

Supplementary Table SI. Mendelian randomization estimates for the association between SGLT2 inhibition, serum metabolites, and kidney stone risk. **(A)** Effect of SGLT2 inhibition on kidney stone risk (univariable MR, β_3). **(B)** Effect of SGLT2 inhibition on eight candidate serum metabolites (univariable MR, β_1). **(C)** Effect of metabolites significantly associated with SGLT2 inhibition on kidney stone risk, adjusted for SGLT2 inhibition (multivariable MR, β_2)

Exposure / Mediator	Outcome	Method	β (95% CI)	P	Q statistic	P heterogeneity	Egger intercept	P intercept
A. SGLT2 inhibition → kidney stone risk (univariable MR; β ₃)								
SGLT2 inhibition	Kidney stone (meta-analysis of UK Biobank & FinnGen)	MR Egger	0.038 (-0.028, 0.103)	0.297	3.514	0.834	-0.020	0.199
		Weighted median	-0.004 (-0.033, 0.025)	0.780	-	-		
		Inverse variance weighted (fixed effects)	-0.007 (-0.029, 0.015)	0.519	5.522	0.701		
		Simple mode	-0.023 (-0.065, 0.019)	0.319	-	-		
		Weighted mode	-0.002 (-0.037, 0.034)	0.930	-	-		
B. SGLT2 inhibition → serum metabolites (univariable MR; β ₁)								
SGLT2 inhibition → Urate		MR Egger	-0.003 (-0.018, 0.012)	0.721	33.173	<0.0001	0.004	0.238
		Weighted median	0.006 (0.000, 0.012)	0.057	-	-		
		<i>Inverse variance weighted (multiplicative random effects)</i>	<i>0.006 (0.000, 0.012)</i>	<i>0.038</i>	<i>38.403</i>	<i>6.69E-05</i>		
		Simple mode	0.004 (-0.008, 0.015)	0.539	-	-		
		Weighted mode	0.005 (-0.005, 0.016)	0.333	-	-		
SGLT2 inhibition → Phosphate		MR Egger	0.000 (-0.015, 0.016)	0.962	5.951	0.203	-0.004	0.274
		<i>Weighted median</i>	<i>-0.013 (-0.020, -0.005)</i>	<i>0.001</i>	-	-		
		<i>Inverse variance weighted (fixed effects)</i>	<i>-0.009 (-0.016, -0.002)</i>	<i>0.011</i>	<i>8.335</i>	<i>0.139</i>		
		Simple mode	-0.014 (-0.026, -0.002)	0.078	-	-		
		<i>Weighted mode</i>	<i>-0.013 (-0.022, -0.004)</i>	<i>0.039</i>	-	-		
SGLT2 inhibition → Calcium		MR Egger	-0.003 (-0.016, 0.010)	0.669	15.486	0.115	0.003	0.291
		<i>Weighted median</i>	<i>0.006 (0.001, 0.012)</i>	<i>0.030</i>	-	-		
		Inverse variance weighted (fixed effects)	0.004 (-0.001, 0.009)	0.119	17.407	0.096		
		Simple mode	0.007 (-0.002, 0.015)	0.161	-	-		
		Weighted mode	0.006 (-0.001, 0.013)	0.115	-	-		
SGLT2 inhibition → Citrate		MR Egger	0.001 (-0.019, 0.022)	0.893	14.359	0.157	0.002	0.648

Exposure / Mediator	Outcome	Method	β (95% CI)	P	Q statistic	P heterogeneity	Egger intercept	P intercept
		Weighted median	0.004 (-0.005, 0.013)	0.373	-	-		
		Inverse variance weighted (fixed effects)	0.006 (-0.001, 0.014)	0.113	14.677	0.198		
		Simple mode	-0.004 (-0.018, 0.010)	0.571	-	-		
		Weighted mode	0.002 (-0.009, 0.013)	0.737	-	-		
	SGLT2 inhibition → Sodium	MR Egger	-0.003 (-0.031, 0.024)	0.834	1.771	0.880	0.002	0.659
		Weighted median	0.004 (-0.008, 0.017)	0.464	-	-		
		Inverse variance weighted (fixed effects)	0.003 (-0.006, 0.013)	0.523	1.991	0.921		
		Simple mode	0.006 (-0.010, 0.023)	0.458	-	-		
		Weighted mode	0.006 (-0.011, 0.024)	0.482	-	-		
	SGLT2 inhibition → Oxalate	MR Egger	0.025 (-0.040, 0.091)	0.467	9.124	0.520	-0.008	0.611
		Weighted median	0.026 (-0.006, 0.058)	0.112	-	-		
		Inverse variance weighted (fixed effects)	0.009 (-0.016, 0.034)	0.475	9.399	0.585		
		Simple mode	0.027 (-0.018, 0.072)	0.265	-	-		
		Weighted mode	0.027 (-0.011, 0.065)	0.186	-	-		
	SGLT2 inhibition → Creatinine	MR Egger	0.001 (-0.019, 0.022)	0.906	11.780	0.019	-0.002	0.751
		Weighted median	0.004 (-0.004, 0.011)	0.330	-	-		
		Inverse variance weighted (multiplicative random effects)	-0.002 (-0.010, 0.006)	0.623	12.119	0.033		
		Simple mode	0.003 (-0.009, 0.015)	0.629	-	-		
		Weighted mode	0.004 (-0.003, 0.011)	0.311	-	-		
	SGLT2 inhibition → Xanthine	MR Egger	-0.003 (-0.024, 0.019)	0.806	0.603	0.896	0.001	0.758
		Weighted median	0.002 (-0.007, 0.010)	0.722	-	-		
		Inverse variance weighted (fixed effects)	0.001 (-0.007, 0.008)	0.894	0.717	0.949		
		Simple mode	0.002 (-0.009, 0.014)	0.706	-	-		
		Weighted mode	0.002 (-0.009, 0.013)	0.739	-	-		
	C. Metabolites → kidney stone risk, adjusted for SGLT2 inhibition (multivariable MR; β ₂)							

Exposure / Mediator	Outcome	Method	β (95% CI)	<i>P</i>	Q statistic	<i>P</i> heterogeneity	Egger intercept	<i>P</i> intercept
Urate	Kidney stone (meta-analysis of UK Biobank & FinnGen)	MR Egger	0.285 (-0.244, 0.815)	0.291	152.629	0.000	0.003	0.705
		<i>Inverse variance weighted (multiplicative random effects)</i>	<i>0.372 (0.096, 0.648)</i>	<i>0.008</i>	<i>153.162</i>	<i>0.000</i>		
		<i>Weighted median</i>	<i>0.287 (0.047, 0.527)</i>	<i>0.019</i>	<i>-</i>	<i>-</i>		
Phosphate	Kidney stone (meta-analysis of UK Biobank & FinnGen)	MR Egger	-0.363 (-4.191, 3.465)	0.853	5.001	0.082	0.013	0.731
		Inverse variance weighted (fixed effects)	0.282 (-0.614, 1.177)	0.538	5.296	0.151		
		Weighted median	-0.279 (-1.641, 1.084)	0.689	-	-		

Bold italic indicates statistical significance ($P < 0.05$). Q statistic = Cochran's Q heterogeneity statistic; *P* heterogeneity = *P*-value for Cochran's Q test; Egger intercept and *P* intercept = MR-Egger intercept test for directional pleiotropy. β_1 = effect of SGLT2 inhibition on the metabolite; β_2 = effect of the metabolite on kidney stone risk, adjusted for SGLT2 inhibition; β_3 = direct effect of SGLT2 inhibition on kidney stone risk.