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ORIGINAL RESEARCH

# Subtype-Specific Causal Effects of Antidiabetic Drug Targets on Ovarian Cancer: Mendelian Randomization and Colocalization Evidence

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**Background:** Ovarian cancer (OC), characterized by a high mortality rate and limited treatment options, underscores the urgent need to identify novel therapeutic targets to advance individualized precision therapy. Exploring the potential of antidiabetic drug target genes as therapeutic candidates may expand the treatment repertoire of diverse OC subtypes.

**Methods:** Leveraging datasets involving the Ovarian Cancer Association Consortium, the eQTLGen consortium, and the Genotype-Tissue Expression database, we implemented an integrated analytical framework combining two-sample Mendelian randomization (MR), summary data-based MR, as well as colocalization analysis to assess the association between target genes of antidiabetic drugs with the risk and survival of different ovarian cancer subtypes. Positive control analysis, replication analysis, MR-Egger regression, Bonferroni correction, and MR-PRESSO outlier test were employed to further validate the robustness of the associations.

**Results:** We systematically analyzed the associations of nine OC phenotypes with the target genes from nine antidiabetic drugs, including sulfonylureas, metformin, alpha-glucosidase inhibitors (AGIs), thiazolidinediones (TZDs), dipeptidyl peptidase 4 inhibitors (DPP4i), glucagon-like peptide-1 analogues (GLP-1A), insulin, sodium-glucose cotransporter 2 inhibitors (SGLT2i) and other drugs. Notably, multiple target genes showed consistent and significant associations with specific OC risk: AKR1A1 with Low grade serous OC; HMGCR and KCNJ11 with clear cell OC; ITGAL and AKR1B1 with mucinous OC; and AKR1A1 and ITGAL with endometrioid OC. Although high grade serous OC risk was linked to certain genes in only one method, its survival was associated with DPP4 in two approaches.

**Conclusion:** This study reveals marked subtype-specific heterogeneity in the genetic relationships between antidiabetic targets and ovarian cancer (OC), pointing to a direction for future translational research into drug repurposing for subtype-specific applications. These findings support a metabolic basis in OC progression and may inform the development of tailored therapeutic strategies based on pathological subtypes.

**Plain Language Summary:**

**Why was this study done?** Ovarian cancer is a serious disease with limited therapeutic options. This study aimed to identify potential new treatment strategies by investigating existing medications. Given established links between diabetes and cancer, we examined whether genes targeted by common diabetes drugs influence the risk of developing different subtypes of ovarian cancer or affect patient survival.

**What did the researchers do and find?** Using two sample Mendelian randomization, summary data-based Mendelian randomization, and colocalization analyses, we evaluated genetic data from large-scale studies to assess relationships between diabetes drug target genes and ovarian cancer subtypes. Our results demonstrate that these associations are highly subtype-specific. For example: Genes targeted by DPP4i (HMGCR) and sulfonylureas (KCNJ11) were linked to the risk of clear cell ovarian cancer. Genes targeted by other drugs were linked to the risk of mucinous (ITGAL, AKR1B1) and endometrioid (AKR1A1, ITGAL) ovarian cancers. DPP4 was associated with the survival of patients with high-grade serous ovarian cancer, which is the most common subtype in ovarian cancer.

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**What do these results mean?** These findings suggest that certain diabetes medications merit further investigation for their potential relevance to the risk and prognosis of specific ovarian cancer subtypes. This lays a conceptual foundation for future studies exploring treatment personalization based on precise molecular subtyping, which may ultimately contribute to more tailored clinical strategies.

**Keywords:** ovarian cancer, antidiabetic target genes, gene expression, mendelian randomization

# Introduction

Ovarian cancer, the most lethal gynecological malignancy, caused over 300,000 new cases and 207,252 deaths globally in 2020, largely due to late diagnosis and drug resistance.[1,2] Although conventional first-line therapy including surgery and platinum-based chemotherapy are initially effective, nearly 70% of patients relapse with platinum-resistant disease. While the introduction of targeted maintenance therapies such as bevacizumab and PARP inhibitors has improved survival, not all patients benefit from these treatments, underscoring the urgent need for novel therapeutic targets.[3] Metabolic reprogramming is a key driver of tumor progression, positioning metabolic pathways as promising targets for novel therapeutic strategies in ovarian cancer.[4]

OC is closely associated with endocrine dysfunction, and endocrine-metabolic factors are known contributors to its pathogenesis.[5] Diabetes mellitus (DM) may increase OC risk by disrupting endocrine homeostasis, although epidemiological studies have reported inconsistent results.[6,7] Systematic reviews provide stronger evidence supporting this association, suggesting that antidiabetic drugs could serve as potential interventions or adjunct therapies for OC.[8] However, studies on metformin's effect on OC prognosis remain conflicting,[9] underscoring the complexity of this relationship and the need for innovative approaches to clarify the underlying mechanisms. Additionally, significant heterogeneity among OC subtypes must be carefully considered in such investigations.

As a robust approach for causal inference, Mendelian randomization (MR) employs genetic variants as instrumental variables (IVs) to assess the causal impact of exposures on outcomes, effectively addressing the issues of confounding bias. Mendelian randomization (MR) has emerged as a powerful tool for inferring causal relationships between exposures and outcomes. By leveraging genetic variants, such as IVs, MR can assess the causal effect of an exposure on an outcome while minimizing confounding bias. IVs are presumed to influence the outcome exclusively via the exposure, without being affected by other confounding factors.[10] Thus, MR mimics the rigor of randomized controlled trials[11] and is particularly advantageous when exposures are difficult or expensive to measure.[12] Consequently, MR has gained widespread recognition in the fields of medical genetics and epidemiological research.

In this study, we employed an integrative approach combining three methods involving two-sample MR, SMR, and colocalization analysis to systematically examine the relationship between antidiabetic target genes and OC. Our aim was to further clarify the potential link between diabetes mellitus and OC, while evaluating the therapeutic potential of antidiabetic targets in shaping the development and prognosis of OC across different pathological subtypes. This comprehensive approach constructs an exploratory framework for prioritizing candidate genes and generating testable hypotheses regarding potential therapeutic targets for OC.

# Methods

## Identification of Antidiabetic Drug Target Genes and Determination of Study Outcomes

The methodological structure of this study is summarized in Figure 1. The DrugBank pharmacogenetics database (https://go.drugbank.com/) was utilized to identify genes associated with nine antidiabetic drugs: sulfonylureas, metformin, alpha-glucosidase inhibitors (AGIs), thiazolidinediones (TZDs), dipeptidyl peptidase 4 inhibitors (DPP4i), glucagon-like peptide-1 analogues (GLP-1A), insulin, sodium-glucose cotransporter 2 inhibitors (SGLT2i), and other drugs Tables S1 and S2 shows a complete overview of all drug target genes.

This study utilized outcome data from a genome-wide association analysis (GWAS) performed by the Ovarian Cancer Association Consortium (OCAC) involving 66,450 European participants, including 25,509 ovarian epithelial cancer

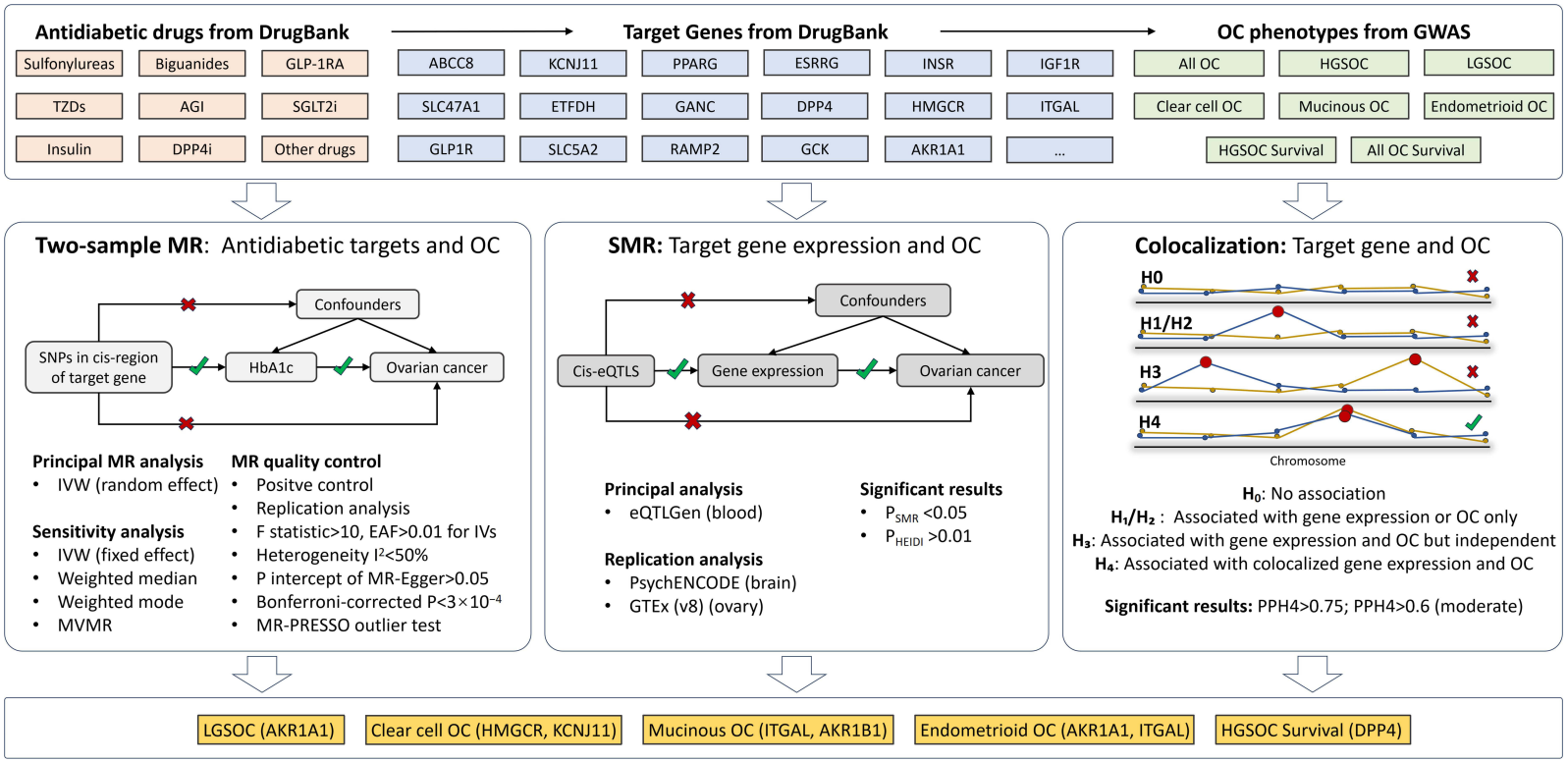


**Figure 1** Diagram outlining a structured framework for investigating the relationship between antidiabetic targets and ovarian cancer. It presents a MR analysis framework utilized to evaluate the causal effects of target genes from nine antidiabetic drugs, obtained from DrugBank, on diverse ovarian cancer phenotypes identified through extensive genome-wide association study of ovarian cancer. The three central sections of the flowchart detail the specific mechanisms and sensitivity analyses associated with three distinct MR analysis methods. The bottom section highlights the target genes and ovarian cancer phenotypes that demonstrate consistent significance across at least two of the three MR analyses, underscoring robust associations. √indicated yes while ×indicated no.

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patients and 40,941 healthy controls (Table S3). This analysis not only included all ovarian epithelial cancers but also specifically examined different pathological subtypes of OC, such as 13307 High grade serous OC (HGSOC) cases, 1012 Low grade serous OC (LGSOC) cases, 1366 Clear cell OC cases, 2810 Endometrioid OC cases, and 2,566 Mucinous OC cases.[13] Additionally, 11,311 patients with clinical prognostic information were utilized for GWAS analysis of overall survival, either for HGSOC cases only, All OC cases or All OC with adjustment for pathological type respectively.[14]

## Two-Sample MR

Two-sample MR studies were selected to identify the impact of Hb1Ac alteration by targeting specific genes using antidiabetic drugs on the risk and prognosis of OC. In MR analyses, genetic variation can serve as an IV if it satisfies the following fundamental conditions: (i) the genetic variation correlates with the exposure; (ii) the variation does not affect the outcome through confounding factors; and (iii) the variation has no direct effect on the outcome but influences it indirectly solely by affecting the exposure (as depicted in the directed acyclic graph in the middle-left of the Figure 1). To meet the requirements, the following is the detailed analysis process.

Initially, single nucleotide polymorphisms (SNPs) within the cis-region (spanning ±500 kb) of the target genes were retrieved from the prior GWAS of HbA1c in the UK Biobank cohort. These SNPs were then analyzed using a clumping window of 100 kb, with a significance threshold of $P< 5 \times 10-8$, effective allele frequency (EAF) > 0.01, r2 < 0.2 and F >10 to eliminate weak IVs. Target genes with at least one valid SNP were screened through TwoSampleMR package (https://mrcieu.github.io/TwoSampleMR/). After removing SNPs in palindromic and compatible alleles, the remaining SNPs were used as IVs for the corresponding target genes (Table S4). The same method was applied during the replication analysis for Two-sample MR quality control. When two neighboring genes shared IVs due to overlapping cis-regions, they were presented together and separated by a slash, such as "VEGFA/SLC29A1". Subsequently, positive control MR analyses were carried out to further exclude target genes that had no significant association with either blood glucose (met-d-Glucose, ebi-a -GCST90014005) or type 2 diabetes mellitus (T2DM) (ebi-a-GCST006867, finn-b-E4_DM2_STRICT). (Tables S3 and S5).

For target genes with at least two effective IVs, the multiplicative random effects inverse variance weighted (IVW) was employed as principal analysis, while Wald ratio MR was used for those with only one IV. To corroborate the results, we performed multiple sensitivity assessments utilizing various methodologies, specifically the IVW with fixed effects, along with weighted median and mode estimation techniques. The final risk ratios (OR) and p-value obtained from these four approaches were compared to verify the robustness and reliability of the results. Two-stage methods, such as the IVW method, are the most effective analytical methods when IV assumptions are met, and thus should typically be used as the primary analytical approach. The weighted median estimator maintains robustness despite the inclusion of potentially invalid instrumental variables. Statistical significance of the weighted mode estimator requires that most comparable causal effects originate from valid instrumental variables. The heterogeneity of IVs was verified using the I2 statistics and Q test. Horizontal pleiotropy was evaluated through MR-Egger regression's intercept examination. MR analyses quantified OC-related effects of per-SD decreases in genetically predicted HbA1c through specific drug targets, with additional scaling to per-SD reduction of random glucose (ebi-a-GCST90014005). Positive control analyses provided conversion coefficients (α) between these measures for each target. The effect of a per-SD reduction in random blood glucose induced by antidiabetic drug targeting of specific genes on OC (scaled β) was then calculated by multiplying β by 1/α. We established dual significance thresholds, with P values below 0.05 indicating nominal significance and values under $3\times10^{-4}$ representing significance after multiple testing correction (Bonferroni correction: 0.05/18×9 to account for multiple comparisons across all drug target-phenotype combinations) to further rule out the possibility of false-positive results. If multiple target genes of an antidiabetic drug all had valid IVs, these genes were included in a combined MR analysis to validate the overall drug effect.

Comprehensive sensitivity testing and quality control procedures were implemented to confirm the stability of the findings. We implemented Multivariate MR (MVMR) to quantify the causal influence of individual exposures on outcomes by leveraging genetic instruments linked to several potentially confounding exposures. This approach helps avoid bias due to confounding factors, demonstrating that genetic variation does not influence outcomes through confounders. Therefore, we applied MVMR analysis (Figure S1) to calculate the effect of Hb1Ac reduction through

targeting specific genes by antidiabetic drugs on different OC phenotypes after adjusting for four confounders: body mass index, systolic blood pressure, smoking status, and alcohol-drinking status. Subsequent replication analysis also examined the association between HbA1c (Within family GWAS consortium, MAGIC), T2DM (DIAGRAM, FinnGen, Sílvia Bonàs-Guarch), and fasting glucose (MAGIC). SNPs within the cis-region (spanning ±500 kb) of the target genes were obtained from the previous GWAS, and weak IVs were removed following the same screening criteria (Table S3). The causal links between drug targets and OC outcomes were further verified through replicated MR methods. Moreover, the presence of pleiotropic SNPs was investigated through MR-PRESSO outlier detection analysis, serving as a complementary sensitivity evaluation.

## SMR

SMR is a summary data-based MR analysis method employed in expression quantitative trait loci (eQTL) research and GWAS studies. It serves to determine whether the impact magnitude of SNPs on the outcome is influenced by gene expression. Through SMR analysis, we investigated the causal links between antidiabetic drug target gene expression and OC subtype-specific outcomes, including disease risk and survival, following the analytical approach represented in Figure 1 central directed acyclic graph. EQTL refers to a class of genetic loci, mostly SNPs, which can significantly influence the level of gene expression. The eQTLGen consortium encompasses gene expression data from 31,684 patients' blood samples and offers genetic variants linked to the expression of those genes. This analysis focused on cis-eQTLs located within a 1-Mb range of the respective gene locations were used as IVs to ensure the correlation between SNPs and target genes. We then utilized heterogeneity in dependent instruments (HEIDI) test to identify linkage disequilibrium in pleiotropic relation and, thereby, to detect the presence of heterogeneity in SMR analyses.

To enhance the comprehensiveness of our gene expression investigation, we integrated eQTL data from the most recently released Genotype-Tissue Expression (GTEx) database. Specifically, data from PsychENCODE (n=1387) and GTEx(v8)-ovary (n=167), derived from brain and ovarian tissues respectively, were used for replication analyses. All of the above-mentioned analysis procedures adopted the preset parameters (https://yanglab.westlake.edu.cn/software/ smr/#SMR&HEIDIanalysis). PSMR < 0.05 was regarded as statistically significant for association, followed by the application of a multiple-test correction threshold (Bonferroni correction: 0.05 divided by total gene count used for SMR analysis) to further eliminate the possibility of false-positive results.

## Colocalization Analysis

Colocalization analysis is an integrative approach aimed at identifying genetic variants that may induce concurrent phenotypic changes in multiple molecules or other complex features. Even if a genetic variant in a specific gene region shows associations with both the exposure and the outcome, this does not confirm that the same variant influences the two. These associations could arise from distinct causal variants correlated through linkage disequilibrium. Colocalization analysis is especially valuable for assessing exposures, such as protein levels and gene expression, especially in MR analyses based on individual gene regions. Thus, colocalization analysis can offer further support in elucidating the biological mechanism underlying the causal relationship between antidiabetic drug target genes and OC outcomes. This analysis employed a Bayesian model, estimating posterior probabilities for five potential scenarios: 1) H0: No connection to either trait; 2) Associated with trait A exclusively; 3) Associated with trait B exclusively; 4) Separate SNPs linked to trait A and trait B independently; 5) A common SNP associated with both trait A and trait B (middle-right of Figure 1). Analyses were carried out utilizing the R package (coloc.abf algorithm, http://cran.rproject.org/web/packages/coloc) with default parameters of p1 = $1 \times 10^{-4}$, p2 = $1 \times 10^{-4}$, and p12 = $1 \times 10^{-3}$. A posterior probability of H4 (PPH4) over 0.75 was considered indicative of a robust colocalization relationship and a PPH4 over 0.6 as evidence of a moderate colocalization association.

Finally, we summarized the performance of all genes in the above three MR analyses and listed the genes that were significantly associated with OC in at least two of them (Figure 1). The SMR analyses in this study were carried out using the smr-1.3.1-win software on a Windows system, while all other analyses were executed using R software (version 4.4.1) with packages including TwoSampleMR, coloc.abf, and others. This study relies on previously published data and publicly available databases. Ethical approval and informed consent were secured from the respective institutional review boards.

# Results

## Two-Sample MR: Screening Effective Drug Target

Antidiabetic drugs were categorized into nine classes based on the DrugBank pharmacogenetics database, and their respective target genes are listed in Tables S1 and S2. A total of 21 target genes were identified as potentially associated with OC outcomes, including genes targeted by sulfonylureas (ABCC8/KCNJ11, ABCB11/LRP2, CPT1A, PPARG, INS, KCNJ1, V-EGFA/SLC29A1), TZDs (PPARG, VEGFA/SLC29A1, ESRRA, RXRB), insulin (ABCB11/LRP2), biguanides (SLC47A1), AGIs (GANC), DPP-4i (HMGCR, ITGAL), GLP-1RA (GLP1R), SGLT2i (SLC5A2, SLC5A1), and other drugs (RAMP1, RAMP2, RAMP3, GCK, AKR1A1) (Table S4). The corresponding SNPs for each target gene and their effects on HbA1c levels are detailed in Table S4. Among these, 18 target genes were selected for subsequent two-sample MR analyses, excluding KCNJ1, ESRRA, and RAMP1, which showed no significant association with blood glucose or T2DM in positive control analyses (Table S5).

## Two-Sample MR: Investigating Antidiabetic Drug Targets on OC

Following a comprehensive analytical approach, which included principal analysis utilizing IVW (multiplicative random effects) or Ward Ratio, sensitivity analyses employing IVW (fixed-effect), weighted median, and weighted mode methods, as well as rigorous quality control screenings (F statistic >10 and EAF > 0.01; Q test for heterogeneity <50%; MR-Egger intercept P > 0.05; Bonferroni-corrected $P < 3\times10^{-4}$), we identified 16 significant targets linked to at least one OC outcome except for GANC and ABCB11/LRP2 (Figure 2A and Figure S2–21 and Table S6). Notably, VEGFA/SLC29A1 and PPARG for sulfonylureas/TZDs, CPT1A and ABCC8/KCNJ11 for sulfonylureas, RXRB for TZDs, SLC5A2 and SLC5A1 for SGLT2i, GLP1R for GLP-1RA, HMGCR and ITGAL for DPP4i, AKR1A1, RAMP2, RAMP3, and GCK for other drugs demonstrated significant associations with at least one OC phenotype and passed the significance threshold after multiple testing correction ($P < 3\times10^{-4}$) (Figure 2A and Figure S2).

The impact of representative drug targets, as determined through primary analysis, on various OC risk and survival outcomes is illustrated in Figure 2A. The per-SD reduction in HbA1c through targeting RXRB by TZDs was related to a decreased risk of All OC (OR: 0.528, 95% CI: 0.413~0.675, $P < 3\times10^{-4}$) and HGSOC (OR: 0.378, 95% CI: 0.26~0.549, $P < 3\times10^{-4}$), indicating a protective effect. Conversely, targeting VEGFA/SLC29A1 with sulfonylureas/TZDs, resulting in a per-SD decrease in HbA1c, was linked to an elevated risk of HGSOC (OR: 2.128, 95% CI: 1.415~3.199, $P < 3\times10^{-4}$), and worse survival for All OC (OR: 0.288, 95% CI: 0.138~0.6, $P < 3\times10^{-4}$) and HGSOC (OR: 0.197, 95% CI: 0.122~0.317, $P < 3\times10^{-4}$). Sulfonylureas/TZDs targeting PPARG were also significantly associated with reduced survival in All OC and an elevated risk of endometrioid (OR: 2.917, 95% CI: 1.596~5.333, $P < 3\times10^{-4}$). The effects of sulfonylureas targeting CPT1A on OC risk varied by pathotype, showing a decreased incidence of LGSOC but an increased incidence of endometrioid OC, alongside a negative correlation with survival in HGSOC (all $P < 3 \times 3\times10^{-4}$). GLP-1RA targeting GLP-1R was associated with improved survival in HGSOC. Additionally, other drugs targeting RAMP2 were linked to an elevated risk of All OC, Clear cell OC, Mucinous OC, and Endometrioid OC, but a reduced risk of LGSOC (all $P < 3\times10^{-4}$). Conversely, targeting AKR1A1 by other drugs was correlated with a higher risk of All OC, HGSOC, LGSOC, and Endometrioid OC, and an increased risk of Mucinous OC, alongside decreased survival in HGSOC and All OC (all $P < 3\times10^{-4}$). DPP4i targeting HMGCR was significantly linked to a higher risk of clear cell OC and reduced survival of All OC patients (all $P < 3\times10^{-4}$).

Sulfonylureas, TZDs, SGLT2i, and DPP4i, which act on multiple target genes, were also found to have significant associations with at least one of the OC phenotypes, although only the associations observed for DPP4i with OC phenotypes passed the multiple correction threshold (Figure 2B and Figure S22–25 and Table S6). Pooled targets of sulfonylureas showed a significant association with a higher risk of endometrioid OC, an elevated risk of LGSOC, as well as reduced survival in HGSOC and All OC subtypes (all $P < 0.05$). TZDs targeting SLC29A1, RXRB, and PPARG, had a protective effect on the HGSOC and All OC subtypes, however the effect was reversed for endometrioid OC (all $P < 0.05$). Moreover, co-targeting SLC5A1 and SLC5A2 by SGLT2i was linked to an elevated risk of All OC and HGSOC (all $P < 0.05$). In contrast, the pooled targets of DPP4i were linked to a reduced risk of mucinous OC and endometrioid OC (all $P < 3\times10^{-4}$).

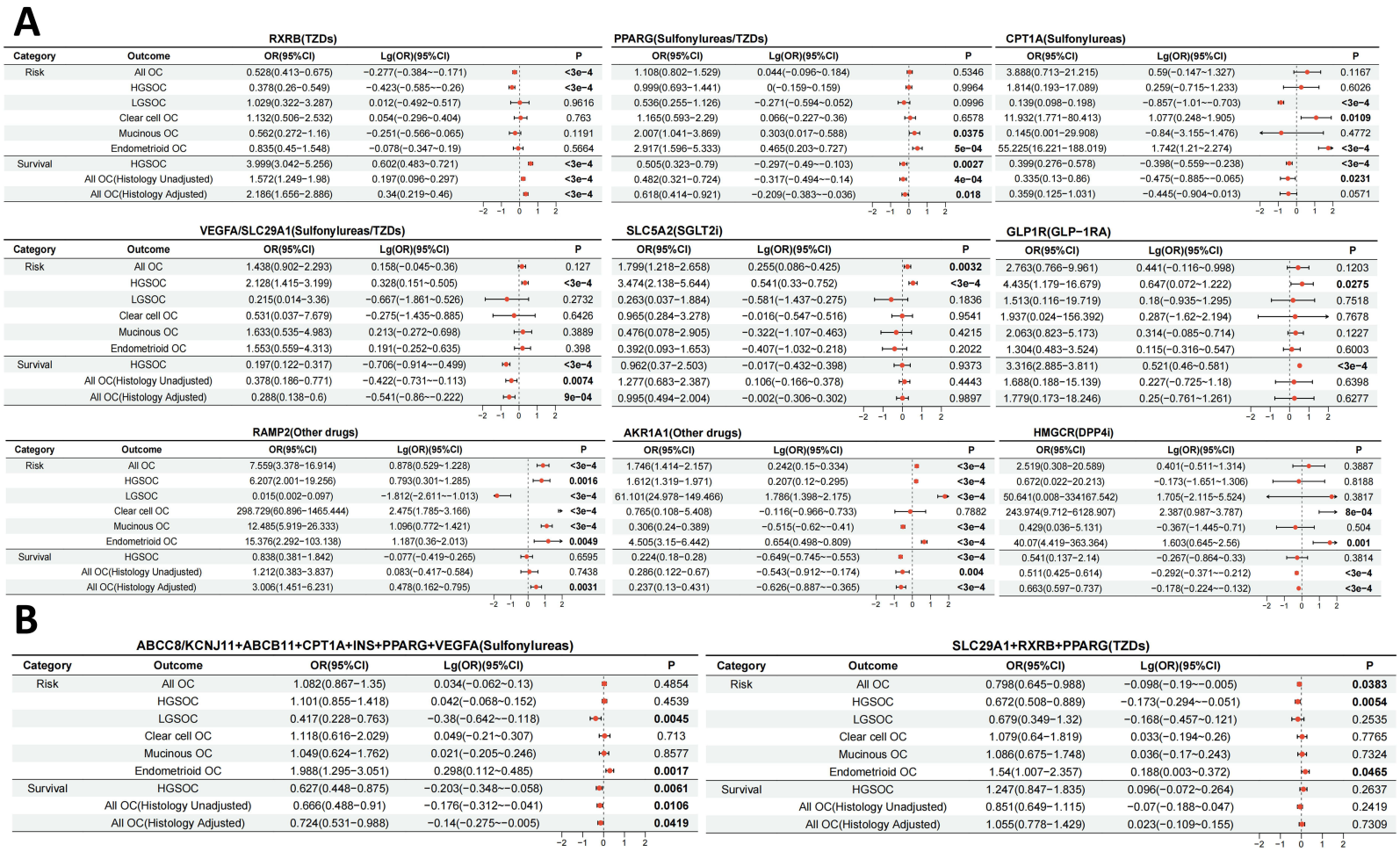


**Figure 2** Forest plots depicting the impact of antidiabetic targets on nine ovarian cancer phenotypes. All analyses were conducted employing the multiplicative random-effects IVW MR approach. The effect estimates, expressed as odds ratios, were calibrated to represent a per-SD reduction in genetically predicted HbA1c levels, reflecting the impact of targeting specific genes with corresponding drugs on ovarian cancer risk and survival. Each plot is annotated with the gene and its related drug class. (**A**) illustrates the results for individual drug targets, while (**B**) summarizes the findings for grouped drug targets within a specific drug category. Additional results for individual and combined targets can be found in Figure S2.

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## Two-Sample MR: Sensitivity Analysis and Quality Control

In the MVMR analysis (Figure S1 and Figure S26), the targets of antidiabetic drugs were further validated to be significantly associated with specific OC subtypes, which was consistent with the principal analysis. Among these, RAMP2 and RXRB were related to both the risk and survival of All OC subtypes. Meanwhile, GCK was only correlated with the risk of All OC ($P < 0.001$). RXRB and GCK were linked to both the risk and survival of HGSOC. Additionally, VEGFA/SLC29A1 ($P < 0.001$), GLP1R ($P < 0.001$), and AKR1A1 ($P < 0.05$) were solely associated with HGSOC survival. Moreover, RAMP2 and GCK were significantly associated with the risk of mucinous OC (all $P < 0.001$). The risk of clear cell OC was found only associated with RAMP2 ($P < 0.001$). ITGAL ($P < 0.001$), AKR1A1 ($P < 0.05$), and PPARG ($P < 0.05$) were all associated with the risk of endometrioid OC.

In terms of the replication analyses (Table S7 and Figure S27 and 28), the associations of GCK with the survival and risk of HGSOC, GCK with the risk of All OC, LGSOC, and mucinous OC, PPARG with the risk of mucinous OC and endometrioid OC, and the survival of HGSOC and All OC in the MR results were replicated at least once. Table S6 provided the MR findings adjusted for random blood glucose levels. The results of the principal analyses were largely consistent with those obtained from the sensitivity analyses using the other three MR methods (Table S6 and Figure S3–25). After the MR-PRESSO analysis (Table S8), the associations of the risk of HGSOC with SGLT2i targeting SLC5A2, as well as TZDs targeting the combined targets of SLC29A1, RXRB, and PPARG, were identified as having potential pleiotropy, although significant in the MR principal analysis.

## SMR: Antidiabetic Drug Target Gene Expression and OC

The eQTLGen (blood) database was utilized for the primary analysis of the SMR (Figure 3). The PsychENCODE (brain) (Figure S29A) and GTEx (v8)-ovary (Figure S29B) databases were employed for replication analyses. First, in the primary analysis, a per-SD increase of ETFDH expression in the blood was associated not only with the risk of All OC (OR: 0.77, 95% CI: 0.63–0.95, $P = 0.013$) and HGSOC (OR: 0.74, 95% CI: 0.58–0.94, $P = 0.013$), but also with the prognosis of HGSOC (OR: 0.71, 95% CI: 0.52–0.97, $P = 0.032$). This finding implies that there may be a more intricate relationship between ETFDH expression and the progression of OC. Moreover, the expression of DDP4 was negatively correlated with the survival of HGSOC (OR: 0.59, 95% CI: 0.38–0.90, $P = 0.015$), and the expression of HMGCR was negatively linked to the risk of HGSOC (OR: 0.73, 95% CI: 0.57–0.94, $P = 0.016$) and All OC (OR: 0.73, 95% CI: 0.57–0.94, $P = 0.016$). The expression of SLC47A1 was associated with the higher risk of Endometrioid OC (OR: 1.38, 95% CI: 1.01–1.87, $P = 0.042$), and the expression of ABCA1 was associated with an increased risk of LGSOC (OR: 4.64, 95% CI: 1.76–12.24, $P = 0.002$). Conversely, HMGCR was negatively linked to the risk of Mucinous OC (OR: 0.36, 95% CI: 0.20–0.66, $P = 0.0008$), and SLC29A1 was negatively related with the risk of Endometrioid OC (OR: 0.39, 95% CI: 0.19–0.82, $P = 0.013$). (Figure 3 and Table S9).

In the replication analyses, AK1B1, CFTR, KCNJ11, and GAA were significantly linked to at least one OC subtype, yet there was no overlap with the principal SMR results. A per-SD increase in AKR1B1 expression in the brain was associated with a significantly increased risk of Mucinous OC (OR: 1.5, 95% CI: 1.14–1.99, $P = 0.004$). CFTR was negatively associated with the risk of All OC (OR: 0.93, 95% CI: 0.87–1.00, $P = 0.043$). KCNJ11 was positively associated with the occurrence of All OC (OR: 1.13, 95% CI: 1.0–1.28, $P = 0.047$) and HGSOC (OR: 1.17, 95% CI: 1.01–1.35, $P = 0.039$). Additionally, a per-SD increase in GAA expression in the ovary was significantly associated with reduced HGSOC survival (OR: 0.92, 95% CI: 0.85–1.00, $P = 0.047$). (Figure S29 and Table S9).

## Colocalization Analysis: Colocalization of the Target Gene Expression with Ovarian Cancer

Colocalization analysis was applied to ascertain whether the connection between the expression of specific genes and OC could be ascribed to the same causal genetic variants (Figure 4 and Figure S30, TableS10). Figure 4A shows that GCK, SLC47A1, CCN3, ETFDH, DPP4, and SIGMAR1 all co-localize with at least one of the OC outcomes, with a PPH4 > 0.75. Simultaneously, the expression of GANAB, PRKAA1, HMGCR, ITGAL, CCN3, INSR, AKR1A1, AKR1B1, CPT1A, KCNJ11, TRPM4, and VEGFA moderately co-localize with OC, with PPH4 > 0.6. Figure 4B and Figure S30

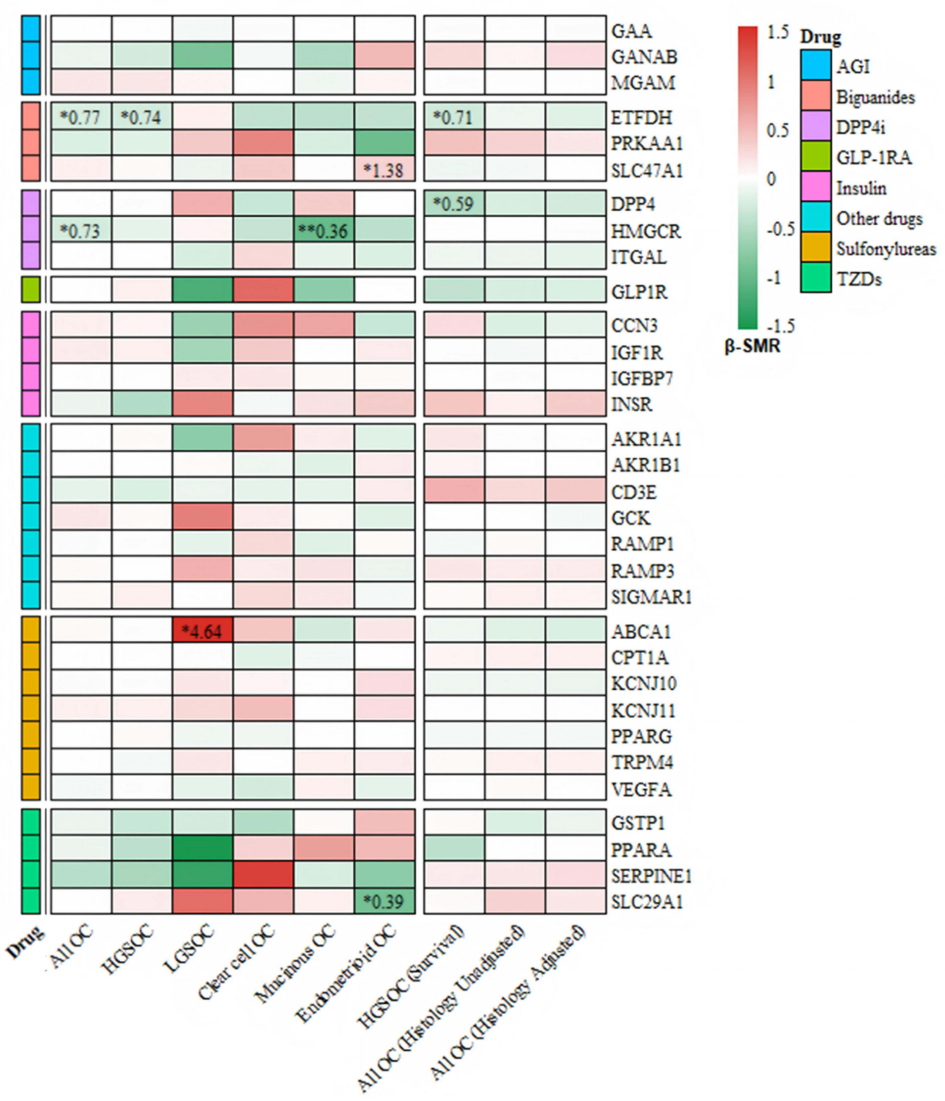


**Figure 3** SMR analysis of antidiabetic targets in ovarian cancer. Figure 3 presents the relationship between the expression of gene expression in blood (sourced from eQTLGen) and nine ovarian cancer phenotypes. Red regions indicate positive correlations, while green regions denote negative correlations. Statistically significant results are presented with asterisks and odds ratios. *indicates significance level (*P < 0.05, **P < 0.05/32, adjusted for multiple testing).

display all the results with PPH4 > 0.75. Among these, both SLC47A1 and CCN3 exhibit a consistent association with Clear cell OC. GCK and ETFDH have been confirmed to have significant colocalization with LGSOC and Mucinous OC, respectively. Additionally, DDP4 is demonstrated to be significantly associated with HGSOC survival, while SIGMAR1 associated with the survival of All OC. However, no antidiabetic target genes were found co-localized to the risk of All OC and HGSOC with PPH4 > 0.6 (Figure 4A).

Following Two-sample MR, SMR and colocalization analysis, the risk of LGSOC, Clear cell OC, Mucinous OC, Endometrioid OC, and the survival of HGSOC were found consistent associations with specific target genes in at least 2 analyses (Figure 1). AKR1A1 targeted by aldose reductase inhibitors showed a significant association with an elevated risk of LGSOC and Endometrioid OC through Two-sample MR and colocalization analysis. Meanwhile, ITGAL targeted by DPP4i was significantly related to the decreased risk of mucinous OC and endometrioid OC. HMGCR (DPP4i) and KCNJ11 (sulfonylureas) were also positively associated with the risk of clear cell OC by Two-sample MR and colocalization analysis. Moreover, through both SMR and colocalization analysis, the expression of AKR1B1 targeted by Aldose reductase inhibitors and DPP4 targeted by DPP4i were consistently associated with an increased risk of mucinous OC and a reduced survival of HGSOC, respectively.


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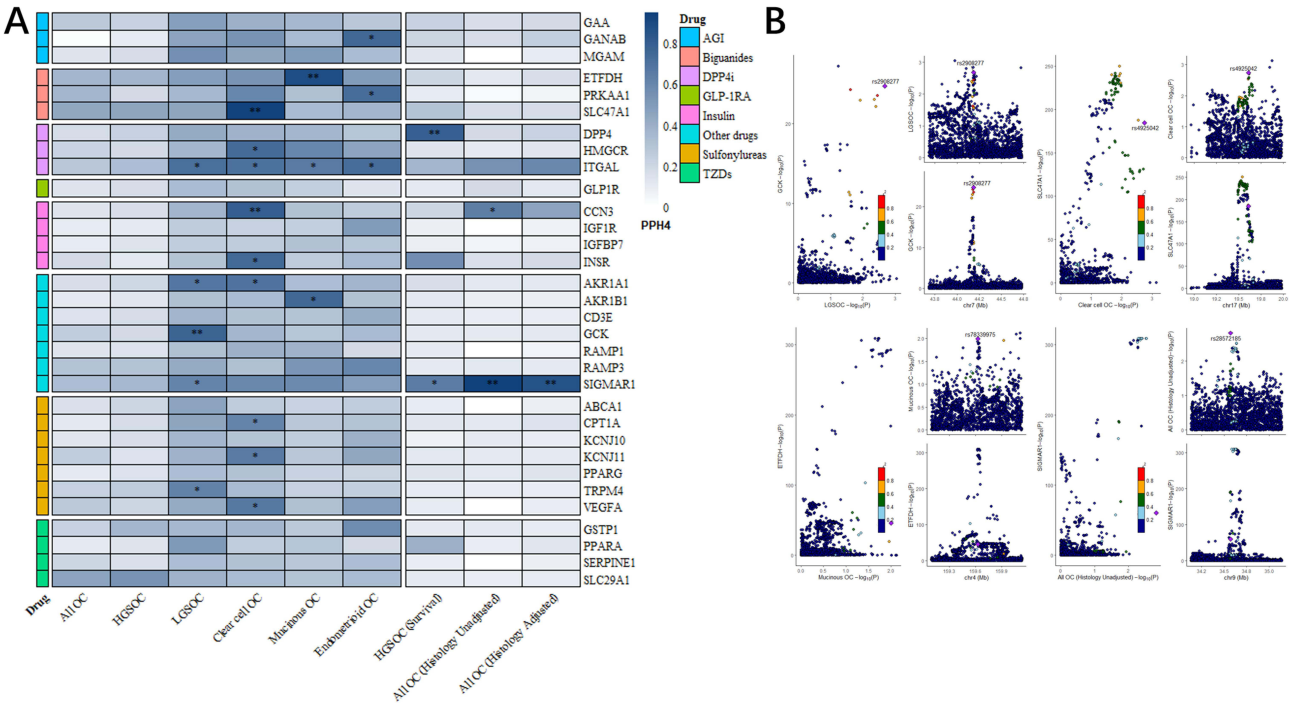


**Figure 4** Colocalization analysis of antidiabetic gene expression and ovarian cancer. (**A**) presents the results of colocalization analysis between putative drug targets and nine ovarian cancer phenotypes. Dark blue shading and asterisks denote robust support for colocalization. **denotes PPH4 > 0.75, while *represents 0.6 < PPH4 < 0.75 in the colocalization analysis. (**B**) and Figure S30 display all results with PPH4 > 0.75, providing further details on significant colocalization findings.

## Discussion

This study investigated the associations between antidiabetic drug target genes and OC risk and survival using three MR methods. It showed that specific antidiabetic targets were consistently linked to the incidence of low-grade serous, clear cell, mucinous, and endometrioid OC (however not HGSOC), as well as to HGSOC survival, supported by at least two MR approaches. These findings suggest that metabolic dysregulation plays a role in OC pathogenesis and support hypotheses for future mechanistic and preclinical investigation of antidiabetic agents against OC.

Extensive research has linked diabetes mellitus to OC development and survival,[15] yet evidence specific to pathological subtypes remains limited. Given the distinct pathophysiology across OC subtypes, we employed MR to analyze GWAS data for each subtype separately. Most subtypes showed associations with antidiabetic drug target genes in multiple MR methods, whereas HGSOC risk was associated only in one method, suggesting potentially stronger links between diabetes and other subtypes. Additionally, SMR and colocalization analyses indicated that higher dipeptidyl peptidase 4 (DPP4) expression, which was reported elevated in OC tissues with conflicting roles in tumor progression,[16,17] was associated with worse survival in HGSOC.

DPP4i-induced per-SD reduction in HbA1c, via targeting HMGCR and ITGAL, was associated with specific OC subtype risks through two-sample MR and colocalization. (3S)-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (HMGCR) catalyzes the transformation of HMG-CoA into mevalonic acid, a rate-limiting reaction in the production of cholesterol and isoprenoids, making it crucial for maintaining cholesterol homeostasis within cells, with higher expression previously linked to better OC prognosis and platinum sensitivity.[18,19] Such metabolic reprogramming could help cancer cells meet the elevated energy and cholesterol needs driven by accelerated tumor growth. In this study, HMGCR inhibition was related to increased clear cell OC risk. Integrins are heterodimeric transmembrane proteins vital for leukocyte trafficking and cell differentiation in inflammation and cancer.[20] Specifically, Integrin Subunit Alpha L (ITGAL) plays a key role in immune and inflammatory responses. Lipid-soluble DPP4i statins can penetrate cell membranes and target ITGAL, potentially exerting antitumor effects.[21] Consistent with this, two-sample MR analysis indicated that DPP4i-mediated inhibition of ITGAL was associated with a lower risk of mucinous and endometrioid ovarian cancer.

Aldo-keto reductase family member A1 and B1 (AKR1A1 and AKR1B1), both targets of aldose reductase inhibitors, were consistently associated with specific OC subtypes in at least two MR methods. AKR1A1 reduces toxic aldehydes to alcohols using NADPH, aiding detoxification and oxidative defense, but also inactivates anthracyclines and may confer chemoresistance.[22–24] Inhibition of AKR1A1 was linked to higher risk of LGSOC and endometrioid OC, suggesting a role in tumor development and treatment resistance. In contrast, AKR1B1 converts glucose to sorbitol and fructose which is vital in tumor glycolysis and growth. AKR1B1 deletion disrupts fructose production, suppressing cancer proliferation and migration.[25,26] Its expression was reported elevated in recurrent HGSOC compared to newly diagnosed patients,[27] and this study also linked higher AKR1B1 expression to increased mucinous OC risk via SMR and colocalization.

Two-sample MR and colocalization analyses found sulfonylureas targeting KCNJ11, the ATP-sensitive inward rectifier potassium channel 11, were correlated with an elevated clear cell ovarian cancer risk. Loss-of-function mutations in KCNJ11 cause hyperinsulinism and sustained insulin release, potentially fueling tumor energy uptake.[28] Sulfonylureas may thus promote tumorigenesis by inhibiting KCNJ11 expression. Although KCNJ11 has been implicated in colorectal and pancreatic cancers,[29,30] its role in ovarian cancer remains poorly understood and warrants further investigation.

When employing the Summary-data-based Mendelian Randomization method to investigate the associations between the expression of antidiabetic drug target genes and the risk and prognosis of different histopathological subtypes of OC, we observed a lack of overlapping results between the principal analysis and replication analysis. This discrepancy could be attributed to several factors. First, certain genes may predominantly function within the immune or hematological systems, influencing OC risk through systemic inflammatory or immunomodulatory mechanisms rather than via local activity in ovarian tissue. Second, ovarian tissue samples in databases such as GTEx are typically smaller in size compared to blood samples, resulting in lower statistical power, which could lead to undetected true positive signals. Finally, eQTLs are inherently tissue-specific; single-nucleotide polymorphisms that serve as eQTLs in blood may not regulate the same genes in ovarian tissue. Identifying tissue-specific gene associations enables a more precise understanding of their mechanisms of action—whether systemic or local—and provides valuable insights for future drug development, such as distinguishing between systemically acting targets and those that require tissue-targeted delivery approaches.

This study aimed to employ two-sample MR, SMR, and colocalization analysis to identify antidiabetic drug target genes with diagnostic and therapeutic potential across different histotypes of ovarian cancer. It should be clarified, however, that all candidate drug target genes ultimately included in our analysis were statistically significant outcomes jointly validated either by two-sample MR combined with colocalization analysis or by SMR together with colocalization analysis. Colocalization analysis serves as a critical step in prioritizing the most reliable MR and SMR signals with the highest biological plausibility. It provides evidence regarding whether the observed associations among genes, phenotypes, and diseases share a common underlying genetic basis, thereby bridging statistical genetic associations with potential biological mechanisms. The colocalization results presented in this study substantially enhance the credibility of our conclusions by effectively minimizing spurious associations attributable to linkage disequilibrium, thus conferring higher priority to the final candidate targets identified. This study has several limitations. First, while multiple sensitivity analyses were applied to strengthen causal inference, residual pleiotropy and inherent biases of MR methods cannot be fully excluded. Second, the predominant use of European populations in genetic analyses may limit generalizability and introduce bias, necessitating cautious interpretation of results. Finally, no drug target showed consistent association with any OC subtype across all three methods, and many were significant in only one approach. Although single-method findings are insufficient to establish causality, they may suggest potential links warranting further validation through larger samples, refined genetic instruments, or additional analytical techniques.

## Conclusion

Through two-sample MR, SMR, and colocalization analyses, we identified consistent associations between specific antidiabetic targets and OC risk: AKR1A1 with LGSOC; HMGCR and KCNJ11 with clear cell OC; ITGAL and AKR1B1 with mucinous OC; and AKR1A1 and ITGAL with endometrioid OC. Although HGSOC risk was linked to certain genes in only one method, its survival was associated with DPP4 in two approaches. These robust connections

underscore the importance of metabolic dysregulation in OC pathogenesis, identifying antidiabetic drug targets as potential candidates for future translational research aimed at subtype-specific therapeutic strategies.

## Abbreviations

OC, Ovarian cancer; MR, Mendelian randomization; SMR, Summary data-based MR; HGSOC, High-grade serous OC; DM, Diabetes mellitus; IV, Instrumental variable; AGIs, Alpha-glucosidase inhibitors; TZDs, Thiazolidinediones; DPP4i, Dipeptidyl peptidase 4 inhibitors; GLP-1A, Glucagon-like peptide-1 analogues; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; GWAS, Genome-wide association analysis; OCAC, Ovarian Cancer Association Consortium; LGSOC, Low grade serous OC; SNP, Single nucleotide polymorphism; EAF, Effective allele frequency; T2DM, Type 2 diabetes mellitus; IVW, Inverse variance weighted; OR, Odd ratio; SD, Standard deviation; MVMR, Multivariate MR; eQTL, Expression quantitative trait loci; HEIDI, Heterogeneity in dependent instruments; GTEx, Genotype-Tissue Expression; PPH4, Posterior probability of H4; DPP4, Dipeptidyl peptidase 4; HMGCR, (3S)-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase; ITGAL, Integrin Subunit Alpha L; AKR1A1, Aldo-keto reductase family member A1; AKR1B1, Aldo-keto reductase family member B1; KCNJ11, ATP-sensitive inward rectifier potassium channel 11.

## Data Sharing Statement

Table S3 showed all the databases applied in this study. GWAS summary data for diverse OC phenotypes, HbA1c, type 2 diabetes, fasting glucose, glucose, body mass index, systolic blood pressure, smoking status and alcohol drinking status are available on https://gwas.mrcieu.ac.uk/datasets/(Table S3). Data from eQTLGen consortium and the GTEx database can be found in https://www.eqtlgen.org/ and https://yanglab.westlake.edu.cn/software/smr/#eQTLsummarydata.

## Ethics Approval and Consent to Participate

This study used previously published data and publicly available databases. The study was conducted in accordance with the local legislation and institutional requirements and approved by the Ethics Committee of the National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences (Approval No.: 25/181-5127). Also, the relevant accession numbers have been included in the manuscript, and further details regarding ethical exemption can be found on the official websites of the respective databases: https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics.

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## Author Contributions

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

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## Disclosure

The authors declare that they have no competing interests.

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