu Z, Chen G. Attenuation of early brain injury and learning deficits following experimental subarachnoid hemorrhage secondary to Cystatin C: possible involvement of the autophagy pathway. *Molecular Neurobiology*. 2014; 49: 1043–1054.
- [39] Zou J, Chen Z, Wei X, Chen Z, Fu Y, Yang X, *et al.* Cystatin C as a potential therapeutic mediator against Parkinson's disease via VEGF-induced angiogenesis and enhanced neuronal autophagy in neurovascular units. *Cell Death & Disease*. 2017; 8: e2854–e2854.
- [40] Krokidis MG. Identification of biomarkers associated with Parkinson's disease by gene expression profiling studies and bioinformatics analysis. *AIMS Neuroscience*. 2019; 6: 333–345.
- [41] Chang D, Nalls MA, Hallgrímsdóttir IB, Hunkapiller J, van der Brug M, Cai F, *et al.* A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nature Genetics*. 2017; 49: 1511–1516.
- [42] Amin F, Khan MS, Bano B. Mammalian cystatin and protagonists in brain diseases. *Journal of Biomolecular Structure and Dynamics*. 2020; 38: 2171–2196.