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Research Article

Bidirectional Causal Relationship between Inflammatory Cytokines and Benign Prostatic Hyperplasia

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Abstract

Objective: This study aimed to establish a genetic correlation between inflammatory cytokines (IC) and benign prostatic hyperplasia (BPH) to present an empirical reference for BPH treatment.

Methods: Single nucleotide polymorphism (SNP) data were derived from two genome-wide association studies of IC and BPH. Forward Mendelian randomization (MR) analysis was carried out by the inverse variance weighting method with IC-related SNPs as the instrumental variable and BPH as the outcome, while the reverse MR analysis used BPH-related SNPs as the instrumental variable and IC as the outcome.

Results: The results from forward MR analysis showed that there was no statistical differences between 51 ICs and BPH at the genetic level (P>0.05). Reverse MR analysis showed that BPH was significantly correlated with one type of IC at the genetic level (P<0.05), while the rest were no statistical differences (P>0.05).

Conclusion: There was no bidirectional relationship between IC and BPH at the genetic level, suggesting that genetic exposure of IC may have no effect on BPH.

Keywords: bidirectional Mendelian randomization, benign prostatic hyperplasia, inflammatory cytokines

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1 INTRODUCTION

Benign prostatic hyperplasia (BPH) is a prevalent benign disease leading to urination disorder in middle-aged and elderly men, with an incidence rate of 50% in men over the age of 60[1]. Despite extensive research, the precise etiology of BPH remains elusive, with current theories suggesting the involvement of genetics, androgens, hormones, cytokines, chemokines, and stem cells. The number of patients receiving treatment for BPH-related lower urinary tract symptoms is steadily increasing, and the associated healthcare costs are escalating exponentially. However, effective treatments for BPH are still lacking[2,3]. Therefore, exploring the etiology and influencing factors of BPH is crucial for its treatment.

Chronic inflammation leading to tissue damage and the release of pro-inflammatory cytokines has been shown to play a significant role in the pathogenesis of BPH[4]. However, the role of inflammatory cytokines (IC) in BPH remains unclear. Several studies have explored the role of IC in BPH[5,6], but the effect of IC on BPH through genetic pathways remains unknown. This is where Mendelian randomization (MR) offers a new analytical method[7,8] to elucidate the relationship between BPH and IC. The MR method is employed in this study to investigate the relationship between BPH and IC, providing a new research direction for BPH treatment. The design of this study includes bidirectional MR to identify the potential association between IC and BPH.

2 METHODS

2.1 Study Design Description

Figure 1 presented brief steps of this bi-directional MR study between IC and BPH. The aggregated statistical data of genome-wide association studies (GWAS) were used for two MR analyses to identify the association between IC and BPH. In the forward MR analysis, IC was set as the exposure factor and BPH as the outcome. In the reverse MR, BPH was set as the exposure factor and IC as the outcome. The core MR assumptions are displayed in Figure 1. This study was based on a public database, so ethical approval is not required.

2.2 MR Tool Variable Selection

The MR analysis tool variable was derived from two different GWAS summary results. Firstly, at the genome-wide significance threshold ($P<5\times10^{-8}$)[9]. Secondly, the independence between the selected single nucleotide polymorphism (SNP) was evaluated according to the paired linkage disequilibrium. When r2>0.001 (the aggregation window is 10,000kb), SNPs associated with multiple SNP and those associated with higher *P* will be deleted[10]. Linkage disequilibrium referred to the association of nonrandom between alleles of different locus. In short, as long as the two genes were not inherited completely independently, they would show some degree of linkage. r2: it was the data between 0 and 1. r2=1 meant that there was a complete linkage disequilibrium relationship between the two SNPs. r2=0 meant that there was a complete linkage equilibrium between the two SNPs, that is, the allocation of the two SNPs was completely random. Kb: the length of the linkage disequilibrium area. r2=0.00110000kb, which meant removing SNPs with r2 greater than 0.001 within 10,000kb. Thirdly, *F*-statistics were calculated to verify the strength of a SNP. When *F*-statistic was greater than 10, SNP was considered to be strong enough to mitigate the impact of potential bias.

2.3 Data Source and Tool Variable Selection of BPH

BPH data was sourced from MRC IEU UK Biobank GWAS pipeline version 2 (https://data.bris.ac.uk/data/dataset/pnoat8cxo0u52p6ynfaekeigi), including 463,010 participants. BPH was the primary diagnosis in these population data. This GWAS was used to identify SNPs related to BPH, which would be selected as IV (see supporting information Table 1).

2.4 Data Source and Tool Variable Selection of IC

IC data was sourced from the UK biobank (https://www.ebi.ac.uk/gwas/downloads/summary-statistics), including 57,013 participants (support information Table 2). The GWAS contained 51 IC types. These 51 different ICs were used for subsequent matching and analysis.

2.5 MR Statistical Analysis

SNPs of IC and BPH were used for the subsequent forward MR analysis and (see support information Table 1) reverse MR analysis (see support information Table 3). The inverse variance weighted (IVW) method, based on all core assumptions of MR, was the major statistical method for estimating the potential bidirectional causal relationship between BPH and IC[7]. When multiple IVS were available, IVW was the most effective analysis method, because it not only considered the specificity of variation and heterogeneity of causal estimation but also conducted a sensitivity analysis, including simple mode, weighted mode, weighted median and MR egger regression method, to evaluate the robustness of research results[11]. However, IV affected the results in other ways, indicating potential pleiotropic effect, and the causal estimation by IVW might be biased. Therefore, MR egger was used for level pleiotropy test. If $P>0.05$, it indicated the absence of pleiotropy. MR heterogeneity testing was used to identify the heterogeneity among SNPs. If there was heterogeneity, the random effect model was used. Otherwise, the fixed effect model was used by default. SNPs were sequentially removed from MR and then analyzed as a whole to observe the impact of a SNP on the whole MR analysis results[12]. Two sample mr (v.0.5.6) in R package (v.4.3.0) was used for

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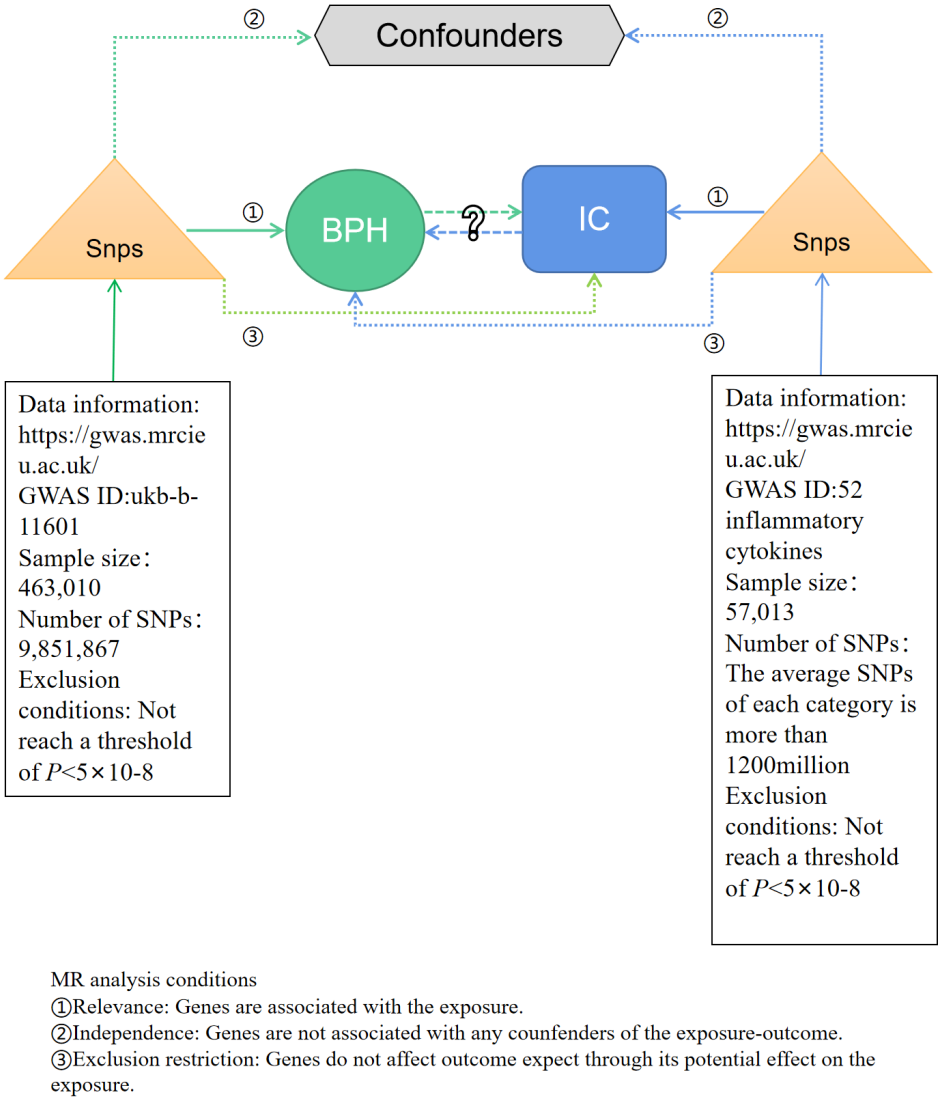

Figure 1. Flow chart of bidirectional MR study. MR analysis depends on three core assumptions ① ② ③. Blue represents positive MR analysis, IC is exposure, and BPH is the result. Green represents reverse MR analysis, BPH is exposure, and IC is the result. IC, inflammatory cytokines; BPH, benign prostatic hyperplasia; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

major statistical analysis and chart making[13]. Odds ratio and 95% confidence interval (CI) indicated the degree of change in the result risk for each additional standard deviation of exposure factors. Statistical significance was set to $P<0.05$[14].

3 RESULTS

3.1 Influence of IC on BPH

IVW results demonstrated that 51 ICs were not significantly correlated with BPH at the genetic level ($P>0.05$) (Table 1). There was no significant level pleiotropy among SNPs (Table 2, global>0.05). According to the results of IVW and MR egger methods, we did not find the association accompanied by significant heterogeneity (Table 3, all P of Cochran's Q>0.05).

3.2 Effect of BPH on IC

IVW results showed that there was no significant correlation between BPH and 50 ICs at the genetic level ($P>0.05$). BPH was significantly correlated with one IC, prot-a-1525 (interleukin-3) at the genetic level ($P<0.05$) (see Table 4 and Figure 2 for the results). From the comprehensive results of the shape trend of the scatter diagram and the forest diagram, we can know that with the increase of BPH exposure, the risk of outcome (interleukin-3) decreases. At the same time, the results of eliminating the forest map one by one did not indicate the existence of a SNP affecting the whole result, indicating that the results of MR analysis were supported by all the included SNPs. There was no significant level pleiotropy between SNPs (Table 5, $P>0.05$). In addition, by combining the Q/P of Cochran in IVW and MR egger methods (Table 6, all P of Cochran's Q>0.05) with the funnel diagram (Figure 2), no significant heterogeneity was found in the correlation.

Table 1. Forward MR IVW

IC	Method	Nsnp	SE	*P*
Interleukin-17	Inverse variance weighted	8	0.002935452	0.214101575
Interleukin-8	Inverse variance weighted	8	0.003114947	0.397882909
Interleukin-7	Inverse variance weighted	8	0.003023686	0.695624136
Interleukin-4	Inverse variance weighted	8	0.003578857	0.617855915
Eotaxin	Inverse variance weighted	8	0.003907043	0.647388117
CCL20	Inverse variance weighted	8	0.001501672	0.8548931
CCL23	Inverse variance weighted	8	0.001579185	0.720815013
CCL25	Inverse variance weighted	8	0.000499833	0.387923314
CCL28	Inverse variance weighted	8	0.001788445	0.071146213
CCL3	Inverse variance weighted	8	0.001146789	0.440303216
CCL4	Inverse variance weighted	8	0.000870495	0.343262869
CXCL1	Inverse variance weighted	8	0.000973279	0.912729576
CXCL10	Inverse variance weighted	8	0.002390156	0.359762644
CXCL11	Inverse variance weighted	8	0.001342559	0.875606701
CXCL5	Inverse variance weighted	8	0.001139594	0.355520072
CXCL6	Inverse variance weighted	8	0.000484907	0.350758675
CXCL9	Inverse variance weighted	8	0.001627542	0.910523837
Interleukin-6	Inverse variance weighted	10	0.001206833	0.721575772
Interleukin-18	Inverse variance weighted	10	0.000943676	0.404782398
Immunoglobulin E	Inverse variance weighted	10	0.002510549	0.699516919
Interleukin-11	Inverse variance weighted	10	0.001445522	0.782413201
Interleukin-12	Inverse variance weighted	10	0.001287695	0.974310917
Interleukin-23	Inverse variance weighted	10	0.001322687	0.805832139
Interleukin-13	Inverse variance weighted	10	0.001215818	0.491209077
Interleukin-16	Inverse variance weighted	10	0.000500872	0.341884533
Interleukin-17A	Inverse variance weighted	10	0.001265806	0.751828598
Interleukin-17C	Inverse variance weighted	10	0.001609783	0.53928419
Interleukin-17F	Inverse variance weighted	10	0.001140915	0.849229352
Interleukin-1 receptor antagonist protein	Inverse variance weighted	10	0.000916442	0.113944661
Interleukin-21	Inverse variance weighted	10	0.002156731	0.905301195
Interleukin-25	Inverse variance weighted	10	0.001443544	0.640599435
Interleukin-27	Inverse variance weighted	10	0.001487102	0.884603613
Interleukin-2 receptor subunit alpha	Inverse variance weighted	10	0.002692621	0.321763241
Interleukin-31	Inverse variance weighted	10	0.002344312	0.513931555
Interleukin-32	Inverse variance weighted	10	0.001763086	0.553350945
Interleukin-34	Inverse variance weighted	10	0.001093875	0.903655417
Interleukin-3	Inverse variance weighted	10	0.002919849	0.381901902
Interleukin-36 alpha	Inverse variance weighted	10	0.001136349	0.930099443
Interleukin-36 beta	Inverse variance weighted	10	0.001343932	0.933077043
Interleukin-36 gamma	Inverse variance weighted	10	0.002185628	0.713737762
Interleukin-5	Inverse variance weighted	10	0.0017555	0.450343516
Interleukin-6 receptor subunit alpha	Inverse variance weighted	10	0.000188177	0.625325369

Interleukin-9	Inverse variance weighted	10	0.002510621	0.553216553
Toll-like receptor 4	Inverse variance weighted	10	0.001635542	0.762943071
MCP-1	Inverse variance weighted	8	0.001897654	0.326612582
TNF-a	Inverse variance weighted	8	0.001605156	0.755275219
CRP	Inverse variance weighted	8	0.0013565	0.684181349
b-NGF	Inverse variance weighted	8	0.00184724	0.707730649
TNF-b	Inverse variance weighted	8	0.001144238	0.546801719
G-CSF	Inverse variance weighted	8	0.001760395	0.831033896
MIF	Inverse variance weighted	8	0.00059689	0.264791729

Table 2. Forward MR Horizontal Pleiotropy

ID Exposure	ID Outcome	SE	*P*
ebi-a-GCST004442	ukb-b-11601	1.27E-04	0.3075908
ebi-a-GCST004445	ukb-b-11601	1.33E-04	0.2322862
ebi-a-GCST004451	ukb-b-11601	1.26E-04	0.399273
ebi-a-GCST004453	ukb-b-11601	1.11E-04	0.7411803
ebi-a-GCST004460	ukb-b-11601	1.17E-04	0.8714405
ebi-a-GCST90000444	ukb-b-11601	1.16E-04	0.8564033
ebi-a-GCST90000445	ukb-b-11601	1.58E-04	0.1935303
ebi-a-GCST90000446	ukb-b-11601	9.37E-05	0.5323358
ebi-a-GCST90000447	ukb-b-11601	1.49E-04	0.3435592
ebi-a-GCST90000448	ukb-b-11601	1.19E-04	0.5946732
ebi-a-GCST90000449	ukb-b-11601	9.70E-05	0.6079453
ebi-a-GCST90000458	ukb-b-11601	1.66E-04	0.5350311
ebi-a-GCST90000459	ukb-b-11601	1.30E-04	0.5232793
ebi-a-GCST90000460	ukb-b-11601	1.11E-04	0.3244389
ebi-a-GCST90000461	ukb-b-11601	1.24E-04	0.9944352
ebi-a-GCST90000462	ukb-b-11601	1.05E-04	0.3578067
ebi-a-GCST90000463	ukb-b-11601	1.49E-04	0.28824
ebi-a-GCST90012005	ukb-b-11601	8.34E-05	0.5435456
ebi-a-GCST90012024	ukb-b-11601	8.49E-05	0.373806
prot-a-1456	ukb-b-11601	1.37E-04	0.7654356
prot-a-1466	ukb-b-11601	9.30E-05	0.1606427
prot-a-1470	ukb-b-11601	9.85E-05	0.613107
prot-a-1472	ukb-b-11601	1.01E-04	0.3474789
prot-a-1475	ukb-b-11601	9.27E-05	0.8263527
prot-a-1479	ukb-b-11601	7.69E-05	0.4965681
prot-a-1480	ukb-b-11601	9.15E-05	0.6243055
prot-a-1483	ukb-b-11601	8.56E-05	0.2301492
prot-a-1485	ukb-b-11601	8.78E-05	0.249381
prot-a-1504	ukb-b-11601	8.71E-05	0.7172722
prot-a-1506	ukb-b-11601	1.50E-04	0.1767558
prot-a-1515	ukb-b-11601	1.08E-04	0.3230504
prot-a-1516	ukb-b-11601	1.13E-04	0.4983363
prot-a-1518	ukb-b-11601	1.16E-04	0.7502979
prot-a-1521	ukb-b-11601	9.77E-05	0.5730969
prot-a-1523	ukb-b-11601	1.35E-04	0.3785118
prot-a-1524	ukb-b-11601	8.77E-05	0.7658137

prot-a-1525	ukb-b-11601	9.24E-05	0.7602778
prot-a-1526	ukb-b-11601	9.82E-05	0.8732425
prot-a-1527	ukb-b-11601	9.76E-05	0.2242442
prot-a-1528	ukb-b-11601	1.32E-04	0.5466671
prot-a-1535	ukb-b-11601	1.24E-04	0.4913327
prot-a-1540	ukb-b-11601	7.71E-05	0.8674261
prot-a-1546	ukb-b-11601	1.12E-04	0.3958118
prot-a-2990	ukb-b-11601	1.44E-04	0.8530817
prot-c-2578_67_2	ukb-b-11601	1.08E-04	0.4217126
prot-c-3722_49_2	ukb-b-11601	1.25E-04	0.8859223
prot-c-4337_49_2	ukb-b-11601	1.26E-04	0.955205
prot-c-4368_8_2	ukb-b-11601	1.17E-04	0.5367686
prot-c-4703_87_2	ukb-b-11601	1.70E-04	0.7176119
prot-c-4840_73_1	ukb-b-11601	1.47E-04	0.6138571
prot-c-5356_2_3	ukb-b-11601	1.01E-04	0.7106364

Table 3. Forward MR Heterogeneity

ID Exposure	ID Outcome	Method	*P*
ebi-a-GCST004442	ukb-b-11601	Inverse variance weighted	0.7611525
ebi-a-GCST004445	ukb-b-11601	Inverse variance weighted	0.6613116
ebi-a-GCST004451	ukb-b-11601	Inverse variance weighted	0.5930875
ebi-a-GCST004453	ukb-b-11601	Inverse variance weighted	0.6046444
ebi-a-GCST004460	ukb-b-11601	Inverse variance weighted	0.5998525
ebi-a-GCST90000444	ukb-b-11601	Inverse variance weighted	0.5787391
ebi-a-GCST90000445	ukb-b-11601	Inverse variance weighted	0.590039
ebi-a-GCST90000446	ukb-b-11601	Inverse variance weighted	0.6650614
ebi-a-GCST90000447	ukb-b-11601	Inverse variance weighted	0.9310135
ebi-a-GCST90000448	ukb-b-11601	Inverse variance weighted	0.646764
ebi-a-GCST90000449	ukb-b-11601	Inverse variance weighted	0.68369
ebi-a-GCST90000458	ukb-b-11601	Inverse variance weighted	0.5761784
ebi-a-GCST90000459	ukb-b-11601	Inverse variance weighted	0.6764405
ebi-a-GCST90000460	ukb-b-11601	Inverse variance weighted	0.5776707
ebi-a-GCST90000461	ukb-b-11601	Inverse variance weighted	0.6782612
ebi-a-GCST90000462	ukb-b-11601	Inverse variance weighted	0.6803399
ebi-a-GCST90000463	ukb-b-11601	Inverse variance weighted	0.5762521
ebi-a-GCST90012005	ukb-b-11601	Inverse variance weighted	0.7759042
ebi-a-GCST90012024	ukb-b-11601	Inverse variance weighted	0.8284255
prot-a-1456	ukb-b-11601	Inverse variance weighted	0.7780214
prot-a-1466	ukb-b-11601	Inverse variance weighted	0.7709993
prot-a-1470	ukb-b-11601	Inverse variance weighted	0.76367
prot-a-1472	ukb-b-11601	Inverse variance weighted	0.7694602
prot-a-1475	ukb-b-11601	Inverse variance weighted	0.8085848
prot-a-1479	ukb-b-11601	Inverse variance weighted	0.8465271
prot-a-1480	ukb-b-11601	Inverse variance weighted	0.7732978
prot-a-1483	ukb-b-11601	Inverse variance weighted	0.7996094
prot-a-1485	ukb-b-11601	Inverse variance weighted	0.7670972
prot-a-1504	ukb-b-11601	Inverse variance weighted	0.9529735
prot-a-1506	ukb-b-11601	Inverse variance weighted	0.7649522

prot-a-1515	ukb-b-11601	Inverse variance weighted	0.7846263
prot-a-1516	ukb-b-11601	Inverse variance weighted	0.765627
prot-a-1518	ukb-b-11601	Inverse variance weighted	0.8531033
prot-a-1521	ukb-b-11601	Inverse variance weighted	0.8041772
prot-a-1523	ukb-b-11601	Inverse variance weighted	0.7972261
prot-a-1524	ukb-b-11601	Inverse variance weighted	0.7650009
prot-a-1525	ukb-b-11601	Inverse variance weighted	0.8346096
prot-a-1526	ukb-b-11601	Inverse variance weighted	0.7643211
prot-a-1527	ukb-b-11601	Inverse variance weighted	0.7642582
prot-a-1528	ukb-b-11601	Inverse variance weighted	0.7766351
prot-a-1535	ukb-b-11601	Inverse variance weighted	0.8173211
prot-a-1540	ukb-b-11601	Inverse variance weighted	0.7865772
prot-a-1546	ukb-b-11601	Inverse variance weighted	0.7972484
prot-a-2990	ukb-b-11601	Inverse variance weighted	0.7724241
prot-c-2578_67_2	ukb-b-11601	Inverse variance weighted	0.691489
prot-c-3722_49_2	ukb-b-11601	Inverse variance weighted	0.5863691
prot-c-4337_49_2	ukb-b-11601	Inverse variance weighted	0.5945791
prot-c-4368_8_2	ukb-b-11601	Inverse variance weighted	0.5915826
prot-c-4703_87_2	ukb-b-11601	Inverse variance weighted	0.6184749
prot-c-4840_73_1	ukb-b-11601	Inverse variance weighted	0.5801843
prot-c-5356_2_3	ukb-b-11601	Inverse variance weighted	0.7255121

Table 4. Reverse MR IVW

ID Exposure	ID Outcome	Method	Nsnp	SE	*P*
ukb-b-11601	ebi-a-GCST004442	Inverse variance weighted	8	3.989997923	0.618714867
ukb-b-11601	ebi-a-GCST004445	Inverse variance weighted	8	5.839792261	0.632711568
ukb-b-11601	ebi-a-GCST004451	Inverse variance weighted	8	5.966260692	0.230726929
ukb-b-11601	ebi-a-GCST004453	Inverse variance weighted	8	3.901383959	0.985311767
ukb-b-11601	ebi-a-GCST004460	Inverse variance weighted	8	3.886916143	0.41244133
ukb-b-11601	ebi-a-GCST90000444	Inverse variance weighted	8	11.22154184	0.874104374
ukb-b-11601	ebi-a-GCST90000445	Inverse variance weighted	8	11.22154184	0.052093007
ukb-b-11601	ebi-a-GCST90000446	Inverse variance weighted	8	11.90989162	0.889576139
ukb-b-11601	ebi-a-GCST90000447	Inverse variance weighted	8	12.05228732	0.561739717
ukb-b-11601	ebi-a-GCST90000448	Inverse variance weighted	8	11.34099825	0.608819274
ukb-b-11601	ebi-a-GCST90000449	Inverse variance weighted	8	11.22154184	0.366957688
ukb-b-11601	ebi-a-GCST90000458	Inverse variance weighted	8	15.27549838	0.765498806
ukb-b-11601	ebi-a-GCST90000459	Inverse variance weighted	8	11.22154184	0.743832644
ukb-b-11601	ebi-a-GCST90000460	Inverse variance weighted	8	11.22154184	0.900698273
ukb-b-11601	ebi-a-GCST90000461	Inverse variance weighted	8	17.47032801	0.456852076
ukb-b-11601	ebi-a-GCST90000462	Inverse variance weighted	8	11.22154184	0.719485811
ukb-b-11601	ebi-a-GCST90000463	Inverse variance weighted	8	11.22154184	0.19542469
ukb-b-11601	ebi-a-GCST90012005	Inverse variance weighted	11	2.839315658	0.429351259
ukb-b-11601	ebi-a-GCST90012024	Inverse variance weighted	11	2.32158884	0.357404456
ukb-b-11601	prot-a-1456	Inverse variance weighted	11	5.311140513	0.642154338
ukb-b-11601	prot-a-1466	Inverse variance weighted	11	5.310812432	0.14282234
ukb-b-11601	prot-a-1470	Inverse variance weighted	11	5.973046559	0.07189565
ukb-b-11601	prot-a-1472	Inverse variance weighted	11	5.311140513	0.972400033
ukb-b-11601	prot-a-1475	Inverse variance weighted	11	7.333932027	0.446795511

ukb-b-11601	prot-a-1479	Inverse variance weighted	11	5.311140513	0.76549001
ukb-b-11601	prot-a-1480	Inverse variance weighted	11	7.659498885	0.849393747
ukb-b-11601	prot-a-1483	Inverse variance weighted	11	5.312157506	0.215935302
ukb-b-11601	prot-a-1485	Inverse variance weighted	11	5.708772477	0.73978062
ukb-b-11601	prot-a-1504	Inverse variance weighted	11	5.780946404	0.492466078
ukb-b-11601	prot-a-1506	Inverse variance weighted	11	5.36913288	0.146802435
ukb-b-11601	prot-a-1515	Inverse variance weighted	11	5.411103207	0.377038934
ukb-b-11601	prot-a-1516	Inverse variance weighted	11	5.311140513	0.775461954
ukb-b-11601	prot-a-1518	Inverse variance weighted	11	5.311140513	0.211713825
ukb-b-11601	prot-a-1521	Inverse variance weighted	11	5.311140513	0.181496567
ukb-b-11601	prot-a-1523	Inverse variance weighted	11	6.280096594	0.794333905
ukb-b-11601	prot-a-1524	Inverse variance weighted	11	5.311140513	0.894032941
ukb-b-11601	prot-a-1525	Inverse variance weighted	11	5.311140513	0.006048732
ukb-b-11601	prot-a-1526	Inverse variance weighted	11	5.312157506	0.590475533
ukb-b-11601	prot-a-1527	Inverse variance weighted	11	5.311140513	0.536628658
ukb-b-11601	prot-a-1528	Inverse variance weighted	11	5.822865106	0.328926843
ukb-b-11601	prot-a-1535	Inverse variance weighted	11	6.388625288	0.794721137
ukb-b-11601	prot-a-1540	Inverse variance weighted	11	6.597614873	0.888034071
ukb-b-11601	prot-a-1546	Inverse variance weighted	11	5.640737349	0.133968345
ukb-b-11601	prot-a-2990	Inverse variance weighted	11	5.312157506	0.315610712
ukb-b-11601	prot-c-2578_67_2	Inverse variance weighted	5	19.25253096	0.74824847
ukb-b-11601	prot-c-3722_49_2	Inverse variance weighted	5	17.38963557	0.881189273
ukb-b-11601	prot-c-4337_49_2	Inverse variance weighted	5	12.03369169	0.798664515
ukb-b-11601	prot-c-4368_8_2	Inverse variance weighted	5	13.25921741	0.916792634
ukb-b-11601	prot-c-4703_87_2	Inverse variance weighted	5	18.19590512	0.920701561
ukb-b-11601	prot-c-4840_73_1	Inverse variance weighted	5	18.08078028	0.803742876
ukb-b-11601	prot-c-5356_2_3	Inverse variance weighted	5	18.67203327	0.793757526

Table 5. Reverse MR Horizontal Pleiotropy

ID Exposure	ID Outcome	SE	*P*
ukb-b-11601	ebi-a-GCST004442	0.0518095	0.42193223
ukb-b-11601	ebi-a-GCST004445	0.07602007	0.329835
ukb-b-11601	ebi-a-GCST004451	0.0799223	0.94195004
ukb-b-11601	ebi-a-GCST004453	0.05071123	0.55834458
ukb-b-11601	ebi-a-GCST004460	0.05055511	0.96798188
ukb-b-11601	ebi-a-GCST90000444	0.14461264	0.26149178
ukb-b-11601	ebi-a-GCST90000445	0.14461264	0.48962242
ukb-b-11601	ebi-a-GCST90000446	0.16200163	0.61371851
ukb-b-11601	ebi-a-GCST90000447	0.15937052	0.45134944
ukb-b-11601	ebi-a-GCST90000448	0.14540474	0.07228067
ukb-b-11601	ebi-a-GCST90000449	0.14461264	0.1941975
ukb-b-11601	ebi-a-GCST90000458	0.21174536	0.83017889
ukb-b-11601	ebi-a-GCST90000459	0.14461264	0.77332733
ukb-b-11601	ebi-a-GCST90000460	0.14461264	0.26839864
ukb-b-11601	ebi-a-GCST90000461	0.24310839	0.95445802
ukb-b-11601	ebi-a-GCST90000462	0.14461264	0.60866866
ukb-b-11601	ebi-a-GCST90000463	0.14461264	0.43863626
ukb-b-11601	ebi-a-GCST90012005	0.03487753	0.48973444
ukb-b-11601	ebi-a-GCST90012024	0.02785514	0.65395994

ukb-b-11601	prot-a-1456	0.06396801	0.23703579
ukb-b-11601	prot-a-1466	0.06398886	0.47440535
ukb-b-11601	prot-a-1470	0.07572	0.87422117
ukb-b-11601	prot-a-1472	0.06396801	0.17844129
ukb-b-11601	prot-a-1475	0.0864342	0.26021111
ukb-b-11601	prot-a-1479	0.06396801	0.25564824
ukb-b-11601	prot-a-1480	0.09522202	0.54722899
ukb-b-11601	prot-a-1483	0.06399811	0.70124936
ukb-b-11601	prot-a-1485	0.07162621	0.65394515
ukb-b-11601	prot-a-1504	0.06395879	0.02188069
ukb-b-11601	prot-a-1506	0.06394594	0.18781891
ukb-b-11601	prot-a-1515	0.06869111	0.93682176
ukb-b-11601	prot-a-1516	0.06396801	0.10243591
ukb-b-11601	prot-a-1518	0.06396801	0.07162234
ukb-b-11601	prot-a-1521	0.06396801	0.25918187
ukb-b-11601	prot-a-1523	0.07304269	0.22146516
ukb-b-11601	prot-a-1524	0.06396801	0.31158527
ukb-b-11601	prot-a-1525	0.06396801	0.25132819
ukb-b-11601	prot-a-1526	0.06399811	0.48413786
ukb-b-11601	prot-a-1527	0.06396801	0.38007206
ukb-b-11601	prot-a-1528	0.06396801	0.07029675
ukb-b-11601	prot-a-1535	0.07662751	0.32396215
ukb-b-11601	prot-a-1540	0.08324986	0.74684853
ukb-b-11601	prot-a-1546	0.07140164	0.82526962
ukb-b-11601	prot-a-2990	0.06399811	0.51998361
ukb-b-11601	prot-c-2578_67_2	0.20341704	0.09380869
ukb-b-11601	prot-c-3722_49_2	0.2921604	0.56737612
ukb-b-11601	prot-c-4337_49_2	0.18681962	0.81555819
ukb-b-11601	prot-c-4368_8_2	0.20579558	0.93534172
ukb-b-11601	prot-c-4703_87_2	0.20549511	0.11599532
ukb-b-11601	prot-c-4840_73_1	0.32319863	0.93218255
ukb-b-11601	prot-c-5356_2_3	0.23684545	0.18214001

Table 6. Reverse MR Heterogeneity

ID Exposure	ID Outcome	Method	*P*
ukb-b-11601	ebi-a-GCST004442	Inverse variance weighted	0.716066045
ukb-b-11601	ebi-a-GCST004445	Inverse variance weighted	0.751450603
ukb-b-11601	ebi-a-GCST004451	Inverse variance weighted	0.498497997
ukb-b-11601	ebi-a-GCST004453	Inverse variance weighted	0.692793128
ukb-b-11601	ebi-a-GCST004460	Inverse variance weighted	0.630138361
ukb-b-11601	ebi-a-GCST90000444	Inverse variance weighted	0.519990211
ukb-b-11601	ebi-a-GCST90000445	Inverse variance weighted	0.979296685
ukb-b-11601	ebi-a-GCST90000446	Inverse variance weighted	0.342832452
ukb-b-11601	ebi-a-GCST90000447	Inverse variance weighted	0.32604413
ukb-b-11601	ebi-a-GCST90000448	Inverse variance weighted	0.424201435
ukb-b-11601	ebi-a-GCST90000449	Inverse variance weighted	0.845300206
ukb-b-11601	ebi-a-GCST90000458	Inverse variance weighted	0.072810575
ukb-b-11601	ebi-a-GCST90000459	Inverse variance weighted	0.967469382
ukb-b-11601	ebi-a-GCST90000460	Inverse variance weighted	0.732754467

ukb-b-11601	ebi-a-GCST90000461	Inverse variance weighted	0.017612757
ukb-b-11601	ebi-a-GCST90000462	Inverse variance weighted	0.685105364
ukb-b-11601	ebi-a-GCST90000463	Inverse variance weighted	0.944569143
ukb-b-11601	ebi-a-GCST90012005	Inverse variance weighted	0.368359806
ukb-b-11601	ebi-a-GCST90012024	Inverse variance weighted	0.999208304
ukb-b-11601	prot-a-1456	Inverse variance weighted	0.564281049
ukb-b-11601	prot-a-1466	Inverse variance weighted	0.51089201
ukb-b-11601	prot-a-1470	Inverse variance weighted	0.244033484
ukb-b-11601	prot-a-1472	Inverse variance weighted	0.575528866
ukb-b-11601	prot-a-1475	Inverse variance weighted	0.03941124
ukb-b-11601	prot-a-1479	Inverse variance weighted	0.794655031
ukb-b-11601	prot-a-1480	Inverse variance weighted	0.022604901
ukb-b-11601	prot-a-1483	Inverse variance weighted	0.611012982
ukb-b-11601	prot-a-1485	Inverse variance weighted	0.316056424
ukb-b-11601	prot-a-1504	Inverse variance weighted	0.294989165
ukb-b-11601	prot-a-1506	Inverse variance weighted	0.420996058
ukb-b-11601	prot-a-1515	Inverse variance weighted	0.408147972
ukb-b-11601	prot-a-1516	Inverse variance weighted	0.522737382
ukb-b-11601	prot-a-1518	Inverse variance weighted	0.786502048
ukb-b-11601	prot-a-1521	Inverse variance weighted	0.60619726
ukb-b-11601	prot-a-1523	Inverse variance weighted	0.173508272
ukb-b-11601	prot-a-1524	Inverse variance weighted	0.714050761
ukb-b-11601	prot-a-1525	Inverse variance weighted	0.462768905
ukb-b-11601	prot-a-1526	Inverse variance weighted	0.809674825
ukb-b-11601	prot-a-1527	Inverse variance weighted	0.792219256
ukb-b-11601	prot-a-1528	Inverse variance weighted	0.283732375
ukb-b-11601	prot-a-1535	Inverse variance weighted	0.15288066
ukb-b-11601	prot-a-1540	Inverse variance weighted	0.11711558
ukb-b-11601	prot-a-1546	Inverse variance weighted	0.335715644
ukb-b-11601	prot-a-2990	Inverse variance weighted	0.928348807
ukb-b-11601	prot-c-2578_67_2	Inverse variance weighted	0.071569084
ukb-b-11601	prot-c-3722_49_2	Inverse variance weighted	0.14198205
ukb-b-11601	prot-c-4337_49_2	Inverse variance weighted	0.813624882
ukb-b-11601	prot-c-4368_8_2	Inverse variance weighted	0.929012656
ukb-b-11601	prot-c-4703_87_2	Inverse variance weighted	0.110747527
ukb-b-11601	prot-c-4840_73_1	Inverse variance weighted	0.114019846
ukb-b-11601	prot-c-5356_2_3	Inverse variance weighted	0.083531295

Figure 2A showed the scatter plot. Each point on the graph represented an IV, the line on each point actually reflecting the 95% CI, the abscissa was the effect of SNP on exposure, the ordinate was the effect of SNP on outcome, and the colored line represented the MR fitting results (light blue for IVW, dark blue for MR egger, light green for simple mode, dark green for weighted medium, and red for weighted mode). Figure 2B showed the forest plot. Each horizontal solid line in the figure reflected the result estimated by a SNP using the Wald ratio method. If the solid line was entirely on the left side of 0, it meant that the result estimated by this SNP was that increased exposure can reduce the risk of the result; If the solid line was entirely on the right side of 0, it meant that the result estimated by this SNP was that increased exposure can increase the risk of the result. Figure 2C was eliminating individual SNPs one by one forest plot. Each horizontal solid line in the figure reflected the result estimated by Wald ratio method after a SNP was eliminated. This method was to test the effect of a SNP on the whole result. Figure 2D was funnel plot. The abscissa in the figure was the value of IVW and MR, the ordinate was the value of tool variable IV, the solid blue line was MR egger, and the light blue line was IVW.

4 DISCUSSION

Despite the extensive research on the role of ICs in BPH,

https://doi.org/10.53964/jmpp.2023012

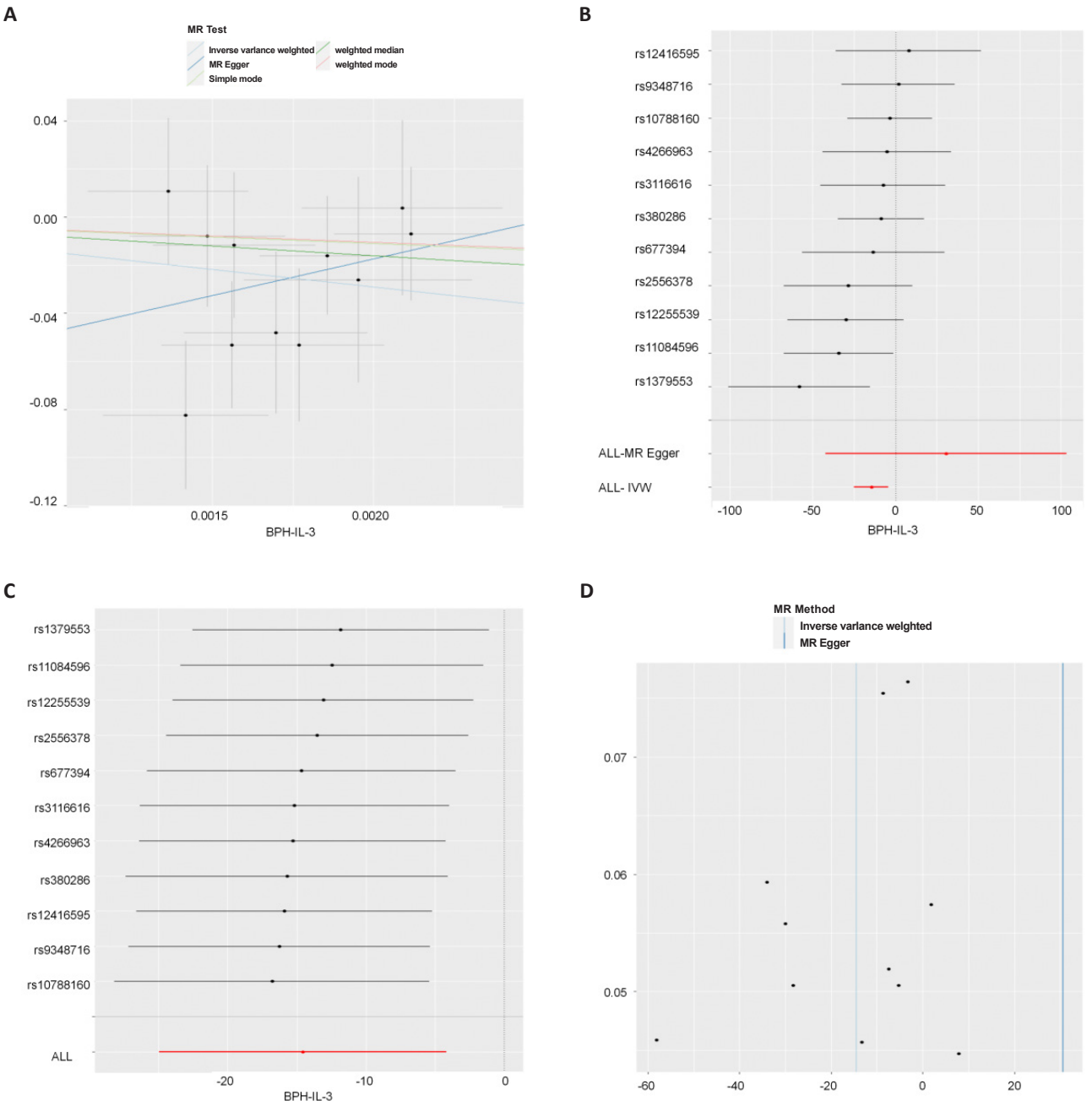

Figure 2. Reverse MR analysis results. A showed the scatter plot. B showed the forest plot. C was eliminating individual SNPs one by one forest plot. D was funnel plot.

our study presented results that contradict the traditionally held belief that the local inflammatory response exacerbated BPH. This discrepancy warranted further investigation and explanation. Previous studies showed that some ICs played a critical role in BPH. However, our study did not find any significant genetic association between ICs and BPH. One possible explanation for this discrepancy could be the inherent limitations of our study, which included a predominantly European study population and database constraints that precluded the inclusion of all ICs. Inflammatory changes often occur in glands of BPH patients[15]. But this process may not play a role through IC directly. Previous studies showed that the above IC has pro-inflammatory effect in various diseases. Studies showed that some ICs also play an important role in BPH. For example, IL-17 in BPH cases increased[16]; The expression of IL-8 was also increased in BPH[17]. IL-4 was associated with BPH[18]. Inflammation was not only affiliated with BPH, but also influenced epigenetics in certain diseases[19]. Epigenetic alterations was observed in BPH patients[20], suggesting the involvement of epigenetics in the pathogenesis and progression of BPH. Epigenetic mechanisms influenced various physiological and pathological processes by modulating the local and global accessibility of the epigenetic code to chromatin, thereby regulating gene expression. The three major well-studied epigenetic codes include DNA methylation, histone modification, and non-coding RNA (ncRNA)[21]. Epigenetics plays a significant

role in numerous diseases such as BPH, cancer, and neurological disorders[22,23]. As the modern evolution of Mendelian genetics, the study of epigenetics is gaining momentum[24]. IC might indirectly have negative effects on BPH through inflammatory environments or epigenetic pathways.

5 CONCLUSION

In this bidirectional MR study, our results indicated that there was no significant genetic bidirectional association between BPH and IC. This suggested that IC may not exert a genetic exposure influence on BPH, contradicting previous studies that suggested otherwise. Further research is needed to elucidate the role of IC in BPH and to validate the findings of this study.

Our findings provided a unique perspective on the genetic interplay between IC and BPH, which could potentially reshape our understanding of BPH's pathophysiology. Given the high prevalence of BPH in the elderly male population and the significant impact on their quality of life, it was crucial to gain a comprehensive understanding of its etiology.

However, our study did not support a significant genetic exposure influence of IC on BPH. This conclusion, while derived from rigorous MR analysis, was in contrast to previous studies, suggesting a complex interplay of genetic and non-genetic factors in BPH's development and progression.

It was also worth noting that our study population was predominantly European, which may limit the generalizability of our findings to other ethnic groups. Future studies involving diverse populations are warranted to confirm our findings and further explore the genetic associations between IC and BPH.

Furthermore, due to database constraints, not all ICs, including those yet undiscovered, were included in this study. As our understanding of ICs continues to expand with ongoing research, future studies should incorporate these additional ICs to provide a more comprehensive view of the relationship between IC and BPH.

In summary, while our study did not find a significant genetic relationship between IC and BPH, it does highlight the need for further research in this area. Understanding the precise role of IC in BPH could have significant implications for the development of novel therapeutic strategies and personalized medicine approaches for BPH management.

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Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

Zhang Z conceived and designed the study. Zhu M conducted data analysis. Zhang Z, Chen Y and Huang S wrote the paper. Huang S reviewed and edited the manuscript. All authors approved the final version of the article. Zhang Z, Huang S and Chen Y contributed equally to this work and are co-first authors.

Data Availability

The datasets generated and analyzed during the current study are available at https://gwas.mrcieu.ac.uk/

Supplementary Materials

The following supporting information can be downloaded at: https://figshare.com/account/home (DOI: 10.6084/m9.figshare.23393915), Tables 1-3.

Abbreviation List

BPH, Benign prostatic hyperplasia
CI, Confidence interval
GWAS, Genome-wide association studies
IC, Inflammatory cytokines
IVW, Inverse variance weighted
MR, Mendelian randomization
SNP, Single nucleotide polymorphism

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