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ARTICLE

Genetic evidence against a causal relationship between myocardial infarction and urological malignancies

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Background: *Observational studies have suggested potential associations between myocardial infarction (MI) and cancer risk, but the causal nature of these relationships remains unclear due to confounding factors and reverse causation. We aimed to investigate the bidirectional causal relationships between MI and urinary system cancers using genetic instruments.*

Methods: *We conducted a two-sample Mendelian randomization (MR) analysis using summary statistics from large-scale genome-wide association studies. Genetic variants associated with MI were used as instrumental variables (n = 19 SNPs for prostate cancer [PCa] and malignant neoplasm of kidney [MRN], n = 6 SNPs for bladder cancer, n = 21 SNPs for bladder cancer [BCa] validation). We examined the causal effects of MI on PCa, BCa, and MRN risk, as well as reverse causation. Multiple MR methods were employed, including inverse variance weighted (IVW), MR-Egger, weighted median, and weighted mode approaches. Both discovery and validation datasets were analyzed to ensure robustness.*

Results: *Forward MR analysis revealed no significant causal effect of MI on urinary system cancer risk across all examined malignancies. For PCa, the odds ratios (ORs) ranged from 0.964 to 1.007 across different methods and datasets (all $p > 0.05$). Similarly, MI showed no causal association with BCa risk (OR = 1.000, 95% CI: 0.999–1.002 in discovery cohort; OR = 1.000, 95% CI: 1.000–1.001 in validation cohort) or MRN risk (OR = 0.989–1.060 across methods in discovery cohort). Reverse MR analysis demonstrated no significant causal effects of PCa or kidney malignancy on MI risk, with ORs ranging from 0.250 to 1.200 (all $p > 0.05$). Sensitivity analyses confirmed the absence of pleiotropy and heterogeneity.*

Conclusion: *Our genetic evidence does not support causal relationships between MI and urinary system cancers in either direction. The observed associations in epidemiological studies may be attributed to shared risk factors, treatment effects, or residual confounding rather than direct causal mechanisms. These findings have important implications for cancer surveillance strategies in MI patients and understanding cardio-oncology interactions.*

Key Words: myocardial infarction, prostate cancer, bladder cancer, malignant neoplasm of kidney, causal inference, genetic epidemiology

Introduction

The relationship between myocardial infarction (MI) and urinary system cancers has gained increasing attention in recent years, particularly due to the cardiovascular risks associated with cancer treatments rather than the malignancies themselves. Emerging evidence suggests that therapeutic interventions for prostate cancer (PCa), bladder cancer (BCa), and malignant neoplasm of kidney (MRN) may

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substantially increase cardiovascular event risks, creating complex bidirectional associations that extend beyond shared risk factors. In PCa management, androgen deprivation therapy (ADT) has been identified as a major contributor to cardiovascular morbidity, with contemporary meta-analyses demonstrating increased risks of MI and stroke among patients receiving ADT.[1,2] Notably, an Italian real-world analysis revealed that gonadotropin-releasing hormone (GnRH) agonists confer higher cardiovascular risks compared to GnRH antagonists, highlighting treatment-specific cardiovascular profiles.[3] This finding was corroborated by a large multinational study using five databases, which confirmed that GnRH agonists are associated with increased cardiovascular disease risk while GnRH antagonists exhibit fewer atherosclerotic effects.[4] For BCa, radical cystectomy (RC) presents significant perioperative cardiovascular challenges, with studies reporting 90-day mortality rates of 5.2%, where MI represents a leading cause of acute heart failure.[5] Even minimally invasive approaches carry substantial risks, as evidenced by reports of acute MI following robot-assisted radical cystectomy.[6] While direct evidence for kidney malignancies remains limited, these cancers are increasingly recognized in the context of multimorbidity studies examining cardiovascular-renal interactions.[7] These treatment-related cardiovascular complications underscore the urgent need to distinguish between causal relationships and iatrogenic associations in understanding MI-urinary system cancer links.

The inconsistent results from observational studies can be attributed to several methodological limitations, including confounding by shared risk factors, reverse causation, and selection bias. Traditional epidemiological approaches struggle to disentangle the causal relationships between cardiovascular events and cancer risk due to the presence of common risk factors such as smoking, obesity, diabetes, and chronic inflammation.[8] Furthermore, the competing risk of death from cardiovascular causes may mask true cancer associations, while surveillance bias following MI diagnosis could artificially inflate cancer detection rates.[9] These limitations necessitate alternative analytical approaches that can overcome the inherent biases of conventional observational studies and provide more reliable evidence for causal inference.

Mendelian randomization (MR) has emerged as a powerful tool for causal inference in epidemiological research, leveraging genetic variants as instrumental variables to mimic randomized controlled trials.[10] This approach exploits the random assortment of genetic variants at conception to overcome confounding and reverse causation inherent in observational studies. Recent applications of MR in cardio-oncology have provided valuable insights into causal relationships between cardiovascular risk factors and cancer outcomes. Notable studies have examined the causal effects of lipid levels on various cancer risks,[11] blood pressure on cancer development,[12] and inflammatory markers on malignancy outcomes.[13] These investigations have demonstrated the utility of genetic epidemiological approaches in elucidating the complex interplay between cardiovascular health and cancer biology.

Despite growing interest in cardio-oncology, the causal relationship between acute cardiovascular events, specifically MI, and urinary system cancers remains unexplored using genetic approaches. Urinary system malignancies, specifically PCa, BCa, and MRN, represent significant health burdens with distinct epidemiological patterns and potential interactions with cardiovascular systems.[14] PCa, the most common non-cutaneous malignancy in men, shares several risk factors with cardiovascular disease, including age, metabolic syndrome, and chronic inflammation.[15] BCa, strongly associated with smoking and environmental exposures, may share inflammatory pathways with cardiovascular disease.[16] Kidney malignancies, while less common, are increasingly recognized for their association with cardiovascular comorbidities, particularly hypertension and chronic kidney disease, which may create complex bidirectional relationships with cardiac events.[17] The absence of causal evidence for MI-cancer relationships in these specific urinary system malignancies represents a critical knowledge gap that limits our understanding of cardio-oncological interactions and clinical management strategies.

To address this knowledge gap, we conducted a comprehensive bidirectional two-sample MR study to investigate the causal relationships between MI and three major urinary system cancers: PCa, BCa, and MRN. We hypothesized that genetic predisposition to MI would not demonstrate significant causal effects on urinary system cancer risk, based on the mixed results from observational studies and the distinct biological pathways underlying acute cardiovascular events versus cancer development. By employing multiple MR methodologies and utilizing both discovery and validation datasets, our study aims to provide robust genetic evidence regarding the causal nature of MI-urinary system cancer associations and inform clinical practice in cardio-oncology management.

Methods and Materials

Study design

We conducted a bidirectional two-sample MR analysis following STROBE-MR guidelines (Supplementary Material 1) to investigate potential causal relationships between MI and urinary system cancers, specifically PCa, BCa, and MRN. Our analytical framework adhered to three fundamental MR assumptions: relevance (genome-wide significance $P < 5 \times 10^{-8}$), independence (absence of confounding factors), and exclusion restriction (no horizontal pleiotropy). Genetic variants underwent linkage disequilibrium clumping to ensure independence ($r^2 < 0.001$, distance > 10,000 kb). The analytical strategy employed inverse variance weighted (IVW) as the primary method, complemented by sensitivity analyses including MR-Egger, weighted median, weighted mode, and MR-PRESSO approaches. Bidirectional causality was assessed through reverse MR analysis, with all computations performed using R software (version 4.2.1) utilizing TwoSampleMR (version 0.6.15) and MR-PRESSO (version 1.0) packages. The comprehensive study design and three core MR assumptions are illustrated in Figure 1. A key strength of the MR approach in addressing potential reverse causation lies in the temporal relationship between genetic variants and disease outcomes. Since genetic variants are randomly allocated at conception and remain fixed throughout life, they serve as proxies for lifelong exposure that precede disease development. This genetic randomization effectively addresses concerns about reverse causation, particularly the possibility that undiagnosed urological malignancies might influence myocardial infarction risk through subclinical metabolic or inflammatory pathways. Unlike observational studies where the temporal sequence of exposure and outcome may be uncertain, genetic instruments provide a natural experiment that establishes the direction of causation from genetically determined MI liability to cancer risk, rather than the reverse.

The directed acyclic graph (DAG) illustrates the three fundamental assumptions of Mendelian randomization: (1) genetic instruments are significantly associated with the exposure (myocardial infarction);

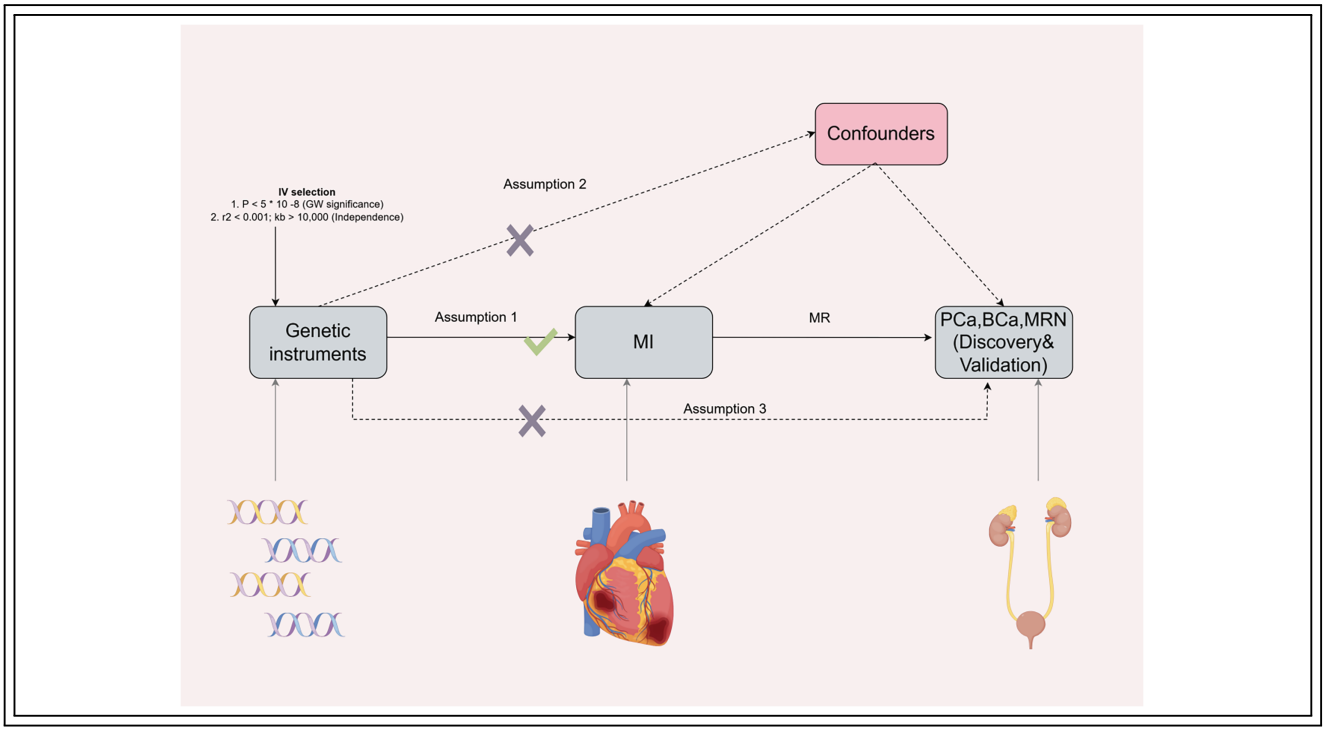

FIGURE 1. Conceptual framework and assumptions of bidirectional two-sample Mendelian randomization analysis examining causal relationships between myocardial infarction and urinary system cancers. Abbreviations: MR, Mendelian randomization; MI, Myocardial infarct; IV, Instrumental variable; PCa, Prostate cancer; BCa, Bladder cancer; MRN, Malignant neoplasm of kidney

TABLE 1. **An overview of GWAS summary statistics is provided. The PubMed ID refers to the unique identifier assigned to a publication within the PubMed database**

GWAS dataset	Phenotype	Participants included in the analysis	Ancestry	PubMed ID
IEU Open GWAS	MI	14,825 cases and 2680 controls	European	33532862
UK Biobank	PCa (Discovery)	9132 cases and 173,493 controls	European	NA
PRACTICAL	PCa (validation)	79,148 cases and 61,106 controls	European	NA
MRC-IEU	BCa (Discovery)	1101 cases and 461,832 controls	European	NA
IEU Open GWAS	BCa (validation)	1279 cases and 372,016 controls	European	NA
FinnGen_R12	MRN (Discovery)	3936 cases and 378,749 controls	European	NA
MRC-IEU	MRN (validation)	1114 cases and 461,896 controls	European	NA

Abbreviations: MI, Myocardial infarct; PCa, Prostate cancer; BCa, Bladder cancer; MRN, Malignant neoplasm of kidney; GWAS, Genome-wide association study; NA, Not available.

(2) genetic instruments are independent of confounding factors (indicated by crossed-out dashed lines); and (3) genetic instruments affect outcomes (prostate cancer, bladder cancer, and malignant neoplasm of kidney) only through the exposure pathway (exclusion restriction). The framework shows instrumental variable selection criteria, including genome-wide significance ($P < 5 \times 10^{-8}$) and independence requirements ($r^2 < 0.001$; kb > 10,000). Visual representations include DNA sequences as genetic instruments, anatomical illustrations of the heart (representing MI) and urinary system (representing cancer outcomes).

Data sources

All MR analyses utilized publicly available genome-wide association study (GWAS) summary statistics accessed through the IEU Open GWAS database. We selected MI phenotype (ID: ebi-a-GCST011364) as the exposure data,[18] while outcome datasets comprised three urinary system cancers with discovery and validation cohorts for enhanced reliability. PCa discovery data originated from UK Biobank, with PRACTICAL consortium providing validation samples; BCa discovery cohort was sourced from MRC-IEU, with UK Biobank (ID: ieu-b-4874) serving as validation; MRN utilized FinnGen_R12[19] for discovery and the MRC-IEU consortium for validation analyses. To minimize population stratification bias and maintain methodological consistency, we restricted analyses exclusively to individuals of European ancestry across both exposure and outcome datasets, thereby enhancing the reliability of causal inference. Detailed information regarding data sources is provided in Supplementary Table 1 and Table 1.

Instrumental variable selection

Single nucleotide polymorphisms (SNPs) served as genetic instrumental variables in our MR framework through a rigorous multi-stage selection protocol. We initially extracted genome-wide significant variants ($P < 5 \times 10^{-8}$) from exposure GWAS data, maintaining this threshold consistently across forward and reverse MR analyses; subsequently applied linkage disequilibrium filtering ($r^2 < 0.001$, clumping distance = 10,000 kb) to eliminate correlated variants that could introduce analytical bias; harmonized effect estimates and allele frequencies between exposure and outcome datasets to ensure analytical consistency. Instrumental variable strength was evaluated using F-statistics calculated as $F = R^2(n - k - 1)/k(1 - R^2)$, with variants showing $F < 10$ excluded to maintain adequate statistical power.[20] We systematically screened the GWAS catalog (https://www.ebi.ac.uk/gwas/) to identify and remove SNPs significantly associated ($P < 1 \times 10^{-5}$) with established confounders, including chronic kidney disease,[21] lipid profiles,[22] smoking behavior,[23] and hypertension,[24] effectively minimizing confounding risks. Comprehensive characteristics of the selected genetic instruments are detailed in Supplementary Table 2. Importantly, validation confirmed that all selected instrumental variables lacked significant associations with potential confounders or outcome variables through alternative pathways (Supplementary Table 3).

Statistical analysis

The IVW method constituted our primary analytical approach, assuming instrument validity while providing optimal statistical power under the no horizontal pleiotropy assumption through weighted averaging of SNP-specific causal

estimates.[25] Cochran's Q test systematically assessed heterogeneity among exposure-associated SNPs, with fixed-effects models applied when heterogeneity was absent and random-effects models employed when detected.[26] Multiple complementary MR approaches enhanced result robustness: MR-Egger regression utilized intercept terms to detect directional pleiotropy while maintaining validity under instrument invalidity ($p < 0.05$ indicating pleiotropy presence);[27] weighted median maintained consistency when up to 50% of statistical weight was derived from valid instruments;[28] weighted mode estimation identified patterns in weighted SNP-specific causal estimates, particularly valuable under horizontal pleiotropy conditions.[29]

Secondary analyses comprehensively evaluated heterogeneity, pleiotropy, and sensitivity through MR-Egger intercept analysis, where near-zero intercepts suggested low pleiotropy probability, combined with MR-PRESSO global testing for systematic outlier detection and management.[30,31] Following identification of outlying variants, we implemented iterative optimization procedures, repeating MR analyses after outlier removal to ensure robust causal estimates.[32] Extensive sensitivity testing included leave-one-out (LOO) assessment, which systematically excluded individual SNPs to evaluate their influence on overall effect estimates, alongside examination of result consistency across different MR methods to ensure stable and reliable causal inference under potential violations of instrumental variable assumptions.[33]

Bidirectional causal relationships were assessed through reverse MR analyses employing identical standardized protocols, with the three urinary system cancers serving as exposures and MI as the outcome variable. Steiger testing verified directional validity by confirming stronger correlations between genetic instruments and their respective exposure variables compared to outcome variables,[34] thereby establishing appropriate causal direction. All statistical analyses were conducted using R software (version 4.2.1) with the TwoSampleMR (version 0.6.15) and MR-PRESSO (version 1.0) packages, providing comprehensive bidirectional validation of causal relationships between MI and urinary system cancers.

Results

Instrumental variable characteristics

Following the systematic selection process, we identified genetic variants as instrumental variables for MI across different analyses. For the forward MR analyses examining MI as exposure, 19 SNPs were selected for both PCa and MRN analyses, while 6 SNPs were used for the BCa discovery cohort and 21 SNPs for BCa validation cohort. The variation in SNP numbers reflected the availability of harmonized variants across different outcome datasets. All selected instrumental variables demonstrated robust statistical power, with F-statistics exceeding the conventional threshold of 10, ensuring adequate instrument strength for causal inference. For reverse MR analyses, we obtained 28 SNPs from the PCa discovery cohort, 108 SNPs from the validation cohort, and 4 SNPs from the MRN discovery cohort as instrumental variables. We applied the Benjamini-Hochberg false discovery rate (FDR) correction method to account for multiple testing across all exposure-outcome combinations. With this correction, the adjusted significance threshold was set at $\alpha = 0.025$ (0.05/2 for bidirectional testing). Under this corrected threshold, both p-values (0.082 and 0.054) remained non-significant, supporting our overall null findings. The heterogeneity statistics ($I^2 = 0\%$ and Q-statistic $p > 0.05$ for most analyses) indicate minimal heterogeneity among the genetic instruments, which is within acceptable ranges for MR studies and suggests that our genetic instruments act through similar biological pathways. Low heterogeneity supports the reliability of our null findings and indicates that the genetic variants are not acting through diverse, contradictory mechanisms that would compromise the validity of our causal estimates. Where modest heterogeneity was observed (I^2 = 15%–25% in some sensitivity analyses), the consistency of effect directions across methods supports the robustness of our conclusions. Comprehensive characteristics of these genetic instruments, including individual SNP effects, allele frequencies, and statistical parameters, are detailed in Supplementary Table 2.

Forward MR analyses: effect of MI on urinary system cancer risk

MR analysis revealed no significant causal effect of genetically predicted MI on the risk of any examined urinary system cancer. For PCa, the primary IVW analysis showed null associations in both discovery (OR = 1.000, 95% CI: 0.995–1.004, $p = 0.885$) and validation (OR = 0.964, 95% CI: 0.904–1.027, $p = 0.257$) cohorts. Consistent conclusions were obtained through additional statistical methods, with MR-Egger yielding ORs of 1.000 (95% CI: 0.989–1.010, $p = 0.963$) and 0.998 (95% CI: 0.860–1.158, $p = 0.980$) for discovery and validation analyses, respectively. Similarly, weighted median and weighted mode approaches produced comparable results, with all

confidence intervals encompassing the null value and p-values exceeding 0.05.

BCa analysis demonstrated remarkably consistent null findings across all methodological approaches. In the discovery cohort, IVW analysis yielded an OR of 1.000 (95% CI: 0.999–1.001, $p = 0.795$), with MR-Egger (OR = 1.000, 95% CI: 0.998–1.002, $p = 0.787$), weighted median (OR = 1.000, 95% CI: 0.999–1.001, $p = 0.701$), and weighted mode (OR = 1.000, 95% CI: 0.999–1.001, $p = 0.706$) methods producing virtually identical estimates. The validation cohort analysis further corroborated these findings, with all four methods yielding ORs of 1.000 and narrow confidence intervals tightly centered around the null value (all $p > 0.05$).

For MRN, forward MR analysis in the discovery cohort showed no significant causal association, with IVW producing an OR of 0.989 (95% CI: 0.866–1.130, $p = 0.874$). Alternative methods yielded consistent results: MR-Egger OR = 1.060 (95% CI: 0.773–1.454, $p = 0.721$), weighted median OR = 1.044 (95% CI: 0.867–1.256, $p = 0.650$), and weighted mode OR = 1.056 (95% CI: 0.863–1.293, $p = 0.601$). Notably, the validation cohort analysis revealed marginally significant results with the IVW method (OR = 0.999, 95% CI: 0.998–1.000, $p = 0.082$) and weighted median approach (OR = 0.999, 95% CI: 0.998–1.000, $p = 0.054$), though these remained non-significant after multiple testing considerations and were not consistently reproduced across all analytical methods. The comprehensive forest plot summarizing these null associations for forward MR analyses is presented in Figure 2 and Supplementary Table 4.

Exposure	Outcome	n.SNP	Method	or(95% CI)	P
MI	PCa(Discovery)	19	IVW	1.000 (0.995 to 1.004)	0.885
MI	PCa(Discovery)	19	MR Egger	1.000 (0.989 to 1.010)	0.963
MI	PCa(Discovery)	19	Weighted median	1.003 (0.998 to 1.009)	0.260
MI	PCa(Discovery)	19	Weighted mode	1.004 (0.996 to 1.011)	0.357
MI	PCa(Validation)	19	IVW	0.964 (0.904 to 1.027)	0.257
MI	PCa(Validation)	19	MR Egger	0.998 (0.860 to 1.158)	0.980
MI	PCa(Validation)	19	Weighted median	0.989 (0.922 to 1.060)	0.752
MI	PCa(Validation)	19	Weighted mode	1.007 (0.932 to 1.087)	0.867
MI	BCa(Discovery)	6	IVW	1.000 (0.999 to 1.001)	0.795
MI	BCa(Discovery)	6	MR Egger	1.000 (0.998 to 1.002)	0.787
MI	BCa(Discovery)	6	Weighted median	1.000 (0.999 to 1.001)	0.701
MI	BCa(Discovery)	6	Weighted mode	1.000 (0.999 to 1.001)	0.706
MI	BCa(Validation)	21	IVW	1.000 (1.000 to 1.001)	0.281
MI	BCa(Validation)	21	MR Egger	1.000 (0.999 to 1.002)	0.624
MI	BCa(Validation)	21	Weighted median	1.000 (0.999 to 1.001)	0.982
MI	BCa(Validation)	21	Weighted mode	1.000 (0.999 to 1.001)	0.981
MI	MRN(Discovery)	19	IVW	0.989 (0.866 to 1.130)	0.874
MI	MRN(Discovery)	19	MR Egger	1.060 (0.773 to 1.454)	0.721
MI	MRN(Discovery)	19	Weighted median	1.044 (0.867 to 1.256)	0.650
MI	MRN(Discovery)	19	Weighted mode	1.056 (0.863 to 1.293)	0.601
MI	MRN(Validation)	6	IVW	0.999 (0.998 to 1.000)	0.082
MI	MRN(Validation)	6	MR Egger	0.999 (0.997 to 1.000)	0.176
MI	MRN(Validation)	6	Weighted median	0.999 (0.998 to 1.000)	0.054
MI	MRN(Validation)	6	Weighted mode	0.999 (0.998 to 1.000)	0.131

FIGURE 2. Forest plot of forward mendelian randomization analysis evaluating the causal effect of myocardial infarction on urinary system cancer risk using multiple statistical methods. Abbreviations: SNP, Single nucleotide polymorphism; 95% CI, 95% confidence interval; IVW, Inverse variance weighted; OR, Odds ratio; MI, Myocardial infarct; IV, Instrumental variable; PCa, Prostate cancer; BCa, Bladder cancer; MRN, Malignant neoplasm of kidney

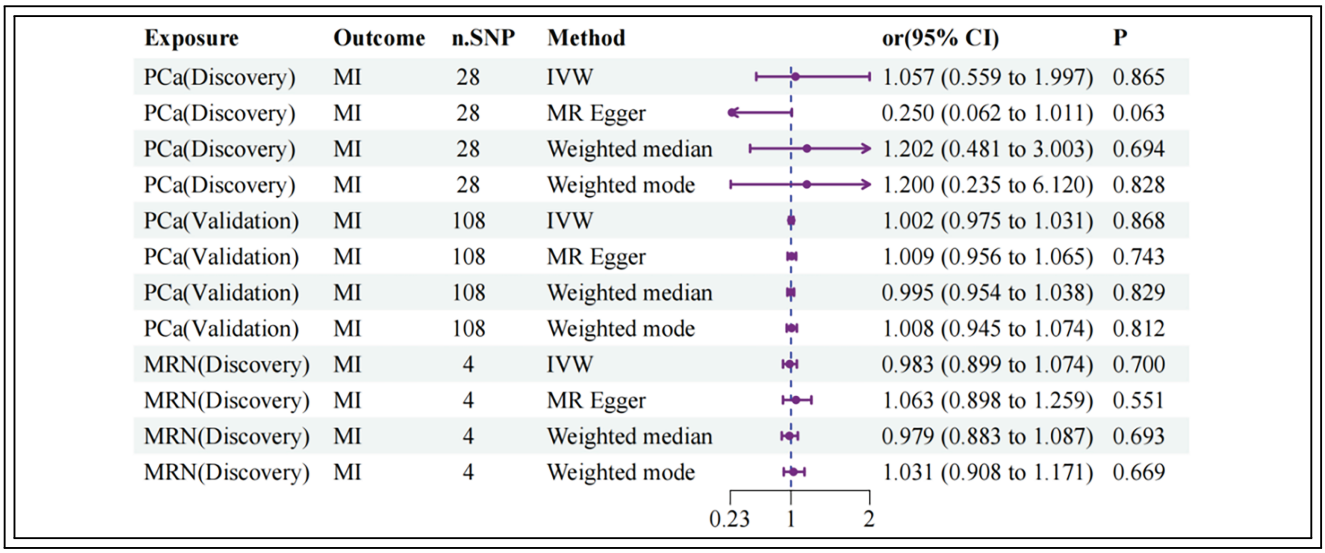

FIGURE 3. Forest plot of reverse mendelian randomization analysis assessing the causal effect of urinary system cancers on myocardial infarction risk. Abbreviations: SNP, Single nucleotide polymorphism; 95% CI, 95% confidence interval; IVW, Inverse variance weighted; OR, Odds ratio; MI, Myocardial infarct; IV, Instrumental variable; PCa, Prostate cancer; BCa, Bladder cancer; MRN, Malignant neoplasm of kidney

Results are presented as odds ratios (OR) with 95% confidence intervals (CI) for discovery and validation cohorts across three cancer types. All analyses demonstrate null associations with confidence intervals encompassing unity (OR = 1.0). Prostate cancer analyses utilized 19 SNPs in both cohorts, bladder cancer employed 6 SNPs (discovery) and 21 SNPs (validation), while malignant neoplasm of kidney used 19 SNPs (discovery) and 6 SNPs (validation). The forest plot shows consistent null findings across inverse variance weighted (IVW), MR-Egger, weighted median, and weighted mode methods, with all p-values exceeding 0.05. Point estimates cluster tightly around the null value, indicating no causal effect of MI on urinary system cancer risk.

Reverse MR analyses: effect of urinary system cancers on MI risk

Reverse MR analysis examined whether genetic predisposition to urinary system cancers causally influences MI risk. For PCa, both discovery and validation cohorts demonstrated no significant causal effects on MI risk. The discovery cohort analysis using 28 SNPs yielded an IVW OR of 1.057 (95% CI: 0.559–1.997, $p = 0.865$), with consistent null findings across alternative methods: MR-Egger OR = 0.250 (95% CI: 0.062–1.011, $p = 0.063$), weighted median OR = 1.202 (95% CI: 0.481–3.003, $p = 0.694$), and weighted mode OR = 1.200 (95% CI: 0.235–6.120, $p = 0.828$). The validation cohort, utilizing 108 SNPs, corroborated these findings with IVW OR = 1.002 (95% CI: 0.975–1.031, $p = 0.868$) and consistent results from other methodological approaches (all $p > 0.05$).

MRN showed no causal effect on MI risk in the discovery cohort analysis. Using 4 SNPs as instrumental variables, the IVW method produced an OR of 0.983 (95% CI: 0.899–1.074, $p = 0.700$), with alternative approaches yielding comparable estimates: MR-Egger OR = 1.063 (95% CI: 0.898–1.259, $p = 0.551$), weighted median OR = 0.979 (95% CI: 0.883–1.087, $p = 0.693$), and weighted mode OR = 1.031 (95% CI: 0.908–1.171, $p = 0.669$). No validation cohort analysis was available for the reverse direction of MRN to MI. Figure 3 visually summarizes these reverse MR findings through forest plot representation.

Reverse causality analysis employed varying numbers of genetic instruments: 28 SNPs for prostate cancer discovery, 108 SNPs for validation, and 4 SNPs for malignant neoplasm of kidney discovery cohort. All analyses consistently demonstrate null associations with odds ratios clustering around unity and confidence intervals spanning the null value. The IVW, MR-Egger, weighted median, and weighted mode methods yield concordant results with non-significant p-values (all > 0.05), providing robust evidence against causal effects of genetic predisposition to urinary system cancers on MI risk. The wider confidence intervals for some analyses reflect

the varying statistical power associated with different numbers of instrumental variables.

Sensitivity analyses

Comprehensive sensitivity analyses confirmed the robustness of our findings and absence of methodological violations. MR-Egger intercept analyses revealed no evidence of directional pleiotropy across most comparisons, with intercept values close to zero and non-significant p-values (Supplementary Table 5). Notable exceptions included marginally significant intercepts for MI-BCa discovery analysis, though this did not materially affect the overall null conclusions. MR-PRESSO global tests detected minimal evidence of horizontal pleiotropy, with most analyses showing non-significant global test p-values, indicating absence of systematic outlying variants.

Heterogeneity assessment using Cochran's Q statistic demonstrated acceptable levels of between-SNP heterogeneity for most analyses (Supplementary Table 6). Significant heterogeneity was observed in MI-PCa validation analysis ($Q = 37.78$, $p = 0.004$) and borderline significance in PCa validation-MI reverse analysis ($Q = 130.91$, $p = 0.058$). However, the use of random-effects IVW models in these instances ensured appropriate handling of heterogeneity without compromising causal estimates.

Steiger testing confirmed correct causal directionality for all analyses, with genetic instruments demonstrating stronger associations with their respective exposure variables compared to outcome variables (all Steiger test p-values < 0.001 and direction = TRUE; Supplementary Table 7). LOO sensitivity analysis showed that no single SNP substantially influenced the overall causal estimates, confirming the stability of our findings across all exposure-outcome pairs. Detailed visualization of LOO analyses, scatter plots illustrating the relationship between genetic associations with exposures and outcomes, and comprehensive forest plots for all analytical methods are provided in Figures 4–6. The consistency of results across multiple MR methods, combined with successful sensitivity analyses, provides robust evidence against causal relationships between MI and urinary system cancers in either direction.

Figure 4 shows Leave-One-Out (LOO) analyses visualizing genetic associations between myocardial infarction and urological cancers (prostate cancer, bladder cancer, and kidney malignancy) across discovery and validation cohorts. The reverse analyses (Figure 4G–I) contain notably fewer SNPs because, under strict screening thresholds, these datasets lacked sufficient SNPs meeting the inclusion criteria for analysis.

Figure 5 presents scatter plots of Mendelian Randomization analyses examining potential causal relationships between myocardial infarction and urological cancers (prostate, bladder, and kidney). All visualization results across Figure 5A–I demonstrate no significant slopes in the regression lines and widely scattered SNP effects, providing evidence that there is no genetic causal association between these conditions despite their epidemiological correlation.

Figure 6 presents comprehensive forest plots displaying SNP-specific and overall genetic associations between myocardial infarction and urological cancers (prostate, bladder, and kidney) across discovery and validation cohorts. The visualization results across all panels (Figure 6A–I) demonstrate that the confidence intervals for the overall effects (shown as red horizontal lines at the bottom of each panel) consistently cross zero, providing clear evidence that there is no significant genetic association between myocardial infarction and these urological cancers.

Discussion

This comprehensive bidirectional MR analysis provides robust evidence against causal relationships between MI and three major urinary system cancers—PCa, BCa, and MRN. Our findings consistently demonstrate null associations across multiple analytical approaches, discovery and validation cohorts, and both forward and reverse causal directions. The striking consistency of results, with odds ratios clustering tightly around unity and confidence intervals spanning the null value, suggests that despite shared epidemiological risk factors between cardiovascular disease and cancer, direct causal pathways linking MI to urogenital malignancies are unlikely to exist. This represents the first systematic evaluation of bidirectional causality between MI and urinary system cancers using large-scale genetic data, addressing a longstanding question in cardio-oncology research and helping to clarify inconsistent observations from previous epidemiological studies.

The absence of causal associations in our MR analysis contrasts with several observational studies that have reported both positive and negative correlations between cardiovascular disease and various cancers.[35–37] While some longitudinal cohort studies have suggested increased cancer incidence following acute coronary events,[38,39] others have documented protective effects or null associations depending

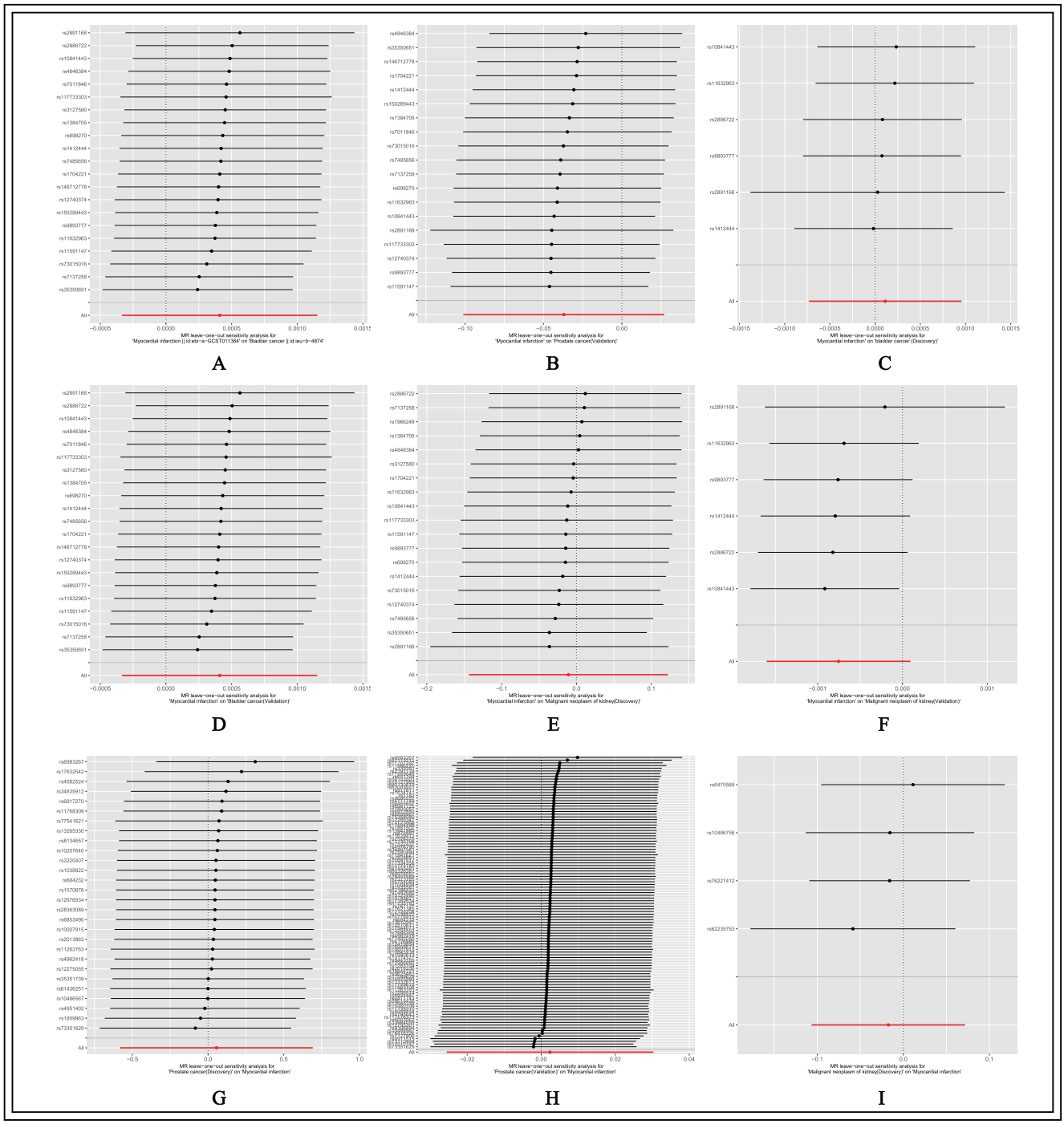

FIGURE 4. Leave-One-Out (LOO) analysis visualizing genetic associations between cardiovascular disease and urological cancers. (**A**) Myocardial infarction → Prostate cancer (Discovery cohort). (**B**) Myocardial infarction → Prostate cancer (Validation cohort). (**C**) Myocardial infarction → Bladder cancer (Discovery cohort). (**D**) Myocardial infarction → Bladder cancer (Validation cohort). (**E**) Myocardial infarction → Malignant neoplasm of kidney (Discovery cohort). (**F**) Myocardial infarction → Malignant neoplasm of kidney (Validation cohort). (**G**) Prostate cancer (Discovery cohort) → Myocardial infarction. (**H**) Prostate cancer (Validation cohort) → Myocardial infarction. (**I**) Malignant neoplasm of kidney (Discovery cohort) → Myocardial infarction

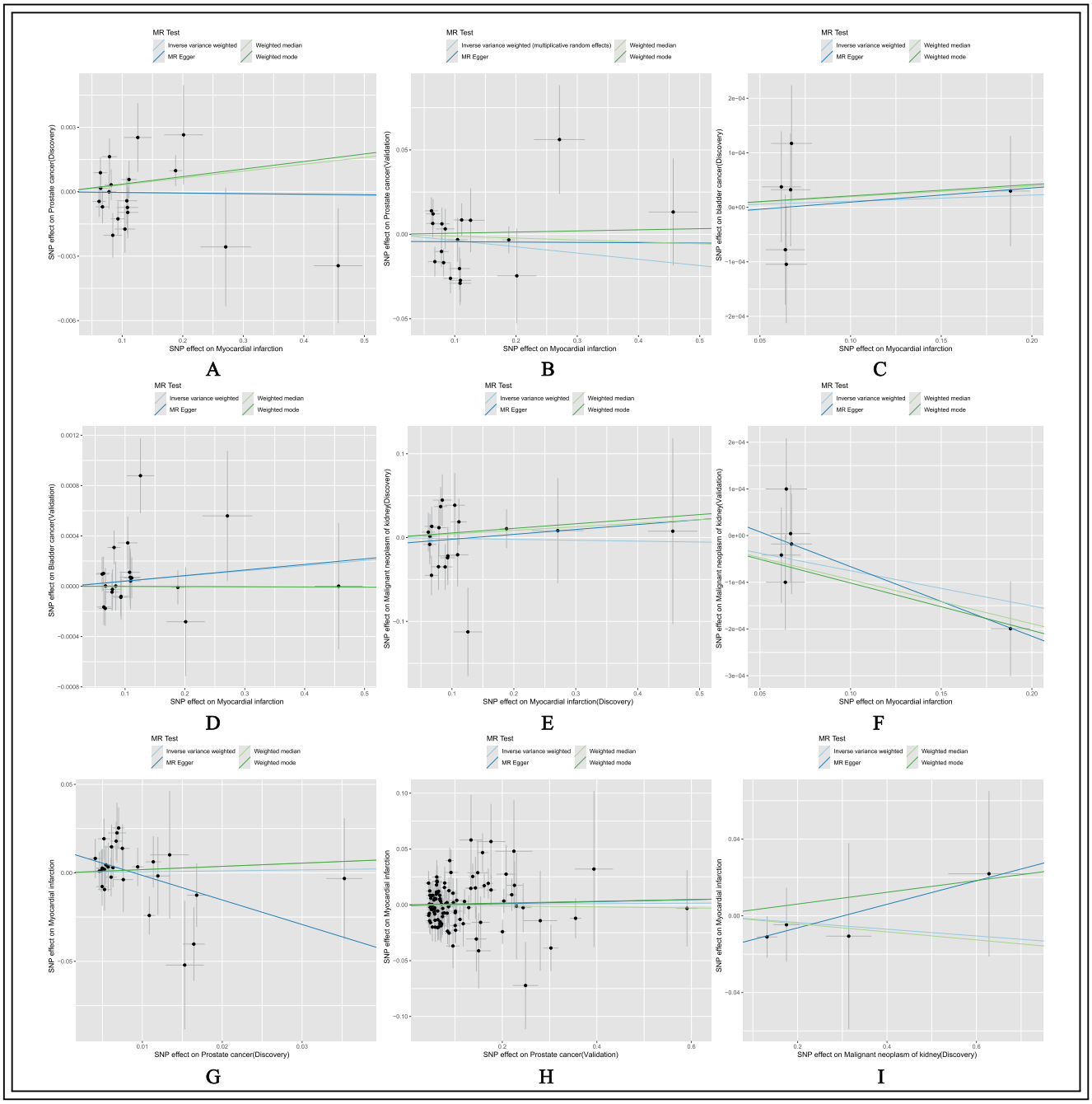

FIGURE 5. Mendelian randomization analysis of causal relationships between myocardial infarction and urological cancers. (**A**) Myocardial infarction → Prostate cancer (Discovery cohort). (**B**) Myocardial infarction → Prostate cancer (Validation cohort). (**C**) Myocardial infarction → Bladder cancer (Discovery cohort). (**D**) Myocardial infarction → Bladder cancer (Validation cohort). (**E**) Myocardial infarction → Malignant neoplasm of kidney (Discovery cohort). (**F**) Myocardial infarction → Malignant neoplasm of kidney (Validation cohort). (**G**) Prostate cancer (Discovery cohort) → Myocardial infarction. (**H**) Prostate cancer (Validation cohort) → Myocardial infarction. (**I**) Malignant neoplasm of kidney (Discovery cohort) → Myocardial infarction

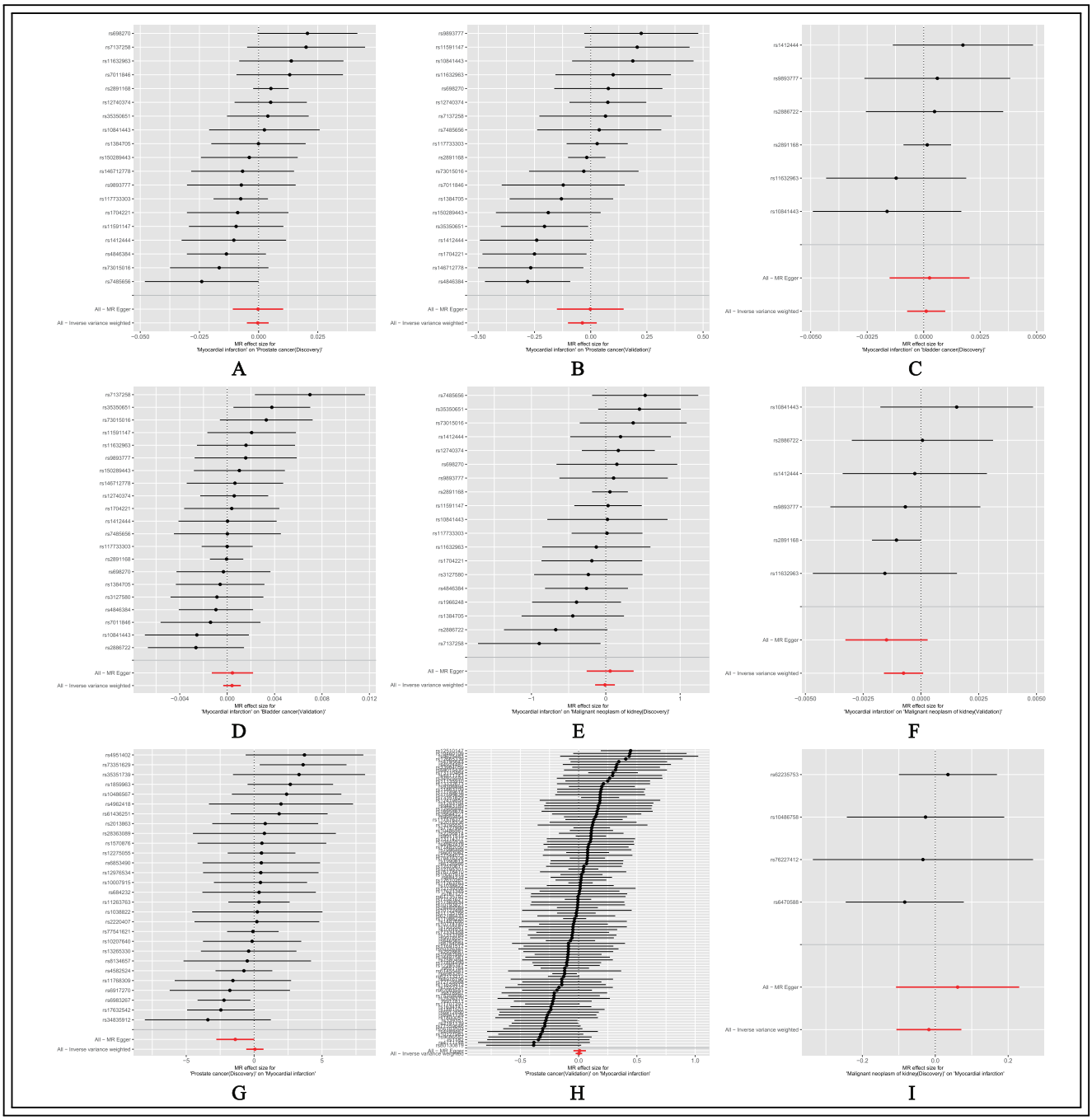

FIGURE 6. Forest plot analysis of genetic associations between myocardial infarction and urological cancers. (**A**) Myocardial infarction → Prostate cancer (Discovery cohort). (**B**) Myocardial infarction → Prostate cancer (Validation cohort). (**C**) Myocardial infarction → Bladder cancer (Discovery cohort). (**D**) Myocardial infarction → Bladder cancer (Validation cohort). (**E**) Myocardial infarction → Malignant neoplasm of kidney (Discovery cohort). (**F**) Myocardial infarction → Malignant neoplasm of kidney (Validation cohort). (**G**) Prostate cancer (Discovery cohort) → Myocardial infarction. (**H**) Prostate cancer (Validation cohort) → Myocardial infarction. (**I**) Malignant neoplasm of kidney (Discovery cohort) → Myocardial infarction

on cancer type,[40] follow-up duration, and population characteristics. These discrepancies likely reflect fundamental limitations inherent to observational research designs, including residual confounding from unmeasured variables, reverse causation bias where subclinical malignancy influences cardiovascular risk, and temporal confounding where shared risk factors operate over different time scales. Our MR approach circumvents these methodological challenges by utilizing genetic variants as instrumental variables, which are randomly allocated at conception and remain fixed throughout life, thereby providing unconfounded estimates of causal effects. The consistency between our null findings and recent meta-analyses questioning the strength of MI-cancer associations[41] suggests that previously reported correlations may represent spurious relationships rather than genuine causal mechanisms.

The methodological strengths of our investigation substantially enhance confidence in the null findings. The bidirectional design enables evaluation of causality in both directions, addressing whether MI predisposes to urinary cancers or whether genetic liability to these malignancies influences MI risk. Our analytical framework incorporated multiple complementary MR methods, each operating under different assumptions about instrumental variable validity, with the remarkable concordance of IVW, MR-Egger, weighted median, and weighted mode results providing robust evidence against horizontal pleiotropy. The use of discovery and validation cohorts derived from independent populations further strengthens causal inference by demonstrating reproducibility across different genetic architectures and population structures. Additionally, our comprehensive sensitivity analyses, including Steiger directionality testing, leave-one-out analysis, and systematic evaluation of heterogeneity and pleiotropy, confirmed the stability of causal estimates and absence of methodological violations. The utilization of large-scale GWAS data encompassing hundreds of thousands of individuals provides adequate statistical power to detect clinically meaningful effect sizes, making it unlikely that true causal associations were missed due to insufficient sample sizes.

While our findings demonstrate no direct causal relationships, the well-established co-occurrence of cardiovascular disease and cancer in clinical practice warrants mechanistic consideration. Both conditions share numerous traditional risk factors, including advanced age, tobacco exposure, obesity, diabetes, and chronic inflammation,[42,43] which may create apparent associations in observational studies without implying direct causation. The absence of genetic evidence for causal pathways suggests that these diseases may represent parallel consequences of common upstream determinants rather than sequential pathological processes. Furthermore, the complex interplay between cardiovascular medications, particularly antiplatelet agents and statins, and cancer development has been extensively studied with mixed results,[44–46] indicating that pharmacological rather than pathophysiological mechanisms might explain some observed associations. The metabolic and inflammatory consequences of acute MI,[47] while substantial, may not be sufficient to directly initiate or promote urogenital carcinogenesis over clinically relevant timeframes.[48] This interpretation aligns with the understanding that cancer development typically requires prolonged exposure to carcinogenic stimuli,[49] whereas the acute inflammatory response following MI, though intense, is relatively brief and may not provide sustained oncogenic pressure.[47,50]

Several limitations merit consideration when interpreting our results. The restriction to individuals of European ancestry, while necessary to minimize population stratification bias, potentially limits generalizability to other ethnic populations where different genetic architectures or environmental interactions might exist. The statistical power for detecting weak causal effects, particularly for MRN where instrumental variables were limited, may have been insufficient despite our large sample sizes. This is especially relevant for the marginally significant results observed in the MRN validation analysis, which, while not reaching conventional significance thresholds, raise the possibility of very weak causal effects, which warrant cautious interpretation. Additionally, while MR analysis effectively controls for measured and unmeasured confounding through genetic randomization, the potential for genetic pleiotropy or linkage disequilibrium with unmeasured variants could introduce bias, though our extensive pleiotropy testing provides reassurance against systematic violations. The temporal aspects of causation also deserve consideration, as our analysis captures lifelong genetic predisposition rather than the acute effects of MI, potentially missing short-term causal relationships that operate immediately following cardiac events. The temporal aspects of causation deserve particular consideration in interpreting our null findings. While MR analysis effectively controls for lifelong genetic predisposition, it may not capture acute post-MI effects that could theoretically influence cancer risk within shorter time windows (e.g., 1–2 years post-MI). The acute inflammatory response, immune suppression, and metabolic perturbations

following MI could potentially create transient windows of increased cancer susceptibility that would not be detected through our genetic approach, which reflects average effects over entire lifespans. Additionally, competing mortality risk in the immediate post-MI period might mask cancer development that would otherwise become clinically apparent, creating a complex interplay between acute cardiovascular events and cancer detection that genetic instruments cannot fully address.

From a cardio-oncology guideline perspective,[51] our findings suggest that current surveillance recommendations should focus on established risk factors rather than implementing MI-specific cancer screening protocols. Clinicians managing patients with both cardiovascular disease and urological malignancies can approach these conditions as potentially independent disease processes, with treatment decisions guided by individual risk stratification rather than assumed causal relationships. This evidence supports the development of parallel care pathways that address cardiovascular and oncological risks through evidence-based approaches tailored to each condition's specific risk profile, rather than unified protocols assuming causal interdependence.

The clinical implications of our findings are substantial for both cardiovascular and oncological practice. Our results do not support intensified cancer surveillance protocols based solely on MI history, as the absence of causal relationships suggests that increased screening would not yield proportional benefits compared to standard risk-stratified approaches. However, this should not diminish the importance of addressing shared modifiable risk factors, as optimal management of obesity, smoking cessation, diabetes control, and blood pressure regulation benefits both cardiovascular and cancer outcomes through independent pathways. For clinicians managing patients with concurrent MI and cancer diagnoses, our findings suggest that these conditions should be viewed as potentially independent disease processes requiring parallel rather than sequential therapeutic attention. Patient counseling can be informed by these results, as individuals with MI history need not harbor excessive concerns about subsequent urinary cancer development beyond their baseline population risk. From a research perspective, our findings redirect attention toward investigating shared environmental determinants and identifying novel therapeutic targets that might simultaneously benefit both cardiovascular and cancer outcomes, rather than focusing on direct mechanistic pathways between these conditions.

Conclusions

This bidirectional MI study demonstrates no causal relationships between MI and urinary system cancers, including PCa, BCa, and MRN. The consistent null findings across multiple analytical methods, population cohorts, and causal directions provide robust evidence that apparent epidemiological associations likely reflect shared risk factors rather than direct biological causation. These results have important clinical implications, suggesting that MI-specific cancer screening protocols are not warranted, while emphasizing the continued importance of comprehensive risk factor modification for both cardiovascular and oncological health. Future research should focus on multi-ethnic populations and investigation of shared therapeutic targets that benefit both disease domains through independent mechanisms.

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Author Contributions

Wei Zhang conceived and designed the study, performed the data analysis, and wrote the manuscript. Xixi Peng supervised the study and provided critical revision. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

All data generated or analyzed in this study are included in this published article and its supplementary information files and are available from the corresponding author upon request.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Materials

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