Causal relationship between obesity, lifestyle factors and risk of benign prostatic hyperplasia: a univariable and multivariable Mendelian randomization study

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Abstract

Background: Obesity (waist circumference, body mass index (BMI)) and lifestyle factors (dietary habits, smoking, alcohol drinking, Sedentary behavior) have been associated with risk of benign prostatic hyperplasia (BPH) in observational studies, but whether these associations are causal is unclear.

Methods: We performed a univariable and multivariable Mendelian randomization study to evaluate these associations. Genetic instruments associated with exposures at the genome-wide significance level ($P < 5 \times 10^{-8}$) were selected from corresponding genome-wide associations studies (n = 216,590 to 1,232,091 individuals). Summary-level data for BPH were obtained from the UK Biobank (14,126 cases and 169,762 non-cases) and FinnGen consortium (13,118 cases and 72,799 non-cases). Results from UK Biobank and FinnGen consortium were combined using fixed-effect meta-analysis.

Results: The combined odds ratios (ORs) of BPH were 1.24 (95% confidence interval (CI), 1.07–1.43, $P = 0.0045$), 1.08 (95% CI 1.01–1.17, $P = 0.0175$), 0.94 (95% CI 0.67–1.30, $P = 0.6891$), 1.29 (95% CI 0.88–1.89, $P = 0.1922$), 1.23 (95% CI 0.85–1.78, $P = 0.2623$), and 1.04 (95% CI 0.76–1.42, $P = 0.8165$) for one standard deviation (SD) increase in waist circumference, BMI, and relative carbohydrate, fat, protein and sugar intake, 1.05 (95% CI 0.92–1.20, $P = 0.4581$) for one SD increase in prevalence of smoking initiation, 1.10 (95% CI 0.96–1.26, $P = 0.1725$) and 0.84 (95% CI 0.69–1.02, $P = 0.0741$) for one SD increase of log-transformed smoking per day and drinks per week, and 1.31 (95% CI 1.08–1.58, $P = 0.0051$) for one SD increase in sedentary behavior. Genetically predicted waist circumference (OR = 1.26, 95% CI 1.11–1.43, $P = 0.0004$) and sedentary behavior (OR = 1.14, 95% CI 1.05–1.23, $P = 0.0021$) were associated with BPH after the adjustment of BMI.

Conclusion: This study supports independent causal roles of high waist circumference, BMI and sedentary behavior in BPH.

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Introduction

Benign prostate hyperplasia (BPH) is a common benign disease in middle-aged and elderly men, appearing in approximately 8% of men by age 40, but up to 90% of men by age 90 [1]. The incident cases of BPH increased by 105.70% from 1990 to 2019 according to the Global Burden of Disease 2019 data [2]. BPH is often underestimated and underdiagnosed. If patients are not treated in time, it may lead to serious complications, such as urinary retention, renal insufficiency and renal failure [3].

Epidemiological studies have reported several potential risk factors for BPH, including obesity [4–6], dietary habits [7–10], smoking [11], alcohol consumption [12–15] and sedentary behavior [16]. However, most of the evidence for the associations have been inconsistent and inconclusive. More importantly, in observational epidemiological studies, reverse causality, misclassification, unobserved confounding, and other biases may largely impede causal inference of these associations. For example, abdominal obesity and overall obesity are strongly related, and their independent association with BPH is unclear. Similarly, smoking and drinking may be overlapping behaviors for individuals, which may introduce residual confounding in traditional observational studies. Identifying the causal association of potentially modifiable risk factors with BPH has important practical implications for exploring the etiology of the disease and for its prevention and management in public health. Mendelian randomization (MR) designs use genetic variation as instrumental variables (IVs) for exposure and enhance causal association [17]. The method can reduce the influence of residual confounding since genetic variants are randomly distributed at conception and therefore unrelated to environmental and self-adopted lifestyle confounders [18]. Furthermore, MR designs can reduce the possibility of reverse causality, since genetic variants could not be altered by disease occurrence and progression.

Therefore, we performed a two-sample univariable and multivariable MR study to evaluate the possible causal associations of abdominal obesity (measured as waist circumference), overall obesity (measured as body mass index (BMI)), lifestyle factors (dietary habits, smoking, alcohol drinking, and sedentary behavior) with risk of BPH.
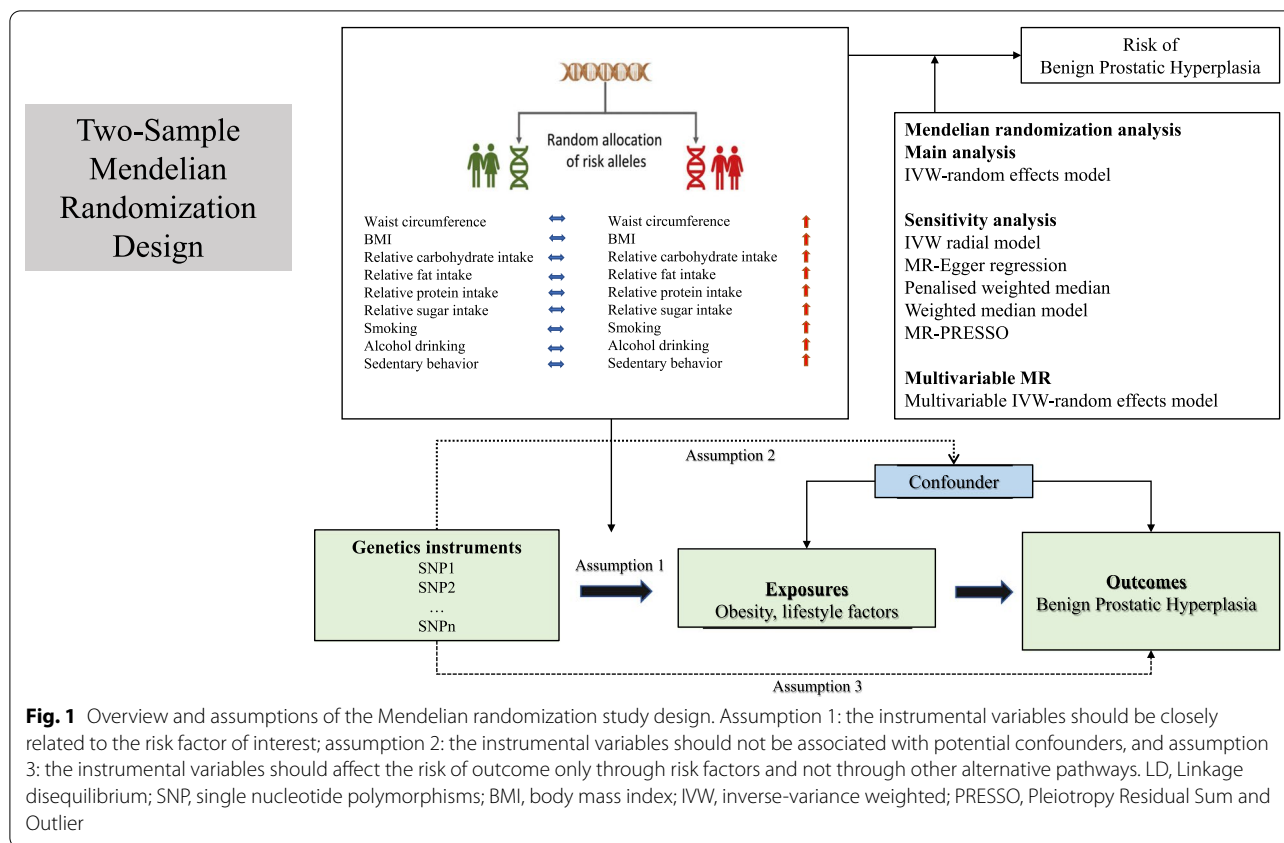
Methods

Study design and genetic instrument selection

Figure 1 shows the study design and the assumptions of MR in our study [19]. This IV analysis mimics randomized controlled trial with respect to the random allocation of single nucleotide polymorphisms (SNPs) in offspring (independent of confounding factors such as sex and age). We obtained the genetic IVs for the exposures from published genome-wide association studies (GWASs) using summary data [20–24]. We selected SNPs that were associated with waist circumference [20], waist circumference adjusted for BMI [20], BMI [21], dietary habits, smoking behaviors [22, 23], alcohol per week [22], and sedentary behavior [24] at the genome-wide significance threshold ($P < 5 \times 10^{-8}$). For dietary habits, four sets of instruments (SNPs for relative carbohydrate, fat, protein and sugar intake) were employed for validation [25]. For smoking behaviors, three sets of instruments (SNPs for smoking initiation [22], smoking per day [22], and lifetime smoking index [23]) were employed for validation. For example, the SNPs for smoking initiation were chosen from a meta-analysis of GWAS with a total of 1,232,091 participants of European ancestry. This phenotype was measured as a binary variable, coded as "1" if they had never been a regular smoker in their life and "2" if they had ever been a regular smoker in their life (current or former). The GWAS of number of cigarettes per day came from the Sequencing Consortium of Alcohol and Nicotine use, 23andMe and UK Biobank. The cigarettes per day was defined as the average number of cigarettes smoked per day both in current smoker and former smoker. The GWAS on the lifetime smoking index included information on duration of smoking, heaviness and cessation, which were combined into a simulated half-life (τ) constant and a lifetime smoking index. We obtained summary-level data of alcohol consumption from a GWAS of number of drinks per week in 941,280 individuals. The GWAS was from several cohorts including deCODE, UK Biobank and 23andMe. Drinks per week was defined as the amount of drinks a study participant reported drinking per week, including different types of alcohol. Detailed information on used data sources, definition, unit, participants included in the analysis, adjusted covariates and identified SNPs are displayed in Additional file 1: Table S1.

We calculated the linkage disequilibrium (LD) between SNPs for every risk factor based on LD reference panel from 1000 Genomes of European populations. We excluded SNPs in LD ($r^2 > 0.001$ and clump window < 10,000 kb) and retained the SNP with the lowest P value. Then, we harmonized the SNPs in the exposure and outcome datasets by coded and reference alleles. Exposure and outcome data are unified into a dataset by removing the allele frequencies of SNPs containing

Fig. 1 Overview and assumptions of the Mendelian randomization study design. Assumption 1: the instrumental variables should be closely related to the risk factor of interest; assumption 2: the instrumental variables should not be associated with potential confounders, and assumption 3: the instrumental variables should affect the risk of outcome only through risk factors and not through other alternative pathways. LD, Linkage disequilibrium; SNP, single nucleotide polymorphisms; BMI, body mass index; IVW, inverse-variance weighted; PRESSO, Pleiotropy Residual Sum and Outlier

palindromes [19]. We defined palindromic SNPs with ambiguous minor allele frequency > 0.45 and < 0.55 [26]. Considering the limited impact of a small proportion of missing generates on the results, a few missing instruments tools in the outcome datasets were not replaced by proxy SNPS. We calculated the proportion of the variance of phenotype explained by whole SNPs and F-statistic [27]. When the corresponding F statistic is > 10, it is considered to be sufficient. We used an online tool to estimate the Power (https://shiny.cnsgenomics.com/mRnd/) [28]. The flow chart of our study is shown in Fig. 2, including the inclusion and exclusion criterion of candidate SNPs for each exposure-outcome pair. Detailed information on genetic instruments are shown in Additional file 1: Table S2.

Data sources for benign prostatic hyperplasia

Summary-level genetic data of GWASs for BPH were acquired from the R5 release of the FinnGen consortium [29] and the UK Biobank study [30] (Additional file 1: Table S1). In the FinnGen consortium, BPH cases were defined by N40 in International Classification of Diseases-Tenth (ICD-10) Revision code and 600 in ICD-8 and ICD-9. The R5 release of the FinnGen consortium data with a total of 13,118 BPH cases and 72,799 non-cases were obtained. In this data set, individuals with undefined sex, high genotype deletion (> 5%), excess heterozygosity (±4 standard deviations ((SDs)), and non-Finnish ancestry were excluded. Correlation tests were adjusted for age, 10 genetic principal components and genotyping batches. In the UK Biobank study, the disease was defined by N40 in ICD-10, self-reported operation codes, and office of population and censuses surveys. Data from the UK Biobank study included 183,888 participants (14,126 BPH and 169,762 non-cases) after exclusion of individuals who had withdrawn consent from the UK Biobank study, individuals with sexual chromosome aneuploidies, and individuals of non-European ancestry. Correlation tests had been adjusted for age and up to 20 main components. Detailed information on quality control refers to the web and cited GWAS papers of FinnGen consortium and the UK Biobank [29, 30].

All cited summary-level data from published GWASs and consortia had been approved by the relevant review committees and the participants involved had given informed consent, and the analytic process was in accordance with the STROBE-MR guidelines [31].
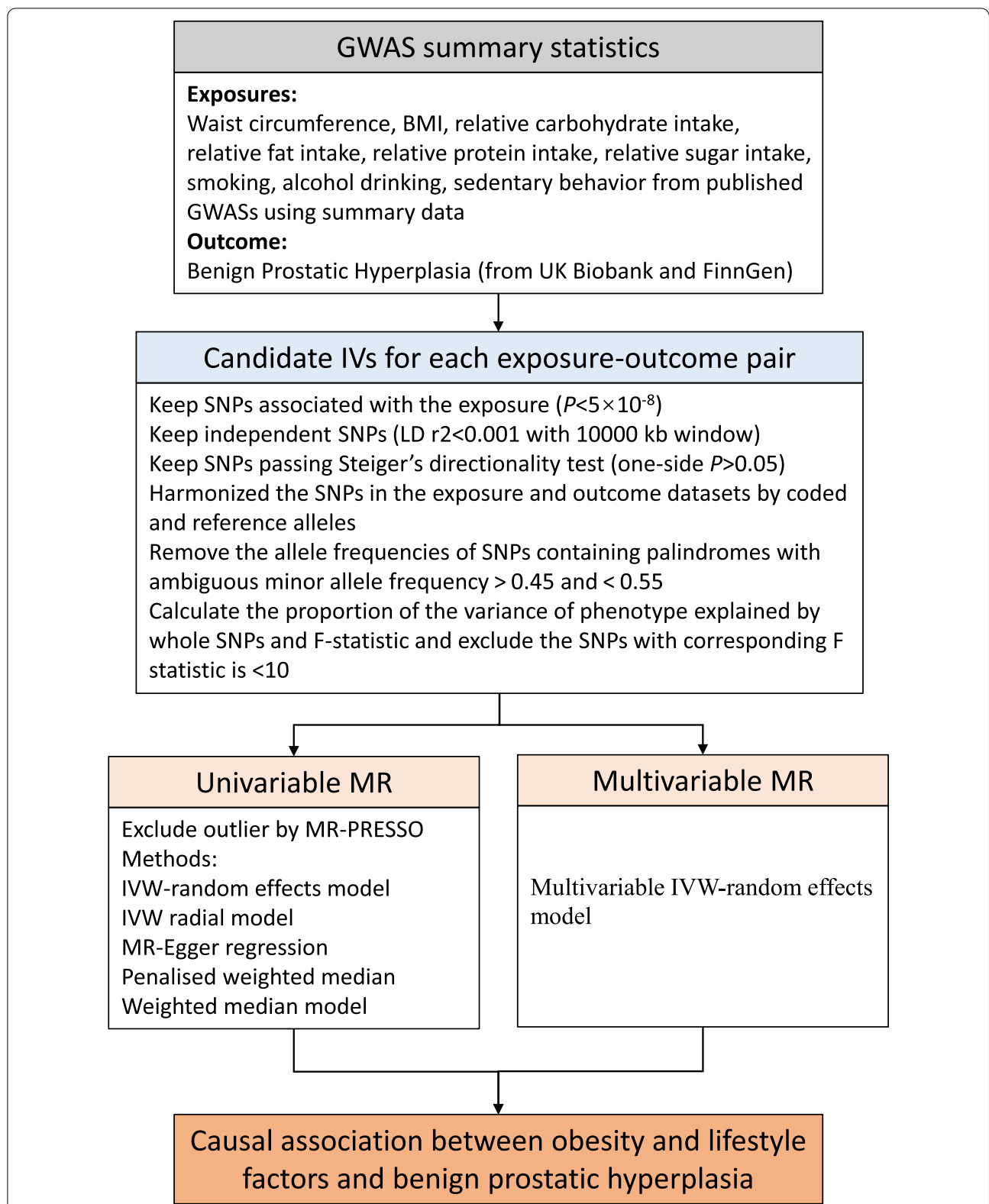
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GWAS summary statistics

Exposures:
Waist circumference, BMI, relative carbohydrate intake, relative fat intake, relative protein intake, relative sugar intake, smoking, alcohol drinking, sedentary behavior from published GWASs using summary data
Outcome:
Benign Prostatic Hyperplasia (from UK Biobank and FinnGen)

Candidate IVs for each exposure-outcome pair

Keep SNPs associated with the exposure ($P<5\times10^{-8}$)
Keep independent SNPs (LD r2<0.001 with 10000 kb window)
Keep SNPs passing Steiger's directionality test (one-side $P>0.05$)
Harmonized the SNPs in the exposure and outcome datasets by coded and reference alleles
Remove the allele frequencies of SNPs containing palindromes with ambiguous minor allele frequency > 0.45 and < 0.55
Calculate the proportion of the variance of phenotype explained by whole SNPs and F-statistic and exclude the SNPs with corresponding F statistic is <10

Univariable MR

Exclude outlier by MR-PRESSO
Methods:
IVW-random effects model
IVW radial model
MR-Egger regression
Penalised weighted median
Weighted median model

Multivariable MR

Multivariable IVW-random effects model

Causal association between obesity and lifestyle factors and benign prostatic hyperplasia

Fig. 2 The flow chart of the inclusion and exclusion criterion of candidate SNPs for each exposure-outcome pair. GWAS, genome-wide association studies; BMI, body mass index; LD, Linkage disequilibrium; IVW, inverse-variance weighted; PRESSO, Pleiotropy Residual Sum and Outlier; MR, Mendelian randomization

Statistical analysis

We applied MR-Steiger analysis to test the direction of the potential causal association between each of the extracted SNPs on the risk factors and BPH [32]. Heterogeneity between the SNPs was evaluated by calculating Cochrane's Q statistic. Heterogeneity was considered to exist when Cochrane Q-derived $P < 0.05$, and we used a random-effect inverse-variance weighted (IVW) model as the main analysis method [33]. Five other sensitivity analysis methods, including the weighted median, MR-Egger regression, penalized weighted median, IVW radial regression and MR-PRESSO (Pleiotropy Residual Sum and Outlier) methods, were performed to assess the robustness of the results [33–35]. The weighted median model provides consistent estimates on the condition that $\geq 50\%$ of the weight in the analysis comes from valid IVs [36]. The MR-Egger regression analysis can detect and correct for directional pleiotropy whereas it compromises power. The P value for the MR-Egger intercept was used to indicate directional pleiotropy. Under the assumption that no more than 50% of the estimated weight of MR effects is derived from multi-effect SNPs, the penalized weighted median method gives consistent estimates of effects, where the weight is depended on the strength of their association with exposure [36]. The IVW radial regression uses modified second-order weights to test and remove outlying SNPs. The MR-PRESSO method can identify outliers and generate estimates after the outliers are removed [37]. The MR-PRESSO distortion test is designed to test the difference in the estimation before and after the outlier correction. A $P < 0.05$ of the distortion test indicates that there is a significant difference in the estimation before and after the outlier correction. To evaluate whether genetic liability to smoking is associated with BPH risk independently of alcohol drinking, a multivariable random-effects IVW model was employed to adjust for genetically predicted alcohol drinking in the analysis of smoking and vice versa [38, 39]. In addition, to assess whether genetic liability to lifestyle factors are associated with BPH risk independently of BMI, we performed multivariable MR analyses by random-effects IVW model with adjustment for genetically predicted BMI. Derived estimates based on the UK Biobank and the FinnGen consortium were summarized using fixed-effects meta-analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of BPH were scaled to per one standard deviation (SD) increase in waist circumference, BMI, relative carbohydrate, fat, protein, and sugar intake, lifetime smoking index and sedentary behavior, one SD increase in prevalence of smoking initiation, and

one SD increase of log-transformed alcoholic smoking per day and drinks per week. To account for multiple testing in our analyses, a Bonferroni-corrected threshold of $P < 0.0046$ ($\alpha = 0.05/11$ exposure factors) was applied. Associations with $P < 0.0046$ were considered significant, and associations with $P \geq 0.0046$ and < 0.05 were considered suggestive. All statistical analyses were conducted using the Mendelian Randomization (0.4.2), TwoSampleMR (0.5.5), MRPRESSO (1.0), MVMR (0.3) and meta (4.11.0) packages in R, version 4.0.3.

Results

The F statistics for IVs and estimated power for all analyses are shown in Additional file 1: Table S3. None of these IVs had an F-statistic below the threshold of 10, indicating that there was low evidence of weak instrument bias in this study. Expected ORs for BPH was estimated for Given a $\alpha = 5\%$ and 80% power in the FinnGen consortium and UK biobank study. The power was low in the analysis of alcohol per week, but adequate for the other studied exposures.

The Steiger-MR indicated that the SNPs explained more variance in exposure than the outcome (all $P > 0.05$), which identified the robustness of the causal effect estimates. No pleiotropy was identified in the analysis of all exposures in the UK Biobank and FinnGen data by the MR-Egger regression (Additional file 1: Table S4). Moderate heterogeneity was found in the analysis of most exposures (P for Cochrane's Q < 0.001) (Additional file 1: Table S4).

Genetically predicted higher waist circumference, waist circumference adjusted for BMI and BMI were associated with a raised risk of BPH in UK Biobank data (Fig. 3). The estimates were retained in FinnGen consortium data, but with wider CIs that span 1.0. The combined ORs of BPH were 1.24 (95% CI 1.07–1.43, $P = 0.0045$), 1.26 (95% CI 1.11–1.43, $P = 0.0004$) and 1.08 (95% CI 1.01–1.17, $P = 0.0175$) for waist circumference, waist circumference adjusted for BMI and BMI, respectively. The association calculated by different methods (the weighted median, MR-Egger regression, penalized weighted median, and IVW radial regression) was directionally consistent (Additional file 1: Figure S1). After removing outliers in the MR-PRESSO analysis, the association between waist circumference, waist circumference adjusted for BMI and BMI and BPH persisted and the P value for the distortion test were above 0.05 (Additional file 1: Table S4).

As for lifestyle factors, in terms of dietary habits, the combined ORs of BPH were 0.94 (95% CI 0.67–1.30, $P = 0.6891$), 1.29 (95% CI 0.88–1.89, $P = 0.1922$), 1.23 (95% CI 0.85–1.78, $P = 0.2623$), and 1.04 (95% CI
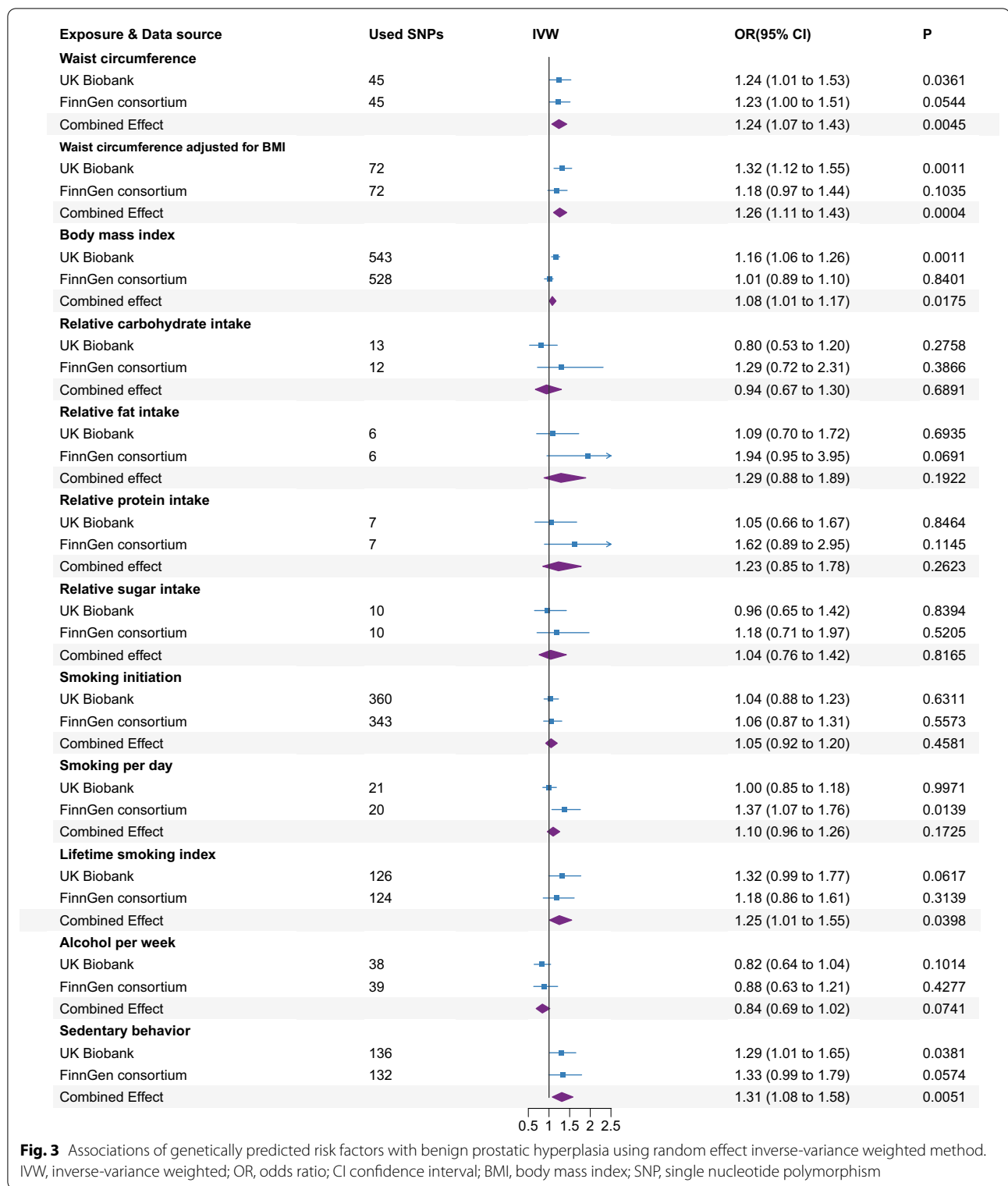
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Exposure & Data source	Used SNPs	IVW	OR(95% CI)	P
Waist circumference				
UK Biobank	45		1.24 (1.01 to 1.53)	0.0361
FinnGen consortium	45		1.23 (1.00 to 1.51)	0.0544
Combined Effect			1.24 (1.07 to 1.43)	0.0045
Waist circumference adjusted for BMI				
UK Biobank	72		1.32 (1.12 to 1.55)	0.0011
FinnGen consortium	72		1.18 (0.97 to 1.44)	0.1035
Combined Effect			1.26 (1.11 to 1.43)	0.0004
Body mass index				
UK Biobank	543		1.16 (1.06 to 1.26)	0.0011
FinnGen consortium	528		1.01 (0.89 to 1.10)	0.8401
Combined effect			1.08 (1.01 to 1.17)	0.0175
Relative carbohydrate intake				
UK Biobank	13		0.80 (0.53 to 1.20)	0.2758
FinnGen consortium	12		1.29 (0.72 to 2.31)	0.3866
Combined effect			0.94 (0.67 to 1.30)	0.6891
Relative fat intake				
UK Biobank	6		1.09 (0.70 to 1.72)	0.6935
FinnGen consortium	6		1.94 (0.95 to 3.95)	0.0691
Combined effect			1.29 (0.88 to 1.89)	0.1922
Relative protein intake				
UK Biobank	7		1.05 (0.66 to 1.67)	0.8464
FinnGen consortium	7		1.62 (0.89 to 2.95)	0.1145
Combined effect			1.23 (0.85 to 1.78)	0.2623
Relative sugar intake				
UK Biobank	10		0.96 (0.65 to 1.42)	0.8394
FinnGen consortium	10		1.18 (0.71 to 1.97)	0.5205
Combined effect			1.04 (0.76 to 1.42)	0.8165
Smoking initiation				
UK Biobank	360		1.04 (0.88 to 1.23)	0.6311
FinnGen consortium	343		1.06 (0.87 to 1.31)	0.5573
Combined Effect			1.05 (0.92 to 1.20)	0.4581
Smoking per day				
UK Biobank	21		1.00 (0.85 to 1.18)	0.9971
FinnGen consortium	20		1.37 (1.07 to 1.76)	0.0139
Combined Effect			1.10 (0.96 to 1.26)	0.1725
Lifetime smoking index				
UK Biobank	126		1.32 (0.99 to 1.77)	0.0617
FinnGen consortium	124		1.18 (0.86 to 1.61)	0.3139
Combined Effect			1.25 (1.01 to 1.55)	0.0398
Alcohol per week				
UK Biobank	38		0.82 (0.64 to 1.04)	0.1014
FinnGen consortium	39		0.88 (0.63 to 1.21)	0.4277
Combined Effect			0.84 (0.69 to 1.02)	0.0741
Sedentary behavior				
UK Biobank	136		1.29 (1.01 to 1.65)	0.0381
FinnGen consortium	132		1.33 (0.99 to 1.79)	0.0574
Combined Effect			1.31 (1.08 to 1.58)	0.0051

0.5 1 1.5 2 2.5

Fig. 3 Associations of genetically predicted risk factors with benign prostatic hyperplasia using random effect inverse-variance weighted method. IVW, inverse-variance weighted; OR, odds ratio; CI confidence interval; BMI, body mass index; SNP, single nucleotide polymorphism

0.76–1.42, $P=0.8165$) for one SD increase in relative carbohydrate, fat, protein, and sugar intake, respectively, in the meta-analysis of data from the UK Biobank and FinnGen consortium (Fig. 3). These null associations

were replicated in the sensitivity analysis and multivariable MR analysis (Additional file 1: Figure S1 and Fig. 4).

As for smoking behaviors, genetic predisposition to smoking initiation (combined OR 1.05, 95% CI 0.92–1.20,
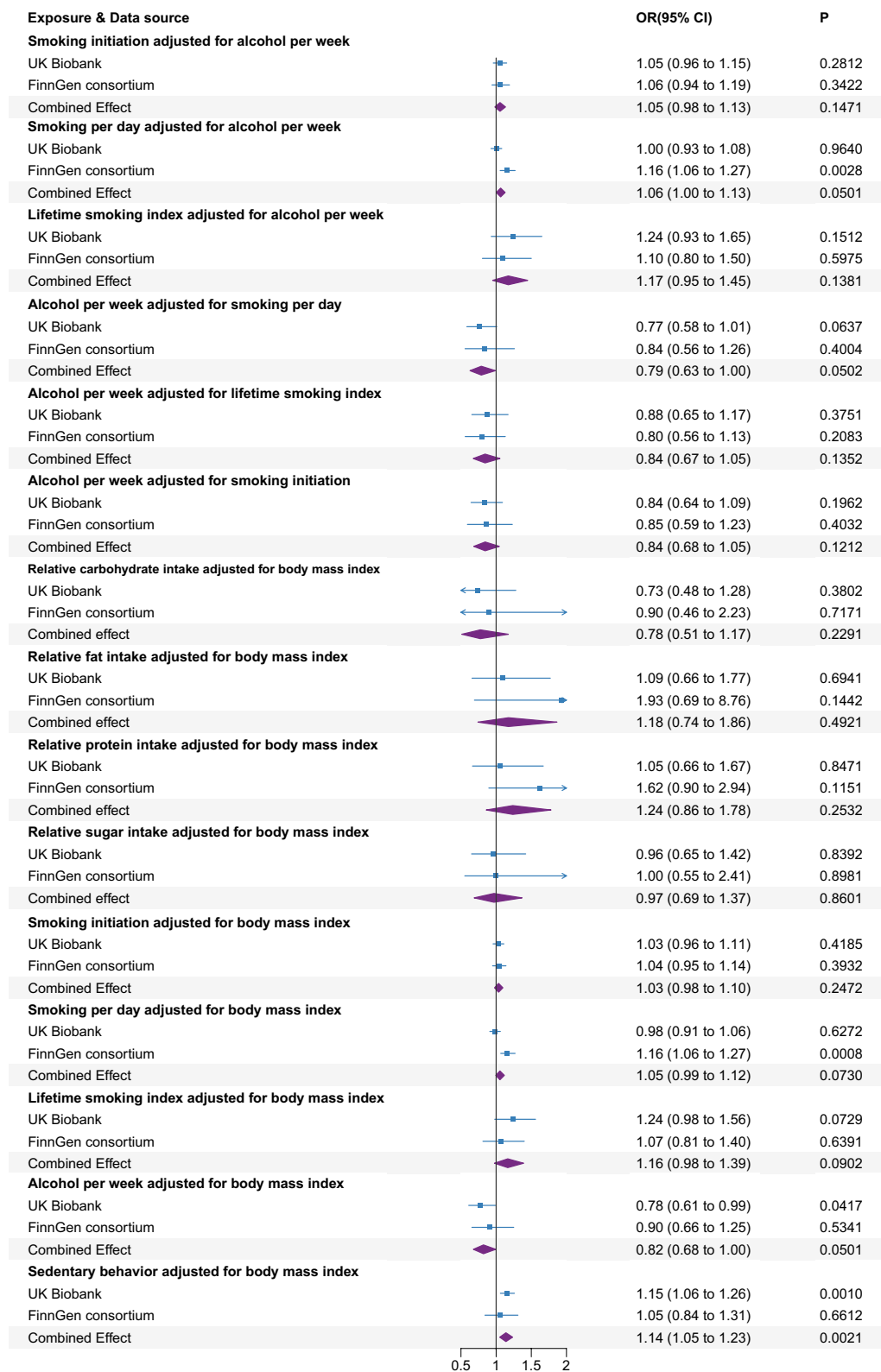
Exposure & Data source	OR(95% CI)	P
Smoking initiation adjusted for alcohol per week		
UK Biobank	1.05 (0.96 to 1.15)	0.2812
FinnGen consortium	1.06 (0.94 to 1.19)	0.3422
Combined Effect	1.05 (0.98 to 1.13)	0.1471
Smoking per day adjusted for alcohol per week		
UK Biobank	1.00 (0.93 to 1.08)	0.9640
FinnGen consortium	1.16 (1.06 to 1.27)	0.0028
Combined Effect	1.06 (1.00 to 1.13)	0.0501
Lifetime smoking index adjusted for alcohol per week		
UK Biobank	1.24 (0.93 to 1.65)	0.1512
FinnGen consortium	1.10 (0.80 to 1.50)	0.5975
Combined Effect	1.17 (0.95 to 1.45)	0.1381
Alcohol per week adjusted for smoking per day		
UK Biobank	0.77 (0.58 to 1.01)	0.0637
FinnGen consortium	0.84 (0.56 to 1.26)	0.4004
Combined Effect	0.79 (0.63 to 1.00)	0.0502
Alcohol per week adjusted for lifetime smoking index		
UK Biobank	0.88 (0.65 to 1.17)	0.3751
FinnGen consortium	0.80 (0.56 to 1.13)	0.2083
Combined Effect	0.84 (0.67 to 1.05)	0.1352
Alcohol per week adjusted for smoking initiation		
UK Biobank	0.84 (0.64 to 1.09)	0.1962
FinnGen consortium	0.85 (0.59 to 1.23)	0.4032
Combined Effect	0.84 (0.68 to 1.05)	0.1212
Relative carbohydrate intake adjusted for body mass index		
UK Biobank	0.73 (0.48 to 1.28)	0.3802
FinnGen consortium	0.90 (0.46 to 2.23)	0.7171
Combined effect	0.78 (0.51 to 1.17)	0.2291
Relative fat intake adjusted for body mass index		
UK Biobank	1.09 (0.66 to 1.77)	0.6941
FinnGen consortium	1.93 (0.69 to 8.76)	0.1442
Combined effect	1.18 (0.74 to 1.86)	0.4921
Relative protein intake adjusted for body mass index		
UK Biobank	1.05 (0.66 to 1.67)	0.8471
FinnGen consortium	1.62 (0.90 to 2.94)	0.1151
Combined effect	1.24 (0.86 to 1.78)	0.2532
Relative sugar intake adjusted for body mass index		
UK Biobank	0.96 (0.65 to 1.42)	0.8392
FinnGen consortium	1.00 (0.55 to 2.41)	0.8981
Combined effect	0.97 (0.69 to 1.37)	0.8601
Smoking initiation adjusted for body mass index		
UK Biobank	1.03 (0.96 to 1.11)	0.4185
FinnGen consortium	1.04 (0.95 to 1.14)	0.3932
Combined Effect	1.03 (0.98 to 1.10)	0.2472
Smoking per day adjusted for body mass index		
UK Biobank	0.98 (0.91 to 1.06)	0.6272
FinnGen consortium	1.16 (1.06 to 1.27)	0.0008
Combined Effect	1.05 (0.99 to 1.12)	0.0730
Lifetime smoking index adjusted for body mass index		
UK Biobank	1.24 (0.98 to 1.56)	0.0729
FinnGen consortium	1.07 (0.81 to 1.40)	0.6391
Combined Effect	1.16 (0.98 to 1.39)	0.0902
Alcohol per week adjusted for body mass index		
UK Biobank	0.78 (0.61 to 0.99)	0.0417
FinnGen consortium	0.90 (0.66 to 1.25)	0.5341
Combined Effect	0.82 (0.68 to 1.00)	0.0501
Sedentary behavior adjusted for body mass index		
UK Biobank	1.15 (1.06 to 1.26)	0.0010
FinnGen consortium	1.05 (0.84 to 1.31)	0.6612
Combined Effect	1.14 (1.05 to 1.23)	0.0021

0.5   1   1.5   2

Fig. 4 Associations of genetically predicted risk factors with benign prostatic hyperplasia using multivariable MR analyses. OR, odds ratio; CI, confidence interval

$P = 0.4581$) and smoking per day (combined OR 1.10, 95% CI 0.96–1.26, $P = 0.1725$) were not associated with BPH in the meta-analysis of data from the UK Biobank and FinnGen consortium (Fig. 3). This null association was replicated in the sensitivity analysis (Additional file 1: Figure S1). In the multivariable MR analysis adjusting for alcohol per week and BMI separately, we also detected no association between genetic susceptibility to smoking initiation and smoking per day and risk of BPH (Fig. 4). A suggestive positive association between genetically predicted lifetime smoking index and BPH was detected in the meta-analysis (combined OR 1.25, 95% CI 1.01–1.55, $P = 0.0398$) (Fig. 4). However, the association did not remain after adjusting for alcohol per week (combined OR 1.17, 95% CI 0.95–1.45, $P = 0.1380$) and BMI (combined OR 1.16, 95% CI 0.98–1.39, $P = 0.0902$), respectively (Fig. 4). In addition, genetically predicted alcohol per week was not associated with BPH neither in a univariable model (combined OR 0.84, 95% CI 0.69–1.02, $P = 0.0741$) or in a multivariable MR analysis adjusting for smoking behaviors and BMI, respectively (Fig. 3, 4, Additional file 1: Figure S1).

However, genetically predicted higher sedentary behavior was associated with an elevated risk of BPH in UK Biobank data (Fig. 3). The estimate was unchanged in FinnGen consortium data, but with a broader CI. The combined ORs of BPH was 1.31 (95% CI 1.08–1.58, $P = 0.0051$) for sedentary behavior. The association was directionally consistent in the sensitivity analyses (Additional file 1: Figure S1). After the adjustment of BMI, a significantly positive association was also found between genetic predisposition to sedentary behavior and risk of BPH (OR = 1.14, 95% CI 1.05–1.23, $P = 0.0021$) (Fig. 4).

Discussion

Our MR study supports that genetic predisposition to higher waist circumference and sedentary behavior are independently and causally associated with the risk of BPH. Suggestive causal association is observed between genetic predisposition to higher BMI and increased risk of BPH. There is no obvious evidence that genetic predisposition to relative carbohydrate, fat, protein, and sugar intake, smoking and alcohol drinking are causally associated with the risk of BPH.

It is reported that obesity, especially visceral obesity, has been associated with BPH in observational studies [40, 41]. A meta-analysis of 7 cohort studies and 12 case–control studies reported a positive association between BPH and BMI [4]. In the subgroup analysis of population-based case–control studies, BMI was associated with a dose–response relationship with BPH, and a marginal positive association was detected between BPH risk with higher BMI. However, some prospective studies have not confirmed the association between BMI and BPH [5, 6]. This difference may be due to the different covariate adjustments and small sample sizes in these studies. In this study, the association between waist circumference and BPH remained after the adjustment for BMI, which suggested that central obesity is a vital risk factor as overall fat mass for BMI. There is a possible mechanism that could explain why obesity itself results in BPH even in metabolically healthy populations. Previous studies have observed that obesity can lead to chronic systemic inflammation and oxidative stress, leading to prostate tissue immune cell infiltration, tissue remodeling and hyperplasia in prostate tissues [40, 42, 43].

A systematic review evaluated myriads of food types and food groups and found consumption of a high-calorie diet, high in starches and red meat may be weakly associated with BPH risk, while a lower-calorie diet, high in polyunsaturated fats and low in saturated fat may be weakly associated with decreased risk [7–10]. The Prostate Cancer Prevention Trial (PCPT) within a cohort of 18,800 patients aged more than 50 years found a diet low in fat and red meat and high in protein may reduce the risk of symptomatic BPH [7]. However, with regard to the role of a high-fat diet, the evidence from the literature is not consistent. Suzuki et al. found that BPH risk was not associated with energy-adjusted total fat intake [8]. The above-mentioned findings led us to emphasize that the exact association between different dietary patterns and BPH has not yet been fully elucidated. Our study did not detect associations between relative carbohydrate, fat, protein, and sugar intake and BPH in the univariable and multivariable analyses after adjusting for BMI, although we could not rule out the possibility that the observed null findings were led by an inadequate power.

Several previous observational studies have reported that smoking confers an aggravated effect on BPH [44, 45], while other studies have found a protective effect [46]. A meta-analysis of 1 case–control study, 6 cohort studies, and 1 cross-sectional study representing data from 44,100 subjects, found no association between smoking and BPH risk, either for current smokers or for ex-smokers [11]. In our study, we did not find statistically significant associations with BPH for genetic predisposition to smoking behaviors in the univariable analyses and multivariable analyses after adjusting for alcohol behavior and BMI, although positive associations were showed in all analyses. More well-powered MR analysis is needed to verify our finding. Nevertheless, several vivo and vitro studies have shown that nicotine may increase activity in the sympathetic nervous system and may cause symptoms of urine storage by increasing the tone of the bladder smooth muscles [45]. Several studies have suggested that smoking may reduce the levels of testosterone, and

this effect could increase the risk of BPH [47–49]. In addition, smoking could cause nutritional imbalance, which may affect bladder and collagen synthesis [50]. It may also affect bladder wall strength and detrusor instability [51].

There are conflicting data on the association between BPH and alcohol consumption in observational studies [12–15]. Several studies have found that mild alcohol intake could increase lower urinary tract symptoms (LUTS) through diuretic effects or increased sympathetic nervous system activity, while moderate and high alcohol consumption may reduce the risk of BPH and complications of severe LUTS by altering androgen levels [52]. A meta-analysis including sixteen studies were conducted and the authors divided total alcohol intake per day into six gm levels [12]. At all six levels, alcohol intake was associated with slightly or significantly reduced likelihood of BPH. However, this finding was majorly based on cross-sectional and case-control studies and therefore were prone to residual confounding (e.g., other alcohol-related behaviors and lifestyles) and misclassification bias. Our study did not detect a negative association between alcohol consumption and BPH in the multivariable analyses after adjusting for smoking behavior and BMI, although our null findings are also at risk by inadequate power.

Several evidences support the role of sedentary behavior in endangering LUTS/BPH [53, 54]. In one large prospective study, men with the highest levels of physical activity were 19% less likely to develop moderate or worse LUTS than men with the lowest level [55]. Men who watched more than 30 h of television (TV) per week were more likely to develop moderate or more severe LUTS than men who watched less than 1 h of TV per week [55]. A cross-sectional study found that reducing sedentary time had a protective effect and reduced the prevalence of BPH [56]. However, their findings were prone to residual confounding from other sedentary related behaviors and lifestyles as well as misclassification bias. In our study, the proportion of time spent sitting throughout life appears to significantly increase the risk of BPH. Our MR study strengthened the causal nature of the positive association between sedentary behavior and BPH and further revealed that this association was independent of BMI. This result has potential implications for the prevention of BPH in ageing societies, where the incidence of BPH is gradually increasing.

MR analysis has three important assumptions [17, 57]. First, the selected IVs should be strongly associated with the exposure. In the present study, we selected SNPs that were associated with the exposures at the genome-wide significance level ($P < 5 \times 10^{-8}$) as IVs from GWASs with large sample sizes. Second, IVs should be independent

of potential confounders. Given the study was based on summary-level data, a thorough examination of the associations between exposures and possible confounders was not possible. However, these IVs were widely used in previous MR studies [58, 59]. Third, the genetic IVs should affect the outcome only via the exposure, not via other alternative pathways. Although we could not completely rule out the possibility that our findings might be biased by horizontal pleiotropy, our results remained consistent across several sensitivity analyses and the MR-Egger and MR-PRESSO analyses detected limited evidence in support of strong pleiotropic effects. This is the first MR study to investigate the casual association between obesity, lifestyle factors and risk of BPH using two-sample MR analyses. The main advantages of this study were the MR design and the large number of cases of BPH. Similar results in two independent populations support the reliability and robustness of our results. In addition, the results remained overall consistent across several sensitivity analyses. The MR directionality test (Steiger method) supported evidence that our genetic IVs influences our exposure before our outcome as opposed to the opposite direction of effect. Moreover, all of the participants recruited in the GWASs were from European descent. Therefore, our findings were unlikely distorted by demographic stratification biases.

Limitations need to be considered in this study. First, a potential concern in any MR study is horizontal pleiotropy. In our study, we did not observe obvious pleiotropic effects in all the analyses of exposures from MR-Egger intercept test. In addition, there were few outliers detected by MR-PRESSO analysis and the associations remained consistent after the removal of outlying SNPs. For smoking and alcohol behavior, we observed no association between genetically predicted smoking behavior and BPH after adjusting for alcohol consumption in the multivariable MR analysis and vice versa. Given the consistent associations of genetic predisposition to high waist circumference, BMI and sedentary behavior with BPH across two data sources and different MR models, it is unlikely that these results are driven by horizontal pleiotropy. Second, overfitting may be a concern, as both smoking and alcohol GWAS contain a certain percentage of data from the UK Biobank. However, sample overlap was unlikely to mislead our results, as our IVs were chosen from large GWASs. Our SNPs were chosen at a strong genome-wide threshold ($P < 5 \times 10^{-8}$) with all estimated F statistics exceeding 10, suggesting that the bias introduced by partial sample overlap should be minimal. Meanwhile, we interpreted the associations based on the results of meta-analyses by FinnGen and UK Biobank, with nearly half of the weights were derived from FinnGen. Third, even though our analyses were based

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on FinnGen and UK Biobank with large sample sizes, we may overlook weak associations, especially exposures consisting of a few SNPS that explain small phenotypic variations. Fourth, for lifestyle factors, whether the observed associations differ by age, metabolic level and other potential factors and BPH severity could not be examined based on summary-level data in this study. Fifth, the population restriction in our study may limit the generality of our findings in other populations. Sixth, for alcohol consumption, the effects of different types of alcohol are indistinguishable, and the nonlinear association could not be evaluated in our present MR analysis. Similarly, the gene-environmental interaction could not be estimated in summary-level genetic statistics. Finally, further validation studies should be performed to explore the association between other risk factors and BPH [60].

BPH is a major prostate disease in men that increase with aging. Previous traditional epidemiological studies with small sample size had explained some common related factors and did not perform causal inference. Therefore, risks of BPH were not fully understood. To validate the causality, we performed a two-sample Mendelian randomization analyses. In conclusion, our study provides MR evidence supporting a significantly causal role of waist circumference and sedentary behavior in BPH. The suggestive association between genetic predisposition to higher BMI and BPH risk needs verification. Dietary habits, smoking and alcohol drinking need confirmation in well-powered studies. Although many of these risks have not been fully studied, they might be beneficial in providing information to assist in counselling of patients and help to form strategies for the prevention of BPH. Meanwhile, in the future studies, identifying comprehensive risk factors on BPH, and developing freely accessible prediction models for the BPH can identify individuals at particular risk and provide decision-making supports for individualized intervention.

Abbreviations

BMI: Body mass index; BPH: Benign prostate hyperplasia; CI: Confidence interval; ICD-10: International Classification of Diseases-Tenth; IV: Instrumental variable; IVW: Inverse-variance weighted; GWASs: Genome-wide association studies; LD: Linkage disequilibrium; LUTS: Lower urinary tract symptoms; MR: Mendelian randomization; OR: Odds ratio; PRESSO: Pleiotropy Residual Sum and Outlier; SD: Standard deviation; SNP: Single nucleotide polymorphism.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-022-03722-y.

Additional file1: Table S1. Detailed information on used studies. **Table S2.** Detailed information on genetic instruments. **Table S3.** Variance explained, average F-statistic, and power calculation. **Table S4.** The results of pleiotropy test, Cochrane's Q and MR-PRESSO. **Figure S1.** Associations of genetically predicted risk factors with benign prostatic hyperplasia

using multiple MR sensitivity analyses. IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval; BMI, body mass index; SNP, single nucleotide polymorphism; MR, Mendelian randomization.

Data availability

The datasets analyzed in this study are publicly available summary statistics. Data used can be obtained upon a reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

All studies had been approved by a relevant ethical review board and participants had given informed consent. Ethical approval was not required because of the public characteristics of the data of GWAS.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Kim EH, Larson JA, Andriole GL. Management of benign prostatic hyperplasia. Annu Rev Med. 2016;67:137–51.
2. Zhu C, Wang DQ, Zi H, Huang Q, Gu JM, Li LY, Guo XP, Li F, Fang C, Li XD, Zeng XT. Epidemiological trends of urinary tract infections, urolithiasis and benign prostatic hyperplasia in 203 countries and territories from 1990 to 2019. Mil Med Res. 2021;8(1):64.
3. Lee SWH, Chan EMC, Lai YK. The global burden of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis. Sci Rep. 2017;7(1):7984.
4. Wang S, Mao Q, Lin Y, Wu J, Wang X, Zheng X, Xie L. Body mass index and risk of BPH: a meta-analysis. Prostate Cancer Prostatic Dis. 2012;15(3):265–72.
5. Kok ET, Schouten BW, Bohnen AM, Groeneveld FP, Thomas S, Bosch JL. Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men: the Krimpen Study. J Urol. 2009;181(2):710–6.

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6.   Burke JP, Rhodes T, Jacobson DJ, McGree ME, Roberts RO, Girman CJ, Lieber MM, Jacobsen SJ. Association of anthropometric measures with the presence and progression of benign prostatic hyperplasia. Am J Epidemiol. 2006;164(1):41–6.

7.   Kristal AR, Arnold KB, Schenk JM, Neuhouser ML, Goodman P, Penson DF, Thompson IM. Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. Am J Epidemiol. 2008;167(8):925–34.

8.   Suzuki S, Platz EA, Kawachi I, Willett WC, Giovannucci E. Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia. Am J Clin Nutr. 2002;75(4):689–97.

9.   Bradley CS, Erickson BA, Messersmith EE, Pelletier-Cameron A, Lai HH, Kreder KJ, Yang CC, Merion RM, Bavendam TG, Kirkali Z. Evidence of the impact of diet, fluid intake, caffeine, alcohol and tobacco on lower urinary tract symptoms: a systematic review. J Urol. 2017;198(5):1010–20.

10. Russo GI, Broggi G, Cocci A, Capogrosso P, Falcone M, Sokolakis I, Gül M, Caltabiano R, Di Mauro M. Relationship between dietary patterns with benign prostatic hyperplasia and erectile dysfunction: a collaborative review. Nutrients. 2021;13(11):4148.

11. Xu H, Fu S, Chen Y, Chen Q, Gu M, Wang Z. Smoking habits and benign prostatic hyperplasia: a systematic review and meta-analysis of observational studies. Medicine (Baltimore). 2016;95(32): e4565.

12. Parsons JK, Im R. Alcohol consumption is associated with a decreased risk of benign prostatic hyperplasia. J Urol. 2009;182(4):1463–8.

13. Rees J. Alcohol consumption decreases risk of BPH. Practitioner. 2009;253(1724):5.

14. Crispo A, Talamini R, Gallus S, Negri E, Gallo A, Bosetti C, La Vecchia C, Dal Maso L, Montella M. Alcohol and the risk of prostate cancer and benign prostatic hyperplasia. Urology. 2004;64(4):717–22.

15. Parsons JK. Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. J Urol. 2007;178(2):395–401.

16. Lee HW, Kim SA, Nam JW, Kim MK, Choi BY, Moon HS. The study about physical activity for subjects with prevention of benign prostate hyperplasia. Int Neurourol J. 2014;18(3):155–62.

17. Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG. Using published data in mendelian randomization: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol. 2015;30(7):543–52.

18. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37(7):658–65.

19. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife. 2018;7:e34408.

20. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Mägi R, Strawbridge RJ, Pers TH, Fischer K, Justice AE, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature. 2015;518(7538):187–96.

21. Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, Yengo L, Ferreira T, Marouli E, Ji Y, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet. 2019;28(1):166–74.

22. Wootton RE, Richmond RC, Stuijfzand BG, Lawn RB, Sallis HM, Taylor GMJ, Hemani G, Jones HJ, Zammit S, Davey Smith G, Munafò MR. Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. Psychol Med. 2020;50(14):2435–43.

23. Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, Datta G, Davila-Velderrain J, McGuire D, Tian C, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat Genet. 2019;51(2):237–44.

24. MRC-IEU. http://app.mrbase.org. Accessed 28 May 2022.

25. Meddens SFW, de Vlaming R, Bowers P, Burik CAP, Linnér RK, Lee C, Okbay A, Turley P, Rietveld CA, Fontana MA, et al. Genomic analysis of diet composition finds novel loci and associations with health and lifestyle. Mol Psychiatry. 2021;26(6):2056–69.

26. Hartwig FP, Davies NM, Hemani G, Davey Smith G. Two-sample Mendelian randomization: avoiding the downsides of a powerful, widely applicable but potentially fallible technique. Int J Epidemiol. 2016;45(6):1717–26.

27. Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol. 2011;40(3):755–64.

28. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. Int J Epidemiol. 2013;42(5):1497–501.

29. The FinnGen consortium. https://www.finngen.fi/fi. Accessed 28 May 2022.

30. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3): e1001779.

31. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, VanderWeele TJ, Higgins JPT, Timpson NJ, Dimou N, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. JAMA. 2021;326(16):1614–21.

32. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. PLoS Genet. 2017;13(11): e1007081.

33. Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. Hum Mol Genet. 2018;27(R2):R195-r208.

34. Bowden J, Spiller W, Del Greco MF, Sheehan N, Thompson J, Minelli C, Davey Smith G. Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the Radial plot and Radial regression. Int J Epidemiol. 2018;47(4):1264–78.

35. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512–25.

36. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40(4):304–14.

37. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet. 2018;50(5):693–8.

38. Rees JMB, Wood AM, Burgess S. Extending the MR-Egger method for multivariable Mendelian randomization to correct for both measured and unmeasured pleiotropy. Stat Med. 2017;36(29):4705–18.

39. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. Am J Epidemiol. 2015;181(4):251–60.

40. Chughtai B, Forde JC, Thomas DD, Laor L, Hossack T, Woo HH, Te AE, Kaplan SA. Benign prostatic hyperplasia. Nat Rev Dis Primers. 2016;2:16031.

41. Li BH, Deng T, Huang Q, Zi H, Weng H, Zeng XT. Body mass index and risk of prostate volume, international prostate symptom score, maximum urinary flow rate, and post-void residual in benign prostatic hyperplasia patients. Am J Mens Health. 2019;13(4):1557988319870382.

42. Parsons JK, Sarma AV, McVary K, Wei JT. Obesity and benign prostatic hyperplasia: clinical connections, emerging etiological paradigms and future directions. J Urol. 2013;189(1):S102-106.

43. Fang C, Wu L, Zhu C, Xie WZ, Hu H, Zeng XT. A potential therapeutic strategy for prostatic disease by targeting the oral microbiome. Med Res Rev. 2021;41(3):1812–34.

44. Prezioso D, Catuogno C, Galassi P, D'Andrea G, Castello G, Pirritano D. Lifestyle in patients with LUTS suggestive of BPH. Eur Urol. 2001;40:19–12.

45. Rohrmann S, Crespo CJ, Weber JR, Smit E, Giovannucci E, Platz EA. Association of cigarette smoking, alcohol consumption and physical activity with lower urinary tract symptoms in older American men: findings from the third National Health And Nutrition Examination Survey. BJU Int. 2005;96(1):77–82.

46. Roberts RO, Tsukamoto T, Kumamoto Y, Rhodes T, Masumori N, Miyake H, Girman CJ, Jacobsen SJ, Lieber MM. Association between cigarette smoking and prostatism in a Japanese community. Prostate. 1997;30(3):154–9.

47. Shaarawy M, Mahmoud KZ. Endocrine profile and semen characteristics in male smokers. Fertil Steril. 1982;38(2):255–7.

48. Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, Deanfield JE. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation. 1993;88(5 Pt 1):2149–55.

49. Huang YC, Chin CC, Chen CS, Shindel AW, Ho DR, Lin CS, Shi CS. Chronic cigarette smoking impairs erectile function through increased oxidative stress and apoptosis, decreased nNOS, endothelial and smooth muscle contents in a rat model. PLoS ONE. 2015;10(10): e0140728.

50. Maserejian NN, Kupelian V, Miyasato G, McVary KT, McKinlay JB. Are physical activity, smoking and alcohol consumption associated with lower urinary tract symptoms in men or women? Results from a population based observational study. J Urol. 2012;188(2):490–5.

51. Knuutinen A, Kokkonen N, Risteli J, Vähäkangas K, Kallioinen M, Salo T, Sorsa T, Oikarinen A. Smoking affects collagen synthesis and extracellular matrix turnover in human skin. Br J Dermatol. 2002;146(4):588–94.

52. van de Borne P, Mark AL, Montano N, Mion D, Somers VK. Effects of alcohol on sympathetic activity, hemodynamics, and chemoreflex sensitivity. Hypertension. 1997;29(6):1278–83.

53. Marshall LM, Holton KF, Parsons JK, Lapidus JA, Ramsey K, Barrett-Connor E. Lifestyle and health factors associated with progressing and remitting trajectories of untreated lower urinary tract symptoms among elderly men. Prostate Cancer Prostatic Dis. 2014;17(3):265–72.

54. Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F, D'Armiento M, Giugliano D. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA. 2004;291(24):2978–84.

55. Mondul AM, Giovannucci E, Platz EA. A prospective study of physical activity, sedentary behavior, and incidence and progression of lower urinary tract symptoms. J Gen Intern Med. 2020;35(8):2281–8.

56. Platz EA, Kawachi I, Rimm EB, Colditz GA, Stampfer MJ, Willett WC, Giovannucci E. Physical activity and benign prostatic hyperplasia. Arch Intern Med. 1998;158(21):2349–56.

57. Boef AG, Dekkers OM, le Cessie S. Mendelian randomization studies: a review of the approaches used and the quality of reporting. Int J Epidemiol. 2015;44(2):496–511.

58. Chen X, Hong X, Gao W, Luo S, Cai J, Liu G, Huang Y. Causal relationship between physical activity, leisure sedentary behaviors and COVID-19 risk: a Mendelian randomization study. J Transl Med. 2022;20(1):216.

59. Xiong J, Yang L, Deng YQ, Yan SY, Gu JM, Li BH, Zi H, Ming DJ, Zeng XT, Wang YB. The causal association between smoking, alcohol consumption and risk of bladder cancer: a univariable and multivariable Mendelian randomization study. Int J Cancer. 2022;151(12):2136–2143.

60. Wu L, Li BH, Wang YY, Wang CY, Zi H, Weng H, Huang Q, Zhu YJ, Zeng XT. Periodontal disease and risk of benign prostate hyperplasia: a cross-sectional study. Mil Med Res. 2019;6(1):34.

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