Low Serum Bilirubin Level as an Independent Predictor of Stroke Incidence: A Prospective Study in Korean Men and Women

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Stroke. 2009;40:3422-3427; originally published online August 27, 2009;
doi: 10.1161/STROKEAHA.109.560649
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Low Serum Bilirubin Level as an Independent Predictor of Stroke Incidence

A Prospective Study in Korean Men and Women

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Background and Purpose—Bilirubin is not only a waste end-product but also an antioxidant. Bilirubin is known to be associated with decrease in cardiovascular risk in men, but its relationship to stroke was not clearly understood.

Methods—Serum bilirubin concentrations were measured in 78 724 health examinees (41 054 men, aged 30–89 years) from 1994 to 2001. The subjects with potential hepatobiliary diseases or Gilbert syndrome were excluded from analysis. Stroke incidence outcome was collected from hospital records of admission attributable to stroke from 1994 to 2007.

Results—Serum bilirubin measurements were divided into 4 levels: 0 to 10.2, 10.3 to 15.3, 15.4 to 22.1, and 22.2 to 34.2 μmol/L. The number of stroke cases was 1137 in men and 827 in women. In Cox proportional hazard models, participants with a higher level of bilirubin showed lower hazard ratios in men with ischemic stroke after adjustment for multiple confounding factors compared to the lowest level of bilirubin (hazard ratio [HR], 0.72; 95% CI, 0.58–0.90 in level 3; HR, 0.66; 95% CI, 0.49–0.89 in level 4; *P* for trend=0.016). The risk of all stroke types also decreased as bilirubin levels increased (HR, 0.81; 95% CI, 0.68–0.97 in level 3; HR, 0.74; 95% CI, 0.58–0.94 in level 4; *P* for trend=0.0071). However, these associations were not seen in hemorrhagic stroke or in women.

Conclusions—These findings suggest that serum bilirubin might have some protective function against stroke risk in men. **(*Stroke*. 2009;40:3422-3427.)**

Key Words: bilirubin ■ hemorrhagic stroke ■ ischemic stroke ■ stroke incidence

As stroke is becoming more prevalent in both developed and developing countries, the prevention of stroke is becoming crucial.[1] In Korea, stroke is the second leading cause of death after cancer.[2]

It has been suggested that bilirubin is not only a waste end-product but also an antioxidant[3–5] that may protect against diseases associated with oxidative stress.[6] In several prospective studies, an inverse relationship has been reported between bilirubin and the following diseases: cardiovascular disease (CVD),[7,8] coronary heart disease,[9] myocardial infarction,[10] ischemic heart disease,[11] and all-cause and cancer mortality in men,[12] although some of them failed to reach statistical significance in CVD.[12] Cross-sectional studies reported similar results with coronary artery disease,[13,14] peripheral vascular disease,[15,16] carotid intimal-medial thickness,[17,18] and stroke.[19] This inverse relationship of bilirubin to CVD was confirmed by meta-analysis,[20] and bilirubin has been discussed as a therapeutic target for CVD.[5,6]

In a recent cross-sectional study, it was shown that total bilirubin and stroke prevalence have an inverse association in the representative national data in which higher bilirubin level was not only associated with reduced stroke prevalence but also associated with favorable stroke outcomes.[19] However, the relationship between bilirubin and stroke has not been fully understood because of limited reports on this issue. Information such as subtypes of stroke or various ethnic groups is also limited.

Therefore, we analyzed the association between serum bilirubin levels and incidences of ischemic, hemorrhagic, and all stroke types in a large prospective cohort study in Korea.

Materials and Methods

Study Population

The initial study population consisted of 122 769 participants who underwent health examinations at 2 health examination centers in Seoul from 1994 to 2001. Among the initial subjects, subjects with missing data in the major variables (n=15 503), hemoglobin level <10 g/dL or >20 g/dL (n=1318), past history of CVD, cerebrovascular accident, cancer, history of kidney disease or serum creatinine >2.0 mg/dL, or past history of admission (n=10 928) were excluded. Among the 95 220 (53 217 men) participants, potential Gilbert syndrome group (total bilirubin >34.2 μmol/L [2.0 mg/dL], aspartate aminotransferase <80 IU/L, alanine transaminase <80 IU/L, gamma glutamyl transpeptidase [GGT] <80 IU/L, and no self-reported history of hepatobiliary disease; n=662) and potential hepatobiliary disease group (total bilirubin >34.2 μmol/L or aspar-

Received June 15, 2009; final revision received July 10, 2009; accepted July 20, 2009.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.109.560649**

tate aminotransferase ≥80 IU/L or aspartate aminotransferase ≥80 IU/L or serum albumin <3.5 g/dL or positive self-reported history of hepatobiliary disease; n=15 834) were also excluded to avoid confounding factors. The definition of the potential Gilbert syndrome group was modified from previous works.[21] The potential hepatobiliary disease group was defined according to the US NHANES study.[19] Finally, 78 724 health examinees (41 054 men, aged 30–89 years) were selected for the analyses. Consent from each examinee was not specially obtained because the data were collected from routine health examinations. The study was approved by the Institutional review board of human research of Yonsei University.

Data Collection

Baseline information was obtained from the health examinations from 1994 to 2001. Each participant completed systemized questionnaires that include smoking habit (never smoker, ex-smoker, or current smoker), alcohol habit (nondrinker or drinker of any amount of alcohol), regular exercise (yes or no), and other characteristics, including history and any medication. The participants' weights, heights, and blood pressures were measured in a standardized manner. The BMI was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic blood pressure were measured in a seated position with a mercury sphygmomanometer or automatic manometer. Fresh fasting serum specimens were analyzed for laboratory tests. Fasting blood glucose, serum cholesterol, liver function tests, and serum bilirubin concentrations were measured by automated biochemical profiling (Hitachi-7600 analyzer, Hitachi Ltd). Bilirubin concentrations were collected in milligram per deciliter units. Serum creatinine was measured by a kinetic rate Jaffe method.

Measurement of Outcome

The outcome variables were incidence of stroke and its subtypes (ischemic, hemorrhagic, and all stroke types) as recorded in hospital admission discharge records from 1994 to 2007 (median follow-up duration, 9.4 years). We ascertained these outcomes from health insurance claim data from the National Health Insurance Corporation and checked fatal cases from the national death certification data.[22,23] Ischemic, hemorrhagic, and all stroke types were defined according to the International Classification of Diseases 10th Revision codes: ischemic stroke, I63-I639; hemorrhagic stroke, I60-I629; and all stroke types, I60-I699. For those individuals with >1 event during the follow-up period, we considered only the first event in our statistical analyses. Morbidity was recorded according to the International Classification of Diseases 10th Revision codes in a standardized manner.[22–24] The accuracy rate of the International Classification of Diseases codes for cerebrovascular diseases in medical insurance claims for men in Korea was reported as 83.0% in 2000.[25]

Statistical Analysis

We classified the concentrations of serum bilirubin into 4 levels: 0 to 10.2, 10.3 to 15.3, 15.4 to 22.1, and 22.2 to 34.2 μmol/L (to convert bilirubin from milligrams per deciliter to micromoles per liter, multiply by 17.1). Type 2 diabetes was defined as participants with self-reported diagnosis of type 2 diabetes or participants with fasting blood glucose levels ≥126 mg/dL. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or a self-reported diagnosis of hypertension.

To examine the differences of baseline characteristics of the 4 levels of bilirubin, age-adjusted ANOVA and χ^2 test were used. The incidence rates per 100 000 person-year were calculated. Partial Pearson correlation coefficients were acquired to determine the relationship between log-transformed bilirubin and other variables with adjustment for age. Log-transformed bilirubin concentrations were used to achieve normal distribution. Cox proportional hazards models were used to estimate the risk of stroke incidence according to serum bilirubin levels. Crude (model I), age-adjusted (model II), and multivariable-adjusted (model III) analyses were performed with consideration for multicollinearity. We adopted the multivariable model used in the Framingham offspring study,[7] in addition to the GGT, a new risk factor for cardiovascular disease mortality.[26] Finally, the hazard ratios (HR) in model III were adjusted for age, smoking (nonsmoker, ex-smoker, current smoker), alcohol (yes or no), exercise (yes or no), alanine transaminase, total cholesterol, type 2 diabetes, hypertension, and GGT. The HR and 95% CI were calculated. All analyses were conducted using SAS statistical software version 9.1 (SAS institute Inc) and performed separately for men and women because frequency rates in the 4 bilirubin levels were different between men and women ($P<0.0001$ by χ^2 test). All statistical tests were 2-sided, and statistical significance was determined as $P<0.05$.

Results

Mean±SD of bilirubin concentration was 15.1±5.6 μmol/L in men (n=41 054) and 11.6±4.7 μmol/L in women (n=37 670; $P<0.0001$). During a 14-year follow-up, a total of 1964 men and women were hospitalized for stroke. Among all the stroke patients, the proportion of patients having ischemic stroke were 63.1% for men and 57.1% for women, respectively.

The mean age of study participants decreased as levels of serum bilirubin in both men and women increased ($P<0.0001$). There was not an even distribution of general characteristics among the 4 bilirubin levels which included age, BMI, alanine transaminase, total cholesterol, and smoking habit. GGT and hypertension in women, alcohol, exercise, and type 2 diabetes in men were also associated with bilirubin levels (Table 1). In age-adjusted partial correlation analysis, aspartate aminotransferase, systolic blood pressure, fasting blood glucose, triglyceride, high-density lipoprotein, serum creatinine, and hemoglobin were also correlated with log-transformed bilirubin concentrations (Table 2).

There was strong multicollinearity among aspartate aminotransferase, alanine transaminase, and GGT, and also between total cholesterol and triglyceride. When we analyzed with several alternate models with or without systolic blood pressure, fasting blood glucose, GGT, BMI, creatinine, hemoglobin, triglyceride, high-density lipoprotein, and cholesterol/high-density lipoprotein ratio,[19] there was no difference in the final results showing the association between bilirubin levels and stroke incidence (data not shown).

In Cox proportional hazard models, participants with higher levels of bilirubin showed lower HR in men with ischemic stroke before and after adjustment for age (model II) or multiple (model III) confounding factors compared with the lowest level of bilirubin (HR, 0.72; 95% CI, 0.58–0.90 in level 3; HR, 0.66; 95% CI, 0.49–0.89 in level 4; P for trend=0.016). The risk for all stroke types also decreased as bilirubin levels increased (HR, 0.81; 95% CI, 0.68–0.97 in level 3; HR, 0.74; 95% CI, 0.58–0.94 in level 4; P for trend=0.0071). However, these associations were not seen in hemorrhagic stroke or in women (Tables 3 and 4).

We also did the Cox proportional hazard analysis with bilirubin as a continuous variable. For ischemic stroke, a 1 μmol/L increment in bilirubin concentration was associated with a 2% reduction of HR (HR, 0.98; 95% CI. 0.97–0.99; $P=0.0138$) and a 1-log bilirubin (μmol/L) increment was associated with a 23% reduction in HR (HR, 0.77; 95% CI. 0.63–0.94) in a multivariate-adjusted model for men. For all stroke types, there was a 1% reduction of HR (HR, 0.99; 95%

Table 1. Baseline Characteristics of the Study Population According to the Bilirubin Levels

	Bilirubin Levels (μmol/L)				
	1 0–10.2	2 10.3–15.3	3 15.4–22.1	4 22.2–34.2	*P*
Men (n=41 054)	5422	16 220	14 099	5313	
Age, yr	48.6±10.5	48.1±10.3	46.9±10.0	45.6±9.8	<0.0001
BMI, kg/m^2	23.6±2.7	23.9±2.7	23.9±2.7	23.7±2.8	<0.0001
ALT, IU/L	26.5±13.2	26.7±13.6	26.2±13.5	25.6±13.3	<0.0001
GGT, IU/L	39.9±39.1	40.4±38.6	40.3±40.6	39.1±44.1	0.1823
Cholesterol, mg/dL	196.4±35.1	199.0±34.2	196.9±33.4	193.2±33.5	<0.0001
Bilirubin, μmol/L	7.6±1.3	12.0±1.4	17.4±1.9	25.7±3.5	<0.0001
Log bilirubin, μmol/L	2.0±0.2	2.5±0.1	2.9±0.1	3.2±0.1	<0.0001
Current smoker	3392 (62.6)	8914 (55.0)	6649 (47.2)	2334 (43.9)	<0.0001
Alcohol drinker	4505 (83.1)	13855 (85.4)	12293 (87.2)	4664 (87.8)	<0.0001
Regular exercise	2490 (45.9)	6808 (42.0)	5969 (42.3)	2318 (43.6)	<0.0001
Type 2 diabetes	425 (7.8)	1119 (6.9)	932 (6.6)	285 (5.4)	<0.0001
Hypertension	1370 (25.3)	3990 (24.6)	3548 (25.2)	1275 (24.0)	0.2810
Women (n=37 670)	13 543	16 172	6318	1637	
Age, yr	48.7±10.2	47.7±10.1	46.2±9.9	45.3±9.8	<0.0001
BMI, kg/m^2	23.3±3.1	23.1±3.1	22.9±3.1	22.5±3.0	<0.0001
ALT, IU/L	17.9±9.6	17.4±9.7	16.9±9.5	16.6±9.8	<0.0001
GGT, IU/L	18.5±16.2	18.0±16.1	17.3±15.4	17.3±17.2	<0.0001
Cholesterol, mg/dL	196.9±36.6	197.0±37.2	193.9±37.3	191.6±37.2	<0.0001
Bilirubin, μmol/L	7.4±1.4	11.6±1.3	17.1±1.8	25.4±3.3	<0.0001
Log bilirubin, μmol/L	2.0±0.2	2.5±0.1	2.8±0.1	3.2±0.1	<0.0001
Current smoker	898 (6.6)	838 (5.2)	275 (4.4)	69 (4.2)	<0.0001
Alcohol drinker	4939 (36.5)	6001 (37.1)	2391 (37.8)	617 (37.7)	0.2645
Regular exercise	7741 (57.2)	9008 (55.7)	3557 (56.3)	914 (55.8)	0.0879
Type 2 diabetes	512 (3.8)	641 (4.0)	240 (3.8)	71 (4.3)	0.6402
Hypertension	3118 (23.0)	3595 (22.2)	1342 (21.2)	324 (19.8)	0.0027

Data are shown as mean±SD for continuous variables and N (percent) for categorical variables. For continuous variables, age-adjusted ANOVA test was used.

ALT indicates alanine transaminase.

Type 2 diabetes: self-reported diagnosis or with fasting blood glucose ≥126 mg/dL; hypertension: self-reported diagnosis, or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

CI, 0.98–1.00; P=0.0382) and a 15% reduction of HR (HR, 0.85; 95% CI, 0.72–0.99; P=0.0358), respectively (data not shown). Similar results were observed when we divided the participants into quartiles (please see Table I, available online at http://stroke.ahajournals.org). We grouped the bilirubin concentrations into 5 levels using the design used in the Framingham offspring study.[7] The multivariable adjusted HR, which compared ischemic stroke in the highest quintile to that in the lowest quintile, showed a significant decrease in men (HR, 0.71; 95% CI, 0.56–0.90), but the HR for all stroke types was not significant (please see Table II).

In men, we saw a protective trend of bilirubin against a risk of hemorrhagic stroke in an unadjusted model for the trend test (P for trend=0.0151), but it disappeared when we adjusted for age and other confounding variables (Table 3).

In women, we found significant associations between bilirubin and stroke in an unadjusted model for ischemic stroke (HR, 0.71; 95% CI, 0.54–0.94 in level 3; P for trend=0.0046) and all stroke types (HR, 0.72; 95% CI, 0.58–0.89 in level 3; P for trend=0.0024). In adjusted models, there was no remaining significant relationship between bilirubin and the various stroke types in women (Table 4).

Discussion

Even after adjusting for age and other well-known risk factors, the serum bilirubin level still was independently associated with the incidence of ischemic and all stroke types dose-dependently in men, but not in women. The result of our study on stroke coincides with previous reports that bilirubin is an independent inverse predictor for CVD.

In previous studies, a U-shape correlation between bilirubin and cardiovascular risk was described[9,11] or suggested.[7,19] In our report, we divided the bilirubin concentrations into 4 levels by a concentration range in contrast to previous studies to provide information on these concentrations. However, we performed alternate grouping to check this issue. Our analysis using the same grouping as the Framingham offspring study[7] showed decreased risk of ischemic stroke in higher bilirubin levels in men. However, there was no significant

Table 2. Age-Adjusted Partial Correlation Coefficients Between Log Bilirubin Concentration and Other Variables Measured

	Men (n=41 054)		Women (n=37 670)	
	Correlation Coefficient	*P*	Correlation Coefficient	*P*
Aspartate aminotransferase	−0.0238	<0.0001	−0.0372	<0.0001
ALT	−0.0374	<0.0001	−0.0160	0.0013
GGT	−0.0075	0.1197	−0.0097	0.0518
Systolic blood pressure	0.0361	<0.0001	0.0157	0.0017
Diastolic blood pressure	−0.0162	0.0008	0.0001	0.9913
Fasting blood glucose	−0.0132	0.0063	0.0176	0.0004
Total cholesterol	−0.0227	<0.0001	0.0136	0.0066
Triglyceride	−0.0739	<0.0001	−0.0953	<0.0001
High-density lipoprotein cholesterol	0.0926	<0.0001	0.0604	<0.0001
Hemoglobin	0.1559	<0.0001	0.1762	<0.0001
BMI	0.0032	0.5066	−0.0348	<0.0001
Serum creatinine	−0.0281	<0.0001	−0.0573	<0.0001

Log-transformed bilirubin concentrations were used to achieve normal distribution.

association between bilirubin and the risk of all stroke types in men. This result implies the possibility that the U-shape was attributable to the lack of analysis for the subtypes of CVD.

In our study, we presented each HR for ischemic, hemorrhagic, and all stroke types rather than total CVD, and found some differences between the results from ischemic stroke and the results from hemorrhagic stroke. A stronger association of bilirubin with the risk of ischemic stroke than with the risk of hemorrhagic stroke may support the antiatherogenic property of bilirubin suggested in previous reports.[19]

Bilirubin has been shown to be a natural antioxidant.[3,4] As an antioxidant, bilirubin demonstrated antiatherogenic function through inhibition of low-density lipoprotein oxidation[27,28] or through inhibition of vascular endothelial activation, which may mediate the antiatherogenic properties of heme oxygenase-1.[29] The antiatherogenic potential of bilirubin was also shown in human studies. Carotid intima-media thickness, a predictor for atherosclerosis, increased in healthy subjects with low bilirubin levels not only in men[17] but also in women.[18]

However, in longitudinal cohort studies, the association between bilirubin and mortality[12] or between bilirubin and cardiovascular disease[7] did not reach statistical significance in women. The Framingham Offspring Cohort reported inverse associations between bilirubin and cardiovascular diseases when they analyzed CVD not specific for coronary heart disease or stroke in men but not in women among 4276 participants during a 22-year follow-up. The multivariate-adjusted HR for risk of CVD for the higher bilirubin group (14.53–17.94 μmol/L) compared to the lowest group was 0.59 (95% CI, 0.39–0.89) in men,[7] which is comparable with our findings (HR, 0.72; 95% CI, 0.58–0.90) of 15.4 to

Table 3. HR and 95% CI for Ischemic, Hemorrhagic, and All Stroke Types According to Bilirubin Levels in Men, 1994–2007 (n=41 054)

	Bilirubin levels (μmol/L)				
	0–10.2	10.3–15.3	15.4–22.1	22.2–34.2	*P*
N (%)	5422 (13.2)	16 220 (39.5)	14 099 (34.3)	5313 (12.9)	
Ischemic stroke					
Cases	145	302	209	61	
Incidence rate	311.4	216.8	171.7	131.9	
Model I	1.00	0.70 (0.57–0.85)	0.55 (0.45–0.68)	0.42 (0.31–0.57)	<0.0001
Model II	1.00	0.73 (0.60–0.89)	0.64 (0.52–0.79)	0.55 (0.41–0.75)	<0.0001
Model III	1.00	0.80 (0.65–0.97)	0.72 (0.58–0.90)	0.66 (0.49–0.89)	0.0016
Hemorrhagic stroke					
Cases	41	118	79	26	
Incidence rate	87.4	84.3	64.6	56.1	
Model I	1.00	0.97 (0.68–1.34)	0.74 (0.51–1.08)	0.64 (0.39–1.05)	0.0151
Model II	1.00	1.00 (0.70–1.42)	0.83 (0.60–1.21)	0.79 (0.48–1.29)	0.1558
Model III	1.00	1.05 (0.73–1.50)	0.87 (0.59–1.27)	0.80 (0.48–1.32)	0.1753
All stroke					
Cases	207	476	349	105	
Incidence rate	446.6	343.3	287.9	227.8	
Model I	1.00	0.77 (0.63–0.91)	0.64 (0.54–0.77)	0.51 (0.40–0.64)	<0.0001
Model II	1.00	0.80 (0.68–0.94)	0.74 (0.62–0.88)	0.65 (0.51–0.82)	0.0001
Model III	1.00	0.86 (0.73–1.01)	0.81 (0.68–0.97)	0.74 (0.58–0.94)	0.0071

Incidence rate=cases/100 000 person-year; model I: unadjusted; model II: adjusted for age; model III: adjusted for age, smoking (nonsmoker, ex-smoker, current smoker), alcohol (yes or no), exercise (yes or no), ALT, GGT, total cholesterol, type 2 diabetes, and hypertension.

Table 4. HR and 95% CI for Ischemic, Hemorrhagic, and All Stroke Types According to Bilirubin Levels in Women, 1994–2007 (n=37 670)

	Bilirubin Levels (μmol/L)				
	0–10.2	10.3–15.3	15.4–22.1	22.2–34.2	*P*
N (%)	13 543 (36.0)	16 172 (42.9)	6318 (16.8)	1637 (4.4)	
Ischemic stroke					
Cases	194	195	67	16	
Incidence rate	166.8	137.8	120.0	110.0	
Model I	1.00	0.82 (0.67–1.00)	0.71 (0.54–0.94)	0.77 (0.39–1.08)	0.0046
Model II	1.00	0.91 (0.75–1.11)	0.93 (0.70–1.23)	0.94 (0.57–1.57)	0.5055
Model III	1.00	0.90 (0.74–1.10)	0.88 (0.67–1.17)	0.91 (0.55–1.52)	0.3253
Hemorrhagic stroke					
Cases	75	99	28	7	
Incidence rate	64.2	69.8	50.0	48.0	
Model I	1.00	1.09 (0.80–1.47)	0.78 (0.50–1.12)	0.75 (0.34–1.62)	0.2782
Model II	1.00	1.17 (0.87–1.58)	0.93 (0.60–1.44)	0.97 (0.45–2.10)	0.9540
Model III	1.00	1.16 (0.86–1.56)	0.90 (0.58–1.34)	0.94 (0.43–2.03)	0.8158
All stroke					
Cases	314	376	109	28	
Incidence rate	270.9	266.8	195.9	192.9	
Model I	1.00	0.98 (0.84–1.14)	0.72 (0.58–0.89)	0.70 (0.48–1.03)	0.0024
Model II	1.00	1.07 (0.92–1.25)	0.90 (0.72–1.12)	0.97 (0.66–1.43)	0.6072
Model III	1.00	1.07(0.92–1.24)	0.87 (0.70–1.09)	0.94 (0.64–1.38)	0.4193

Incidence rate=cases/100 000 person-year; model I: unadjusted; model II: adjusted for age; model III: adjusted for age, smoking (nonsmoker, ex-smoker, current smoker), alcohol (yes or no), exercise (yes or no), ALT, GGT, total cholesterol, type 2 diabetes, and hypertension.

22.1 μmol/L for ischemic stroke. These differences in men and women may be attributable to lifestyle factors, including tobacco, alcohol, or diet. Postmenopausal women and men accumulate higher levels of stored iron than young women,[30] and high dietary intake of heme iron has been known to be associated with increased coronary heart disease risk.[31] We cannot exclude a potential effect of iron load to the heme oxygenase-1 and bilirubin pathway.[29]

Defining hyperbilirubinemic subgroup and excluding potential liver disease patients was pointed as a key step to clarify the inverse associations between bilirubin and stroke in discussions from other published works.[32] We modified the exclusion criteria of the NHANES study: a report on active liver diseases, 2-times higher than normal value of alanine transaminase, bilirubin >34.2 μmol/L, or albumin <3.5 mg/dL, and adjustment for alcohol intake.[19] We also excluded the potential Gilbert syndrome group because it has been known that they had lower prevalence and incidence of coronary heart diseases and had higher high-density lipoprotein and antioxidant levels.[6] However, we could not find any difference in the risk of stroke among the potential Gilbert syndrome group, the potential hepatobiliary disease group, and the main analysis group in our additional analysis. When we calculated HR without excluding them (n=95 220), the results did not differ from that reported.

This study has several limitations. The representation of our participants is limited and the variables of stroke prognosis or dietary intake are lacking. We also cannot rule out selection bias in our volunteers who may have had healthier lifestyles. Bilirubin concentration was measured only once, but we thought the possibility of confounders from biliary disease might be minimal because we excluded subjects with abnormal liver enzymes and with histories of hepatobiliary diseases. The accuracy rate for cerebrovascular diseases in medical insurance claims for men was reported previously,[25] but there were limited data for women.

It was reported that among the stoke cases, ≈15% of the cases were hemorrhagic stroke, 70% of the cases were cerebral infarction, and 15% of the cases were transient ischemic attack (TIA).[33] We did not include TIA in the all stroke types category because TIA patients are likely to be missed from the admission record because of the mild, transient symptom.

Our study has a few strengths. First, we analyzed a large population with men and women. Second, we excluded subjects with potential hepatobiliary diseases or Gilbert syndrome. Third, the characteristics of participants were homogenous because they were all urban middle class. Finally, we clarified the specific risk for the subgroups of stroke, including ischemic and hemorrhagic stroke.

Bilirubin assay is available in many laboratories and is not expensive. The results in this large cohort study support the potential role of bilirubin to predict stroke. Our findings suggest that serum bilirubin might have some protective function against stroke in men. Further studies are needed to confirm the association of bilirubin with stroke. A larger

sample size or longer follow-up time might have detected significant findings in the risk of hemorrhagic stroke, as well as in the risk of any type of stroke in women. Clarification of the protective bilirubin cut-off level and intervention trials may answer the question of the potential for bilirubin as a therapeutic target for CVD.

Acknowledgments

The authors are indebted to the staff of the Korean National Health Insurance Corporation, particularly Mungyu Park, the deputy director.

Sources of Funding

This study was supported by a grant of the Seoul R&BD Program, Republic of Korea (10526). Also, this research was supported by a grant from the Korea Institute of Oriental Medicine (KIOM, K09200). The funding sources had no role in the design and conduct of the study.

Disclosures

None.

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