Association between serum bilirubin concentration and Parkinson's disease: a meta-analysis

Jia-Ning Jin[1], Xian Liu[2], Ming-Juan Li[1], Xin-Ling Bai[1], An-Mu Xie[1]

[1]Department of Neurology, Affiliated Hospital of Qingdao University, Qingdao, Shandong 266003, China;
[2]Department of Internal Medicine, Affiliated Hospital of Qingdao University, Qingdao, Shandong 266003, China.

Abstract

Background: The antioxidant effects of bilirubin in Parkinson's disease (PD) have recently gained much attention from the research community. However, results from these studies have been conflicting. This meta-analysis is conducted to assess the relationship between the serum bilirubin concentration and the risk of PD.

Methods: Two reviewers performed a systematic literature search across five databases (MEDLINE, PubMed, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials). The case-control studies regarding bilirubin levels in PD patients published up to April 2020 were included. These studies were subjected to rigorous scrutiny and data extraction to determine the standard mean difference (SMD) and the 95% confidence interval (CI), which were analyzed using the Stata V.12.0 statistical software.

Results: A total of eight studies which included 1463 PD cases and 1490 controls were incorporated into our meta-analysis. SMD analysis showed that there was a higher total bilirubin (TBIL) and direct bilirubin (DBIL) levels in PD patients compared with controls (for TBIL, SMD: 0.300, 95% CI: 0.050–0.549, $P = 0.018$; for DBIL, SMD: 0.395, 95% CI: 0.102–0.688, $P = 0.008$). However, no significant relationship was found between the serum indirect bilirubin and PD patients (SMD: −0.223, 95% CI: −0.952–0.505, $P = 0.548$). A subgroup analysis based on ethnicity indicated that the serum TBIL was higher in PD patients of Caucasian descent in contrast to matched healthy controls (SMD: 0.511, 95% CI: 0.324–0.698, $P = 0.000$, $I^2 = 58.0\%$).

Conclusion: Higher serum bilirubin levels in PD patients suggest that bilirubin might play a role in the pathogenesis of PD and have the potential to be utilized as a biochemical marker for PD diagnosis and treatment.

Keywords: Parkinson's disease; Bilirubin; Heme oxygenase; Serum bilirubin concentration

Introduction

Parkinson's disease (PD) is the second most commonly encountered neurodegenerative disease following Alzheimer's disease with 1% to 2% prevalence in people over 65 years old.[1] The pathological features found to correlate with signs and symptoms of PD are the progressive degeneration of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies.[2] The clinical features of PD consist of both non-motor and motor features, with four primary symptoms being: bradykinesia, static tremor, rigidity, and postural imbalance.[1] Previous studies have shown that oxidative stress is related to the progression of neuronal damage, highlighting its potential role in the pathogenesis of PD.[3]

Heme oxygenase (HO) is one of the main antioxidant enzymes in the oxidative regulation system and is closely related to the occurrence of mammalian central nervous system (CNS) diseases.[4] There is increasing evidence demonstrating the neuroprotective effect of HO in various diseases and models of CNS injury. Additionally, HO was found to be significantly over-expressed in dopaminergic cells damaged by oxidative stress and has been documented to participate in Lewy body modification in degenerative dopaminergic neurons of PD.[5] Heme is catabolized to free iron, carbon monoxide (CO), and biliverdin in the presence of HO, with biliverdin reductase converting biliverdin into bilirubin.[6,7] Previous studies have suggested that total bilirubin (TBIL) can be used as a marker of HO functional activity.[8] Bilirubin has long been considered to be a potentially cytotoxic metabolite; however, recent studies have brought to light its potential antioxidant effects. It has been shown that bilirubin, as the only natural fat-soluble antioxidant in the human body, possesses stronger anti-lipid peroxidation capacity in comparison to vitamin E analogs.[9] While several studies have indicated that moderate concentrations of bilirubin impart neuroprotective effects in PD cell models, the

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001300

Correspondence to: Dr. An-Mu Xie, Department of Neurology, Affiliated Hospital of Qingdao University, No. 16 Jiangsu road, Qingdao, Shandong 266003, China
E-Mail: xieanmu@163.com

Chinese Medical Journal 2021;134(6)
Received: 12-12-2020 **Edited by:** Yan-Jie Yin and Xiu-Yuan Hao

underlying biological mechanisms have yet to be fully established. Therefore, we conducted a meta-analysis to explore the relationship between serum bilirubin concentration and PD to determine its utility as a diagnostic and prognostic marker in PD.

Methods

In the present study, we performed the meta-analysis under the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (http://www.prisma-statement.org).[10]

Search strategy

Two investigators performed a systemic literature search on the following databases — MEDLINE, PubMed, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. The case-control studies published from database establishment to April 2020 were selected. The retrieval formula was composed of the following keywords and terms: (bilirubin OR BIL) AND (Parkinson's Disease OR Parkinson Disease OR Primary Parkinsonism). In addition, this retrieval included all article forms with no language restrictions. We also screened the reference list of the original studies and conducted a manual review to further obtain potentially qualified studies.

Inclusion and exclusion criteria

The inclusion criteria encompassed the following: (1) case–control studies; (2) diagnosis of PD made by an experienced neurologist following the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria; (3) sufficient data of serum TBIL concentration for PD and healthy controls. Studies were excluded based on the following criteria: (1) not a case-control study (including animal experiment, *in vitro* experiment, pharmacoeconomic research, drug metabolism research); (2) overlapping samples of the same research center; (3) incomplete data information; (4) samples taken from patients before a diagnosis of PD; (5) the article was a case report, meta-analysis, review, or abstract from the conference.

Data extraction

Based on the inclusion and exclusion standards, two researchers independently reviewed the full text of all included studies and extracted the following relevant information: first author, age, ethnicity, gender, publication time, the number of samples, and serum TBIL concentration data of PD and controls (including subgroup analysis data). The differences between the data extracted by the two researchers were reviewed by the third researcher.

Quality assessment

We used the Newcastle-Ottawa Scale (NOS) standard to evaluate the quality of each study.[11] Three aspects were assessed: subject selection, inter-group comparability, and exposure factor measurement. The full NOS score is 9 points, with a score ≥ 6 indicating high quality.

Statistical analysis

Stata version 12.0 statistical software (Stata Corp., College Station, TX, USA) was used in our article for all data processing and analysis. The primary data extracted in this study were sample size, as well as the mean and standard deviation of serum bilirubin concentration. Due to the different measurement units of the bilirubin concentration in the included studies, a significant difference was observed between the mean and standard deviation of these results, so the standard mean difference (SMD) and 95% confidence interval (CI) were selected as the effective size (ES) for statistical analysis for continuous outcomes. A forest plot was used to show the characteristics of the results of various studies. $P < 0.05$ indicated a statistically significant difference. We used the Q test and I^2 statistics to analyze the heterogeneity of the included studies. The fixed-effect model was employed for data combination if $P \geq 0.05$ and $I^2 \leq 50\%$ which indicated that there was no statistical difference in heterogeneity between the studies. The random-effect model was adopted if the converse was true.[12,13] Egger test was used to assess publication bias.[14] A P-value of Egger test of < 0.05 indicated the potential of publication bias. To further investigate the potential influencing factors of heterogeneity, we conducted a subgroup analysis of the whole study based on gender and ethnicity. In addition, we also performed statistical analyses for relevant indicators [serum direct bilirubin (DBIL) and serum indirect bilirubin] when at least two research outcomes were available for calculation. Furthermore, a sensitivity analysis was carried out to assess the stability of the results. Repeated data analyses were performed, with each done after removing one study at a time.

Results

Characteristics of eligible studies

A total of 14,977 related records were initially retrieved through each database. Two hundred and nine documents were left after screening for title and abstract. A further 201 articles were excluded after a complete review of journal text based on the following reasons: the main subjects were not PD patients ($n = 191$); no case-control study ($n = 7$); lack of necessary data information ($n = 1$); case report or review ($n = 2$). Therefore, eight published clinical case-control studies were incorporated into our meta-analysis, included 2953 individual research subjects consisting of 1463 PD cases and 1490 healthy controls.[15-22] Figure 1 shows the flowchart for the study selection process and reasons for elimination. The subjects of these eligible studies were mainly Asian and Caucasian people. Table 1 summarizes some of the essential characteristics of the included studies.

Quantitative synthesis

Serum TBIL

Eight research papers provided information on serum TBIL concentration. After a comprehensive data analysis of included studies, our meta-analysis indicated that there was a significant relationship between serum TBIL and PD

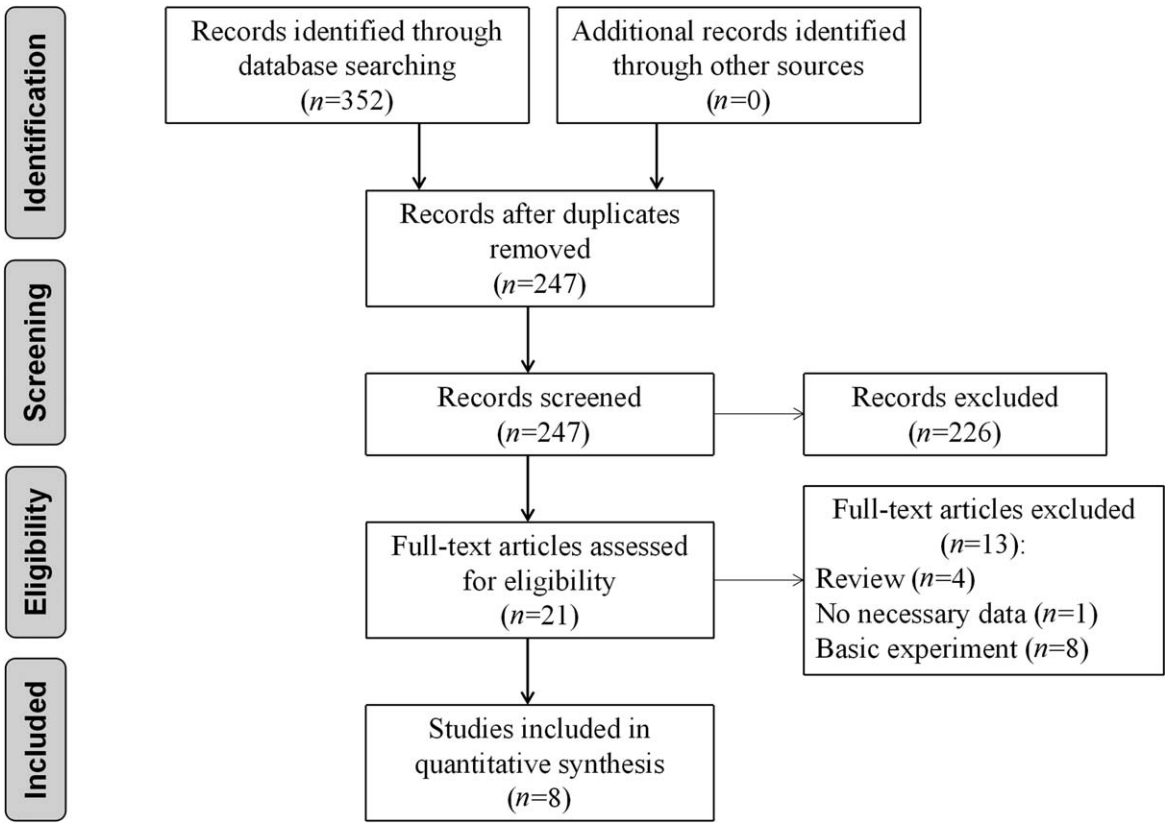

Figure 1: Flowchart of the selection process for studies included in the meta-analysis.

Table 1: Primary characteristics of included studies.

Author	Publication year	Country	Sample size (*n*)		TBIL (μmol/L)		DBIL (μmol/L)		IBIL (μmol/L)		Male-TBIL (μmol/L)		Female-TBIL (μmol/L)		NOS
			Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	
Scigliano *et al*	1997	Italy	255	224	0.69 ±0.27	0.60 ± 0.25	–	–	–	–	–	–	–	–	8
Moccia *et al*	2015	Italy	75	75	0.74 ± 0.25	0.51 ± 0.29	–	–	–	–	0.79 ± 0.25	0.58 ± 0.32	0.64 ± 0.22	0.42 ± 0.20	8
Qin *et al*	2015	China	425	460	12.10 ± 3.99	12.30 ± 3.34	3.73 ± 1.46	3.15 ± 0.98	8.36 ± 2.81	9.15 ± 2.57	12.70 ± 4.13	13.22 ± 3.24	10.96 ± 3.49	10.61 ± 2.83	8
Bolner *et al*	2016	Italy	44	21	0.83 ± 0.34	0.64 ± 0.20	–	–	–	–	–	–	–	–	7
Macias-Garcia *et al*	2019	Spain	420	435	0.56 ± 0.26	0.45 ± 0.22	–	–	–	–	–	–	–	–	8
Lee *et al*	2019	China	105	62	0.73 ± 0.25	0.64 ± 0.28	–	–	–	–	–	–	–	–	8
Songsomboon *et al*	2020	Thailand	61	135	7.92 ± 3.67	6.59 ± 2.78	3.39 ± 1.45	3.33 ± 1.16	4.52 ± 2.48	3.26 ± 1.82	–	–	–	–	8
Li *et al*	2020	China	78	78	12.94 ± 3.87	15.45 ± 6.33	6.43 ± 3.37	4.63 ± 1.97	6.51 ± 4.03	10.82 ± 4.61	13.26 ± 3.73	16.46 ± 6.85	12.30 ± 4.17	13.44 ± 4.60	7

Data are presented as *n* or mean ± standard deviation. DBIL: Direct bilirubin; IBIL: Indirect bilirubin; NOS: Newcastle-Ottawa Scale; TBIL: Total bilirubin.

patients. Compared to healthy control subjects, the serum TBIL concentration was markedly higher in PD patients. This relationship was of high statistical significance (SMD: 0.300, 95% CI: 0.050–0.549, $P = 0.018$, Table 2, Figure 2). However, we detected high heterogeneity between the included studies through I^2 statistics ($I^2 = 89.5\%$); therefore, a random-effect model was selected for a comprehensive analysis of the data.

Serum DBIL and indirect bilirubin

To further explore the causes of elevated serum TBIL concentration in PD patients, we conducted a meta-analysis with the random-effect model of the relationship between serum DBIL and serum indirect bilirubin and PD patients, only three works of literature provided relevant data. Interestingly, our meta-analysis found that the

Table 2: Meta-analysis of the association between serum bilirubin concentration and the risk of Parkinson's disease.

Items	Study (*n*)	Random-effect model			Heterogeneity	Egger test
		SMD	95% CI	*P*	I^2 (%)	*P*
TBIL	8	0.300	0.050–0.549	0.018	89.5	0.612
DBIL	3	0.395	0.102–0.688	0.008	75.9	0.802
IBIL	3	−0.223	−0.952–0.505	0.548	96.0	0.936
Ethnicity						
Caucasian	4	0.511	0.324–0.698	0.000	58.0	0.368
Asian	4	0.057	−0.286–0.399	0.746	86.1	0.717
Gender						
Male	3	−0.008	−0.604–0.587	0.978	90.3	0.814
Female	3	0.286	−0.341–0.913	0.371	84.3	0.774

CI: Confidence interval; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; NOS: Newcastle-Ottawa Scale; SMD: Standard Mean Difference; TBIL: Total bilirubin.

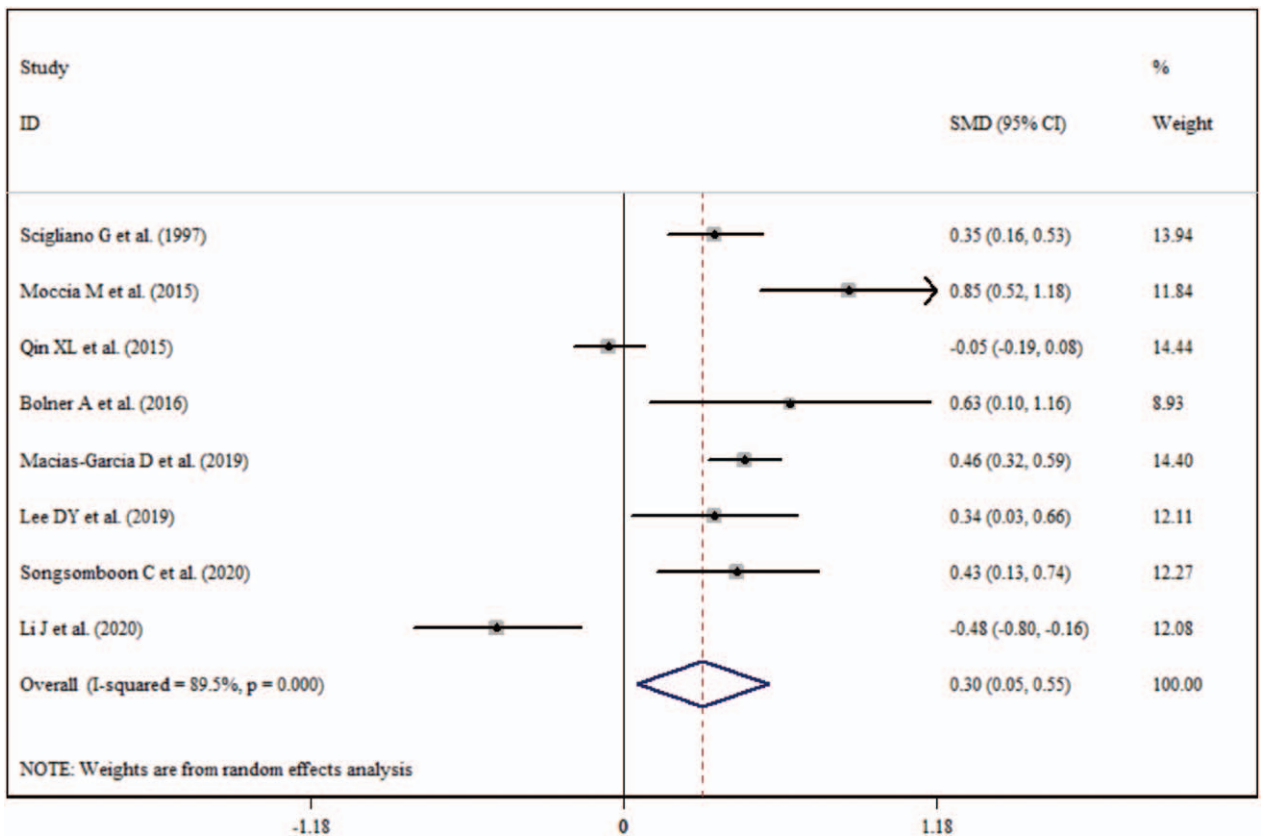

Figure 2: Forest plot displaying the association between the bilirubin and the risk of Parkinson's disease in the whole population.

concentration of serum DBIL was significantly higher in patients who had PD compared with healthy controls (SMD: 0.395, 95% CI: 0.102–0.688, $P = 0.008$, $I^2 = 75.9\%$, Table 2). This was consistent with the above serum TBIL results. In contrast, no significant relationship was found between the concentration of serum indirect bilirubin and PD patients (SMD: −0.223, 95% CI: −0.952–0.505, $P = 0.548$, $I^2 = 96.0\%$, Table 2).

Subgroup analysis

To further investigate the potential influencing factors of heterogeneity, we conducted a subgroup analysis of the whole study based on gender and ethnicity. When subgroup analysis using gender (male and female) as the main considering factor, no significant statistical difference was found in the concentration of serum TBIL between the two groups (for male, SMD: −0.008, 95% CI: −0.604–0.587, $P = 0.978$, $I^2 = 90.3\%$; for female, SMD: 0.286, 95% CI: −0.341–0.913, $P = 0.371$, $I^2 = 84.3\%$, Table 2). Additionally, the subgroup analysis according to ethnicity (Caucasian population and Asian population) indicated that the serum TBIL concentration was notably higher in PD patients in the Caucasian population than matched healthy controls with significant statistical significance (SMD: 0.511, 95% CI: 0.324–0.698, $P = 0.000$, $I^2 = 58.0\%$, Table 2, Figure 3). On

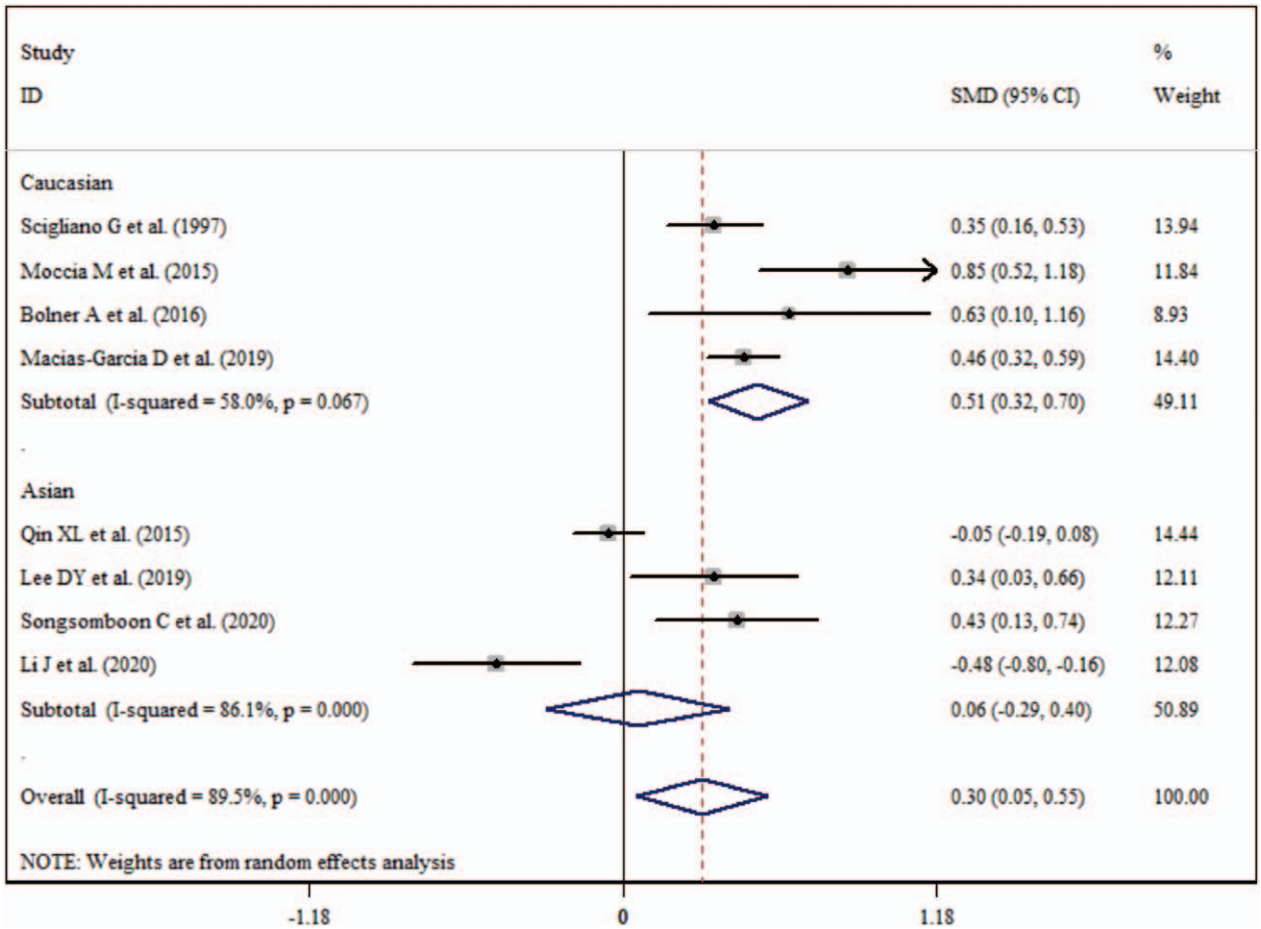

Figure 3: Forest plot displaying the association between the bilirubin and the risk of Parkinson's disease in the Caucasian and the Asian population.

the contrary, the association between TBIL and PD was not observed in the Asian population (SMD: 0.057, 95% CI: −0.286–0.399, $P = 0.746$, $I^2 = 86.1\%$, Table 2, Figure 3).

Publication bias

The publication bias was tested by Egger test and the *P* value of Egger test in each analysis was all >0.05 [Table 2], which indicated the lack of any significant publication bias in our meta-analysis.

Sensitivity analysis

Sensitivity analysis showed that there was no substantial change in the combined SMD and 95% CI [Figure 4], which suggested that the results of this study possessed high stability with slight influence affected by each literature.

Discussion

This meta-analysis confirmed that there was a statistically significant association between the serum bilirubin concentration and the risk of PD. Both serum TBIL and DBIL were significantly increased in PD patients compared with control groups. This relationship was not observed between serum indirect bilirubin and PD, which may be explained by the small number of the incorporated literature and the lack of large samples for statistical analysis. In addition, ethnicity appeared to play a role in the relationship between serum bilirubin and PD. In the Caucasian population, a significant association between serum TBIL and PD patients was found, which is consistent with the results of the total population results. Unfortunately, this phenomenon was not recorded in the Asian population. This difference could be attributed to the selection criteria of each study, as well as genetic and environmental differences between different races. Interestingly, in the two studies,[16,19] the conclusion was completely opposite to that of other researchers. We considered that this may be related to differences in regions, environments, and lifestyles. Due to the large sample sizes of the above two studies, they have had an important impact on the subgroup analysis of the Asian population, so the relationship between bilirubin and PD in the Asian population still needs further verification. Further studies with larger samples are needed to verify this phenomenon. In addition, another subgroup analysis based on gender did not reveal a significant statistical difference, which suggested that gender did not affect bilirubin levels in PD patients.

Bilirubin is the only endogenous lipid-soluble antioxidant in the human body, with recent evidence highlighting its antioxidant effect.[7] In a trial on patients with silent cerebral infarction (SCI), it was found that the increase in bilirubin levels was positively correlated with the lower risk of SCI.[23] In neurodegenerative diseases, the reduction

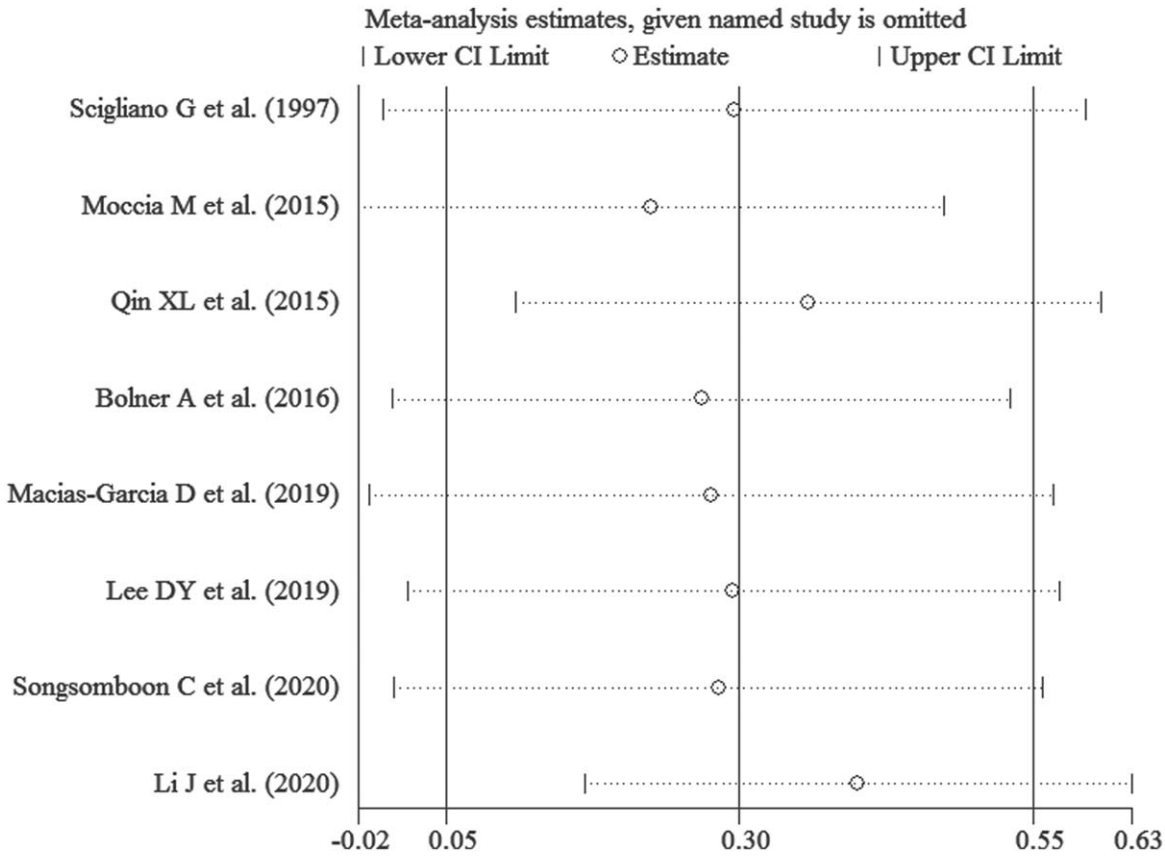

Figure 4: Sensitivity analysis of the studies on bilirubin and Parkinson's disease.

of bilirubin levels in patients with amyotrophic lateral sclerosis and Alzheimer's disease was associated with an increased risk of disease.[24,25] However, the results of studies on the neuroprotective effect of bilirubin in PD are conflicting. Scigliano *et al*[22] conducted the first retrospective study on the relationship between PD and bilirubin and showed that the PD patients receiving levodopa treatment had significantly higher levels of bilirubin in contrast to untreated PD patients and control groups, but there was no significant difference between the treatment group and the control group. This difference was considered to be related to dopamine replacement therapy. Nevertheless, in a small sample study, Moccia *et al*[21] suggested that newly diagnosed and untreated PD patients also possessed higher bilirubin levels, and after 2 years of follow-up, they found that bilirubin levels were negatively correlated with the levodopa daily dose (LEDD). Similarly, Macias-Garcia *et al*[17] performed a larger sample study of PD patients at different disease stages and found that PD patients had higher bilirubin levels and the concentration of serum TBIL was negatively related to the severity of PD. Similar conclusions were determined from two studies in Finland and Thailand, but three cross-sectional studies conducted in the Chinese Han population were in disagreement. Through this meta-analysis, we consider that the increased bilirubin concentration in PD patients might be related to the overexpression of heme oxygenase 1 (HO-1) in the CNS in the early stages of PD. HO-1 is a stress-responsive enzyme of heme and had a neuroprotective effect in the CNS. Some studies confirmed that HO-1 played an important role in regulating the oxidative balance of neurodegenerative disease brain.[26-28] HO-1 was the main enzyme that regulated the production of bilirubin, and its overexpression could increase the concentration of bilirubin, thus exerting an antioxidant role in the brain.

Our meta-analysis comprehensively screened all the studies related to bilirubin and PD in existing published articles, rigorously extracted and processed the data to be analyzed using standardized statistical methods. We believe that these data form a foundation for future-related studies. The outcomes obtained suggested that bilirubin may play an important role in the pathogenesis of PD, which may prompt future researchers to increase attention on this subject matter. Additionally, further investigations regarding the utility of bilirubin as a biomarker in diagnosing PD may be performed based on the outcomes of this study.

This study contains several limitations. First of all, we detected high heterogeneity among the included studies, which suggested that the results obtained should be interpreted with caution. Our meta-analysis also includes studies published in English, thus the language bias needs to be taken into account. The current study was not registered, but we strictly followed the guidelines for meta-analysis to minimize the selection bias. In addition, since all included works of literature are retrospective studies, the differences in case selection and environmental resources between different research centers give rise to inevitable

selection bias in this research. Due to the possible limitations mentioned above, large-scale studies on a larger and more diverse population are needed to reassess the relationship between the bilirubin and PD, and more biological trials are needed to explore the underlying biological function of bilirubin in PD.

In the present meta-analysis, a higher concentration of serum TBIL and DBIL was found in PD patients. Our results can provide a reference for high-quality experiments to further explore the role of bilirubin in PD.

Funding

This work was supported by a grant from the National Natural Science Foundation of China (No. 81971192).

Conflicts of interest

None.

References

1. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, *et al*. Parkinson disease. Nat Rev Dis Primers 2017;3:17013. doi: 10.1038/nrdp.2017.13.
2. Dickson DW. Neuropathology of Parkinson disease. Parkinsonism Relat Disord 2018;46 (Suppl 1):S30–S33. doi: 10.1016/j.parkreldis.2017.07.033.
3. Olanow CW. Levodopa: effect on cell death and the natural history of Parkinson's disease. Mov Disord 2015;30:37–44. doi: 10.1002/mds.26119.
4. Barone E, Di Domenico F, Mancuso C, Butterfield DA. The Janus face of the heme oxygenase/biliverdin reductase system in Alzheimer disease: It's time for reconciliation. Neurobiol Dis 2014;62:144–159. doi: 10.1016/j.nbd.2013.09.018.
5. Castellani R, Smith MA, Richey PL, Perry G. Glycoxidation and oxidative stress in Parkinson disease and diffuse Lewy body disease. Brain Res 1996;737:195–200. doi: 10.1016/0006-8993(96)00729-9.
6. Ziberna L, Martelanc M, Franko M, Passamonti S. Bilirubin is an endogenous antioxidant in human vascular endothelial cells. Sci Rep 2016;6:29240. doi: 10.1038/srep29240.
7. Yamamoto N, Izumi Y, Matsuo T, Wakita S, Kume T, Takada-Takatori Y, *et al*. Elevation of heme oxygenase-1 by proteasome inhibition affords dopaminergic neuroprotection. J Neurosci Res 2010;88:1934–1942. doi: 10.1002/jnr.22363.
8. McCarty MF. Serum bilirubin may serve as a marker for increased heme oxygenase activity and inducibility in tissues — A rationale for the versatile health protection associated with elevated plasma bilirubin. Med Hypotheses 2013;81:607–610. doi: 10.1016/j.mehy.2013.07.013.
9. Wu TW, Fung KP, Yang CC. Unconjugated bilirubin inhibits the oxidation of human low density lipoprotein better than trolox. Life Sci 1994;54:477–481. doi: 10.1016/0024-3205(94)90140-6.
10. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1. doi: 10.1186/2046-4053-4-1.
11. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–605. doi: 10.1007/s10654-010-9491-z.
12. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect 2014;20:123–129. doi: 10.1111/1469-0691.12494.
13. Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 2005;28:123–137. doi: 10.1002/gepi.20048.
14. Jin ZC, Zhou XH, He J. Statistical methods for dealing with publication bias in meta-analysis. Stat Med 2015;34:343–360. doi: 10.1002/sim.6342.
15. Songsomboon C, Tanprawate S, Soontornpun A, Wantaneeyawong C, Louthrenoo W. Serum uric acid, serum uric acid to serum creatinine ratio and serum bilirubin in patients with Parkinson's disease: A case-control study. J Clin Med Res 2020;12:172–179. doi: 10.14740/jocmr4079.
16. Li J, Zhao L, Wang Z, Zhao X, Wu J. Association of serum indirect bilirubin concentrations with motor subtypes of Parkinson's disease. Neurodegener Dis 2020;19:1–7. doi: 10.1159/000505852.
17. Macias-Garcia D, Mendez-Del Barrio C, Jesus S, Labrador MA, Adarmes-Gomez A, Vargas-Gonzalez L, *et al*. Increased bilirubin levels in Parkinson's disease. Parkinsonism Relat Disord 2019;63:213–216. doi: 10.1016/j.parkreldis.2019.01.012.
18. Lee DY, Oh M, Kim SJ, Oh JS, Chung SJ, Kim JS. Bilirubin-related differential striatal [18F]FP-CIT uptake in Parkinson disease. Clin Nucl Med 2019;44:855–859. doi: 10.1097/rlu.0000000000002749.
19. Qin XL, Zhang QS, Sun L, Hao MW, Hu ZT. Lower serum bilirubin and uric acid concentrations in patients with Parkinson's disease in China. Cell Biochem Biophys 2015;72:49–56. doi: 10.1007/s12013-014-0402-x.
20. Bolner A, Micciolo R, Bosello O, Nordera GP. A panel of oxidative stress markers in Parkinson's disease. Clin Lab 2016;62:105–112. doi: 10.7754/clin.lab.2015.150538.
21. Moccia M, Picillo M, Erro R, Longo K, Amboni M, Santangelo G, *et al*. Increased bilirubin levels in de novo Parkinson's disease. Eur J Neurol 2015;22:954–959. doi: 10.1111/ene.12688.
22. Scigliano G, Girotti F, Soliveri P, Musicco M, Radice D, Caraceni T. Increased plasma bilirubin in Parkinson patients on L-dopa: evidence against the free radical hypothesis? Ital J Neurol Sci 1997;18:69–72. doi: 10.1007/bf01999565.
23. Li RY, Cao ZG, Zhang JR, Li Y, Wang RT. Decreased serum bilirubin is associated with silent cerebral infarction. Arterioscler Thromb Vasc Biol 2014;34:946–951. doi: 10.1161/atvbaha.113.303003.
24. Ilzecka J, Stelmasiak Z. Serum bilirubin concentration in patients with amyotrophic lateral sclerosis. Clin Neurol Neurosurg 2003;105:237–240. doi: 10.1016/s0303-8467(03)00031-3.
25. Kim TS, Pae CU, Yoon SJ, Jang WY, Lee NJ, Kim JJ, *et al*. Decreased plasma antioxidants in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2006;21:344–348. doi: 10.1002/gps.1469.
26. Schipper HM. Heme oxygenase expression in human central nervous system disorders. Free Radic Biol Med 2004;37:1995–2011. doi: 10.1016/j.freeradbiomed.2004.09.015.
27. Schipper HM, Song W, Zukor H, Hascalovici JR, Zeligman D. Heme oxygenase-1 and neurodegeneration: Expanding frontiers of engagement. J Neurochem 2009;110:469–485. doi: 10.1111/j.1471-4159.2009.06160.x.
28. Peng F, Yang Y, Liu J, Jiang Y, Zhu C, Deng X, *et al*. Low antioxidant status of serum uric acid, bilirubin and albumin in patients with neuromyelitis optica. Eur J Neurol 2012;19:277–283. doi: 10.1111/j.1468-1331.2011.03488.x.

How to cite this article: Jin JN, Liu X, Li MJ, Bai XL, Xie AM. Association between serum bilirubin concentration and Parkinson's disease: a meta-analysis. Chin Med J 2021;134:655–661. doi: 10.1097/CM9.0000000000001300