

Sodium-glucose cotransporter 2 inhibitors and kidney stones: a Mendelian randomisation study

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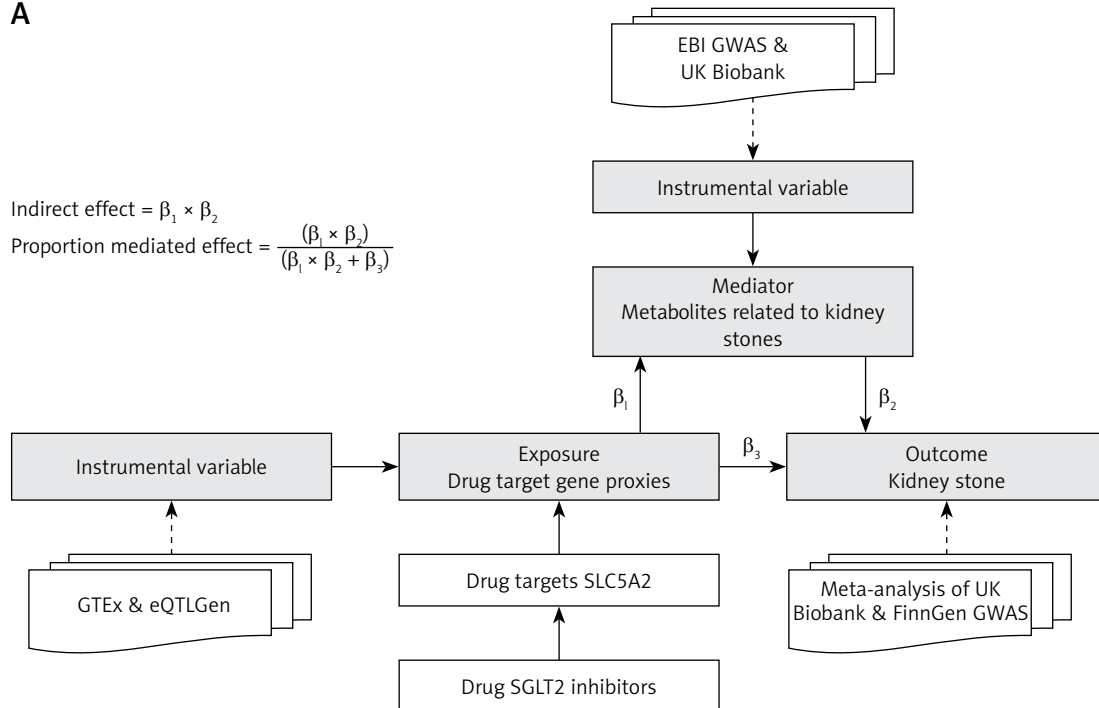
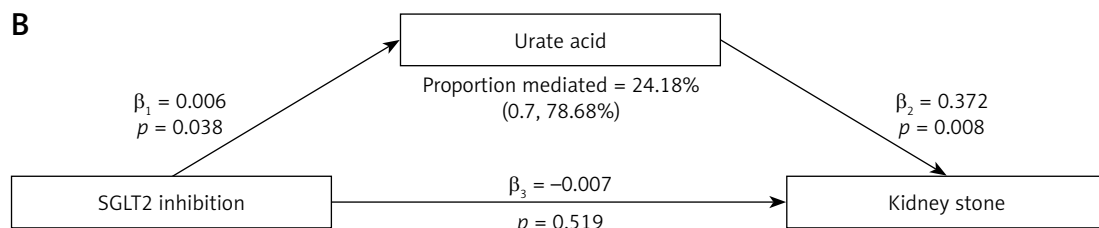
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Renal stone disease affects a large proportion of the population worldwide and imposes a considerable burden on healthcare systems [1]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucose-lowering agents with established cardiorenal benefits [2] now widely used across the type 2 diabetes population [3], have been proposed to reduce the risk of nephrolithiasis. Observational cohorts in patients with type 2 diabetes reported lower stone incidence among SGLT2 inhibitor users than among users of other glucose-lowering drugs [4, 5], but a meta-analysis of randomised trials found no significant association [6]. These conflicting findings largely derive from retrospective, diabetes-only cohorts relying on adverse-event reporting rather than confirmed diagnoses, so the causal relationship remains unclear. We therefore applied a two-step Mendelian randomisation (MR) approach, which is less prone to confounding and reverse causation than observational designs [7], to test whether genetically proxied SGLT2 inhibition causally affects kidney stone risk, and whether such an effect is mediated by serum metabolites implicated in stone formation.

Methods. Study design. MR relies on three core assumptions: genetic instruments must be robustly associated with the exposure, independent of confounders, and affect the outcome only through the exposure (no horizontal pleiotropy) [7], an approach increasingly applied across disease areas [8]. We performed a two-step MR analysis: SGLT2 inhibition (exposure) was first assessed for its effect on eight candidate serum metabolites (mediators); the effect of the significant mediators on kidney stone risk (outcome) was then estimated using multivariable MR adjusting for SGLT2 inhibition, and the indirect effect was calculated with the product-of-coefficients method [9]. Genetic proxies for SGLT2 inhibition were derived from single nucleotide polymorphisms (SNPs) associated with expression of the drug-target gene SLC5A2 (from GTEx and the eQTLGen Consortium) that were also significantly correlated with glycated haemoglobin (HbA1c) levels in 344,182 non-diabetic UK Biobank participants. Twelve independent SNPs were retained as instruments, all with F-statistics above 11, well above the conventional threshold for weak instruments [10]. The overall study design is summarised in Figure 1 A.

Data sources. Kidney stone outcomes were obtained from the UK Biobank (5530 cases/415,001 controls), FinnGen release R10 (10,556

A**B**

Calculated by the product coefficient method, the indirect effect of SGLT2 inhibition on the risk of kidney stones through urate was odds ratio = 1.0022 (95% CI [1.0001, 1.0061]), with the mediating effect accounting for 24.2% of the total effect (95% CI [0.7%, 78.7%]).

Figure 1. Overview of the study design and main findings. **A** – Overview of the basic assumptions and main design of the two-step Mendelian randomisation (MR) study. **B** – Summary of the mediation MR analysis showing the effect of SGLT2 inhibition on kidney stone risk through serum urate, using the meta-GWAS of the UK Biobank and FinnGen cohorts

cases/400,681 controls), and a fixed-effects meta-analysis of both. Eight serum metabolites previously linked to stone formation—urate, citrate, sodium, calcium, oxalate, phosphate, creatinine, and xanthine—were obtained from the IEU OpenGWAS project and evaluated as candidate mediators.

Statistical analysis. Inverse-variance weighting (IVW) served as the primary analysis, supported by MR-Egger, weighted median, simple mode, and weighted mode estimators [11, 12]; heterogeneity was assessed with Cochran's Q and pleiotropy with the MR-Egger intercept. Analyses used the TwoSampleMR R package and followed STROBE-MR reporting guidelines [13].

Results. Genetically proxied SGLT2 inhibition showed no direct association with kidney stone risk ($\beta = -0.007$, 95% CI: $-0.029, 0.015$, $p = 0.519$; Table I, Supplementary Table SI A), a null result

that was consistent across the UK Biobank, FinnGen, and meta-analysis outcomes and across all five MR methods. Among the eight candidate mediators, SGLT2 inhibition was significantly associated with urate ($\beta = 0.006$, 95% CI: $0.000-0.012$, $p = 0.038$) and phosphate ($\beta = -0.009$, 95% CI: -0.016 to -0.002 , $p = 0.011$), with no evidence of directional pleiotropy for either (MR-Egger intercept $p = 0.238$ and 0.274 , respectively; Table I, Supplementary Table SI B). In multivariable MR adjusting for SGLT2 inhibition, only urate remained significantly associated with kidney stone risk ($\beta = 0.372$, 95% CI: $0.096-0.648$, $p = 0.008$), although with significant heterogeneity ($Q = 153$, $p < 0.001$; Table I, Supplementary Table SI C). The indirect effect of SGLT2 inhibition on kidney stones mediated through urate corresponded to an odds ratio of 1.0022 (95% CI: $1.0001-1.0061$),

Table 1. Primary Mendelian randomisation estimates for the three key associations between SGLT2 inhibition, serum urate, and kidney stone risk (inverse-variance-weighted method)

Association	β (95% CI)	P-value
SGLT2 inhibition → kidney stones	−0.007 (−0.029, 0.015)	0.519
SGLT2 inhibition → urate	0.006 (0.000, 0.012)	0.038
Urate → kidney stones (adjusted for SGLT2 inhibition)	0.372 (0.096, 0.648)	0.008

Full results for all eight candidate metabolites, all five MR methods, and heterogeneity/pleiotropy statistics are provided in Supplementary Table S1.

accounting for 24.2% (95% CI: 0.7–78.7%) of the total effect (Figure 1 B). Because the total effect of SGLT2 inhibition on kidney stone risk was not statistically significant, this mediation proportion should be interpreted with caution and does not represent a clinically meaningful pathway.

Discussion. Our findings indicate that genetic variation in the SGLT2 inhibition target is not directly associated with kidney stone risk, consistent with a prior meta-analysis of randomised trials [6]. Although SGLT2 inhibition showed statistically significant associations with urate and phosphate, and urate in turn showed a weak positive association with stone risk, the magnitude of these effects was small and unlikely to be clinically meaningful. This suggests that the lower nephrolithiasis incidence reported among SGLT2 inhibitor users in some observational cohorts [4, 5] may be attributable to other mechanisms, such as improved glycaemic control or increased urine volume, rather than a direct pharmacological effect on stone-related metabolites. Unlike previous observational studies, which were almost entirely confined to diabetic cohorts [4, 5, 14], our genetic instruments are valid regardless of diabetes status – a key advantage that partially addresses the evidence gap left by non-diabetic populations, given that SGLT2 inhibitor trials remain largely restricted to diabetic patients. Similar reductions in nephrolithiasis risk have been reported with empagliflozin in trial-based analyses [15], reinforcing that pharmacological benefits observed in diabetic cohorts may not reflect the direct causal pathway suggested by our null genetic findings. A protein-protein interaction analysis (STRING database) [16] suggested a plausible, if minor, biological connection underlying the modest urate signal, consistent with our overall conclusion that SGLT2 inhibition has no clinically meaningful direct effect on kidney stone risk.

This study has several limitations. We examined only eight metabolites with adequate GWAS coverage, and we were unable to assess other stone-relevant factors such as cystine or struvite, owing to a lack of well-powered GWAS data for these traits. Significant heterogeneity detected by Cochran's Q may still introduce residual bias despite our multiple sensitivity analyses, and, as with any MR study, our estimates reflect lifelong

genetic exposure rather than the pharmacological effect of initiating therapy in middle age, which may differ from lifelong exposure in both magnitude and clinical relevance. Kidney stone formation is also influenced by diet and fluid intake, modifiable factors that genetic instruments cannot capture and that could mask or amplify any pharmacological effect. Our analysis was also restricted to individuals of European ancestry, which may limit generalisability to other populations.

A further methodological strength of our study is that, because it relies on germline genetic variation rather than clinical exposure to the drug, it inherently includes both individuals with and without type 2 diabetes. This partially compensates for the fact that current SGLT2 inhibitor trials are conducted almost exclusively in diabetic patients, where hyperglycaemia itself is a competing driver of stone risk – by increasing urinary calcium excretion and lowering urinary pH [17, 18] – and may obscure any direct drug effect. The consistency of our null finding for the direct effect across three independent outcome sources (UK Biobank, FinnGen, and their meta-analysis) and five statistical methods further strengthens confidence in this result, even though the study cannot fully substitute for a randomised trial.

In conclusion, our two-step MR analysis found no evidence that SGLT2 inhibitors meaningfully reduce or increase kidney stone risk, either directly or through the examined metabolic pathways, and any urate-mediated effect appears too small to be clinically relevant. Dedicated prospective trials in both diabetic and non-diabetic populations are needed before SGLT2 inhibitors can be recommended as a preventive strategy for nephrolithiasis.

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Ethical approval

Not applicable. Publicly available, de-identified GWAS summary statistics were used; ethical approval and participant consent were obtained in the original studies.

Conflict of interest

The authors declare no conflict of interest.

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