Type 2 Diabetes Mellitus and the Risk of Prostate Cancer: A Mendelian Randomization Study

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Abstract

Purpose

The purpose of this study is to address the current uncertainty surrounding the causal relationship between type 2 diabetes mellitus (T2DM) and prostate cancer. By employing Mendelian randomization studies, we aim to eliminate the influence of confounding factors and clarify the relationship between T2DM and prostate cancer. Understanding the causal effect will contribute to the improvement of prevention and control strategies for both conditions in clinical practice.

Methods

European population-derived summary data from Genome-Wide Association Studies (GWAS) was utilized to investigate the relationship between T2DM and prostate cancer. T2DM data from 148,726 patients with T2DM and 965,732 controls were included, as well as prostate cancer data from 30,945 prostate cancer patients and 368,725 controls, totaling 399,670 samples. T2DM was utilized as an exposure indicator, and significant and independent SNPs were screened as instrumental variables. A two-sample Mendelian Randomization (MR) approach was used to evaluate the link between T2DM and prostate cancer in the overall sample. Five different methods, including Inverse Variance Weighting (IVW) and MR-Egger, were implemented in the analysis process to establish causal associations. IVW was selected as the main analysis method, and gender heterogeneity was detected by the Cochran Q test.

Results

Our analysis revealed a positive correlation between T2DM and prostate cancer in the overall population (IVW, OR = 7.88; 95% CI: 6.95–8.93, P < 0.005), indicating a causal relationship.

Conclusion

Our findings suggest that T2DM does increase the risk of prostate cancer and that a causal relationship between the two does exist.

Introduction

Diabetes is a metabolic disease characterized by high levels of blood sugar and is among the most prevalent chronic illnesses in humans. T2DM represents over 90% of diabetic cases. Symptoms of T2DM typically manifest after the age of 35 to 40 and are often accompanied by a significant decrease in the body’s ability to produce insulin. While some patients may respond to oral medications that stimulate insulin secretion, others may require insulin injections in the later stages of the disease. The global
incidence of T2DM has risen to 463 million, signifying a worrisome increase\(^1\). Notably, numerous human cancers, including those affecting the endometrium\(^2\), pancreas\(^3\), colon\(^4\), and thyroid\(^5\), have been linked to diabetes, displaying a positive correlation. However, the relationship between diabetes and prostate cancer has generated conflicting perspectives. Some reports have suggested that a history of diabetes may be associated with a reduced risk of prostate cancer based on follow-up studies\(^6\). Similarly, meta-analyses have arrived at parallel conclusions\(^7\)–\(^10\). Conversely, other researchers have posited the opposite conclusion, emphasizing a positive correlation between diabetes and prostate cancer through clinical data collection and meta-analysis\(^11\). Moreover, studies have indicated that the coexistence of T2DM and other metabolic abnormalities (dyslipidemia, hypertension, obesity) is linked to a more rapid progression of prostate cancer\(^12\)–\(^13\).

In response to the inconsistencies among previous studies, we will employ Mendelian randomization (MR) as a novel research method to further investigate the existence and nature of the correlation between T2DM and prostate cancer. MR is a causal inference technique grounded in the fundamental principles of genetic variation. It utilizes the influence of randomly assigned genotypes on phenotypes in nature to infer the impact of biological factors on diseases. This simulation of genotype distribution closely resembles a randomized controlled trial (RCT). An advantageous aspect of MR is that an individual's genotype is determined at conception and remains constant throughout their lifetime, thereby eliminating the issue of reverse causation linked to genotypes. Additionally, MR serves as a research method wherein genetic information acts as an instrumental variable, minimizing the influence of confounding factors. Unlike traditional epidemiological research, MR can establish the causal relationship and directionality, whether positive or negative, between exposure and outcome, going beyond mere association. The aforementioned strengths of MR have facilitated its widespread application in various domains, including cardiovascular disease\(^14\) and drug research and development\(^15\). Consequently, we conducted an MR study utilizing the latest human genome database to better evaluate the impact of T2DM on prostate cancer.

**Method**

**1 Study Design**

This study aimed to investigate the causal link between prostate cancer risk and T2DM. In conducting 2-sample Mendelian randomization (2SMR) analysis, genetic variants must fulfill three major assumptions of Mendelian randomization studies: 1) robustly linked with T2DM, 2) unrelated to any confounding factors of T2DM and prostate cancer, and 3) associated with outcomes achieved through other methods, as depicted in Fig. 1 and supported by Not relevant. We comprehensively searched the gwas catalog database (https://www.ebi.ac.uk/gwas/) as well as the Ieu Open GWAS Project database (https://gwas.mrcieu.ac.uk/) to match the most suitable summary data of exposure and outcome. To avoid errors arising from stratification effects of factors such as ancestry and population, we selected
participants with European ancestry in the cohort. In this study, we aimed to utilize GWAS data with a larger sample size and a greater number of SNPs for identifying appropriate studies.

2 Genetic instrumental variables for T2DM and prostate cancer data sources

The study identified T2DM-associated SNPs in individuals of European ancestry through GWAS catalog analysis, specifically the GWAS-id "GCST010555". The dataset comprised 148,726 T2DM patients and 965,732 healthy controls of European descent. To ensure that the selected SNPs were strongly linked to T2DM, biologically and statistically reasonable SNPs meeting the criteria of genomic significance, with a length parameter excluding linkage disequilibrium set at 1000kb, were chosen. Preliminary analysis included SNPs with a threshold p < 5e-08 and a linkage disequilibrium threshold of r² < 0.001. The Radial MR package was utilized to assess SNP heterogeneity, removing those with significant heterogeneity and ultimately obtaining the SNPs significantly associated with T2DM as instrumental variables. Prostate cancer data, the outcome indicator of this study, were obtained from the Ieu database (Ieu Open GWAS Project) with the Ieu ID ukb-b-7773, encompassing 399,670 samples, including 30,945 prostate cancer patients and 368,725 healthy controls.

3 Methods and Models of 2SMR

Among the methods used in two-sample Mendelian randomization analysis, five are relatively mainstream and commonly used, these include inverse variance weighting (IVW), MR-Egger, weighted median, weighted mode, and sample mode. IVW is the primary analysis method within these five, given its capability to not only analyze the causal relationship between exposure and outcome but also to assess heterogeneity in SNPs. The other four methods were utilized for supplementary analysis. The IVW principle involves using the reciprocal of the variance of each filtered effective instrumental variable as a weight to conduct a weighted calculation, assuming the validity of all instrumental variables. The result is the weighted average of the effect values of all instrumental variables. MR-Egger serves as a method to detect horizontal pleiotropy in instrumental variables, particularly irrelevant horizontal pleiotropy, by assessing the presence or absence of the intercept term, or the significance of the P value of the intercept term. The intercept term is used to gauge the average pleiotropy between instrumental variables, and when the intercept term is 0 or the statistical p-value is not significant, it indicates no bias in the instrumental variables. Weighted median regression is currently the mainstream method for addressing "coherence level pleiotropy." MR-Egger and weighted median are both considered simultaneously to help minimize potential false positives in the study. The weighted median statistical method complements the MR-Egger regression approach.

4 Leave-one-out sensitivity and heterogeneity analysis

The principle of leave-one-out sensitivity analysis is to systematically eliminate each SNP included in the analysis and calculate the cumulative effect of the remaining SNPs to assess if alterations in the causal relationship between heterogeneity, exposure, and outcome can be attributed to any specific SNP.
Cochran's Q statistic and a statistical p-value (with a threshold of 0.05) are employed to evaluate if there exists a significant heterogeneous association in all SNP causal relationships. If the p-value exceeds 0.05, it indicates the absence of such an association. Consequently, the smaller the heterogeneity, the more reliable the MR estimate.

5 MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) analysis

This study employs MR-PRESSO to examine the horizontal pleiotropy of genetic instrumental variables (IVs) and rectify biased results stemming from outliers. Initially, MR-PRESSO is utilized to ascertain the presence of heterogeneity and outliers. Should these factors be identified, the outliers are subsequently excluded, and pleiotropy correction is conducted once again. Finally, the MR-PRESSO distortion test is applied to evaluate the alteration in causality following the removal of outliers\textsuperscript{[18]}

Result

1 Selection of instrumental variables

This study employed the Twosample package to conduct an initial screening of single nucleotide polymorphisms (SNPs) with genome-wide significance, taking into account correlation and independence. Subsequently, the Radial MR package was utilized to further differentiate each of the initially screened SNPs. Through qualitative testing, a total of 168 SNPs from participants of European ancestry were ultimately identified as instrumental variables. Each SNP is characterized by its chr, Position, chroeffect_allele, other_allele, beta, eaf, se, and p values. A comprehensive summary of the SNP details is provided in Supplementary Table 1.

2 Mendelian randomization assessment between T2DM and prostate cancer

This study employed five 2SMR methods, namely inverse-variance weighted (IVW), Mendelian randomization-Egger (MR-Egger), weighted median, and weighted mode (simple mode). Upon conducting the calculations, it was discovered that all methods demonstrated a positive causal relationship and presented statistically significant differences (OR > 1, p < 0.001). Preliminary analysis reveals that T2DM in the population, as an exposure factor, may influence the risk of prostate cancer as an outcome factor. Table 1 and Fig. 2 present the OR values, confidence intervals, and P values for all five methods.
Table 1
Genetically predicted associations between T2DM and risk of prostate cancer

<table>
<thead>
<tr>
<th>Methods</th>
<th>OR</th>
<th>95% CI of OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inverse-variance Weighted</td>
<td>7.88</td>
<td>6.95 ~ 8.93</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>MR-Egger</td>
<td>7.15</td>
<td>6.05 ~ 8.43</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Simple mode</td>
<td>10.13</td>
<td>8.29 ~ 12.38</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Weighted median</td>
<td>10.00</td>
<td>9.00 ~ 11.09</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Weighted mode</td>
<td>10.13</td>
<td>8.78 ~ 11.69</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

3 Sensitivity and heterogeneity analysis results

To further judge the credibility of Mendelian randomization studies, it is necessary to further judge the sensitivity and heterogeneity of the results. \( p < 5 \times 10^{-8} \) was selected to screen SNPs at the genome-wide significance level to satisfy the first condition of the Mendelian hypothesis. The results of heterogeneity analysis showed that there was statistical heterogeneity \((p < 0.05)\) in both inverse-variance weights and MR-egger analysis (Table 2 and Supplementary Fig. 1), so the random effects IVW model was used. Leave-one-out analysis shows that although there is rs76895963 that is higher than the overall value, it does not change the overall direction (all error bars are on the right side of 0), so there is no single SNP that makes T2DM have an overall impact on abnormal sperm. There is a significant impact (Supplementary Fig. 2).

Table 2
Heterogeneity statistics of two-sample Mendelian randomization analysis

<table>
<thead>
<tr>
<th>Method</th>
<th>Q value</th>
<th>Degrees of freedom</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inverse-variance weights</td>
<td>1269</td>
<td>167</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>MR-egger</td>
<td>1245</td>
<td>166</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

4 Pleiotropy Statistics

Moreover, the results of the pleiotropy analysis demonstrated no significant horizontal pleiotropy through MR-Egger \((p > 0.05)\) (Table 3). This indicates that the estimated causal relationship between T2DM and prostate cancer risk remains unaltered by potential confounders. Furthermore, the MR-PRESSO analysis substantiated these outcomes by confirming the absence of significant pleiotropic effects and outliers (Supplementary Table 2).
Table 3
Pleiotropy statistics of two-sample Mendelian randomization analysis

<table>
<thead>
<tr>
<th>Method</th>
<th>Egger regression intercept</th>
<th>Standard error</th>
<th>Directionality p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR-egger</td>
<td>0.000365</td>
<td>0.0002</td>
<td>0.076</td>
</tr>
</tbody>
</table>

Discussion

Diabetes, a prevalent chronic disease, is known for its detrimental impact, arising not solely from the disease itself but also from associated complications stemming from abnormal blood sugar levels. The damage caused by diabetes extends to vital organs and blood vessels, resulting in serious conditions such as stroke, blindness, heart attack, kidney failure, and skin ulcers[19]. Furthermore, the high-sugar environment created by diabetes within the human body has been shown to stimulate the growth of certain cancer cells, including those in the endometrium[2], pancreas[3], colon[4], thyroid[5], and other types of cancers.

Controversies persist in the literature regarding the relationship between diabetes and prostate cancer. Some scholars contend that no statistical difference exists in the clinical symptoms and classification of prostate cancer between diabetics and non-diabetics[20]. At the same time, meta-analyses have yielded diverging outcomes indicating a reduced risk of developing prostate cancer for diabetes patients, however, this association has been shown to have little or no impact on the progression of the disease[21]. It should be noted that this meta-analysis was limited by the small number of papers included and a restricted clinical sample. Various studies have suggested a negative correlation between diabetes and prostate cancer, but this conclusion can be impacted by the ethnicity of the participants, with a positive correlation evident between these two conditions among Asian populations[10]. This finding stresses the significance of genetic factors in determining the relationship between diabetes and prostate cancer, thus calling attention to the potential of investigating novel genetic markers or pathways to shed light on this topic further.

However, several studies have presented contrasting findings, suggesting that diabetes may have a detrimental impact on the prognosis of prostate cancer and escalate the mortality rate among prostate cancer patients[11]. These studies imply that the relationship between diabetes and prostate cancer is intricate and necessitates further and in-depth investigation. Due to the extensive duration of the disease cycle in diabetic patients, the study of this disease inevitably involves the incorporation of numerous confounding factors. For instance, diabetic individuals commonly endure obesity[22], and obesity has been linked to an increased risk of prostate cancer. This association indicates a positive correlation with the heightened susceptibility to the disease, and obesity may serve as a significant risk factor for PCa[23]. The impact of long-term use of hypoglycemic drugs on prostate cancer development in patients warrants consideration. Metformin, a commonly prescribed drug for T2DM, has been associated with a reduced risk of prostate cancer in some studies[24]. Its mechanism of action in various tumor types involves the activation of the AMP kinase pathway, p53 activation, downregulation of cyclin D1, and inhibition of
HER2 oncoprotein expression. Inhibitory effects have been observed in preclinical models of prostate\cite{25}, breast\cite{26}, pancreas\cite{27}, lung\cite{28}, and colon\cite{29} cancer.

Given the influence of confounding factors such as obesity, drug effects, and deliberate changes in living and eating habits following the diagnosis of T2DM, some studies have indicated the necessity of employing experimental designs with fewer interfering factors to further elucidate the association between diabetes mellitus (DM) and prostate cancer (PCa)\cite{21}. In this study, we leverage the methodology of Mendelian randomization research to investigate the impact of T2DM on prostate cancer and to analyze whether a causal relationship exists between the two at a genetic level. This approach allows the analysis results to mitigate many confounding factors in the development of the disease, thereby providing a more convincing demonstration of the relationship between T2DM and prostate cancer\cite{30}.

This study utilized the most recent extensive summary data from public resources in GWAS and IEU databases to examine the impact of T2DM on prostate cancer through a two-sample Mendelian analysis approach. From a genetic standpoint, it was observed that an increase in T2DM in the population considerably raises the incidence of prostate cancer. Throughout the analysis process, we strictly adhered to the three major assumptions of Mendelian randomization: firstly, we employed a stringent criterion (p < 5E-08) to establish a strong correlation, thereby preliminarily excluding SNPs, thus ensuring a strong correlation between SNPs and exposure factors; secondly, we carried out linkage disequilibrium analysis (R2 < 0.001) to further enhance the screening of SNPs, guaranteeing their independence from confounding factors; finally, to comply with the "exclusivity hypothesis," sensitivity analysis was conducted, specifically involving sex-based and MR-PRESSO analyses, both demonstrating the absence of horizontal pleiotropy, thus ensuring that SNPs solely impact outcomes through exposure factors.

This study also has several limitations. Firstly, the analysis was only conducted on data from the European population, which may limit the generalizability of the findings to the broader human population. Secondly, there might be an insufficiency of prostate cancer cases, and the inclusion of additional cases may introduce bias. Thirdly, the study could not establish correlations between different stages of prostate cancer due to the lack of detailed data. This limitation prevents a more refined conclusion regarding the causal relationship between T2DM and prostate cancer.

Declarations

Supplementary data

Supplemental data for this article is available online.

Conflict of interest statement:

Authors declare no conflict of interests in this paper.
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Author Contribution

S. N., Z. Z., B. L., X. C., and J. W. designed the study and were responsible for data analysis and interpretation. S. N. and Z. Z. collected the data and drafted the manuscript. J. W., B. L., and X. C. critically reviewed the manuscript. S. N. was responsible for the statistical analysis of the full-text data. J. W. and X. C. were responsible for important data and key issues in the text and were the guarantors and contributors of critical revisions to the manuscript. All authors had free access to all data in the study, were responsible for the integrity of the data and the accuracy of the data analysis, and read and approved the final version of the manuscript accepted for publication.

References


Schematic diagram of MR analysis. It can be estimated by 2TSMR analysis: whether the hypothetical outcome (prostate cancer) is caused by exposure (T2DM). Genetic variants used in the 2TSMR analysis must meet three assumptions: a) be strongly associated with T2DM, b) be not associated with any confounder of T2DM and abnormal spermatozoa, c) be not related to the relevant outcomes obtained through other methods.
Figure 2

Scatter plot of estimated individual odds of T2DM with prostate cancer as the outcome (including trend lines derived from 5 different 2SMR methods), used to represent the causal relationship between the two.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• supplementarydata.doc