# No genetic causal links detected between antihypertensive medications and bladder cancer: insights from a trans-ancestry, drug-target Mendelian randomization analysis

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Bladder cancer (Bca) is a malignant condition that affects the urinary bladder and typically originates from the urothelial cells that line the bladder. Muscle-invasive bladder cancer (MIBC) has a relatively high risk of progression and metastasis [1]. The global annual number of cases of bladder cancer exceeds 500,000 [2]. This disease primarily affects adults, with the majority of diagnoses occurring in individuals over the age of 55. Symptoms commonly experienced by patients include gross or microscopic hematuria (the presence of blood in the urine), which can be quite distressing [3].

In recent years, antihypertensive drugs, as a core strategy for the primary and secondary prevention of cardiovascular diseases (CVDs), have formed a multilevel evidence chain because of their benefits in reducing all-cause mortality and major adverse cardiovascular events (MACEs). A Global Burden of Disease (GBD) study revealed that hypertension remains the leading modifiable risk factor for death worldwide, and systematic blood pressure-lowering treatment can significantly reverse this trend [4]. Against this backdrop, the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC) have clearly set blood pressure control (systolic blood pressure < 130 mm Hg) as the primary goal of hypertension management, emphasizing the need to develop individualized plans on the basis of the characteristics of drug classes and patient features [5]. A substantial amount of evidence-based support has been obtained for the role of antihypertensive drugs in reducing the risk of cardiovascular diseases and all-cause mortality. The renin–angiotensin–aldosterone system (RAAS) inhibitors include ACEIs and ARBs. Both the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) and IDNT (Irbesartan Diabetic Nephropathy Trial) studies have shown that losartan and irbesartan demonstrate cardiovascular (CV) benefits, reducing the incidence of cardiovascular-related death, congestive heart failure, myocardial infarction, and cerebrovascular events. Furthermore, in a real-world study of elderly hypertensive patients in Italy, current users of calcium channel blockers significantly reduced the risk of CV events, hos-

AMS

pitalization, and mortality [6]. A systematic review from the Cochrane Library [7] also revealed that, compared with placebo, β-blockers were associated with a lower total incidence of CVD.

Numerous epidemiological observational studies have explored the association between the use of antihypertensive medications and the risk of bladder cancer, but the findings have been inconsistent. For example, a case-control study from Taiwan Province, China [8], reported a significant association between the use of diuretics and any type of urinary tract cancer; however, a population-based case-control study from Los Angeles [9] reported that the use of high doses of diuretics was not associated with the occurrence of Bca. These conflicting results may be related to methodological biases in traditional pharmacoepidemiologic studies; for example, if confounding factors such as smoking, alcohol consumption, diet, and obesity of study participants are not adjusted for, residual confounding may arise, thereby affecting the reliability of the study outcomes.

Drug-target Mendelian randomization (MR), a research method that utilizes genetic approaches to investigate the causal relationship between drug targets and disease outcomes, can avoid the confounding biases present in traditional pharmacoepidemiologic studies, thus allowing for inferences about whether drug targets have a causal

effect on diseases. Therefore, the objective of this study was to conduct a comprehensive drug-target-based MR analysis to systematically assess the causal relationships between various classes of antihypertensive medications (Supplementary Table SII) and bladder cancer, with the study population including individuals of European and East Asian descent.

**Methods.** This study conforms to the MR_STROBE reporting guidelines (Supplementary Table SI) and is predicated on the three fundamental assumptions of MR (Figure 1). A schematic representation of the study's methodology is depicted in Figure 1. The data sources utilized in this research are specified in Supplementary Table SIII. Primary analysis of bladder cancer outcomes in Europeans was conducted via the FinnGen Biobank dataset, with replication analysis performed by the Neale Lab. For East Asians, the bladder cancer outcome study was based on data from the China Kadoorie Biobank (CKB).

In accordance with the previously published MR study [10], for European participants, the present study utilized the largest GWAS summary dataset on bladder cancer, which was freely accessible from the FinnGen Biobank. In total, the dataset includes 2,682 cases and 26,795 controls related to Bca outcomes, predominantly identified through ICD-10 codes (ICD-O-3). During the
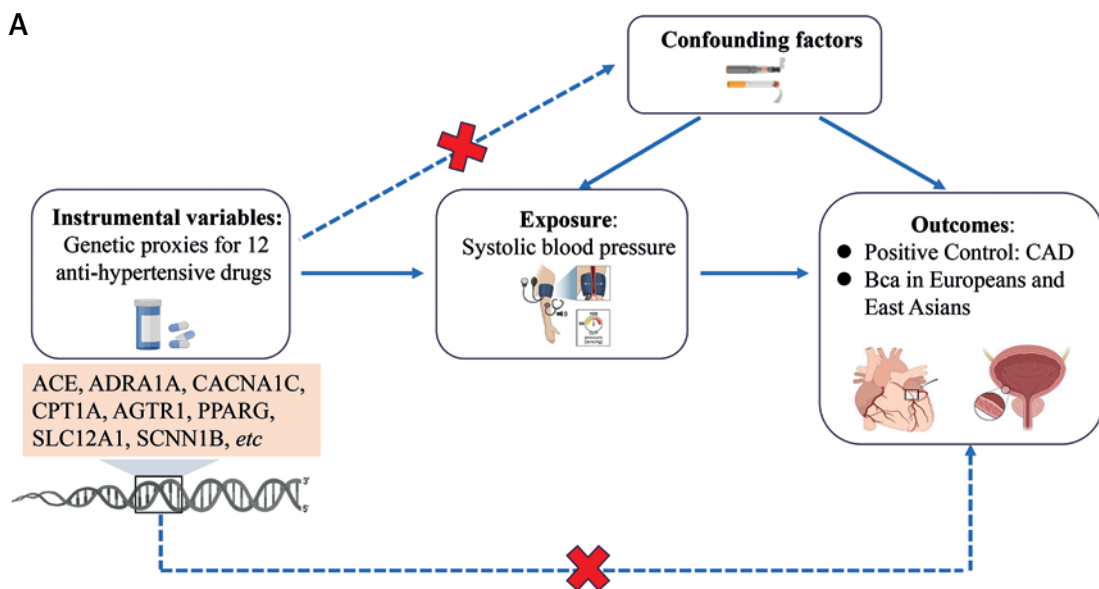


**Figure 1. A** – Three key assumptions of Mendelian randomization (MR) were used in this study: (1) the instrumental variables (genetic proxies for 12 antihypertensive drugs) are not related to the confounders (dashed line and red ✖); (2) the instrumental variables (genetic proxies for 12 antihypertensive drugs) are related to the exposure factor (systolic blood pressure) (solid line); and (3) the instrumental variables (genetic proxies for 12 antihypertensive drugs) are not directly related to the outcome (skin cancer) (dashed line and red ✖)

*EUR – Europeans, EAS – East Asians, SBP – systolic blood pressure, ACEI – angiotensin-converting enzyme inhibitors, BBs – β-adrenoceptor blockers, CCBs – calcium channel blockers, ARB – angiotensin-II receptor antagonists, ANBs – adrenergic neuron blockers, Cas – centrally acting antihypertensives, LDs – loop diuretics, PSDs – potassium-sparing diuretics (PSDs) and aldosterone antagonists, Ris – renin inhibitors, AABs – α-adrenoceptor blockers, TDs – thiazides and related diuretics, vasodilator antihypertensives, CAD – coronary artery disease, Bca – bladder cancer.*
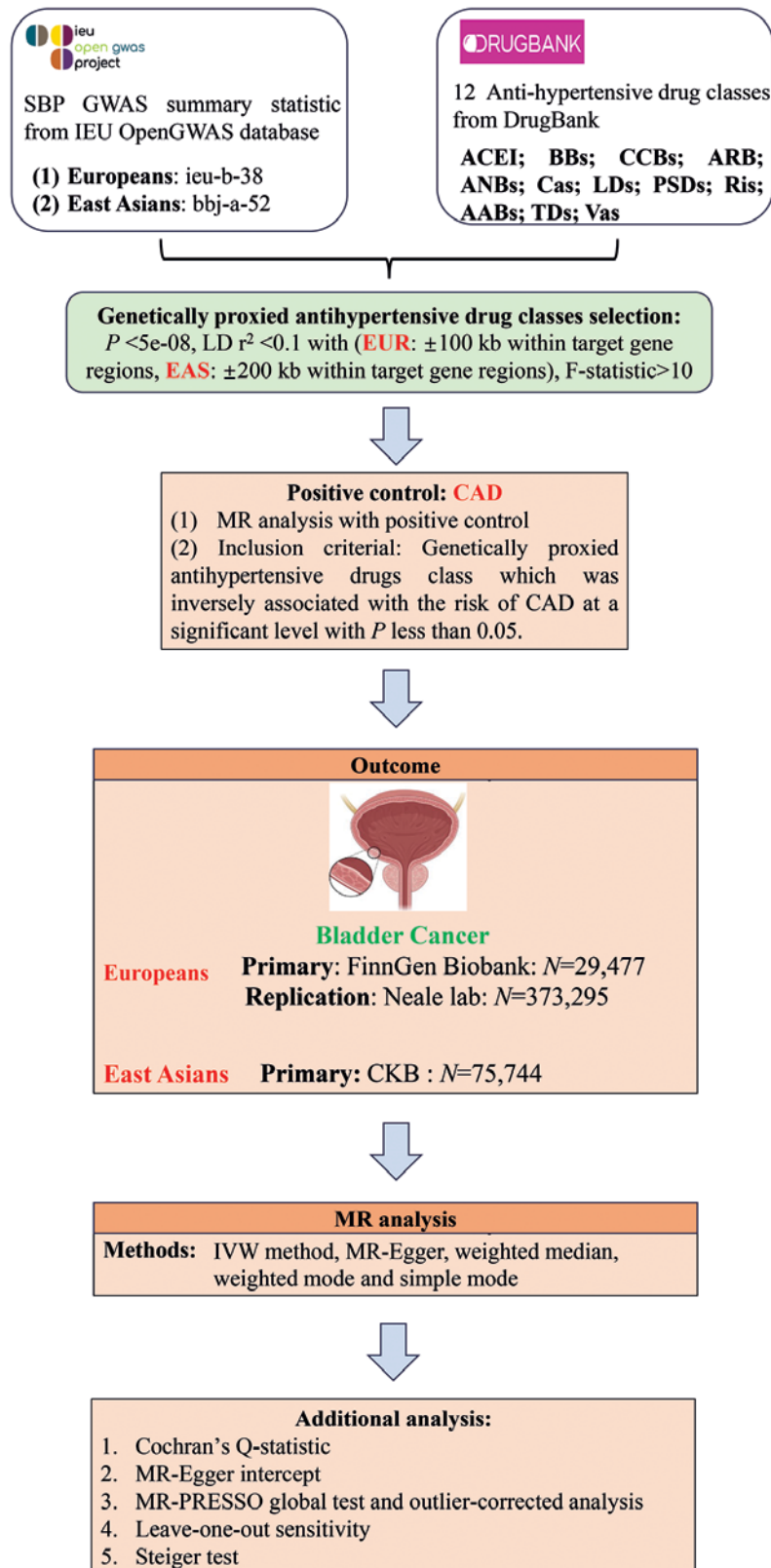
**B**



**Figure 1.** Cont. **B** – Flowchart of the overview of Mendelian randomization (MR) analysis

*EUR – Europeans, EAS – East Asians, SBP – systolic blood pressure, ACEI – angiotensin-converting enzyme inhibitors, BBs – β-adrenoceptor blockers, CCBs – calcium channel blockers, ARB – angiotensin-II receptor antagonists, ANBs – adrenergic neuron blockers, Cas – centrally acting antihypertensives, LDs – loop diuretics, PSDs – potassium-sparing diuretics (PSDs) and aldosterone antagonists, Ris – renin inhibitors, AABs – α-adrenoceptor blockers, TDs – thiazides and related diuretics, vasodilator antihypertensives, CAD – coronary artery disease, Bca – bladder cancer.*

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replication analysis, for bladder cancer, the genetic data are from the Neale laboratory, which conducted a GWAS on 361,194 Europeans (Ncase = 1,554, Ncontrol = 359,640), identifying a total of 10,267,743 SNPs. The genetic data for bladder cancer in East Asian populations are from the China Kadoorie Biobank (CKB) [11], which performs a GWAS on 75,744 Chinese populations. More details are summarized in Supplementary Table SIII.

Supplementary Tables SIV and SV summarize the genetic proxy information for antihypertensive medications in European and East Asian populations, respectively. Supplementary Table SVI includes antihypertensive drugs that are significantly negatively associated with CAD and were selected for further analysis to explore their causal relationship with Bca. Notably, in the analysis of East Asian populations, following the harmonization of data for genetically predicted exposure (BBs) and the outcome of bladder cancer, it was observed that the associated single-nucleotide polymorphisms (SNPs) (rs10885532, rs180912, and rs78006240) presented palindromic structures and intermediate allele frequencies. Consequently, genetically predicted exposures (BBs) in East Asian populations were excluded from further analysis.

For statistical analysis, the IVW approach was used as the primary method for MR analysis. In this MR study, we conducted multiple tests (evaluating various antihypertensive medicines) with Bonferroni correction. In MR studies, the inverse variance weighted (IVW) method is a widely utilized statistical approach for estimating causal
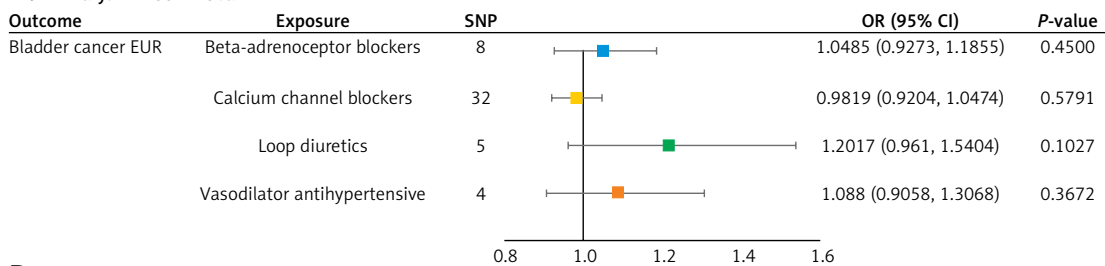
effects [12]. This method operates by calculating a weighted average of the effect estimates from multiple genetic variants (e.g., single nucleotide polymorphisms – SNPs), where the weights correspond to the inverse of the variance (i.e., the squared standard errors) of each genetic variant's effect estimate. Specifically, the IVW approach employs a regression model that excludes an intercept term and incorporates the inverse of the outcome variance as weights during fitting. This methodology assumes that all genetic variants serve as valid instrumental variables (IVs) and satisfy three core MR assumptions: (1) the relevance assumption, (2) the independence assumption, and (3) the exclusion restriction assumption. When these assumptions hold, the IVW method provides consistent and unbiased estimates of the causal effect.

Sensitivity analysis in MR studies involves reassessing the robustness of the causal relationship. This includes methods such as the Cochran's Q test to assess heterogeneity and horizontal pleiotropy of IVs [13]. Confounding analysis in MR studies ensures that genetic instruments are not associated with other factors (such as smoking alcohol, drinking, diet, and obesity) that could influence the outcome. This investigation typically involves the use of reverse MR methods [14].

Further methodological details are described in the Supplementary Methods.

**Results.** In the primary MR analysis, the MR results indicated no statistically significant associations between genetically predicted BBs, CCBs, LDs and Vas and a high risk of Bca in European



**A.** Primary: FinnGen Biobank

| Outcome | Exposure | SNP | | OR (95% CI) | *P*-value |
|---|---|---|---|---|---|
| Bladder cancer EUR | Beta-adrenoceptor blockers | 8 | | 1.0485 (0.9273, 1.1855) | 0.4500 |
| | Calcium channel blockers | 32 | | 0.9819 (0.9204, 1.0474) | 0.5791 |
| | Loop diuretics | 5 | | 1.2017 (0.961, 1.5404) | 0.1027 |
| | Vasodilator antihypertensive | 4 | | 1.088 (0.9058, 1.3068) | 0.3672 |

**B.** Replication: Neale lab

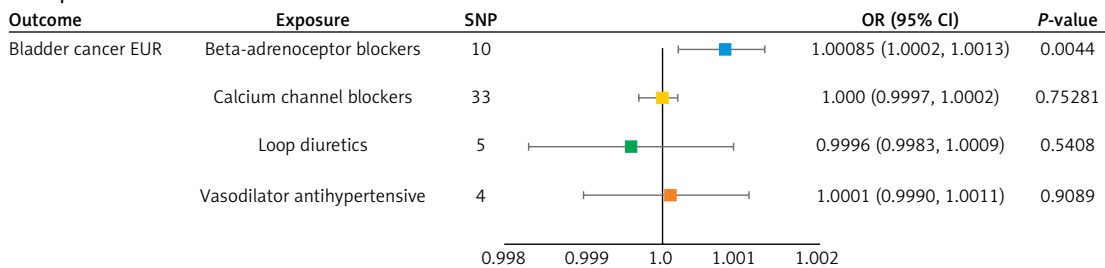| Outcome | Exposure | SNP | | OR (95% CI) | *P*-value |
|---|---|---|---|---|---|
| Bladder cancer EUR | Beta-adrenoceptor blockers | 10 | | 1.00085 (1.0002, 1.0013) | 0.0044 |
| | Calcium channel blockers | 33 | | 1.000 (0.9997, 1.0002) | 0.75281 |
| | Loop diuretics | 5 | | 0.9996 (0.9983, 1.0009) | 0.5408 |
| | Vasodilator antihypertensive | 4 | | 1.0001 (0.9990, 1.0011) | 0.9089 |

**Figure 2. A** – Forest plot map of Mendelian randomization (MR) analysis, utilizing genetic proxies for four classes of antihypertensive drugs, demonstrating their association with the risk of bladder cancer. The primary outcome is based on data from the FinnGen Biobank. **B** – Forest plot map of MR analysis, using genetic proxies for four classes of antihypertensive drugs, illustrating their association with the risk of bladder cancer. The secondary outcome is derived from the Neale lab dataset
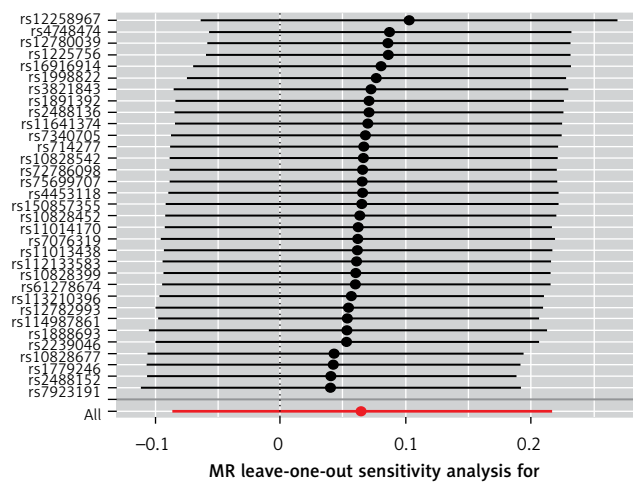
## C. Leave-one-out sensitive analysis

Primary: FinnGen Biobank

1. Beta-adrenoceptor blockers
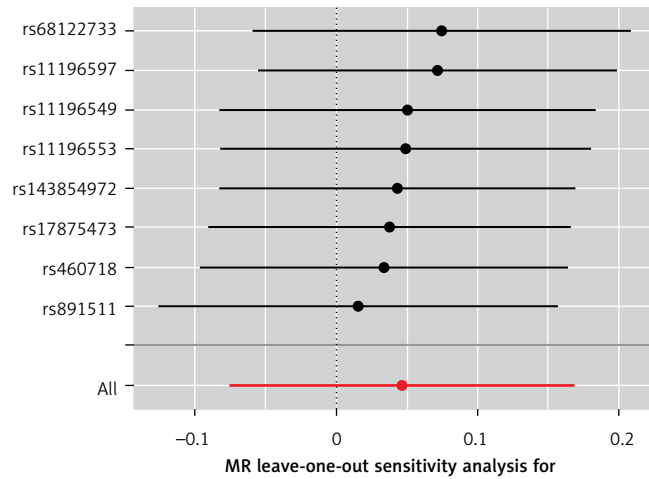


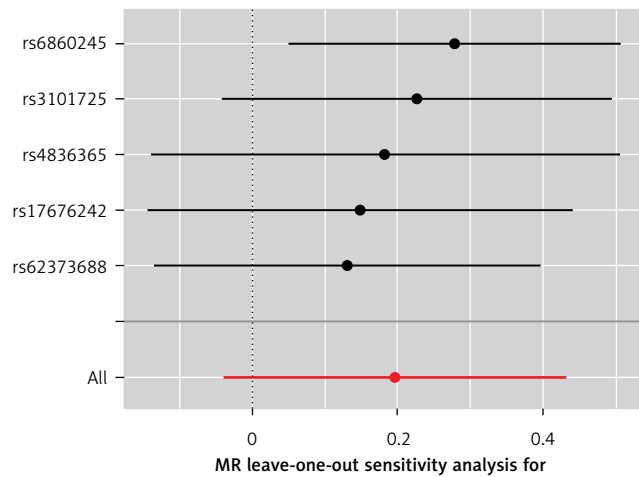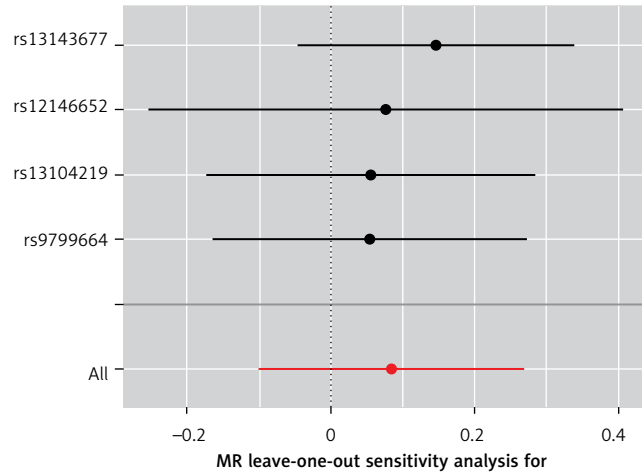2. Calcium channel blockers



3. Loop diuretics



**Figure 2.** Cont. **C** – Leave-one-out analysis was conducted for the following antihypertensive drug classes: (1) β-adrenoceptor blockers, (2) calcium channel blockers, (3) loop diuretics, and (4) vasodilator antihypertensives. This analysis was applied to both the primary analysis of bladder cancer risk in the FinnGen Biobank and the replication analysis in the Neale lab

4. Vasodilator antihypertensives

Replication: Neale lab
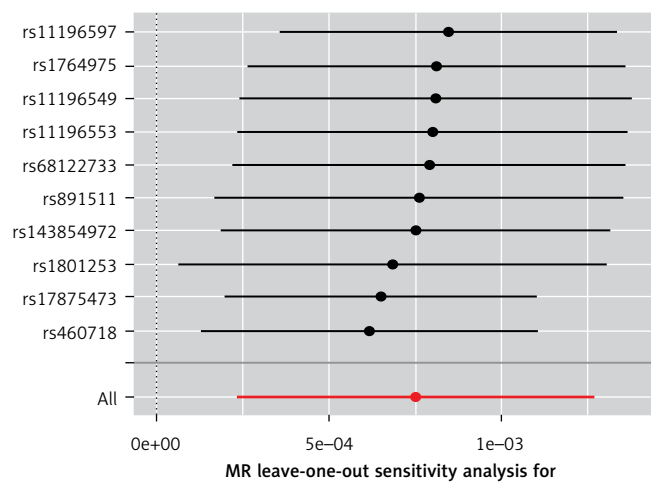1. Beta-adrenoceptor blockers

2. Calcium channel blockers

**Figure 2.** Cont. **C** – Leave-one-out analysis was conducted for the following antihypertensive drug classes: (1) β-adrenoceptor blockers, (2) calcium channel blockers, (3) loop diuretics, and (4) vasodilator antihypertensives. This analysis was applied to both the primary analysis of bladder cancer risk in the FinnGen Biobank and the replication analysis in the Neale lab

3. Loop diuretics



4. Vasodilator antihypertensives



**D.** Confounding analysis in Neale lab

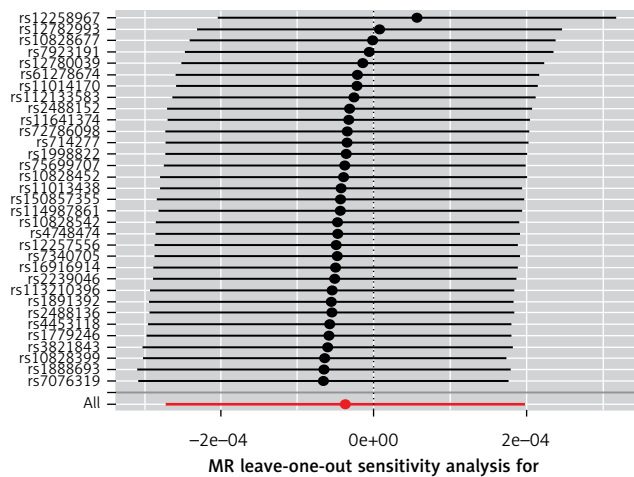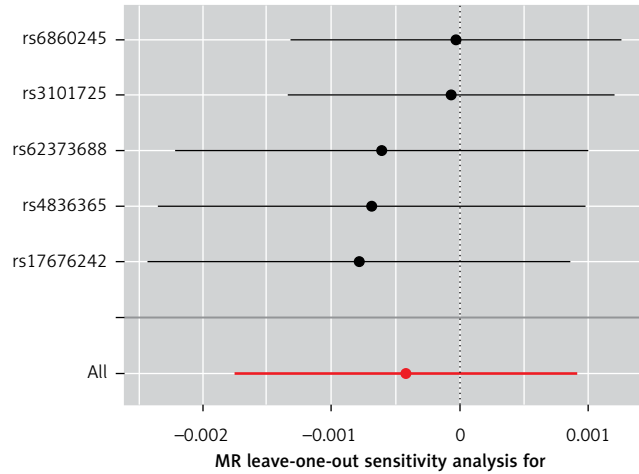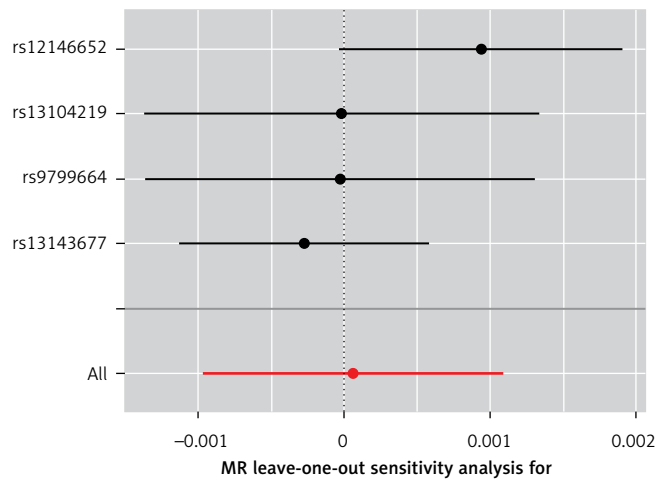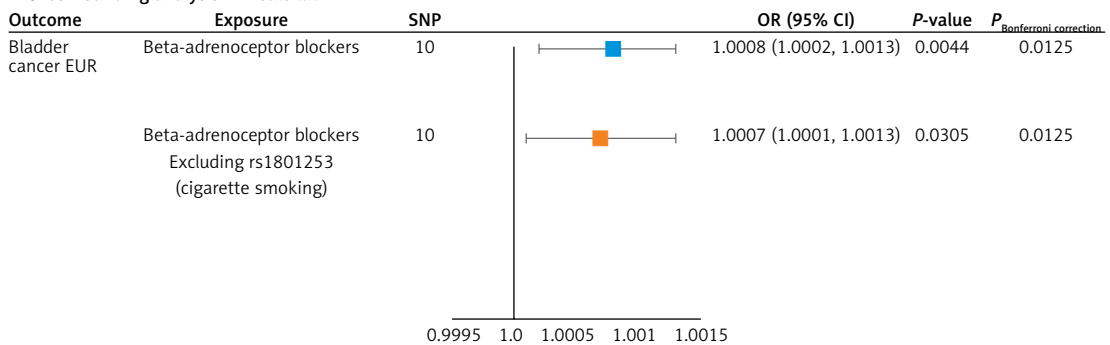| Outcome | Exposure | SNP | | OR (95% CI) | P-value | $P_{Bonferroni\ correction}$ |
|---|---|---|---|---|---|---|
| Bladder cancer EUR | Beta-adrenoceptor blockers | 10 | | 1.0008 (1.0002, 1.0013) | 0.0044 | 0.0125 |
| | Beta-adrenoceptor blockers Excluding rs1801253 (cigarette smoking) | 10 | | 1.0007 (1.0001, 1.0013) | 0.0305 | 0.0125 |

0.9995   1.0   1.0005   1.001   1.0015

**Figure 2.** Cont. **C** – Leave-one-out analysis was conducted for the following antihypertensive drug classes: (1) β-adrenoceptor blockers, (2) calcium channel blockers, (3) loop diuretics, and (4) vasodilator antihypertensives. This analysis was applied to both the primary analysis of bladder cancer risk in the FinnGen Biobank and the replication analysis in the Neale lab. **D** – Confounding analysis was conducted to assess the impact of genetic proxies for β-adrenoceptor blockers, specifically focusing on the inclusion or exclusion of the rs1801253 (rs1801253: cigarette smoking), on the association with bladder cancer risk in the replication data from the Neale lab

populations, utilizing the outcome dataset from the FinnGen Biobank (EUR$_{\text{—FinnGen Biobank}}$: $P_{\text{IVW\_BBs}}$ = 0.4500, $P_{\text{IVW\_CCBs}}$ = 0.5791, $P_{\text{IVW\_LDs}}$ = 0.1027, and $P_{\text{IVW\_Vas}}$ = 0.3672) (Figure 2 A and Supplementary Table SVII). The results of four additional MR analyses are presented in Supplementary Table SVII.

In subsequent replication analysis, interestingly, a harmful effect of genetically proxied BB drugs was observed in the European Bca population from the Neale laboratory dataset (OR$_{\text{IVW\_BBs}}$ = 1.0008, 95% CI (1.0002, 1.0013), $P_{\text{IVW\_BBs}}$ = 0.0044). For other antihypertensive drugs, including CCBs, LDs,

and Vas, no significant associations with the risk of European Bca populations from the Neale laboratory dataset were observed (EUR$_{\text{Neale laboratory}}$: $P_{\text{IVW\_CCBs}} = 0.7528$, $P_{\text{IVW\_LDs}} = 0.5408$, and $P_{\text{IVW\_Vas}} = 0.9089$) (Figure 2 B).

LOO analysis further confirmed the stability of the aforementioned findings, which were derived from both the primary and replication analyses (Figure 2 C).

In the confounding analysis, one pleiotropic SNP (rs1801253 pertaining to smoking in the beta-adrenoceptor blockers, NHGRI-EBI GWAS catalog in ontology accessions: EFO:0006336 and referenced by PMID:29455858) confirmed by Ensemble Asian (https://asia.ensembl.org/) (outcome: bladder cancer risk in the replication dataset from the Neale laboratory) was identified, and following the elimination of this specific SNP, the findings remained in alignment with previously identified significant relationships ($P_{\text{IVW}} = 0.0305$) (Figure 2 D). However, this statistically significant correlation did not successfully pass the Bonferroni correction test (the threshold of $P_{\text{Bonferroni\_correction}}$ was

0.0125) (Figure 2 D). Therefore, further validation through confounding analysis and Bonferroni correction revealed that this statistically significant genetic association was not confirmed in the European bladder cancer population from the Neale laboratory dataset. The current evidence from MR studies still does not substantiate the association between genetically proxied BB drugs and bladder cancer in the European population.

Furthermore, in the East Asian population, no statistically significant correlation was found between genetically proxied CCBs or LDs and a higher risk of Bca ($P_{\text{IVW\_CCBs}} = 0.6493$ and $P_{\text{Wald\_ratio\_LDs}} = 0.5815$) (Supplementary Table SVIII).

Additional analysis confirmed that there was no heterogeneity ($P_{\text{heterogeneity}} > 0.05$), horizontal pleiotropy ($P_{\text{Intercept}} > 0.05$ and $P_{\text{MRPRESSO\_Global\_Test}} > 0.05$) (Table I), or reverse causality in our MR study involving European populations ($P_{\text{Steiger\_filtering}} < 0.05$ and correct causal direction = True) (Table I). However, owing to the limited number of SNPs included, the pleiotropy of LDs and CCBs in the East Asian population could not be detected. Additionally, the heterogeneity of LDs could not be

**Table I.** Heterogeneity, horizontal pleiotropy test and Steiger filtering

| Ancestry | Drugs | Heterogeneity | | | Pleiotropy | | MRPRESSO | Steiger filtering |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | Method | $Q$ value | $Q\_P$-value | Intercept | $P$-value | Global Test ($p$-value) | |
| Europeans | B-adrenoceptor blockers | MR Egger | 3.934 | 0.686 | −0.0066 | 0.941 | 0.798 | $P = 4.48E\text{-}31$ TRUE |
| | | Inverse variance weighted | 3.940 | 0.787 | | | | |
| | Calcium channel blockers (CCBs) | MR Egger | 15.523 | 0.986 | −0.0271 | 0.308 | 0.984 | $P = 1.062422e\text{-}112$ TRUE |
| | | Inverse variance weighted | 16.599 | 0.984 | | | | |
| | Loop diuretics | MR Egger | 2.250 | 0.522 | −0.191 | 0.197 | 0.940 | $P = 3.133567e\text{-}10$ TRUE |
| | | Inverse variance weighted | 4.977 | 0.290 | | | | |
| | Vasodilator antihypertensives | MR Egger | 2.250 | 0.522 | −0.191 | 0.197 | 0.178 | $P = 6.384450e\text{-}16$ TRUE |
| | | Inverse variance weighted | 4.977 | 0.290 | | | | |
| East Asians | Calcium channel blockers (CCBs) | Inverse variance weighted | 0.050 | 0.824 | N/A | N/A | N/A | $P = 0.01970104$ TRUE |
| | Loop diuretics | MR Egger | N/A | N/A | N/A | N/A | N/A | $P = 1.867287e\text{-}05$ TRUE |
| | | Inverse variance weighted | N/A | N/A | | | | |

calculated because of the insufficient number of SNPs included.

**Discussion.** A study by Shoji-Asahina *et al.* [15] revealed that, compared with patients with a systolic blood pressure of 120–129 mm Hg, the risk of cardiovascular events and all-cause mortality was significantly greater in elderly patients over 75 years of age with a systolic blood pressure below 120 mm Hg or above 150 mm Hg. These findings indicate that appropriate blood pressure control is crucial for reducing cardiovascular events and all-cause mortality. In addition, the clinical guidelines of the ESC and AHA/ACC emphasize the importance of antihypertensive drugs in reducing cardiovascular events and all-cause mortality [5].

The potential carcinogenic effects of antihypertensive drugs add to the psychological burden of patients with cardiovascular diseases taking medication. Cardiovascular diseases are the leading cause of death worldwide, and discontinuing necessary antihypertensive treatment due to fear of the potential carcinogenic effects of antihypertensive drugs may increase the risk of death for cardiovascular patients [16]. However, there is currently inconsistency in the results regarding the correlation between the use of antihypertensive drugs and cancer risk. Wang *et al.* [17] conducted a population-based cohort study in Shanghai, China, to investigate the relationship between antihypertensive drugs and cancer risk. The study revealed that calcium channel blockers (CCBs) were moderately associated with increased total cancer risk. In contrast, Copland *et al.* [18] conducted a network meta-analysis comparing the effects of different antihypertensive drugs with those of placebos and reported that no excess cancer risk was associated with any type of antihypertensive drug.

In previous observational studies, patients used more than one antihypertensive drug over a period of time, making it impossible to determine the impact of a single antihypertensive drug on bladder cancer. In addition, previous observational studies have shortcomings, such as recall bias, short follow-up periods (less than 10 years), and poor patient medication adherence, which still results in inconsistencies in the research findings regarding the use of antihypertensive drugs and the risk of bladder cancer [19].

This drug-targeted MR study, which uses SNPs associated with various antihypertensive drugs as IVs, can investigate the associations between the lifelong use of a single drug target of antihypertensive drugs and the risk of bladder cancer, avoiding the influence of confounding factors and reverse causality. The results of this study show that these antihypertensive drugs do not have a genetic causal relationship with the risk of bladder cancer. This result has been verified in both European and Asian populations.

Interestingly, preclinical experimental studies have shown that β-blockers (BBs) can regulate inflammation and block norepinephrine, which is closely related to cancer promotion and metastasis in the tumor environment, as well as cAMP-dependent intracellular signal transduction, to reduce tumor proliferation and migration [20]. However, the significant association observed in the Neale laboratory dataset appears to be very weak. There are several reasons for this.

First, in genetic association studies, the effect sizes of newly discovered significant genetic variants are often overestimated, and effect size attenuation occurs in independent validation or replication studies [21].

Second, the importance of pleiotropy in MR studies needs to be considered, and pleiotropic SNPs should be removed to clarify the true association between exposure and outcome. Smoking is an important risk factor for bladder cancer [22]. Smoking can lead to the accumulation of harmful chemicals in the urine, which may damage the bladder membrane and increase the risk of cancer. Smokers have a significantly greater risk of bladder cancer than nonsmokers do, possibly because of DNA damage and inflammatory responses caused by smoking. The SNP rs1801253 is located in the ADRB1 gene (encoding the β1-adrenergic receptor), and the polymorphism at this site leads to a difference in the amino acid at position 389 of the receptor protein. Carriers of Arg389 are more sensitive to β-blockers and may be more sensitive to smoking-induced tachycardia. The SNP rs1801253 is closely related to smoking behavior and was identified as a potential confounder in this MR study. A genetic polymorphism (rs1801253) may have pleiotropy; that is, it may affect multiple traits or outcomes. In the Neale laboratory dataset, the pleiotropy of rs1801253 (closely related to smoking) may confound the association between BBs and bladder cancer risk. In the validation dataset (from the Neale laboratory dataset), after removing the pleiotropic SNP (rs1801253) closely related to smoking, the association between genetically proxied beta-blockers and the risk of bladder cancer in the European population changed from OR = 1.0008 (95% CI: 1.0002–1.0013, $p$ = 0.0044) to OR = 1.0007 (95% CI: 1.0001–1.0013, $p$ = 0.0305). The $p$-value of 0.0305 after removing the pleiotropic SNP (rs1801253) did not reach the Bonferroni-corrected significance level ($P_{Bonferroni\_Correction}$ = 0.0125). This finding indicates that the association between BBs and bladder cancer risk is no longer significant after rs1801253 is

removed, which further supports the possibility that smoking is a confounder. In addition, this result also indicates that the weak significant association between BBs and bladder cancer risk may not be robust or clinically meaningful. Similarly, Jiang *et al.* [9], on the basis of a case-control study of the Los Angeles population, noted that the treatment of hypertension, including the use of diuretics, may have some interaction with the risk of bladder cancer, and this interaction may be influenced by individual genetic background. Therefore, when the relationship between diuretics and the risk of bladder cancer is considered, individual genetic susceptibility and lifestyle factors, such as smoking, need to be considered.

In this study, the use of the Bonferroni correction can enhance the credibility of the research results. The Bonferroni correction method has also been widely used in previous antihypertensive drug-targeted Mendelian randomization studies [23, 24]. Moreover, although multiple comparisons were made in this study, the number of comparisons was relatively small, so the use of Bonferroni correction in this study can effectively control the type I error rate without excessively affecting the statistical power. The results of this MR study are also consistent with the clinical study results of Xie *et al.* [25], and a case-control study in a clinical population did not find a significant association between BBs and bladder cancer risk.

In conclusion, the weak significant association between genetic proxies of BBs and bladder cancer risk observed in the Neale laboratory dataset may be the result of the combined effects of smoking as a confounder, Bonferroni correction, genetic pleiotropy, and other factors. Future studies should use larger sample sizes and more genetic tool variables to verify this association and consider the potential confounding effects of smoking and other lifestyle factors. In addition, the clinical significance of this association should be carefully evaluated to determine its practical application value in clinical practice.

Previously, Fan *et al.* [26] applied drug-targeted MR methods to explore the correlation between genetic proxies for calcium channel blockers (CCBs) and cancer risk. The study revealed that under the Bonferroni correction threshold ($p = 0.003$), there was no significant correlation between genetic proxies for CCBs and the risk of any type of tumor. This study included data from two specific European bladder cancer databases (FinnGen and Neale lab) and once again confirmed that there was no significant correlation between genetic proxies for CCBs and the risk of bladder cancer. Furthermore, the results of this study further revealed that, in addition to the European bladder cancer population, no associations were found between genetic proxies for calcium channel blockers and bladder cancer in the East Asian population, which further supplements the previous MR study results of Fan *et al.* [26].

The magnitude of associations is another aspect that needs to be discussed in this study. In the Neale laboratory dataset, the results for genetic proxies of beta-blockers and the risk of bladder cancer in the European population were OR = 1.0008, 95% CI: 1.0002–1.0013, $p = 0.0044$. The OR value in the study is close to 1, which seems to lack evidence of a strong association.

First, in MR studies, the odds ratio (OR) obtained is significantly different from that in observational studies in terms of result interpretation. Although the OR value in MR studies can reflect the direction and general magnitude of the causal relationship, it cannot be directly equated with the OR value in observational studies. The genetic variants used in MR studies are determined at conception and are lifelong and do not change over time; thus, they cannot represent the disease status at a specific moment [27]. Therefore, the OR value in MR studies is not equivalent to that in observational studies. A larger OR value in MR studies does not necessarily indicate a stronger causal relationship in observational studies. In summary, the OR value in MR studies mainly provides the direction of the causal effect (positive or negative) and preliminary evidence, but its magnitude needs to be interpreted with caution. The OR value in MR essentially estimates the 'lifetime average causal effect' of exposure on outcomes, which is different from the situation in observational studies that depend on time–event dynamics [28].

Second, the genetic effect size explained by the SNPs screened in GWAS is mostly within 10%. We used these SNPs for MR, and the changes caused by genetic effect modification were actually small. In addition, the genetic variations derived from GWASs are population effects and represent the average level of the population, which is different from that of specific clinical populations or individuals.

Third, in the GWAS database, the OR values in the UK Biobank, MRC-IEU, and Neale laboratory datasets are relatively small, which is related to the use of the BOLT-LMM model in these databases. This model did not perform indexing of OR values. However, the OR values in the FinnGen database did not show the above phenomenon.

For example, Goławski M *et al.* [29] used the Mendelian randomization method to explore the association between Lp(a) and T2D. The GWAS data for Lp(a) were downloaded from the Neale laboratory dataset, and the concentrations of ge-

netically predicted Lp(a) were not associated with type 2 diabetes (OR = 1.008; 95% CI: 0.991–1.026; $p = 0.362$). For studies with exposure data from the Neale laboratory dataset, the OR values are also very small.

Zhou *et al.* [30] used the Mendelian randomization method to explore the association between hip or knee osteoarthritis and frailty. The GWAS data concerning hip osteoarthritis and knee osteoarthritis were obtained from the UK Biobank dataset. The IVW analysis revealed a statistically significant association between hip osteoarthritis and knee osteoarthritis with frailty (OR = 1.082, 95% CI: 1.0532–1.1125, $p = 1.36 \times 10^{-8}$). Although there was an association between hip osteoarthritis, knee osteoarthritis, and frailty ($p = 1.36 \times 10^{-8}$), the OR value was very close to 1, at only 1.082.

Zeng *et al.* [31] used the Mendelian randomization method to explore the association between circulating micronutrients and the risk of stroke. Carotene was extracted from the UK Biobank dataset. The IVW analysis demonstrated that circulating carotene was not significantly associated with the risk of stroke (OR = 1.014, 95% CI: 0.850–1.209; $p = 0.879$). For studies with exposure data from the UK Biobank, the OR values are also very small. Therefore, this MR study is similar to previous studies [29–31], using the FinnGen database results as the primary analysis and the Neale laboratory dataset results as the secondary analysis.

The majority of participants were of European or East Asian descent, limiting the applicability of the results to other ethnic groups [32]. Second, in the East Asian population, the limited number of included single-nucleotide polymorphisms (SNPs) may result in insufficient statistical power to detect pleiotropy and heterogeneity for LDs and CCBs. This limitation hampers our in-depth understanding of the potential associations between these medications and bladder cancer in East Asian populations.

In conclusion, this study revealed no evidence supporting a genetic causal relationship between antihypertensive medications and bladder cancer in both European and Asian population while confirming their irreplaceable role in reducing cardiovascular risk and all-cause mortality.

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## Ethical approval

Not applicable.

## Conflict of interest

The authors declare no conflict of interest.

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