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Association Between Obstructive Sleep Apnea and Prostate Cancer: NHANES and the Mendelian Randomization Study

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Background: Obstructive sleep apnea is a common condition worldwide, and prostate cancer is the most prevalent cancer among men. However, the link between OSA and prostate cancer remains unclear. This study aims to explore the relationship between OSA and prostate cancer.

Methods: Initially, a multivariable regression analysis was conducted to control for potential confounders and assess the impact of OSA on the risk of developing prostate cancer. Subsequently, age-stratified analyses were performed to further investigate the relationship between OSA and prostate cancer across different age groups. Finally, Mendelian randomization was employed to evaluate the causal relationship between OSA and prostate cancer risk.

Results: The multivariable regression analysis of the NHANES data showed no significant association between OSA and prostate cancer after controlling for age, smoking habits, hypertension, diabetes, cardiovascular diseases, stroke, alcohol consumption, body mass index (OR = 0.83; 95% CI: 0.46–1.48; p = 0.49). However, age-stratified analysis revealed a significant negative correlation between OSA and prostate cancer in the younger population (<60 years) (OR = 0.07; 95% CI: 0.01–0.74; p = 0.03), whereas no significant association was found in the elderly population (≥60 years) (OR = 1.01; 95% CI: 0.69–1.49; p = 0.96). Finally, our Mendelian randomization results did not find a causal relationship between OSA and prostate cancer (OR = 0.992; 95% CI: 0.876–1.124; p = 0.906).

Conclusion: The findings indicate that while there is no significant association between OSA and prostate cancer in the overall analysis, a significant negative correlation exists in the younger population. The lack of significant association in the Mendelian randomization analysis may be due to the inability to perform age stratification. Further prospective studies and mechanistic research are needed to better understand the biological mechanisms underlying this association.

Keywords: obstructive sleep apnea, prostate cancer, national health and nutrition examination survey, mendelian randomization

Introduction

Prostate cancer is the most prevalent cancer among men. The etiology of prostate cancer is multifactorial, involving genetic, environmental, and lifestyle factors.[1] Obstructive sleep apnea (OSA) is a prevalent condition worldwide, affecting over 4% of men and 2% of women, characterized by recurrent partial or complete upper airway obstruction during sleep. This condition is associated with various adverse health outcomes, including cardiovascular diseases, and metabolic disorders.[2,3]

Several studies have investigated the potential link between OSA and cancer, suggesting that one of the key features of OSA—intermittent hypoxia—might promote tumor progression and metastasis through mechanisms such as increased angiogenesis, oxidative stress, and inflammation.[4,5] However, the relationship between OSA and prostate cancer remains unclear, with conflicting results reported in the literature. Fang et al indicated that, based on data from the National Health Insurance database in Taiwan, the risk of prostate cancer in patients with obstructive sleep apnea is significantly

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higher than that in the control group.[6] In contrast to Fang et al, Wu et al's study found no significant impact of obstructive sleep apnea on the risk of prostate cancer.[7] Conversely, in a nationwide large health insurance database, OSA appeared to increase the risk of only a few cancer types, including pancreatic cancer, kidney cancer, and melanoma, while the risk of prostate cancer was lower among OSA patients.[8]

The National Health and Nutrition Examination Survey (NHANES) provides valuable datasets for epidemiological studies, offering comprehensive health information representative of the US population. Utilizing the NHANES database, we aim to investigate the association between OSA and prostate cancer, employing multivariate regression analysis to adjust for potential confounding factors. Additionally, we seek to explore the impact of stratifying this relationship by different factors.

To complement the observational findings from NHANES, we employ Mendelian Randomization (MR) as an analytical method. MR uses genetic variations as instrumental variables to infer causal relationships between exposures and outcomes, thereby reducing the likelihood of confounding and reverse causality.[9]

Therefore, to explore the relationship between the two, we analyzed data from the NHANES database spanning from 2001 to 2010. Additionally, to determine if there is a causal relationship, we conducted a two-sample Mendelian Randomization analysis.

Materials and Methods

Study Population in NHANES

NHANES is a cross-sectional survey that has been updated and released every two years since 1999, employing a rigorous, stratified, multistage probability sampling design to ensure national representativeness. In the current observational study, we used data from the NHANES 2001–2010 cycles, spanning five survey periods. Detailed inclusion and exclusion criteria are provided in Figure 1.

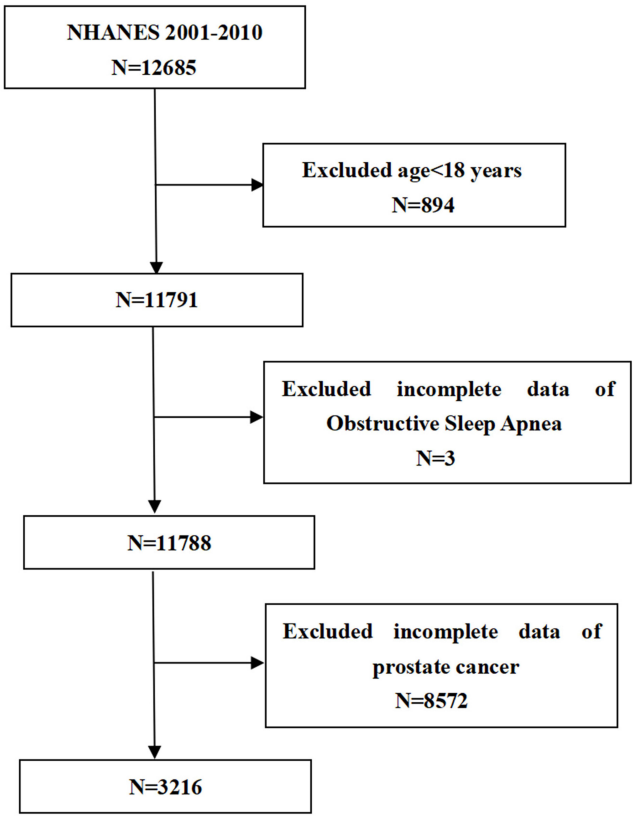

Figure 1 Flowchart of NHANES.

Exposure and Outcome Definitions

In this study, OSA was used as the exposure variable. The presence of obstructive sleep apnea symptoms was determined using answers to three yes/no questions: (1) frequent snoring (three or more nights weekly); (2) episodes of snorting, gasping, or breath stopping (three or more nights weekly); and (3) excessive daytime sleepiness occurring 16–30 times a month despite sleeping at least seven hours on average during weekdays or work nights. Participants who reported any of these symptoms were considered to have OSA. The identification of prostate cancer was based on responses to a single question: "Have you ever been told by a doctor or health professional that you have prostate cancer?"

Covariates

The multivariable-adjusted models encompassed a summary of the potential covariates that could introduce confounding factors into the relationship between OSA and prostate cancer. The covariates included age (years), smoking status (never/former/current), hypertension, diabetes, cardiovascular disease (CVD), stroke, alcohol intake (never/former/mild/moderate/heavy), body mass index. Comprehensive information regarding the measurement procedures for the study variables can be accessed publicly at www.cdc.gov/nchs/nhanes/.

Assumptions and Data Sources of Two-Sample MR

In Mendelian Randomization (MR) studies, it is critical that the instrumental variables (IVs) used meet three criteria: (1) they must be strongly associated with OSA, (2) they should not relate to any confounders between the exposure and the outcome, and (3) they must affect prostate cancer only through their interaction with the exposure.[10] We sourced the genetic instruments for OSA from FinnGen's latest release 10 (https://r10.fnngen.fi/), with data including 43,901 cases and 366,484 controls. We obtained genetic data on prostate cancer from the PRACTICAL Consortium (https://gwas.mrcieu.ac.uk/), which conducted a large study including 79,148 cases and 61,106 controls of European ancestry, ultimately including 20,346,368 SNPs.[11]

Selection of Genetic Instruments

In our study, we selected single-nucleotide polymorphisms (SNPs) that showed a robust correlation with obstructive sleep apnea (OSA) to serve as instrumental variables (IVs), applying a significance threshold of $p < 5x10^{-8}$. To ensure the independence of these SNPs, linkage disequilibrium (LD) clumping was conducted. This involved identifying SNPs with r^2 less than 0.01 and at least 50,00 kb apart. SNPs that were palindromic were excluded, and harmonization was achieved between alleles affecting the exposure and outcome in our datasets. Additionally, we utilized the Phenoscanner database (http://www.phenoscanner.medschl.cam.ac.uk/) to remove any SNPs that exhibited pleiotropic effects, thereby addressing potential confounders in the exposure-outcome relationship.

Statistical Analysis

Cross-Sectional Study

We applied the NHANES sampling weights to address the intricacies of the complex multistage cluster survey design according to CDC protocol. Odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship between obstructive sleep apnea (OSA) and prostate cancer were estimated using two distinct multivariable logistic regression models. The first model did not adjust for any covariates, and the second model included adjustments for age, smoking habits, hypertension, diabetes, cardiovascular diseases, stroke, alcohol consumption and body mass index. We also conducted a subgroup analysis using stratified multivariate regression, which considered a range of demographic and health-related factors. An interaction term was used to examine the variability in associations across different subgroups using the log-likelihood ratio test model. Statistical significance was determined using a p-value of 0.05. All statistical analyses and graphical representations were performed using Stata version 17 and R version 4.3.1.

MR

Our Mendelian randomization study used a variety of research methods, including the inverse variance weighting (IVW) method, MR-Egger, weighted median, and MR-Pleiotropy residuals and outliers (MR-PRESSO) test. IVW is used as the predominant analytical method used to verify causality because of its robust causal estimation, which is chosen as the primary method for all

Mendelian randomization.[12] We used MR-Egger regression and weighted medians to enhance the credibility of the IVW results.[13,14] In addition to this, we used the Cochran Q test to test for the presence of heterogeneity in the selected SNPs and the MR-Egger intercept to test for the presence of horizontal pleiotropy.[15,16] The MR-PRESSO test provides a comprehensive assessment of heterogeneity to identify potential outliers in the SNP data in order to exclude these outliers from distorting the results.[17]

BWMR is an efficient statistical method for causal inference based on summary statistics. To address the prevalence of polygenic structure as well as pleiotropy, we adopted Bayesian-weighted Mendelian randomization (BWMR) to remove the uncertainty associated with weak effects as well as pleiotropy for the purpose of enhancing the robustness of IVW results.[18]

All statistical analyses were conducted using the"Two Sample M" package (version 0.5.6) in R software (version 4.3.1).

Results

Baseline Characteristics of Participants

Table 1 shows the participants' baseline demographic characteristics. A total of 3216 participants were enrolled in our study. The average age of the participants was 56.35 ± 0.38 years. The overall mean incidence of prostate cancer was

Table 1 Baseline Characteristics of Participants

	Overall	Without OSA[f]	With OSA	p value
Age (years)	56.35(0.38)	57.33(0.50)	54.51(0.40)	< 0.0001
Age (years)				< 0.0001
<60	64.79	61.1	71.73	
≥60	35.21	38.9	28.27	
Prostate cancer (%)				0.02
No	96.72	96.3	97.51	
Yes	3.28	3.7	2.49	
Smoke (%)				0.93
Never	40.53	40.73	40.2	
Former	36.9	36.61	37.46	
Current	22.54	22.66	22.34	
Hypertension (%)				0.15
No	50.64	52	48.11	
Yes	49.36	48	51.89	
Diabetes (%)				0.38
No	69.7	74.38	71.64	
DM[a]	18.22	18.34	20.77	
IFG[b]	7.01	7.28	7.59	
CVD[c](%)				0.67
No	85.36	85.14	85.78	
Yes	14.64	14.86	14.22	
Stroke (%)				0.65
No	95.47	95.99	95.62	
Yes	4.12	4.01	4.38	
Alcohol (%)				0.17
Never[d]	5.63	6.83	4.18	
Former[d]	21.16	21.44	23.53	
Mild[d]	42.25	43.34	46.03	
Moderate[d]	11.18	12.44	10.4	
Heavy[d]	15.19	15.95	15.86	
BMI[e]	29.08(0.16)	28.31(0.14)	30.53(0.32)	< 0.0001

Notes: The survey-weighted mean (standard deviation) was used for continuous variables. For categorical variables, the survey weighted percentages. [a]Diabetes mellitus. [b]Impaired Fasting Glycaemia.[c]Cardiovascular disease. [d]Never corresponds to <12 drinks in lifetime; Former corresponds to ≥12 drinks in 1 year and did not drink last year, or did not drink last year but drank ≥12 drinks in lifetime; Mild corresponds to 2 drinks/day; Moderate corresponds to 3 drinks/day; Heavy corresponds to 4 drinks/day [e]Body mass index; units are kg/m^2. [f]Obstructive Sleep Apnea.

Table 2 Association of Obstructive Sleep Apnea with Prostate Cancer

	OR (95% CI), p value	
	Model 1[a] (n =3216)	**Model 2[b] (n =3216)**
Prostate cancer OSA[c]		
Without	Reference	Reference
With	0.66(0.47,0.93) 0.02	0.83(0.46,1.48) 0.49

Notes: aModel 1: No covariates were adjusted. bModel 2: Adjusted for age, smoking status, hypertension, diabetes, alcohol intake, stroke, cardiovascular disease, body mass index. [c]Obstructive Sleep Apnea.

3.28%, and varying rates of prostate cancer were based on the presence of OSA. (prostate cancer: 3.7% without OSA and 2.49% With OSA; p = 0.02).

NHANES of Obstructive Sleep Apnea and Prostate Cancer

In Model 1, which did not include any adjustments for variables, there was a negative link between obstructive sleep apnea (OSA) and prostate cancer (OR = 0.66; 95% CI: 0.47–0.93; p=0.02). However, in Model 2, after adjusting for age, smoking habits, hypertension, diabetes, cardiovascular diseases, stroke, alcohol consumption, and body mass index, no significant association was found between OSA and prostate cancer (OR = 0.83; 95% CI: 0.46–1.48; p = 0.49) (Table 2).

Subgroup Analysis

A subgroup analysis was conducted to assess the strength of the relationship between OSA and prostate cancer (Figure 2). We detected interactions between age, smoking habits, hypertension, diabetes, cardiovascular diseases, stroke,

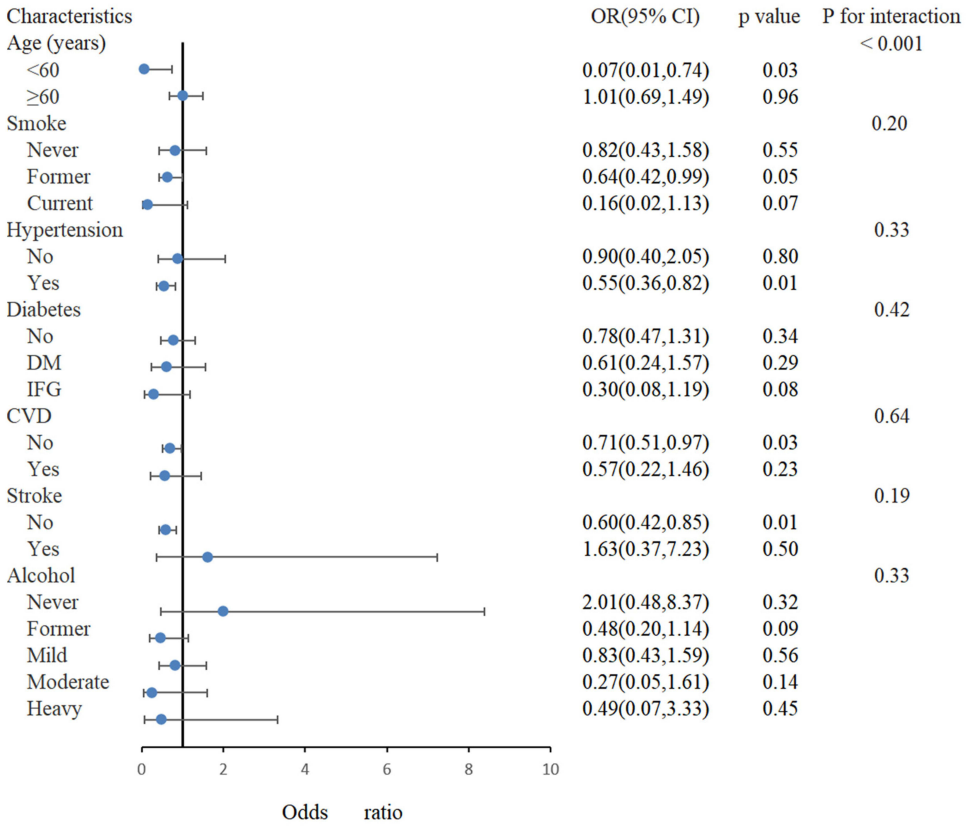

Figure 2 Subgroup analysis (forest plots).

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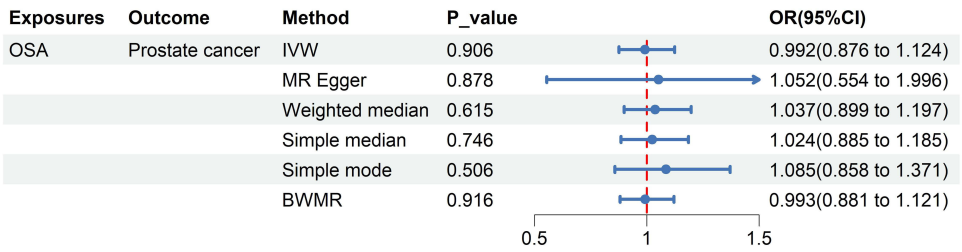

Figure 3 Causal relationship between Obstructive sleep apnea with prostate cancer.

and alcohol consumption. The age-stratified analysis revealed a significant negative correlation between OSA and prostate cancer in the younger population (OR = 0.07; 95% CI: 0.01–0.74; p = 0.03), whereas no significant association was found in the elderly population (OR = 1.01; 95% CI: 0.69–1.49; p = 0.96). No statistically significant correlation with the p-value for interaction was observed, suggesting that there was no dependency on factors such as smoking habits, hypertension, diabetes, cardiovascular diseases, stroke, and alcohol consumption (p for interaction >0.05).

Results of Two-Sample MR Analysis

We rigorously screened all data and the final genetic instrumental variables included in the analyses had F-values greater than 10, indicating that the genetic instrumental variables of OSA are less likely to be affected by bias from weak instrumental variables. Subsequently, a selected set of SNPs was used as genetic instrumental variables in Mendelian randomization (MR) studies, as detailed in Supplementary Table 1. We did not observe a significant causal relationship between OSA and prostate cancer (OR = 0.992; 95% CI: 0.876–1.124; p = 0.906) and the results of our Bayesian Mendelian randomization analysis remained consistent (OR = 0.993; 95% CI: 0.881–1.121; p = 0.916). The results of the analyses for all methods can be found in Figure 3. Although our Cochran's Q statistic showed presence of heterogeneity, both MR-Pleiotropy residuals as well as MR-PRESSO suggested the absence of horizontal pleiotropy, as shown in Table 3. Scatter plots, leave-one-out plots, forest plots and funnel plots pertinent to MR are available in Figures 4–7.

Discussion

This study used the NHANES database to explore the relationship between OSA and prostate cancer. Multivariable regression analysis showed no significant association between OSA and prostate cancer after controlling for confounders. However, age-stratified analysis revealed a negative correlation between OSA and prostate cancer in individuals under 60, while no significant relationship was found in those over 60. The lack of significant association in the Mendelian randomization analysis may be due to the inability to perform age stratification. These findings offer new insights into the OSA-prostate cancer connection.

Intermittent hypoxia (IH) is a core feature of obstructive sleep apnea (OSA) in clinical pathophysiology. Chronic cyclical severe hypoxia (30–90 seconds) is considered a primary mechanism leading to the adverse systemic outcomes of OSA. Intermittent hypoxia (IH) can induce the production of hypoxia-inducible factor-1α (HIF-1α), which plays a crucial role in tumor metastasis and angiogenesis. The overexpression of HIF-1α in prostate cancer cells further suggests a potential link between obstructive sleep apnea (OSA) and prostate cancer.[19,20] In addition, chronic hypoxic conditions are also involved in the early development of prostate cancer, playing a key role in tumor proliferation and hormone-refractory progression.[21–24]

Table 3 Heterogeneity and Pleiotropy Test

Exposure	Heterogeneity Test			Pleiotropy Test			MR-PRESSO
	Q	*df*	Q-pval	Egger-Intercept	SE	p-value	p-value
Obstructive Sleep Apnea	28.132	17	0.043	0.003	0.016	0.857	0.908

Notes: Q, Cochrane's heterogeneity statistic; *df*, degrees of freedom.

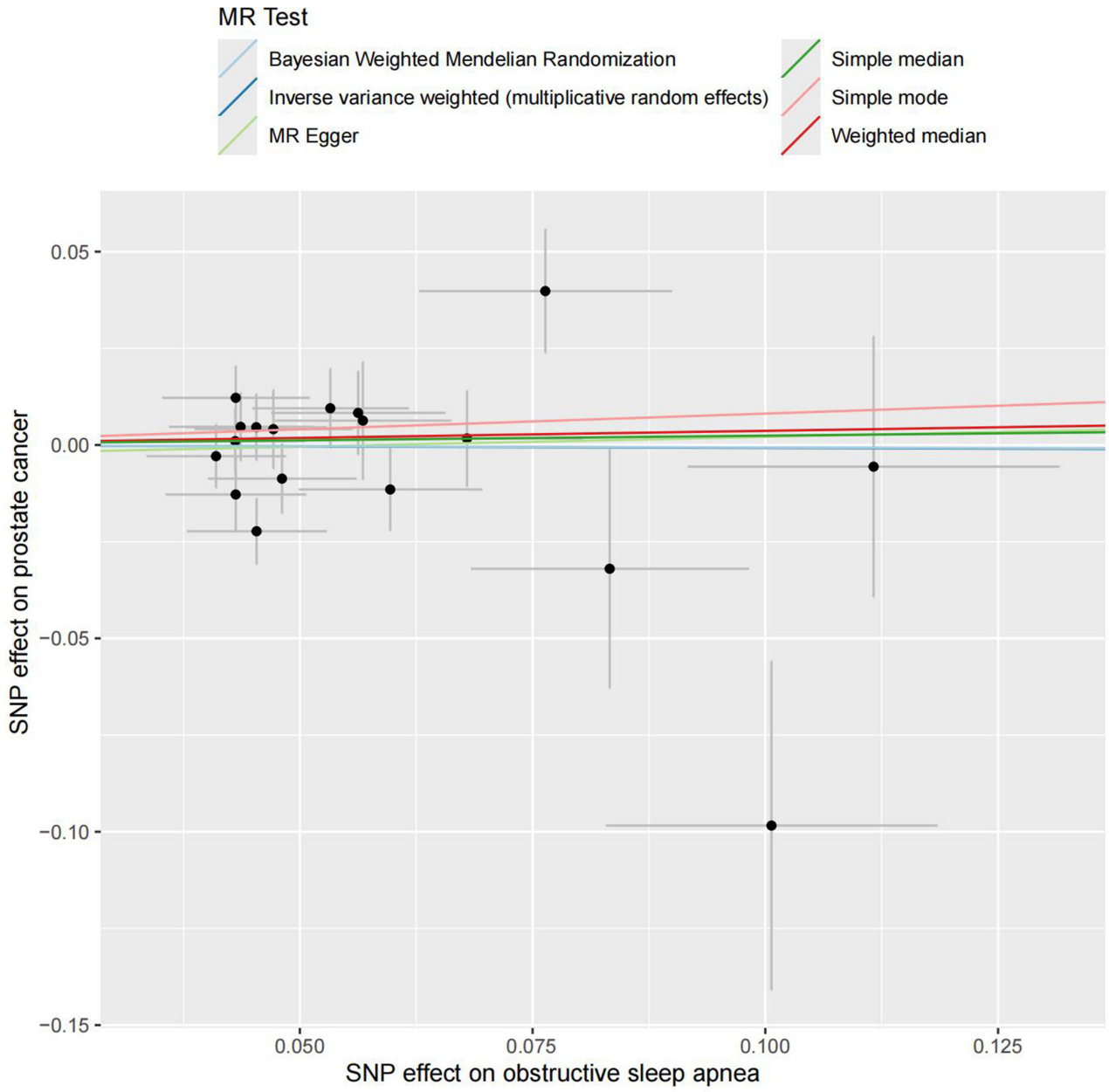

Figure 4 The scatter plot for MR analyses of causal associations between obstructive sleep apnea SNPs and prostate cancer.

The desaturation-reoxygenation sequence results in oxidative stress and the production of reactive oxygen species (ROS).[25] Elevated ROS levels lead to increased expression of adhesion molecules,[26] leukocyte activation,[27] and systemic inflammation.[28] Oxidative stress, systemic inflammation, and sympathetic activation underlie the significant cardiovascular and metabolic complications in OSA. Thus, OSA should be regarded as a systemic disease, with IH causing detrimental effects throughout the organism.

However, some arguments suggest that hypoxia exposure may also lead to beneficial adaptations in the body, protecting it from various pathological conditions. For decades, athletes have used hypoxic training as a strategy to enhance performance, with methods and techniques becoming increasingly sophisticated.[29] Interestingly, epidemiological data indicate that living at moderate altitudes may be associated with lower obesity rates.[30–32] Although IH is generally considered harmful in OSA, some findings suggest that moderate OSA might offer protection against ischemia-reperfusion events.[33,34] In this context, IH could enhance the number and function of endothelial progenitor cells,

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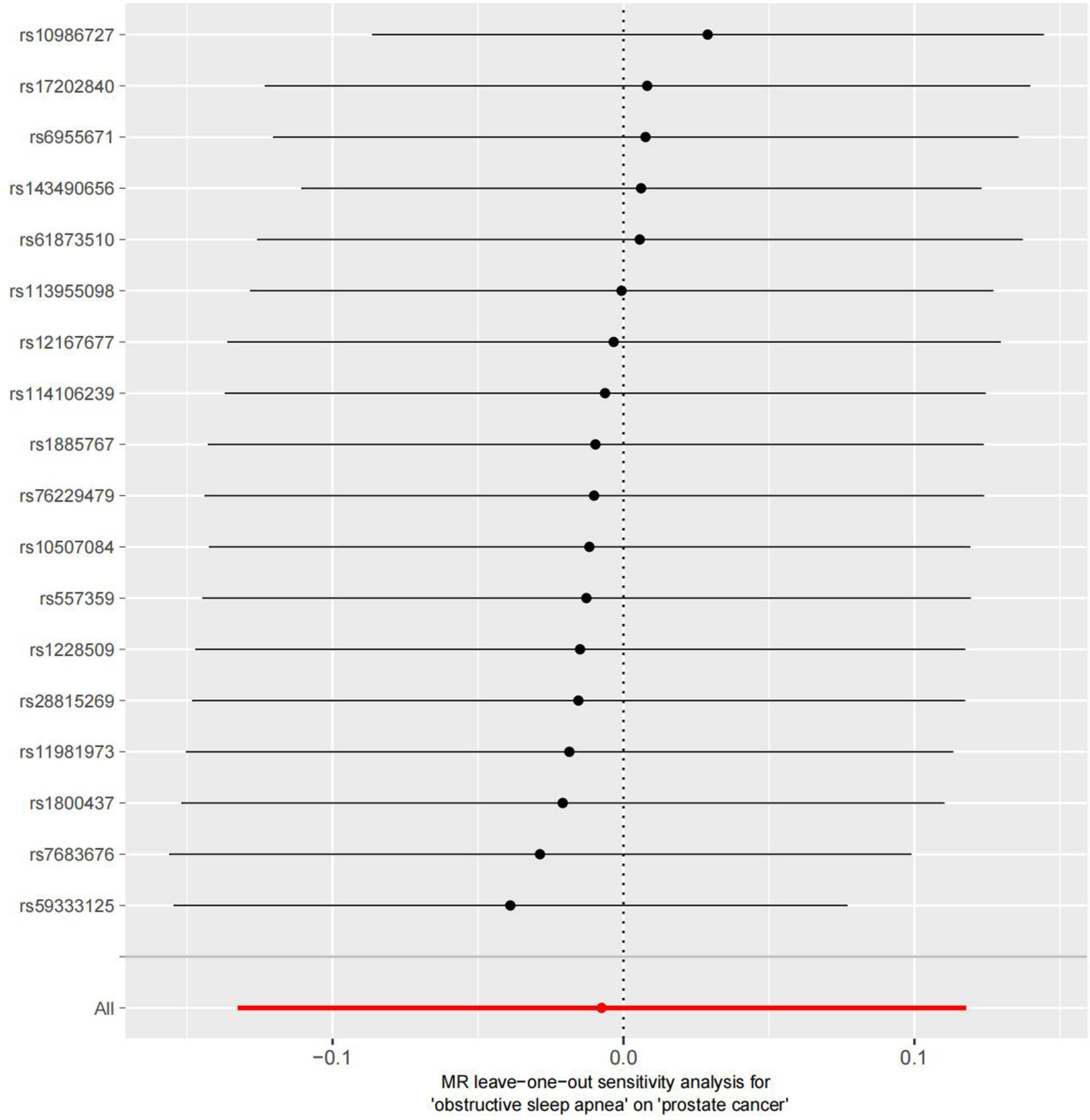

Figure 5 Leave-one-out sensitivity analysis for prostate cancer using SNPs associated obstructive sleep apnea.

promoting angiogenesis and coronary collateral vessels.[35] These factors could potentially reduce the incidence of prostate cancer.

In elderly men, the ratio of estrogen to androgen increases significantly parallel to the decrease in testosterone (T) levels.[36] Recent studies suggest that not only low T levels but also an increase in estrogen may promote the progression of prostate cancer.[37] This may obscure age-specific associations observed in younger populations. Specifically, age-related hormonal differences may play an important role: younger men typically have higher levels of testosterone and dihydrotestosterone, and endocrine alterations related to OSA at this stage may not exert strong pro-carcinogenic effects.[38] In addition, younger individuals generally have fewer comorbidities and more active immune surveillance, which may counteract some of the tumor-promoting effects of intermittent hypoxia. By contrast, older men are more

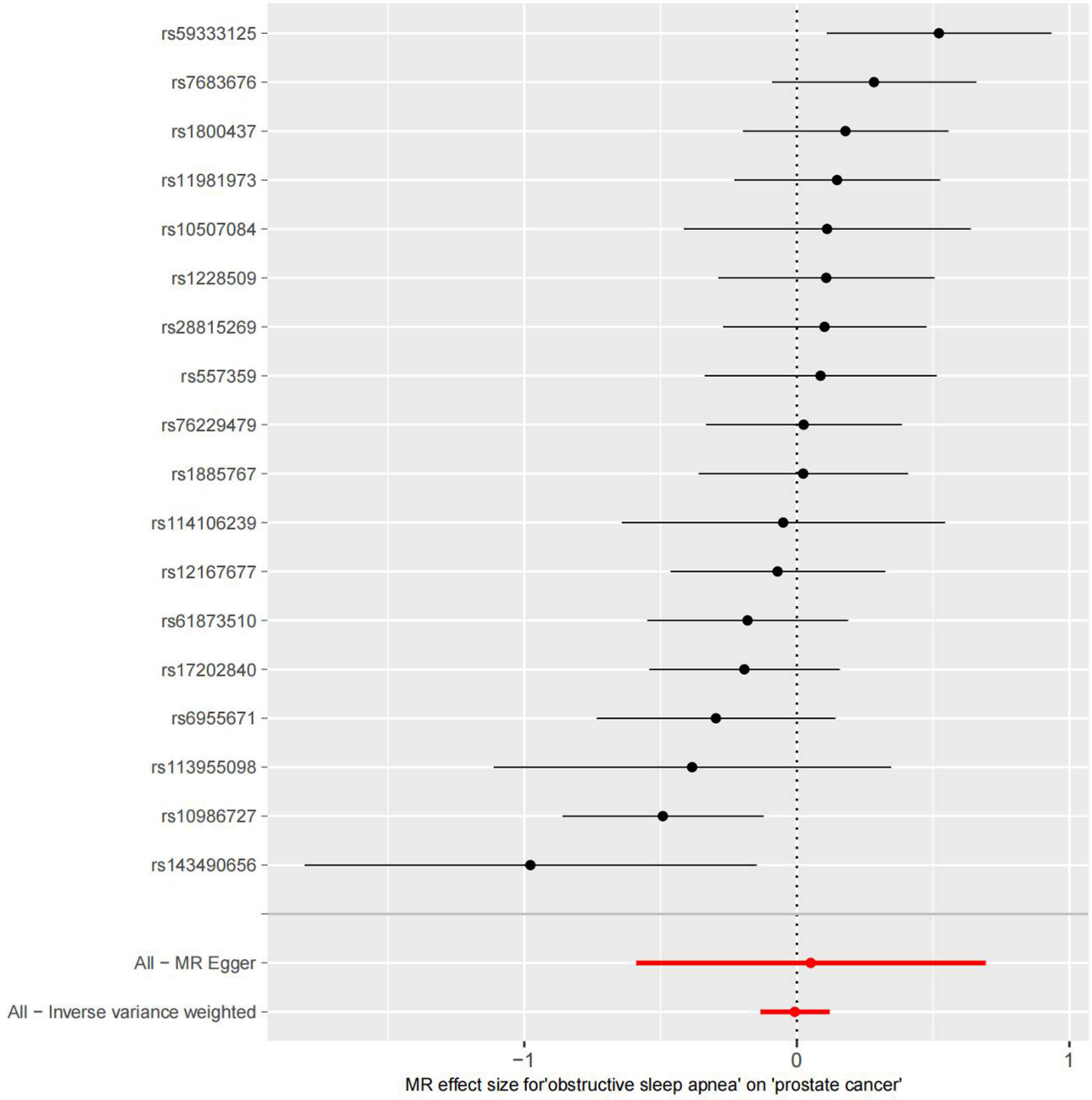

Figure 6 The forest plots for MR analyses of causal associations between obstructive sleep apnea SNPs and prostate cancer.

susceptible to immunosenescence, and the cumulative burden of hypoxia and oxidative stress may amplify cancer risk.[39,40] Furthermore, the higher prevalence of comorbidities and metabolic dysfunction in older populations could further contribute to cancer development.[41] These mechanisms provide a plausible biological explanation for the observed age-specific associations.

Compared to the findings of Fang et al, who reported a significantly higher risk of prostate cancer in OSA patients based on data from the Taiwan National Health Insurance Database,[6] this may be due to the lack of adjustment for certain confounding factors in their study. In contrast, our overall results align with Wu et al, who found no significant impact of OSA on prostate cancer.[7] This discrepancy might be due to the lack of age-stratified analysis in their study. When we stratified by age, we discovered a negative correlation between OSA and prostate cancer in individuals under 60, consistent with findings from a large, nationally representative health insurance database.[8]

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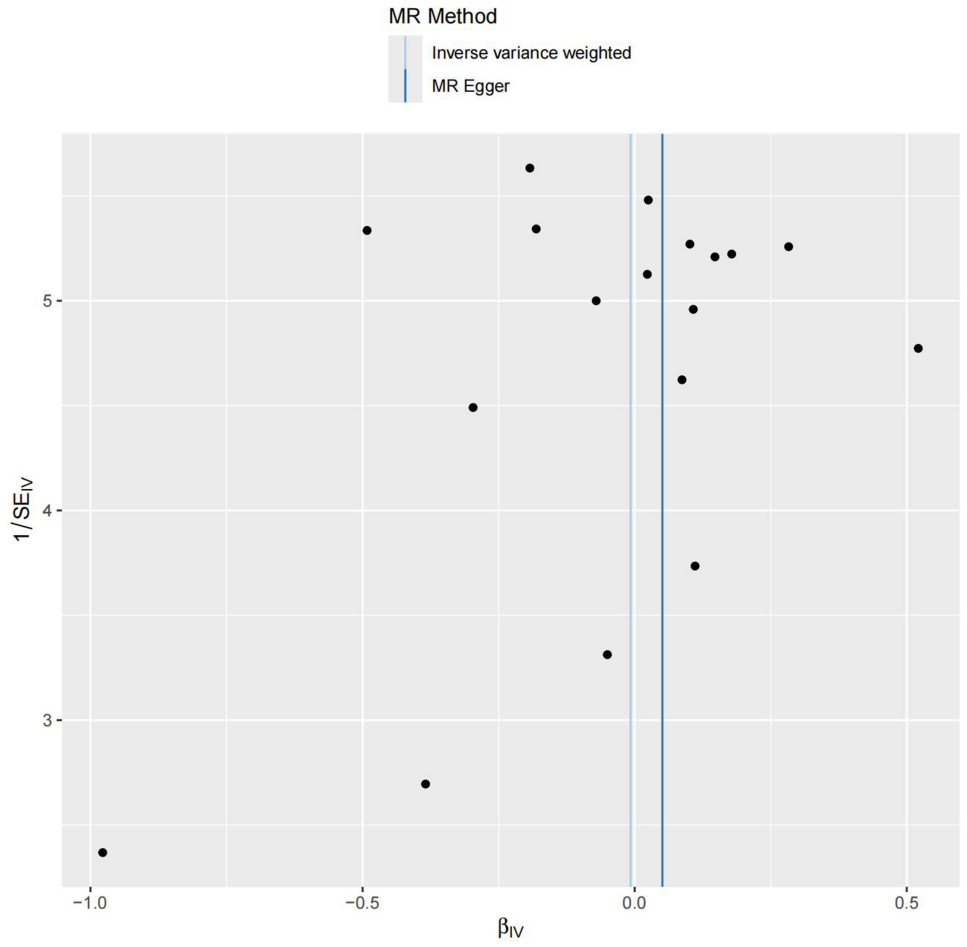

Figure 7 The funnel plot for MR analyses of causal associations between obstructive sleep apnea SNPs and prostate cancer.

Although our MR analyses did not provide evidence for a causal relationship, these null findings are still clinically informative. They suggest that the associations observed in previous observational studies may be due to confounding or bias rather than a direct causal link, and therefore should be interpreted with caution in clinical practice. Further large-scale and well-designed studies are warranted before firm clinical recommendations can be made.

This study has several strengths: First, it utilizes the nationally representative NHANES data, providing a large sample size and good external validity. Second, it employs Mendelian Randomization to systematically explore the relationship between OSA and prostate cancer, offering more robust causal inferences. However, there are limitations: The cross-sectional design limits causal determination, and despite Mendelian Randomization, statistical power constraints remain, such as the inability to perform age stratification. NHANES data reliance on self-reporting introduces potential bias, future studies incorporating objective diagnostic approaches are warranted to validate and strengthen our findings. Future GWAS using objectively defined OSA phenotypes based on polysomnography could provide more accurate and reliable insights into the genetic architecture of the disorder. This study is based on cross-sectional prevalence data and lacks stratification by OSA severity, which may introduce selection bias. Future studies using longitudinal incidence data and incorporating OSA severity will help to better elucidate the age- and severity-dependent associations between OSA and prostate cancer. Additionally, small subgroup sample sizes in stratified analyses may affect the stability and reliability of statistical results.

Conclusion

The findings indicate that while there is no significant association between OSA and prostate cancer in the overall analysis, a significant negative correlation exists in the younger population. This suggests that age may play a crucial moderating role in

the relationship between OSA and prostate cancer. The lack of significant association in the Mendelian randomization analysis may be due to the inability to perform age stratification. Further prospective studies and mechanistic research are needed to better understand the biological mechanisms underlying this association.

Data Sharing Statement

This study utilized publicly available datasets for analysis. The original contributions made to the research are outlined in the article/Supplementary material; for additional inquiries, please contact the corresponding author.

Ethics Approval

The Ethics Committee of the affiliated hospital of North Sichuan Medical College strictly adheres to the Declaration of Helsinki and the International Ethical Guidelines for Health-related Research Involving Humans, performing independent ethical review responsibilities. This study uses legally obtained publicly available data, meeting the conditions for exemption from review as stated in the Ethical Review Methods for Life Sciences and Medical Research Involving Humans.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no relevant conflicts of interest for this work.

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