Original Article

Causal relationship between renal function and risk of esophageal cancer: insights from Mendelian randomization

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Background: Previous studies have indicated a potential correlation between renal function and risk of cancer. However, establishing a causal relationship is challenging. To address this, we employed Mendelian randomization (MR), a novel method that utilizes genotype data to simulate randomized trial groups, to investigate whether there is a causal correlation between renal function and the esophageal cancer (EC) risk.

Methods: MR analysis was conducted with the individual-level data on EC from the UK Biobank published dataset. Genetic instruments were derived from single nucleotide polymorphisms (SNPs) extracted from publicly available genome-wide association studies. Furthermore, leave-one-out sensitivity analysis was performed to assess the impact of individual SNPs.

Results: In our MR analysis, we examined 39,475,182 SNPs associated with various renal functional indexes from public databases. Based on the primary causal effects model using MR analyses with the inverse variance weighted method, the genetically predicted cystatin C [odds ratio (OR) =1.0005, 95% confidence interval (CI): 1.0000–1.0009; P=0.05] and creatinine (OR =1.0016, 95% CI: 1.0002–1.0031; P=0.02) demonstrated a significant association with higher risk of EC. However, we found no evidence of an association between urinary albumin and glomerular filtration rate with the risk of EC.

Conclusions: Our research provides strong evidence for the association of decreased renal function to a potential risk of EC. However, it is crucial to recognize the necessity for additional large-scale prospective studies to validate this discovery and establish a comprehensive understanding of the causal relationships between renal function and EC.

Keywords: Esophageal cancer (EC); renal function; Mendelian randomization (MR); causal association

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Introduction

Esophageal cancer (EC) is a malignant tumor that forms in the tissues lining the esophagus (1). Due to the aggressiveness of EC, the prognosis of EC patients is poor, and the overall 5-year survival rate of EC is still lower than 30% (2,3). Therefore, early detection is crucial for better treatment outcomes. Furthermore, promoting awareness, early screening, and identifying novel EC risk factors are vital steps in reducing the impact of EC on global health.

The kidneys play a pivotal role in preserving the body's overall health, as they filter waste products and toxins from the blood, maintain fluid balance, and control electrolyte levels. Proper renal function is indispensable

for eliminating excess water, salts, and waste materials, thus ensuring a stable internal environment (4). Maintaining optimal renal function is essential for overall well-being and preventing the development of various health conditions. Any impairment in renal function may affect the body's ability to eliminate toxins and potentially influence tumor development (5). Recent studies have suggested potential relationship between renal function and various types of tumors (6,7). However, the specific impact of renal function on the development of EC remains unclear.

Mendelian randomization (MR) is a robust statistical technique employed in genetic epidemiology to establish causal relationships between an exposure and an outcome based on genetic variation. By utilizing genetic variants as instrumental variables, MR mimics a randomized controlled trial setting and helps overcome limitations of traditional observational studies, like confounding and reverse causation (8). This approach has been pivotal in examining the impact of modifiable risk factors on various diseases, providing crucial insights for public health and medical interventions. To explore causality, we conducted a MR analysis using genetic variants identified in recent genome-wide association studies (GWAS). Specifically, our study aims to investigate the potential causal relationship between renal function and the risk of EC. By leveraging the wealth of genetic data available, we aim to shed light on this complex relationship and contribute to a better understanding of EC development. We present this article in accordance with the STROBE-MR reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1764/rc).

Highlight box

Key findings

- The study demonstrates a causal link between decreased renal function, specifically elevated levels of cystatin C and creatinine, and an increased risk of esophageal cancer (EC). This provides concrete evidence of the impact of renal health on EC susceptibility.

What is known and what is new?

- Research has established a correlation between renal function and the occurrence and progression in various tumors. However, there remains a lack of studies investigating the relationship between renal function and the incidence of EC, and the causal relationship therein remains unknown.
- We observed a noteworthy association between elevated levels of cystatin C and creatinine and a potential elevation in the risk of EC. Nevertheless, our investigation did not yield significant effects concerning urinary albumin and glomerular filtration rate in relation to EC risk.

What is the implication, and what should change now?

- The evidence of a causal relationship between renal function deterioration and increased EC risk underscores the importance of kidney health in EC prevention strategies. It suggests that interventions aimed at improving renal health could be a novel and effective approach to reducing EC risk. Future research should focus on validating these findings and exploring targeted interventions to mitigate EC risk through renal function improvement.

Methods

Study design

Figure 1 illustrates the study design and presents the three fundamental assumptions of MR as follows: (I) the strong and reliable association between single nucleotide polymorphisms (SNPs) and essential renal function indicators [cystatin C, creatinine, urinary albumin, and glomerular filtration rate (GFR)]; (II) the impact of SNPs on EC is exclusively mediated through renal function; (III) the independence of SNPs from known confounding factors.

Data sources

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We conducted a comprehensive MR analysis using publicly available GWAS data from populations with European ancestry. The GWAS summary data included 13,586,047 SNPs for cystatin C, 12,087,816 SNPs for creatinine, 11,684,850 SNPs for urinary albumin, and 2,116,469 SNPs for GFR, respectively. Moreover, 8,970,465 SNPs associated with EC were obtained from the GWAS summary data bas. To assess the relationship between cystatin C, creatinine, urinary albumin, GFR, and genetic variants, we carefully selected SNPs based on specific criteria. All the included SNPs reached the genome-wide significance threshold ($P<5\times10^{-8}$). SNPs were considered suitable genetic instruments for evaluation if their r^2 value was less than 0.001 and the clumping distance exceeded 10,000 kb. This rigorous selection ensured that the chosen SNPs were independent and not in linkage disequilibrium with each other. Furthermore, we evaluated the strength of the selected SNPs using the F-statistic. SNPs with an F-statistic value greater than 10 were deemed sufficiently robust to minimize the impact of potential bias in our analysis (9). Before conducting the MR analysis, we performed

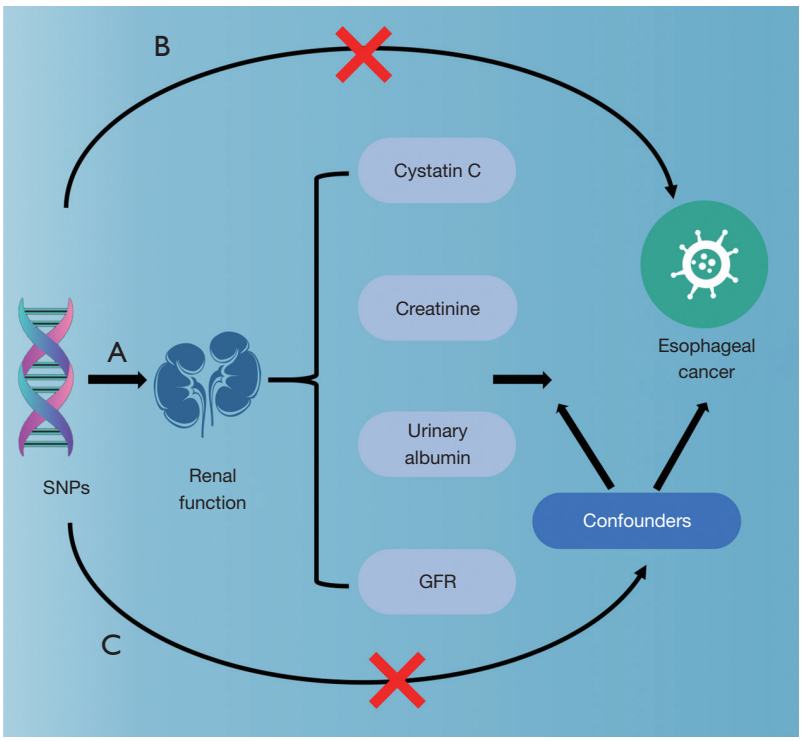

Figure 1 Three key assumptions of the mendelian randomization study. (A) SNPs are strongly associated with renal function; (B) SNPs only affect EC through renal function; (C) SNPs are independent of known confounders. SNP, single-nucleotide polymorphism; GFR, glomerular filtration rate; EC, esophageal cancer.

data-harmonization to ensure that the chosen SNPs had consistent alleles associated with both exposures and outcomes. This step was crucial to maintain the validity of our results. By utilizing these stringent procedures and high-quality data, we aimed to provide reliable and meaningful insights into the genetic associations between cystatin C, creatinine, urinary albumin, GFR, and EC.

MR analysis

To investigate the heterogeneity among the instrumental variables (IVs) included in our analysis, we calculated Cochrane's Q-value. This helped us understand the variability and potential sources of heterogeneity in the data. Additionally, to mitigate the influence of confounding factors, we carefully screened SNPs in the PhenoScanner GWAS database. If an SNP was found to be associated with confounders ($P<1\times10^{-5}$), we excluded it from the MR analysis to ensure the validity of our results [such as age, hypertension (HTN), diabetes mellitus (DM), autoimmune diseases, genetic disorders, medications and toxins, infections, urinary tract obstructions, chronic kidney disease (CKD), lifestyle factors, obesity, and dehydration].

Statistical analyses

In this study, we employed the inverse-variance weighted (IVW) method as the primary approach for MR. Additionally, we assessed the effects using two other MR statistical methods: weighted median and MR-Egger. To ensure the robustness of our findings and potential horizontal pleiotropy, we also utilized the MR-Egger method, enabling the assessment of horizontal pleiotropy and evaluation of result consistency. Further, we performed a leave-one-out sensitivity analysis to assess the influence of individual SNPs on the overall estimates. This analysis allowed us to identify any particularly influential SNPs that could significantly impact our results. The results were presented as odds ratios (ORs) with their associated 95% confidence intervals (95% CIs). All analyses were conducted using MR packages within the R programming language, renowned for their reliability and accuracy in MR studies.

Table 1 Details of studies and datasets used for Mendelian randomization analyses

Trait	Sample size	GWAS ID	Year	Population	SNPs
Cystatin C	NA	ukb-d-30720_irnt	2018	European	13,586,047
Creatinine	NA	met-c-850	2016	European	12,087,816
Urinary albumin	382,500	ebi-a-GCST006586	2018	European	11,684,850
GFR	133,413	ebi-a-GCST003372	2016	European	2,116,469
EC	372,756	ieu-b-4960	2021	European	8,970,465

GWAS, genome-wide association studies; SNPs, single-nucleotide polymorphisms; GFR, glomerular filtration rate; EC, esophageal cancer; NA, not applicable.

Results

SNP selection and validation

In this study, we considered a collection of studies published between 2016 and 2021, predominantly conducted on European populations. The IVs used in our analysis demonstrated genome-wide significance levels, with F-statistics greater than 10, indicating their robustness as genetic instruments. The details of these IVs information are shown in Table S1.

Cystatin C and EC risk

The details of the studies and datasets utilized for MR analyses are presented in *Table 1*. Our investigation employed several analytical methods, including IVW, MR-Egger, and Weighted Median. The IVW analysis indicated a positive association between genetically predicted cystatin C and an increased risk of EC, with an OR of 1.0005 (95% CI: 1.0000–1.0009; P=0.05). Similarly, the MR-Egger analysis also demonstrated a positive correlation with an OR of 1.0007 (95% CI: 1.0001–1.0013; P=0.03), suggesting consistency in the results. The Weighted Median method showed an OR of 1.0006 (95% CI: 0.9999–1.0012; P=0.10), aligning with the direction of effect from IVW and MR-Egger methods, though statistical significance was not detected (*Figure 2*). Assessment of heterogeneity using Cochrane's Q value revealed no significant heterogeneity in the analyses (P=0.61), indicating the reliability and consistency of the findings. Moreover, the MR-Egger analysis provided no evidence of horizontal pleiotropy (P=0.32), further strengthening the validity of the results (*Table 2*). We visually presented the results in *Figure 3* (scatter plot) and Figure S1 (forest plot) for easy interpretation. Additionally, we conducted a leave-one-out sensitivity analysis, which indicated that no individual SNP had a significant influence on the overall estimates, as shown in Figure S2.

Creatinine and EC risk

The IVW method provided compelling evidence of a significant correlation between creatinine levels and a higher risk of EC (OR =1.0016, 95% CI: 1.0002–1.0031; P=0.02). Consistent with this, both the Weighted Median method (OR =1.0015, 95% CI: 0.9997–1.0032; P=0.10) and MR-Egger method (OR =1.0054, 95% CI: 0.9964–1.0144; P=0.33) also indicated a similar direction of effect though statistical significance was not detected (*Figure 2*). Moreover, we observed no significant heterogeneity (P=0.91) or evidence of horizontal pleiotropy (P=0.47) based on the results presented in *Table 2*. These findings support the reliability and validity of our MR analysis. We graphically depicted the MR results in *Figure 3* (scatter plot) and *Figure 4* (forest plot) for visual clarity and comprehensive representation of the associations. *Figure 5A* shows the results of leave-one-out sensitivity analysis that individual SNPs did not exert a significant influence on the overall estimates.

Urinary albumin and EC risk

The IVW (OR =0.9997, 95% CI: 0.9962–1.0031; P=0.85), Weighted Median (OR =0.9998, 95% CI: 0.9951–1.0045; P=0.93), and MR-Egger (OR =0.9963, 95% CI: 0.9884–1.0042; P=0.37) (*Figure 2C*) methods revealed that urinary albumin had no significant association with EC risk, and no evidence of heterogeneity (P=0.41) or horizontal pleiotropy (P=0.36) was detected (*Table 2*). The results from the leave-one-out sensitivity analysis, as shown in *Figure 5B*, reaffirmed that no individual SNP exerted undue influence on the overall estimates.

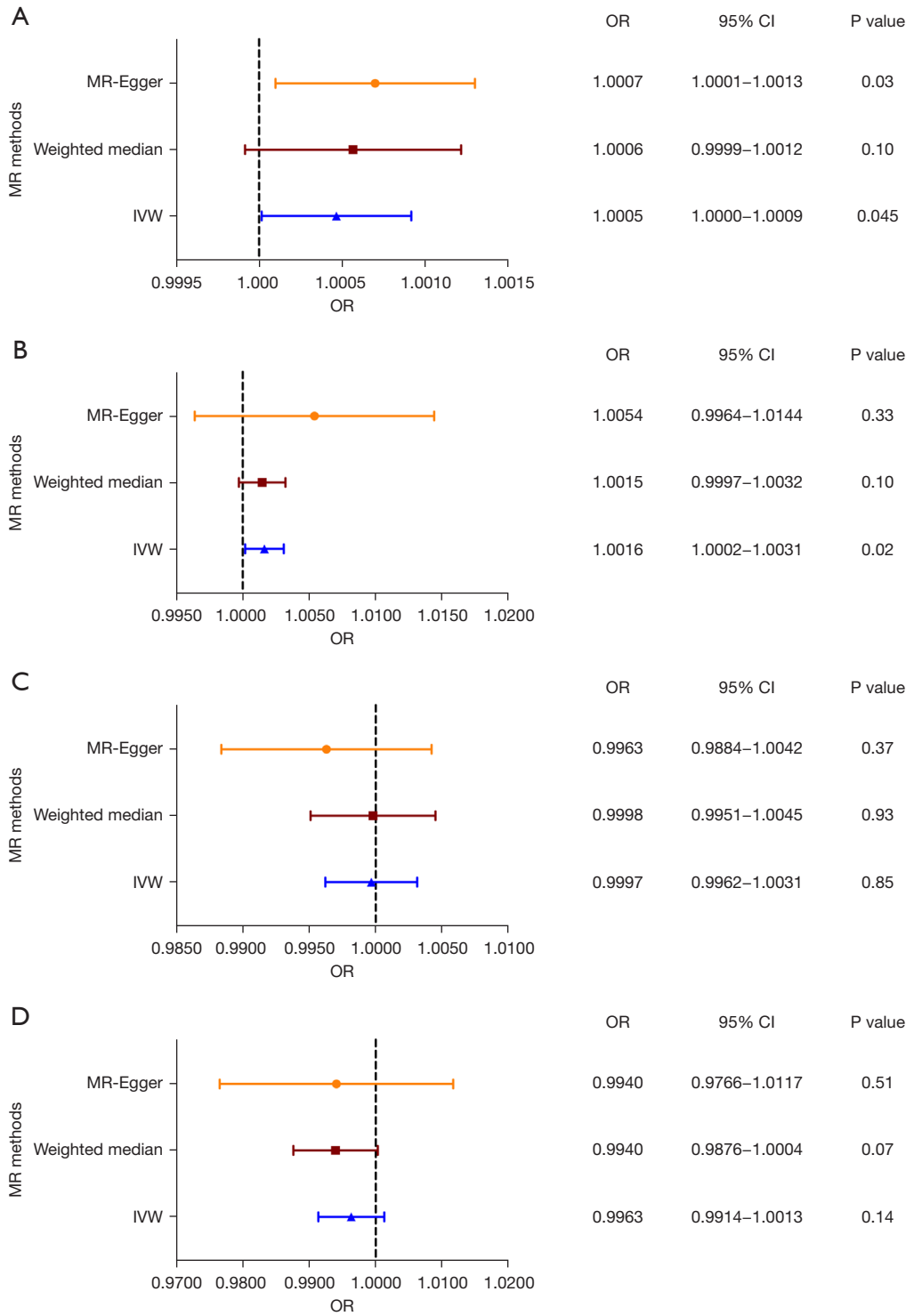

Figure 2 Associations of genetically predicted renal function with EC. (A) Cystatin C; (B) creatinine; (C) urinary albumin; (D) GFR. MR, Mendelian randomization; IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval; EC, esophageal cancer; GFR, glomerular filtration rate.

GFR and EC risk

Figure 2D shows the results of IVW (OR =0.9963, 95% CI: 0.9914–1.0013; P=0.14), Weighted Median (OR =0.9940, 95% CI: 0.9876–1.0004; P=0.07), and MR-Egger (OR =0.9940, 95% CI: 0.9766–1.0117; P=0.51) methods of GFR and EC risk, no statistical significance was detected. The heterogeneity analysis indicated no heterogeneity (P=0.16). Furthermore, there was no evidence of horizontal pleiotropy (P=0.78) (*Table 2*). The consistency of the findings was visually demonstrated through the scatter plot in *Figure 3D* and the forest plot in *Figure 4C*. Additionally, the leave-one-out sensitivity analysis provided reassurance that no individual SNP disproportionately influenced the overall estimates (*Figure 5C*).

Table 2 Pleiotropy and heterogeneity test

Expose	Pleiotropy		Heterogeneity	
	Intercept	P	Q	P
Cystatin C	<0.001	0.32	255.057	0.61
Creatinine	<0.001	0.47	1.010	0.91
Urinary albumin	<0.001	0.36	26.056	0.41
GFR	<0.001	0.78	46.513	0.16

GFR, glomerular filtration rate.

Discussion

In this comprehensive MR analysis, our aim was to explore the genetic evidence for potential causal relationships between renal function and EC risk. The results of our investigation demonstrated significant associations between cystatin C, creatinine, and EC risk. However, we did not find evidence of a causal association between urinary albumin, GFR, and EC risk. These findings provide valuable insights into the potential role of specific renal

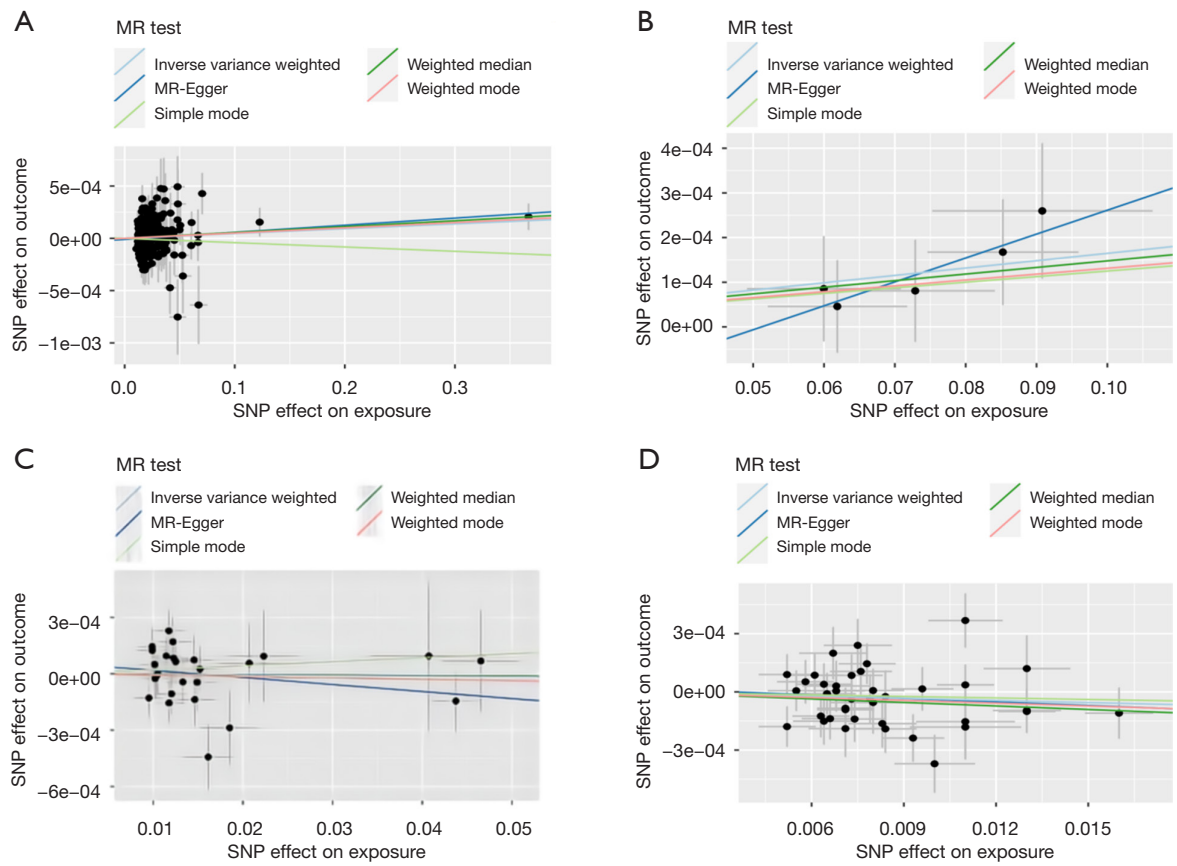

Figure 3 Scatter plots of the association of renal function and EC. (A) Cystatin C; (B) creatinine; (C) urinary albumin; (D) GFR. MR, Mendelian randomization; SNP, single-nucleotide polymorphism; EC, esophageal cancer; GFR, glomerular filtration rate.

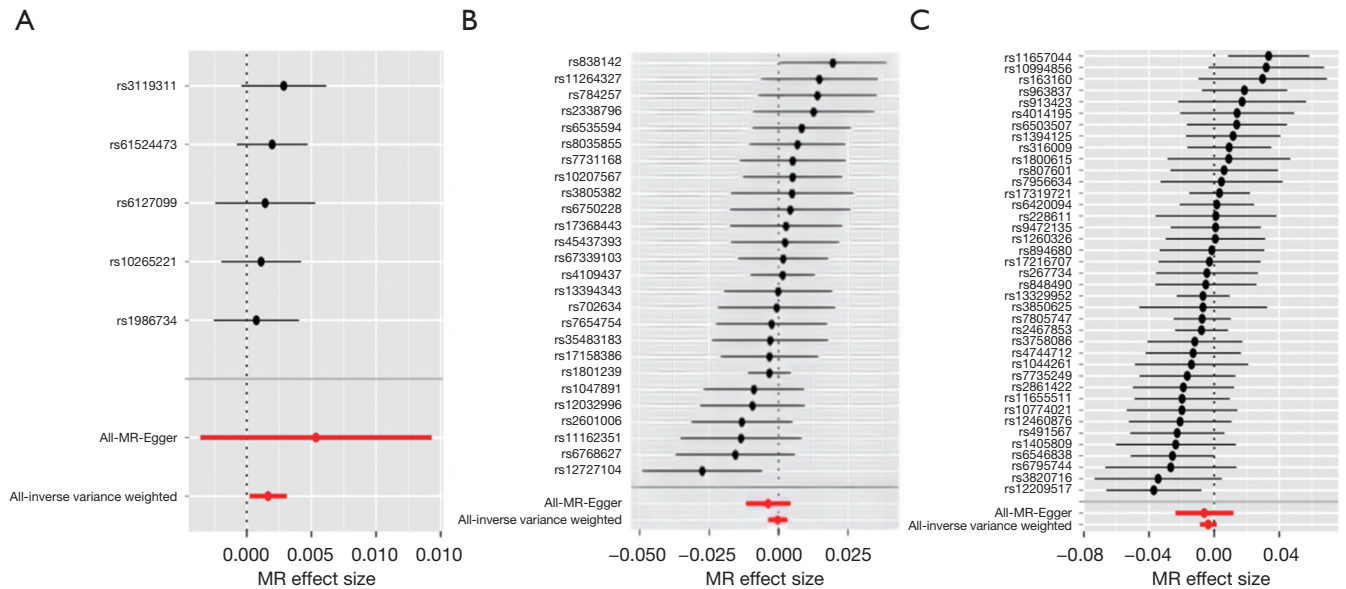

Figure 4 Forest plots of the association of renal function and EC. (A) Creatinine; (B) urinary albumin; (C) GFR. MR, Mendelian randomization; EC, esophageal cancer; GFR, glomerular filtration rate.

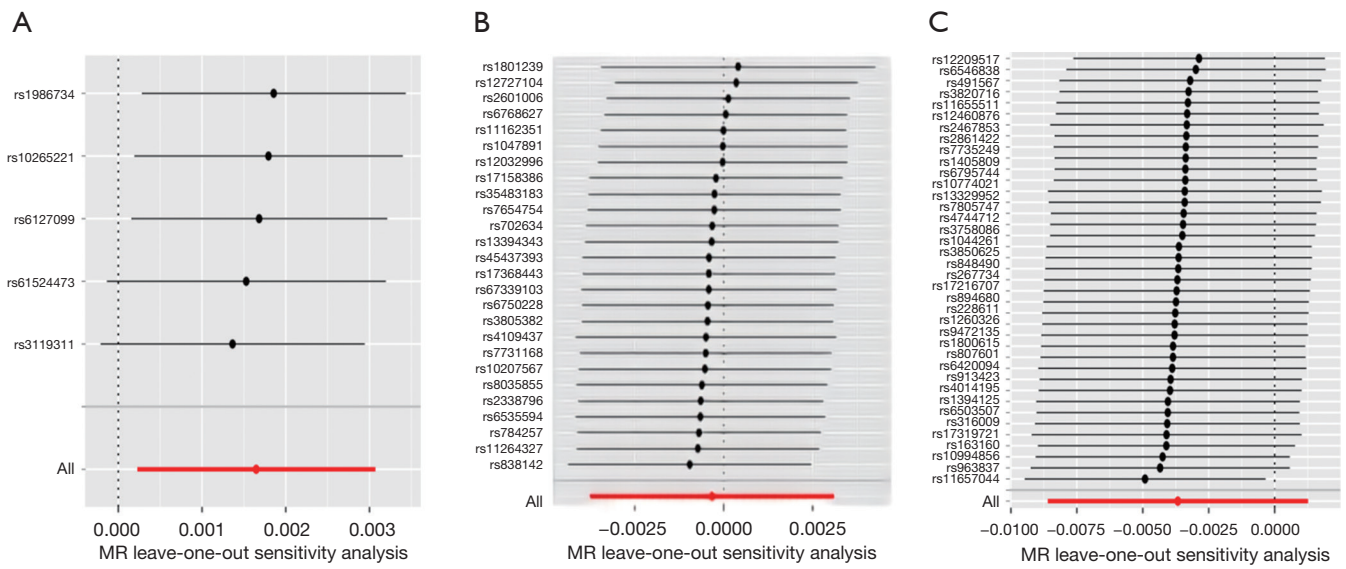

Figure 5 Leave-one-out sensitivity analysis of renal function and EC. (A) Creatinine; (B) urinary albumin; (C) GFR. MR, Mendelian randomization; EC, esophageal cancer; GFR, glomerular filtration rate.

function biomarkers in the development of EC.

The correlation between renal function and tumor development has garnered significant attention in medical research. Numerous studies have explored the potential correlation between renal function and tumor risk. Existing research has revealed that individuals with compromised renal function, as evidenced by elevated levels of biomarkers such as cystatin C and creatinine, may face an augmented likelihood of developing specific types of tumors. Dikovskaya *et al.* demonstrated in their study that serum ratio of cystatin C to cystatin S-type neutral (cystatin SN) appears to be a robust indicator of the presence of uveal melanoma (10).

Guo *et al.* found that clear cell renal cell carcinoma patients with decreased cystatin C level were likely to have a better prognosis compared with patients having an elevated cystatin C level (11). Zeng *et al.* demonstrated in their study that cystatin C immunostaining in EC tissues was increased compared to that of adjacent normal tissues (12). The study conducted by Jung *et al.* proved that at the time of cancer diagnosis, creatinine-cystatin C ratio significantly associates with survival and hospitalization in cancer patients (13). Yan *et al.* demonstrated that serum cathepsin B and cystatin C levels were of diagnostic significance in EC. The ratio of serum cystatin C/cathepsin B was prognostic for the survival of EC patients (14). These findings highlight the potential involvement of cystatin C and kidney dysfunction in the process of tumorigenesis. Moreover, investigations have also delved into the impact of kidney diseases, including CKD, on the incidence and outcomes of various cancers. Kitchlu *et al.* demonstrated that patients with kidney disease, especially those with urologic cancers and myeloma, experienced a significant increase in cancer-related mortality (15). In patients with renal cell carcinoma, preoperative CKD was proved to be correlated with more aggressive features and poorer prognosis (16). Furthermore, there is also substantial evidence suggesting that impaired renal function could exert influence over tumor progression and response to treatment in certain scenarios (17,18). Nonetheless, the role of renal function as a potential risk factor for EC remains enigmatic. Consequently, there is a pressing need to employ MR analysis to validate this hypothesis. In contrast to traditional observational studies, MR analysis is endowed with greater resilience against confounding variables or reverse causation, thereby yielding conclusions of heightened reliability. Thus, MR analysis has the potential to yield insights into the intricate correlation between renal function and the risk of EC.

Creatinine and cystatin C are considered markers of kidney function, reflecting the filtration efficiency of the kidneys. However, beyond their role in renal health, these biomarkers can also serve as indicators of systemic physiological and pathological processes potentially related to cancer risk. In our study, significant associations between the levels of creatinine and cystatin C with EC risk suggest a deeper biological link. Drawing on previous literature, our biochemical hypothesis for how impaired kidney function (indicated by elevated creatinine and cystatin C) could lead to esophageal carcinogenesis includes: (I) systemic inflammation: kidney dysfunction can induce a pro-inflammatory state, characterized by increased levels of cytokines and inflammatory markers. Chronic inflammation is a well-documented factor in tumorigenesis, potentially promoting the occurrence and progression of cancers, including EC (19). (II) Immune system dysfunction: impaired kidney function might alter immune surveillance and response capabilities, reducing the efficiency of eliminating precancerous cells and cancer cells (20). (III) Oxidative stress: reduced renal clearance leading to the accumulation of waste products can cause oxidative stress, resulting in DNA damage and promoting genetic mutations, thereby leading to cancer development (21). These interconnected pathways suggest that elevated levels of creatinine and cystatin C, as manifestations of renal dysfunction, might indirectly increase EC risk through systemic effects on inflammation, immune function, and oxidative stress. Our findings underscore the complex interplay between kidney function markers and cancer risk, highlighting the need for further research to unravel the intricate mechanisms involved (22). In our study, no association was found between GFR or urinary albumin and EC risk, which may be due to the specificity of these markers in reflecting different aspects of renal and systemic health. While levels of creatinine and cystatin C are influenced by glomerular filtration and may be affected by muscle mass and other systemic factors, they might be more closely related to systemic pathologies affecting cancer risk. In contrast, GFR and urinary albumin, as comprehensive indicators of kidney function, indicate renal damage or stress and may not directly or sufficiently capture systemic pathophysiological changes related to cancer risk. This distinction suggests that the pathways linking renal dysfunction to EC risk may be more specifically related to the systemic effects reflected by creatinine and cystatin C, rather than the renal function state per se, as indicated by GFR and urinary albumin.

This MR analysis has some noteworthy limitations that require consideration. Firstly, while MR-Egger intercept tests did not reveal evidence of pleiotropy, it remains challenging to entirely rule out the influence of potential directional pleiotropy. Secondly, the GWASs utilized in this study predominantly consisted of individuals of European descent, potentially limiting the generalizability of our findings to other ethnicities. Notably, the major pathological type of EC patients in European countries differs from those in East Asian countries. Thirdly, renal functional indexes evaluated in this MR: cystatin C, creatinine, urinary albumin and GFR in the original GWAS lacked detailed information and these four indicators might

not fully reflect the function of kidney. Further research and clinical investigations are warranted to fully understand the underlying mechanisms.

Conclusions

Our MR analysis provided compelling evidence of a causal relationship between renal function and the risk of EC. Specifically, we observed that elevated levels of cystatin C and creatinine were associated with a potential increase in EC risk. However, we did not find significant effects for urinary albumin and GFR in relation to EC risk. These findings underscore the importance of renal function in influencing EC susceptibility and emphasize the potential impact of improving kidney health on EC prevention strategies. Addressing and ameliorating renal function could open new avenues for developing targeted approaches to mitigate EC risk and enhance overall cancer prevention efforts.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1764/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1764/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1764/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). No patients were involved in the design, recruitment, or conduct of this study, so ethical approval was not needed.

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