Supplementary Table 9. Effect modification by different types of bilirubin and corresponding cut-off concentrations for presence of effect modification

Modifying factor	Outcome	Factor	n	*P* for interaction	Cut-off concentrations (μmol/L)
TBIL	Presence of CSVD (Wardlaw)*	Hypertension	3,061	0.041	22.4
	Presence of CSVD (Rothwell)*	Hypertension	3,061	0.022	22.3
	Total CSVD burden (Wardlaw)†	Hypertension	3,061	0.278	
	Modified total CSVD burden (Rothwell)†	Hypertension	3,061	0.056	
IBIL	Presence of CSVD (Wardlaw)*	Hypertension	3,061	0.014	13.8
	Presence of CSVD (Rothwell)*	Hypertension	3,061	0.004	13.8
	Total CSVD burden (Wardlaw)†	Hypertension	3,061	0.182	
	Modified total CSVD burden (Rothwell)†	Hypertension	3,061	0.028	15.2
DBIL	Presence of CSVD (Wardlaw)*	Hypertension	3,061	0.081	
	Presence of CSVD (Rothwell)*	Hypertension	3,061	0.101	
	Total CSVD burden (Wardlaw)†	Hypertension	3,061	0.503	
	Modified total CSVD burden (Rothwell)†	Hypertension	3,061	0.223	

Results of presence of CSVD were estimated by binary logistic regression model. Results of CSVD burden were estimated by ordinary least squares regression model. The product term of hypertension state and bilirubin concentrations was included in the model to assess the effect modification by bilirubin. Cut-off concentrations were available when there was statistically significant effect modification (*P* for interaction <0.05). All models were adjusted for age, sex, body mass index, current smoking, current drinking, diabetes, dyslipidemia, antihypertensive medication, antiplatelet medication, anticoagulant medication, and alanine aminotransferase and aspartate aminotransferase levels.

TBIL, total bilirubin; IBIL, indirect bilirubin; DBIL, direct bilirubin; CSVD, cerebral small vessel disease.

*Presence of CSVD was defined as total CSVD or modified total CSVD burden scores ≥1; †Total and modified total CSVD burdens were classified as grade 0 (total or modified total CSVD burden score 0), grade 1 (total or modified total CSVD burden score 1), grade 2 (total or modified total CSVD burden score 2–3), or grade 3 (total or modified total CSVD burden score ≥4).

Supplementary Table 10. Effect modification by TBIL in participants stratified by identified cut-off concentrations from the Johnson–Neyman analyses

Outcome	Group	N	n (%)	Adj. OR (95% CI)	*P*	*P* for interaction
Presence of CSVD (Wardlaw)*	Participants with TBIL ≤22.4 μmol/L					
	No hypertension	1,542	324 (21.0)	Ref.		0.077
	Hypertension	1,188	492 (41.4)	1.65 (1.29–2.11)	<0.001	
	Participants with TBIL >22.4 μmol/L					
	No hypertension	202	63 (31.2)	Ref.		
	Hypertension	129	55 (42.6)	1.21 (0.60–2.46)	0.596	
Presence of CSVD (Rothwell)*	Participants with TBIL ≤22.3 μmol/L					
	No hypertension	1,538	480 (31.2)	Ref.		0.053
	Hypertension	1,188	643 (54.1)	1.72 (1.36–2.16)	<0.001	
	Participants with TBIL >22.3 μmol/L					
	No hypertension	206	82 (39.8)	Ref.		
	Hypertension	129	66 (51.2)	0.86 (0.43–1.70)	0.659	

All models were adjusted for age, sex, body mass index, current smoking, current drinking, diabetes, dyslipidemia, antihypertensive medication, antiplatelet medication, anticoagulant medication, and alanine aminotransferase and aspartate aminotransferase levels. The product term of hypertension state and TBIL group was included in the model to assess the effect modification by TBIL.

TBIL, total bilirubin; Adj., adjust; OR, odds ratio; CI, confidence interval; CSVD, cerebral small vessel disease; Ref., reference.

*Presence of CSVD was defined as total CSVD or modified total CSVD burden scores ≥1.