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Metformin and the risk of malignant tumors of digestive system: a mendelian randomization study

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Abstract

Background Observational studies suggest that metformin may reduce the risk of malignant tumors of the digestive system (MTDS), but these findings are often confounded by bias and unmeasured variables. Recent meta-analyses have questioned these associations, emphasizing the need for robust causal inference.

Methods Mendelian randomization (MR) was used to evaluate the causal relationship between metformin and MTDS. Genetic variants associated with metformin's molecular targets were selected from GTEx, eQTLGen, and UK Biobank and validated using genetic colocalization to ensure instrument validity. GWAS summary statistics for MTDS, encompassing up to 314,193 controls and 6,847 colorectal cancer cases, were obtained from FinnGen and EBI. The primary analysis employed the inverse-variance weighted (IVW) method, supplemented by MR-Egger, weighted median, and weighted mode analyses. Bonferroni correction was applied to adjust for multiple testing across 14 cancer types.

Results Genetically proxied metformin use was associated with an increased risk of colorectal cancer (OR = 2.38, 95%CI = 1.38–4.09, $P = 0.0018$) and related subtypes. No causal relationship was found for hepatocellular carcinoma, gastric cancer, pancreatic cancer, or other digestive system cancers. The robustness of these findings was supported by sensitivity analyses, which indicated no significant pleiotropy, and leave-one-out tests.

Conclusion This study provides robust genetic evidence that metformin use increases the risk of colorectal cancer, challenging its role as a preventive agent for digestive cancers. These findings emphasize the need for clinicians to carefully evaluate the risks and benefits of metformin, particularly in populations at higher risk for colorectal cancer. Future research should focus on delineating the mechanisms underlying this association to optimize the use of metformin in clinical practice.

Keywords Metformin, Malignant tumors, Mendelian randomization

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Introduction

Malignant tumors of digestive system (MTDS) currently exhibit high incidence and mortality rates, with over 4.8 million new cases and 3.4 million deaths reported annually [1]. These malignancies rank as the leading cause of cancer-related deaths worldwide and represent a significant public health challenge. Projections based on age demographics and global population growth indicate a steep rise in incidence and mortality, with new cases anticipated to increase by 58% to 7.5 million and deaths expected to rise by 73% to 5.6 million by the year 2040 [2].

The exploration of metformin, widely used for type 2 diabetes (T2DM) treatment, as a potential cancer prevention or treatment drug began with an observational study in 2005 [3], indicating that metformin use could reduce cancer incidence, which spurred extensive basic, observational, and clinical studies. Some studies indicated that metformin exerts anticancer effects through its influence on multiple biological pathways, including activation of AMPK [4, 5], inhibition of mTOR [4, 5], regulation of cell cycle and apoptosis [6, 7], targeting of cancer stem cells [4, 7], metabolic reprogramming [4, 5], and modulation of inflammation and immunity [4, 7]. Numerous observational studies suggesting that metformin may reduce the risk of MTDS, including colorectal cancer [8, 9], hepatocellular carcinoma [10], and gastric cancer [11]. However, these findings often stem from observational designs, which are inherently limited by confounding factors, selection bias, and challenges in accurately controlling for variables like glycemic control, medication adherence, and co-therapies. Recent meta-analyses have highlighted these inconsistencies, calling into question the robustness of earlier conclusions [12, 13]. Specifically, Zeng et al. found no significant reduction in hepatocellular carcinoma risk with metformin use after adjusting for concurrent medications like statins and aspirin, pointing to substantial heterogeneity among studies [12]. Similarly, Bai et al. categorized the evidence linking metformin to reduced gastric cancer risk as weak, emphasizing methodological limitations in the included studies and the need for more robust data [13].

Given these limitations, Mendelian randomization (MR) offers a compelling alternative for establishing causal inferences. Unlike traditional observational methods, MR uses genetic variants as instrumental variables to proxy the exposure of interest, effectively mimicking the random allocation seen in clinical trials. This reduces bias from confounders and avoids the limitations inherent in observational studies. Specifically, MR allows for more reliable causal inferences in situations where randomized controlled trials (RCTs) are logistically or ethically difficult to conduct. By leveraging genetic data, MR provides an opportunity to evaluate the effects of metformin on cancer risk, free from the confounding influences of lifestyle factors, medication adherence, and other biases. In this study, we analyzed the relationship between metformin and 14 types of MTDS using a two-sample MR and validated our findings across different Genome Wide Association Study (GWAS) datasets, further confirming our results.

Methods

Genetic instrument selection

Figure 1 provides the overall design of the study. To investigate the causal relationship between metformin and MTDS, we identified genetic proxies for metformin based on its known molecular targets. Based on previous study [14], we identified seven targets of metformin: AMPK, MC1, MG3, GDF15, GLP1/GCG, FBP1, and ADCY1. These targets encompass pathways critical to metformin's pharmacological effects, including glucose metabolism, energy homeostasis, and metabolic signaling. The inclusion of these genes was based on a thorough literature review to ensure biological relevance and completeness. We then identified single nucleotide polymorphisms (SNPs) associated with these genes from three databases: GTEx [15], eQTLGen [16], and the study by Zheng et al. [17]. SNPs were included if they were associated with the expression of these target genes ($P<0.05$).

To refine these instruments, we cross-referenced SNPs with data from the UK Biobank, focusing on those associated with glycated hemoglobin (HbA1c) levels ($P<0.05$) as a marker of metformin exposure. Genes linked to HbA1c levels were prioritized to ensure that genetic variants reflected metformin's glucose-lowering effects. Variants associated with HbA1c but unrelated to the seven target genes were excluded, ensuring biological relevance and reducing potential pleiotropy.

Genetic colocalization was used to ensure that the same genetic variants influenced both the expression of the target genes and HbA1c levels. This approach examines whether two traits (e.g., gene expression and HbA1c levels) share a common causal variant in the same genomic region. Specifically, we used the coloc R package, which calculates posterior probabilities for five hypotheses: (1) no association with either trait, (2) association with trait 1 only, (3) association with trait 2 only, (4) association with both traits but with different causal variants, and (5) association with both traits and a shared causal variant. A posterior probability ≥ 0.8 for hypothesis 5 (shared causal variant) was considered evidence of colocalization [18, 19]. This step ensures that the selected SNPs are robust proxies for metformin exposure, reducing the risk of bias from horizontal pleiotropy.

To ensure the validity of our MR approach, we addressed key assumptions rigorously. For the relevance assumption, we calculated F-statistics for the selected

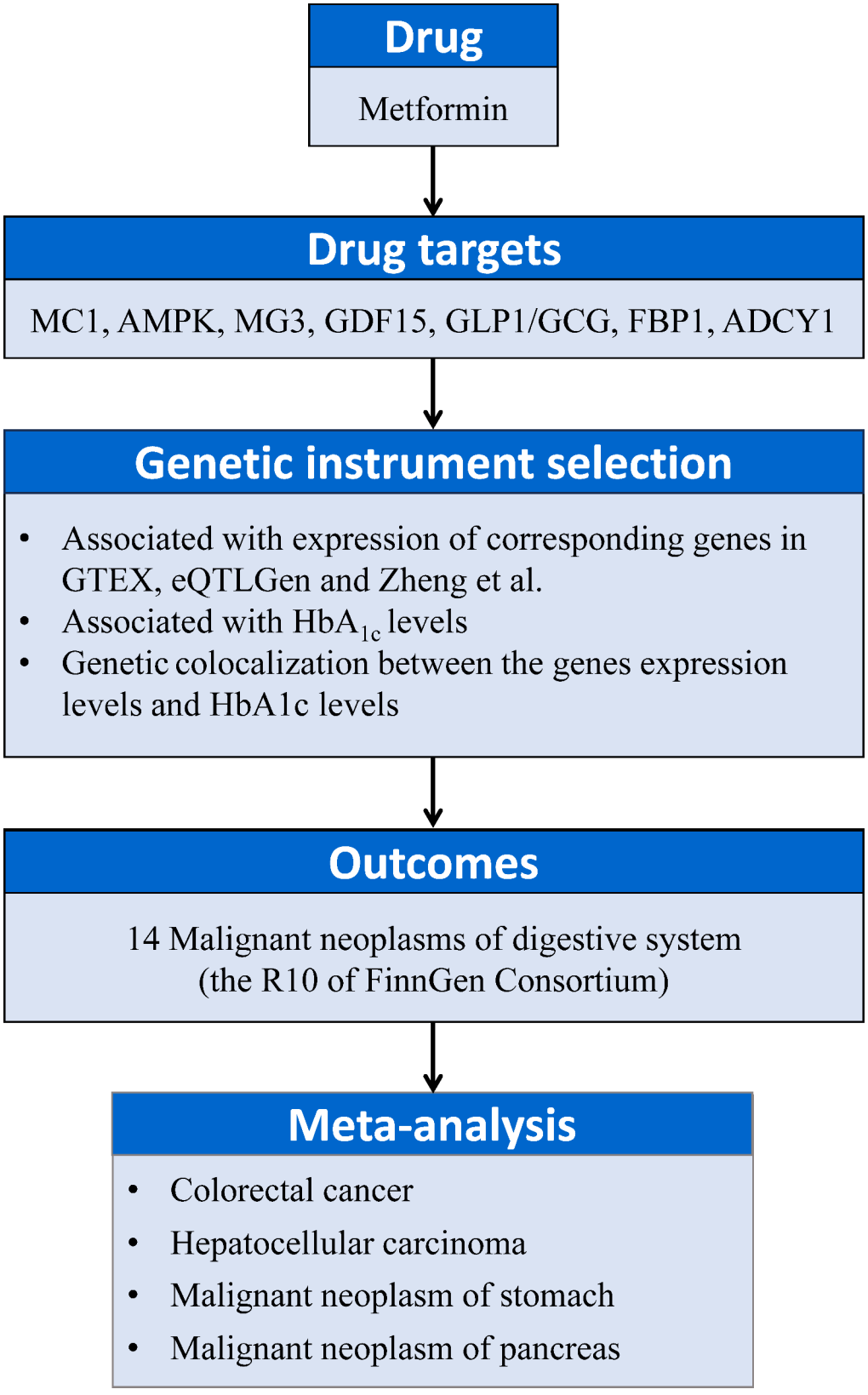

Fig. 1 Study design overview

SNPs, ensuring values exceeded 10 to confirm strong instruments and minimize weak instrument bias. For independence, genetic colocalization was performed to verify that the selected SNPs influence both HbA1c levels and gene expression via the same causal variant, thereby reducing the likelihood of confounding. To satisfy the exclusion restriction assumption, we assessed horizontal pleiotropy using MR-Egger regression by evaluating the intercept, which indicates pleiotropic effects. Sensitivity analyses, including weighted mode and weighted median approaches, were conducted as these methods are robust to invalid instruments. To address potential bias from population stratification, we derived all data from individuals of predominantly European ancestry and applied principal component adjustments in the original GWAS to control for population structure.

Study outcomes

To comprehensively evaluate the relationship between metformin and MTDS, we included a broad range of cancer types as outcome variables. The GWAS summary statistics for MTDS were obtained from the 10th release of the FinnGen consortium, including colon adenocarcinoma (3,212 cases, 314,193 controls), malignant neoplasm of colon (4,143 cases), colorectal adenocarcinoma (5,610 cases), colorectal cancer (6,847 cases), hepatocellular carcinoma (500 cases), malignant neoplasm of oesophagus (619 cases), adenocarcinoma and ductal carcinoma of pancreas (731 cases), malignant neoplasm of pancreas (1,626 cases), adenocarcinoma and papilloma adenocarcinoma of rectum (2,437 cases), adenocarcinoma, papilloma adenocarcinoma and mucinous carcinomas of rectum (2, 545 cases), malignant neoplasm of rectum (2,490 cases), malignant neoplasm of small intestine (525 cases), adenocarcinoma and papillary adenocarcinoma of stomach (792 cases), and malignant neoplasm of stomach (1,423 cases). GWAS summary statistics for colorectal cancer (ebi-a-GCST90018588), hepatocellular carcinoma (ebi-a-GCST90041897), gastric cancer (ebi-a-GCST90018849), and pancreatic cancer (ebi-a-GCST90018893) were selected from European Bioinformatics Institute (EBI) for use in the meta-analysis. While prior evidence linking metformin to certain cancers may be limited, these cancers were included to explore potential novel associations given metformin's systemic effects on metabolism, inflammation, and cell growth pathways. This exploratory approach ensures that our analysis captures a comprehensive range of potential effects, addressing gaps in the existing literature. By including all major digestive cancers with available GWAS data, we aim to provide a holistic understanding of metformin's potential role across the spectrum of MTDS.

Statistical analyses

To evaluate the potential effects of metformin on MTDS, we employed the inverse-variance weighted (IVW) method as our primary measurement approach, which provides statistical efficiency and effectively minimizes bias. Additionally, we performed supplementary analyses using alternative methods like MR Egger, weighted mode, and weighted median that can be used to cross-validate results, address potential biases, and ensure the robustness of causal inferences [20, 21]. To evaluate the genetic variability across different diseases, we applied Cochran's Q test, which helps to identify significant differences in genetic effects. This test is useful for detecting whether the observed variations in results are beyond what would be expected by chance, thus highlighting potential heterogeneity among the genotypes. Additionally, we employed MR-Egger regression to address the issue of horizontal pleiotropy. MR-Egger regression is particularly advantageous in this context because it allows for the detection and adjustment of such pleiotropic effects, ensuring that the causal relationship we estimate is not biased by these confounding pathways. While multivariable MR can address specific confounders by incorporating additional exposures, this method was not applied in our study due to the lack of comprehensive GWAS data for potential confounders across all cancer types. Future studies with richer datasets may incorporate multivariable MR to further validate these findings. To ensure the robustness of our MR results, we implemented a leave-one-out strategy. This approach involves sequentially excluding each instrumental variable one at a time and recalculating the causal estimate. By doing so, we can determine whether our overall findings are unduly influenced by any single IV, which helps to confirm the stability and reliability of our results. Furthermore, we used funnel plots to evaluate the distribution of effect estimates. Funnel plots are instrumental in assessing the symmetry of these estimates around the overall effect size. This visual tool helps us to identify and address any underlying issues, thereby ensuring the integrity of our findings. Given the analysis of multiple cancer types, we applied Bonferroni correction to adjust for multiple testing. This correction ensures that the overall type I error rate is controlled. Specifically, the nominal significance threshold ($P<0.05$) was divided by the number of cancer outcomes analyzed ($n=14$), resulting in an adjusted threshold of $P<0.0036$. Results exceeding this corrected threshold are considered statistically significant, while results below $P<0.05$ but above the corrected threshold are interpreted as suggestive and warranting further investigation.

Results

The genetic instruments that are associated with both the metformin target genes and HbA1c levels are listed in Supplementary Tables 1–7. The final genetic instruments determined through genetic colocalization are shown in Supplementary Table 8. Using T2DM as a positive reference outcome sufficiently validated the effectiveness of our genetic instruments (Supplementary Table 9).

IVW analysis showed that genetically proxied metformin increased the risk of colorectal cancer (OR=2.38, 95%CI=1.38–4.09, P=0.0018), colorectal adenocarcinoma (2.41, 1.34–4.34, 0.0032), malignant neoplasm of colon (2.88, 1.47–5.67, 0.0021), and colon adenocarcinoma (2.76, 1.29–5.91, 0.0091). After applying Bonferroni correction (P<0.0036), associations for colorectal cancer, colorectal adenocarcinoma, and malignant neoplasm of the colon remained statistically significant. However, the association for colon adenocarcinoma did not meet the adjusted significance threshold and is considered suggestive. However, no causal relationship was found with hepatocellular carcinoma (0.69, 0.09–5.32, 0.7228), malignant neoplasm of oesophagus (3.64, 0.65–20.35, 0.1415), adenocarcinoma and ductal carcinoma of pancreas (1.42, 0.29–6.88, 0.664), malignant neoplasm of pancreas (1.01, 0.36–2.89, 0.9791), adenocarcinoma and papilloma adenocarcinoma of rectum (1.39, 0.52–3.68, 0.5085), adenocarcinoma, papilloma adenocarcinoma and mucinous carcinomas of rectum (1.47, 0.55–3.92, 0.4438), malignant neoplasm of rectum (1.74, 0.65–4.69, 0.2703), malignant neoplasm of small intestine (6.32, 0.92–43.24, 0.0604), adenocarcinoma and papillary adenocarcinoma of stomach (1.13, 0.25–5.19, 0.873), and malignant neoplasm of stomach (0.94, 0.30–2.95, 0.9216) (Fig. 2, Supplementary Fig. 1).

Meta-analysis indicated that genetically proxied metformin increased the risk of colorectal cancer (1.71, 1.23–2.37, 0.0013), while there was no statistically significant association with hepatocellular carcinoma (1.21, 0.16–9.24, 0.8564), malignant neoplasm of stomach (0.94, 0.59–1.4, 0.6869), and malignant neoplasm of pancreas (1.01, 0.51–2.7, 0.7216) (Fig. 3).

Cochran's Q test indicated that there was no significant heterogeneity in the association between target genes and 14 types of MTDS (Supplementary Table 10). MR-Egger regression analysis revealed horizontal pleiotropy with colon adenocarcinoma for the target genes, but no significant horizontal pleiotropy was observed in other analyses (Supplementary Table 11). Additionally, the leave-one-out analysis demonstrated that the results were stable and dependable by sequentially excluding each instrumental variable (Supplementary Fig. 2). Meanwhile, the funnel plot revealed that there was no substantial bias affecting the analysis (Supplementary Fig. 3).

Discussion

In this study, we assessed the impact of seven metformin targets on MTDS. The results indicate that metformin use does not reduce the risk of these cancers and may even increase the risk of colorectal cancer. To date, although many studies suggest that metformin use may reduce the incidence of MTDS, most of these studies are likely subject to biases and confounding factors [22], and their results should be interpreted with caution. Our study provides evidence comparable to that of a randomized controlled trial, which does not support the use of metformin for the prevention of MTDS.

The initial study linking metformin use to colorectal cancer risk emerged in 2004 [23]. Following this, numerous population-based studies, case-control cohort investigations, and meta-analyses have explored the connection between metformin use and CRC risk. The findings have been varied, with some studies indicating a reduced risk [24–27], others finding no significant association [28, 29], and a few suggesting an increased risk of CRC [30, 31]. For individuals with diabetes but not on antidiabetic medication, the incidence rates of colorectal cancer and hepatocellular carcinoma are increased. When using metformin, the incidence rates of colorectal cancer in women and hepatocellular carcinoma in men decrease to non-diabetic levels [25]. A meta-analysis incorporating four observational studies suggested that metformin treatment is significantly associated with a reduced risk of colorectal cancer in patients with T2DM [32]. However, a multicenter study indicated that metformin did not reduce the incidence of colorectal cancer in diabetic patients [28]. A large case-control analysis using the General Practice Research Database indicated that metformin use is not associated with a reduced risk of colorectal cancer, and long-term use may even increase the risk of colorectal cancer [30].

In fact, there is no consistent conclusion regarding the relationship between metformin and other MTDS. Surprisingly, a meta-analysis showed that metformin is associated with a roughly 70% reduction in the risk of hepatocellular carcinoma in patients with T2DM, but there was evidence indicating significant heterogeneity among the studies included by the authors [33]. However, another meta-analysis showed that the use of metformin is not associated with a reduced risk of hepatocellular carcinoma [12]. A meta-analysis of 7 cohort studies including 591,077 patients found that metformin therapy significantly reduced the incidence of gastric cancer compared to other treatments [34]. Additionally, a pooled analysis combining data from 3 case-control studies within the Stomach Cancer Pooling Project found no significant link between chronic metformin use and gastric cancer [35].

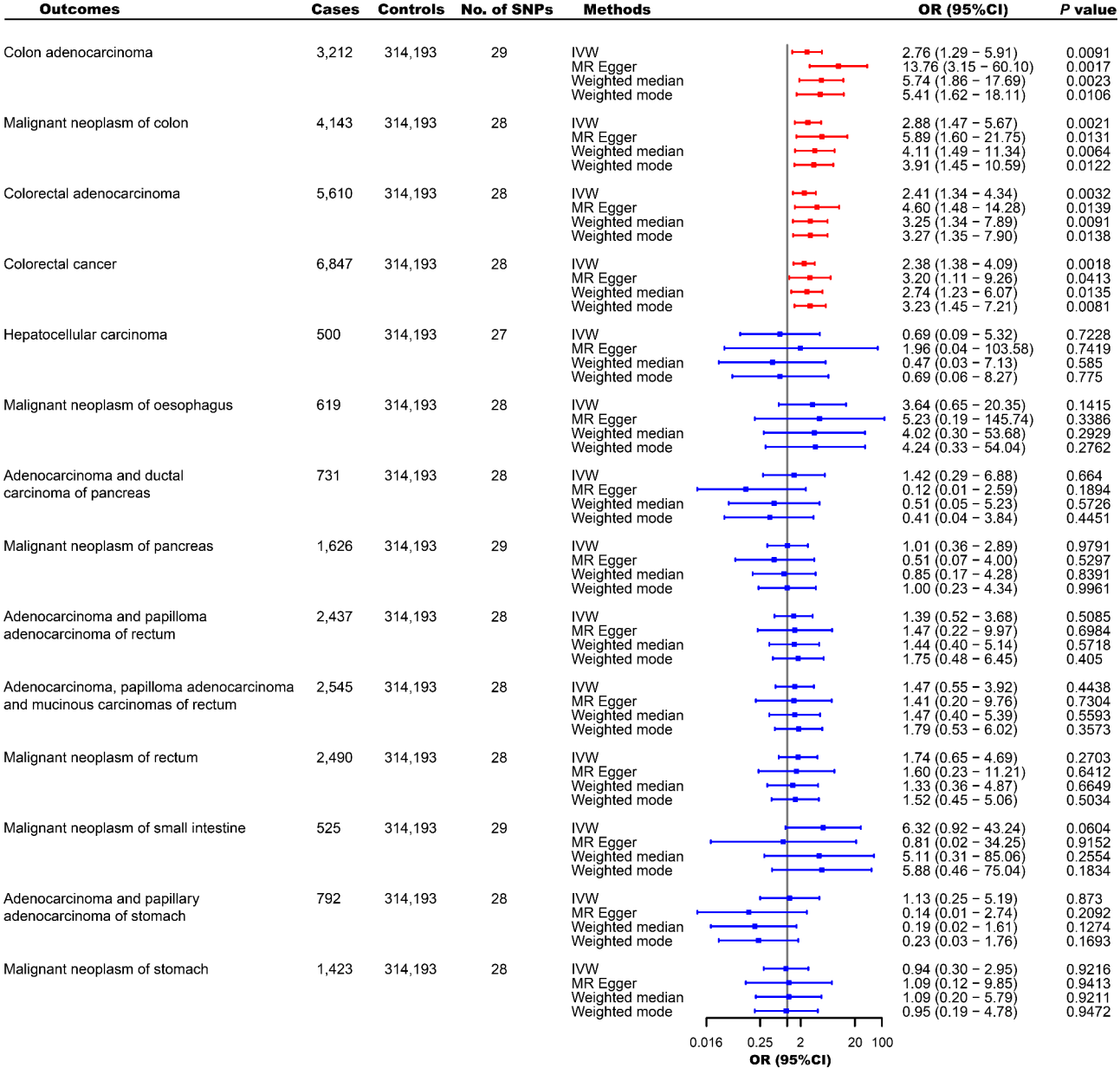

Fig. 2 Association between genetically predicted metformin targets genes and malignant neoplasm of digestive system

It is important to note that the majority of current research on metformin and cancer consists of observational studies, often utilizing historical medical records or insurance data, rather than being specifically designed to assess metformin's impact on cancer. The data on dosage, duration, and temporal changes in metformin treatment, as well as other adjunctive therapies (including insulin, sulfonylureas, and other medications), are often incomplete. These studies are frequently affected by immortal time bias, selection bias, and other confounding factors, potentially leading to an overestimation of metformin's benefits on cancer incidence and outcomes. While some randomized clinical trials have recently emerged to evaluate metformin as an adjunct therapy for various cancers, no definitive benefits on cancer have been demonstrated. A recent meta-analysis comprising nine randomized trials found that, compared to anticancer therapy alone, the use of metformin as an adjunctive anticancer treatment did not enhance tumor response or extend overall survival [36]. Recently, a large phase 3 placebo-controlled trial involving 3,649 women with high-risk operable breast cancer found no difference in invasive disease-free survival or cancer mortality between those who received adjuvant metformin and those who received standard therapy [37]. A phase 2 single-arm trial found that adjuvant metformin treatment

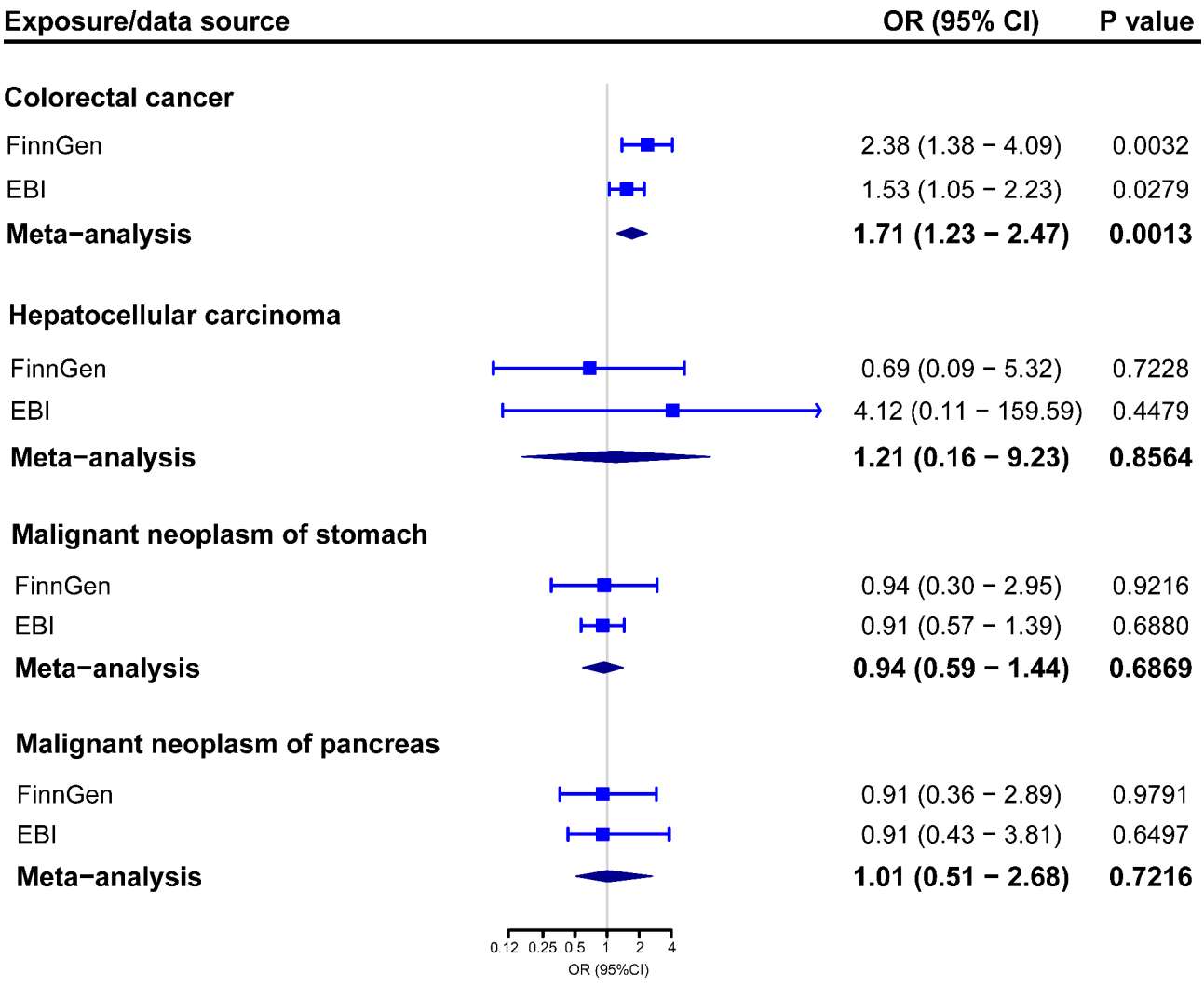

Fig. 3 Meta-analysis of the association between genetically predicted metformin targets genes and malignant neoplasm of digestive system

for colorectal cancer achieved disease control in 41% of participants [38], higher than the control rates seen in previous studies with monotherapy [39]. However, evidence indicates that such trials are often subject to time-related biases and confounding factors [40, 41].

The mechanisms by which metformin might increase colorectal cancer risk are complex and multifactorial, reflecting its diverse biological effects. One critical factor is metformin's influence on gut microbiota composition. While metformin-induced changes in microbiota have been associated with improved glucose homeostasis, they may also result in the overproduction of potentially carcinogenic metabolites, such as secondary bile acids and pro-inflammatory cytokines. These metabolites can disrupt the intestinal epithelial barrier, leading to chronic inflammation—a well-established driver of colorectal tumorigenesis. Additionally, metformin's systemic glucose-lowering effects reduce circulating insulin levels, which is generally protective against cancer driven by insulin signaling. However, in colorectal tissues, metformin may exert paradoxical, localized effects by altering insulin signaling pathways. Specifically, metformin might enhance insulin resistance within epithelial cells, inadvertently promoting hyperactivation of the PI3K/AKT/mTOR pathway—a signaling axis frequently dysregulated in colorectal cancer [42]. This pathway is known to stimulate cellular proliferation and survival, creating a pro-tumorigenic environment in the colon. Furthermore, metformin's effects on metabolic and inflammatory pathways may vary depending on tissue type. For example, in hepatocellular carcinoma, metformin appears to exert anti-inflammatory effects and inhibit cell growth via AMPK activation and mTOR inhibition [43]. However, in colorectal tissues, its influence on local inflammation and microbiota may override these protective effects, resulting in divergent outcomes. These findings align with prior studies showing variability in metformin's effects across cancer types, highlighting the

need for tissue-specific mechanistic studies. It is important to note that the mechanisms discussed here are speculative and based on existing literature. Our study is focused on causal inference through MR, and while we propose potential mechanisms, we did not directly test these biological processes. These mechanisms should be considered as hypotheses to guide future research. Direct experimental validation of these proposed pathways is necessary to fully understand the role of metformin in colorectal cancer and its broader implications for cancer prevention. Future research should integrate microbiome analysis, insulin signaling assays, and metabolic profiling to disentangle these dynamics. This will be crucial for optimizing metformin's therapeutic use while mitigating potential risks in colorectal cancer [22].

Our study suggests that, in addition to its well-established role in glycemic control, metformin may also have an unintended effect on cancer risk—particularly increasing the risk of colorectal cancer. While metformin remains a cornerstone in diabetes management, these findings underscore the need for clinicians to be cautious in prescribing metformin for cancer prevention in patients with T2DM, particularly in those at risk for colorectal malignancies. The dual effects of metformin—both as a glucose-lowering agent and as a potential modulator of cancer risk—raise important questions for clinical practice. Given that patients with diabetes are already at higher risk for various cancers, particularly those of the digestive system, the potential pro-carcinogenic effects of metformin in certain tissues must be carefully considered. If future studies confirm that metformin increases the risk of colorectal cancer, alternative therapies or adjunctive treatments may be needed for patients with high cancer risk. Additionally, these findings suggest the importance of continued monitoring and personalized treatment strategies for diabetic patients, where cancer risk is an added concern.

Strengths and limitations

Our study has several advantages. First, there are currently no well-designed large randomized controlled trials that investigate the relationship between metformin use and MTDS. MR studies can avoid time-related biases and confounding factors, providing evidence comparable to randomized controlled trials. Second, although some MR studies have explored the link between metformin and certain tumors, their selection of metformin instrumental variables was not rigorous, as they only used the UK Biobank population taking metformin as a basis [44]. The IVW method was used as the primary approach for causal inference due to its efficiency under the assumption that all genetic instruments are valid and free from horizontal pleiotropy. However, this assumption may not always hold, as unmeasured pleiotropy could introduce bias. To address this, we conducted complementary sensitivity analyses, including MR-Egger regression, weighted median, and weighted mode methods, which provide robust causal estimates even when some instruments are invalid. The consistency of results across these methods, coupled with the absence of significant pleiotropy indicated by the MR-Egger intercept test, supports the robustness of our findings. The genetic instruments used in this study were rigorously selected and validated through genetic colocalization and F-statistics exceeding 10, minimizing the risk of weak instrument bias. While the IVW method assumes no directional pleiotropy, the robustness of our findings across multiple methods provides confidence that pleiotropic effects are unlikely to drive the observed associations. Finally, we conducted a meta-analysis using different GWAS datasets, which enhances the persuasiveness of our study. However, our study has some limitations. First, the specific mechanisms by which metformin might increase the risk of colorectal cancer are still unknown. Second, the GWAS data we analyzed come from European populations, and the results may not be generalizable to other ethnic groups. Third, we were unable to conduct subgroup analyses, such as examining the effect of metformin on malignant tumors specifically in diabetic patients. Fourth, the datasets we utilized (GTEx, eQTLGen, Zheng et al., FinnGen, and EBI) provide summary-level genetic data, but do not include detailed clinical or phenotypic information for each participant. While demographic information such as age, sex, and ethnicity were available for most datasets, other important variables, including diabetes prevalence and comorbidities, were not consistently reported. Lastly, the lack of significant associations for cancers other than colorectal cancer could partly reflect limited statistical power due to smaller case numbers in the underlying GWAS datasets. For instance, cancers such as hepatocellular carcinoma and small intestine cancer had relatively few cases compared to colorectal cancer, potentially reducing the precision of causal estimates. However, the consistency of these null results across multiple sensitivity analyses and the robustness of our genetic instruments provide confidence that these findings are not artifacts of insufficient power. Future studies with larger GWAS datasets may provide further clarification of these potential associations.

Conclusions

In conclusion, our study did not find that metformin can reduce the risk of malignant neoplasm of digestive system; instead, it increased the risk of colorectal cancer. To confirm and extend the findings of this study, future research should explore several key directions. First, MR studies incorporating non-European populations are needed to enhance the generalizability of the results, as

our analysis relied on European datasets. Second, dose-response relationships for metformin should be investigated to determine optimal doses for potential cancer prevention or treatment. This could guide more targeted clinical trials. Third, multivariable MR approaches and further stratified analyses could provide insights into the interaction between metformin use, metabolic status, and other cancer risk factors. These strategies could refine future randomized clinical trial designs and ensure their relevance to broader populations and specific patient subgroups.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01573-9.

Supplementary Material 1

Supplementary Material 2

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Author contributions
PL: Conceptualization, methodology, formal analysis, validation, and writing-original draft. JX and JX: Data curation, validation and writing-review & editing. JZ: Conceptualization, project administration, supervision and writing-review & editing.

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Data availability
The datasets generated and analyzed during the current study are publicly available. Genetic data used for instrument selection were obtained from the GTEx (https://gtexportal.org/home/), eQTLGen (https://www.eqtlgen.org/), and UK Biobank (https://www.ukbiobank.ac.uk/) datasets. The GWAS summary statistics for malignant tumors of the digestive system (MTDS) were sourced from the FinnGen consortium (https://www.finngen.fi/en) and the European Bioinformatics Institute (EBI) GWAS Catalog (https://www.ebi.ac.uk/gwas/). All data are accessible to researchers upon appropriate application and agreement with the respective repositories.

Declarations

Ethics approval and consent to participate
We utilized publicly available GWAS summary-level data in our research, and all the original studies involved in our analysis had obtained approval from their respective Institutional Review Boards or local ethics committees.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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