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ABOUT COVER

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Basic Study

Diabetes mellitus and prostate cancer risk: A mendelian randomization analysis

Jian-Xu Yuan, Qing Jiang, Sheng-Jie Yu

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Abstract

BACKGROUND

Some studies have directed towards an association between diabetes mellitus (DM) and prostate cancer (PCa); however, this specific relationship remains inconclusive. In recent years, Mendelian randomization (MR) has become a widely used analytical method for inferring epidemiological causes.

AIM

To investigate the potential relationship between DM and PCa using MR.

METHODS

We downloaded relevant data on "diabetes" and "PCa" from the IEU OpenGWAS project database, performed three different methods to conduct MR, and carried out sensitivity analysis for verification.

RESULTS

The results indicated that DM was an independent risk factor for PCa. The odds ratio (OR) values obtained using the inverse variance weighted method in this study were as follows: OR = 1.018 (95% confidence interval: 1.004-1.032), $P = 0.014$.

CONCLUSION

We found that DM could increase the incidence rate of PCa.

Key Words: Prostate cancer; Diabetes mellitus; Mendelian randomization analysis; Risk factors; Genome-wide association study

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Core Tip: Diabetes mellitus (DM) is a chronic metabolic disease caused by many factors. Prostate cancer (PCa) is a common malignant tumor in men and is the second leading cause of cancer death. The Mendelian randomization (MR) method uses genetic variation as an instrumental variable to detect and quantify causal relationships, which can avoid the impact of confounding factors on the accuracy of the research results. This makes it more reliable than observational study or even randomized controlled trial. This study aimed to clarify the relationship between DM and PCa using MR analysis. Through MR analysis of a large sample with three different methods, this study found that DM was an independent risk factor for PCa, providing new directions for the prevention and treatment of PCa.

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INTRODUCTION

Diabetes mellitus (DM) is a major chronic disease worldwide, causing huge burden and harm to patients and their families[1,2]. Currently, prevention is the primary treatment for DM. Its occurrence and development are related to many factors such as diet, lifestyle, and environment[3-5]. Prostate cancer (PCa) is one of the most common cancers worldwide and the second most common cancer in men[6]. In recent years, the diagnostic and treatment modalities for PCa have greatly improved. However, its incidence rate is steadily increasing, and the age of onset has been decreasing[7]. Currently, the recognized high-risk factors for PCa include age, family history, and ethnic background[8]. Some exogenous factors (such as obesity, diabetes, metabolic syndrome, and dietary factors) are also reportedly associated with PCa; however, this remains inconclusive[9,10]. Given the huge burden of PCa on human health, it is important to identify relevant high-risk factors for its prevention and treatment. This study aimed to investigate the effects of DM on PCa.

Mendelian randomization (MR) is a data analysis method that has been widely used in inferring epidemiological etiology in recent years. It can strengthen causal inference using genetic variation as an instrumental variable (IV). This analysis method is based on the Mendelian inheritance law, so the association between genes and diseases is free from the interference of the postpartum environment, socioeconomic status, behavioral factors, and other common confounding factors, and the resulting causal sequence is reasonable and closer to a real situation[11]. This research method is conceptually similar to a randomized controlled study in which genetic variations are randomly assigned during gamete formation before being interfered with by any confounding factors and are evenly distributed within the population. Alleles are fixed among individuals and do not change with disease occurrence or development. Therefore, the causal inference obtained from MR is not easily affected by residual confounding factors or reverse causality[12-14]. In this study, we obtained sufficient genome-wide association study (GWAS) data from relevant databases and performed a study to assess the impact of DM on PCa based on MR.

MATERIALS AND METHODS

Study design

The premise of MR analysis is that IVs must meet three preconditions: (1) Exposure correlation (correlation hypothesis); (2) no common cause with the outcome (independence assumption); and (3) outcome related only through exposure (excluding restriction assumptions). Based on these criteria, we performed MR to explore the causal relationship between DM and PCa. The entire process of the study primarily included five steps: (1) Fetching exposure factor GWAS data, (2) sifting appropriate IVs, (3) inputting the outcome GWAS data and drawing single nucleotide polymorphisms (SNPs) of the above IVs, (4) preprocessing the exposure factor and outcome GWAS data to ensure consistency in format, and (5) conducting MR and sensitivity analysis.

Data source

SNPs associated with DM were downloaded from the IEU OpenGWAS project database, using phenotype "DM" in this study. Its GWAS ID was "ukb-a-306," the sample size was 336473 and included 10894596 SNPs. The pooled data for prostate cancer was obtained from the GWAS phenotyped "PCa" (GWAS ID: ukb-a-57; sample size: 337159; SNPs' number: 10894596), which was also derived from the IEU OpenGWAS project database. The research data were open and transparent, and could be downloaded directly from relevant websites; therefore, no additional ethical declaration or consent was required.

Selection of IV

We screened SNPs under the genome-wide significance threshold ($P < 5 \times 10^{-8}$) related to exposure interest as potential SNPs, visualized the results of the correlation analysis, and generated Manhattan plots. In both graphs, the red lines represented the filtering conditions of $P < 5 \times 10^{-8}$ (Figure 1). Next, we used a clump function ($r^2 = 0.001$, kb = 10000) to

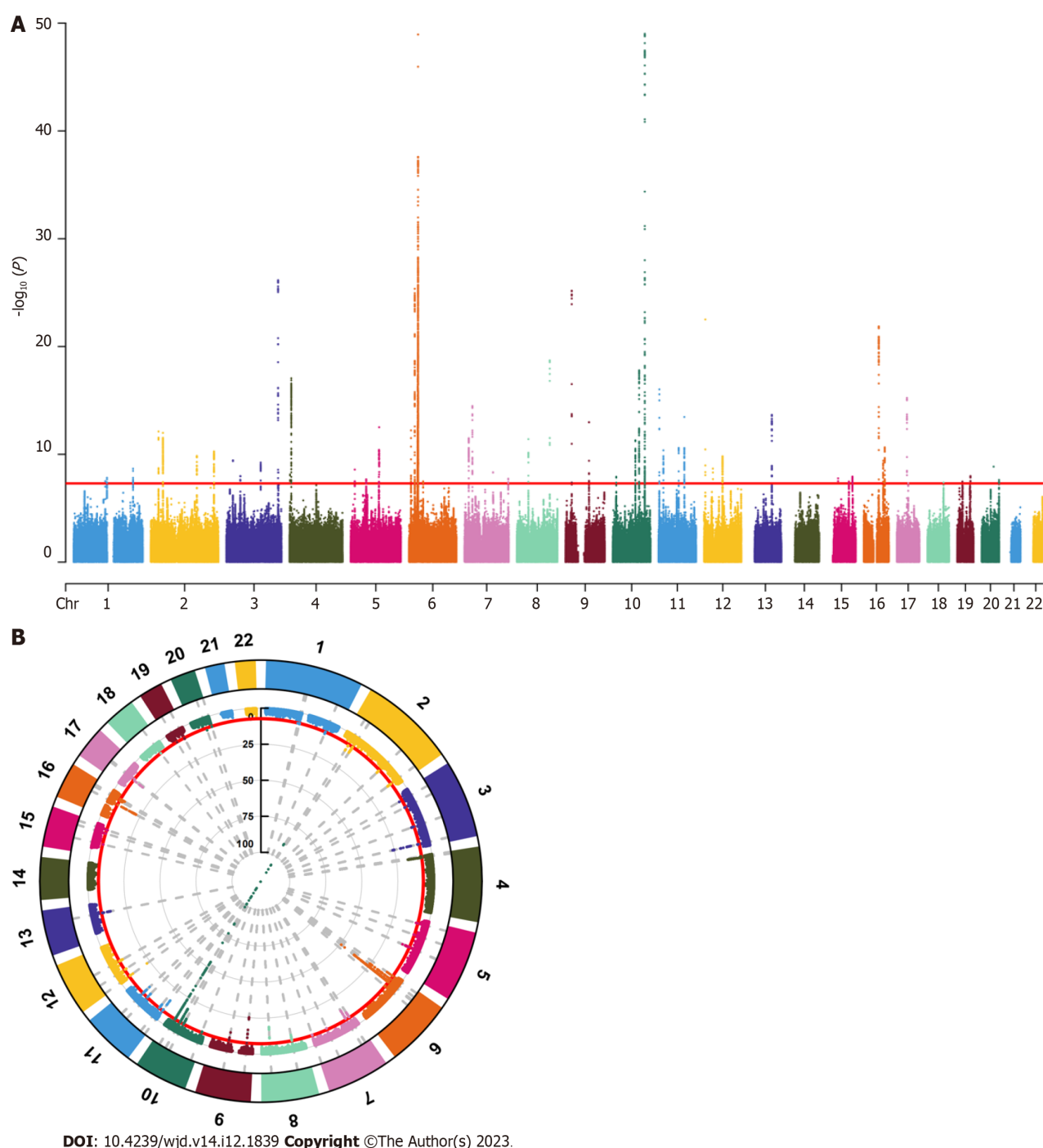


Figure 1 Selection of instrumental variables. A: Manhattan plot (line graph); B: Manhattan plot (cyclic graph). The red lines represent the filtering conditions of $P < 5 \times 10^{-8}$.

eliminate linkage disequilibrium between the selected SNPs. Further F-statistics were employed to evaluate the effect of weak IVs[15,16], when the F-statistic was less than 10, the genetic variation was considered a weak IV and might have caused bias in the research results. After removing the weak IVs, we created a comprehensive web-based genotype-phenotype association database (“phenoScanner”) to further investigate whether the remaining SNPs were related to potential risk factors for PCa, such as long-term bedridden diseases and serious diseases[17,18]. For SNPs associated with confounding factors, we conducted manual screening at the genome-wide significance level $P < 5 \times 10^{-8}$ to remove them. After obtaining the remaining SNPs, relevant adjustments were made to ensure that the impact of the IVs on exposure and outcomes corresponded to the same effector alleles. Finally, we removed SNPs with palindromic sequences whose orientation could not be determined and incompatible SNPs, and used the remaining SNPs as IVs for MR analysis.

MR analysis

To avoid the impact of potential pleiotropy, we employed three different MR methods to assess the causal effect between DM and PCa: The inverse variance weighted (IVW), weighted median, and weighted mode methods. Among them, the

result of the IVW method was considered to be the main result, as the IVW method assumed that all IVs were valid[19-21]. The results of the MR analysis were visualized as the corresponding plots.

Sensitivity analysis

To demonstrate the reliability of the results, we conducted a sensitivity analysis to evaluate pleiotropy and heterogeneity. First, Cochran's Q test was performed to detect potential heterogeneity. When $P < 0.05$, Cochran's Q statistic evaluated the heterogeneity between genetic variation and the heterogeneity that considered. The results were visualized as corresponding funnel plots. Subsequently, we performed MR-Egger intercept tests to evaluate the horizontal pleiotropy, when $P < 0.05$, there was pleiotropy in the result. If pleiotropy occurred, further analysis and identification of the source of pleiotropy were conducted through MR-PRESSO analysis. Finally, leave-one-out analysis was conducted to evaluate whether the causal relationship obtained in the study depended on or leaned towards a single SNP[22].

RESULTS

IVs

Through this screening process, we ultimately screened 49 SNPs as IVs for MR analysis. The F-statistic of all IVs was > 10 , indicating the absence of weak IVs bias (Table 1).

MR analysis

MR is a data analysis technique used in epidemiological studies to evaluate causal inferences. It uses genetic variation as the IVs in nonexperimental data to estimate the causal relationship between the exposure factors and outcomes of interest. Using the fixed nature of genes and Mendelian laws of inheritance, the MR analysis results were not affected by common confounding factors such as the postnatal environment, socio-economic factors, and behavioral habits. The causal relationship derived from MR is more reasonable and reliable.

The results of all three MR methods used for analysis revealed that DM was positively correlated with the incidence of PCa. Specifically, using the IVW method as the main analysis method, the OR values obtained in this study were $OR = 1.018$ (95%CI: 1.004-1.032), $P = 0.014$. Based on these results, we plotted corresponding scatter and forest plots (Figure 2).

Sensitivity analysis

Finally, to verify the reliability of the results further, we performed a sensitivity analysis to examine the heterogeneity and pleiotropy of our conclusions. Cochran's Q test results showed no heterogeneity in the IVs included in the study ($P > 0.05$), and the corresponding funnel plot was shown in Figure 3. MR-PRESSO analysis did not find significant pleiotropy in the conclusion nor did it screen for SNPs with outliers ($P > 0.05$). The test results of the leave-one-out method indicated that the causal relationship between DM and PCa did not depend on or lean towards any single SNP.

DISCUSSION

DM is a chronic metabolic disease caused by many factors[23,24]. Many studies indicate that the best treatment is to prevent the occurrence of diabetes by maintaining a healthy weight and increasing physical activity[25-27]. PCa is a common malignant tumor in men and is the second leading cause of cancer death[28]. Because of its inconspicuous development, most PCa patients are undiagnosed in the early stages[29]. In addition, because of the heterogeneity of tumor cells, approximately 90% of patients present with local or systemic metastasis at the time of diagnosis, losing the opportunity for radical surgery[30,31]. Therefore, early prevention of PCa and implementation of effective intervention measures are particularly important and can significantly improve patient prognosis.

The relationship between DM and PCa has long been the focus of research. Some scholars believe that DM is a protective factor for patients with PCa, whereas others believe that it is a high-risk factor for PCa. Evidence supporting both hypotheses has been reported; thus far, no conclusions have been reached. Epidemiological investigations have shown that the risk of cancer (including liver cancer, pancreatic cancer, colorectal cancer, breast cancer, and endometrial cancer) in patients with DM increases significantly, and the risk of cancer mortality also increases significantly[32]. In a 14 year cross-sectional study, Saewai *et al*[33] found that the long-term risk of PCa was significantly increased in patients with DM. Other studies have shown that obesity and DM are independent risk factors for PCa and may have synergistic effects, further increasing the risk of invasive PCa[34,35]. Another study also found that advanced PCa with DM was associated with a worse prognosis and a greater risk of metastasis[36]. Sánchez-Maldonado *et al*[37] confirmed that functional type 2 DM-related mutations may affect the risk of PCa at the genetic level. Kingshott *et al*[38] also found that DM could directly affect regulatory growth factors related to cancer, and that changing living habits might significantly reduce the risk of prostate and other cancers. Relevant research has shown that patients with DM have a higher risk of recurrence[39]. However, compared with other drugs, the use of metformin in patients with DM can significantly reduce the risk of new-onset PCa, which also proves that intervention in the development of DM has a positive impact on the prevention and treatment of PCa[40,41].

The MR method uses genetic variation as an IV to detect and quantify causal relationships, which can avoid the impact of confounding factors on the accuracy of the research results. This makes MR study more reliable than observational study or even randomized controlled trial. This study aimed to clarify the relationship between DM and PCa using MR.

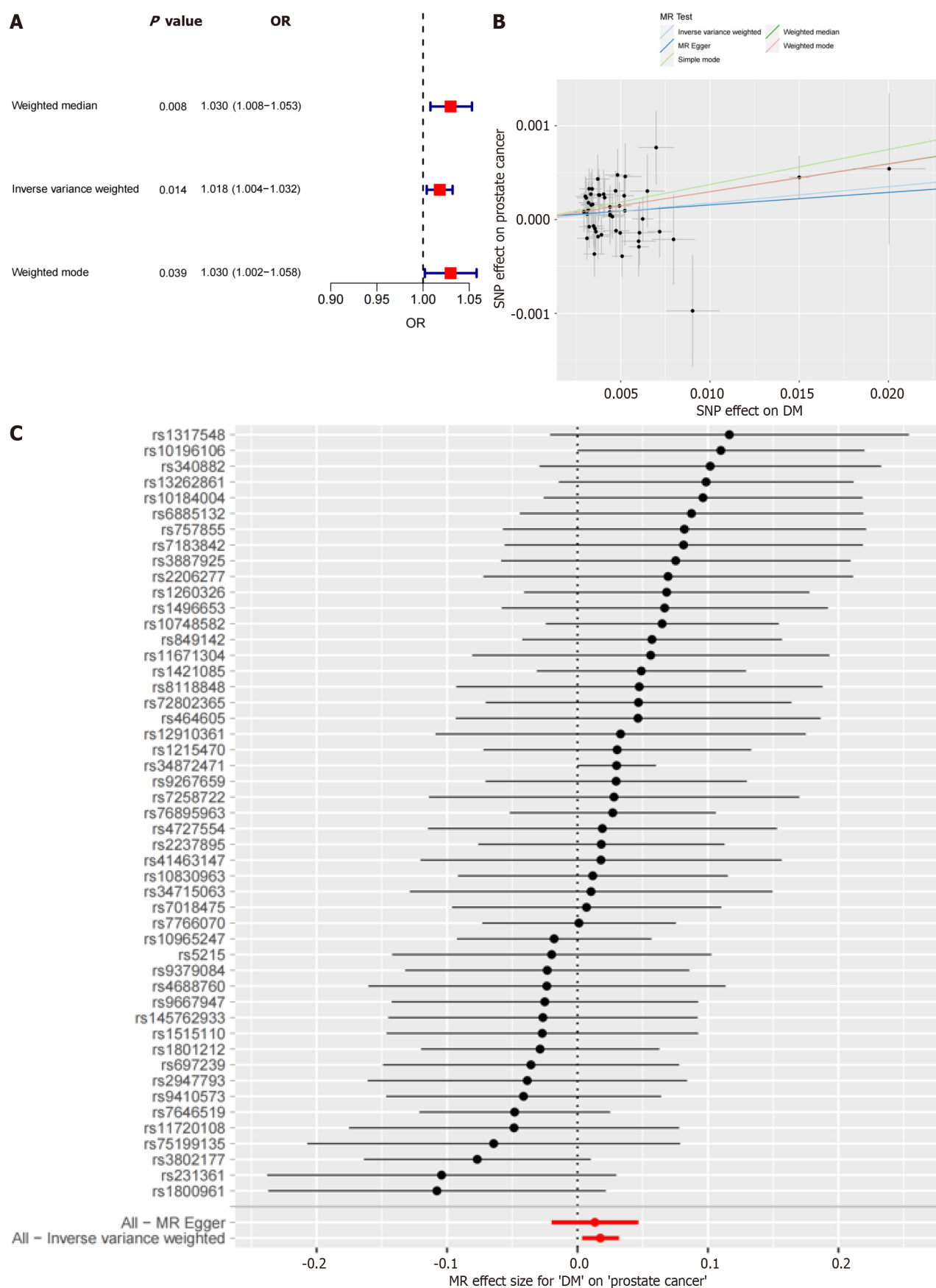


Figure 2 Mendelian randomization analysis. A: Forest plot of three mendelian randomization methods; B: Scatter plot; C: Forest plot for each single nucleotide polymorphism. DM: Diabetes mellitus; MR: Mendelian randomization; SNP: Single nucleotide polymorphism.

Table 1 49 Single nucleotide polymorphisms selected

SNP	Outcome	Exposure	P val. exposure
rs10184004	PCa	DM	1.42E-10
rs10196106	PCa	DM	1.02E-12
rs10748582	PCa	DM	1.61E-18
rs10830963	PCa	DM	3.45E-14
rs10965247	PCa	DM	6.65E-26
rs11671304	PCa	DM	1.03E-08
rs11720108	PCa	DM	5.75E-10
rs1215470	PCa	DM	2.17E-14
rs1260326	PCa	DM	7.61E-13
rs12910361	PCa	DM	3.34E-08
rs1317548	PCa	DM	1.19E-08
rs13262861	PCa	DM	3.90E-12
rs1421085	PCa	DM	1.36E-22
rs145762933	PCa	DM	3.85E-11
rs1496653	PCa	DM	3.66E-10
rs1515110	PCa	DM	5.35E-11
rs1800961	PCa	DM	1.40E-09
rs1801212	PCa	DM	8.72E-18
rs2206277	PCa	DM	3.23E-08
rs2237895	PCa	DM	9.39E-17
rs231361	PCa	DM	4.68E-09
rs2947793	PCa	DM	1.52E-10
rs340882	PCa	DM	2.14E-09
rs34715063	PCa	DM	1.72E-08
rs34872471	PCa	DM	3.60E-151
rs3802177	PCa	DM	1.90E-19
rs3887925	PCa	DM	4.88E-09
rs41463147	PCa	DM	1.51E-08
rs464605	PCa	DM	2.08E-08
rs4688760	PCa	DM	1.03E-08
rs4727554	PCa	DM	4.59E-09
rs5215	PCa	DM	1.49E-10
rs6885132	PCa	DM	2.60E-09
rs697239	PCa	DM	5.00E-12
rs7018475	PCa	DM	3.02E-14
rs7183842	PCa	DM	1.15E-08
rs7258722	PCa	DM	3.37E-08
rs72802365	PCa	DM	2.26E-11
rs75199135	PCa	DM	4.11E-08
rs757855	PCa	DM	1.83E-08
rs7646519	PCa	DM	7.02E-27

rs76895963	PCa	DM	3.07E-23
rs7766070	PCa	DM	4.38E-26
rs8118848	PCa	DM	2.38E-08
rs849142	PCa	DM	3.31E-15
rs9267659	PCa	DM	4.84E-15
rs9379084	PCa	DM	6.03E-13
rs9410573	PCa	DM	1.04E-13
rs9667947	PCa	DM	2.55E-11

DM: Diabetes mellitus; SNP: Single nucleotide polymorphism; PCa: Prostate cancer.

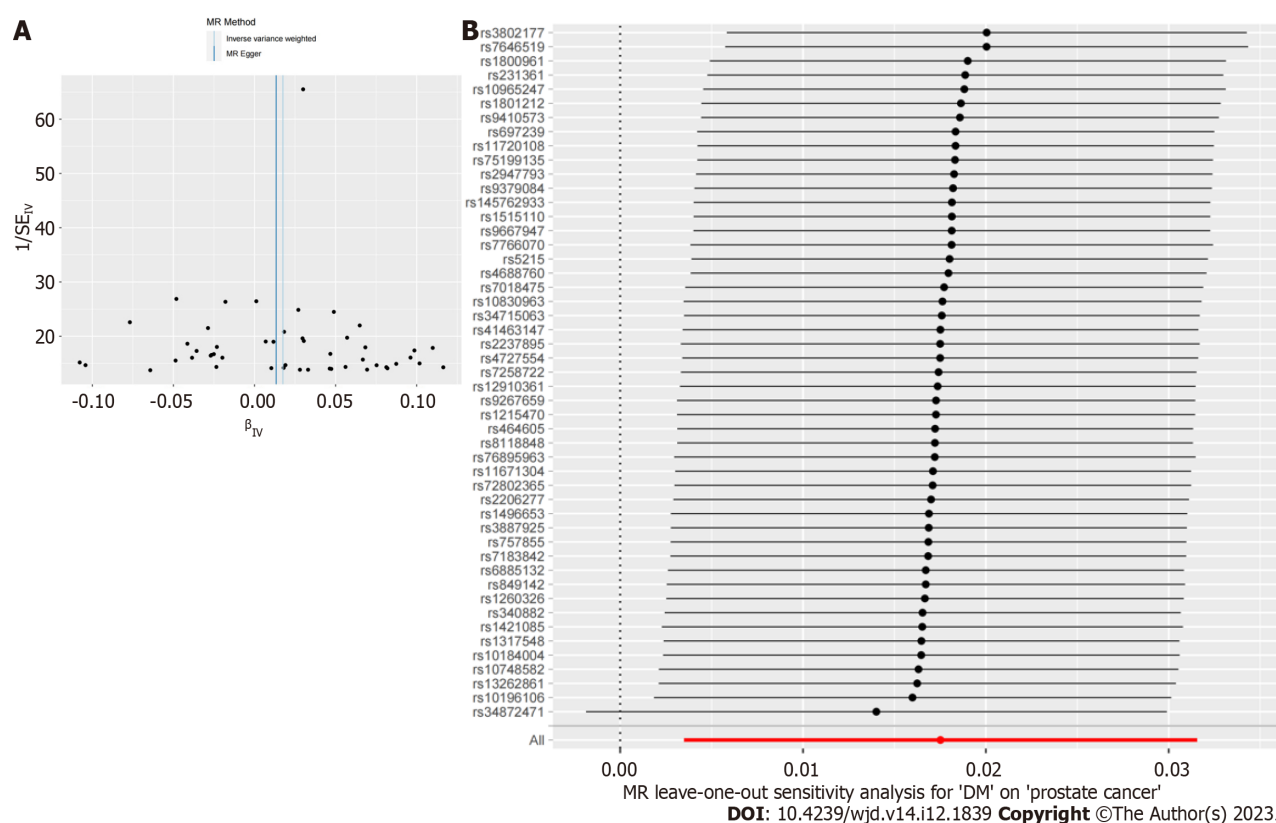


Figure 3 Sensitivity analysis. A: Funnel plot; B: The result of leave-one-out method. DM: Diabetes mellitus; IV: Instrumental variable.

Compared to the previous observational study, this study explored the potential causal relationship between DM and PCa using three different MR methods. Through MR analysis, we found that DM was a high-risk factor for PCa, which was consistent with previous clinical experience and the results of numerous studies. The results of the sensitivity analysis validation also indicated that the obtained results were reliable. The results of the three MR methods showed that DM increased the risk of PCa. Based on the results of this study, we could conduct early clinical screening of high-risk (DM) populations, control their weight, and strengthen their exercises to further reduce the incidence rate of PCa. DM has already been regarded as a high-risk factor for PCa in some clinical guidelines and academic researches, and our results could also provide a theoretical basis.

This study had some limitations. First, the GWAS dataset obtained in our study was from the same population (European) and could be supplemented in subsequent studies to further expand the coverage of the research results. Second, DM and PCa could be divided into many subtypes, and future research should further explore the relationship between these subtypes. Third, we excluded only SNPs associated with known confounding factors, and future research was needed to further exclude other unknown confounding factors. Finally, it should be noted that the results of MR research could only partially explain the causal effect of DM on PCa. Other methods were needed to prove this result in the future.

CONCLUSION

Through MR analysis of a large sample, this study found that DM was an independent risk factor for PCa, providing new directions for the prevention and treatment of PCa.

ARTICLE HIGHLIGHTS

Research background

Some studies have shown a relationship between diabetes mellitus (DM) and prostate cancer (PCa); however, this specific relationship remains inconclusive.

Research motivation

Mendelian randomization (MR) has been a widely used analytical method in recent years for inferring epidemiological causes. We believe that MR can explain the causal relationship between DM and PCa.

Research objectives

Find the causal relationship between DM and PCa.

Research methods

We downloaded the relevant data from a public database, used three different MR methods, and conducted a sensitivity analysis for validation.

Research results

These results indicated that DM was an independent risk factor for PCa. The odds ratio (OR) values obtained using the inverse variance weighted method in this study were as follows: OR = 1.018 (95% confidence interval: 1.004-1.032), $P = 0.014$.

Research conclusions

Through MR analysis of a large sample, this study found that DM was an independent risk factor for PCa, providing new directions for the prevention and treatment of PCa.

Research perspectives

This study investigated the potential relationship between DM and PCa using MR.

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FOOTNOTES

Author contributions: Jiang Q designed the research plan; Yuan JX wrote the first draft; Yuan JX and Yu SJ participated in data collection and analysis; Yu SJ made revisions to the manuscript; all authors contributed to the article and approved the submitted version.

Conflict-of-interest statement: All authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Data sharing statement: Publicly available datasets were analyzed in this study. The data are as follows: IEU OpenGWAS project: <https://gwas.mrcieu.ac.uk/datasets/ukb-a-57/>; <https://gwas.mrcieu.ac.uk/datasets/ukb-a-306/>.

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