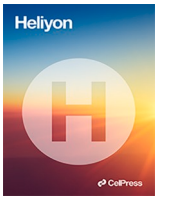
Heliyon 10 (2024) e36053

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Association between serum total bilirubin with Parkinson's disease among American adults (NHANES 1999 to 2018)

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ARTICLE INFO

Keywords:
Serum total bilirubin
Parkinson's disease
NHANES
Cross-sectional study
L-shaped

ABSTRACT

Background: Currently, the existing evidence on the correlation between serum total bilirubin (STB) and Parkinson's disease (PD) is insufficient. The objective of this study was to clarify the relationship between STB levels and PD within the US (United States) population.

Methods: A cross-sectional analysis was conducted using data from 25,637 participants in the National Health and Nutrition Examination Survey (NHANES) 1999–2018. Weighted logistic regression, smooth curve fitting, subgroup analysis, and sensitivity analyses were employed to validate the research objectives.

Results: Among all eligible subjects, the mean age was 57.11 ± 11.78 years. The prevalence of PD was 1.18 % overall, with 47.86 % in males. After adjusting for multiple variables, the odds ratio [OR] (95 % confidence interval [CI]) for PD associated with STB levels in T2 and T3 were 0.59 (95 % CI = 0.40–0.85, $p = 0.006$) and 0.67 (95 % CI = 0.45–0.99, $p = 0.045$), respectively, when compared to STB levels in T1. The analysis using restricted cubic splines (RCS) indicated an L-shaped relationship between STB levels and the prevalence of PD (p for nonlinearity = 0.004), with the lowest risk observed at 10.84 μmol/L. Comparable patterns of association were noted in subgroup analyses. Furthermore, consistent findings were derived from additional sensitivity analyses.

Conclusions: Our study findings indicated that the level of STB is significantly negatively correlated with the prevalence of PD. Therefore, more prospective studies need to be designed to prove the causal relationship between them.

1. Introduction

Parkinson's disease (PD) refers to a clinical syndrome marked by bradykinesia, cogwheel rigidity, resting tremor, a slow shuffling gait, and postural instability [1]. After Alzheimer's disease, PD ranks as the second most prevalent neurodegenerative disorder, constituting a significant societal concern and global priority. Projections anticipate a twofold increase in its incidence over the next 30

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https://doi.org/10.1016/j.heliyon.2024.e36053
Received 22 April 2024; Received in revised form 7 August 2024; Accepted 8 August 2024
Available online 9 August 2024

years [2–5]. The prevalence of PD is projected to surge from 6.9 million individuals in 2015 to 14.2 million by 2040 [6]. The pathogenesis and risk factors of PD are constantly being explored. Consequently, a thorough understanding of PD and its associated factors could aid in the prevention and management of the condition, thus enhancing the prognosis and quality of life for those affected.

Oxidative stress and neuroinflammation are key factors in the pathogenesis of PD [7–10]. Serum bilirubin, recognized for its potent antioxidant and anti-inflammatory properties, has garnered attention in recent studies [11–16]. As an antioxidant molecule, bilirubin can protect dopaminergic neurons from the effects of oxidative stress by scavenging free radicals [17]. Additionally, in an in vitro PD model, bilirubin prevents dopamine cell death by acting on tumor necrosis factor-α (TNFα) through its anti-inflammatory properties [14]. Moreover, bilirubin exerts its effects indirectly. The production of bilirubin depends on the decomposition reaction of heme catalyzed by heme oxygenase (HMOX) [18]. HMOX catalyzes the conversion of heme into biliverdin, which is then further reduced to bilirubin [18]. Studies have confirmed that HMOX1 and its products are believed to protect astrocytes and microglia from the effects of oxidative stress, apoptosis, and increased inflammation [18–21]. At the genetic level, a study found an association between the dominant locus of HMOX1 rs2071747 and PD [22]. Existing research suggested that bilirubin might serve as a biochemical marker for the diagnosis and treatment of PD [11,23]. However, some study results are contradictory. One study from Italy and two studies from Spain have found elevated levels of serum total bilirubin (STB) in early PD patients [23–25]. Additionally, a meta-analysis showed that total bilirubin and direct bilirubin levels are higher in PD patients compared to the control group [11]. Yet, in the Japanese population, STB levels exhibited a decrease in PD patients with a specific disease duration compared to controls [26]. And studies from China suggest that serum bilirubin levels are lower in PD patients [27]. Besides, Jayanti S. et al. discussed bilirubin as a promising therapy for PD [10].

However, a comprehensive exploration of the association between STB concentrations and PD risk in the US population remains lacking. Given the potential implications of this association in clinical settings, our study sought to explore the potential involvement of STB in PD among adult population in the US, through a cross-sectional study in NHANES.

2. Materials and methods

2.1. Study population

All survey data can be accessed through the NHANES website. NHANES, conducted on a two-year cycle, is a large-scale, nationally representative study of the US population, employing a multi-stage and stratified sampling design [28]. In this study, we enrolled 101,311 subjects from 10 consecutive NHANES survey cycles conducted between 1999 and 2018. To maintain age consistency, individuals younger than 40 years (65,059 participants) were excluded. Furthermore, 31 pregnant participants, 72 participants with missing PD data, and 3,975 participants without STB data were also excluded. Subsequently, 6,537 study participants were excluded due to missing data on other relevant variables. This led to a final study population of 25,637 individuals. The recruitment process is illustrated in Fig. 1.

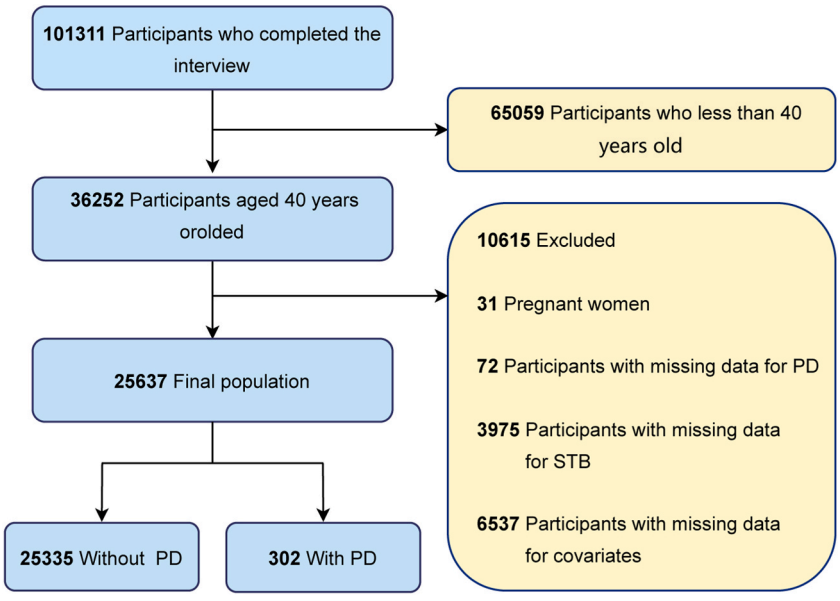

Fig. 1. Flowchart depicting the selection strategy. PD, Parkinson's disease; STB, Serum Total Bilirubin.

2.2. Diagnosis of PD

In this study, PD was used as the outcome variable. Individuals diagnosed with PD were identified by categorizing prescriptions under the "Second Level Category Name" as "ANTIPARKINSON AGENTS" in the Prescription Medications document. This determination relied on participants' responses to inquiries regarding prescribed medications. Due to the constraints of medications and codes included in NHANES, the classification of PD required individuals to be actively undergoing treatment for the condition. Individuals who did not disclose the use of antiparkinsonian medication were classified as non-PD participants. The disease definition utilized in this study aligns with the criteria established in previous research [29].

2.3. Measurement of STB

Measured using NHANES Laboratory Procedures, the study's dependent variable, STB level (mmol/L), was determined [30]. In brief, STB, in a strongly acidic environment, STB, when combined with a solubilizing agent, interacts with 3,5-dichlorophenyl diazonium. The intensity of the resulting red azo dye correlates directly with the level of STB, allowing for photometric measurement at 546 nm [30].

2.4. Measurements of other covariates

Drawing from existing literature and clinical practice, we assessed a range of potential covariates [29,31], encompassing age, sex, race/ethnicity, marital status, family income, education level, body mass index (BMI), smoking status, alcohol consumption, presence of coronary heart disease, stroke, hypertension, and diabetes. Structured data collection in NHANES encompasses certain sociodemographic information. Participants provided self-reports on age, sex, race/ethnicity, and education. Marital status was delineated as either married/living with a partner or living alone. Race/ethnicity classifications included Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Hispanic, and Other Race. Educational achievement was classified into three categories: Less than high school, High school or equivalent, and Above high school. Family income was categorized into three groups according to the poverty income ratio (PIR): low (PIR $\leq$1.3), moderate (PIR $>$1.3 to 3.5), and high (PIR $>$3.5) [32]. According to previous literature, smoking status was categorized as follows: individuals who smoked fewer than 100 cigarettes in their lifetime were classified as never smokers. Individuals who currently smoked and consumed more than 100 cigarettes in their lifetime and currently smoked were categorized as current smokers. Individuals who had smoked more than 100 cigarettes in their lifetime but currently did not smoke were classified as former smokers [33]. Self-reported drinking status was classified as follows: never drinkers (consumed $<$12 drinks in their lifetime), former drinkers (consumed $\geq$12 drinks in one year but did not drink in the last year, or did not drink in the last year but consumed $\geq$12 drinks in their lifetime), mild drinkers (females consuming $\leq$1 and males consuming $\leq$2 drinks per day), moderate drinkers (females consuming $\leq$2 and males consuming $\leq$3 drinks per day), or heavy drinkers (females consuming $\geq$3 and males consuming $\geq$4 drinks per day) [28]. Trained health technologists conducted measurements of weight and height in accordance with the anthropometry procedure manual. Subsequently, BMI was calculated as weight in kilograms divided by the square of height in meters. Both coronary heart disease and stroke were self-reported by participants. In calculating the average blood pressure for hypertension, the following protocol was followed [33]: ① Diastolic readings of zero were excluded from the calculation of the diastolic average. ② If all diastolic readings were zero, the average was recorded as zero. ③ In the case of only one blood pressure reading obtained, that single reading served as the average. ④ If multiple blood pressure readings were available, the initial reading was consistently omitted from the average calculation. The diagnostic criteria for diabetes include the following indicators: ① receiving a diagnosis of diabetes from a doctor. ② having a glycohemoglobin HbA1c level of $\geq$6.5 %. ③ fasting glucose level of $\geq$7.0 mmoL/l. ④ random blood glucose level of $\geq$11.1 mmoL/l. ⑤ 2-h Oral Glucose Tolerance Test blood glucose level of $\geq$11.1 mmoL/l. ⑥ utilization of diabetes medication or insulin [34].

2.5. Statistical analyses

Due to the intricate sampling framework and the deployment of mobile examination centers (MEC), it is imperative to incorporate the MEC weights into our analysis. The sampling weights were determined as follows: 1999–2002 wt were 2/10 $\times$ 4 year MEC weight, and 2003–2018 wt were 1/10 $\times$ 2 year MEC weight. All normally distributed continuous variables were reported as mean $\pm$ standard deviation (SD), while categorical variables were presented as frequencies (%). Chi-square test was employed for categorical variables, One-Way ANOVA test was utilized for variables with normal distribution, while Kruskal-Wallis H test was applied for variables with skewed distribution to examine differences among various STB groups. The impact of STB on PD was assessed through binary weighted logistic regression models, reporting OR and 95 % CI with adjustments made for major covariates. Four models were constructed for analysis: Model 1 included no covariate adjustments. Model 2 was further adjusted for age, sex, and race/ethnicity in addition to the variables in Model 1. Model 3 incorporated additional adjustments for marital status, education level, and family income based on Model 2. Lastly, Model 4 (the primary model) included additional adjustments for BMI, smoking status, drinking status, coronary heart disease, stroke, hypertension, and diabetes, building upon Model 3. Multivariable weighted regression models were employed to conduct tests for trend, incorporating the median value of each STB tertile as a continuous variable in the analysis. To explore whether there exists a potential nonlinear dose-response association between STB and PD, we utilized RCS to generate smooth curves. In this model, STB was utilized as a continuous variable with 3 knots (10th, 50th, and 90th percentiles), as recommended by Harrell. The presence of non-linearity was evaluated through a likelihood ratio test, contrasting the model containing solely a linear term against

the model integrating both linear and cubic spline terms. Subgroup analysis was conducted to investigate the association between STB and PD based on subgroup variables. Interaction across subgroups was assessed using the likelihood ratio test. Missing data, which constituted less than 20 % of the dataset, were addressed through listwise deletion during the analysis process. Additionally, sensitivity analyses were conducted using a complete-case analysis approach. Several sensitivity analyses were conducted to evaluate the stability of the study findings and evaluate the potential impact of different association inference models on our conclusions. Effect sizes and corresponding p-values were calculated from all these models and subsequently reported and compared. Analysis was conducted using R Statistical Software (Version 4.2.2, The R Foundation) and the Free Statistics analysis platform (Version 1.9, Beijing, China).

3. Results

3.1. Baseline characteristics

After rigorous screening based on the inclusion and exclusion criteria, the analysis included a total of 25,637 patients. Among them, the overall prevalence of PD disease was 1.18 %. The weighted sample represents 105.57 million people in the US (Table 1). The table shows the weighted numbers for each group. In this study, STB levels were divided into three categories: tertile (T)1 (0–8.55 μmol/L),

Table 1
The base line characteristics by tertiles of the STB in the NHANES 1999–2018 cycles, weighted.

Characteristics	Total (weighted)	STB (μmol/L)			
		T1 (0–8.55)	T2 (8.60–11.97)	T3 (12.00–121.41)	*P* value
NO. (ten thousand)	10557.17	3423.36	3514.38	3619.43	
Age (year), Mean (SD)	57.11 ± 11.78	56.64 ± 11.50	57.37 ± 11.75	57.32 ± 12.06	0.0095
Sex, n (%)					
Male	5053.11 (47.86)	1121.70 (32.77)	1565.28 (44.54)	2366.12 (65.37)	<0.0001
Female	5504.07 (52.14)	2301.66 (67.23)	1949.10 (55.46)	1253.31 (34.63)	
Race/ethnicity, n (%)					
Non-Hispanic White	7973.31 (75.53)	2422.68 (70.77)	2656.93 (75.60)	2893.69 (79.95)	<0.0001
Non-Hispanic Black	975.48 (9.24)	398.17 (11.63)	329.16 (9.37)	248.14 (6.86)	
Mexican American	587.93 (5.57)	216.80 (6.33)	195.09 (5.55)	176.03 (4.86)	
Other Hispanic	445.19 (4.22)	175.62 (5.13)	140.70 (4.00)	128.88 (3.56)	
Other Race	575.27 (5.45)	210.09 (6.14)	192.49 (5.48)	172.69 (4.77)	
Marital status, n (%)					
Married/Living with a partner	7269.40 (68.86)	2210.79 (64.58)	2387.63 (67.94)	2670.98 (73.80)	<0.0001
Living alone	3287.77 (31.14)	1212.57 (35.42)	1126.75 (32.06)	948.45 (26.20)	
Family income, n (%)					
≤1.30	1799.82 (17.05)	696.73 (20.35)	618.27 (17.59)	484.82 (13.40)	<0.0001
1.31–3.50	3612.87 (34.22)	1231.71 (35.98)	1200.00 (34.15)	1181.16 (32.63)	
>3.50	5144.48 (48.73)	1494.93 (43.67)	1696.11 (48.26)	1953.44 (53.97)	
Education level, n (%)					
Less than high school	1751.34 (16.59)	605.76 (17.70)	630.35 (17.94)	515.23 (14.24)	<0.0001
High school or equivalent	2557.26 (24.22)	860.43 (25.13)	863.27 (24.56)	833.56 (23.03)	
Above high school	6248.57 (59.19)	1957.17 (57.17)	2020.76 (57.50)	2270.64 (62.73)	
BMI (kg/m^2), Mean (SD)	29.24 (6.51)	30.19 (7.27)	29.25 (6.44)	28.34 (5.63)	<0.0001
Smoking status, n (%)					
never	5341.14 (50.59)	1703.49 (49.76)	1740.26 (49.52)	1897.39 (52.42)	<0.0001
former	3282.21 (31.09)	963.26 (28.14)	1082.44 (30.80)	1236.51 (34.16)	
current	1933.82 (18.32)	756.61 (22.10)	691.68 (19.68)	485.54 (13.41)	
Drinking status, n (%)					
never	1181.50 (11.19)	423.32 (12.37)	405.42 (11.54)	352.76 (9.75)	0.0002
former	1915.79 (18.15)	607.73 (17.75)	678.83 (19.32)	629.23 (17.38)	
current	7459.89 (70.66)	2392.31 (69.88)	2430.13 (69.15)	2637.45 (72.87)	
Coronary heart disease, n (%)					
No	9991.08 (94.64)	3256.85 (95.14)	3331.11 (94.79)	3403.12 (94.02)	0.0427
Yes	566.09 (5.36)	166.52 (4.86)	183.27 (5.21)	216.31 (5.98)	
stroke, n (%)					
No	10138.04 (96.03)	3272.99 (95.61)	3368.46 (95.85)	3496.59 (96.61)	0.013
Yes	419.13 (3.97)	150.37 (4.39)	145.92 (4.15)	122.84 (3.39)	
Hypertension, n (%)					
No	5307.50 (50.27)	1684.80 (49.21)	1732.85 (49.31)	1889.85 (52.21)	0.0048
Yes	5249.67 (49.73)	1738.56 (50.79)	1781.53 (50.69)	1729.58 (47.79)	
Diabetes, n (%)					
No	8644.71 (81.88)	2709.30 (79.14)	2898.26 (82.47)	3037.15 (83.91)	<0.0001
Yes	1912.46 (18.12)	714.06 (20.86)	616.12 (17.53)	582.28 (16.09)	
Parkinson's disease, n (%)					
No	10440.51 (98.89)	3371.00 (98.47)	3483.29 (99.12)	3586.22 (99.08)	0.0017
Yes	116.67 (1.11)	52.36 (1.53)	31.09 (0.88)	33.21 (0.92)	

STB, Serum Total Bilirubin; T, Tertiles; SD, standard deviation; BMI: body mass index.

T2 (8.60–11.97 μmol/L), and T3 (12.00–121.41 μmol/L), based on tertiles.

Participants in the highest STB tertile tended to be older, comprised more males, had a higher proportion of non-Hispanic whites, were more likely to be married or living with a partner, possessed greater wealth, attained higher levels of education, had lower BMI values, were fewer current smokers, were more current drinkers, had a higher prevalence of coronary heart disease, were less likely to have experienced stroke, hypertension, diabetes, and PD, in contrast to those in the lowest STB tertile ($p < 0.05$) (Table 1).

3.2. Relationship between TBS and PD

Univariate weighted logistic regression analysis revealed associations between PD and variables including age, race/ethnicity, family income, stroke, hypertension, and diabetes ($p < 0.05$) (Table 2).

In multivariable weighted logistic regression analyses, upon examination of STB using tertiles, a notable inverse association between STB and PD was noted after adjusting for potential confounders. In contrast to individuals in the lowest STB tertile (T1), those in the middle (T2) and highest (T3) tertiles demonstrated adjusted OR for PD of 0.59 (95 % CI = 0.40–0.85, p value = 0.006) and 0.67 (95 % CI = 0.45–0.99, P value = 0.045), respectively (Table 3). These results indicated a respective reduction of 41 % and 34 % in the prevalence of PD when comparing T2 and T3 to T1. Moreover, a smoothing function analysis was utilized to estimate the possible dose-response connection between STB and PD prevalence. After accounting for confounding variables, an observation of a non-linear association between STB and PD was made (p for nonlinearity = 0.004, Fig. 2 A). The correlation between STB and PD demonstrated an L-shaped curve, with the nadir of risk occurring at 10.84 μmol/L (Table 4).

3.3. Subgroup, sensitivity and additional analyses

In addition, subgroup analysis revealed no evidence of effect modification or interaction based on common risk factors of PD (p for interaction >0.05) (Table 5, Fig. 3).

Moreover, we expanded the population to include individuals over 20 years old. After excluding missing data, we performed weighted multivariable logistic regression calculations, and the results were consistent with the main study (Table 6, Fig. 2 B).

Additionally, we conducted a separate analysis for young onset PD cases. According to the literature, some scholars use 40 years as the dividing line for young onset PD (YOPD), while others define patients who develop the disease before the age of 50 as YOPD and those who develop it after the age of 50 as late onset PD (LOPD) [35]. Therefore, after addressing missing values, we conducted weighted multivariable logistic regression calculations for the 20–39 and 20–49 age groups in the NHANES database. In the multivariable weighted logistic regression analysis, STB was assessed as a continuous variable and potential confounders were controlled for. It was found that there was a significant inverse linear relationship between STB and PD in both the 20–39 and 20–49 age groups [OR (95 % CI) were 0.91 (0.85–0.98) and 0.97 (0.93–1.02), respectively] (Table 7, Fig. 2C and D).

For sensitivity analysis, we performed multiple imputations for missing values of participant covariates using five sets of imputations, and selected one set for multivariable logistic regression analysis. In the meantime smoothed curve fitting was performed. Multifactorial analyses yielded results consistent with analyses that removed individuals with missing covariates (Table 8). Consistent results were also obtained in the RCS (Fig. 2 E).

Table 2
Association of covariates with PD, weighted.

Variable	OR (95 % CI)	P value	Variable	OR (95 % CI)	P value
Age (year)	1.02 (1.01–1.04)	<0.001	**Smoking status**		
Sex			never	1 (Ref)	
Male	1 (Ref)		former	0.75 (0.55–1.02)	0.066
Female	1.34 (1.00–1.79)	0.05	now	1.25 (0.85–1.84)	0.253
Race/ethnicity			**Drinking status**		
Non-Hispanic White	1 (Ref)		never	1 (Ref)	
Non-Hispanic Black	0.77 (0.55–1.08)	0.133	former	1.35 (0.87–2.10)	0.173
Mexican American	0.61 (0.43–0.86)	0.005	now	0.79 (0.50–1.25)	0.311
Other Hispanic	0.78 (0.39–1.57)	0.489	**Coronary heart disease**		
Other Race	0.49 (0.21–1.14)	0.098	No	1 (Ref)	
Marital status			Yes	1.4 (0.81–2.42)	0.226
Married/Living with a partner	1 (Ref)		**Stroke**		
Living alone	1.24 (0.89–1.71)	0.203	No	1 (Ref)	
Family income			Yes	3.35 (2.19–5.13)	<0.001
≤1.30	1 (Ref)		**Hypertension**		
1.31–3.50	0.85 (0.62–1.17)	0.317	No	1 (Ref)	
>3.50	0.48 (0.32–0.73)	<0.001	Yes	1.43 (1.04–1.95)	0.027
Education level			**Diabetes**		
High school or less	1 (Ref)		No	1 (Ref)	
Some College	0.81 (0.49–1.33)	0.403	Yes	1.45 (1.04–2.02)	0.028
College graduate	0.8 (0.54–1.17)	0.24	**STB (umol/L)**	0.96 (0.93–1.00)	0.065
BMI (kg/m^2)	1.02 (1.00–1.04)	0.058	/	/	/

OR, odds ratio; CI, confidence interval; BMI: body mass index; STB, Serum Total Bilirubin.

Table 3
Association between STB tertiles and PD, weighted.

STB tertiles	No. (unweighted)	OR (95 % CI)							
		Model 1	*P* value	Model 2	*P* value	Model 3	*P* value	Model 4	*P* value
T1 (0 ~ 8.55)	8378	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
T2 (8.60 ~ 11.97)	8709	0.57 (0.40–0.83)	0.003	0.57 (0.39–0.82)	0.003	0.58 (0.40–0.84)	0.004	0.59 (0.40–0.85)	0.006
T3 (12.00 ~ 121.41)	8550	0.6 (0.41–0.86)	0.006	0.6 (0.41–0.88)	0.01	0.62 (0.42–0.9)	0.019	0.67 (0.45–0.99)	0.045
Trend test	25637		0.007		0.01		0.018		0.038

OR, odds ratio; CI, confidence interval; STB, Serum Total Bilirubin; T, Tertiles; Ref, Reference.
aModel 1: with no covariate adjustment.
bModel 2: adjusted for Age, Sex, Race/Ethnicity.
cModel 3: Model 2 + Marital status, Education level, Family income.
dModel 4: Model 3 + BMI, Smoking status, Drinking status, Coronary heart disease, Stroke, Hypertension, Diabetes.

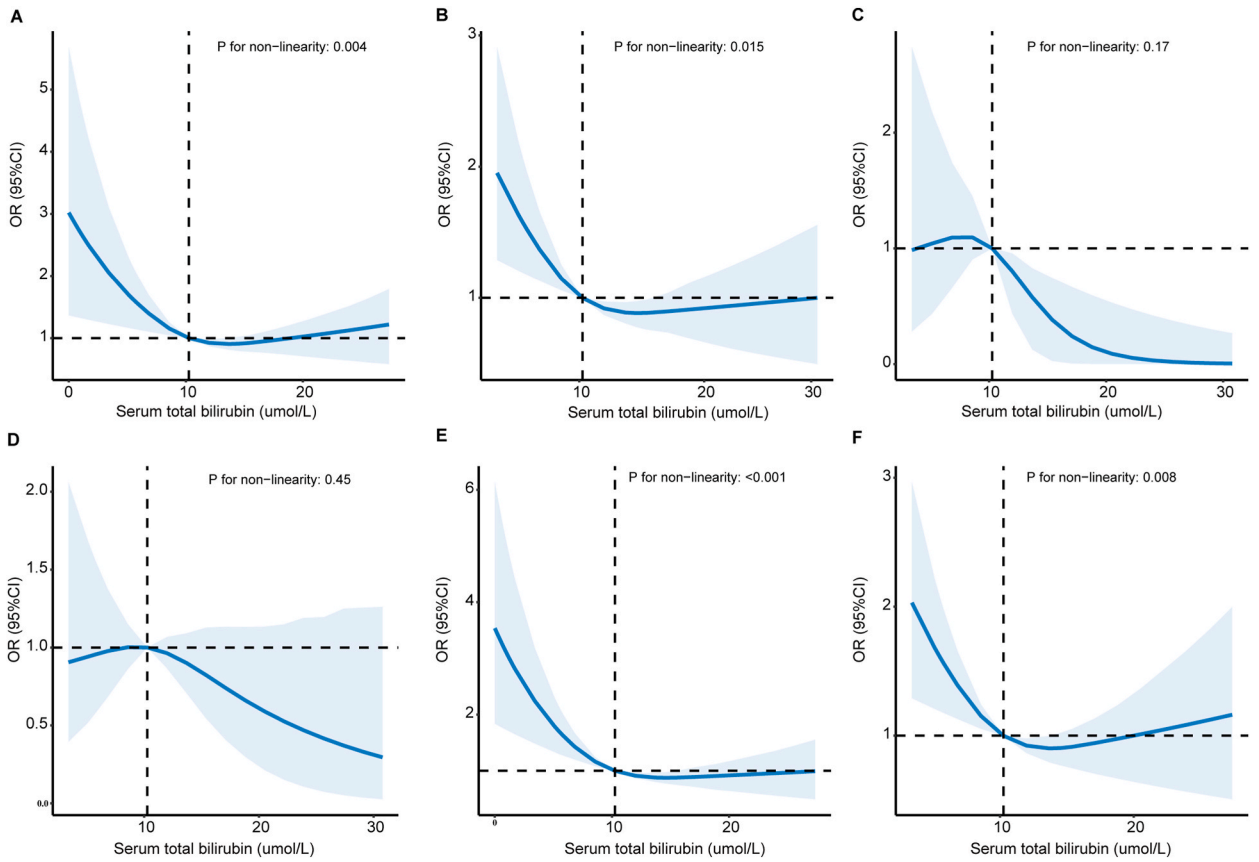

Fig. 2. A: Association between the serum total bilirubin and Parkinson's disease odds ratio, weighted. B: Association between the serum total bilirubin and Parkinson's disease odds ratio among individuals over 20 years old, weighted. C: Association between serum total bilirubin and Parkinson's disease odds ratio among individuals aged 20–39 years, weighted. D: Association between serum total bilirubin and Parkinson's disease odds ratio among individuals aged 20–49 years, weighted. E: Association between serum total bilirubin and the odds ratio of Parkinson's disease after multiple imputation, weighted. F: Association between serum total bilirubin and the odds ratio of Parkinson's disease after excluding abnormal liver function values, weighted. OR, odds ratio; CI, confidence interval. Solid and dashed lines represent the predicted value and 95 % confidence intervals. They were adjusted for age, sex, race/ethnicity, marital status, family income, education level, body mass index, smoking status, drinking status, coronary heart disease, stroke, hypertension and diabetes. Only 99 % of the data is shown.

Table 4
Threshold effect analysis of the relationship of STB with PD.

STB (μmol/L)	Adjusted Model	
	OR (95 % CI)	*P* value
<10.84	0.90 (0.84–0.96)	0.002
≥10.84	1.02 (0.98–1.06)	0.291
Likelihood ratio test		0.003

STB: Serum total bilirubin; OR, odds ratio; CI, confidence interval. Adjusted for socio-demographic (age, sex, race/ethnicity, marital status, family income, education level), body mass index, smoking status, drinking status, coronary heart disease, stroke, hypertension, and diabetes. Only 99 % of the data is displayed.

Table 5
Subgroup analysis of the association between STB and PD, weighted.

Subgroup	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value	*P* for interaction
Age, year					**0.31**
40 ~ 60			**≥ 60**		
T1 (0–8.55)	1 (Ref)		1 (Ref)		
T2 (8.60–11.97)	0.56 (0.32–0.99)	0.05	0.62 (0.37–1.05)	0.07	
T3 (12.00–121.41)	0.59 (0.33–1.06)	0.08	0.73 (0.45–1.20)	0.22	
Trend test		0.06		0.24	
Sex					**0.392**
Male			**Female**		
T1 (0–8.55)	1 (Ref)		1 (Ref)		
T2 (8.60–11.97)	0.44 (0.25–0.77)	0.005	0.69 (0.44–1.09)	0.11	
T3 (12.00–121.41)	0.48 (0.28–0.82)	0.01	0.86 (0.50–1.48)	0.58	
Trend test		0.02		0.42	
Marry status					**0.733**
Married/Living with a partner			**Living alone**		
T1 (0–8.55)	1 (Ref)		1 (Ref)		
T2 (8.60–11.97)	0.63 (0.37–1.08)	0.09	0.50 (0.29–0.86)	0.01	
T3 (12.00–121.41)	0.65 (0.38–1.13)	0.13	0.68 (0.38–1.20)	0.18	
Trend test		0.13		0.13	
Family income					**0.335**
≤ 1.30			**> 1.30**		
T1 (0–8.55)	1 (Ref)		1 (Ref)		
T2 (8.60–11.97)	0.79 (0.42–1.49)	0.47	0.52 (0.33–0.83)	0.01	
T3 (12.00–121.41)	0.58 (0.29–1.15)	0.12	0.67 (0.42–1.08)	0.1	
Trend test		0.13		0.1	
Education, year					**0.771**
≤ 12			**> 12**		
T1 (0–8.55)	1 (Ref)		1 (Ref)		
T2 (8.60–11.97)	0.63 (0.33–1.20)	0.16	0.55 (0.33–0.92)	0.02	
T3 (12.00–121.41)	0.84 (0.46–1.54)	0.57	0.56 (0.34–0.91)	0.02	
Trend test		0.5		0.02	
BMI, kg/m^2					**0.508**
< 24			**≥ 24**		
T1 (0–8.55)	1 (Ref)		1 (Ref)		
T2 (8.60–11.97)	0.52 (0.21–1.32)	0.17	0.61 (0.41–0.90)	0.01	
T3 (12.00–121.41)	0.86 (0.36–2.02)	0.72	0.60 (0.40–0.91)	0.02	
Trend test		0.72		0.01	

OR, odds ratio; CI, confidence interval; Ref, Reference; BMI: body mass index.

Furthermore, we excluded individuals with liver dysfunction (ALT and AST >40 U/L) and performed weighted multivariable logistic regression calculations. The results were consistent with the main study (Table 9, Fig. 2 F).

4. Discussion

To our knowledge, in this comprehensive retrospective cross-sectional study utilizing large NHANES datasets from 1999 to 2018, we consistently observed a negative correlation between STB levels and the prevalence of PD. Notably, restricted cubic splines analysis indicated an L-shaped relationship between STB levels and PD risk (p for nonlinearity < 0.05), with the lowest risk observed at 10.84 μmol/L. These results remained consistent across various clinical subgroups and in sensitivity analyses. These findings carry significant clinical implications.

Until now, only a restricted number of studies have explored the connection between PD and STB. For example, a cross-sectional case-control study enrolled consecutive PD patients in Italy [24]. Initially, In a study utilizing propensity score matching (PSM), 75 de

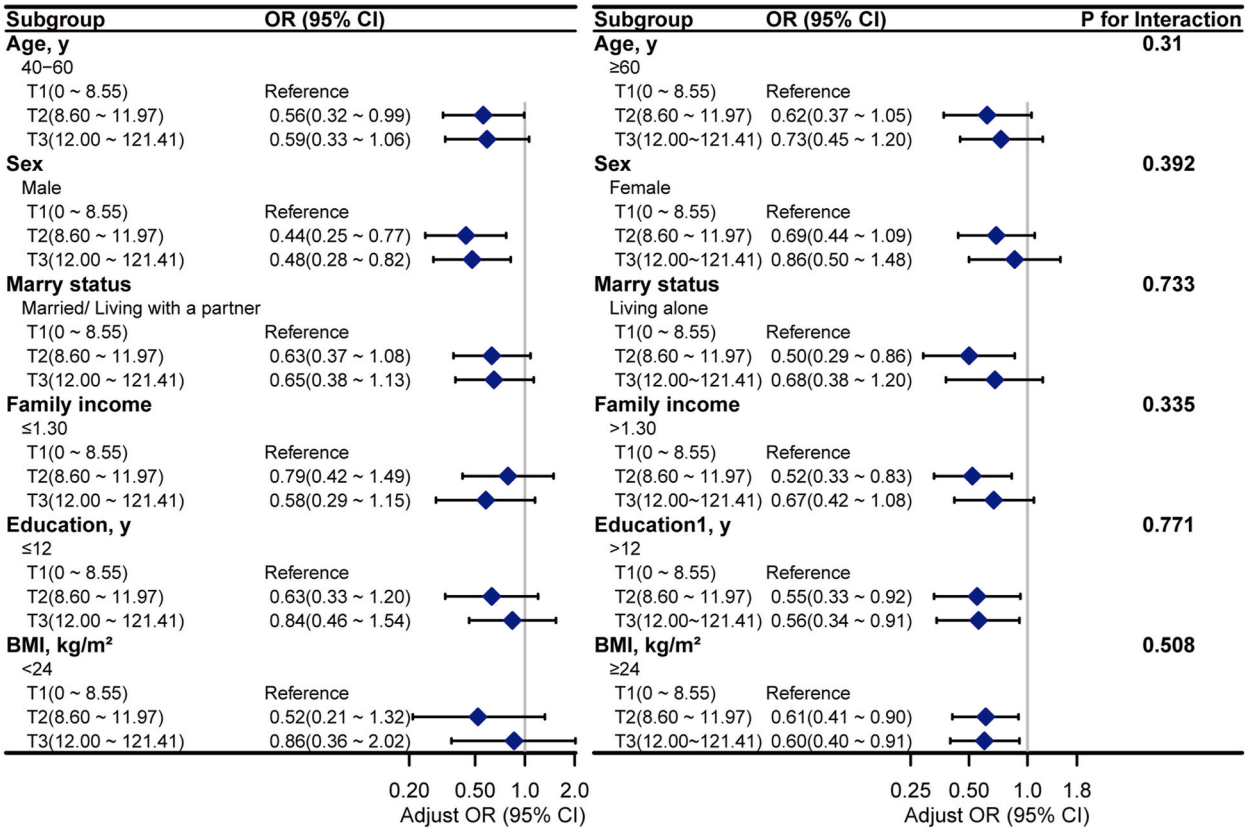

Fig. 3. Association between the serum total bilirubin and Parkinson's disease according to basic features. OR, odds ratio; CI, confidence interval; y, years; T, Tertiles; BMI: body mass index. Except for the stratification component itself, each stratification factor was adjusted for all other variables (age, sex, race/ethnicity, marital status, family income, education level, body mass index, smoking status, drinking status, coronary heart disease, stroke, hypertension and diabetes).

Table 6
Association between STB tertiles and PD among individuals over 20 years old, weighted.

STB tertiles	No. (unweighted)	OR (95 % CI)			
		Crude Model	*P* value	[a]Adjusted Model	*P* value
T1 (0 ~ 8.55)	8378	1 (Ref)		1 (Ref)	
T2 (8.60 ~ 11.97)	8709	0.66 (0.47–0.92)	0.016	0.66 (0.46–0.93)	0.018
T3 (12.00 ~ 121.41)	8550	0.56 (0.39–0.79)	0.001	0.63 (0.43–0.91)	0.014
Trend test	25637		0.002		0.014

STB, Serum Total Bilirubin; OR, odds ratio; CI, confidence interval; T, Tertiles; Ref, Reference.
[a] Adjusted Model: Adjusted for sociodemographic (age, sex, race/ethnicity, marital status, family income, education level), body mass index, smoking status, drinking status, coronary heart disease, stroke, hypertension and diabetes.

Table 7
Association between STB and young onset PD, weighted.

Variable	No. (unweighted)	No. (PD)	OR (95 % CI)			
			Crude Model	*P* value	[a]Adjusted Model	*P* value
20 ~ 39 (year)	12606	39	0.89 (0.83–0.96)	0.002	0.91 (0.85–0.98)	0.013
20 ~ 49 (year)	19325	97	0.94 (0.90–0.99)	0.019	0.97 (0.93–1.02)	0.269

PD, Parkinson's disease; OR, odds ratio; CI, confidence interval.
[a] Adjusted Model: Adjusted for sociodemographic (age, sex, race/ethnicity, marital status, family income, education level), body mass index, smoking status, drinking status, coronary heart disease, stroke, hypertension and diabetes.

Table 8
Associations STB tertiles with PD, after multiple interpolation of missing values, weighted.

Variable	STB (umol/L)		
	T1 (0–6.84)	T2 (8.55–10.30)	T3 (11.97–220.59)
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
NO. (unweighted)	6783	10571	14820
Model 1	1 (Ref)	0.72 (0.49–1.05)	0.49 (0.35–0.68)
Model 2	1 (Ref)	0.72 (0.49–1.05)	0.49 (0.34–0.69)
Model 3	1 (Ref)	0.72 (0.49–1.06)	0.50 (0.35–0.72)
Model 4	1 (Ref)	0.73 (0.50–1.07)	0.54 (0.38–0.77)

STB, Serum Total Bilirubin; T, Tertiles; OR, odds ratio; CI, confidence interval; Ref, Reference.
aModel 1: with no covariate adjustment.
bModel 2: adjusted for Age, Sex, Race/Ethnicity.
cModel 3: Model 2 + Marital status, Education level, Family income.
dModel 4: Model 3 + BMI, Smoking status, Drinking status, Coronary heart disease, Stroke, Hypertension, Diabetes.

Table 9
Association between STB tertile and PD, after excluding abnormal liver function values, weighted.

Variable	STB (umol/L)		
	T1 (0–6.84)	T2 (8.55–10.30)	T3 (11.97–121.41)
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
NO. (unweighted)	4635	7770	10791
Crude Model	1 (Ref)	0.73 (0.45–1.18)	0.60 (0.40–0.91)
[a]Adjusted Model	1 (Ref)	0.73 (0.45–1.19)	0.65 (0.42–1.00)

STB, Serum Total Bilirubin; T, Tertiles; OR, odds ratio; CI, confidence interval; Ref, Reference.
[a] Adjusted Model: Adjusted for sociodemographic (age, sex, race/ethnicity, marital status, family income, education level), body mass index, smoking status, drinking status, coronary heart disease, stroke, hypertension and diabetes.

novo PD subjects were paired with 75 healthy controls [24]. Following adjustments for age and sex, higher bilirubin levels were detected in PD patients [24]. Over a 2-year follow-up, associations emerged between bilirubin levels with both the Unified Parkinson's Disease Rating Scale Part III and levodopa-equivalent daily dosage [24]. Furthermore, a case-control study gathered plasma samples from 137 patients in Spain, which included 35 age-matched controls, 29 individuals with newly diagnosed PD, 35 with established PD, and 38 with essential tremor [23]. The study revealed elevated plasma or serum bilirubin and/or biliverdin levels in PD patients, suggesting their potential utility as biomarkers. Bilirubin, among other markers, exhibited good predictive accuracy in distinguishing de novo PD and advanced PD from controls and individuals with essential tremor [23]. Additionally, bilirubin, along with other factors, was identified as a potential biomarker capable of distinguishing PD from both controls and individuals with ET [23]. Similarly, the study comprised 420 PD patients and 435 healthy controls, with the patients in Spain [25]. Research has indicated a significant elevation in bilirubin levels among PD patients in comparison with controls. Additionally, within the PD patient cohort, bilirubin levels exhibited a negative correlation with disease duration [25]. Elevated bilirubin levels were observed in PD patients with Hoehn & Yahr stage $\leq$3. Nevertheless, this study indicated that bilirubin levels in PD patients were not associated with treatment [25]. Moreover, JN et al. conducted a meta-analysis comprising 8 studies with a total of 1463 PD cases and 1490 controls. The analysis revealed higher levels of total bilirubin and direct bilirubin in PD patients in contrast to controls, as indicated by the standardized mean difference. However, no significant correlation was observed between serum indirect bilirubin and PD patients [11]. An ethnicity-based subgroup analysis conducted within the study center revealed elevated STB levels in PD patients of Caucasian descent contrasted with controls matched healthy controls [11]. Additionally, a metabolomics-based investigation reported significantly reduced levels of bilirubin in the PD profile relative to those in normal controls. The PD cohort comprised 35 individuals with idiopathic PD, including 18 men, with a mean age of 69.1 $\pm$ 10.8 years, an average disease duration of 8.82 $\pm$ 4.3 years (ranging from 1 to 18 years), and a mean Hoehn-Yahr stage of 2.9 $\pm$ 1.1. All PD participants received outpatient treatment at Juntendo University in Tokyo, Japan [26].

However, the correlation between bilirubin and PD has not been extensively explored in the US.In our study population, we confirmed a negative correlation between STB levels and PD within the NHANES 1999–2018 dataset. In this study, participants in the highest tertile of STB demonstrated a relative decrease in the prevalence of PD in contrast to those in the lowest tertile. It is noteworthy that our findings are not entirely consistent with previous reports. What might be the reasons for this discrepancy?

Upon reviewing the literature, we noted that previous studies have indicated relatively high STB levels in patients with newly diagnosed PD [23–25], while levels tend to be somewhat lower in patients with PD of a certain disease duration [26]. In our study, individuals were classified as having PD if they were actively undergoing treatment for the condition. Conversely, Participants who didn't report taking any anti-Parkinsonian medications were categorized as not having PD. This implies that the PD cohort included in our study may have had the disease for an extended duration, potentially influencing the levels of serum STB in their bodies, which could also be impacted by Parkinson's treatment medications. Previous research has identified a negative connection between

bilirubin levels and disease duration in PD patients [25]. In a study, after a 2-year follow-up, the levodopa equivalent daily dosage exhibited a negative relationship with bilirubin levels [24]. Therefore, our study results may be consistent with those of previous research. In our analysis of NHANES data from 1999 to 2018, we consistently observed an L-shaped association with PD, even after adjusting for confounding factors such as age, sex, marital status, race/ethnicity, education level, family income, smoking status, drinking status, BMI, and baseline diseases. Further research is warranted to validate our findings and explore the intricate relationship and potential mechanisms in greater depth. Interestingly, there was a significant connection between STB and the prevalence of PD, and this association remained consistent across different subtypes, including age, gender, marital status, education level, family income, and BMI. Moreover, our results were generally robust according to sensitivity analyses.

Mechanistically, research has confirmed that elevated STB levels in PD patients may be due to multiple pathways, including antioxidant and anti-inflammatory effects, thereby providing neuroprotection. Oxidative stress is recognized as a primary pathogenic mechanism in PD [36]. Evidence highlights bilirubin's role as an endogenous lipid-soluble antioxidant in the human body [37]. The existing evidence suggesting that HMOX is among the major antioxidant defense systems in mammals, operating within various oxidative pathways. In the presence of HMOX, heme undergoes degradation, resulting in the production of free iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin by biliverdin reductase [37,38]. Previous research has demonstrated the utility of total bilirubin as a marker for HMOX functional activity [39]. Postmortem investigations have revealed increased immunoreactivity of HMOX1 in individuals with PD [37]. Therefore, several studies speculate that the increase in bilirubin may be due to the overexpression of HMOX as a compensatory response to oxidative stress occurring in the early stages of PD [24,25]. Studies have indicated that levels of HMOX1 protein in the midbrain are regulated by proteasome activity, and elevations resulting from proteasome inhibition offer neuroprotection [37]. In addition, bilirubin has emerged as an in vivo homeostatic, antioxidant, anti-inflammatory factor, and even a hormone. A substantial body of clinical and experimental evidence suggests a relationship between the outset and development of PD and inflammation [14]. Regarding the anti-inflammatory properties of bilirubin, it may prevent the death of dopaminergic neurons in an in vitro model of PD by modulating TNFα [14]. The anti-inflammatory capacity of bilirubin has attracted attention in nanomedicine, where studies on bilirubin-loaded nano-delivery approaches have exhibited promising outcomes in diverse contexts such as tumors and metabolic syndrome.

Our study possesses several strengths. Firstly, our study may assist future researchers in providing new evidence for bilirubin as a potential biomarker for the diagnosis and progression of PD. Secondly, it utilized a representative sample of the US population from NHANES, ensuring robustness and generalizability to the broader population. Thirdly, rigorous control for confounding variables, including sociodemographic factors and relevant medical history, was conducted. Additionally, subgroup and sensitivity analyses were performed, yielding consistent findings.

This study also has some limitations. To begin with, the causal relationship between STB and PD is difficult to determine due to the cross-sectional nature of this study. Moreover, due to the nature of the NHANES database, diagnosing PD patients solely based on the use of anti-Parkinsonian medication may lead to potential misdiagnosis. Furthermore, we can only determine if a patient has PD based on the oral medication information provided by the NHANES database. The NHANES database does not provide information on the severity of PD, therefore, we were unable to study the potential association between disease severity and bilirubin levels. Consequently, the specific course of the disease and the type of medication given and the amount of medication taken and the course of medication taken were also variable in our study. Therefore, large stratified studies on the correlation between STB and PD should be done in the future, including the rigorous design of the disease course of PD, disease severity and the strict control of the type and dosage of medication.

5. Conclusions

Our study findings indicated that the level of STB is significantly negatively correlated with the prevalence of PD. Therefore, more prospective studies need to be designed to prove the causal relationship between them.

Data availability

Data used for this study are available on the NHANES website: https://wwwn.cdc.gov/nchs/nhanes/.

Ethics statement

The survey plan and study procedure were approved by the Ethics Review Board of the National Center for Health Statistics. The document confirming this approval can be accessed via the download link provided: https://www.cdc.gov/nchs/nhanes/irba98.htm. It is titled "National Center for Health Statistics Ethics Review Board Approval". The ethical approval number is the National Center for Health Statistics Institutional Review Board/Ethics Review Board Protocol Number or Description. The ethical approval numbers for the data spanning from 1999 to 2018 are as follows: Protocol #98-12 (NHANES 1999–2004), Protocol #2005-06 (NHANES 2005–2010), Protocol #2011-17 (NHANES 2011–October 26, 2017), and Protocol #2018-01 (Effective beginning October 26, 2017). Participants provided written informed consent. Our study, which involved secondary data analysis from the NHANES, was exempt from institutional review.

Funding

This work was supported by the Jilin Provincial Science and Technology Department (NO. 20220204006YY) and Jilin Province Development and Reform Commission (NO. 2022C041-2).

CRediT authorship contribution statement

Jing Su: Writing – original draft, Methodology. **Liming Liu:** Writing – review & editing, Methodology. **Dalong Wu:** Supervision, Project administration, Funding acquisition. **Ruonan Wang:** Supervision, Investigation, Data curation, Conceptualization. **Zihan Wang:** Supervision, Investigation, Data curation, Conceptualization. **Enshuo Fan:** Visualization, Validation, Software. **Qiaoli Xu:** Supervision, Investigation, Data curation, Conceptualization. **Qingyuan Wang:** Visualization, Validation, Software, Conceptualization. **Chunyu Shen:** Visualization, Validation, Software. **Dexi Zhao:** Supervision, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We extend our sincere gratitude to all those who have contributed to this work. Special thanks are owed to Dr. Jie Liu from the Department of Vascular and Endovascular Surgery at the Chinese PLA General Hospital, for his invaluable consultation on study design, statistical assistance, and insightful comments on the manuscript.

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