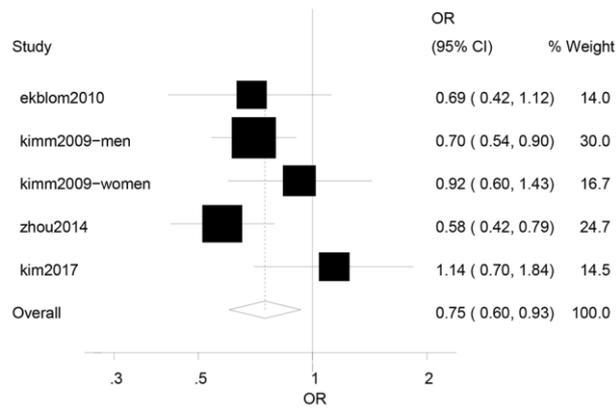


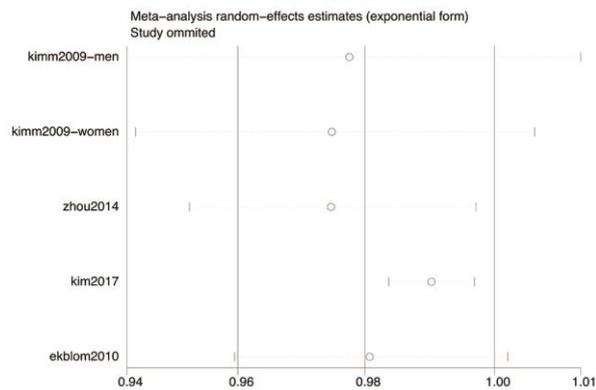
Searching strategy

The following searching strategy, using a combination of controlled vocabulary (MeSH) and free text terms, was used for PubMed, and was modified for the other databases searched.

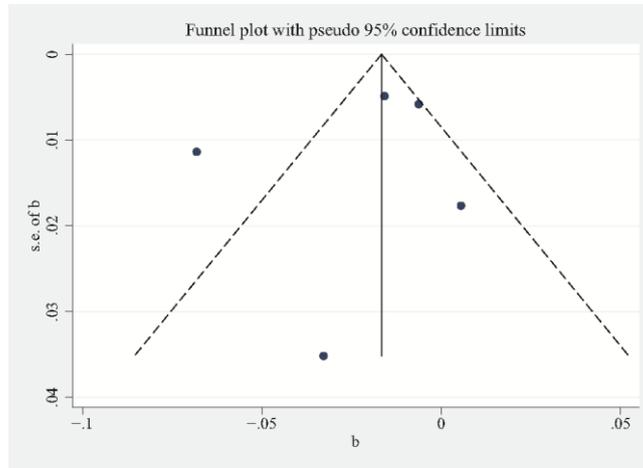
1. "stroke" [MeSH Terms]
2. "cerebral infarction" [MeSH Terms]
3. "brain ischemia" [MeSH Terms]
4. stroke* OR (brain infarct*) OR (cerebral infarct*) OR (brain ischemia) OR (brain ischaemia) OR (cerebral ischemia) OR (cerebral ischaemia) OR (cerebrovascular accident*) OR cva OR (cerebrovascular disorder*) OR (cerebrovascular disease*) OR (brain embol*) OR (brain thromb*) OR (cerebral embol*) OR (cerebral thromb*) OR (intracerebral embol*) OR (intracerebral thromb*) OR (intracranial embol*) OR (intracranial thromb*) OR apoplexy OR ictus
5. "cerebrovascular disorders" [MeSH Terms]
6. "cerebral hemorrhage" [MeSH Terms]
7. "intracranial hemorrhages" [MeSH Terms]
8. (brain haemorrhage*) OR (brain hemorrhage*) OR (cerebral haemorrhage*) OR (cerebral hemorrhage*) OR (intracerebral haemorrhage*) OR (intracerebral hemorrhage*) OR (intracranial haemorrhage*) OR (intracranial hemorrhage*)
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10. (bilirubin [mh] OR (bilirubin* [tiab]))
11. 9 and 10
12. limit 11 to human
13. limit 12 to English



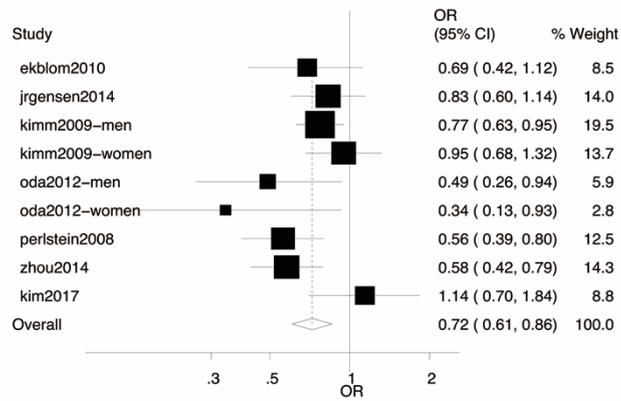
Supplementary Fig. I. Forest plot of the blood total bilirubin level (highest vs. lowest) and the risk of ischemic stroke. Squares indicate study-specific odds ratios; horizontal lines indicate 95% CIs; the diamond indicates the summary odds ratio estimate with its 95% CI.



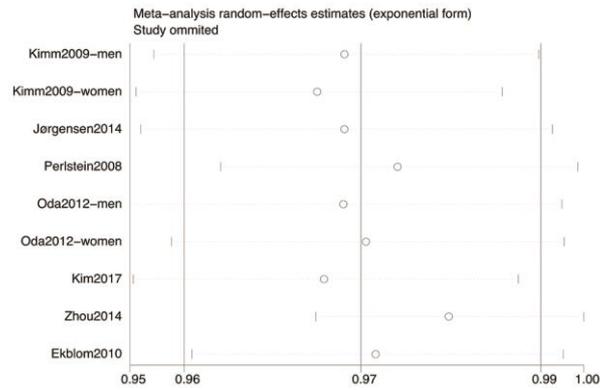
Supplementary Fig. II. The pooled OR of per 1 $\mu\text{mol/L}$ increment in the bilirubin level and the risk of ischemic stroke by omitting each single study among all included studies (Impact Analysis).



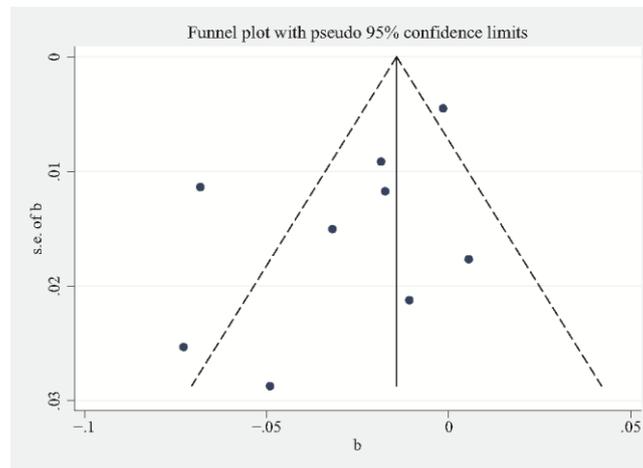
Supplementary Fig. III. Funnel plot of publication bias for ischemic stroke.



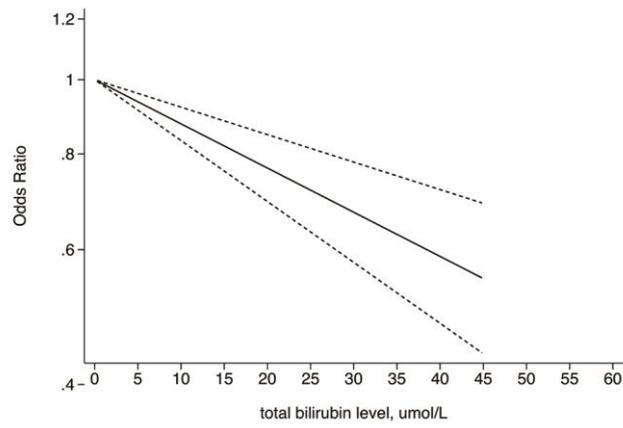
Supplementary Fig. IV. Forest plot of the circulating total bilirubin level (highest vs. lowest) and the risk of all types of stroke. Squares indicate study-specific odds ratios; horizontal lines indicate 95% CIs; the diamond indicates the summary odds ratio estimate with its 95% CI.



Supplementary Fig. V. The pooled OR of per 1 μ mol/L increment in the bilirubin levels and risk of all types of stroke by omitting each single study among all included studies (Impact Analysis).



Supplementary Fig. VI. Funnel plot of publication bias for all types of stroke.



Supplementary Fig. VII. Linear dose-response relationship analysis between the bilirubin level and the risk of all types of stroke. The solid and short dashed lines represent the estimated OR and its 95% CI (per 1 $\mu\text{mol/L}$ increment).

Supplementary Table I Risk of Bias Assessment

<i>Observational studies</i>	Bias due to confounding	Bias in participant selection	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Kim et al,2017	moderate risk	moderate risk	low risk	moderate risk	low risk	low risk	low risk	moderate risk
Zhou et al,2014	moderate risk	moderate risk	low risk	moderate risk	low risk	low risk	low risk	moderate risk
Jørgensen et al,2014	moderate risk	moderate risk	low risk	moderate risk	low risk	low risk	low risk	moderate risk
Oda and Kawai,2012	moderate risk	moderate risk	low risk	moderate risk	low risk	low risk	low risk	moderate risk
Ekblom et al,2010	moderate risk	moderate risk	low risk	moderate risk	low risk	low risk	low risk	moderate risk
Kimm et al,2009	moderate risk	moderate risk	low risk	moderate risk	low risk	low risk	low risk	moderate risk
Perlstein et al,2008	moderate risk	moderate risk	low risk	moderate risk	low risk	low risk	low risk	moderate risk

Risk of Bias in non-randomised studies-of interventions (ROBINS-I) tool was used for observational studies. Each domain was classified as low risk, moderate risk, serious risk, and critical risk or not interpretable. An overall bias assessment was then made using the same scale.

Supplementary Table II Subgroup analyses and meta-regression analyses of the circulating total bilirubin

level and the risk of ischemic stroke as well as dose-response analysis

subgroups	No. of studies	Odds ratio (95% CI)	I ² (%)	<i>P</i> for heterogeneity	<i>P</i> for heterogeneity (meta regression)
All studies	5	0.978(0.957,0.999)	84.3	<0.001	-
Gender					0.851
Male	2	0.984(0.974,0.993)	31.8	0.226	
Female	2	0.992(0.981,1.003)	53.1	0.144	
Study type					0.485
Cohort study	2	0.988(0.981,0.995)	36.0	0.211	
Case-control study	1	0.968(0.903,1.037)	-	-	
Cross-sectional study	2	0.968(0.901,1.040)	91.9	<0.001	
age					0.544
≥60	2	0.968(0.901,1.040)	91.9	<0.001	
<60	3	0.988(0.981,0.995)	0.0	0.384	
Sample size					0.468
≥2000	2	0.988(0.981,0.995)	36.0	0.211	
<2000	3	0.968(0.917,1.022)	83.9	0.002	

Supplementary Table III The pooled OR of 1 $\mu\text{mol/L}$ increment in the bilirubin level and the risk of ischemic stroke by omitting each single study among all included studies (Impact Analysis).

Study omitted	e ^{coef.}	[95% Conf.	Interval]
Kimm2009-men	.97519296	.9384383	1.0133871
Kimm2009-women	.97227961	.93990737	1.0057669
Zhou2014	.97215909	.94879752	.99609584
Kim2017	.98872912	.98169887	.99580973
Ekblom2010	.9785192	.95621318	1.0013456
Combined	.9777249	.95677198	.99913668

Supplementary Table IV Subgroup analyses and meta-regression analyses of the circulating total

bilirubin level and the risk of all types of stroke, dose-response analysis

subgroups	No. of studies	Odds ratio (95% CI)	I ² (%)	P for heterogeneity	P for heterogeneity (meta regression)
All studies	9	0.974(0.956,0.992)	80.1	<0.001	-
Gender					0.834
Male	3	0.982(0.966,0.998)	0.0	0.863	
Female	3	0.981(0.951,1.012)	65.7	0.054	
Study type					0.192
Cohort study	3	0.996(0.988,1.004)	0.0	0.424	
Case-control study	1	0.952(0.900,1.007)	-	-	
Cross-sectional study	5	0.965(0.939,0.992)	79.2	0.001	
age					0.868
≥60	3	0.972(0.932,1.015)	87.5	<0.001	
<60	6	0.978(0.960,0.996)	65.5	0.013	
Sample size					0.415
≥2000	6	0.982(0.967,0.997)	61.7	0.023	
<2000	3	0.963(0.915,1.014)	83.8	0.002	

Supplementary Table V The pooled OR of 1 μ mol/L increment in the bilirubin level and the risk of all

stroke by omitting each single study among all included studies (Impact Analysis). OR: odds ratios.

Study omitted	e ^{coef.}	[95% Conf.	Interval]
Kimm2009-men	.97206402	.95282364	.9916929
Kimm2009-women	.96933383	.95103282	.98798704
Jørgensen2014	.97207254	.95151573	.9930734
Perlstein2008	.97742462	.9595657	.9956159
Oda2012-men	.97196746	.95040876	.99401516
Oda2012-women	.9742344	.95462048	.99425125
Kim2017	.96999681	.9507671	.98961538
Zhou2014	.98260623	.96917135	.99622732
Ekblom2010	.97521889	.95664972	.99414849
Combined	.97372218	.95587315	.9919045