Correlation between benign prostatic hyperplasia and comorbidities: a systematic analysis integrating global burden of disease and mendelian randomization study

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Abstract

Background Benign prostatic hyperplasia (BPH) is a common chronic condition in elderly men. Observational studies have identified several comorbidities associated with BPH. However, these studies are limited by various confounding factors and do not clearly explain the association between BPH and its comorbidities. We investigated the association between BPH and comorbidities using the Global Burden of Disease (GBD) database combined with Mendelian randomization (MR) methods.

Methods Through an extensive PubMed search, we identified 22 diseases associated with BPH and selected 9 significant comorbidities from the GBD database for a detailed correlation analysis. We also considered socio-economic and environmental influences on BPH. Utilizing the GWAS database, we gathered data on BPH and 20 comorbidities, employing the Linkage Disequilibrium Score Regression (LDSC) method to unearth genetic connections. Causality was determined through both univariable and multivariable bidirectional MR analyses, supplemented by Steiger directionality tests to confirm causation. The study's integrity was fortified by employing various MR models and conducting rigorous sensitivity analyses. The synthesis of GBD data with LDSC and MR findings offered a nuanced understanding of the BPH-comorbidity nexus. Additionally, we explored the genetic basis and the role of mediating factors between BPH and comorbidities through phenome-wide association studies (PheWAS), colocalization analysis, and mediation MR.

Results Correlation analysis of GBD data found associations of prostate cancer, chronic kidney disease and depression with BPH. LDSC results indicated that prostatitis and bladder cancer are related to BPH. Two associations were replicated in bidirectional univariable MR, linking BPH with a higher risk of prostatitis and prostate cancer.

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conducted sensitivity analyses to confirm the robustness of the results and all Steiger directionality tests were correct. Multiple multivariable MR models validated these results. PheWAS analysis showed that outliers in MR do not significantly impact MR results. Through colocalization analysis, three shared loci between BPH and both prostatitis and prostate cancer were identified. Mediation analysis found that, after adjusting for BPH, fruit consumption was associated with a lower risk of prostatitis, and morning person and chronotype were associated with a lower risk of prostate cancer.

Conclusions This study uncovered associations between BPH and various comorbidities, emphasizing the causal relationships between BPH, prostatitis, and prostate cancer. Our research provides a new perspective in understanding the comorbid associations of BPH.

Keywords Benign prostatic hyperplasia, Comorbidities, Mendelian randomization analysis, Causality, Global burden of disease

Introduction

Benign Prostatic Hyperplasia (BPH) is a common urological condition in elderly men [1]. Patients with BPH not only frequently experience lower urinary tract symptoms (LUTS) but may also suffer from a range of comorbidities, posing a significant threat to their quality of life [2, 3]. Epidemiological studies have meticulously delineated comorbidities associated with BPH, encompassing not just prostate diseases but also various systemic illnesses such as prostatitis, [4] prostate cancer, [5] erectile dysfunction, [6], diabetes [7] and hypertension [8]. Yet, the intricate web of interactions between BPH and its comorbidities is obfuscated by myriad confounding factors, including socio-economic and environmental variances.

The Global Burden of Disease (GBD) study, the most expansive and detailed global disease analysis initiative to date, aggregates and harmonizes health data across diverse geographies and demographics, offering a comparative perspective on health detriments attributed to numerous diseases, injuries, and risk factors [9]. The most current version has been updated with data up to 2019. GBD harmonizes data from various countries and regions, making it comparable. [10] Thus, the GBD study overcomes some limitations of previous epidemiological studies. Mendelian Randomization (MR) assesses the causal relationships between different risk factors and diseases through closely related genetic variations [11]. Compared to observational studies, MR uses the random allocation of genetic variations, reducing the impact of confounding factors, and can examine potential causal relationships between BPH and its comorbidities. [12] Building upon this, multivariable MR employs genetic variants associated with various risk factors to concurrently estimate the causal influence of each factor on the outcomes, [13] thereby uncovering the complex interrelations between BPH, intermediary factors, and comorbid conditions.

Previously, GBD studies comprehensively assessed the temporal and geographical patterns of the BPH burden. In most regions worldwide, the absolute burden of BPH is rising at an alarming rate [10]. We expanded the exploration of the connections between BPH and its comorbidities, assessing the impact of socio-economic, environmental factors and lifestyle on BPH. Previous MR explorations, such as the work by Du et al., have pinpointed specific comorbid associations, notably between BPH and bladder cancer [14]. Our systematic approach advances this discourse by integrating GBD and MR data, offering a holistic view of the BPH-comorbidity landscape.

Method

Study design

Figure 1 provides an overview of our study design. Our investigation began with a detailed search of the PubMed database, identifying 22 diseases associated with BPH. Building on this, we selected 9 comorbidities from the GBD database for extensive correlation analysis using the Pearson coefficient. We explored the impact of economic, environmental, and lifestyle variables on the incidence of BPH. Subsequently, data regarding BPH and 20 comorbidities were sourced from the GWAS database, with the selection criteria for these comorbidities detailed in Supplementary Notes 1 and Supplementary Table 1. Using Linkage Disequilibrium Score Regression (LDSC), we assessed the genetic associations between BPH and its comorbidities, established causality through univariable and bidirectional Mendelian Randomization (MR), and confirmed the directions of causation using Steiger directionality tests. Our analytical rigor was further enhanced by the deployment of various MR models, multivariable MR models, and sensitivity analyses. We then integrated GBD data with LDSC and MR findings to comprehensively assess the connections between BPH and its comorbidities. Finally, we embarked on elucidating potential pathways linking BPH with comorbidities through Phenome-Wide Association Studies (PheWAS), colocalization analysis, and mediation MR.
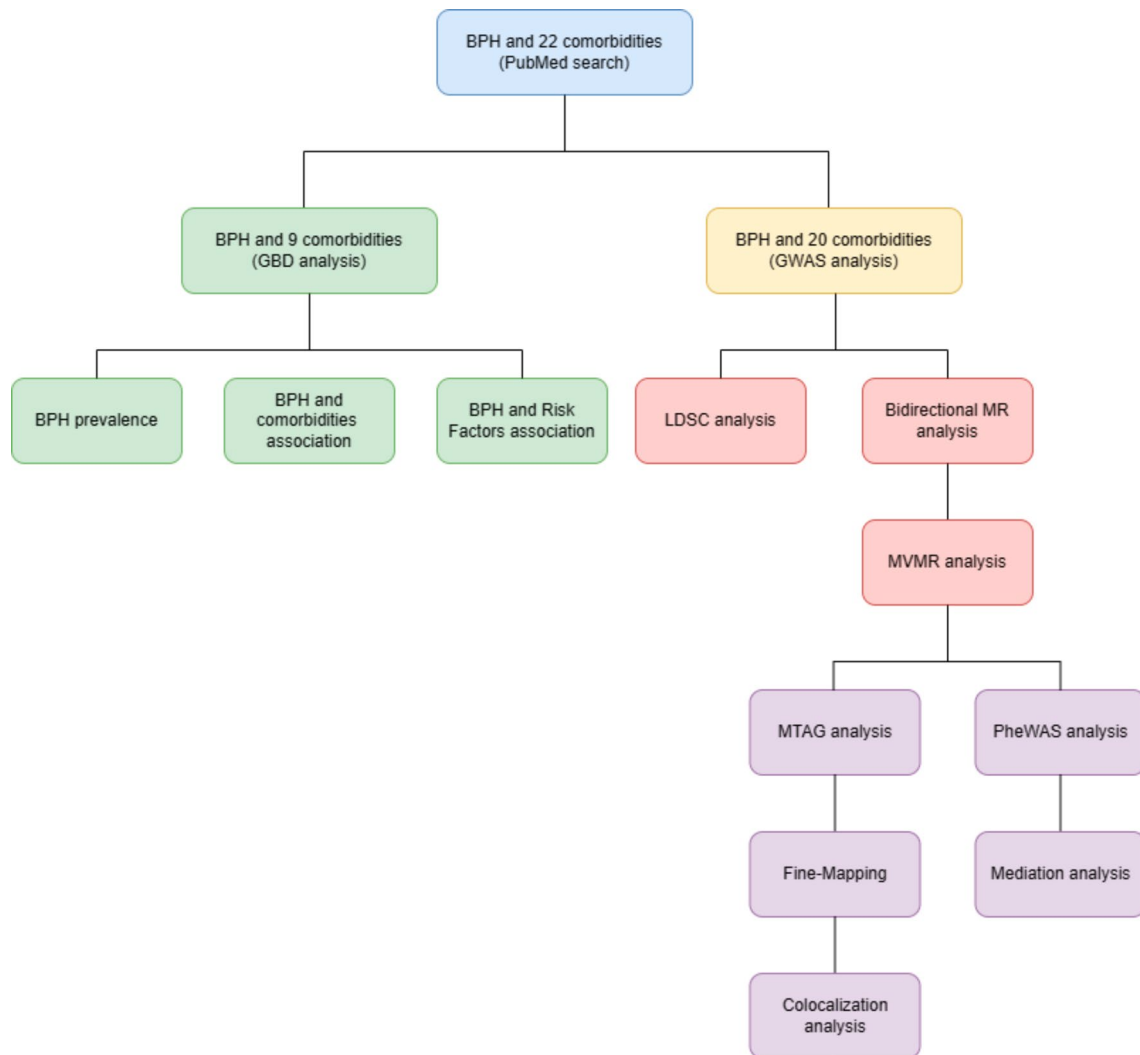
Fig. 1 Study design overview. BPH = benign prostatic hyperplasia; GBD = Global Burden of Disease; GWAS = genome-wide association study; LDSC = Linkage disequilibrium score regression; MR = Mendelian Randomization; MVMR = Multivariable Mendelian; PheWAS = Phenome-Wide Association Studies; MTAG = Multi-Trait Analysis of GWAS

GBD data source

The foundation of our data on BPH and the selected comorbidities is the GBD Database, spearheaded by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington. This collaborative effort encompasses contributions from over 9,000 researchers worldwide, cataloging 370 diseases and injuries from 1990 to 2019 across 201 countries, segmented by age and gender. Detailed methodology: https://www.healthdata.org/sites/default/files/files/Projects/GBD/March2020_GBD%20Protocol_v4.pdf. The classification and sources of risk factors, including socio-economic, environmental and lifestyle variables, are detailed in Supplementary Tables 3 and Supplementary Table 4.

GBD data analysis

Prior to the GBD data analysis, we employed periodic prevalence estimates from the GBD study to delineate and evaluate the relationships between global BPH incidence and comorbidities from 1990 to 2019. A stratified model facilitated our evaluation of these connections by age, and we quantified the impact of various risk factors on BPH incidence using Pearson correlation analysis. The formulas for calculating periodic prevalence and Pearson correlation analysis are in the Supplementary Note 3 and Supplementary Note 4. This analytical process was executed using MATLAB software (R2023a) and R (v4.3.1).

GWAS data source

The summary-level genetic data for BPH is sourced from the FinnGen consortium's Release 8 (R8) and the UK Biobank data (Supplementary Table 5). In FinnGen's R8 data,

individuals with unclear gender, high genotype missing rate (>5%), extreme heterozygosity (±4 standard deviations), and non-Finnish ancestry were excluded based on age, ten principal genetic components, and genotyping, resulting in 26,358 BPH cases and 110,070 controls. The UK Biobank study adjusted for age and up to twenty principal components, excluding individuals who withdrew consent, those with aneuploidy of sex chromosomes, and non-European ancestry, yielding 6,505 BPH cases and 202,303 controls. For detailed information on quality control, please refer to the data source websites and GWAS papers [15, 16].

Selection of genetic instruments

The genetic instruments used for MR analysis must meet the following three criteria: [17] (1) The Single Nucleotide Polymorphism (SNP) should be associated with BPH, (2) The SNP should not be correlated with confounding factors, and (3) The SNP must influence comorbidities through exposure that has no direct link. Therefore, we chose SNPs from exposures with $P < 5 \times 10^{-8}$, ensuring a significant association between the SNP and exposure. For prostatitis datasets, only one exposure with $P < 5 \times 10^{-8}$ was selected, potentially resulting in weak instrumentation; thus, we chose a threshold of $P < 5 \times 10^{-6}$ to select genetic instruments [18]. We excluded SNPs with linkage disequilibrium (LD) (r2 > 0.001 and block window < 10,000 kb) (Supplementary Table 6). We calculated the F-statistics and the power of the MR based on the proportion of variance explained by these instrumental variables [19]. The methods and results for the F-statistic calculation and MR power assessment are detailed in the Supplementary Table 7.

LDSC method

LDSC is a method that uses GWAS data to estimate heritability and genetic correlation, examining the relationship between test statistics and LD, thereby distinguishing polygenicity and confounding bias [20, 21]. This method can be implemented through the R package, ldscr (https://github.com/mglev1n/ldscr) [22]. In this study, we used cross-trait LDSC to estimate genetic correlations, examining the genetic relationship between BPH and its comorbidities.

Univariable MR analysis

Before conducting MR analysis, we eliminated allele frequencies containing palindromic SNPs to harmonize exposures and outcomes. The Inverse Variance Weighted (IVW) method was used as the primary MR analysis technique [23]. MR-Egger, Weighted mode, Weighted median, MR-PRESSO and MR-RAPS methods were employed as supplements. These techniques relax assumptions regarding horizontal pleiotropy and weak

instruments, ensuring the robustness of our MR inferences [24–28]. The specific strengths and limitations of each method are reported in the Supplementary Note 6.

Furthermore, we conducted several sensitivity analyses to ensure the robustness of the causal estimates. The Cochran Q of the IVW method was used to assess heterogeneity in individual causal effects, with a p-value < 0.05 indicating the presence of heterogeneity [29]. We also used MR-Egger regression to detect potential directional pleiotropy based on its intercept. A non-zero MR-Egger intercept indicates the presence of horizontal pleiotropy [25, 30]. MR-PRESSO identifies potential outliers that could bias MR-IVW results. Leave-one-out analysis and scatterplots were used to assess whether the effect estimates were influenced by individual variants.

All statistical analyses were performed using the TwoSampleMR v0.4.22 [30], MVMR v0.5.0 [31], MR-RAPS v0.2.0 [24] and MR-PRESSO v1.0.0 [28] packages in R v4.3.1 software.

Multivariable MR analysis

Multivariable MR (MVMR) analysis uses multiple phenotypes as exposures to assess the role of potential mediating variables identified in univariable MR, thereby better interpreting the results of univariable MR. Complete details are provided in Supplementary Notes 8. Firstly, testosterone levels are crucial for the onset and progression of prostate diseases. Testosterone may mediate the causal relationship between BPH and comorbidities; thus, we included total testosterone levels and bioavailable testosterone levels as mediators in MVMR. Secondly and thirdly, we utilized key factors affecting BPH from the GBD data analysis as the second and third types of mediator models.

PheWAS analysis

Some SNPs in the exposure may be related to other pleiotropic pathways, and excluding these SNPs could affect the variance efficiency of the results. Therefore, we examined outliers in bidirectional MR and conducted PheWAS analyses on these outliers to explore whether their associated phenotypes could serve as mediating factors. We then tested the impact of manually removing these outliers on the overall MR analysis. Complete details are provided in Supplementary Notes 7.

MTAG, fine-mapping and colocalization analysis

The MTAG (Multi-Trait Analysis of GWAS) method integrates data from GWAS of correlated traits to enhance statistical power, taking into account the potential overlap between GWAS datasets [32]. We utilized MTAG for cross-trait meta-analysis to identify loci significant in both traits, thus discovering new SNPs with strong signals. Significant loci were marked as those reaching

genome-wide significance thresholds ($P\_meta < 5 \times 10^{-8}$) and suggestive significance levels (single-trait $p < 5 \times 10^{-3}$) in both traits [33].

After identifying important shared loci between traits, we applied a Bayesian algorithm, the Probability of Causal SNP Identification (PICS). This algorithm uses linkage data from the 1000 Genomes Project to explore the 99% credible set of causal SNPs within a 500 kb radius around the index, which are used for downstream analysis [34]. To investigate whether shared loci exist between BPH, prostatitis, and prostate cancer, we conducted a colocalization analysis. The results of the Bayesian colocalization analysis indicated that a P(H4) > 0.5 is interpreted as evidence supporting shared genetic variants [35]. Complete details are provided in Supplementary Notes 9.

Mediation analysis
To further understand the role of mediating factors between BPH and its comorbidities, we applied mediation analysis. First, we assessed the impact of BPH on each mediator. We utilized MVMR to estimate the effects of each mediator on prostate cancer and prostatitis, while adjusting for the genetic effects of the instruments on BPH [13]. For the individual mediating effects of each risk factor, we employed the product of coefficients method to estimate the indirect effects [36]. Specifically, we estimated the impact of BPH on each mediator separately, then multiplied the BPH mediating effects by the mediating effects of the mediator on the outcome adjusted for BPH [37]. We calculated the proportion of the total effect mediated by each risk factor by dividing the indirect effect by the total effect.

Ethics approval
Summary data sourced from GBD [9], the GWAS Catalog project [38] and the Integrated Epidemiology Units OpenGWAS (IEU OpenGWAS) project [39] have been granted necessary permissions by respective review boards, in addition to having received informed consent from individual participants. Given the publicly accessible characteristics of this aggregate data, further ethical approval is not required.

Results
GBD disease associations
Figure 2 shows the associations between BPH and 9 comorbidities. Here, we analyzed the periodic incidence rates of BPH and these 9 comorbidities to explore the interrelations between these diseases. After age-stratifying the incidence of BPH for 1990 and 2019, we found that BPH most frequently occurs in individuals aged 70–75 years (See Supplementary Fig. 1, Supplementary Fig. 2). Correlation analysis results indicate a positive association between the overall prevalence of BPH and

chronic kidney disease, prostate cancer, and a negative association with depression. (Fig. 2A) The network graph shows that these associations are more pronounced in individuals over 70 years of age. (Fig. 2B)

Analysis of risk factors
The incidence rate of BPH is influenced by various factors including societal, environmental, and lifestyle elements. After analyzing 28 socio-environmental factors, age has emerged as one of the significant influencing factors and is the most critical determinant of disease burden in patients with BPH. PM2.5, years of education, Human Development Index, Social Development Index, life expectancy, and unsafe drinking water have been identified as significant factors. Age-segmented analysis revealed that the influence of years of education, Human Development Index, Social Development Index, and life expectancy on BPH gradually diminishes after the age of 60, while the effects of PM2.5 and unsafe drinking water remain consistent across different age groups. Detailed information is provided in Supplementary Fig. 3 and Supplementary Fig. 4. Among 36 lifestyle factors, smoking, alcohol consumption, sugar intake, and daily egg consumption are closely related to BPH. The impact of smoking remains consistent across different age stages, while the effects of other factors gradually diminish with increasing age. Detailed information is provided in Supplementary Fig. 5 and Supplementary Fig. 6.

Evaluation of instrumental variables
In the datasets derived from GWAS for BPH and 20 comorbidities, we identified 3-215 SNPs for subsequent MR analysis (Supplementary Table 6). All these SNPs had F-statistics > 10, indicating great statistical power. Detailed information can be found in Supplementary Table 7.

LDSC
We conducted 232 LDSC computations for BPH and 20 comorbidities, applying Bonferroni correction with a significance level of 2.38×10^{-4}. Figure 3 shows the genetic associations between benign prostatic hyperplasia and 20 comorbidities. The strongest association was observed between BPH and prostatitis (UK Biobank, Correlation = 0.938, $p < 0.001$; FinnGen, Correlation = 0.896, $p < 2.38 \times 10^{-4}$). This was followed by the correlation between BPH data from the UK Biobank and FinnGen (Correlation = 0.938, $p < 2.38 \times 10^{-4}$). The association between BPH and bladder cancer was also noted (UK Biobank, Correlation = 0.319, $p = 0.057$; FinnGen, Correlation = 0.434, $p = 0.012$). The association between BPH and chronic kidney disease was not strong (UK Biobank, Correlation = 0.011, $p = 0.645$; FinnGen, Correlation = -0.025, $p = 0.183$), but there was a certain association with

A.

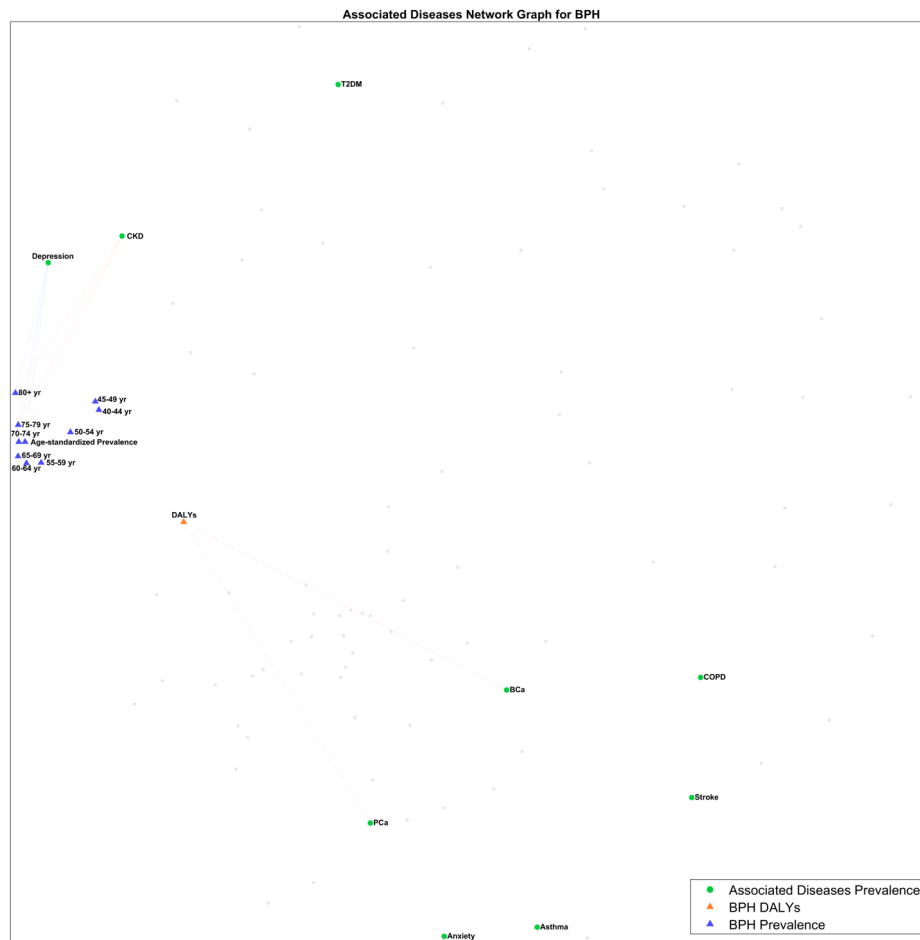|	BPH-Prev	BPH-DALYs	BPH-Prev.40-44	BPH-Prev.45-49	BPH-Prev.50-54	BPH-Prev.55-59	BPH-Prev.60-64	BPH-Prev.65-69	BPH-Prev.70-74	BPH-Prev.75-79	BPH-Prev.80+
T2DM-Prev	0.150	-0.040	-0.064	-0.062	-0.004	0.063	0.103	0.134	0.163	0.199	0.238
CKD-Prev	0.393	0.091	0.180	0.194	0.257	0.309	0.345	0.377	0.400	0.429	0.456
Stroke-Prev	-0.048	-0.273	-0.035	-0.022	-0.079	-0.135	-0.127	-0.092	-0.061	0.002	0.122
PCa-Prev	0.222	0.449	0.104	0.048	0.147	0.256	0.276	0.257	0.239	0.196	0.104
BCa-Prev	0.000	0.430	0.213	0.196	0.153	0.095	0.046	0.008	-0.016	-0.048	-0.099
COPD-Prev	0.072	0.238	0.309	0.266	0.189	0.100	0.057	0.050	0.056	0.064	0.068
Asthma-Prev	-0.030	0.142	-0.064	-0.124	-0.071	0.003	0.014	-0.001	-0.015	-0.047	-0.110
Depression-Prev	-0.407	-0.261	-0.307	-0.333	-0.360	-0.364	-0.368	-0.386	-0.409	-0.431	-0.433
Anxiety-Prev	-0.059	0.148	-0.078	-0.133	-0.086	-0.020	-0.014	-0.037	-0.054	-0.079	-0.128

B.

Fig. 2 Correlation between benign prostatic hyperplasia (BPH) prevalence and Disability-Adjusted Life Years (DALYs) and socioeconomic and environmental factors. (**A**) Heat map showing correlation coefficients comparing BPH prevalence and DALYs with socioeconomic and environmental factors. (**B**) Network diagram describing the association between BPH and socioeconomic and environmental factors. T2DM = Diabetes Mellitus Type 2; CKD = Chronic Kidney Disease; Stroke = Stroke; PCa = Prostate Cancer; BCa = Bladder Cancer; COPD = Chronic Obstructive Pulmonary Disease; Asthma = Asthma; Depression = Depressive Disorders; Anxiety = Anxiety Disorders; BPH = Benign Prostatic Hyperplasia
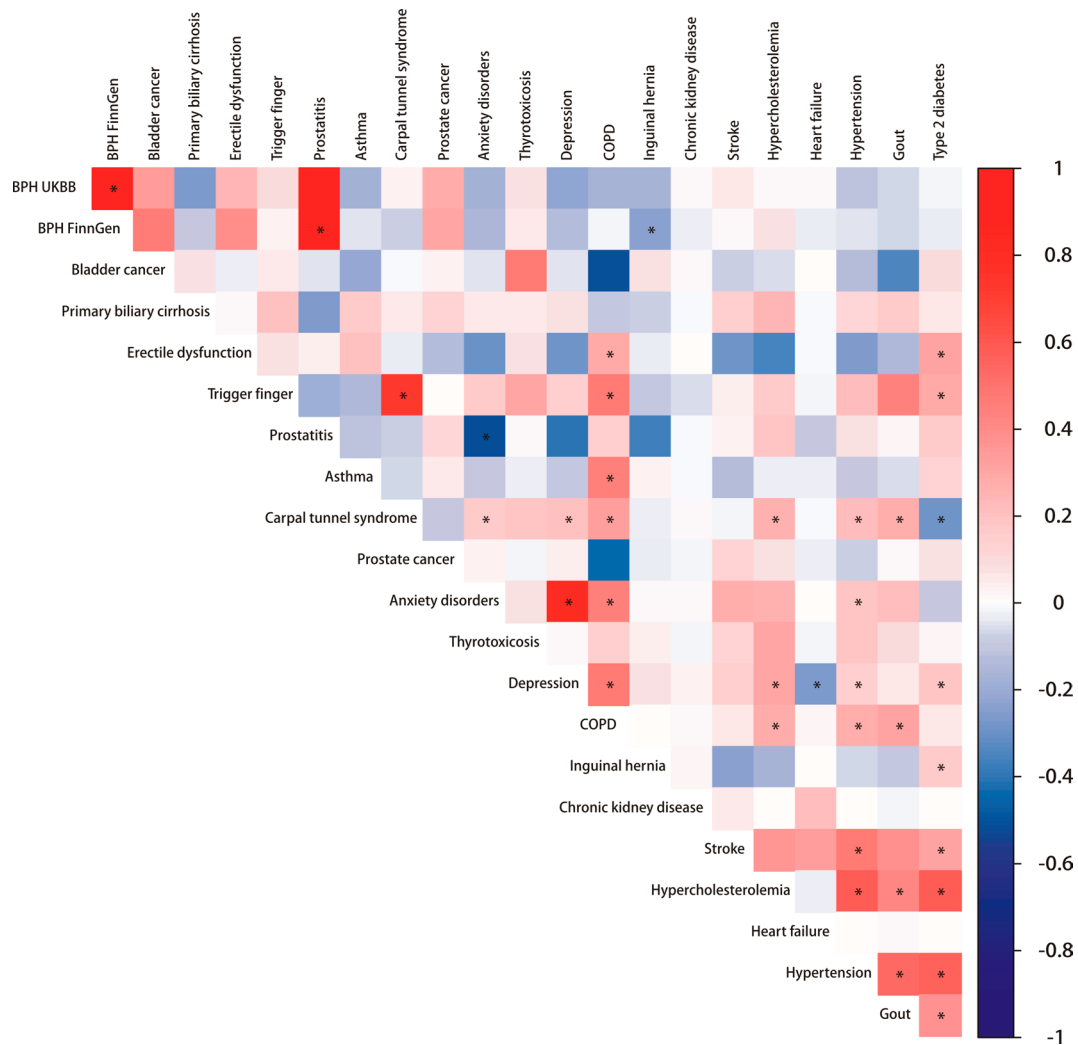
Fig. 3 Genetic associations between benign prostatic hyperplasia and 20 comorbidities. Inside the square is the genetic correlation estimate Rg, and the depth of the color represents the strength of the association. Asterisks indicate significance ($p < 2.38 \times 10^{-4}$). BPH = Benign prostatic hyperplasia; UKBB = UK Biobank; COPD = Chronic obstructive pulmonary disease

depression (UK Biobank, Correlation = 0.210, $p = 0.051$; FinnGen, Correlation = 0.123, $p = 0.023$) (See Supplementary Table 19).

Bidirectional univariable MR analysis
Figure 4 shows the results of preliminary MR analysis. In the bidirectional MR, 3 out of 40 associations were replicated (Supplementary Table 8), with all Steiger directionality tests being correct. BPH (UK Biobank) was associated with an increased risk of prostate cancer (odds ratio (OR), 1.009; 95% confidence interval (95%CI), 1.004 to 1.014; $p < 0.001$, IVW) and a higher risk of prostatitis (OR, 1.255; 95% CI, 1.116 to 1.411; $p < 0.001$, IVW). (Fig. 4A) Similar results were observed for BPH (FinnGen database) with prostate cancer (OR, 1.032; 95% CI, 1.019 to 1.045; $p < 0.001$, IVW) and prostatitis (OR, 1.702; 95% CI, 1.495 to 1.938; $p < 0.001$, IVW).(Fig. 4B)

The fixed-effect meta-analysed MR estimates for BPH on prostate cancer and prostatitis outcomes across both cohorts verified the above results.In subsequent sensitivity analyses, the results of BPH (UK Biobank) with the risk of prostatitis showed no heterogeneity or potential horizontal pleiotropy. Other results showed heterogeneity but no horizontal pleiotropy (Supplementary Table 10). All Steiger direction tests are correct. (Supplementary Table 9) Leave-one-out plots and scatterplots support these analyses (Supplementary Fig. 7, Supplementary Fig. 8).

The association of prostate cancer with increased risk of BPH (UK Biobank, OR, 10.842; 95% CI, 4.724 to 24.885; $p < 0.001$, IVW) (FinnGen, OR, 17.884; 95% CI, 9.653 to 33.133; $p < 0.001$, IVW) was noted. Although the result of prostate cancer being associated with an increased risk of BPH was significant in other MR
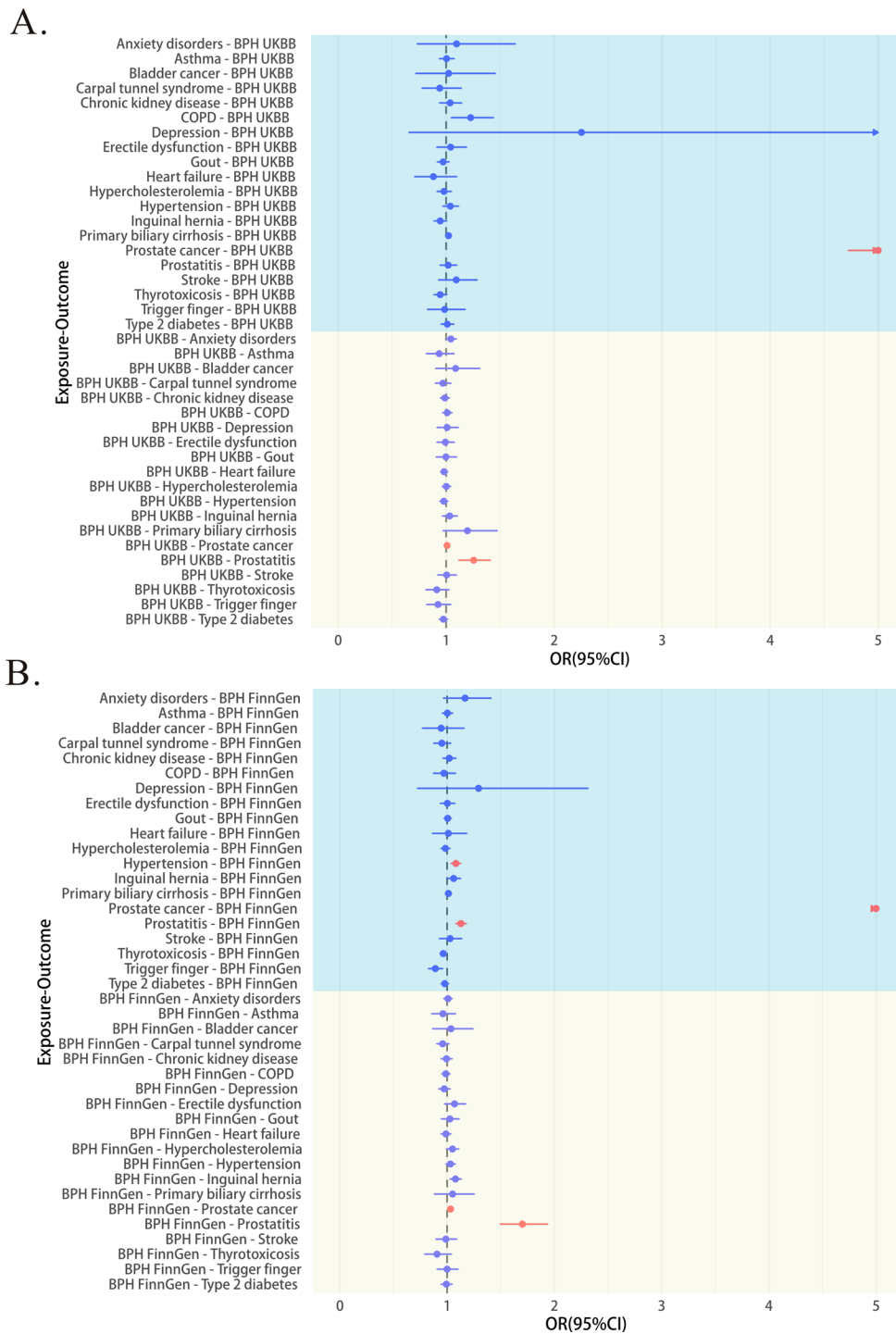
Fig. 4 Gene-predicted associations between benign prostatic hyperplasia (BPH) and comorbidities in two-sample Mendelian randomization (MR) analysis (inverse variance weighting (IVW) method). Red indicates significance (*p* < 0.05) and blue indicates not significance (*p* > 0.05). The circle represents the odds ratio (OR), the horizontal line indicates the range between the 95% upper and lower confidence limits, and the arrow shows that the 95% UCL exceeds the boundary. If the arrow is to the left of the OR, it means the 95% lower confidence limit also exceeds the boundary. BPH = Benign prostatic hyperplasia; UKBB = UK Biobank; COPD = Chronic obstructive pulmonary disease; OR = Odds ratio

models, the OR values varied widely, and pleiotropy tests suggested the possibility of horizontal pleiotropy. Therefore, we do not consider there to be a causal relationship between prostate cancer and the risk of BPH.

Bidirectional multivariable MR analysis

We ultimately included five traits as mediators, dividing them into three groups (bioavailable testosterone, education level, family income, smoking, drinking). The specific reasons for inclusion and exclusion are in Supplementary Note 8. When using bioavailable testosterone as a mediator, the results of the MVMR for prostate cancer and prostatitis remained statistically significant, across UK Biobank data, FinnGen data, and meta-analysed MR. When using education level and family income as mediators, the results of the MVMR for prostate cancer and prostatitis also remained statistically significant. When using cigarettes per day and drinks per week as mediators, the results of the MVMR for BPH and prostate cancer (UK Biobank, OR, 1.062; 95% CI, 0.950 to 1.187; $p=0.289$, IVW) and prostatitis (UK Biobank, OR, 1.002; 95% CI, 0.998 to 1.007; $p=0.363$, IVW) were no longer significant. However, in FinnGen's BPH data, meta-analysed MR, and for prostate cancer (FinnGen OR, 1.024; 95% CI, 1.014 to 1.034; $p<0.001$, IVW) (Meta OR, 1.006; 95% CI, 1.002 to 1.011; $p=0.003$, IVW) and prostatitis (FinnGen OR, 1.715; 95% CI, 1.530 to 1.921; $p<0.001$, IVW) (Meta OR, 1.343; 95% CI, 1.240 to 1.454; $p<0.001$, IVW) the results still showed statistical significance. Detailed information can be found in Supplementary Tables 15–18.

Combined analysis

The GWAS datasets are predominantly from European populations, while the GBD data encompasses analysis from 201 countries worldwide. Considering the ethnic differences, we chose to analyze the GBD data from European regions, with detailed regional divisions outlined in Supplementary Table 20. Nevertheless, this does not imply that the GBD European data is entirely consistent with the LDSC data sources, as the GBD data is derived from administratively defined countries and regions, not ethnic groups. Since the initial GBD data focused on 9 comorbidities, our combined analysis also concentrated on these 9 diseases.

After integrating the GBD global results, GBD European results, LDSC (BPH from UK Biobank), LDSC (BPH from FinnGen), and MR results, we found a consistent association between prostate cancer and BPH across various scenarios (GBD Global, Correlation=0.222; GBD Europe, Correlation=-0.265; LDSC, UK Biobank, Correlation=0.271; LDSC, FinnGen, Correlation=0.289). This suggests that BPH is also associated with a higher risk of prostate cancer. Detailed data is available in Supplementary Table 21.

PheWAS analysis

We utilized the MR-PRESSO outlier test and found that the outliers in each two-sample MR were different (Supplementary Table 13). Therefore, we selected the outliers from the two associations that were replicated for PheWAS analysis, including any phenotypes containing terms "prostate", "age", "prostate specific antigen (PSA)", "urine", "obesity," "Body Mass Index (BMI)," and "waist-to-hip ratio". The specific process is detailed in Supplementary Note 17. The PheWAS results showed that most traits were related to non-cancerous prostate diseases, with no new traits discovered (Supplementary Table 14). Nevertheless, we chose to remove them and assess their impact on the marginal OR estimates in MR before and after. In the univariable IVW method, removing outlier SNPs for prostate cancer as an outcome (Meta, OR, 1.012; OR, 1.011) did not significantly change the marginal OR value. For prostatitis as an outcome (Meta, OR, 1.440; OR, 1.500), the marginal OR value slightly increased. Specific details can be found in Supplementary Table 8.

MTAG, fine-mapping and colocalization analysis

In the MTAG analysis, we identified 439 genetic loci associated with BPH (UKBB) and prostatitis, 127 genetic loci associated with BPH (UKBB) and prostate cancer, 120 genetic loci associated with BPH (FinnGen) and prostatitis, and 113 genetic loci associated with BPH (FinnGen) and prostate cancer (Supplementary Table 22). For each shared locus identified through cross-trait meta-analysis, we extracted a list of genetic variants within a 500 kb radius around the index SNP to provide candidate genes for downstream analysis (Supplementary Table 23). Based on these genetic variants, we selected independent SNPs for colocalization analysis between BPH and prostatitis, and prostate cancer. Specifically, of the 7 independent loci for BPH (UKBB) and prostatitis, one shared SNP was found; of the 5 independent loci for BPH (FinnGen) and prostatitis, one shared SNP was found; of the 5 independent loci for BPH (FinnGen) and prostate cancer, one shared SNP was found; no independent shared loci were found between BPH (UKBB) and prostate cancer (Supplementary Table 24).

Mediation analysis

No genetic predictors of BPH were found to be associated with individual mediators (>Supplementary Table 26). After adjusting for BPH, fruit consumption was associated with a lower risk of prostatitis (UK Biobank, OR, 0.560; 95% CI, 0.380 to 0.970; $p=0.010$, IVW) (FinnGen, OR, 0.528; 95% CI, 0.312 to 0.894; $p=0.017$, IVW);

chronotype (FinnGen, OR, 0.975; 95% CI, 0.954 to 0.996; $p=0.020$, IVW) and morning person (FinnGen, OR, 0.985; 95% CI, 0.973 to 0.998; $p=0.028$, IVW) were associated with a lower risk of prostate cancer (Supplementary Table 27). These analyses indicate that these mediating factors did not participate in the processes linking BPH with prostate cancer or prostatitis, thus no indirect effects or their proportions were calculated.

Discussion

In our analysis of GBD data, we observed a notable positive correlation between the prevalence of BPH and both chronic kidney disease and prostate cancer, alongside a negative correlation with depression. The incidence of BPH predominantly affects individuals aged between 70 and 75 years. Influential factors such as environmental pollution (PM2.5), alcohol, cigarette, educational attainment, indices of human and social development, life expectancy, and access to clean water have all been identified as significant determinants related to the occurrence of BPH. Our LDSC analysis pinpointed prostatitis as having the most substantial linkage to BPH, followed by bladder cancer. While the connection with chronic kidney disease appeared tenuous, a definitive link with depression was established. Bidirectional two-sample MR analysis further corroborated BPH's association with an elevated risk of prostate cancer and prostatitis, findings that were consistent across diverse datasets. The inclusion of bioavailable testosterone, cigarettes per day, drinks per week, educational level, and family income as mediators in multivariable MR analysis sustained the results aligned with those from univariable MR. PheWAS analysis indicated that outliers in MR do not significantly impact MR results. Through MTAG, fine-mapping, and colocalization analysis, three shared loci between BPH and both prostatitis and prostate cancer were identified. Mediation analysis found that, after adjusting for BPH, fruit consumption was associated with a lower risk of prostatitis, and morning person and chronotype were associated with a lower risk of prostate cancer.

The global incidence of BPH cases increased from 51.10 million in 2000 to 94 million in 2019, indicating a growing disease burden year by year [10]. The impact of BPH on patients is not only reflected in its prevalence but also in its association with various comorbidities. Previous studies have found that BPH is related to falls and depression, and there is a decline in sleep and psychological conditions [40]. Some comorbidities of BPH, such as chronic kidney disease, depression, and anxiety, can also affect the quality of life of patients' families [40, 41]. Hence, a systematic exploration into the connections between BPH and its comorbidities is crucial for optimally allocating medical resources towards diseases closely linked with BPH.

Some of the associations we found in our GBD, LDSC, and MR analyses are consistent with previous studies. A cohort study in Sweden, which followed 86,626 participants over 26 years, found that patients with BPH had an increased risk of prostate cancer (a 10% increase in incidence after two years of follow-up) [42]. In a randomized, double-blind, placebo-controlled study, it was reported that 77.6% of BPH patients have chronic inflammation [43]. A retrospective study also indicated that BPH with varying degrees of lower urinary tract symptoms (LUTS) is significantly associated with chronic kidney disease [44]. An observational study conducted in Italy suggests that a low intake of fruits is associated with an increased incidence of chronic prostatitis [45]. Previous MR analysis also indicated that genetically predicted morning chronotype is associated with a reduced risk of prostate cancer [46]. Therefore, our study further validates the existence of these associations.

However, our study did not replicate the significant link between BPH and depression in middle-aged and older men as reported in some cross-sectional studies, suggesting regional variations in the strength of these associations [47]. Similarly, we found no evidence of a causal relationship between BPH and depression. One possible factor leading to this discrepancy could be the treatment conditions of BPH patients. Some patients treated with 5-alpha-reductase inhibitors have reported long-term adverse effects on sexual function, such as erectile dysfunction and libido reduction, which may be linked to the emergence of depression [48]. Compared to patients who underwent drug treatments, those who underwent transurethral resection of the prostate (TURP) had fewer post-treatment anxiety, depression, and psychiatric complications [49]. On the other hand, our results suggest that this association may vary in strength across different regions, as we found differences in association strength between European and global populations in our GBD data analysis. Unfortunately, due to the lack of comprehensive GWAS datasets for other populations (besides Europeans), we were unable to examine differences in the association between BPH and comorbidities across different ethnicities.

Potential mechanisms linking BPH with prostate cancer include hormonal dependency, the effect of androgen antagonists, chronic inflammation, metabolic disorders, and genetic variations [50, 51]. Androgens are crucial for both the normal and abnormal growth and development of the prostate, as well as the onset, progression, and metastasis of prostate cancer [52]. However, we adjusted for bioavailable testosterone in the multivariable MR, and the results indicated that bioavailable testosterone does not affect the association between BPH and prostate cancer. This could also explain why prostate cancer is occasionally discovered incidentally among male subgroups

undergoing TURP for symptomatic BPH [53]. The nearest gene to the shared loci we identified between BPH and prostate cancer is SLC25A37, a mitochondrial-associated gene that is significantly associated with fatigue during external beam radiation therapy in prostate cancer patients [54].

While the role of inflammatory infiltration in the prostate is well-documented, the precise mechanisms connecting BPH with prostatitis require further elucidation [55]. One possible mechanism is that an increase in prostate volume can cause urinary obstruction, which in turn promotes epithelial injury and infection. Inflammation also increases the oxygen demand of proliferating cells, leading to a relative hypoxic state in the prostate, exacerbating tissue damage [56]. Ultimately, the prostate enters a vicious cycle, with prostatic diseases progressing more rapidly. Our MR results support the notion that the development of BPH and prostatitis begins with an increase in prostate volume. Although we identified the shared genes BBS7 and NR2F1 between BPH and prostatitis, these genes are currently believed to be primarily associated with two genetic diseases [57, 58].

Compared to similar previous studies, this study has several significant advantages. The GBD and MR design reduced confounding factors, enhancing the persuasiveness of our results. The consistency of MR results from two independent populations strengthens the reliability and robustness of our study findings. Additionally, the results of multiple MR sensitivity analyses were largely consistent. On the other hand, all participants in the GWAS were of European ancestry, reducing the likelihood of population stratification bias affecting our MR study results.

However, the study is not without limitations. Firstly, the difference in data sources between GBD and GWAS necessitates cautious interpretation of the associations between BPH and comorbidities, especially where there is a significant discrepancy in association strength between GBD data analysis and LDSC analysis. Secondly, horizontal pleiotropy is a key issue in the reliability of any MR results. To mitigate this bias, we employed multiple MR methods under various assumptions throughout the process and used meta-analysis to combine analyses from two different databases. MR-Egger regression tests indicated no clear directional pleiotropy in most tested associations. Additionally, while we had large-scale summary statistics, only a very limited number of SNPs were available as genetic instruments for some diseases [18]. This led to lower statistical power, particularly given our more lenient threshold ($P < 5 \times 10^{-6}$). Further MR studies are needed to validate these associations once more effective genetic tools are available. Then, BPH data from FinnGen and UK Biobank, and some comorbidity data, also included content from these datasets, which might introduce bias due to sample overlap [59]. However, we expect this will not significantly impact our results' interpretation, as our overlapping samples are from large biobanks and all instrument F statistics were over 10, minimizing bias due to sample overlap. Additionally, previous studies have reported associations between BPH and certain infectious diseases; the clinical symptoms of BPH are associated with worsened conditions in COVID-19, and variations in the presence of Gardnerella vaginalis (GV), Human tumor virus (HPV) and Herpes Simplex Virus type 2 (HSV-2) have been observed in the tissues of patients with BPH and prostate cancer [60–63]. However, due to the lack of related GBD and GWAS data, we were unable to explore these associations.

In summary, this study observed associations between BPH and various comorbidities, which helps to focus more on diseases with stronger associations when assessing the health status of patients with BPH.

Abbreviations

BPH	Benign prostatic hyperplasia
GBD	Global burden of disease
MR	Mendelian randomization
LDSC	Linkage disequilibrium score regression
HDI	Human development index
SDI	Social development index
LUTS	Lower urinary tract symptoms
PheWAS	Phenome-wide association studies
IHME	Institute for health metrics and evaluation
SNPS	Single nucleotide polymorphism
LD	Linkage disequilibrium
IVW	Inverse variance weighted
MVMR	Multivariable Mendelian randomization
IEU OpenGWAS	Integrated epidemiology units OpenGWAS
TURP	Transurethral resection of the prostate
MTAG	Multi-trait analysis of GWAS
PICS	Probabilistic identification of causal SNPs

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Author contributions
Study conception and design: Z.F.S. and B.Q.S.; data acquisition and analysis: Z.F.S., Z.K.C., H.Y. and Z.L.C.; drafted the manuscript: Z.F.S., H.Y., Z.L.C. and Z.K.C.; interpreted data and made critical revisions of the manuscript: W.H.C., Y.P.C., H.J.W., Y.F.L., H.Y.L., Z.M.L., X.B.H., D.F.Q and B.Q.S. All authors read and approved the final manuscript.

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Declarations

Conflict of interest
All authors declare no competing interest.

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