Coffee and Caffeine Consumption and Risk of Kidney Stones: A Mendelian Randomization Study

Shuai Yuan and Susanna C. Larsson

Rationale & Objective: Coffee and caffeine consumption have been associated with a lower risk of kidney stones in observational studies. We conducted a Mendelian randomization study to assess the causal nature of these associations.

Study Design: Mendelian randomization analysis.

Setting & Participants: Independent genetic variants associated with coffee and caffeine consumption at the genome-wide significance level were selected from previously published meta-analyses as instrumental variables. Summary-level data for kidney stones were obtained from the UK Biobank study (6,536 cases and 388,508 noncases) and the FinnGen consortium (3,856 cases and 172,757 noncases).

Exposure: Genetically predicted coffee and caffeine consumption.

Outcome: Clinically diagnosed kidney stones.

Analytical Approach: Mendelian randomization methods were used to calculate causal esti-

mates. Estimates from the 2 sources were combined using the fixed-effects meta-analysis methods.

Results: Genetically predicted coffee and caffeine consumption was associated with a lower risk of kidney stones in the UK Biobank study, and the associations were directionally similar in the FinnGen consortium. The combined odds ratio of kidney stones was 0.60 (95% CI, 0.46-0.79; *P* < 0.001) per a genetically predicted 50% increase in coffee consumption and 0.81 (95% CI, 0.69-0.94; *P* = 0.005) per a genetically predicted 80-mg increase in caffeine consumption.

Limitations: Genetic influence on kidney stone risk via pathways not involving coffee or caffeine.

Conclusions: Using genetic data, this study provides evidence that higher coffee and caffeine consumption may cause a reduction in kidney stones.

Kidney stone disease is a common problem that afflicts up to around 15% of the population.[1] Habitual coffee[2-8] and caffeine[9] consumption have been associated with a reduced risk of kidney stones in a large

to determine the potential causal associations of coffee and caffeine consumption with risk of kidney stones.

Editorial, p. 3

---

body of observational studies. Nevertheless, whether these associations are causal has not been established due to the possibility of confounding in observational studies and the lack of data from randomized controlled trials.

Employing genetic variants as instrumental variables for an exposure (eg, coffee consumption), the Mendelian randomization design can strengthen the causal inference.[10] The approach can minimize residual confounding because genetic variants are randomly allocated at conception and thus generally unrelated to confounders, such as environmental and self-adopted factors.[10] The random allocation of effect allele in the Mendelian randomization design resembles the randomization process in randomized controlled trials. In addition, the method can diminish reverse causation because genetic variants used to proxy the effect of the exposure cannot be modified by the onset and progression of the outcome.[10] Here, we conducted a Mendelian randomization (MR) study

Methods

Study Design

MR analysis is an instrumental variable analysis with the use of genetic variants as instrumental variables.[11] There are 3 important assumptions of MR analysis (Fig 1). The first assumption is that the genetic variants proposed as instrumental variables should be robustly associated with the exposure; the second assumption indicates that the used genetic variants should not be associated with any confounders; and the third assumption is that the selected genetic variants should affect the risk of the outcome merely through the risk factor, not via alternative pathways.[10] The present study was based on publicly available summary-level data from large genome-wide association studies and consortia.

Genetic Instrument Selection

Fifteen single-nucleotide polymorphisms (SNPs) associated with coffee consumption at the genome-wide significance level ($P < 5 \times 10^{-8}$) were obtained from a meta-analysis of 4 genome-wide association studies (GWAS) on coffee consumption with up to 375,833 individuals of European ancestry (~89% from the UK Biobank study).[12]

PLAIN-LANGUAGE SUMMARY

This Mendelian randomization study based on genetic data from 2 large studies found evidence to support causal associations between higher coffee and caffeine consumption and lower risk of kidney stones. Along with previous traditional epidemiological data, these findings suggest that coffee and caffeine consumption may prevent kidney stone disease.

Twelve independent SNPs ($r^2 < 0.01$ and clump distance > 10,000 kb) were used as instrumental variables for coffee consumption. The effect sizes for the SNP-coffee associations were scaled to a 50% increase (eg, an increase from 1 cup to 1.5 cups). Two variants associated with caffeine consumption at $P < 5 \times 10^{-8}$ were used as instrumental variables for caffeine consumption from a meta-analysis of 6 GWAS including 9,876 individuals of European ancestry.[13] Summarized statistics (ie, beta coefficients and standard errors) for SNPs associated with caffeine consumption were derived from a GWAS on 4,460 women[14] and scaled to an 80-mg increase (equivalent to the caffeine dose from 1 cup of coffee). Caffeine consumption was measured from coffee, tea, and cola consumption via a self-reported questionnaire.[14] Selected SNPs explained around 0.5% and up to 1.3% phenotypic variance on average for coffee and caffeine consumption, respectively.[12,14] Detailed information on SNPs for coffee and caffeine consumption is shown in Table 1.

Data Source for Kidney and Ureteral Stones

Summary-level data for the associations of coffee- and caffeine-associated SNPs with kidney stones were derived from the UK Biobank study[15] and the FinnGen consortium.[16] In UK Biobank, cases with kidney stones were defined by the *International Classification of Diseases, 10th Revision* (ICD-10), Office of Population and Censuses Surveys, and self-reported operation codes. GWAS was performed on 6,536 cases and 388,508 controls of European ancestry with the adjustment for sex, age, and the genotyping platform.[17] In FinnGen, cases were defined by N20 in ICD-10 and 592 in ICD-8 and ICD-9. The fourth release of the FinnGen consortium data was used with 3,856 cases and 172,757 noncases after the removal of individuals with ambiguous gender, high genotype missingness (>5%), excess heterozygosity (±4 SD), and non-Finnish ancestry. Association tests had been adjusted for age, sex, genetic principal components, and genotyping batch. Individuals who had withdrawn consent were excluded in both data sources.

Statistical Analysis

The inverse-variance weighted (IVW) method was used as the main statistical model.[18] We used the IVW with random effects method to estimate the associations for genetically predicted coffee consumption and the IVW fixed-effects method (for analysis with <3 SNPs) to estimate the associations for genetically predicted caffeine consumption. The causal estimates were calculated by meta-analyzing SNP-specific Wald ratio estimates (ie, the beta coefficient for the effect of the SNP on the outcome divided by the beta coefficient for the effect of the SNP on the exposure) using a random- or fixed-effects inverse variance method that weights each ratio by its standard error.[11] The standard error of the ratio estimate is estimated using the delta method.[18] Estimates from the UK Biobank and FinnGen were combined using the fixed-effect meta-analysis method.

Three sensitivity analyses, including the weighted median,[19] MR-Egger[20] and MR-PRESSO[21] approaches, were performed. Assuming that at least 50% of the SNPs are valid, the weighted median method can generate consistent causal estimates.[19] The MR-Egger regression can detect and correct for possible pleiotropy, and the P value of the intercept > 0.05 indicates no horizontal pleiotropic effects.[20] The MR-PRESSO method can detect outliers and provide a causal estimate after the removal of corresponding outliers.[21] The F statistic was calculated to measure the strength of instrument in the analyses in the UK Biobank study given a large sample overlap between the exposure and outcome data.[22] Cochrane Q value was used to assess the heterogeneity among estimates of SNPs in each analysis. All analyses were 2-sided and performed using the TwoSampleMR[23] and MR-PRESSO[21] packages in R software (version 4.0.2).
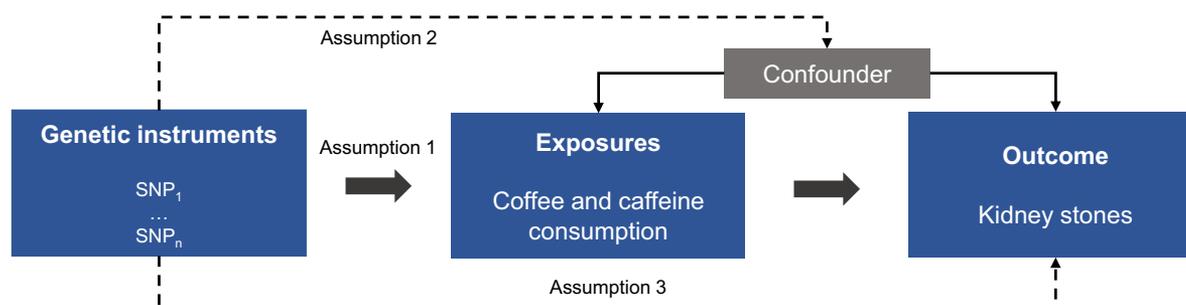

Figure 1. Study design overview. Abbreviation: SNP, single-nucleotide polymorphism.

Table 1. Associations of Single-Nucleotide Polymorphisms With Coffee or Caffeine Consumption and Kidney Stones

SNP	Nearby Gene	EA	NEA	EAF	Coffee or Caffeine Consumption			Kidney Stones in UKBB			Kidney Stones in FinnGen		
					Beta	SE	P	Beta	SE	P	Beta	SE	P
Coffee consumption													
rs2472297	CYP1A1/2	T	C	0.27	4.540	0.170	5.19×10^{-155}	−0.025	0.019	0.2	−0.015	0.028	0.6
rs4410790	AHR	C	T	0.63	3.940	0.150	5.59×10^{-141}	−0.032	0.018	0.07	−0.049	0.025	0.05
rs1057868	POR	T	C	0.29	1.970	0.160	5.26×10^{-33}	−0.025	0.019	0.2	0.014	0.024	0.6
rs73073176	LOC101927630	C	T	0.87	2.310	0.220	5.56×10^{-25}	−0.065	0.025	0.01	−0.005	0.042	0.9
rs1260326	GCKR	C	T	0.61	1.360	0.150	2.62×10^{-19}	−0.069	0.017	<0.001	−0.081	0.025	0.001
rs34060476	MLXIPL	G	A	0.13	1.890	0.220	5.06×10^{-18}	−0.024	0.025	0.3	0.079	0.035	0.02
rs66723169	MC4R	A	C	0.23	1.470	0.180	9.88×10^{-17}	−0.011	0.020	0.6	0.016	0.031	0.6
rs10865548	TMEM18	G	A	0.83	1.540	0.190	4.46×10^{-15}	−0.021	0.023	0.4	−0.080	0.032	0.01
rs2330783	SPECC1L-ADORA2A	G	T	0.99	4.530	0.630	1.57×10^{-12}	−0.158	0.073	0.03	−0.208	0.142	0.1
rs597045	OR8U8	A	T	0.69	1.070	0.160	6.62×10^{-11}	0.006	0.019	0.7	−0.021	0.027	0.4
rs574367	SEC16B	T	G	0.21	1.050	0.180	8.06×10^{-09}	0.013	0.021	0.6	−0.033	0.031	0.3
rs1956218	AKAP6	G	A	0.56	0.820	0.150	3.62×10^{-08}	−0.009	0.017	0.6	−0.022	0.024	0.4
Caffeine consumption													
rs4410790	AHR	C	T	0.62	0.150	0.017	2.36×10^{-19}	−0.021	0.018	0.2	−0.049	0.025	0.05
rs2470893	CYP1A1	T	C	0.31	0.120	0.016	5.15×10^{-14}	−0.032	0.018	0.07	−0.018	0.027	0.5

Abbreviations: EA, effect allele; EAF, effect allele frequency; NEA, noneffect allele; SE, standard error; SNP, single-nucleotide polymorphism.

Ethics Approval

All studies included in the GWAS cited here were approved by a relevant review board. The present MR analyses were approved by the Swedish Ethical Review Authority (2019-02793).

Results

The F statistic was 159 for the association for coffee consumption in the UK Biobank. Genetically predicted coffee and caffeine consumption was inversely associated with a risk of kidney stones in the UK Biobank study, and the associations were directionally similar in the FinnGen consortium (Fig 2). After meta-analysis of the 2 data sources, the odds ratio of kidney stone disease was 0.57 (95% CI, 0.39-0.82; P = 0.003) per genetically predicted 50% greater coffee consumption and 0.86 (95% CI, 0.77-0.96; P = 0.008) per genetically predicted 80 mg greater caffeine consumption. The results for coffee consumption in relation to kidney stones remained consistent in sensitivity analyses (Table 2). We detected mild heterogeneity but no evidence of pleiotropy in the MR-Egger regression (P for the intercept > 0.2). MR-PRESSO analyses detected 2 outliers in the FinnGen consortium, respectively. The association remained after outlier removal (Table 2).

Discussion

The present MR study revealed inverse associations of genetically predicted coffee and caffeine consumption with risk of kidney stones in a combined sample of 7,396 cases and 530,411 noncases, which supported findings from most but not all observational studies.[2-5,7,9] In a recent systematic review, large-scale, population-based studies found that coffee consumption was associated with a lower risk of urinary stones, with similar associations for caffeinated and decaffeinated coffee consumption.[7] Caffeine intake showed an independent association with a lower risk of incident kidney stones in an analysis including 217,883 individuals from 3 studies.[9] Furthermore, a cohort study including 194,095 participants reported an approximately 26% lower risk of developing kidney stones in individuals who consumed ≥1 serving per day of caffeinated coffee compared with those who consumed <1 serving per week.[8]

However, in a case-control study including 39 patients with calcium stones, caffeine intake showed a positive association with calcium oxalate stone formation.[24] A cross-sectional study in US adults also found caffeine intake mostly derived from coffee consumption was linearly associated with an increased risk of recurrent kidney stones.[25] The discrepancy across these studies might be caused by residual confounding, such as coffee-correlated traits and recall bias.

There are several underlying mechanisms supporting inverse associations of coffee and caffeine consumption with kidney stones. Caffeine exerts diuretic properties by adenosine receptors in the kidney.[26] Adequately compensated by water intake, the caffeine contained in coffee beverages results in an increase in urine flow, which represents an important protective factor against the development of kidney stones. Caffeine can also reduce calcium oxalate crystal adhesion on the apical surface of renal tubular epithelial cells.[27] In addition, coffee plants are rich in citric acid; urinary citrate is a known inhibitor
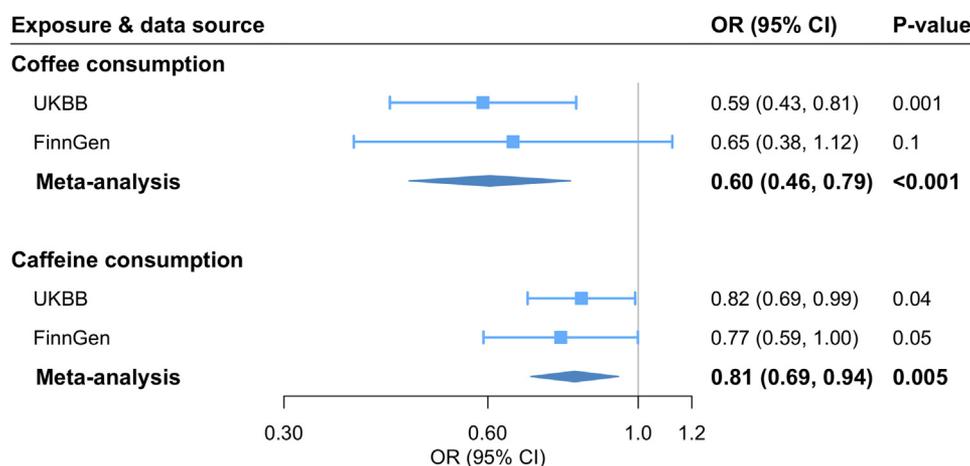
Exposure & data source	OR (95% CI)	P-value
Coffee consumption		
UKBB	0.59 (0.43, 0.81)	0.001
FinnGen	0.65 (0.38, 1.12)	0.1
Meta-analysis	**0.60 (0.46, 0.79)**	**<0.001**
Caffeine consumption		
UKBB	0.82 (0.69, 0.99)	0.04
FinnGen	0.77 (0.59, 1.00)	0.05
Meta-analysis	**0.81 (0.69, 0.94)**	**0.005**

OR (95% CI)

Figure 2. Association of genetically predicted coffee and caffeine consumption with risk of kidney stones. Estimates were obtained from the inverse-variance weighted methods. ORs for kidney stone disease were scaled to genetically predicted 50% of increase in coffee consumption and 80-mg increase in caffeine consumption. Abbreviations: FinnGen, FinnGen Consortium; OR, odds ratio; UKBB, UK Biobank.

of renal stone formation.[28] Other bioactive compounds in decaffeinated coffee, such as trigonelline, may generate similar protective effects like caffeine.[29]

There are strengths and limitations in this study. The major merit is the MR design, which strengthened the causal inference in the associations of coffee and caffeine consumption with risk of kidney stones. Additionally, we examined these associations in 2 independent populations, and the consistent results guaranteed the robustness of findings. We confined the studied population to individuals of European ancestry, which limited the population bias, whereas this might on the other side limit the generalizability of our findings to other populations. There was a large overlap in sample between exposure and outcome data, which might make the model overfitting and the causal estimates toward observational associations.[22] However, the F statistic > 10 indicated that the bias caused by sample overlap was likely to be minimal.

The important limitation is possible horizontal pleiotropy, which means that genetic instruments influence risk of kidney stones not via coffee or caffeine consumption but via other pathways. However, traits that are genetically correlated with coffee consumption, such as obesity and smoking, appear to increase risk of kidney stone disease[30,31] and are therefore unlikely to bias inverse associations between coffee consumption and kidney stone formation. Another pleiotropic factor may be daily fluid intake, which is likely to be positively correlated with coffee and caffeine consumption and inversely associated with risk of kidney stone disease.[5] The genetic variants selected for caffeine consumption are involved in caffeine metabolism and have been shown to be associated with caffeine metabolites in previous studies.[13,32]

In conclusion, this MR study provides genetic evidence in support of causal inverse associations of coffee and caffeine consumption with kidney stones. Increasing coffee and caffeine consumption may be a prevention strategy for kidney stones.

Table 2. Association of Genetically Predicted Coffee Consumption With Risk of Kidney Stones in Sensitivity Analyses

Method	Value	P
Source: UKBB		
Weighted median method	OR, 0.68 (95% CI, 0.50-0.93)	0.02
MR-Egger regression	OR, 0.71 (95% CI, 0.38-1.34)	0.3
MR-PRESSO method	NA	NA
Cochrane Q	18	
Intercept in MR-Egger regression	—	0.5
Source: FinnGen		
Weighted median method	OR, 0.71 (95% CI, 0.44-1.15)	0.2
MR-Egger regression	OR, 0.96 (95% CI, 0.33-2.78)	0.9
MR-PRESSO method	OR, 0.65 (95% CI, 0.44-0.98)	0.07
Cochrane Q	26	
Intercept in MR-Egger regression	—	0.4

Two outliers were detected in the MR-PRESSO analysis in FinnGen. No outlier was observed in the MR-PRESSO analysis in UKBB. Abbreviations: CI, confidence interval; FinnGen, FinnGen Consortium; OR, odds ratio; MR, Mendelian randomization; NA, not applicable; UKBB, UK Biobank.

Article Information

Authors' Full Names and Academic Degrees: Shuai Yuan, BMed, MMedSc, and Susanna C. Larsson, PhD.

Authors' Affiliations: Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm (SY, SCL); and Unit of Medical Epidemiology,

Department of Surgical Sciences, Uppsala University, Uppsala (SCL), Sweden.

Address for Correspondence: Susanna C. Larsson, PhD, Institute of Environmental Medicine, Karolinska Institutet, Nobelsväg 13, Stockholm, 17177, Sweden. Email: susanna.larsson@ki.se

References

1. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol*. 2010;12(2-3):e86-96.
2. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Stampfer MJ. Prospective study of beverage use and the risk of kidney stones. *Am J Epidemiol*. 1996;143(3):240-247.
3. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Beverage use and risk for kidney stones in women. *Ann Intern Med*. 1998;128(7):534-540.
4. Goldfarb DS, Fischer ME, Keich Y, Goldberg J. A twin study of genetic and dietary influences on nephrolithiasis: a report from the Vietnam Era Twin (VET) Registry. *Kidney Int*. 2005;67(3):1053-1061.
5. Littlejohns TJ, Neal NL, Bradbury KE, Heers H, Allen NE, Turney BW. Fluid intake and dietary factors and the risk of incident kidney stones in UK Biobank: a population-based prospective cohort study. *Eur Urol Focus*. 2020;6(4):752-761.
6. Barghouthy Y, Corrales M, Doizi S, Somani BK, Traxer O. Tea and coffee consumption and pathophysiology related to kidney stone formation: a systematic review. *World J Urol*. 2020;39(7):2417-2426.
7. Barghouthy Y, Corrales M, Doizi S, Somani BK, Traxer O. Tea and coffee consumption and the risk of urinary stones—a systematic review of the epidemiological data. *World J Urol*. Published online January 17, 2021, doi: 10.1007/s00345-020-03561-w.
8. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Soda and other beverages and the risk of kidney stones. *Clin J Am Soc Nephrol*. 2013;8(8):1389-1395.
9. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Caffeine intake and the risk of kidney stones. *Am J Clin Nutr*. 2014;100(6):1596-1603.
10. Burgess S, Thompson SG. *Mendelian Randomization: Methods for Using Genetic Variants in Causal Estimation*. Chapman & Hall/CRC Press; 2015.
11. Burgess S, Small DS, Thompson SG. A review of instrumental variable estimators for Mendelian randomization. *Stat Methods Med Res*. 2017;26(5):2333-2355.
12. Zhong VW, Kuang A, Danning RD, et al. A genome-wide association study of bitter and sweet beverage consumption. *Hum Mol Genet*. 2019;28(14):2449-2457.
13. Cornelis MC, Kacprowski T, Menni C, et al. Genome-wide association study of caffeine metabolites provides new insights to caffeine metabolism and dietary caffeine-consumption behavior. *Hum Mol Genet*. 2016;25(24):5472-5482.
14. McMahon G, Taylor AE, Davey Smith G, Munafò MR. Phenotype refinement strengthens the association of AHR and CYP1A1 genotype with caffeine consumption. *PLoS One*. 2014;9(7):e103448.
15. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.
16. The FinnGen consortium. The R4 release of FinnGen study. Accessed January 15, 2021. https://finngen.gitbook.io/documentation/
17. Howles SA, Wiberg A, Goldsworthy M, et al. Genetic variants of calcium and vitamin D metabolism in kidney stone disease. *Nat Commun*. 2019;10(1):5175.
18. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658-665.
19. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304-314.
20. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512-525.
21. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693-698.
22. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genet Epidemiol*. 2016;40(7):597-608.
23. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *Elife*. 2018;7:e34408.
24. Massey LK, Sutton RA. Acute caffeine effects on urine composition and calcium kidney stone risk in calcium stone formers. *J Urol*. 2004;172(2):555-558.
25. Sun Y, Wang D, Zhou Q. Caffeine intake and the risk of recurrent kidney stones in adults, an analysis of 2007-2014 National Health and Nutrition Examination Surveys. *Eur J Nutr*. 2020;59(6):2683-2692.
26. Rieg T, Steigele H, Schnermann J, Richter K, Osswald H, Vallon V. Requirement of intact adenosine A1 receptors for the diuretic and natriuretic action of the methylxanthines theophylline and caffeine. *J Pharmacol Exp Ther*. 2005;313(1):403-409.
27. Peerapen P, Thongboonkerd V. Caffeine prevents kidney stone formation by translocation of apical surface annexin A1

crystal-binding protein into cytoplasm: in vitro evidence. *Sci Rep*. 2016;6:38536.

28. Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Biyani CS. Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database Syst Rev*. 2015;10:CD010057.

29. Arai K, Terashima H, Aizawa S, et al. Simultaneous determination of trigonelline, caffeine, chlorogenic acid and their related compounds in instant coffee samples by HPLC using an acidic mobile phase containing octanesulfonate. *Anal Sci*. 2015;31(8):831-835.

30. Jones P, Karim Sulaiman S, Gamage KN, Tokas T, Jamnadass E, Somani BK. Do lifestyle factors including smoking, alcohol, and exercise impact your risk of developing kidney stone disease? Outcomes of a systematic review. *J Endourol*. 2021;35(1):1-7.

31. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. *JAMA*. 2005;293(4):455-462.

32. Cornelis MC, Monda KL, Yu K, et al. Genome-wide meta-analysis identifies regions on 7p21 (AHR) and 15q24 (CYP1A2) as determinants of habitual caffeine consumption. *PLoS Genet*. 2011;7(4):e1002033.

Coffee and Caffeine Consumption and Risk of Kidney Stones

Population	Design & Analysis	Results

Genome-wide association studies on coffee and caffeine consumption and kidney stones

Exposures
- **Coffee:** 375,833 individuals
- **Caffeine:** 9,876 individuals

Outcome: kidneys stones
- **UK Biobank:** 6,536 cases and 388,508 non-cases
- **FinnGen:** 3,856 cases and 172,757 non-cases

Mendelian Randomization Analysis
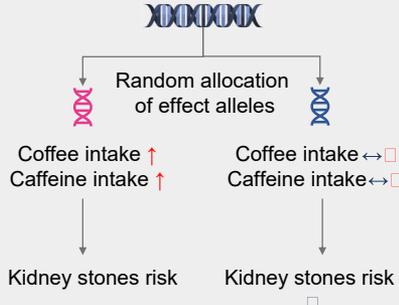
Random allocation of effect alleles

Coffee intake ↑
Caffeine intake ↑

Coffee intake ↔□
Caffeine intake ↔□

Kidney stones risk

Kidney stones risk □

Genetically predicted coffee and caffeine intake ↑
Risk of kidney stones ↓

Coffee consumption
- UKBB
- FinnGen
- **Meta-analysis**

Caffeine consumption
- UKBB
- FinnGen
- **Meta-analysis**
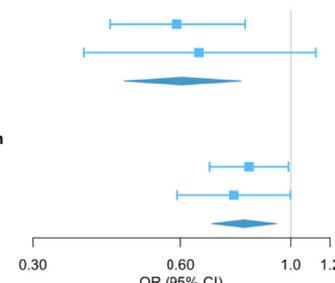
0.30   0.60   1.0 1.2
OR (95% CI)

CONCLUSION: This study provides genetic evidence in support of causal inverse associations of coffee and caffeine consumption with kidney stones.