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Serum total bilirubin level, prevalent stroke, and stroke outcomes: National Health and Nutrition Examination Survey

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Abstract

Background—Bilirubin inhibits experimental atherosclerosis, is inversely associated with carotid plaque burden, and confers neuroprotection in experimental stroke. Clinical data addressing the association of bilirubin with stroke are not available. We hypothesized that higher bilirubin levels would be associated with reduced stroke prevalence and improved stroke outcomes.

Methods—We used the National Health and Nutrition Examination Survey 1999–2004, a nationally representative cross-sectional examination of the United States civilian population, to examine the association of bilirubin with stroke. Of 13,214 adult participants with data on stroke history, serum total bilirubin level, and stroke risk factors, 453 reported a history of stroke. Of these, 138 reported an adverse stroke outcome, defined as a long-term health problem or disability due to stroke. We performed multivariable logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CI) with adjustment for demographic characteristics and stroke risk factors.

Results—After multivariable adjustment, a 1.71 umol/L (0.1 mg/dL) increment in bilirubin level was associated with a 9% reduced odds of stroke (OR 0.91, 95% CI: 0.86, 0.96) among all participants, and was associated with a 10% reduced odds of an adverse stroke outcome (OR 0.90, 95% CI: 0.80, 1.00) among participants with a history of stroke.

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Conclusions—These results suggest that higher serum total bilirubin level is associated with reduced stroke prevalence and improved stroke outcomes. Our findings support the hypotheses that bilirubin may protect from stroke events and from neurologic damage in stroke.

Keywords

Stroke; bilirubin; epidemiology; nutrition survey; National Health and Nutrition Examination Survey; heme oxygenase

Stroke is the third leading cause of death and a leading cause of disability in the United States[1]. While much progress has been made in identifying risk factors for stroke, little is known about factors that modulate stroke risk. Bilirubin, long considered merely metabolic waste but now recognized as having important antioxidant, anti-inflammatory, and neuroprotectant properties, has emerged as a possible endogenous defense mechanism against stroke[2–4]. The inhibitory actions of bilirubin in experimental atherosclerosis, the ability of bilirubin to prevent arterial thrombosis, and the inverse association of bilirubin with carotid atherosclerotic plaque suggest that higher bilirubin levels may be associated with a reduced risk of stroke[5–7]. Additionally, the ability of bilirubin to protect from neuronal injury in experimental acute ischemic stroke suggests that bilirubin may limit neurologic damage once a stroke has occurred[3, 8]. We therefore hypothesized that individuals with higher serum total bilirubin levels would be less likely to have suffered a stroke event, and that higher bilirubin levels would be associated with a more favorable stroke outcome among stroke survivors. To test these hypotheses, we examined the cross-sectional association of serum total bilirubin level with prevalent stroke and adverse stroke outcomes in the National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional examination of the United States population.

MATERIALS AND METHODS

The NHANES, conducted by the National Center for Health Statistics (NCHS), is a program of studies designed to assess the health and nutritional status of children and adults in the United States. The 1999–2004 NHANES was reviewed and approved by the NCHS Institutional Review Board. Informed consent was obtained from all participants. The NHANES detailed interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical examinations, physiological measurements, and laboratory tests administered by highly trained medical personnel. Of the 15,332 participants aged $\geq$ 20 years, 21 were missing data regarding stroke history and an additional 2,041 were missing serum total bilirubin level. Fifty-six of the remaining participants were missing data for a key covariate, allowing 13,214 participants to be included in this analysis.

Laboratory methods

Serum total bilirubin, creatinine, alanine aminotransfersase (ALT), aspartate aminotransferase (AST), albumin and glucose were determined by automated biochemical profiling (Beckman Synchron LX20); fractionation of total bilirubin was not performed in NHANES, and bilirubin levels were recorded in mg/dL. C-reactive protein (CRP) was quantified by latex-enhanced nephelometry. Total cholesterol and high-density lipoprotein (HDL) cholesterol were measured by automated enzymatic assay (Hitachi 704 Analyzer serviced by Roche Diagnostics, Indianapolis). Total homocysteine was measured by the Abbott Homocysteine assay. Hemoglobin was measured by the Beckman Coulter MAXM Instrument.

Definitions

Stroke prevalence and adverse stroke outcomes—Prevalent stroke was defined based upon the response to the question, 'Has a doctor or other health professional ever told you that you have had a stroke'. We defined a participant as having an adverse stroke outcome if the participant reported that stroke was the source of a long-term health problem or disability. As part of the 'Physical Function' questionnaire of the home interview portion of the examination, participants were asked a series of questions to determine whether they had a long-term health problem (not including pregnancy) that caused any long-term physical, mental, or emotional problem or illness[9]. If a subject reported a health problem, he or she was asked to identify the source of this; stroke was included in the list of health problems for the subject to choose from. Examples of health problems specifically queried are difficulty with working, memory, managing money, and walking a quarter mile. The online supplement contains full details of the questionnaire.

Other characteristics—Self-reported race/ethnicity was defined as non-Hispanic white, non-Hispanic black, Mexican-American, or other. A diagnosis of hypertension, hypercholesterolemia, and diabetes mellitus were defined as previously described[10]. Body weight was considered normal, overweight, or obese if the body mass index (BMI) was < 25, 25–29.9, or ≥ 30 kg/m^2, respectively. CRP level was categorized as low (< 1 mg/L), intermediate (1–3 mg/L), or high (> 3 mg/L) as suggested by Centers for Disease Control and Prevention / American Heart Association guidelines[11]. Participants were characterized as active, former, or never smokers[10]. The presence of active liver disease was determined by the subject's answer to the questions 'Has a doctor or other health professional ever told you that you have liver disease?' and 'Do you still have a liver condition?'. For further information about data collection, the reader is referred to the NHANES homepage (http://www.cdc.gov/nchs/nhanes.htm).

Statistical analysis

Analyses were performed with SAS version 9.1 (SAS Institute Inc) and SUDAAN version 9.0.1 (Research Triangle Institute) to account for the complex sample structure. Subject characteristics are reported as percentage and 95% confidence intervals (CI) or as mean and 95% CI. We examined the likelihood of stroke associated with a 1.71 μmol/L (0.1 mg/dL) increase in bilirubin level and with a 1-standard deviation increment bilirubin level; the standard deviation of bilirubin was 5.3 μmol/L (0.31 mg/dL). The association of bilirubin with stroke was also examined by tertiles of bilirubin level. We chose to use tertiles of bilirubin due to the relatively small number of events. We used logistic regression to estimate odds ratios (ORs) and 95% CI. Covariates in multivariable analysis were age, race/ethnicity, gender, smoking status, hypertension, diabetes, and total cholesterol to HDL cholesterol ratio. We individually considered BMI, CRP, hemoglobin and homocysteine as confounders, with a predetermined cutoff of a change in the bilirubin effect estimate of ≥ 20% indicating significant confounding. Additional adjustment for a quadratic term did not demonstrate an important non-linear relationship between bilirubin and stroke, and log transformation did not improve the fit of bilirubin in determining odds of stroke.

A priori we analyzed the interaction between bilirubin level and gender and between bilirubin level and smoking[10]. To address a possible influence from liver disease, we repeated the analysis first excluding participants who reported active liver disease, and second by additionally excluding participants with laboratory evidence suggestive of undiagnosed liver disease (AST or ALT > 2x gender-specific upper limit of normal, bilirubin > 34.2 μmol/L (2.0 mg/dL), or albumin < 35 g/L (3.5 mg/dL)). We additionally adjusted for alcohol intake in participants who had this data available (n = 12,361).

To determine whether bilirubin level was associated with adverse stroke outcome, multivariable logistic regression of adverse stroke outcome was performed among participants diagnosed with stroke. Multivariable adjustment and sensitivity analyses were the same as described above. Log transformation improved the fit of bilirubin in determining the odds of adverse stroke outcome in the multivariable adjusted model. For this outcome we therefore also report the results of the analysis using log-transformed bilirubin, but focus on the results of analysis using untransformed bilirubin so that the effect estimate is more easily understood.

RESULTS

Participant characteristics associated with lower bilirubin levels included female sex, non-Hispanic black race/ethnicity, hypercholesterolemia, and active smoking (Table 1). The distribution of bilirubin levels demonstrated a small right tail (Figure 1). Participant characteristics associated with prevalent stroke included older age, hypertension, diabetes and hypercholesterolemia.

The association of bilirubin with prevalent stroke

Of the 13,214 participants included in this analysis, 453 reported a history of stroke (2.5%, 95% CI: 2.2, 2.9). The mean serum total bilirubin level was significantly lower among participants with (12.1 μmol/L, 95% CI: 11.8, 12.3) (0.63 mg/dL, 95% CI 0.60–0.66) compared to those without (10.8 μmol/L, 95%: CI 10.3,11.3) (0.71 mg/dL, 95% CI: 0.69, 0.72) a history of stroke.

A 1.71 μmol/L (0.1 mg/dL) increment in serum total bilirubin level was associated with a 9% reduced odds of stroke (0.91, 95% CI: 0.86, 0.96) after adjustment for age, gender, race/ethnicity, smoking, hypertension, diabetes, and total:HDL cholesterol ratio. The effect estimate for a 1-standard deviation increment in bilirubin was an OR of 0.72 (95% CI: 0.63,0.82). In addition, we found that the odds of stroke decreased progressively with increasing tertile of bilirubin level; in particular, the second and highest compared with the lowest tertile of bilirubin was associated with a 24 and 44% reduced odds of stroke after multivariable adjustment (OR 0.76, 95% CI: 0.55,1.06, and OR 0.56, 95% CI: 0.39, 0.80, $P_{trend} = 0.002$, respectively) (Figure 2). The inverse association of bilirubin with stroke prevalence remained after excluding participants with a bilirubin level above the reference range (OR 0.90, 95% CI: 0.84, 0.95), indicating that the association was present within the range of clinically normal bilirubin levels.

We did not find evidence for significant confounding by BMI, CRP, homocysteine, or duration of fasting prior to blood draw (known to influence bilirubin levels). Moreover, the association of bilirubin with stroke did not vary by fasting status (≥ 8 hours versus < 8 hours) ($P_{interaction} = 0.53$) or whether the venous blood sample was drawn as part of the morning, afternoon or evening examination session did not modify the results ($P_{interaction} = 0.17$). Excluding participants with diagnosed active liver disease (n = 174) and additionally for laboratory evidence suggestive of possible undiagnosed liver disease (n = 1075), the association of bilirubin with stroke remained (OR 0.90, 95% CI: 0.85, 0.95, and OR 0.89, 95% CI: 0.85, 0.94, respectively). Additional adjustment for alcohol intake did not change the association of bilirubin with stroke (OR 0.91, 95% CI: 0.85, 0.97). Sex did not significantly alter the association of bilirubin with stroke ($P_{interaction} = 0.06$), nor did smoking status ($P_{interaction} = 0.72$).

The association of bilirubin with adverse stroke outcome

Among the 453 participants who reported a history of stroke, 138 (26.4%, 95% CI: 22.2, 31.1) reported a long-term physical, mental, or emotional problem or illness as a consequence of stroke (defined as an adverse stroke outcome). Participants with an adverse stroke outcome

tended to be male, older, and have a greater burden of stroke risk factors, but these differences were not significant (Table 2). Among participants with a history of stroke, a 1.71 μmol/L (0.1 mg/dL) increment in bilirubin level was associated with a 10% reduced odds of an adverse stroke outcome (OR 0.90, 95% CI : 0.80, 1.00) after multivariable adjustment. Log transformation improved the fit of bilirubin in determining the odds of an adverse stroke outcome (log-transformed bilirubin OR 0.44, 95% CI: 0.22, 0.89). In addition, we found that the odds of an adverse stroke outcome tended to decrease progressively with increasing tertile of bilirubin level; in particular, the second and highest compared with the lowest tertile of bilirubin were associated with a 13 and 44% reduced odds of an adverse stroke outcome after multivariable adjustment (OR 0.87, 95% CI: 0.48, 1.58, and OR 0.55, 95% CI: 0.31, 0.98, respectively, $P_{trend} = 0.06$) (Figure 3).

DISCUSSION

Experimental data suggests that bilirubin may limit stroke events by inhibiting atherosclerosis, thrombosis and vascular injury, and that bilirubin may limit neuronal damage once a stroke has occurred. We found that bilirubin level was inversely associated with stroke prevalence in over 13,000 participants in a nationally representative community-based cohort of United States adults. Specifically, the highest tertile of bilirubin level was associated with a 44% reduced odds of stroke. Additionally, among those participants with a history of stroke, those with higher bilirubin levels were less likely to report a long term health problem or disability due to stroke, suggesting that higher bilirubin levels are associated with more favorable stroke outcomes. These findings support the hypothesis that bilirubin may be an important endogenous defense mechanism against stroke events and may protect neurologic injury in the setting of stroke.

Bilirubin, once considered simply the metabolic end product of heme degradation by heme-oxygenase (HO), has emerged as an important endogenous anti-inflammatory and antioxidant molecule[10]. Bilirubin may, in fact, be the most abundant endogenous antioxidant in mammalian tissues[4, 12].

The antioxidant and anti-inflammatory qualities of bilirubin may protect from stroke events by limiting the development of atherosclerotic vascular disease. Bilirubin inhibits several aspects of atherogenesis, including LDL oxidation, monocyte migration, vascular smooth muscle cell proliferation, vascular inflammation, vascular reactive oxygen species generation and endothelial dysfunction[2, 13, 14]. That the antiatherogenic properties of bilirubin may be relevant to stroke is demonstrated by the strong inverse association of bilirubin level with carotid atherosclerotic plaque[7]. In addition to inhibiting atherosclerosis, bilirubin may also prevent stroke by inhibiting thrombus formation[6, 15]. It is important to note that carbon monoxide, another product of heme catabolism by HO, also has important roles in cardiovascular homeostasis[13].

Beyond possibly preventing stroke events, bilirubin may limit neurologic injury in once a stroke has occurred. In experimental acute ischemic stroke, overexpression of HO attenuates injury, and knockout of HO substantially worsens neuronal damage[8, 16]. Bilirubin appears to account for the neuroprotection offered by HO, as the neurotoxic effect of HO deletion is reversed by restoring even low concentrations of bilirubin[8]. The cytoprotection offered by bilirubin greatly exceeds that of glutathione and exceeds that which would be expected based on its intracellular concentration because of rapid recycling by biliverdin reductase: bilirubin can protect from a 10,000-fold excess of oxidants[3]. The increased expression of biliverdin reductase in experimental stroke further supports a role neuroprotective role for bilirubin in this setting[17]. Available human data indirectly supports a role for bilirubin limiting neuronal

damage in stroke, as low plasma antioxidant capacity is associated with high lesion volume and neurological impairment in stroke[18].

Bilirubin may protect not only from cerebrovascular disease but also more broadly from cardiovascular disease. Several investigators have found a strong inverse correlation between bilirubin level and coronary artery disease in men[19]. That bilirubin may broadly protect from cardiovascular disease is further supported by a prospective study of 1780 individuals followed up for 24 years. A 1.71 μmol/L (0.1 mg/dL) increase in bilirubin decreased cardiovascular disease risk by 10%, though the number of non-coronary events was relatively small[20]. Additionally, bilirubin is strongly inversely associated with lower extremity peripheral arterial disease[10].

The NHANES sampling methodology makes these results generalizable to the United States adult population. Participants are carefully characterized, allowing adjustment for several important covariates. Several limitations do warrant consideration. The diagnosis of stroke was made by self-report, a potential source of misclassification. We are not aware that the self-report of stroke has been validated within the NHANES cohort, but others have found that self-report of a physician diagnosis of stroke can be accurate[21]. It has also been shown that self-report of outcomes following stroke can be accurate[22], though the NHANES interview was not specifically designed to address stroke outcomes. Another potential source of error is that the bilirubin level was determined only once in each participant, and bilirubin exhibits significant within-subject variation[23]. Additionally, the antioxidant properties of bilirubin may differ depending upon whether it is conjugated or unconjugated; in NHANES fractionation of bilirubin was not performed[24]. The cross-sectional nature of the NHANES cohort does not allow for determination of the temporal association of bilirubin with stroke or allow any conclusion regarding causation. That the prospective association of bilirubin with cardiovascular disease may be U-shaped supports the need for prospective studies of bilirubin and stroke[25, 26]. NHANES does not have information regarding the type of stroke; it is possible that bilirubin is most strongly associated with a particular stroke subtype. Experimental data, as reviewed above, suggests that bilirubin might specifically protect from atherothrombotic stroke events, and might specifically limit neurologic damage in acute ischemic stroke, but this is speculative.

Should future work confirm that higher bilirubin level is associated with lessened stroke risk and improved stroke outcomes, interventions that increase bilirubin levels, perhaps by the induction of heme-oxygenase or by the inhibition of UDP-glucuronosyltransferase (coined ‘iatrogenic Gilbert syndrome’), may be appropriate investigational strategies for the prevention and/or treatment of stroke[27, 28].

Summary

In this nationally representative cross-sectional survey of United States adults, serum total bilirubin level was inversely associated with prevalent stroke, and individuals with a history of stroke and higher bilirubin levels were less likely to have suffered an adverse stroke outcome. These results are consistent with the hypotheses that the vasculoprotective properties of bilirubin may provide protection from stroke events, and that the neuroprotective capacity of bilirubin may limit neurologic injury in the setting of stroke. Therapeutic strategies to increase either tissue or circulating bilirubin levels may one day be used in the prevention and/or treatment of stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; CI, Confidence interval; CRP, C-reactive protein; HDL, High-density lipoprotein; HO, Heme oxygenase; NHANES, National Health and Nutrition Examination Survey; OR, Odds ratio.

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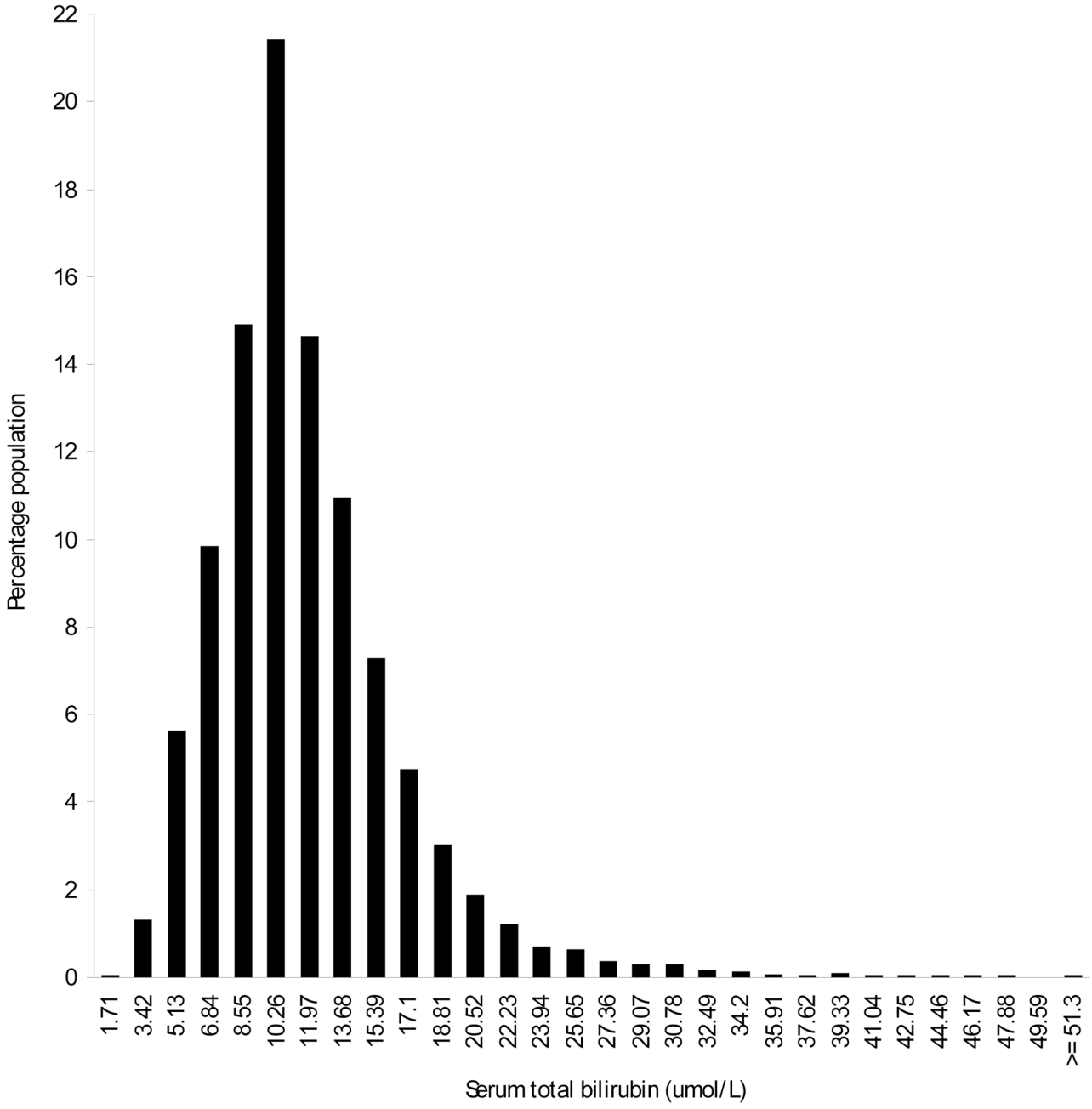

Figure 1. The distribution of bilirubin levels in the analytical sample (n = 13,214)
To convert bilirubin from umol/L to mg/dL, multiply by 0.058. National Health and Nutrition Examination Survey 1999–2004.

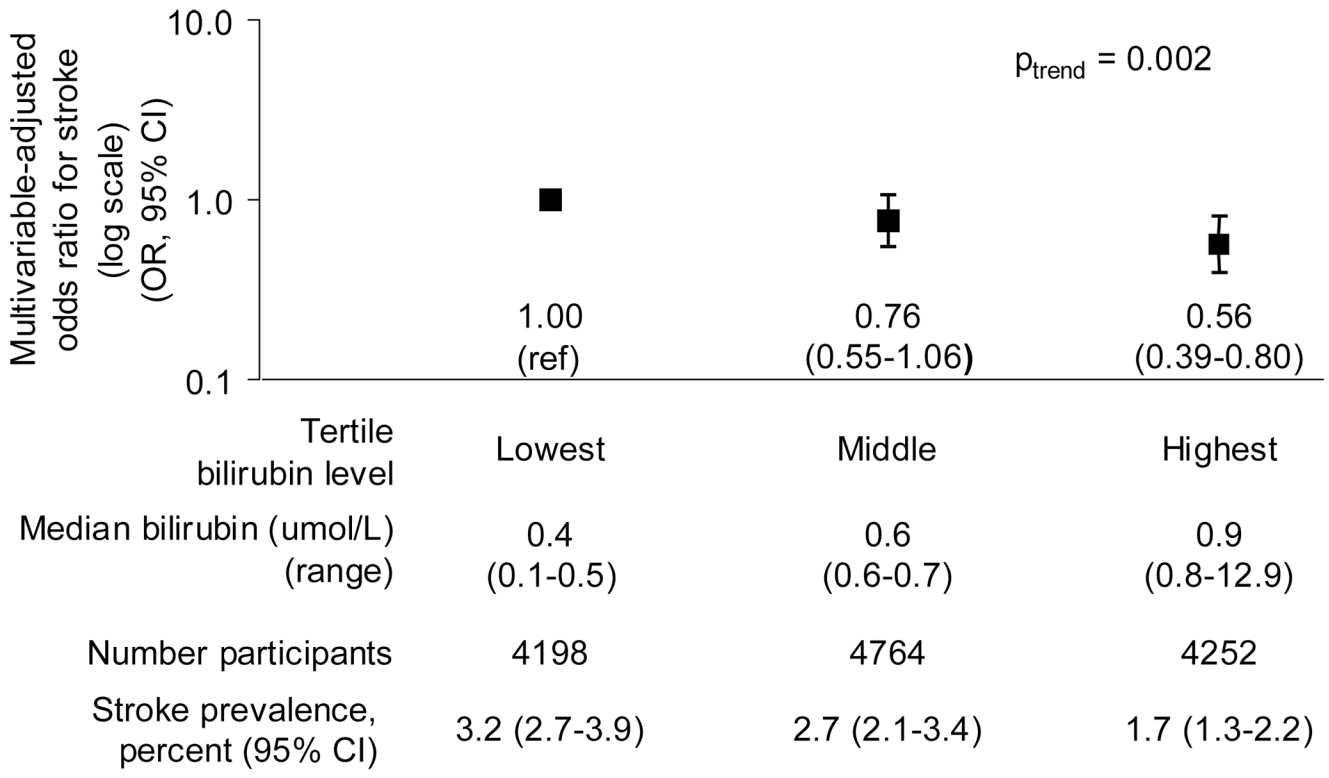

Figure 2. Multivariable-adjusted odds ratio for stroke among all participants

Age, sex, race/ethnicity, smoking, hypertension, total:HDL cholesterol ratio, and diabetes were adjusted for. Odds ratios and 95% confidence intervals (CI) estimated by logistic regression. Y-axis is log scale. The stroke prevalence estimates are unadjusted. To convert bilirubin from umol/L to mg/dL, multiply by 0.058. National Health and Nutrition Examination Survey 1999–2004. OR : Odds ratio. CI : Confidence interval.

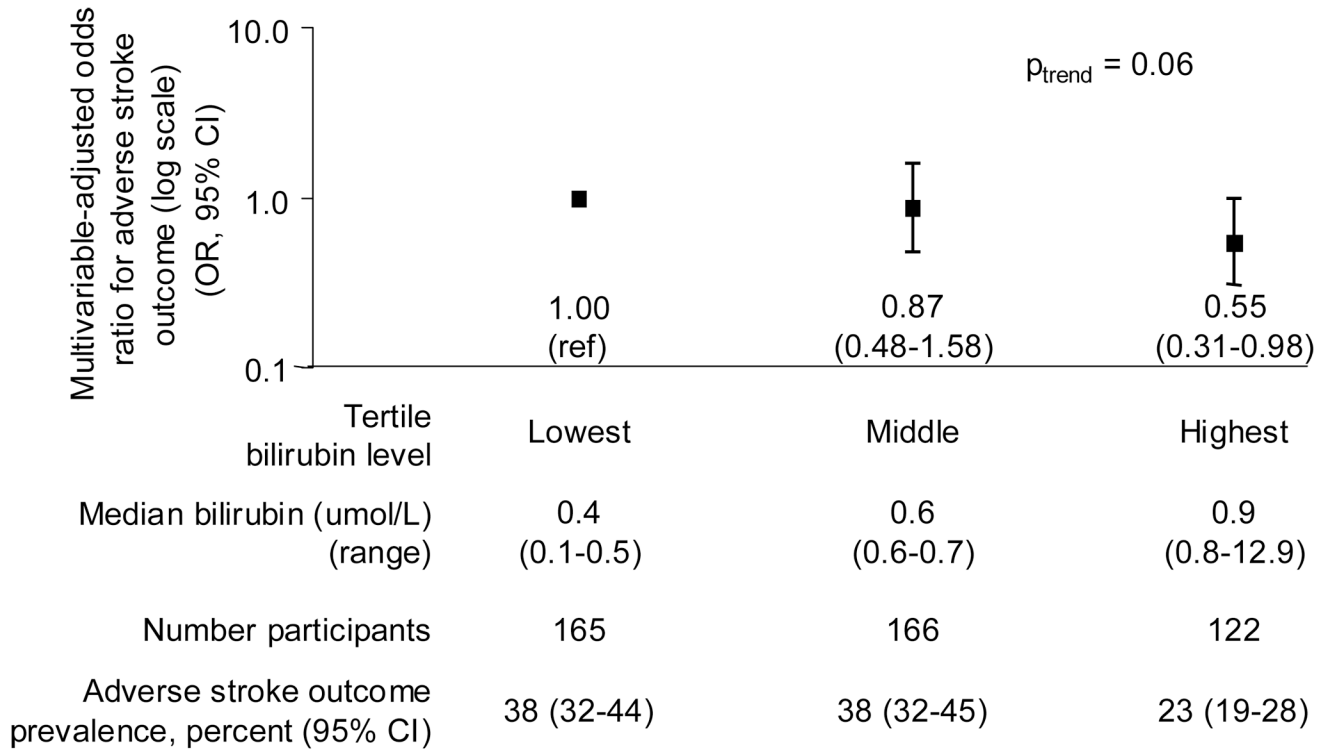

Figure 3. Multivariable-adjusted odds of an adverse stroke outcome among stroke survivors

Age, sex, race/ethnicity, smoking, hypertension, total:HDL cholesterol ratio, and diabetes were adjusted for. Odds ratios and 95% confidence intervals (CI) estimated by logistic regression. Y-axis is log scale. The adverse stroke outcome prevalence estimates are unadjusted. To convert bilirubin from umol/L to mg/dL, multiply by 0.058. National Health and Nutrition Examination Survey 1999–2004. OR : Odds ratio. CI : Confidence interval.

Table 1

Association of serum bilirubin and prevalent stroke with participant characteristics.

Characteristic	Frequency within study population*, mean (95% CI)	Serum total bilirubin level (umol/L)**, mean (95% CI)	Stroke prevalence (%), percentage (95% CI)
Age group (years)			
20–39	39.4 (37.8–40.1)	12.1 (11.8–12.5)	0.5 (0.3–0.8)
40–59	38.3 (37.0–39.6)	12.0 (11.8–12.1)	1.7 (1.3–2.3)
60 or over	22.3 (21.2–23.5)	12.1 (11.8–12.5)	7.3 (6.4–8.3)
Gender			
Male	48.1 (47.4–48.9)	13.7 (13.3–13.9)	2.1 (1.8–2.5)
Female	51.9 (51.1–52.6)	10.6 (10.4–10.8)	2.8 (2.3–3.4)
Race/ethnicity			
Non-Hispanic White	72.6 (69.1–75.9)	12.3 (12.0–12.5)	2.6 (2.2–3.1)
Non-Hispanic Black	10.5 (8.7–12.7)	11.1 (10.6–11.3)	2.9 (2.3–3.7)
Mexican American	7.3 (5.7–9.2)	12.0 (11.6–12.3)	1.2 (0.8–1.7)
Other	9.6 (7.3–12.4)	11.8 (11.1–12.7)	1.9 (1.1–3.3)
Hypertension			
No	65.1 (63.5–66.6)	12.1 (12.0–12.5)	0.9 (0.6–1.2)
Yes	34.9 (33.4–36.5)	12.0 (11.6–12.1)	5.5 (4.8–6.3)
Diabetes mellitus			
No	91.4 (90.7–92.1)	12.1 (11.8–12.3)	2.0 (1.7–2.4)
Yes	8.6 (7.8–9.2)	11.6 (11.3–12.0)	7.5 (6.0–9.2)
Hypercholesterolemia			
No	64.3 (63.0–65.5)	12.3 (12.0–12.5)	1.7 (1.4–2.1)
Yes	35.3 (34.1–36.5)	11.6 (11.5–12.0)	3.9 (3.2–4.7)
Smoking status			
Never	49.1 (47.3–50.9)	12.3 (12.0–12.7)	2.2 (1.8–2.8)
Former	27.3 (25.8–28.8)	12.5 (12.3–12.8)	3.0 (2.5–3.8)
Active	23.6 (22.0–25.3)	11.1 (10.6–11.3)	2.4 (1.7–3.2)
Stroke			
No	97.5 (97.1–97.8)	12.1 (11.8–12.3)	n/a
Yes	2.5 (2.2–2.9)	10.8 (10.3–11.3)	n/a

* Analytical sample of 13,214 adult participants from the National Health and Nutrition Examination Survey, 1999–2004.

** To convert bilirubin from umol/L to mg/dL, multiply by 0.058.

Table 2

Characteristics of stroke survivors by adverse stroke outcome.

Characteristic	Participants with stroke history, without an adverse stroke outcome (n = 315) mean (95% CI)	Participants with stroke history, with an adverse stroke outcome (n = 138) mean (95% CI)
Age group (years)		
20–39	8.4 (2.1–5.0)	7.4 (2.9–17.7)
40–59	29.0 (22.9–35.9)	19.0 (11.5–29.8)
60 or over	62.6 (55.7–69.0)	73.6 (60.4–83.7)
Gender		
Male	37.7 (31.9–44.0)	49.7 (37.3–62.0)
Female	62.3 (56.0–68.2)	50.4 (38.0–62.7)
Race/ethnicity		
Non-Hispanic White	78.3 (71.2–84.1)	72.0 (61.5–80.5)
Non-Hispanic Black	10.1 (6.8–14.5)	19.4 (13.3–27.4)
Mexican American	3.3 (1.8–6.1)	3.9 (2.0–7.6)
Other	8.3 (4.3–15.6)	4.8 (1.2–16.9)
Hypertension		
No	25.3 (19.8–31.9)	16.9 (9.9–27.4)
Yes	74.7 (68.2–80.2)	83.1 (72.6–90.1)
Diabetes mellitus		
No	76.8 (69.5–82.7)	67.3 (56.9–76.3)
Yes	23.2 (17.3–30.5)	32.7 (23.7–43.1)
Hypercholesterolemia		
No	45.2 (37.8–52.8)	42.8 (33.6–52.6)
Yes	54.8 (47.2–62.2)	57.2 (47.4–66.4)
Smoking status		
Never	43.2 (34.4–52.4)	46.7 (36.7–56.9)
Former	33.5 (26.2–41.8)	33.5 (24.2–44.2)
Active	23.3 (17.3–30.7)	19.9 (11.9–31.3)