2. Supplementary method section

2.1. Ethics approval statement

The statistical data for all GWAS summary-level data originated from studies that were openly accessible and had already acquired ethical review board authorizations.

2.2. Data sources

2.2.1. Target genes for classes of antihypertensive drugs

We identified 12 antihypertensive drug classes in the British National Formulary (BNF Legacy. BNF July 2017: BNF Legacy. https://www.medicinescomplete.com/mc/bnflegacy/64/.): adrenergic neurone blocking drugs; alpha-adrenoceptor blockers, angiotensin- converting enzyme inhibitors, angiotensin-II receptor blockers, beta-adrenoceptor blockers, calcium channel blockers, centrally acting antihypertensive drugs, loop diuretics; potassium-sparing diuretics and aldosterone antagonists, renin inhibitors, thiazides and related diuretics, and vasodilator antihypertensives. Target genes of active ingredients in each class of antihypertensive drugs were identified using DrugBank database. The list of 12 antihypertensive drugs and their target genes was described in **Supplementary Table S2**.

2.2.2 Genetic proxies for anti-hypertensive drugs

We chose systolic blood pressure (SBP) as the biomarker because each of the 12 classes of anti-hypertensive drugs were shown to reduce levels of hypertension. For European ancestry, the GWAS meta-analysis of UK Biobank and the International Consortium of Blood Pressure [1] included SBP measurement for 757,601 European participants, which consisted of 299,024 participants from the International Consortium of Blood Pressure constituting 77 independent cohorts and 458 577 participants from UK Biobank. The genetic association estimates for SBP were adjusted for sex, age, age-squared, BMI and antihypertensive medication use. For East Asian ancestry, the GWAS of Japan Biobank [2] included SBP measurement for 136,597 East Asian participants (controlled for sex, age, age squared, the top ten principal components, status of 47 diseases and smoking status) **(Supplementary Table S3)**.

In terms of European ancestry, as mentioned in a previous report [3], we have selected single-nucleotide polymorphisms (SNPs) within the drug target gene region (± 100kB). These SNPs, associated with SBP ($P< 5\times10^{-8}$), serve as proxies for the perturbation of drug targets. Beforehand, we have applied clumping to ensure that only SNPs with a pairwise linkage disequilibrium threshold of $r^2 < 0.1$, using the 1000 Genomes European reference panel, are considered. To assess the associations in East Asians, we used genetic variants that are located near (± 200 kb) or within these drug target genes. Moreover, we selected genetic variants with a linkage disequilibrium (LD) threshold of $r^2 < 0.1$ based on the East Asian 1000 Genomes panel. For both ancestries, proxy single nucleotide polymorphisms (SNPs) with LD ($r^2 >0.8$) were used as substitutes for absent SNPs in our study [4]. Subsequently, the F-statistic [formula: $(R^2/(1-R^2)) \times ((N - K - 1)/K)$] was calculated for each exposure to assess the strength of the selected SNPs. SNPs with an F-statistic less than 10 were eliminated to avoid potential bias from weak IVs [5]. Lastly, SNPs with inconsistent alleles

between the exposure and outcome samples, as well as palindromic SNPs, were discarded.

2.2.3 Outcome data

In this research, we utilized coronary artery disease (CAD) as a control outcome for positive comparison. To gather data on CAD among Europeans, we relied on a meta-analysis of Genome-Wide Association Studies (GWASs) conducted by the CARDIoGRAMplusC4D consortium and UK Biobank [6]. This analysis included a sample size of 547,261 CAD cases and 424,528 healthy controls. Similarly, for East Asians, we obtained the genetic associations of CAD from a GWAS performed on 212,453 individuals with East Asian ancestry. The sample for this analysis were obtained from the BBJ consortium (**Supplementary Table S3**) [7].

In accordance with the previously published MR study [8], for European participants, the present study primarily utilized the largest GWAS summary data on bladder cancer, which was freely accessed 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 replication analysis, for bladder cancer, the genetic data are from Medical Research Council Integrative Epidemiology Unit (MRC-IEU), who 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 China Kadoorie Biobank (CKB) [9], who performed a GWAS on 75,744 Chinese populations. More details are summarized in **Supplementary Table S3**.

2.3. Statistical analysis

To validate the efficacy of SNPs as genetic proxies for antihypertensive medications, our study focused on using genetically proxied antihypertensive drug classes as the exposures and CAD as the control outcome. The IVW high-efficiency approach was applied as the primary analysis to assess the effects of antihypertensive drugs on the risk of bladder cancer across the two ethnic groups [10]. Complementary approaches including MR-Egger, weighted median, weighted mode, and simple mode were also utilized to evaluate the robustness of results [11, 12]. Inconsistent results between the main method and complementary methodologies were resolved by giving precedence to the IVW method. A Bonferroni correction was applied when interpreting the *P* value for statistical significance [0.05/ 4 (4 antihypertensive drugs×1 outcome) = 0.0125] for Europeans and [0.05/ 2 (2 antihypertensive drugs×1 outcome) = 0.0250] for East Asians. To evaluate the strength of the causal link between antihypertensive drugs and the bladder cancer outcome in our primary analysis, we performed an additional confounding analysis. In this study, we included smoking as a potential covariate in confounding analysis [13].

Steiger filtering can infer the causal direction for an identified SNP between exposure and outcome through estimating and comparing the proportion of variance explained in each. The heterogeneity of the instrumental variables (IVs) was evaluated using Cochrane's Q test. The MR-Egger intercept test was used to test for horizontal pleiotropy, which refers to the extent to which IVs affect outcomes not through exposure but through other factors. A leave-one-out sensitivity analysis was performed, in which the effect of exposure on the results was recalculated after removing each IV individually. If removing any IV did not result in a significant change in outcome, the MR results were considered stable. All statistical analysis were conducted using the

'TwoSampleMR', 'MVMR', 'MRPRESSO', and 'MendelianRandomization' packages (R version 4.1.2).

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