Chronic Kidney Disease Does Not Causally Increase the Risk of Cholelithiasis: Evidence from Mendelian Randomization

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Abstract: Background: Chronic kidney disease (CKD) and cholelithiasis are both prevalent conditions that may share metabolic risk factors. However, the causal relationship between CKD and cholelithiasis remains unclear. Methods: A two-sample Mendelian randomization (MR) analysis was conducted using genome-wide association study (GWAS) summary statistics to assess the potential causal effect of CKD on cholelithiasis. Genetic variants significantly associated with CKD were selected as instrumental variables. The inverse variance weighted (IVW) method served as the primary analysis, supplemented by MR-Egger and weighted median approaches. Sensitivity analyses included assessments of pleiotropy, heterogeneity, and leave-one-out stability. Results: MR analysis showed no significant causal effect of CKD on cholelithiasis (IVW OR = 0.948, 95% CI: 0.835–1.077, P = 0.414). Sensitivity analyses found no evidence of pleiotropy or heterogeneity, and leave-one-out analysis supported the robustness of the findings. Conclusion: This MR analysis found no evidence supporting a causal effect of CKD on the risk of developing cholelithiasis. The results suggest that genetic liability to CKD does not significantly increase the likelihood of gallstone formation. Further investigations across diverse populations are warranted to confirm these findings and to explore potential shared pathways underlying both conditions.

***Keywords*:** Genetic variants; Chronic kidney disease; Cholelithiasis; Risk factors

1. Introduction

Chronic kidney disease (CKD) is a progressive condition defined by the presence of structural or functional kidney impairment persisting over time, most commonly manifested by a sustained reduction in glomerular filtration rate or the presence of markers of kidney damage. It represents one of the most pressing global health burdens of the twenty-first century [1,2]. CKD develops silently in its early stages, yet gradually leads to a wide array of systemic complications as kidney function declines. Patients with CKD often face disturbances of mineral metabolism, electrolyte imbalances, impaired immune responses, and profound cardiovascular risk. In advanced stages, renal replacement therapies such as dialysis or transplantation become necessary, imposing substantial physical, psychological, and financial burdens [3,4]. Beyond these direct consequences, CKD exerts far-reaching effects on multiple organ systems, including the gastrointestinal and hepatobiliary systems, thereby extending its clinical significance well beyond the kidney itself. The recognition of CKD as a systemic disorder has prompted increasing attention toward its broader complications, many of which are underexplored but highly relevant for patient outcomes.

Cholelithiasis is among the most common hepatobiliary disorders encountered in clinical practice. It refers to the formation of stones within the gallbladder or biliary tract, typically composed of cholesterol, bile pigments, or mixed components. While often clinically silent, cholelithiasis can give rise to a spectrum of complications ranging from biliary colic and acute cholecystitis to choledocholithiasis, cholangitis, and pancreatitis [5-7]. These events may result in recurrent hospitalizations, the need for surgical intervention, and in severe cases, significant morbidity or mortality. The disease is strongly associated with metabolic factors such as obesity, diabetes, and dyslipidemia, and it exhibits notable variation by sex, age, and ethnicity. The clinical burden of cholelithiasis extends beyond acute episodes, as it may contribute to chronic hepatobiliary dysfunction and increase the long-term risk of other gastrointestinal complications. Consequently, understanding the determinants of cholelithiasis has been a major focus of hepatobiliary and metabolic research.

Recent findings suggest that the hepatobiliary system may be frequently involved in CKD, although the patterns appear to vary according to treatment modality. In a retrospective evaluation of patients at different stages of kidney dysfunction, hepatosteatosis was observed more often in those undergoing hemodialysis compared with peritoneal dialysis, while the occurrence of cholelithiasis was elevated overall but showed no clear differences across treatment groups. The same study also noted that acute cholecystitis tended to be more frequent in patients receiving hemodialysis compared with those not yet on dialysis [8]. These observations indicate that hepatobiliary complications are not uncommon in CKD, but the exact

nature of the association with cholelithiasis remains uncertain. Confounding factors, underlying metabolic disturbances, and dialysis-related influences may all contribute, making it difficult to determine whether the relationship is causal or simply reflects overlapping risks.

Mendelian randomization (MR) provides an approach to strengthen causal inference by using genetic variants as proxies for modifiable exposures. Through the random allocation of alleles at conception, MR reduces confounding and reverse causation, offering insights that complement conventional observational research [9,10]. In the present work, we apply a two-sample MR framework to examine the potential causal link between CKD and cholelithiasis using genome-wide association data. This analysis may help to clarify whether the observed relationship reflects a direct causal pathway or shared underlying mechanisms, thereby contributing to a more nuanced understanding with possible clinical relevance.

2. Material and methods

2.1 Summary statistics data for chronic kidney disease and cholelithiasis

The summary genome-wide association study (GWAS) data for CKD and cholelithiasis were obtained from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/). The CKD dataset (ebi-a-GCST003374) included 117,165 individuals of European ancestry, with 12,385 cases and 104,780 controls, and a total of 2,179,497 single-nucleotide polymorphisms (SNPs). The cholelithiasis dataset (finn-b-K11_CHOLELITH) comprised 19,023 cases and 195,144 controls of European ancestry, with 16,380,452 SNPs. Importantly, these datasets are independent, minimizing the risk of sample overlap and ensuring the robustness of the MR analyses.

2.2 Selection of instrumental variables

Following the three core assumptions of MR, we first extracted SNPs strongly associated with CKD at a genome-wide significance level of $p < 5 \times 10^{-8}$. To ensure independence among instruments, clumping was performed with $r^2 < 0.001$ within a 10,000-kb window [11,12]. Instrumental strength was then assessed using the F-statistic, calculated as $F=\left(\frac{n-1-k}{k}\right)\times\frac{R^2}{1-R^2}$), where n is the sample size, k is the number of variants, and R^2 represents the variance explained by the instruments. All instrumental variables used in this study had F-statistics greater than 10, thereby avoiding weak instrument bias [13].

2.3 Two-sample Mendelian randomization analysis

A two-sample MR analysis was performed to investigate the potential causal association between CKD and cholelithiasis. The primary analysis applied the inverse variance weighted (IVW) method to estimate odds ratios (ORs) with corresponding 95% confidence intervals (CIs). To test the robustness of the results, complementary MR approaches, including MR-Egger regression and the weighted median method, were also conducted [14]. The analysis was designed to evaluate whether genetic susceptibility to CKD may influence the risk of cholelithiasis.

2.4 Statistical methods

Sensitivity analyses were performed to assess the stability of the MR estimates. The MR-Egger intercept and the MR pleiotropy residual sum and outlier (MR-PRESSO) global test were applied to detect potential horizontal pleiotropy, with $P > 0.05$ indicating no significant pleiotropic effect. Heterogeneity among the instruments was examined using Cochrane's Q statistic, where $P > 0.05$ suggested the absence of notable heterogeneity [15,16]. In addition, a leave-one-out approach was used to evaluate whether any single SNP had a disproportionate influence on the overall causal estimates. All analyses were carried out using the "TwoSampleMR" package in R.

3. Results

The MR analysis indicated no significant causal association between genetically predicted CKD and the risk of cholelithiasis (IVW OR = 0.948, 95% CI: 0.835–1.077, P = 0.414) (Figure 1). The scatter plot results are presented in Figure 2.

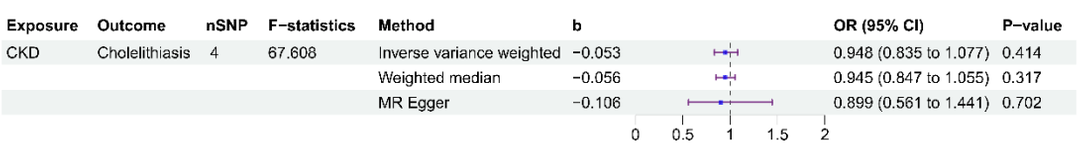

Figure 1. MR estimates of CKD on the risk of cholelithiasis.

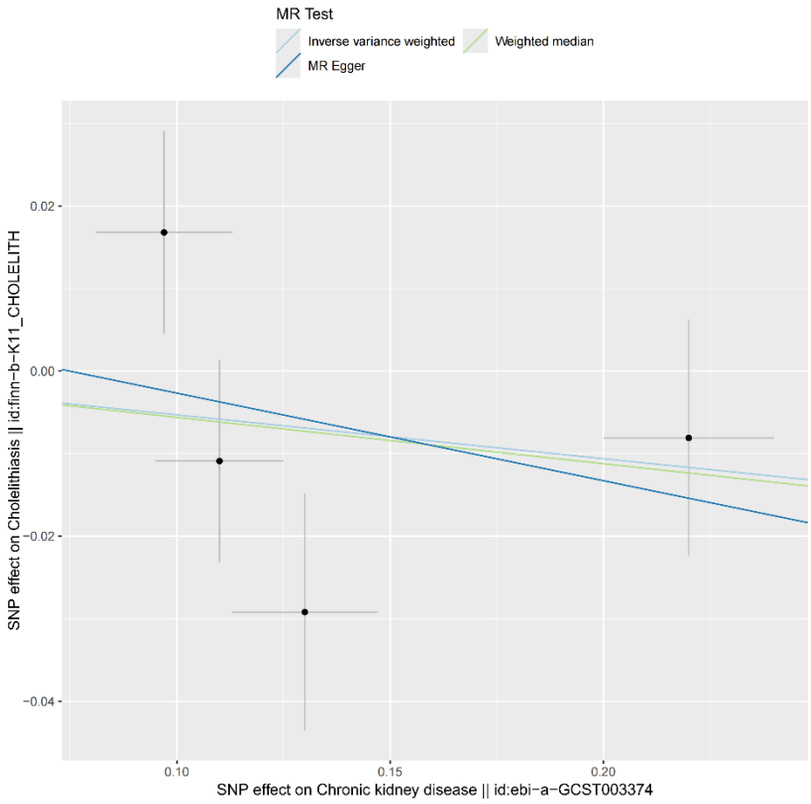

Figure 2. MR scatter plot of the causal effect of CKD on cholelithiasis.

The sensitivity analyses showed no significant heterogeneity among the genetic instruments according to Cochran's Q test (P = 0.119). Furthermore, the MR-Egger intercept test (P = 0.837) and the MR-PRESSO global test (P = 0.236) indicated no evidence of horizontal pleiotropy.

The leave-one-out analysis showed that sequentially removing individual SNPs had little influence on the overall causal estimates (Figure 3). This suggests that the findings were not materially affected by any single variant.

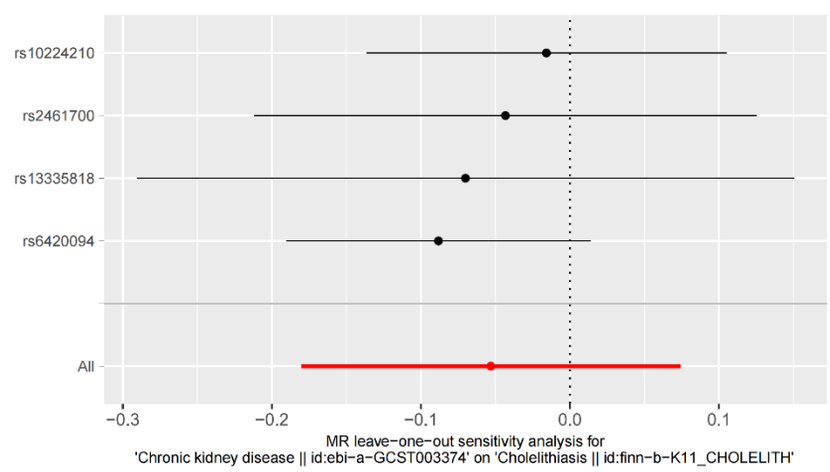

Figure 3. Leave-one-out analysis of the causal effect of CKD on cholelithiasis.

4. Discussion

The present MR analysis did not provide evidence to support a causal relationship between CKD and cholelithiasis. Specifically, genetic liability to CKD did not appear to increase the risk of developing cholelithiasis, suggesting that the associations previously observed in conventional epidemiological studies may not reflect direct causality.

CKD is a progressive disorder characterized by the gradual loss of renal function and associated systemic complications.

It is recognized as a major global health burden, contributing not only to renal morbidity but also to cardiovascular disease, metabolic alterations, and gastrointestinal manifestations [17,18]. Cholelithiasis, in turn, represents one of the most prevalent hepatobiliary conditions worldwide and is associated with significant morbidity when symptomatic, leading to complications such as biliary colic, acute cholecystitis, and pancreatitis. Both CKD and cholelithiasis share a constellation of metabolic risk factors, including obesity, insulin resistance, hypertension, and dyslipidemia [19-21]. Furthermore, patients with advanced CKD or those undergoing renal replacement therapy may be exposed to metabolic disturbances, medication effects, and altered bile composition, which may contribute to gallstone formation. This has raised the possibility of a meaningful link between CKD and cholelithiasis. Clarifying this potential relationship is clinically important, as it could inform screening practices, risk stratification, and management strategies for a large and vulnerable patient population. Against this background, our MR study provides additional evidence by leveraging genetic data to test for causality, thereby complementing and extending existing knowledge.

The lack of a significant causal association in our MR analysis may have several explanations. First, CKD might not exert a direct biological effect on gallstone formation; instead, both conditions may simply coexist due to shared metabolic pathways without a direct causal link. Second, the genetic instruments used for CKD, while robust, may not fully capture the diverse mechanisms and subtypes of kidney dysfunction, leaving open the possibility that subtle causal effects remain undetected. Third, potential pleiotropy or interactions with environmental exposures could have diluted or masked a true but modest relationship. Fourth, our analysis was restricted to individuals of European ancestry, which may limit the generalizability of the findings to other populations with different genetic backgrounds and environmental exposures. These considerations highlight the need for cautious interpretation of the current findings and suggest that further integration of genetic, mechanistic, and clinical research will be valuable in refining our understanding of the interplay between CKD and cholelithiasis.

5. Conclusion

In summary, this MR study did not support a causal effect of CKD on the risk of cholelithiasis. While the results provide genetic evidence that helps to clarify an important clinical question, they should be interpreted with caution given potential methodological and population-related limitations. Future studies should aim to integrate genetic, mechanistic, and longitudinal clinical data across diverse ancestries in order to better clarify the complex interactions between renal dysfunction and hepatobiliary disease.

Data Sharing Statement

The analysis was based on publicly available data sources. A detailed account of the study's original contributions can be found in the main text. Additional information is available from the corresponding author upon request.

Ethics Approval

As all datasets employed in this study were sourced from publicly accessible repositories, no further ethical approval or informed consent was necessary.

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Disclosure

The authors report no conflicts of interest in this work.

References

[1] Qin K, Qing J, Wang Q, Li Y. Epidemiological shifts in chronic kidney disease: a 30-year global and regional assessment. BMC Public Health. 2024;24(1):3519. Published 2024 Dec 18. doi:10.1186/s12889-024-21065-9

[2] Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. Lancet. 2021;398(10302):786-802. doi:10.1016/S0140-6736(21)00519-5

[3] Yi TW, Levin A. Sex, Gender, and Cardiovascular Disease in Chronic Kidney Disease. Semin Nephrol. 2022;42(2):197-207. doi:10.1016/j.semnephrol.2022.04.009

[4] Hodgin JB, Maity S, Kretzler M, Sharma K. Pathology of Chronic Kidney Disease and Spatial Metabolomics. Semin Nephrol. 2024;44(6):151579. doi:10.1016/j.semnephrol.2025.151579

[5] Wang HH, Portincasa P, Liu M, Wang DQ. Genetic Analysis of ABCB4 Mutations and Variants Related to the Pathogenesis and Pathophysiology of Low Phospholipid-Associated Cholelithiasis. Genes (Basel). 2022;13(6):1047. Published 2022 Jun 11. doi:10.3390/genes13061047
[6] Ye Z, Xie J, Ni X, et al. Physical activity and risk of cholelithiasis: a narrative review. Front Med (Lausanne). 2024;11:1485097. Published 2024 Dec 16. doi:10.3389/fmed.2024.1485097
[7] Petrola Chacón CG, Vilallonga R, González López Ó, et al. Analysis of the Management of Cholelithiasis in Bariatric Surgery Patients: a Single-Center Experience. Obes Surg. 2022;32(3):704-711. doi:10.1007/s11695-021-05883-z
[8] Karahan D, Şahin İ. Evaluation of hepatosteatosis and gallstone disease in patients with chronic kidney disease. Hemodial Int. 2024;28(3):343-350. doi:10.1111/hdi.13151
[9] Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. Nat Rev Methods Primers. 2022;2:6. doi:10.1038/s43586-021-00092-5
[10] Verduijn M, Siegerink B, Jager KJ, Zoccali C, Dekker FW. Mendelian randomization: use of genetics to enable causal inference in observational studies. Nephrol Dial Transplant. 2010;25(5):1394-1398. doi:10.1093/ndt/gfq098
[11] de Leeuw C, Savage J, Bucur IG, Heskes T, Posthuma D. Understanding the assumptions underlying Mendelian randomization. Eur J Hum Genet. 2022;30(6):653-660. doi:10.1038/s41431-022-01038-5
[12] Xue H, Liu S, Zeng L, Fan W. Causal effect of systemic lupus erythematosus on psychiatric disorders: A two-sample Mendelian randomization study. J Affect Disord. 2024;347:422-428. doi:10.1016/j.jad.2023.11.033
[13] Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37(7):658-665. doi:10.1002/gepi.21758
[14] Boehm FJ, Zhou X. Statistical methods for Mendelian randomization in genome-wide association studies: A review. Comput Struct Biotechnol J. 2022;20:2338-2351. Published 2022 May 14. doi:10.1016/j.csbj.2022.05.015
[15] Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: A review. Res Synth Methods. 2019;10(4):486-496. doi:10.1002/jrsm.1346
[16] Nguyen K, Mitchell BD. A Guide to Understanding Mendelian Randomization Studies. Arthritis Care Res (Hoboken). 2024;76(11):1451-1460. doi:10.1002/acr.25400
[17] Qing X, Jiang J, Yuan C, Xie K, Wang K. Temporal trends in prevalence and disability of chronic kidney disease caused by specific etiologies: an analysis of the Global Burden of Disease Study 2019. J Nephrol. 2024;37(3):723-737. doi:10.1007/s40620-024-01914-x
[18] Krishnan A, Teixeira-Pinto A, Lim WH, et al. Health-Related Quality of Life in People Across the Spectrum of CKD. Kidney Int Rep. 2020;5(12):2264-2274. Published 2020 Oct 3. doi:10.1016/j.ekir.2020.09.028
[19] Dan WY, Yang YS, Peng LH, Sun G, Wang ZK. Gastrointestinal microbiome and cholelithiasis: Current status and perspectives. World J Gastroenterol. 2023;29(10):1589-1601. doi:10.3748/wjg.v29.i10.1589
[20] Koller T, Kollerova J, Hlavaty T, Huorka M, Payer J. Cholelithiasis and markers of nonalcoholic fatty liver disease in patients with metabolic risk factors. Scand J Gastroenterol. 2012;47(2):197-203. doi:10.3109/00365521.2011.643481
[21] Talha A, Abdelbaki T, Farouk A, Hasouna E, Azzam E, Shehata G. Cholelithiasis after bariatric surgery, incidence, and prophylaxis: randomized controlled trial. Surg Endosc. 2020;34(12):5331-5337. doi:10.1007/s00464-019-07323-7