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Causal association between non-steroidal anti-inflammatory drugs use and the risk of benign prostatic hyperplasia: a univariable and multivariable Mendelian randomization study

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Abstract

Background The results of earlier observational research on the relationships between the usage of non-steroidal anti-inflammatory medicines (NSAIDs) and the risk of benign prostatic hyperplasia (BPH) have been inconsistent.

Methods To assess these associations, we performed both univariable and multivariable Mendelian randomization (MR) studies. Instrumental variables (IVs) associated with exposures at the significance level ($p < 5 \times 10^{-6}$) were selected from a comprehensive meta-analysis conducted by the United Kingdom Biobank (UKB). Summary data for BPH were obtained from the FinnGen consortium, which comprised 30,066 cases and 119,297 controls. Sensitivity analyses were performed to evaluate heterogeneity and pleiotropy.

Results We found evidence by univariable MR (UVMR) that genetically predicted NSAIDs use increased the risk of BPH (odds ratio [OR] per unit increase in log odds NSAIDs use: 1.164, 95% confidence interval [CI]: 1.041–1.302, $p = 0.008$). After controlling for inflammation in multivariable MR (MVMR), the link persisted (OR: 1.165, 95% CI: 1.049–1.293, $p = 0.004$). There were no indications of potential heterogeneity and pleiotropy in UVMR and MVMR analyses.

Conclusion The results of the MR estimates suggest that genetically predicted NSAIDs use may elevate the risk of BPH. This outcome prompts the imperative for deeper exploration into potential underlying mechanisms.

Keywords Benign prostatic hyperplasia, Non-steroidal anti-inflammatory drugs, Mendelian randomization, Causal association, Genetic epidemiology

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Introduction

Benign prostatic hyperplasia (BPH) manifests as a prevalent affliction among the middle-aged and elderly male populace. Meticulous investigations into prostate histopathology through post-mortem samples have unveiled an annual surge, ranging from 41 to 90%, in the cohort of men bearing a histological diagnosis of BPH. Additionally, a noteworthy 50% of men aged between 51 and 60 years evince pathological attributes concomitant with BPH [1]. Globally, the year 2019 bore witness to a staggering 94.0 million prevalent cases of BPH, in stark contrast to the 51.1 million cases recorded in 2000 [2]. Evidently, the absolute burden of BPH is escalating at a disquieting pace throughout most regions of the world. Neglecting to address this condition could have a significant impact on one's quality of life [3].

Numerous studies have elucidated inflammation as one of the perilous factors contributing to the onset of BPH [4–6]. Non-steroidal anti-inflammatory drugs (NSAIDs) are primarily harnessed for their antipyretic, analgesic, anti-inflammatory, and anti-rheumatic properties [7]. The quelling of inflammatory pathways by NSAIDs holds the potential to abate and arrest the progression of BPH [8]. Given the common prevalence of both BPH and NSAIDs usage among elderly males, fathoming their interrelationship assumes paramount significance. Nevertheless, the extant corpus of literature concerning this domain remains somewhat limited, yielding findings that have engendered discordant outcomes [9, 10]. Several investigations have illuminated the potential benefits of NSAIDs usage in ameliorating BPH or lower urinary tract symptoms (LUTS) [11–14]. Conversely, some observational studies have indicated a higher likelihood of BPH development among male individuals using NSAIDs [15–17]. Additionally, certain inquiries have been unable to establish a significant correlation between NSAIDs use and BPH or LUTS [18–20]. The incongruous nature of these findings highlights the potential limitations of observational studies in establishing causal inferences, encompassing concerns such as reverse causality, unobserved confounding, and various biases [21]. Furthermore, a significant challenge in these studies involves disentangling the direct impact of the drug on the onset of BPH or LUTS from the underlying, presumably systemic inflammatory process that triggers the utilization of NSAIDs [10]. Consequently, this has compelled us to embark on pioneering methodologies, in quest of a profound comprehension of veritable causality.

The application of Mendelian randomization (MR) has garnered widespread recognition in unveiling plausible causal connections between exposures and outcomes [22]. This sophisticated approach leverages genetic variations linked to environmental exposures as instrumental variables (IVs) to meticulously examine the intricate relationship between such exposures and their respective outcomes. Genetic variants, being randomly allocated during conception, are preferred as candidate IVs owing to their inherent immunity to potential confounding effects arising from environmental factors [23]. Given the prevailing uncertainty surrounding the causal linkage between NSAIDs use and BPH, the present study adopts the univariable MR (UVMR) design, delving into the potential causal effect of NSAIDs, salicylic acid, and its derivatives, as well as anilides use on BPH, while making judicious use of comprehensive genomewide association study (GWAS) data. In order to address concerns regarding systemic inflammation acting as a potential confounding factor, the analysis strategically incorporates multivariate MR (MVMR), thereby effectively mitigating bias attributable to inflammation.

Materials and methods

Study design

The study design overview is depicted in Fig. 1. Employing a two-sample MR design, we systematically evaluated the causal association between NSAIDs usage and BPH. To ensure a compelling MR design, three fundamental assumptions must be met:(1) IVs exhibit robust associations with the exposures; (2) IVs are not associated with any potential confounding factors; (3) genetic instruments exert their sole impact on the outcome through the relevant exposures. The verification of the last two assumptions, jointly known as horizontal pleiotropy, can be accomplished through diverse statistical methodologies [24]. This study adheres to the reporting guidelines of Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) (Additional file 1: STROBE MR checklist).

Data sources

Summary GWAS data concerning the utilization of NSAIDs were extracted from a comprehensive meta-analysis conducted by the United Kingdom Biobank (UKB) [25]. The medication categories were determined by classifying them according to the active ingredient, utilizing the Anatomical Therapeutic Chemical (ATC) Classification System. Subsequently assigned to 23 medication-taking traits by their respective active ingredients. Anti-inflammatory medications were categorized into three groups, encompassing NSAIDs (M01A), acetylsalicylic acid (N02BA), and acetaminophen (N02BE) (Additional file 3: Table S1). The UKB assessment encompassed a total of 502,616 participants who possessed medication records, and approximately 73% of them contained non-blank medication information. The average age of participants upon attending the assessment center was 56.53 years, while the mean body mass index

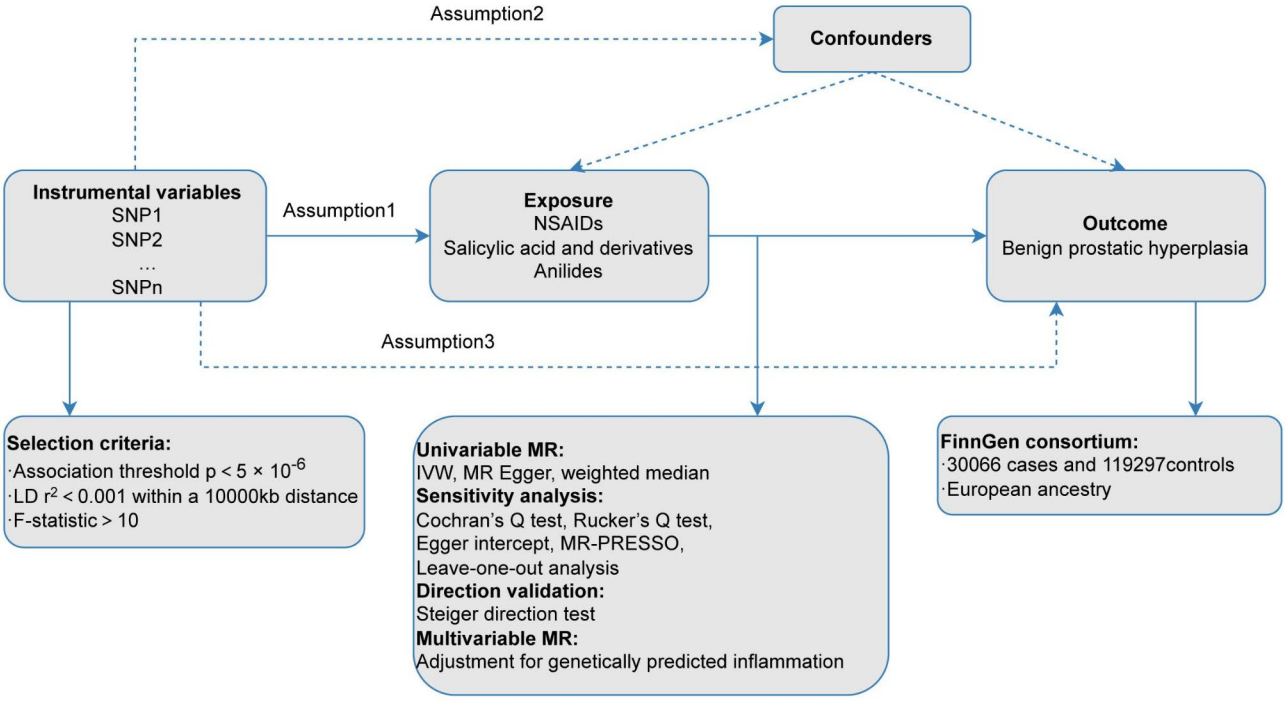

Fig. 1 The study design overview for analyzing the causal effects of NSAIDs use on the risk of BPH using Mendelian randomization. Assumption 1: instrumental variables (IVs) exhibit robust associations with the exposures; Assumption 2: IVs are not associated with any potential confounding factors; Assumption 3: genetic instruments exert their sole impact on the outcome through the relevant exposures. SNP: single nucleotide polymorphisms, NSAIDs: non-steroidal anti-inflammatory drugs, LD: linkage disequilibrium, MR: Mendelian randomization, IVW: inverse variance weighted

(BMI) of the participants was 27.43. The proportion of individuals using medication demonstrated an increasing trend with age. We used Interleukin-17 (IL-17) as a blood biomarker of inflammation. The GWAS data for plasma protein IL-17 were obtained from the study by Zhao et al. ($n = 14{,}824$, of European descent) [26]. Plasma proteins were quantified using the Olink Target-96 Inflammation immunoassay panel. Normalized Protein eXpression (NPX) values represent Olink's normalized relative units on a log2 scale [26].

In order to address sample overlap, BPH summary statistics from the FinnGen consortium's R9 release were obtained [27]. The N40 code in the International Classification of Diseases-10th Revision (ICD-10), as well as the 600 code in ICD-8 and ICD-9, were used within the FinnGen consortium to identify BPH patients. 30,066 BPH cases and 119,297 persons categorized as controls were included in the R9 release of the FinnGen consortium data. For additional information pertaining to the utilized data sources, definitions, units, participant details, population characteristics, and adjusted covariates, please refer to Additional file 3: Table S1.

Univariable Mendelian randomization analysis

We put in place a rigorous screening process for IVs to guarantee the reliability of the results of the MR study. Initially, we changed the threshold to p-value $< 5 \times 10^{-6}$ due to the small number of single nucleotide polymorphisms (SNPs) achieving genome-wide significance for medication, following the approach employed by Rosoff et al. [28]. In order to reduce linkage disequilibrium (LD), we simultaneously defined a threshold of $r^2 = 0.001$ and the breadth of the LD region = 10,000 kb. Furthermore, the F-statistic for each SNP was determined using the ($F = \beta^2/SE^2$), and those with an F-statistic of less than 10 were excluded to lessen the effects of weak instrumental bias. Subsequently, the exposure SNPs were then retrieved from the outcome statistics, and those related to the BPH ($p < 1 \times 10^{-5}$) were disregarded. To find and exclude SNPs associated with confounding variables, we utilized the PhenoScanner V2 database (http://www.phenoscanner.medschl.cam.ac.uk, accessed on 25 June 2023). Previous literature has demonstrated that metabolic syndrome, inflammation, and sex steroid hormones are among the main risk factors for BPH [29, 30]. Finally, data harmonization was performed to ensure compatibility. Incompatible alleles and palindromic SNPs with intermediate allele frequencies were discarded from this study.

For UVMR analysis, the causal relationship between the use of NSAIDs and BPH was assessed using a variety of analyses. The main MR analyses involved utilizing the random effects inverse variance weighted (IVW) method, which yields highly precise estimates while assuming all

SNPs are valid instruments. In cases where the results exhibit homogeneity, the fixed effects IVW method offers a more reliable causal evaluation. MR-Egger regression can be estimated while accounting for horizontal pleiotropy, albeit with a slight reduction in precision [31, 32]. The weighted median method yields a valid causal assessment even when up to 50% of the information is derived from erroneous IVs [33].

Heterogeneity was examined using Cochran's Q statistic and Rucker's Q statistic, with a significance threshold of p-value > 0.05 indicating the absence of heterogeneity [34]. The intercept term from the MR-Egger regression approach was used to evaluate directional pleiotropy [31]. Additionally, the MR pleiotropy residual sum and outlier (MR-PRESSO) test were utilized to identify outliers and potential pleiotropy, with a global test p-value > 0.05 indicating no potential pleiotropy [35]. Finally, a leave-one-out analysis was conducted to investigate the influence of a single SNP on the outcomes of the genetic evaluation and assess the robustness of the MR findings. Furthermore, we conducted the Steiger directionality test to verify if the observed causal relationships were affected by reversed causation [36]. A Steiger p-value > 0.05 suggests a potential bias in the direction of causal inference. The risk of BPH per unit increase in the log odds of using NSAIDs was calculated using the MR estimations, which were shown as odds ratios (OR). We calculated the statistical power of our primary MR estimates at a significance level of 0.05 using an on-line calculator (https://shiny.cnsgenomics.com/mRnd/) [37].

Multivariable Mendelian randomization analysis

In examining whether there was an independent relationship between the genetic prediction of NSAIDs use and the risk of BPH, we conducted MVMR analyses, adjusting for genetically predicted IL-17 levels. We identified IVs that were associated with IL-17 levels at a significance threshold of p-value $< 5 \times 10^{-6}$. We next eliminated duplicate and correlated SNPs (LD region = 10,000 kb; $r^2 = 0.001$). Following this, we combined the SNPs on medication use and IL-17 levels, extracting SNP effects and accompanying standard errors (SE) from the exposure and outcome GWAS data. Then we used the "MVMR" package to calculate the overall F-statistic of the IVs. Finally, data harmonization was performed.

For the MVMR analysis, we used the random effects IVW, weighted median, and MR-Egger analyses [38, 39]. Cochran's Q statistic and Rucker's Q statistic were used to assess the heterogeneity of the MVMR analysis, while the Egger intercept was used to assess pleiotropy. The MVMR-PRESSO test was also utilized to find outliers and possible pleiotropy.

A Bonferroni-corrected criterion of p-value < 0.0167 ($\alpha = 0.05/3$ exposure factors) was utilized in this research to account for multiple tests. Significance was attributed to associations with p-value < 0.0167, whereas those with p-value ≥ 0.0167 and < 0.05 were considered suggestive. All analyses were two-sided and carried out utilizing "TwoSampleMR" package (version 0.5.7), "MendelianRandomization" package (version 0.8.0), "MVMR" package (version 0.4), and "MRPRESSO" package (version 1.0) within the R software (version 4.3.1).

Results

In the UVMR analysis, 37, 32 and 36 SNPs were identified to be IVs for NSAIDs, salicylic acid and its derivatives and anilines, respectively, following the stringent screening process for IVs. The F-statistics for these SNPs varied from 21 to 65, indicating the absence of weak IVs (Additional file 3: Table S2-4). In the MVMR analysis, 47, 44 and 49 SNPs were identified with F-statistics > 10, respectively. The harmonized data was presented in Additional file 3: Table S5-7 for reference.

Univariable Mendelian randomization analysis

The random effects IVW method revealed that the genetically predicted NSAIDs use was linked to an elevated risk of BPH (OR: 1.164, 95% CI: 1.041–1.302, $p = 0.008$) (Fig. 2, Additional file 2: Fig. S1A). Similar results were obtained with the fixed effects IVW method (OR: 1.164, 95% CI: 1.053–1.287, $p = 0.003$). The MR-Egger regression and weighted median methods provided consistent estimates in terms of direction and magnitude, providing further support for the robustness of the causal association. Additionally, a suggestive positive relationship between the genetically predicted anilides usage and the risk of BPH was found (Fig. 2, Additional file 2: Fig. S2A). The MR estimates of the causal relationship between anilides use and BPH remained consistent using the MR models of the random effects IVW method (OR: 1.127, 95% CI: 1.014–1.253, $p = 0.027$), fixed effects IVW method (OR: 1.127, 95% CI: 1.014–1.253, $p = 0.027$), and weighted median (OR: 1.168, 95% CI: 1.005–1.358, $p = 0.043$). MR-Egger regression estimates were also consistent in terms of direction and magnitude. However, we could not discover any proof that genetically predicted salicylic acid and derivatives increased the risk of BPH (random effects IVW method, OR: 0.987, 95% CI: 0.892–1.093, $p = 0.801$).

Comprehensive sensitivity analyses, as presented in Table 1, were performed to assess the reliability of the MR analyses. Heterogeneity was evaluated using Cochran's Q statistic (MR-IVW) and Rucker's Q statistic (MR Egger), with p-value > 0.05 (Table 1), along with the assessment of funnel plot symmetry (Additional file 2: Fig. S1B, Fig. S2B), indicating the absence of heterogeneity. The MR-Egger intercept analysis yielded a p-value > 0.05, suggesting no evidence of horizontal pleiotropy. The

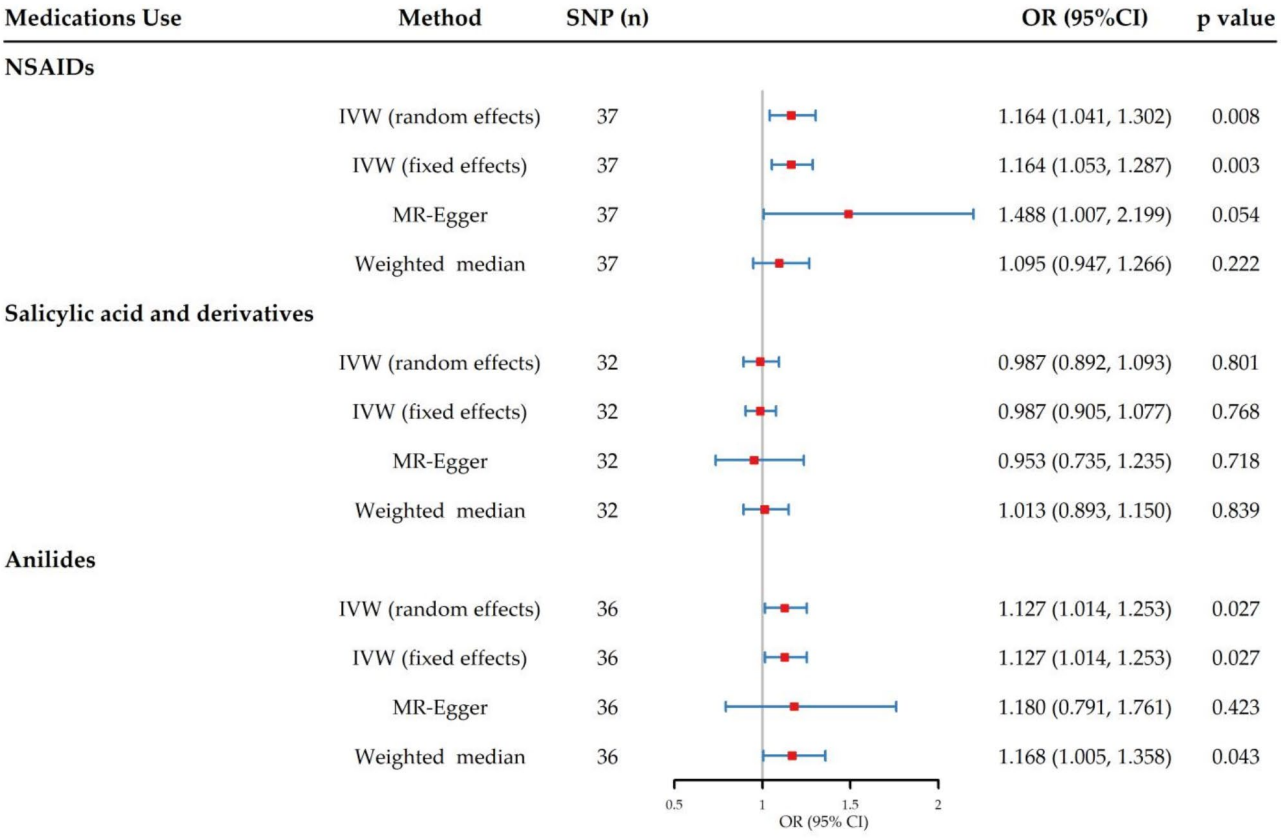

Fig. 2 UVMR analysis results of medications use (NSAIDs, salicylic acid, and anilides) and BPH. OR: odds ratio, CI: confidence interval

Table 1 Sensitivity analysis of the MR analysis results of medications use and BPH

Medications Use	Heterogeneity Test		Pleiotropy Test	MR-PRESSO
	Cochran's Q Test (*p* value)	Rucker's Q Test (*p* value)	Egger Intercept (*p* value)	Global Test
	IVW	MR-Egger	MR-Egger	*p* value
NSAIDs	0.159	0.182	0.208	0.184
Salicylic acid and derivatives	0.088	0.071	0.774	0.129
Anilides	0.526	0.480	0.817	0.532

NSAIDs: non-steroidal anti-inflammatory drugs, IVW: inverse variance weighted, MR-PRESSO: MR pleiotropy residual sum and outlier

Table 2 Steiger direction test from medications use to BPH

Exposure	NSAIDs	Salicylic acid and derivatives	Anilides
Direction	TRUE	TRUE	TRUE
Steiger *p* value	2.269×10^{-61}	1.039×10^{-87}	1.640×10^{-62}

MR-PRESSO test demonstrated that the MR analyses for medication use and BPH was not affected by potential pleiotropy or outliers (Global Test $p>0.05$). Furthermore, the leave-one-out analysis indicated that the MR results remained robust in the absence of any high-influence SNP (Additional file 2: Fig. S1C, Fig. S2C). Additionally, to further establish the direction of the association between medication use and BPH, a Steiger test was performed (Table 2). The Steiger p-value showed that the detected causal correlations were not skewed by reverse causation. Overall, the thorough sensitivity studies demonstrated that neither pleiotropy nor heterogeneity had an impact on the MR estimations.

Multivariable Mendelian randomization analysis

In the context of MVMR analysis, we investigated whether the association between medication and a reduced risk of BPH was affected by inflammation. After adjusting for IL-17 levels, the causal effect of genetically predicted NSAIDs use on BPH persisted, with estimates observed in the IVW analysis (OR: 1.165, 95% CI: 1.049–1.293, $p=0.004$) (Fig. 3). MR-Egger and Weighted median method had the same direction, although the p-value is not significant. When IL-17 levels were taken into account, the causal estimates of genetically predicted

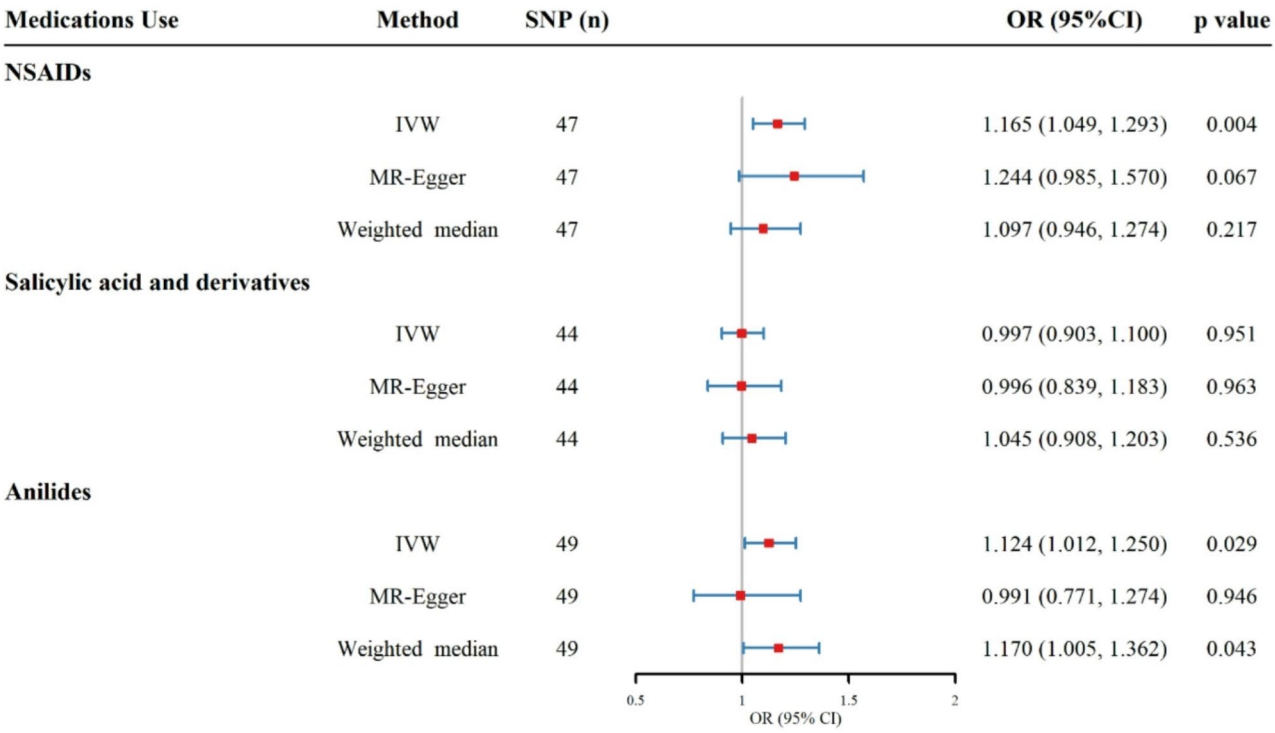

Fig. 3 MVMR analysis results of medications use (NSAIDs, salicylic acid, and anilides) and BPH

salicylic acid and derivatives use and anilides use on BPH remained statistically non-significant.

MVMR analysis showed no evidence of heterogeneity (Additional file 3: Table S8). The MR-Egger intercept analysis once again did not indicate the existence of horizontal pleiotropy. Moreover, the MVMR-PRESSO test in MVMR did not find any outliers or potential pleiotropy.

Discussion

Our study revealed a positive association between genetically predicted NSAIDs use and an elevated risk of BPH, even after adjusting for inflammation. In contrast, no substantial indications were discovered, connecting the usage of salicylic acid and derivatives, as well as anilides, to the risk of BPH. Remarkably, this MR study stands as the inaugural exploration into the causal influence of NSAIDs use on BPH, to the utmost extent of our cognizance.

Previous investigations concerning NSAIDs usage and BPH risk have been scarce, and each study exhibits distinct characteristics that hinder direct comparisons with our findings, thereby leading to limited interpretability. Notably, our outcomes diverge from those of earlier conducted randomized controlled trials (RCTs), which found no connection with the risk of BPH [20]. According to a different meta-analysis, COX-2 inhibitors may provide temporary relief for male LUTS-related symptoms [40]. However, no significant differences in changes to the total prostate volume were observed among the patients [40]. It is imperative to acknowledge that RCTs usually entail a meticulously selected study population, potentially posing challenges in generalizing the outcomes to broader populations. Furthermore, the primary endpoints in their study focused on the International Prostate Symptom Score (IPSS) or maximum urinary flow (QMax), which differed from the primary outcomes in our present study. St. Sauver et al. [11] found a noteworthy negative correlation between NSAIDs use, particularly aspirin, and multiple indirect and direct indicators of BPH, including IPSS, QMax, prostate volume, and prostate-specific antigen (PSA) level. In their research, NSAIDs utilization was ascertained through structured interviews at baseline and questionnaires during follow-up, with only men who reported using NSAIDs at the start were deemed exposed. Kang et al. [17] conducted a cross-sectional study, wherein they found that regular use of aspirin and ibuprofen in the preceding year was linked to a higher likelihood of having a history of BPH that has been medically diagnosed (OR: 1.2, 95% CI: 1.1–1.3). However, the temporal relationships between NSAIDs usage and BPH endpoints remained unclear in their study, and the slight increase in risk observed might potentially be attributed to uncontrolled confounding variables. In another cohort study, the use of any NSAIDs, aspirin, and non-aspirin NSAIDs was shown to be strongly related to an elevated risk of BPH [15]. These relationships were

marginally lessened by controls for NSAIDs indications and baseline IPSS, but they all lost their significance. In this study, incident BPH was referred to as prolonged, clinically significant BPH symptoms or as surgical or medicinal therapy. Only the beginning of NSAIDs usage was considered, so continued use was assumed. Conventional observational studies suffer from limitations such as reverse causality, residual confounding, and limited sample sizes, which restrict the extent to which we can understand the impact of NSAIDs use on BPH to date. As a consequence, the potential influence of NSAIDs use on BPH remains inadequately elucidated.

Our discoveries have broadened the comprehension of the association between NSAIDs usage and BPH in various dimensions. Principally, our findings enhance the existing observational literature, indicating that the utilization of NSAIDs potentially heightens the risk for BPH. Specifically, our investigation delves into the connection between the usage of NSAIDs (excluding aspirin and acetaminophen), salicylic acid and its derivatives (primarily aspirin), and anilides (mainly acetaminophen) in the context of BPH. Secondly, our study, conducted within the framework of MR, provides compelling evidence supporting a causal association between genetically predicted NSAIDs use (excluding aspirin and acetaminophen) and an elevated risk of BPH. The strength of this causal inference was reinforced by consistently aligned effect estimates obtained through various MR methods, including IVW, MR-Egger, and weighted median. Although the precise mechanism underlying this phenomenon remains unclear, a case-control study discovered that NSAIDs use was linked to a greater incidence of acute urinary retention (AUR) even after adjusting for AUR risk factors (OR: 2.02, 95% CI: 1.23–3.31) [41]. However, the risk of getting AUR was not shown to be higher in patients who were already using acetylsalicylic acid. The Italian spontaneous reporting system (SRS) database also noted a connection between NSAIDs usage and the incidence of AUR [42]. It is possible that prostaglandins may trigger slow tonic contractions of bladder muscle strips, and pretreatment with prostaglandin inhibitors could reduce muscle tone and contractility [43]. An alternative perspective is that NSAIDs may be prescribed for the initial symptoms of AUR, potentially introducing a protopathic bias [41]. Notably, there was no correlation between acetylsalicylic acid usage and the risk of developing AUR, which could be related to the fact that it is often used at low cardioprotective dosages [41]. Lastly, distinguishing between the use of medication for managing systemically symptomatic inflammatory processes that might be causative of BPH and any potential direct effect of the drug itself poses a challenge [10]. The likelihood of causal bias arising from indications for NSAIDs use has been previously discussed in the literature [15, 16]. However, in our study, even after controlling for inflammation in the MVMR analysis, genetically predicted NSAIDs use remained strongly associated with BPH, suggesting that causal bias due to an individual's systemic inflammation is unlikely. This points to a potential direct contribution of NSAIDs use to an increased risk of BPH. In conclusion, further investigations are necessary to validate the effects of NSAIDs on BPH and to delve deeper into the underlying mechanisms.

There are several significant advantages to this two-sample MR study examining the relationship between genetically predicted NSAID use and BPH. Firstly, by sourcing exposure data from the UKB and outcome data from the FinnGen consortium, we effectively avoid any overlapping sample sizes, ensuring the validity of our analyses. Secondly, to ensure robustness, we employed complementary MR methods to thoroughly scrutinize potential violations of MR assumptions. Notably, the Steiger test provided support for the notion that IVs influence exposure before the outcome, rather than the opposite direction of effect. Additionally, a salient virtue of this study emanates from the remarkable homogeneity characterizing the participants in the GWAS, all sharing European heritage. This approach minimizes the susceptibility of introducing biased results due to demographic stratification biases. The utilization of summary genetic associations sourced from the largest GWAS further amplifies measurement precision through the integration of larger sample sizes. Lastly, a notable strength in this work lies in the implementation of MVMR. By adjusting for systemic inflammation, MVMR allows us to derive a direct effect of genetically predicted NSAIDs use on BPH, while simultaneously accounting for potential confounding factors arising from inflammation.

This study is subject to several limitations that warrant consideration. Firstly, despite utilizing the largest GWAS on NSAIDs use, we only identify a small number of SNPs that met genome-wide significance, possibly leading to potentially weak IVs. In order to counteract this, we lowered the statistical cutoff ($p < 5 \times 10^{-6}$) and included more SNPs while guaranteeing that all of them had F-statistics > 10. Secondly, owing to the representation of each drug usage phenotype as binary variables (use/non-use), the capacity to discern potential dose-dependent alterations in the risk associated with NSAIDs use remains constrained. Thirdly, it is possible that the genetic variants associated with NSAIDs medication use could also be related to underlying diseases or inflammation, which may influence BPH risk, thereby potentially impacting the study results. Fourthly, data-driven IVs selection may introduce bias into the causal estimate in the summary statistics for drug usage from specific GWAS studies, which may restrict their ability to identify genetic

connections [44]. Fifthly, our MR analyses may currently lack sufficient statistical power. As shown in Additional File 2: Fig. S3, the statistical power for a causal inference with an odds ratio (OR) of 1.164 was approximately 0.5. Although the power increases as the OR approaches 1.488, it remains below the commonly accepted threshold of 80%. Future studies leveraging larger GWAS datasets will be essential to validate these findings. Sixthly, the exclusive inclusion of individuals of European ancestry necessitates cautious extrapolation of the findings to other demographic groups. Finally, although the MR method demonstrates excellent performance in causal inference, we caution that the findings of this MR study should be further validated through robust RCTs to confirm the existence of causal relationships.

Conclusions

In summary, our MR analyses present compelling evidence for a causal effect of the genetically predicted NSAIDs use on the heightened risk of BPH, and this causal relationship remains evident even after excluding inflammation. These findings impart novel perspectives on the underlying correlation between NSAIDs use and BPH, thereby potentially prompting clinicians to exercise heightened vigilance in the monitoring and management of BPH among patients employing NSAIDs.

Abbreviations

BPH	Benign prostatic hyperplasia
NSAIDs	Non-steroidal anti-inflammatory drugs
LUTS	lower urinary tract symptoms
MR	Mendelian randomization
IVs	Instrumental variables
UVMR	Univariable Mendelian randomization
GWAS	Genomewide association study
MVMR	Multivariate MR
UKB	United Kingdom Biobank
ATC	Anatomical Therapeutic Chemical
Il-17	Interleukin-17
ICD-10	International Classification of Diseases—10th Revision
SNPs	Single nucleotide polymorphisms
LD	linkage disequilibrium
IVW	Inverse variance weighted
MR-PRESSO	MR pleiotropy residual sum and outlier
OR	Odds ratio
SE	Standard errors
RCTs	Randomized controlled trials
IPSS	International Prostate Symptom Score
PSA	Prostate-specific antigen
AUR	Acute urinary retention
SRS	Spontaneous reporting system

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-025-02128-1.

Additional file 1: STROBE MR checklist.

Additional file 2: **figure S1**. Association between genetically predicted non-steroidal anti-inflammatory drugs use and benign prostatic hyperplasia presented in (A) scatter plot, (B) funnel plot, (C) leave-one-out sensitivity analysis, and (D) forest plot. **Figure S2**. Association between genetically predicted anilides use and benign prostatic hyperplasia presented in (A) scatter plot, (B) funnel plot, (C) leave-one-out sensitivity analysis, and (D) forest plot. Figure S3. Power calculation of Mendelian randomization analysis.

Additional file 3: **table S1**. Detailed information on used studies. Table S2. Characteristics of the genetic variants used as the instrumental variables for NSAIDs. **Table S3**. Characteristics of the genetic variants used as the instrumental variables for salicylic acid and derivatives. **Table S4.** Characteristics of the genetic variants used as the instrumental variables for anilides. **Table S5.** Characteristics of the genetic variants in multivariate MR analysis used as the instrumental variables for NSAIDs. **Table S6.** Characteristics of the genetic variants in multivariate MR analysis used as the instrumental variables for salicylic acid and derivatives. **Table S7.** Characteristics of the genetic variants in multivariate MR analysis used as the instrumental variables for anilides. **Table S8.** Sensitivity analysis of the multivariate MR results of medications use and BPH.

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Author contributions

Conceptualization: Z.H.P, T.C and Z.L.L; Formal analysis: Z.H.P, M.R.L and M.X.H; Funding acquisition: Z.L.L; Investigation: J.L, J.H.D and Y.W.W; Methodology: M.R.L and M.X.H; Project administration: T.C and Z.L.L; Resources: Y.D, C.Y and Z.H.L; Software: Z.H.P, M.R.L and M.X.H; Supervision: T.C and Z.L.L; Validation: M.R.L; Visualization: Z.H.P; Writing– original draft: Z.H.P; Writing– review & editing: M.R.L and M.X.H. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets for IL-17 levels can be found in GWAS Catalog (https://www.ebi.ac.uk/gwas/publications/37563310). The summary statistics for drug use are available in GWAS Catalog (https://www.ebi.ac.uk/gwas/publications/31015401). The summary statistics for BPH are available at the FinnGen consortium (https://www.finngen.fi/fi).

Declarations

Ethics approval and consent to participate

All data sources were derived from publicly available summary-level data, so no informed patient consent was required to release the summary-level data. The ethics committee of the Second Affiliated Hospital of Xi'an Jiaotong University waived the need for ethical approval and informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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