Diabetes Mellitus and Pancreatic Cancer: Investigation of Causal Pathways Through Mendelian Randomization Analysis

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Abstract

Objective: This study was aimed at investigating the association between diabetes mellitus and susceptibility to pancreatic cancer by using Mendelian randomization (MR) methods and an extensive human genome-wide association study (GWAS) dataset.

Methods: The publicly accessible MR Base database was used to obtain the complete genome, relevant research findings, and summary data pertaining to diabetes mellitus and pancreatic cancer. Genetic variables, specifically single-nucleotide polymorphisms closely associated with diabetes mellitus, were selected for analysis. Four methods—inverse variance weighted (IVW) analysis, weighted median analysis, weighted mode, and MR-Egger regression—were used. Statistical analysis was conducted to explore the potential association between diabetes mellitus and susceptibility to pancreatic cancer.

Results: The results of the IVW analysis (OR = 11.56519319, 95% CI 1.275068624–104.8992116, P = 0.0296) indicated a significant causal relationship between diabetes and elevated pancreatitis risk. Furthermore, the absence of horizontal pleiotropic effects (Egger intercept = 0.29, P = 0.384) and heterogeneity (P = 0.126) suggested that the observed association was not influenced by confounding factors. Sensitivity analysis and other statistical methods also supported the conclusion that genetic pleiotropy did not introduce bias to the findings.

Conclusion: A causal relationship exists between diabetes mellitus and the occurrence of pancreatic cancer. People with diabetes mellitus are at high risk of pancreatic cancer and should receive early screening. The IGF signaling pathway may be a key mediator of the effects of diabetes on pancreatic cancer pathogenesis.

Keywords

Causal relationship, diabetes mellitus, pancreatic cancer, mendelian randomization.

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Introduction

Diabetes mellitus (DM), a metabolic disorder, arises from a combination of genetic and environmental factors [1]. Its enduring complications, including renal failure, diabetic heart disease, stroke, foot ulcer, and diabetic retinopathy, pose substantial burdens on people worldwide, and are increasing in prevalence [2]. According to the International Diabetes Federation, the number of Chinese adults affected by diabetes mellitus is estimated to be 109 million, whereas the worldwide prevalence is 415 million [3].

Pancreatic cancer (PC), like DM, poses a major threat to human well-being. The prevalence of PC is progressively increasing at an annual rate of 1%, and its fatality rate remains alarmingly elevated [4]. According to a 2020 report published by the World Health Organization, the prevalence of PC in Asia is approximately 47.1%, surpassing that in Europe, which has the second-highest prevalence, at 28.3% [5]. In the comprehensive tumor rankings for China, the incidence and mortality rates of PC are eighth and sixth highest, respectively. These rates surpass the global average morbidity (12th) and mortality (7th) levels. The challenging nature of early diagnosis for PC substantially affects patient prognosis. Reports have indicated that 80% of patients with PC are diagnosed in advanced stages involving tumor metastasis and invasion, thus resulting in lost opportunities for curative surgery [6]. Hence, timely identification and diagnosis of PC, and immediate intervention, are crucial to increase the likelihood of survival. The relationship between PC and DM has garnered substantial attention in the academic community. Extensive research has indicated that people with DM

and elevated blood glucose levels have elevated susceptibility to developing PC [7]. Furthermore, DM onset within 2–3 years before PC diagnosis may be attributable to a paraneoplastic phenomenon triggered by the release of inflammatory mediators by cancerous cells [8]. In addition, a causal association has been demonstrated between PC and the onset of DM, thus refuting a causal connection between long-term DM and PC [9]. Therefore, the relationship between DM and PC is complex, and debates regarding its causality and directionality are ongoing.

Mendelian randomization (MR) is an epidemiological experimental method in which publicly available databases are used to analyze causal relationships between exposure factors and outcomes. Single-nucleotide polymorphisms (SNPs) are used as instrumental variables (IVs) to investigate the presence of a causal association between an exposure and outcome [10]. SNPs are the most common type of heritable variation in humans, accounting for more than 90% of all known polymorphisms. SNPs have been used to varying degrees in population genetics, ecology, the pharmaceutical industry, forensic science, cancer, hereditary diseases, and even evolutionary studies [10]. The present investigation used aggregated data from a published genome-wide association study (GWAS) [11]. GWAS is a method for conducting multi-center, large-sample, iterative validation of gene-disease association studies at the genome-wide level. Given that alleles are randomly assigned during meiosis, MR is comparable to a natural randomized controlled trial, thus enabling controlling for confounding factors. Moreover, genetic variants are present from birth, thereby mitigating reverse causation and offering robust evidence of causal inference. Therefore, this study used MR analysis to reevaluate the association between diabetes and PC risk, to provide insights to guide early PC diagnosis.

Materials and methods

The analyses conducted in this study relied on publicly accessible GWAS data; therefore, supplementary ethical approval and informed consent were not required. The flowchart describes the study process (**Figure 1**).

Data source

The exposure data used in the GWAS on DM were obtained from the publicly accessible MR Base database (http://app.mrbase.org/), under accession ukb-b-18009. This dataset encompasses a substantial cohort of 249,710 people, consisting of 43,244 cases and 206,466 controls. Within this dataset, a total of 9,185,867 genetic variants were analyzed. The outcome data for the GWAS on PC were likewise acquired from MR Base database accession ieu-a-822. This dataset included 3,835 participants, comprising 18,964 cases and 1,939 controls, and encompassed a comprehensive set of 521,863 genetic variants. However, importantly, both datasets consisted of participants from only European populations.
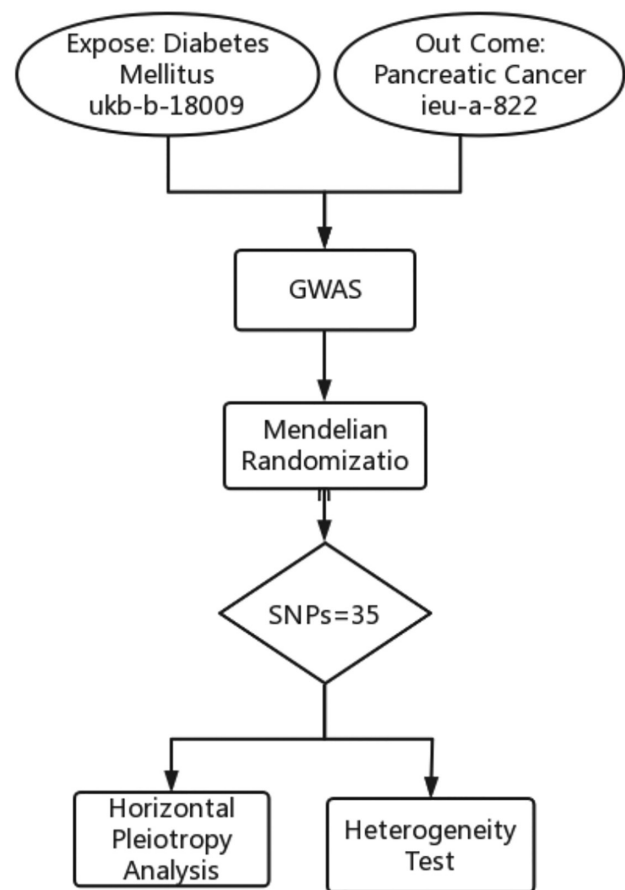

Figure 1 Flowchart of this study.

Research design

This study used a two-sample MR design to investigate the causal relationship between DM and PC, with DM serving as the exposure and PC serving as the outcome. The research methods comprised three steps: (1) examining the significant associations between the IV and DM, (2) assessing the absence of any potential confounding factors associated with the IV, and (3) determining the lack of significant association between the IV and PC, as depicted in **Figure 2**.

A significance threshold of $P < 1 \times 10^{-8}$ was used to determine DM GWAS-identified loci demonstrating genome-wide significance. To ensure accuracy of the results, we analyzed SNPs with genetic significance across the entire set and excluded SNPs in linkage disequilibrium. In particular, SNPs with an r^2 value > 0.01 in conjunction with the most prominent SNP within a 5000 kb span were omitted. Next, we used the Phenoscanner database (http://www.phenoscanner.medschl.cam.ac.uk/) to sequentially retrieve information on each SNP. The retrieved information was then assessed to determine whether the SNP had previously been documented to be linked with metabolites and disease traits at significance levels of $P < 5 \times 10^{-8}$ and $r^2 > 0.8$. The potency of each SNP was evaluated with the F-statistic, computed according to formula 1. Formula 2 outlines the calculation of the R^2 value. Additionally, we assessed whether each SNP had previously been associated with a recognized risk factor for PC. If the SNP was found to be relevant, it was excluded,
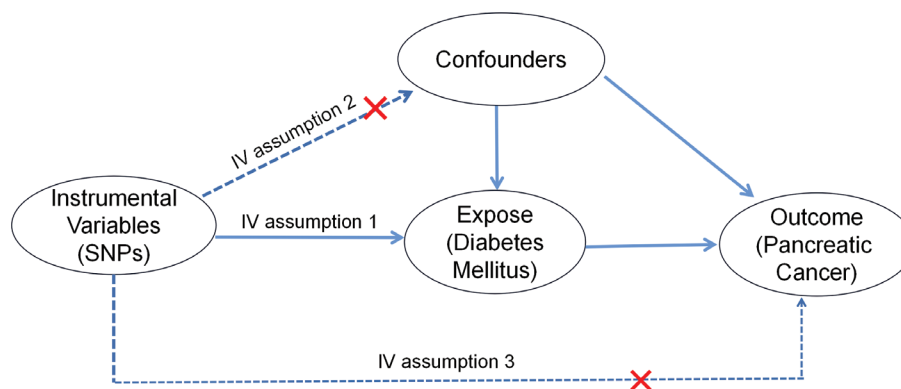
Figure 2 Three assumptions for IVs in MR analysis.

to avoid violating the second assumption of IV analysis. Finally, in cases in which a SNP was unavailable, a surrogate SNP was used as a replacement, provided that the presence of a palindromic structure did not introduce any ambiguity.

$$F-Static = \frac{\lfloor R^2(N-2) \rfloor}{(1-R^2)} \quad (1)$$

$$R^2 = \frac{2*(Beta)^2*EAF*(1-EAF)}{2*(Beta)^2*EAF*(1-EAF)+2*(SE)^2*N*EAF*(1-EAF)} \quad (2)$$

where N is the number of exposed samples included in GWAS studies, R^2 is the degree to which IV explains exposure (the determinant of the regression equation), beta is the effect size of each allele for each SNP and phenotypic association, SE is the standard deviation of beta, and EAF represents the effect allele frequency.

Mendelian randomization analysis

The inverse variance weighted (IVW) method was used to conduct two-sample MR analysis. The robustness of the IVW results was assessed through alternative approaches, including MR-Egger regression, the weighted median (WM), and the weighted median method (WMM).

Horizontal pleiotropy analysis and heterogeneity testing

The intercept of the MR-Egger model can enable examination of the potential presence of horizontal pleiotropic effects associated with the IV [12]. Given that MR-Egger assumes the inclusion of an intercept term in the model, values near zero suggest minimal disparity between the causal effects estimated by MR-Egger and IVW, thereby indicating the absence of horizontal pleiotropy among the IVs. In contrast, a substantial deviation from zero for the intercept term may suggest the existence of horizontal pleiotropy among the IVs. Additionally, we used the Cochran Q statistic to assess the presence of heterogeneity. If the P-value of the Cochran Q test reached statistical significance, the findings were

considered to exhibit heterogeneity. Additionally, a leave-one-out analysis was conducted to determine the reliability of the overall effect. This analysis evaluated the influence of the remaining SNPs on the overall causal estimation, excluding individual SNPs in a sequential manner.

Statistical methods

The statistical tests used in this analysis were two-sided, with a significance threshold of P < 0.05. The results of the MR analysis are presented as odds ratios (OR) and 95% confidence intervals (CIs). To visually represent the outcomes obtained with the coefficient ratio method, MR method, and leave-one-out analysis, we used forest plots and scatterplots. All statistical analyses were conducted in R software (version 4.0) with the packages TwoSampleMR (version 0.5.5), readr (version 1.4.0), and data.table (version 1.13.2).

Results

Instrumental variables

On the basis of the screening criteria used in the two-sample MR investigation, we incorporated a comprehensive set of 35 SNPs as IVs. Notably, each F-statistic associated with the instrumental exposure surpassed the threshold of 10, thereby indicating successful mitigation of the influence of weak IVs on the outcomes (**Table 1**).

Mendelian randomization results

Table 2 presents the results for four MR methods used to assess the causal relationship between DM and PC. The results obtained with the IVW method suggested that people with DM might have elevated risk of developing PC (OR=1.808, 95% CI: 0.091–35.776, P=0.030). Similarly, the WM method yielded comparable results. Although the results of the WM method did not reach statistical significance because of limited statistical power, a consistent direction of effect was observed with the IVW method,

Table 1 Details of SNPs Associated with Diabetes and Pancreatic Cancer

Rsid	Chromosome	EA	OA	Position	EAF	Exposure					Outcome				
						β	SE	P	R²	F	β	SE	P	R²	F
rs10096381	8	T	G	10831868	0.519982	−0.00700709	0.00106833	5.40E-11	1.72E-04	43.01907469	0.0407178	0.0489458	0.405495	1.80E-04	0.691689524
rs11212197	11	A	G	107344724	0.326494	0.00623969	0.00113638	4.00E-08	1.21E-04	30.14917173	0.0735292	0.0522872	0.15947	5.15E-04	1.976525224
rs11760498	7	A	G	106419296	0.174535	0.00926984	0.00141491	5.70E-11	1.72E-04	42.92233758	0.0750147	0.0644385	0.244385	3.53E-04	1.354476006
rs12154627	7	C	T	130438214	0.493833	−0.00810955	0.00107529	4.60E-14	2.28E-04	56.87728	−0.00330546	0.0488892	0.945518	1.19E-06	0.004568897
rs1275986	2	A	C	26912079	0.616567	−0.0140618	0.00109576	1.10E-37	6.59E-04	164.6825069	0.0446836	0.049457	0.36666	2.13E-04	0.815857337
rs12926550	16	A	G	81510742	0.316953	−0.00781637	0.00114854	1.00E-11	1.85E-04	46.3142345	0.0433468	0.0527456	0.411234	1.76E-04	0.675017545
rs1401982	12	A	G	89989599	0.591633	0.00757356	0.00108408	2.80E-12	1.95E-04	48.80608791	0.101479	0.0493356	0.0396232	1.10E-03	4.228681544
rs1427298	2	T	C	145214421	0.42856	−0.00631014	0.00108523	6.10E-09	1.35E-04	33.80889133	0.0322736	0.0482919	0.504066	1.16E-04	0.446395379
rs1581717	6	A	C	51838263	0.482706	0.00595773	0.00106209	2.00E-08	1.26E-04	31.46556373	0.0241071	0.0469516	0.608142	6.87E-05	0.263489065
rs1722883	7	C	T	134215403	0.470715	−0.00616213	0.00107003	8.50E-09	1.33E-04	33.16395568	−0.0176549	0.0474966	0.710269	3.60E-05	0.13809531
rs17514846	15	A	C	91416550	0.470029	0.00915834	0.00107361	1.50E-17	2.91E-04	72.76741556	−0.057841	0.0479072	0.227107	3.80E-04	1.456946012
rs17608766	17	C	T	45013271	0.144532	0.00918956	0.00151101	1.20E-09	1.48E-04	36.98718503	0.0379699	0.0712614	0.593976	7.40E-05	0.283755088
rs2023843	7	T	C	27243221	0.926089	0.0184205	0.002034	1.30E-19	3.28E-04	82.01578635	−0.0164637	0.0886552	0.852422	8.99E-06	0.034468304
rs2293607	3	C	T	169492101	0.243213	−0.00688	0.00123956	2.90E-08	1.23E-04	30.80621141	−0.0258308	0.0548406	0.638024	5.78E-05	0.221740371
rs2341599	4	A	G	156441314	0.659813	−0.00641773	0.00112369	1.10E-08	1.31E-04	32.61867935	0.0251127	0.0503502	0.618424	6.49E-05	0.248632484
rs2977324	8	G	T	76725867	0.700562	0.00703342	0.0011681	1.70E-09	1.45E-04	36.25513927	0.0438474	0.0532649	0.409945	1.77E-04	0.677296625
rs305226	1	G	A	89307261	0.617782	−0.00611639	0.00109575	2.40E-08	1.25E-04	31.15759315	−0.0973082	0.0503052	0.0529273	9.75E-04	3.73978443
rs3824869	11	C	T	47407439	0.636175	−0.00670491	0.00110877	1.50E-09	1.46E-04	36.56785562	0.0864297	0.0505933	0.0873233	7.60E-04	2.91684564
rs4705716	5	A	G	114434126	0.515575	−0.00683232	0.00106405	1.40E-10	1.65E-04	41.22957397	−0.0756938	0.0477514	0.112951	6.55E-04	2.511434464
rs4968782	17	A	G	61548948	0.619265	−0.00723084	0.00110106	5.10E-11	1.73E-04	43.12727857	0.0449974	0.0488101	0.356608	2.22E-04	0.849432546
rs57541197	10	A	G	63551773	0.145028	−0.0172185	0.00151088	4.40E-30	5.20E-04	129.8754923	−0.140182	0.0738204	0.057339	9.39E-04	3.604169162
rs604723	11	C	T	100610546	0.724763	0.0127554	0.00119841	1.90E-26	4.53E-04	113.2853727	0.000300045	0.053769	0.994818	8.12E-09	3.11231E-05
rs6468801	8	A	C	102841031	0.772347	0.00750863	0.00127552	3.90E-09	1.39E-04	34.65320317	0.0582649	0.0591676	0.324576	2.53E-04	0.969213724
rs7187250	16	A	C	53818460	0.392792	0.00765214	0.00109059	2.30E-12	1.97E-04	49.23107436	0.111184	0.0487069	0.0224528	1.36E-03	5.208072976
rs7220198	17	A	G	79375998	0.352773	−0.00695497	0.00112097	5.50E-10	1.54E-04	38.49453375	−0.120474	0.0495315	0.0149445	1.54E-03	5.912853934
rs73306876	20	G	A	57740605	0.11739	0.016946	0.00166166	2.00E-24	4.16E-04	104.0031743	0.00468899	0.0711161	0.94723	1.13E-06	0.004345064
rs7340705	3	C	T	53734531	0.322676	0.00654432	0.00114561	1.10E-08	1.31E-04	32.63262301	0.0516432	0.0507654	0.308846	2.70E-04	1.034341895
rs740746	10	A	G	115792787	0.732751	0.010855	0.00120719	2.40E-19	3.24E-04	80.85463459	0.0277824	0.0538512	0.606098	6.94E-05	0.266024846
rs74461587	5	G	A	122460332	0.132329	0.008673	0.00156919	3.30E-08	1.22E-04	30.54809628	0.0214679	0.065583	0.743024	2.79E-05	0.107095203
rs7701003	5	G	A	157849295	0.371692	−0.0113922	0.001101	4.30E-25	4.29E-04	107.0624273	−0.141218	0.0499362	0.00455743	2.09E-03	8.025345233
rs7911644	10	T	C	18475947	0.330189	0.00684792	0.00113424	1.60E-09	1.46E-04	36.45053943	0.0365248	0.0501657	0.46664	1.38E-04	0.529828591
rs880315	1	C	T	10796866	0.340613	0.0101807	0.00112809	1.80E-19	3.26E-04	81.4449766	0.0193123	0.0497404	0.697498	3.93E-05	0.150668652
rs908951	16	T	C	89734349	0.431483	−0.00948115	0.00107981	1.60E-18	3.09E-04	77.09458349	0.0182328	0.0486966	0.707538	3.66E-05	0.140114444
rs9375459	6	T	C	127176162	0.43725	0.0109051	0.00107183	2.60E-24	4.14E-04	103.5151723	−0.0138961	0.0472946	0.769653	2.25E-05	0.086285178
rs9394951	6	T	C	43352898	0.565819	−0.00769548	0.00107235	7.20E-13	2.06E-04	51.49853053	−0.0105442	0.0478655	0.825673	1.27E-05	0.048501539

Rsid: identification code for reference single-nucleotide polymorphism; EA: effect allele; OA: other alleles; EAF: effect allele frequency; SE: standard error.

Original Article

Table 2 Mendelian Randomization Results in Diabetes Mellitus and Pancreatic Cancer

Method	Nsnp	β	SE	OR	Lower 95%	Upper 95%	P
MR-Egger	35	−0.6772	3.719	0.508037508	0.000346912	743.9992301	0.8566
Weighted median	35	0.5922	1.523	1.807961559	0.09136617	35.7760974	0.6974
Inverse variance weighted	35	2.448	1.125	11.56519319	1.275068624	104.8992116	0.0296
Weighted mode	35	−0.2474	2.355	0.7808283	0.007725722	78.91726301	0.9169

Nsnp: number of SNPs; SE: standard error; OR: odds ratios; β: effect size of each allele for each SNP and phenotypic association.

thus indicating a potential trend toward elevated PC risk in people with DM (OR=11.565, 95% CI: 1.000–1.264, P=0.9694).

Furthermore, we conducted computations and visualizations to determine both individual IV and combined causal effect estimates. The outcomes of the MR statistical approach and the causal effects derived from the individual IVs are summarized as a forest plot (**Figure 3**). The dots in the plot indicate the calculated beta values, and the horizontal line represents the 95% CI of beta. The red line indicates the estimated causal effect obtained through the MR method. Notably, the horizontal line corresponding to the IVW method in the figure did not intersect with the dotted line, thereby indicating statistical significance.

Figure 4 displays scatterplots illustrating the causal effect estimates for individual SNPs and the four MR methods. Each black dot corresponds to an IV, with the abscissa denoting the SNP's effect on DM and the ordinate representing its effect on PC. The extended vertical and horizontal lines depict the 95% CI of the IV's causal effect on the respective disease. The slopes of the four colored lines indicate the estimated values of the causal effects, as determined by the four MR methods.

Cochran's Q test showed no heterogeneity in effect estimates for all IVs (Q_{Egger}=42.58, P_{Egger}=0.1227, I^2_{Egger}=0.225; Q_{IVW}=43.58, P_{IVW}=0.1257, I^2_{IVW}=0.220; **Table 3**). In Cochran's Q test, $I^2 > 25\%$ and $p < 0.05$ indicated significant heterogeneity.
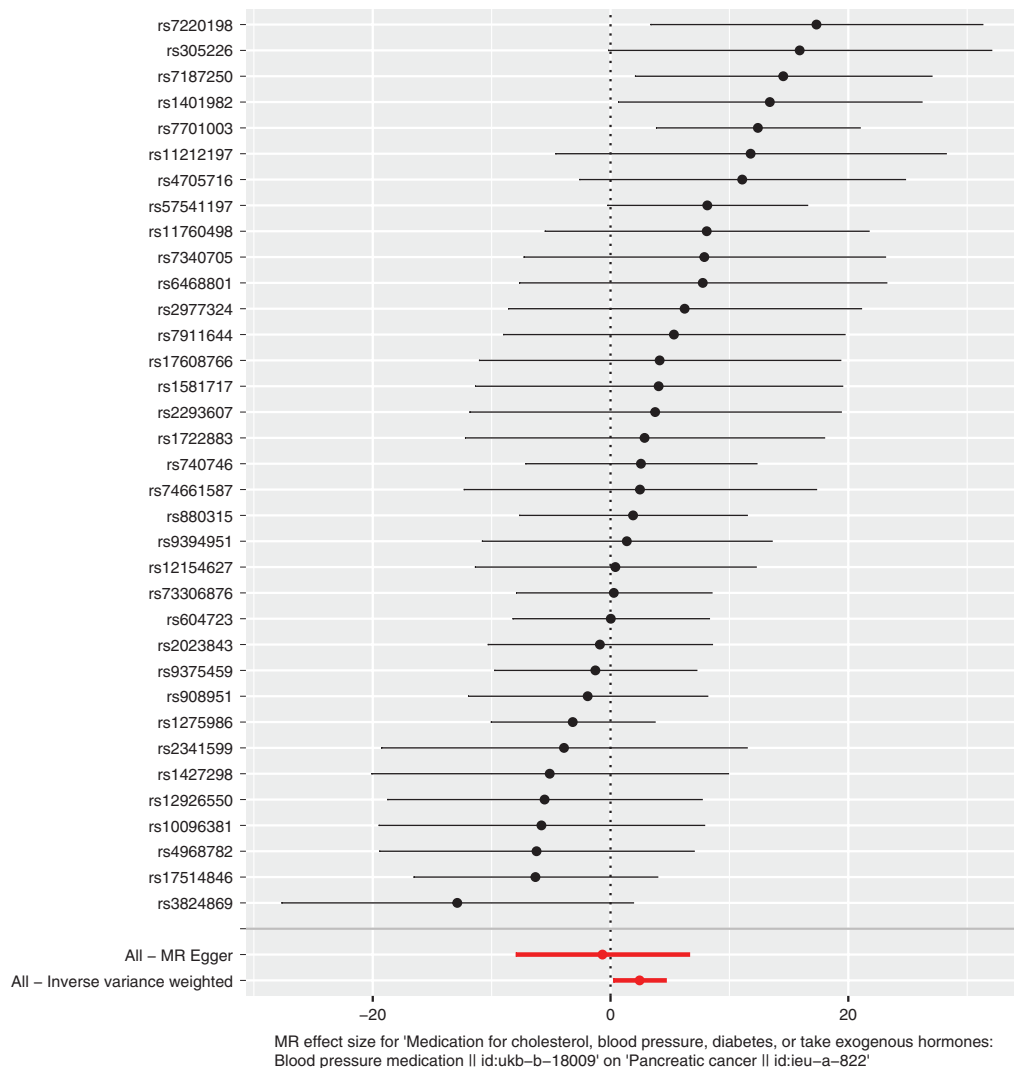
Figure 3 Forest plot of estimated causal effects of diabetes mellitus–associated SNPs on pancreatic cancer.
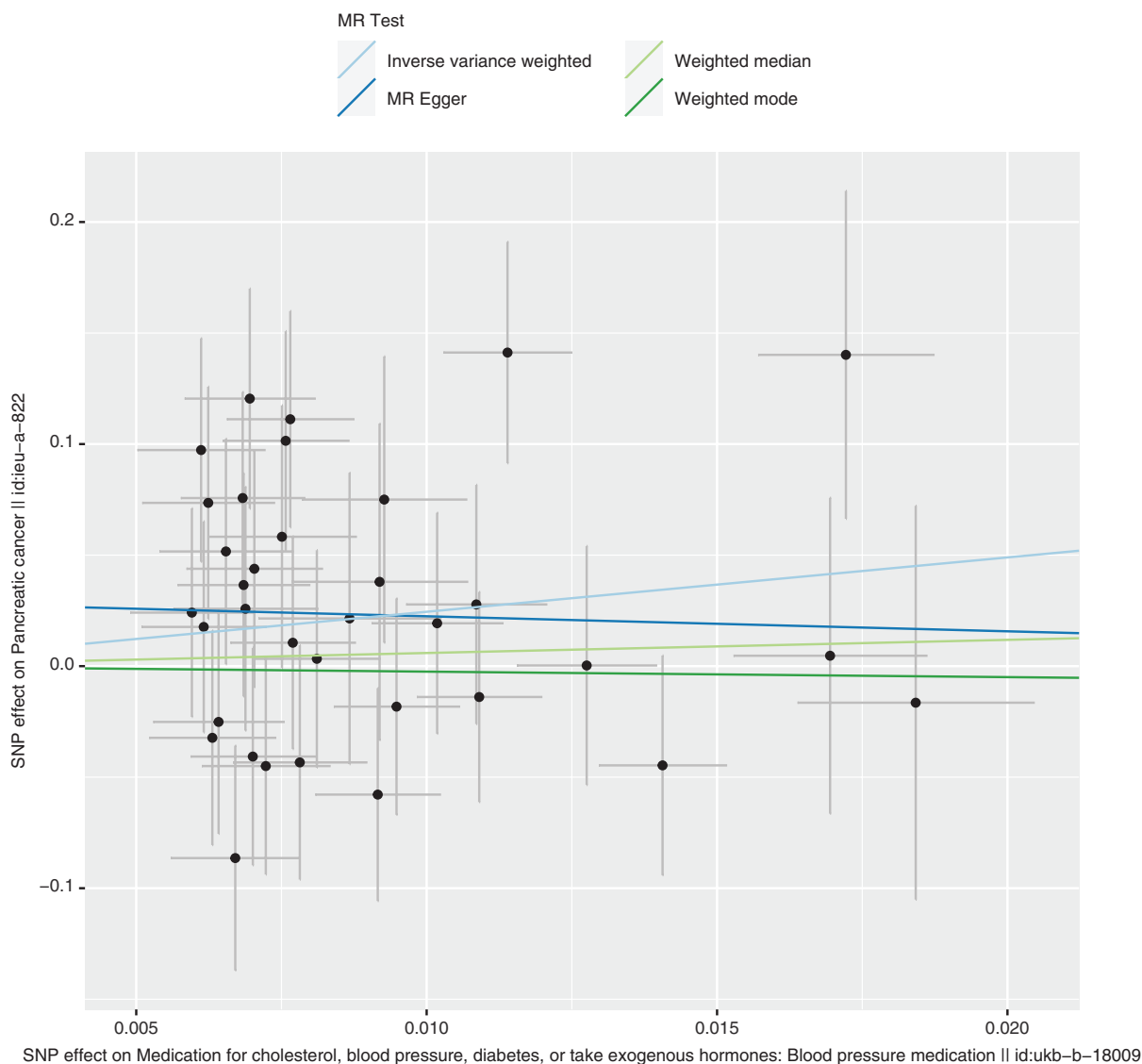
Figure 4 Scatterplot of estimated causal effects of diabetes mellitus–associated SNPs on pancreatic cancer.

Table 3 Cochran's Q Test Results

| Method	Q	df	I²	P
Inverse variance weighted	43.58	34	0.219825608	0.1257
MR-Egger	42.58	33	0.224988257	0.1227

The MR-Egger regression intercept indicated no directional pleiotropic effects in the relationship between DM and PC (MR-Egger intercept=0.029, P=0.384). Additionally, the funnel plot analysis demonstrated that the scatter points representing the causal association effect were symmetrically distributed when SNPs were individually used as variables, thus suggesting an absence of potential bias in the findings (**Figure 5**).

The outcomes of leave-one-out analysis are presented as a forest plot (**Figure 6**). The black line indicates the effects of all SNPs remaining after exclusion of the respective SNP. In contrast, the red line illustrates the cumulative effect without elimination of any SNPs. The dots and horizontal lines represent the beta value of the effect and its 95% CI. The SNPs rs1401982, rs7701003, rs7220198, and rs57541197 were

excluded. The remaining SNPs were situated to the right of the dashed line, thereby demonstrating the strength of the findings and their independence from the effect of a solitary SNP.

Discussion

PC is a profoundly malignant neoplasm affecting the digestive system. It is the fourth leading cause of cancer-associated mortality in the United States and is projected to became the second leading cause by 2030 [13]. Early detection through screening is critical for mitigating mortality rates. However, because of the relatively low prevalence of PC, routine screening of asymptomatic patients through conventional methods is not economically advantageous and has poor compliance. Numerous investigations have been aimed at identifying cohorts at high risk [14]. However, a family history of PC is currently the only indication considered for PC screening [15]. Therefore, better identification of high-risk groups is necessary to enable early PC diagnosis and treatment.
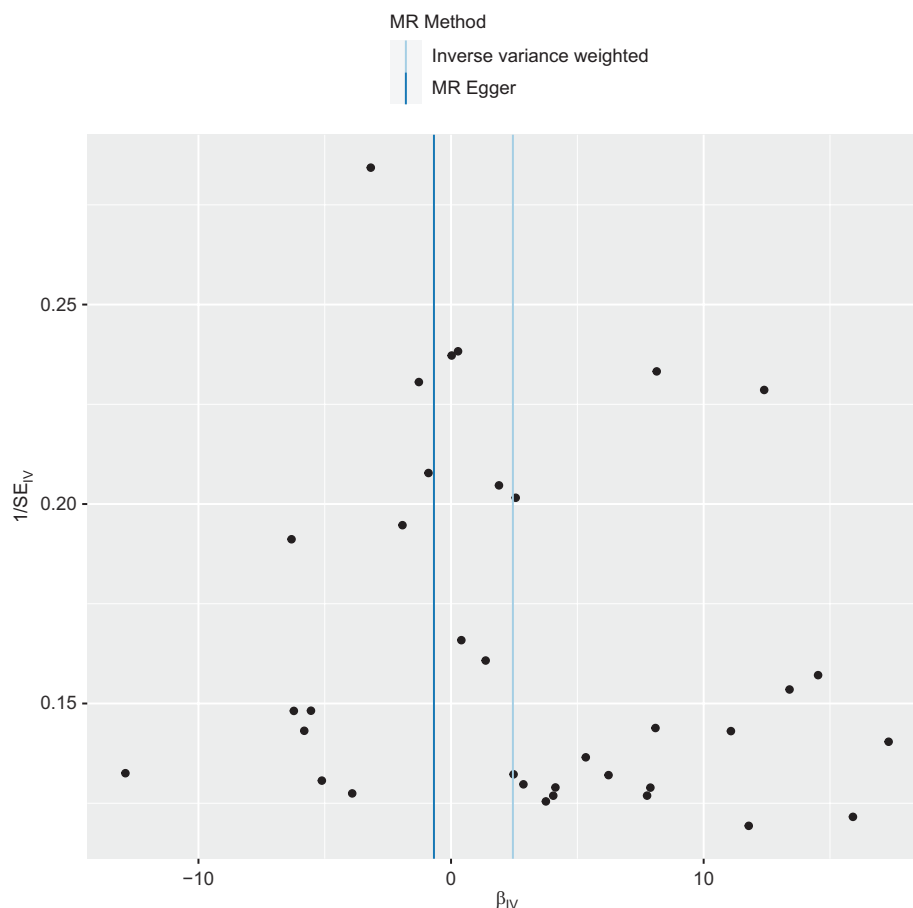
Figure 5   Mendelian randomization funnel plot.

The association between DM and PC risk has been a longstanding topic of academic investigation. Recent DM onset has been demonstrated to serve as an indicator for certain diseases, particularly PC, and can aid in identifying patients with heightened susceptibility to this condition [16]. However, the relationship between DM and PC is further complicated by the ability of PC itself to induce DM development. Consequently, risk studies must exclude any patients who have acquired diabetes as a consequence of PC, as well as those who have pre-existing DM. It is additionally worth investigating the potential resistance of patients diagnosed with DM towards being categorized as part of a high-risk cohort for early screening of PC.

The main aim of this study was to investigate the possible presence of a causal link between DM and PC. Previous research efforts have been impeded by the impracticability of conducting randomized controlled trials, thus limiting the ability to adequately control for confounding variables. Consequently, the findings from previous observational studies might have been influenced by confounding bias or reverse causality, thereby preventing consistent conclusions from being drawn. Our research used a GWAS-based MR method to address potential confounding variables and reverse causality, thereby allowing for investigation of the causal relationship between DM and PC at the genetic level. In contrast to previous studies, our results provide supplementary evidence that strengthens the argument that DM increases vulnerability to PC, thereby conclusively establishing DM as a risk factor for PC. Elena et al. have conducted

a retrospective study indicating an association between DM and PC risk. Additionally, clinical studies [17] have suggested that approximately 50% of patients with PC are diagnosed with DM, and the duration of DM correlates with PC. These investigations have provided valuable insights into potential epidemiological links between DM and PC. Nevertheless, caution is necessary when interpreting these observational findings. In the present study, we used a two-sample MR analysis to investigate the association between DM as the exposure factor and PC as the outcome event. Our analysis revealed no indications of horizontal pleiotropy and demonstrated homogeneity among IVs. Consequently, we used the IVW method as the primary outcome measure, supplemented by the WM approach for additional analysis. The findings of this study provide substantial evidence supporting an elevated risk of PC in people with DM; establish a causal relationship between DM and PC; and suggest elevated PC susceptibility among people with DM.

The correlation between DM and PC continues to be a topic of ongoing scholarly discourse. Previous research has suggested that insulin-like growth factor (IGF) and insulin play crucial roles in regulating energy metabolism and growth. In vitro studies have shown that excess insulin promotes the survival and proliferation of PC cells [18]. The IGF system, which includes IGF, its receptors, and associated binding proteins [19], is frequently characterized by elevated insulin and IGF-1 in people with type 2 DM [20]. In a prospective study conducted on European populations, researchers have observed a significant association between elevated IGF-1 or
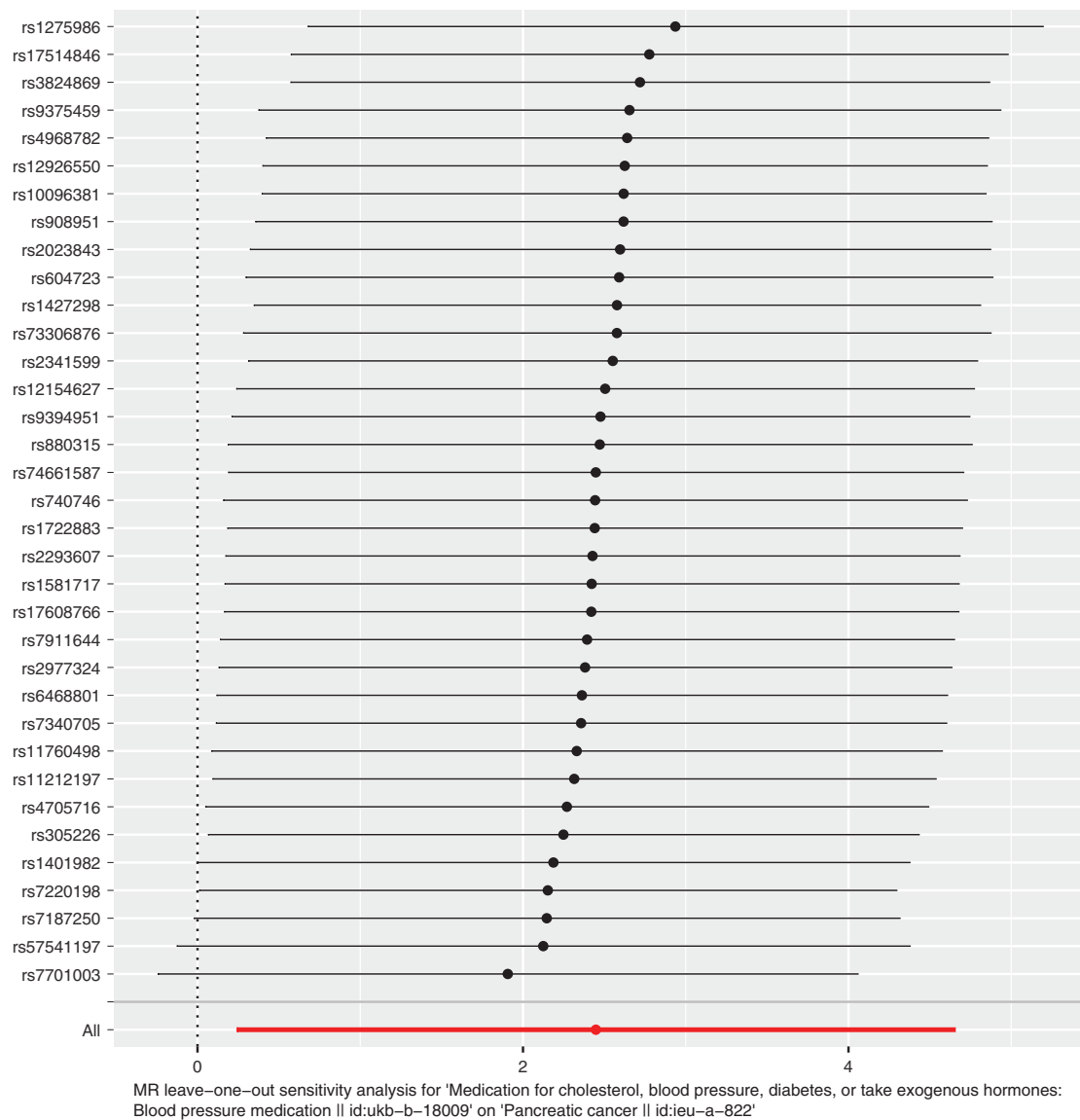
Figure 6 Results of leave-one-out analysis of diabetes mellitus and pancreatic cancer.

diminished IGF-BP3 in the serum and susceptibility to PC [21]. Experimental investigations have further demonstrated that the introduction of exogenous insulin or IGF-1 stimulates the proliferation of PC cell lines [22]. This proliferative effect is mediated by activation of the MAPK pathway through binding of insulin and IGF-1 to their receptors IR and IGF-1R, respectively [22]. Additionally, PI3K pathway activation enhances the anti-apoptotic capabilities of cancer cells [22]. Additional research has demonstrated that a ketogenic diet has the potential to mitigate transient feedback hyperglycemia in the context of tumor treatment involving PI3K inhibitors [23]. This finding has major implications for anti-tumor therapy in patients with insulin resistance or diabetes mellitus. Moreover, elevated metabolic stress protein TRB3 in tumor cells has multifaceted effects on insulin/IGF-mediated production of reactive oxygen species, apoptosis, and tumor cell autophagy inhibition through its interaction with P62, thereby facilitating tumor initiation and progression [24]. Moreover, hyperglycemia may lead to oxidative stress, which is caused by an imbalance between reactive oxygen species and antioxidants [25]. Most patients diagnosed with DM have elevated blood glucose levels, which stimulate the generation of reactive oxygen species [26], thereby augmenting the invasiveness of cancerous cells and facilitating the initiation and progression of PC. Oxidative stress and inflammatory conditions have been postulated to be early stages in the development insulin resistance, accompanied by heightened levels of oxidative stress and inflammatory markers [27, 28], such as nuclear factor-κB and diverse signal transduction molecules and transcriptional activation proteins that activate signaling pathways and subsequently stimulate PC progression [29]. On the basis of the aforementioned analysis, we propose that inhibition of the IGF signaling pathway might potentially mitigate susceptibility to PC in people with diabetes.

This study has several limitations that should be acknowledged. First, the samples used in this study consisted of solely people of European ancestry. Thus, future studies must include samples from participants of other rases, such as those with Asian and African ancestry. Second, the data obtained in this study were derived from GWAS summaries, thereby precluding the exclusion of potential confounding factors such as alcohol consumption and smoking. Finally,

the precise mechanism through which diabetes increases the likelihood of PC remains elusive; therefore, further investigation is warranted to support our findings.

Conclusion

This study used MR research methods to establish a causal relationship between DM and the occurrence of PC. Individuals diagnosed with DM are a high-risk population requiring early screening for PC. The IGF signaling pathway potentially plays a crucial role in mediating the influence of DM on PC development. Therefore, timely medication interventions must be prioritized to prevent PC progression in patients with DM.

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Availability of data and materials

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Authors' contributions

Xie Hui, Zuliang Deng, and Tan Tao designed the study; Wenxing Long and Hanping Duan searched the data; Xie Hui, Zuliang Deng, and Tan Tao analyzed and interpreted the literature and made major contributions in writing the manuscript. Xie Hui and Tan Tao revised the manuscript.

Conflict of interest statement and consent for publication

The authors have no ethical, legal, or financial conflicts associated with the article. All authors have read and approved the manuscript for publication.

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