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Protective effect of antidiabetic drugs against male infertility: evidence from Mendelian randomization

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Abstract

Background The global prevalence of diabetes has been steadily increasing, with a growing number of younger individuals being affected. Over recent decades, various antidiabetic drugs have been repurposed for treating conditions beyond diabetes. However, the effects of antidiabetic drugs on male infertility (MIF) remain inadequately elucidated. This Mendelian randomization (MR) study aims to clarify the potential impact of antidiabetic drugs on the risk of MIF.

Method We designed a comprehensive analytical workflow involving two-sample MR and summary-based MR (SMR) to assess the causal relationship between antidiabetic drug targets and MIF. First, instrumental variables were obtained based on HbA1c levels and gene expression levels. Then, MR analysis was performed after selecting positive target genes from four blood glucose level and type 2 diabetes (T2DM) datasets. Finally, we applied SMR analysis to validate and expand upon the previous conclusions. Additionally, sensitivity analyses were conducted to evaluate the robustness of the results.

Results Seven drug targets associated with five antidiabetic drugs were identified as significantly related to MIF. In the two-sample MR, the following drugs were found to reduce MIF risk through their respective significant targets: metformin (*GPD1*: IVW OR 0.007, 95% CI 0.000–0.204, $P=0.004$), *SGLT2* inhibitors (SGLT2i) (*SLC5A1*: IVW OR 0.048, 95% CI 0.004–0.585, $P=0.017$), insulin and its analogs (*IGF1R*: IVW OR 0.773, 95% CI 0.648–0.922, $P=0.004$), and sulfonylureas (*TRPM4*: IVW OR 0.869, 95% CI 0.766–0.985, $P=0.028$; *CTPA1*: IVW OR 0.838, 95% CI 0.741–0.947, $P=0.005$). In SMR analysis, antidiabetic drugs targeting the genes *CPE* ($P=0.03$, HEIDI = 0.970) and *TRPM4* ($P=0.028$, HEIDI = 0.746) were found to significantly reduce the risk of MIF.

Conclusion Our study indicates that metformin, SGLT2i, insulin and its analogs, as well as sulfonylureas, may offer potential therapeutic benefits for MIF. Specifically, six antidiabetic drug target genes *GPD1*, *SLC5A1*, *IGF1R*, *TRPM4*, *CPT1A*, and *CPE* may play a role in the progression of MIF. These findings have significant implications for the development of personalized precision therapies for MIF.

Keywords Antidiabetic drugs, Male infertility, Mendelian randomization, Drug targets

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Introduction

Clinical infertility is defined as the inability of a couple to conceive after 12 months of regular unprotected intercourse, with male infertility (MIF) contributing to 30–50% of cases [1]. Common causes of MIF include testicular dysfunction, impaired sperm function [2], endocrine disorders [3], metabolic syndrome [4], lifestyle factors such as smoking and obesity [5], and exposure to ionizing radiation [6, 7]. Among them, semen quality is widely considered a key determinant of MIF [8]. Approximately half of MIF patients exhibit abnormalities in semen parameters due to various causes, including reductions in sperm concentration, total count, morphology, and motility [9, 10]. Standard treatments include drug and hormone therapy, surgical interventions, assisted reproductive techniques, and surgical sperm retrieval [11]. However, conception remains a challenge for many couples. Therefore, identifying effective therapeutic targets and exploring novel treatments is of urgent importance.

Antidiabetic drugs regulate blood glucose through various mechanisms and are widely prescribed in clinical practice for diabetes management. Recently, lots of these agents have been shown to benefit conditions beyond glycemic control [12]. Studies suggest that antidiabetic drugs may influence the development of MIF through multiple pathways; however, the precise mechanisms remain unclear [13].

Mendelian randomization (MR) is a method that uses genetic variation as an instrumental variable (IV) to infer causal relationships between exposures and outcomes. Because genetic variations are randomly assigned at conception, prior to disease onset, MR minimizes potential bias from confounding factors [14]. Additionally, by incorporating genetic colocalization and variations associated with drug target mRNA expression, MR can be employed to investigate the relationship between drug exposure and disease outcomes [15].

The aim of this study is to evaluate the causal effect of antidiabetic drugs on MIF using MR and to further investigate the impact of gene expression associated with antidiabetic drugs on MIF. This approach offers new insights into potential therapeutic targets for MIF.

Method

Identification and validation of antidiabetic drug targets

Based on prior studies, we identified effective targets of antidiabetic drugs through three steps [14, 16, 17]. Firstly, we determined the genetic targets of eight classes of commonly prescribed antidiabetic drugs using the DrugBank pharmacogenomics database (Tables S1 and S2). Secondly, we obtained IVs for these targets within the cis-regions (± 500 kb) from a genome-wide association study (GWAS) of glycated hemoglobin (HbA1c) in the UK Biobank population. The criteria for selecting IVs were $P < 5 \times 10^{-8}$ and $r^2 < 0.2$. During this process, we found that some target genes located in overlapping cis-regions shared the same IVs, so these genes were merged and labeled with slashes (e.g., "*ABCC8/KCNJ11*," "*ABCB11/LRP2*," "*KCNJ8/ABCC9*," and "*VEGFA/SLC29A1*"). Finally, as no single GWAS dataset contained IVs for all drug targets associated with HbA1c, blood glucose levels, or type 2 diabetes (T2DM), we retrieved IVs for these gene targets from three non-Biobank GWAS datasets: HbA1c data from the Within Family GWAS Consortium (https://gwas.mrcieu.ac.uk/datasets/ieu-b-4842), T2DM data from Sílvia Bonàs-Guarch (https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005413), and fasting glucose data from MAGIC (https://gwas.mrcieu.ac.uk/datasets/ieu-b-114) (Table S3).

To validate the effectiveness of the identified drug targets, we used four datasets related to blood glucose levels and T2DM as positive controls. Targets that showed no association with any of the positive control results were excluded from further analysis (Table S7).

Additionally, we identified single nucleotide polymorphisms (SNPs) associated with the expression levels of target genes for antidiabetic drugs from the eQTLGen Consortium (https://www.eqtlgen.org) as IVs (Table S4). To ensure the correlation between genetic variants and changes in gene expression, we included only cis-expression quantitative trait loci (cis-eQTLs) located within 500 kb of the target genes in this analysis [18]. To minimize bias caused by weak IVs, we calculated the F-statistic for these SNPs using the following formulas: $F = R^2 \times (N - 2)/(1 - R^2)$; $R^2 = \beta^2/(\beta^2 + se^2 \times (N - 1))$. F-statistic of over 10 indicates no weak instrumental bias. (Tables S5 and S6).

The research process is illustrated in Fig. 1. All of these datasets primarily consist of European ancestry samples and are available on the MRC IEU OpenGWAS platform (https://gwas.mrcieu.ac.uk/) (Table S7).

Determination of the male infertility

The data of MIF comes from FinnGen research, which integrates the genotype data from Finnish Biobank and the digital health records of Finnish Health Registry. MIF is diagnosed by doctors, including azoospermia, oligospermia and unspecified MIF. In addition, patients with reproductive organ cancer were excluded [19].

Mendelian randomization analysis

We employed two-sample MR to assess the causal effects of each antidiabetic drug target on MIF. This method enables the separation of the specific effects of drug targets from those of blood glucose levels. As illustrated in

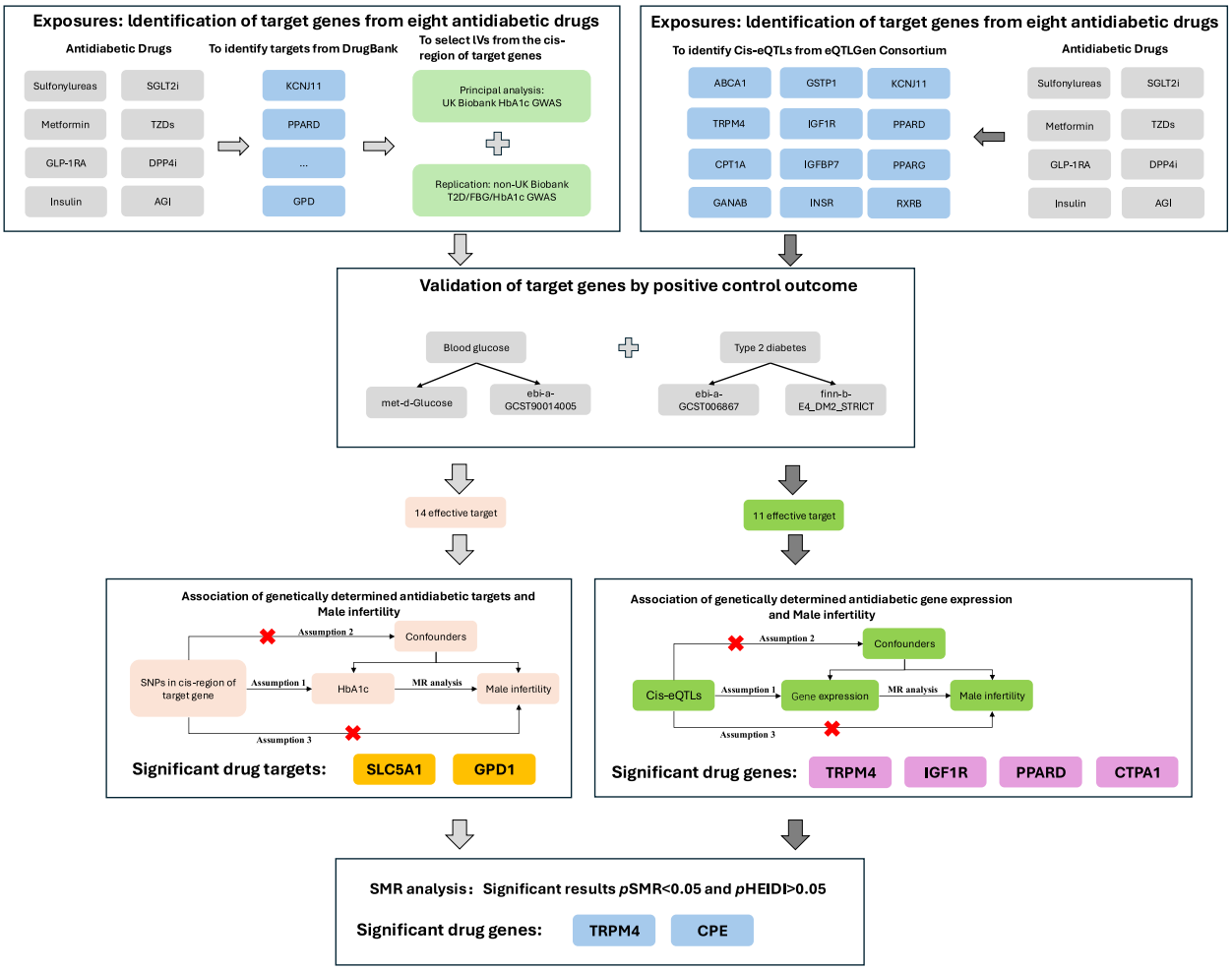

Fig. 1 Study design overview

the MR causal diagram (Fig. 1), this approach relies on three key assumptions: (1) the SNPs must be associated with the risk factor (relevance assumption); (2) the SNPs must not be influenced by confounders related to the risk factor-outcome association (independence assumption); and (3) the SNPs must affect the outcome only through the risk factor (exclusion restriction assumption).

The primary method used was the inverse variance weighted (IVW) approach, with results cross-verified using MR-Egger, Weighted Median, Simple Mode, and Weighted Mode methods to ensure robustness. The weighted median and simple mode methods provide reliable estimates even when a subset of genetic instruments may be invalid, as long as the proportion of invalid instruments does not exceed 50%. The weighted mode method is considered robust when most causal effect estimates derive from valid instruments. Additionally, for target genes with fewer than three valid SNPs, the Wald Ratio method was primarily used for analysis. These methods were employed in parallel to address potential violations of the IV assumptions.

Random effects IVW was used to account for potential bias arising from high heterogeneity among the IVs. To assess heterogeneity, Cochran's Q statistic was calculated using both the MR-Egger and IVW methods. A *p*-value greater than 0.05 indicates the absence of significant heterogeneity. Additionally, the intercept from MR-Egger regression was used to test for horizontal pleiotropy. MR-PRESSO analysis was also performed to detect and correct specific IV outliers (potential pleiotropic SNPs) as an additional sensitivity analysis. Furthermore, a leave-one-out analysis was conducted to evaluate the influence of individual SNPs on the causal effect of the exposure on the outcome [20]. Given that this study aims to broadly explore the potential association between antidiabetic drug target genes and male infertility, we employed a relatively liberal false discovery rate (FDR) for multiple testing correction. Specifically, a corrected *P*-value of

< 0.1 suggests a potential causal relationship between the exposure and the outcome, while a corrected *P*-value of < 0.05 indicates a statistically significant causal relationship [21–23].

According to the mechanisms of action of antidiabetic drugs against different targets in the DrugBank database (Table S2), odds ratios (OR) were adjusted accordingly. For targets classified as agonists or those with unknown mechanisms (e.g., Modulator, Agonist, Activator, Substrate, Unknown, and Other), the original OR was used. For inhibitory targets (e.g., Blocker, Inhibitor, Antagonist, and Inverse Agonist), the reciprocal of the original OR was used as the adjusted OR.

The MR analyses were conducted using the TwoSampleMR package (version 0.5.7) with default parameters (https://mrcieu.github.io/TwoSampleMR/).

Summary-based mendelian randomization

We assessed the effects of all eight antidiabetic drugs (including *DPP4* inhibitors) on gene expression using the Summary-Based Mendelian Randomization (SMR) method to investigate the association between gene expression related to antidiabetic drug targets and the risk of MIF. The SMR method utilizes the SNP most strongly associated with cis-eQTLs as the primary instrumental variable. The main results are presented as the OR for MIF per standard deviation increase in gene expression. To determine whether the observed association between gene expression and MIF is driven by linkage effects (i.e., the eQTL SNP being in linkage disequilibrium with another SNP that independently affects the disease outcome, potentially violating MR assumptions), we conducted a heterogeneity in dependent instruments (HEIDI) test. A *p*-value below 0.05 in the HEIDI test suggests that the association may be driven by a linkage effect rather than gene expression regulation. The SMR analysis was performed using default parameters (https://yanglab.westlake.edu.cn/software/smr/#SMR&HEIDIanalysis).

Result

Identification of antidiabetic drug targets

Based on HbA1c levels, we identified 17 potential targets associated with MIF across eight antidiabetic drug groups: sulfonylureas (*ABCB11*, *ABCC8/KCNJ11*, *CPT1A*, *KCNJ1*, *INS*, *KCNJ8/ABCC9*, *LRP2/ABCB11*, *VEGFA/SLC29A1*), TZDs (*PPARG*, *RXRB*, *VEGFA/SLC29 A1*, *ESRRA*, *SERPINE1*), AGIs (*GANC*), GLP-1RAs (*GLP-1R*), metformin (*GPD1*), *SGLT2* inhibitors (SGLT2i) (*SLC5A1*, *SLC5A2*), and insulin (*LRP2/ABCB11*).

Based on gene expression levels, we identified 12 potential target genes associated with MIF from the eQTLGen Consortium: *ABCA1*, *TRPM4*, *CPT1 A*, *GANAB*, *GSTP1*, *IGF1R*, *IGFBP7*, *INSR*, *KCNJ11*, *PPARD*, *PPARG*, and *RXRB*.

Validation of antidiabetic drug targets

Four datasets related to T2DM and blood glucose levels were used for positive control testing. Among the target genes identified based on HbA1c levels, 14 passed the positive control test (Table S8). Similarly, 11 target genes identified based on gene expression levels passed the positive control test (Table S9). Genes that passed the positive control test were included in subsequent analyses.

The impact of antidiabetic medications on male infertility

MR analysis was performed on the SNPs identified based on HbA1c levels. A total of two drug targets were significantly associated with MIF: the target of SGLT2i, *SLC5A1* (IVW: OR 0.048, 95% CI 0.004–0.585, *P* = 0.017, FDR = 0.092), and the target of metformin, *GPD1* (IVW: OR 0.007, 95% CI 0.000–0.204, *P* = 0.004, FDR = 0.030). Further analysis of the effects of these two drugs revealed that both SGLT2i (IVW: OR 0.099, 95% CI 0.021–0.463, *P* = 0.003) and metformin (IVW: OR 0.007, 95% CI 0.000–0.204, *P* = 0.004) remained significantly negatively associated with MIF risk (Table 1). These results suggest that the use of metformin and SGLT2i may have a potential protective effect on MIF. The effects of each drug target's SNPs on MIF are shown in Fig. 2 and Table S10.

MR analysis was also performed on the SNPs identified based on gene expression levels. We found that the gene expression of *IGF1R* (IVW: OR 0.773, 95% CI 0.648–0.922, *P* = 0.004, FDR = 0.027), *TRPM4* (IVW: OR 0.869, 95% CI 0.766–0.985, *P* = 0.028, FDR = 0.085), and *CPT1 A* (IVW: OR 0.838, 95% CI 0.741–0.947, *P* = 0.005, FDR = 0.027) was negatively correlated with MIF risk. Conversely, *PPARD* (IVW: OR 2.257, 95% CI 1.105–4.611, *P* = 0.025, FDR = 0.085) was positively correlated with MIF risk (Table 2). The effects of each drug target gene on MIF are shown in Fig. 3 and Table S11.

Summary-based mendelian randomization

In the SMR analysis, *TRPM4* (*P* = 0.028, HEIDI = 0.746) was further validated as potentially beneficial for MIF. Additionally, the expression of the *CPE* gene in human testicular tissue showed a negative correlation with MIF (*P* = 0.030, HEIDI = 0.970), suggesting that increased expression of *CPE* may reduce the risk of MIF (Table S12).

Table 1 Mendelian randomization analysis results of antidiabetic drug target genes screened based on glycated hemoglobin (HbA1c)

Target gene	Method	nSNP	OR	LCI95	UCI95	P.val	Q.pval	MR-PRESSO	MR-Egger	FDR
SGLT2i	MR Egger	22	0.902	0.005	151.240	0.969	0.907	0.911	0.385	0.969
	Weighted median	22	0.094	0.011	0.812	0.032				0.148
	Inverse variance weighted	22	0.099	0.021	0.463	0.003	0.907			0.030
	Simple mode	22	0.016	< 0.001	0.703	0.044				0.520
	Weighted mode	22	0.102	0.004	2.740	0.188				0.376
GPD1	MR Egger	4	2.282	< 0.001	1.114E + 09	0.943	0.997	0.969	0.626	0.969
	Weighted median	4	0.011	< 0.001	0.499	0.020				0.143
	Inverse variance weighted	4	0.007	< 0.001	0.204	0.004	0.954			0.030
	Simple mode	4	0.011	< 0.001	1.921	0.186				0.520
	Weighted mode	4	0.011	< 0.001	1.379	0.165				0.376
SLC5A1	MR Egger	9	0.039	< 0.001	3433.101	0.593	0.304	0.388	0.971	0.969
	Weighted median	9	0.007	< 0.001	0.194	0.003				0.049
	Inverse variance weighted	9	0.048	0.004	0.585	0.017	0.401			0.092
	Simple mode	9	0.006	< 0.001	1.173	0.094				0.520
	Weighted mode	9	0.007	< 0.001	0.774	0.073				0.376

This table presents the Mendelian randomization (MR) analysis results of antidiabetic drug target genes, which were screened based on their association with HbA1c. The analysis evaluates the potential causal association between these target genes and male infertility. Key statistical metrics provided include the odds ratio (OR) with corresponding 95% confidence intervals (LCI95–UCI95) and *p*-values (P.val) to assess the significance of the associations. Additionally, the table includes the number of single nucleotide polymorphisms (nSNP) used in each MR method, heterogeneity test results (Q.pval), and sensitivity analyses using MR-PRESSO and MR-Egger methods to detect potential pleiotropy and instrumental variable validity. The false discovery rate (FDR) is also reported to adjust for multiple comparisons and ensure the robustness of the findings. A *p*-value ($P < 0.05$) and an FDR < 0.1 indicate a significant causal relationship between the target gene and male infertility

Sensitivity analysis

All antidiabetic drug target genes that exhibited a significant association with MIF in this study successfully passed the heterogeneity and horizontal pleiotropy tests, further strengthening the robustness of our findings. Detailed results of the sensitivity analysis are provided in Tables S10 and S11.

Discussion

Our study identified seven significant antidiabetic drug targets associated with MIF across five classes of antidiabetic drugs: metformin (*GPD1*), SGLT2i (*SLC5A1*), sulfonylureas (*TRPM4*, *CTPA1*), insulin and its analogs (*IGF1R*, *CPE*), and TZDs (*PPARD*). Notably, the targets of metformin, SGLT2i, sulfonylureas, and insulin analogs were negatively associated with MIF, suggesting potential benefits of these drugs in the treatment of infertility. In contrast, the TZD target *PPARD* was positively associated with MIF. However, the mechanisms through which *PPARD* and TZDs exert their effects remain unclear, complicating efforts to define their precise role in MIF. Further in-depth studies are needed to validate and clarify their impact.

Metformin, an oral antidiabetic agent, is one of the most widely prescribed drugs globally [24]. Beyond its primary role in glycemic control, metformin has demonstrated immune-modulatory, anti-aging, anti-inflammatory, and antimicrobial properties [25, 26]. Studies indicate that metformin enhances antioxidant enzyme activity, reduces testicular oxidative stress and inflammation, inhibits apoptosis, and increases sperm concentration and motility [27, 28], thereby improving fertility in diabetic rat models [29]. Further animal studies have shown that metformin dose-dependently increases sperm motility, mitigates testicular damage, reduces mitochondrial injury, and reverses apoptosis, possibly by inhibiting oxidative stress [30]. In diabetic rats, tail vein administration of 200 mg/kg metformin significantly improved sperm count, motility, morphology, and spermatogenesis, alongside reduced malondialdehyde levels and elevated total antioxidant capacity, ultimately improving fertility[31]. In a clinical study involving 100 diabetic men, Zaidi et al. reported improvements in sperm motility and morphology in the metformin-treated group[32].Another study involving 45 men diagnosed with metabolic syndrome and oligoasthenoteratozoospermia demonstrated significant improvements in sperm concentration, motility, and morphology after six months of 850 mg metformin administered three times daily [4]. Additionally, an in vitro study conducted in Pakistan found that metformin enhanced antioxidant capacity and improved sperm count, morphology, and motility in semen samples from 44 infertile men [33]. Our findings suggest that metformin may improve MIF by inhibiting *GPD1* and exerting antioxidant, anti-apoptotic, and mitochondrial-protective effects. However, further research is required to fully elucidate the precise mechanisms involved.

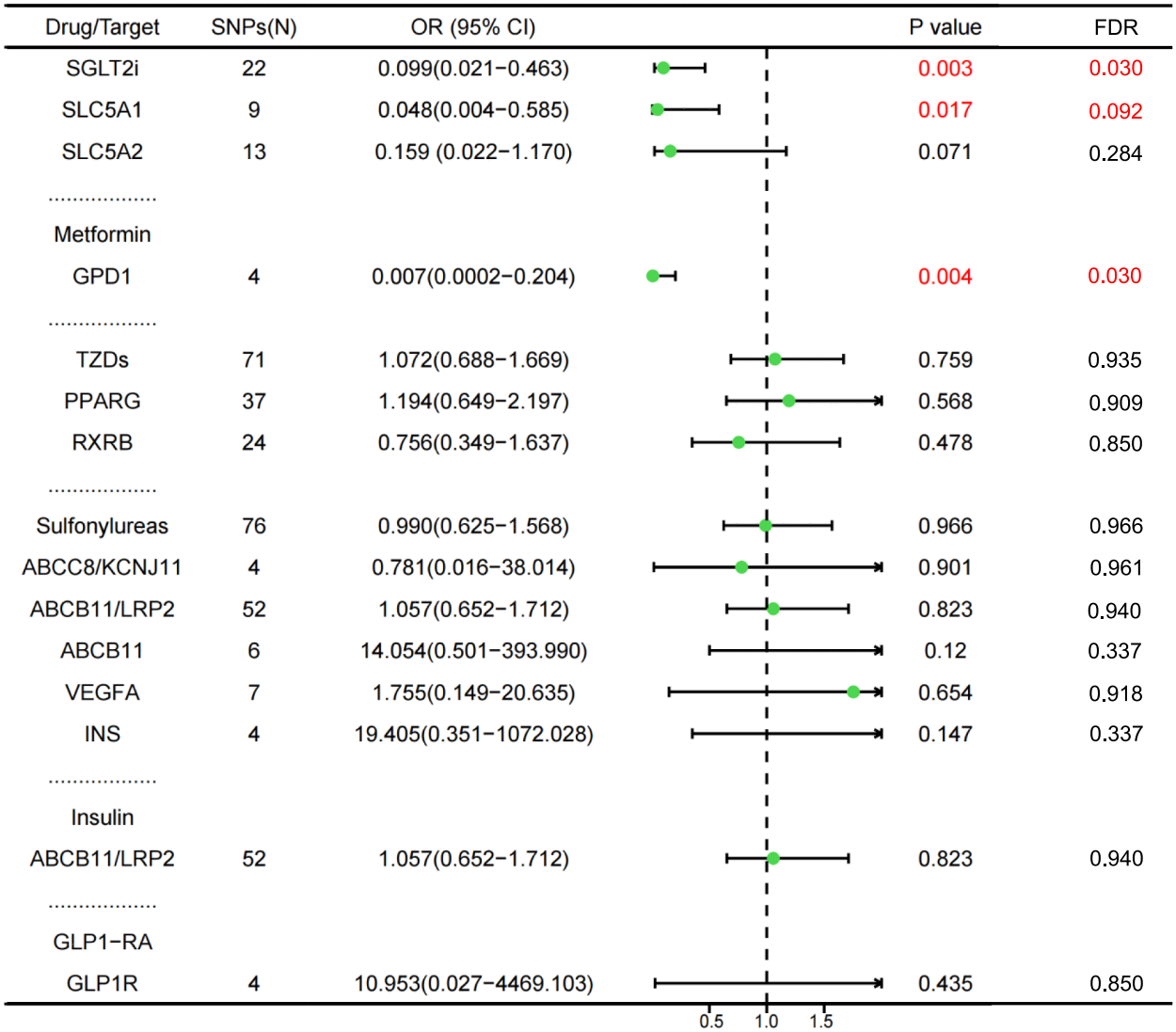

Fig. 2 The forest plot of the effect of antidiabetic drug targets on male infertility risk

SGLT2i, a newer class of oral antidiabetic drugs [34], reduce blood glucose levels by inhibiting *SLC5A1* and *SLC5A2* in the renal tubules and intestines, thereby decreasing glucose reabsorption[35]. Increased expression of *SLC5A1* has been associated with oxidative stress and mitochondrial dysfunction [36], which could impact male fertility.

Numata S. et al.'s study found that sperm motility is dependent on *SLC5A1*, and inhibition of this protein significantly decreases sperm's straight-line velocity, curvilinear velocity, average path velocity, beat-cross frequency, and amplitude of lateral head displacement, without affecting sperm capacitation [37]. In subsequent studies, they found that *SLC5A1* enhances glucose uptake in sperm, with total motility in *SLC5A1*-deficient mice decreasing by 17%. Interestingly, male mice with *SLC5A1* knockout remained fertile and exhibited normal sperm morphology and count[38]. These findings suggest that while inhibition of *SLC5A1* may impair sperm motility, it does not appear to affect overall fertility.

Sulfonylureas function as insulin secretagogues, lowering blood glucose levels by directly stimulating pancreatic β-cells to secrete insulin in a glucose-independent manner [39]. The sulfonylurea receptors (*SUR*) are key regulatory subunits of ion channels, with *SUR1* forming a non-selective cation channel in association with *TRPM4*. Recent studies suggest that *TRPM4* overexpression may contribute to endothelial cell inflammation and injury [40, 41], as well as oxidative stress, mitochondrial dysfunction, and excessive production of reactive oxygen

Table 2 Mendelian randomization analysis results of antidiabetic drug target genes screened based on gene expression levels

Target gene	Method	nSNP	OR	LCI95	UCI95	P.val	Q.pval	MR-PRESSO	MR-Egger	FDR
IGF1R	MR Egger	40	0.908	0.576	1.431	0.679	0.987	0.987	0.459	0.967
	Weighted median	40	0.767	0.590	0.997	0.047				0.174
	Inverse variance weighted	40	0.773	0.648	0.922	0.004	0.988			0.027
	Simple mode	40	0.738	0.466	1.167	0.201				0.553
	Weighted mode	40	0.776	0.546	1.102	0.165				0.468
PPARD	MR Egger	7	3.809	0.633	22.924	0.204	0.953	0.941	0.561	0.561
	Weighted median	7	2.688	1.111	6.504	0.028				0.174
	Inverse variance weighted	7	2.258	1.105	4.611	0.025	0.960			0.085
	Simple mode	7	2.771	0.784	9.797	0.165				0.553
	Weighted mode	7	2.826	0.765	10.443	0.170				0.468
TRPM4	MR Egger	33	1.045	0.781	1.397	0.769	0.476	0.478	0.178	0.967
	Weighted median	33	0.852	0.719	1.010	0.065				0.179
	Inverse variance weighted	33	0.869	0.766	0.985	0.028	0.432			0.085
	Simple mode	33	1.000	0.794	1.260	0.997				0.997
	Weighted mode	33	0.875	0.738	1.037	0.133				0.468
CTPA1	MR Egger	47	0.761	0.598	0.969	0.032	0.408	0.462	0.372	0.353
	Weighted median	47	0.829	0.695	0.990	0.039				0.174
	Inverse variance weighted	47	0.838	0.741	0.947	0.005	0.415			0.027
	Simple mode	47	0.775	0.570	1.053	0.110				0.553
	Weighted mode	47	0.845	0.668	1.070	0.168				0.468

This table presents the Mendelian randomization (MR) analysis results of antidiabetic drug target genes, which were screened based on gene expression levels. The analysis evaluates the potential causal association between these target genes and male infertility. Key statistical metrics provided include the odds ratio (OR) with corresponding 95% confidence intervals (LCI95–UCI95) and *p*-values (P.val) to assess the significance of the associations. Additionally, the table includes the number of single nucleotide polymorphisms (nSNP) used in each MR method, heterogeneity test results (Q.pval), and sensitivity analyses using MR-PRESSO and MR-Egger methods to detect potential pleiotropy and instrumental variable validity. The false discovery rate (FDR) is also reported to adjust for multiple comparisons and ensure the robustness of the findings. A *p*-value ($P < 0.05$) and an FDR < 0.1 indicate a significant causal relationship between the target gene and male infertility

species [42, 43] Consequently, *TRPM4* inhibition by sulfonylureas may help mitigate these forms of cellular damage, potentially reducing the risk of MIF.

However, existing studies on the effects of sulfonylureas on male reproductive function have yielded inconsistent results. Naveen Kumar et al. reported that administering 7.5 mM sulfonylurea led to an immediate and irreversible loss of sperm motility in human sperm samples [44]. In contrast, Rabbani et al. observed a reduction in the number of abnormal sperm in diabetic rats treated with sulfonylureas [45], and Nelli et al. reported increased sperm count and motility, along with a decrease in abnormal sperm, in diabetic rats treated with sulfonylureas [46]. Notably, these studies differ in drug dosage and species studied, which may introduce potential biases.

The *IGF1/IGF1R* signaling pathway plays a crucial role in reproductive function [47]. Animal studies have shown that activation of *IGF-1/IGF1R* promotes sperm survival, proliferation, and the differentiation of germ cells [48]. In human studies, *IGF1R* mRNA levels in semen are positively correlated with sperm concentration and total count [49]. Additionally, in men with infertility, sperm lacking IGF1R exhibit reduced capacitation [50]. Abnormalities in the *IGF1R* locus, such as those observed in cryptorchidism and genital defects, further highlight the importance of *IGF1/IGF1R* signaling for testicular development and male fertility [51]. *CPE*, which regulates sperm Ca^{2+} influx during capacitation, is positively correlated with sperm motility and fertilization rates[52]. Male mice with *CPE* mutations demonstrate reduced fertility [53].

TZDs, synthetic agonists of peroxisome proliferator-activated receptor γ (*PPARG*) [54], are commonly used to treat *T2DM*. *PPARG* is expressed in human sperm and testicular cells [55], indicating that TZDs may influence fertility. Additionally, *PPARD*, a member of the PPAR family, inhibits the ligand-induced transcriptional activity of *PPARA* and *PPARG* [56]. PPARs are involved in regulating inflammation and oxidative stress [57], and TZDs may disrupt this balance, potentially affecting male fertility.

This study has several limitations. First, the MIF data in the FinnGen dataset were derived from electronic health records, which may not fully align with contemporary diagnostic criteria, potentially affecting their accuracy. Second, our MR analysis relied on HbA1c as a biomarker, which could introduce biases due to variations in red blood cell characteristics. Additionally, the

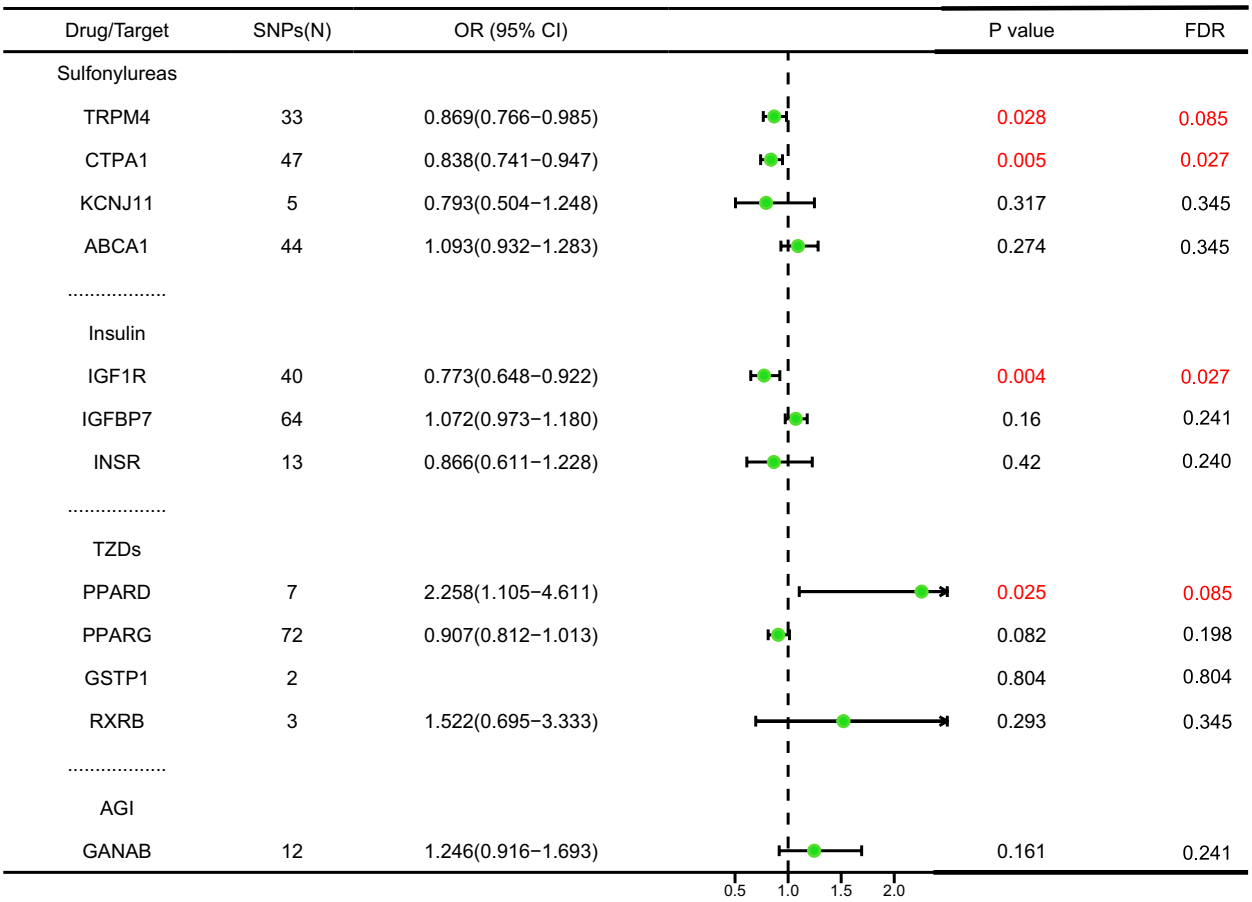

Fig. 3 The forest plot of the effect of cis-eQTLs for antidiabetic drug targets on male infertility risk

study's findings are based on individuals of European ancestry, and further validation in other populations is necessary to assess the generalizability of these results. Furthermore, although this study primarily employed the IVW method as the principal analytical approach, discrepancies observed among different analytical methods suggest potential bias, necessitating circumspect evaluation. Additionally, this study serves as a preliminary investigation into the relationship between antidiabetic drug targets and male infertility. While we validated the reliability of our conclusions using multiple analytical methods, we did not perform a colocalization analysis, which may introduce potential bias. Therefore, we strongly recommend that future MR studies incorporate colocalization analyses to enhance the robustness and reliability of the findings.

Despite these limitations, our findings have a significant impact on clinical practice. Recognizing the potential role of antidiabetic drugs and their target genes on MIF provides a new exploration direction for the treatment of MIF. At the same time, for male diabetic patients with fertility tendency, it holds significant value to choose appropriate antidiabetic drugs to control blood sugar and protect fertility.

Conclusion

In conclusion, our study supports the potential therapeutic role of antidiabetic drugs and their target genes in the treatment of MIF. Specifically, metformin, SGLT2i, sulfonylureas, insulin, and its analogs may contribute to the alleviation of MIF, whereas the effects of TZDs appear to be more complex. Notably, six antidiabetic drug target genes *GPD1, SLC5A1, IGF1R, TRPM4*, *CPT1A*, and *CPE* play a pivotal role in the interaction between antidiabetic drugs and male infertility. Given the diverse mechanisms of action of these drugs, large-scale, multicenter clinical trials are essential to evaluate their therapeutic efficacy and elucidate the underlying molecular pathways. Such investigations are crucial for validating the potential of antidiabetic drugs as a treatment strategy for MIF.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01700-0.

Supplementary material 1: Supplementary Table 1. Drug targets of all antidiabetic drugs from the DrugBabank.

Supplementary material 2: Supplementary Table 2. The information on drug target genes associated with antidiabetic medications.

Supplementary material 3: Supplementary Table 3. Summary of SNPs Selected Based on HbA1c Levels, Within Family GWAS Consortium, Sílvia Bonàs-Guarch and MAGIC.

Supplementary material 4: Supplementary Table 4. The cis-eQTL information from the eQTLGen consortium.

Supplementary material 5: Supplementary Table 5. Summary of SNPs Selected Based on HbA1c Levels.

Supplementary material 6: Supplementary Table 6. Summary of SNPs Selected Based on gene expression levels.

Supplementary material 7: Supplementary Table 7. Details of all data sources in this study.

Supplementary material 8: Supplementary Table 8. The positive control test results for target genes screened at the gene expression level.

Supplementary material 9: Supplementary Table 9. The positive control test results for target genes screened at the HbA1c level.

Supplementary material 10: Supplementary Table 10. The result of Mendelian randomization analysis between the target genes screened based on HbA1c level and the male infertility.

Supplementary material 11: Supplementary Table 11. The result of Mendelian randomization analysis between the target genes screened based on gene expression level and the male infertility.

Supplementary material 12: Supplementary Table 12. The results of SMR.

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Author contributions
Qingfu Deng participated in the design of the study, Yuqi Li, Chunyang Meng and Tao Zhou conducted the data acquisition, and drafted the manuscript. Yuqi Li, Zhiyu Liu and Qilong Wu interpreted and analyzed the data. Chunyang Meng and Xinyao Zhu performed the statistical analysis. All authors read and approved the final version of the manuscript.

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Availability of data and materials
The datasets used in this study are all publicly available.

Declarations

Ethics approval and consent to participate
This study used de-identified public summary-level data that can be downloaded for free. All the GWAS studies utilized in this study were authorized by their respective institutional ethics committees.

Informed consent
Not applicable.

Competing interests
The authors declare no competing interests.

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