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Causality between insulin use and malignant tumors of the digestive system: a two-sample mendelian randomized study

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Abstract

Background Existing cohort studies show no association between insulin use and cancers of the digestive system, while numerous meta-analyses suggest that insulin use increases the risk of digestive system tumours. This study uses two-sample Mendelian randomization (MR) to further investigate the causal relationship between the two.

Methods We selected single nucleotide polymorphisms (SNPs) strongly associated with insulin use as instrumental variables and used aggregated statistics on digestive system neoplasms as the outcome event. The primary method of analysis was inverse variance weighting (IVW), supplemented by weighted median, MR-Egger regression, weighted mode and simple mode methods. The reliability of the study was assessed by heterogeneity testing, pleiotropy analysis and sensitivity analysis.

Result A total of 8 SNPs associated with insulin use were included as instrumental variables. Random-effects IVW analysis showed an association between insulin use and increased risk of colorectal cancer (OR = 1.1037, 95%CI = 1.0183–1.1962, $P = 0.016$). No statistically significant association was found between insulin use and the development of other digestive system tumours. The results were unaffected by pleiotropy and heterogeneity, and the reliability of the findings was confirmed by sensitivity analysis.

Conclusion Our Mendelian randomization study suggests an association between insulin use and an increased risk of CRC, with no clear association observed for other digestive system tumours. However, further MR studies with larger sample sizes from genome-wide association study (GWAS) data are needed to verify this association.

Keywords Digestive system tumours, Insulin use, Mendelian randomization

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Introduction

Digestive system cancers are are a leading global health problem, with high morbidity and mortality rates that present significant challenges. In 2020, there will be more than 5 million new cases and more than 3.5 million deaths, accounting for more than a quarter of all cancer-related mortality [1], representing not only a major threat to human health, but also an enormous socio-economic burden [2, 3]. The aetiology of these cancers includes both genetic factors and lifestyle-related risks such as increased BMI, Helicobacter pylori infection, high alcohol consumption, smoking and poor dietary habits [4–6]. Early diagnosis and treatment are important, but so are preventive measures such as adopting healthy lifestyle habits and reducing alcohol consumption.

In recent years, rapid advances in science, technology and socioeconomics have significantly changed people's diets and lifestyles. Decreased physical activity and increased consumption of foods high in sugar have contributed to an annual increase in the incidence of diabetes, leading to a corresponding increase in the use of exogenous insulin [7]. A number of studies suggest that insulin use may increase the risk of cancer in people with diabetes [8–10]. In particular, a prospective study by Campbell et al. showed that men with type 2 diabetes had an increased risk of CRC compared with the non-diabetic population (RR: 1.24; 95%CI: 1.08–1.44). This risk was further increased in diabetic patients using insulin (RR: 1.36; 95%CI: 1.05–1.78), although insulin use was not associated with an increased risk of CRC in female patients [11]. Conversely, other studies have found no association between insulin use and the risk of digestive system tumours [12, 13].

The conflicting conclusions of existing studies may be due to limited sample sizes and potential confounding factors. Therefore, more clinical trials are needed to determine whether there is a causal relationship between insulin use and gastrointestinal cancers.

Mendelian randomization (MR), a widely utilized method in recent years, offers a valuable approach to infer causal relationships between exposures and diseases. MR employs SNPs as IVs to ascertain these causal links. By leveraging the random allocation of alleles from parents, akin to randomized controlled trials, MR significantly mitigates the impact of confounding variables on study outcomes [14]. Moreover, MR circumvents the influence of environmental and behavioral factors on genetic variants, thus avoiding confounding biases and reverse causality issues. This method provides a more precise tool for evaluating the causal associations between exposures and diseases [15, 16]. Given the inconsistencies in prior research findings, this study employs a two-sample Mendelian randomization approach to investigate the potential causal relationship between insulin use and digestive system cancer.

Materials and methods

Study design

In this research, we employed a two-sample MR study to explore the potential causal link between insulin use and digestive system cancers, with a particular focus on CRC. The MR method was selected for its capacity to utilize genetic variants as IVs, which minimizes confounding and reverse causation biases typically present in observational studies.The MR approach is underpinned by the concept that genetic variants, such as SNPs, are randomly allocated, akin to a randomized controlled trial, thus reducing the impact of various confounding factors. This study is founded on three key assumptions essential for the validity of MR methods: the relevance assumption, which demands a significant correlation between the IVs and insulin use; the exclusivity assumption, which stipulates that the IVs should not be associated with any confounders between insulin use and cancer outcomes; and the independence assumption, which asserts that IVs influence cancer outcomes solely through insulin use, without other biological pathways involved. The study design process for this trial and the three key assumptions for Mendelian randomization are shown in Fig. 1.

Data sources

Exposure and outcome data for our study were sourced from the OpenGWAS database, which is accessible at https://gwas.mrcieu.ac.uk/. We utilized the Neale Lab GWAS dataset (ukb-a-153), encompassing 337,159 Europeans, with 3,319 insulin users as cases and 333,840 non-users as controls. Insulin use was evaluated through questionnaires, medical records, and prescription data, all of which were subjected to stringent quality control for accuracy and reliability. For our primary outcome, CRC, we extracted data from the UK Biobank (ieu-b-4965), comprising 377,673 Europeans, including 5,657 CRC patients and 372,016 without CRC. CRC was defined using EFO terminology: EFO:0005842 for "colorectal cancer" and EFO:1,001,951 for "colorectal carcinoma," both referring to adenocarcinomas of the colon or rectum. To mitigate sample overlap bias, our digestive system cancer dataset was compiled from various consortia, including IEU, UKB, EBI, and FinnGen, and was based on genetic information from the European population. Further details and GWAS data sources for the variables are presented in Table 1. To prevent bias from population stratification, our study exclusively included individuals of European descent. The GWAS IDs can be queried at the OpenGWAS database, which offers open-access, unrestricted data.

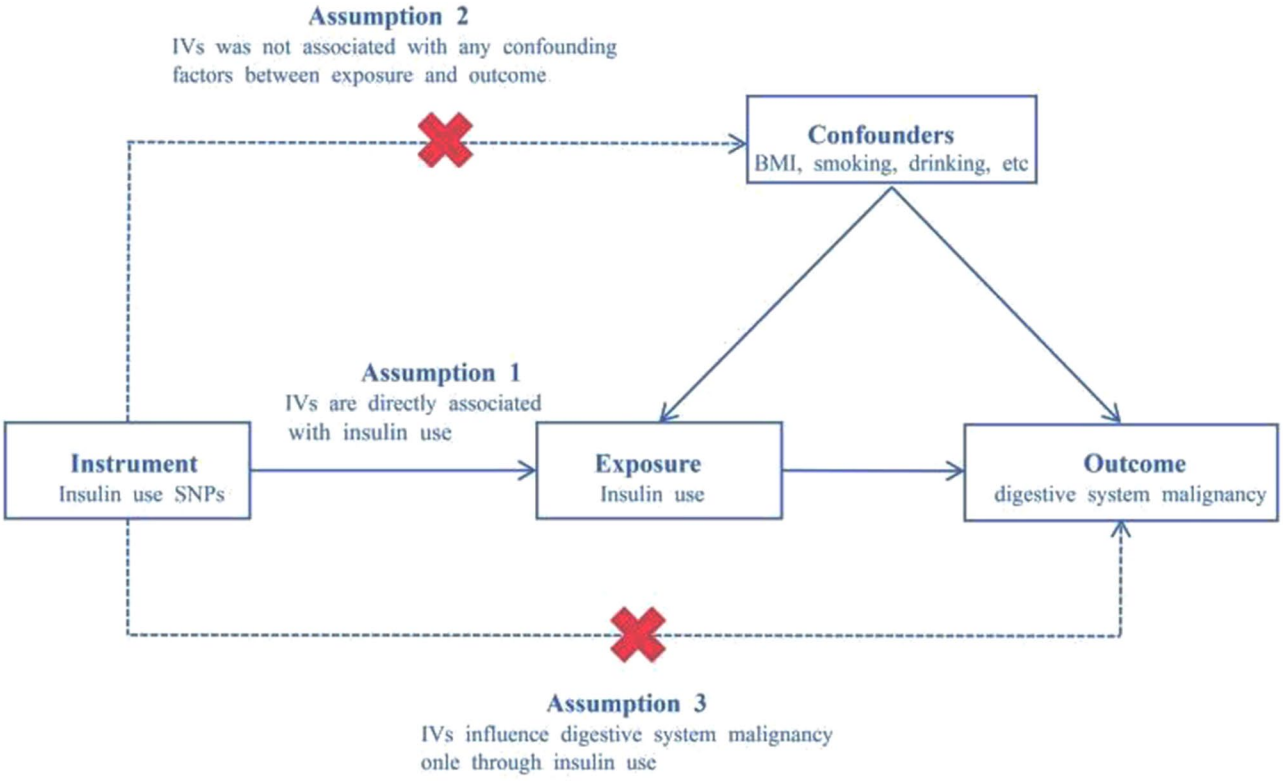

Fig. 1 The design process and three assumptions of the TSMR Study

Table 1 Detailed information and sources of GWAS datea for the included variables

Exposure/ Outcome	GWAS ID	Sample size	Case group	Control group	Consortium	Population source	Data source link
Exposure							https://gwas.mrcieu.ac.uk/
Insulin use	ukb-a-153	337,159	3,319	333,840	Neale Lab	European	
Outcome							
CRC	ieu-b–4965	377,673	5,657	372,016	UK Biobank	European	
Small intestine	ukb-a-56	337,159	156	337,003	Neale Lab	European	
Gastric	ebi-a-GCST90018849	476,116	1,029	475,087	EBI	European	
Liver	finn-b-C3_LIVER_INTRAHEPATIC_BILE_DUCTS	218,792	304	218,488	FinnGen	European	
Esophagus	ieu-b-4960	372,756	740	372,016	UK Biobank	European	
Pancreas	ebi-a-GCST90018893	476,245	1,196	475,049	EBI	European	

NA: Not available; CRC: Colorectal cancer

Sample size

In genome-wide association studies (GWAS), determining an adequate sample size is essential for ensuring adequate statistical power. We estimated the effect size between insulin use and CRC risk, assuming a linear relationship and setting our statistical power at 80% (1-β) and a significance level (α) of 0.05, which aligns with common research standards.Using the formula $n=(\frac{Z_{1-\alpha/2}+Z_{1-\beta}}{\text{Effect size}})^2\times\frac{1}{\text{Var}}$. To ensure adequate statistical power in our GWAS, we calculated the required sample size using established parameters: a critical value of 1.96 for a two-tailed test at $\alpha=0.05$ and a corresponding value of 0.84 for achieving 80% power. We aimed to detect the smallest effect size, determined from prior meta-analyses [17–20], which yielded an average odds ratio (OR) of 1.59. Using the formula Effect Size=ln(OR), we found a minimum effect size of 0.47. We considered the variances of insulin use (0.00974) and CRC (0.01478), opting for the larger variance of 0.01478 to ensure a sufficiently large sample size. Applying these values to the sample size formula, we estimated a need for approximately 2401 samples to detect the effect size between insulin use and CRC risk. However, our actual datasets far

Table 2 Detailed information and intensity evaluation of SNPs were included in this study

SNP	EA	OA	BETA	SE	*P*	*N*	chr	Position	R^2	F-statistic
rs1064173	A	G	0.00824	0.00028	7.46E-193	337,159	6	32,627,480	9.67E-04	879
rs114355928	T	G	0.00818	0.00071	1.56E-30	337,159	6	32,265,881	1.99E-05	132
rs3129886	C	T	0.00414	0.00028	3.70E-50	337,159	6	32,410,576	2.20E-04	222
rs6679677	A	C	0.00387	0.00040	1.42E-22	337,159	1	114,303,808	4.66E-05	96
rs689	T	A	0.00292	0.00027	6.08E-28	337,159	11	2,182,224	1.31E-04	120
rs7744001	A	G	-0.00269	0.00026	4.27E-25	337,159	6	32,626,086	1.21E-04	107
rs7903146	T	C	0.00238	0.00026	2.42E-19	337,159	10	114,758,349	8.83E-05	81
rs9380190	C	T	-0.00204	0.00034	1.85E-09	337,159	6	30,769,565	2.41E-05	36

Table 3 Pleiotropy and heterogeneous analysis of the causal relationship between insulin use and digestive system malignancy

Outcomes	Heterogeneity test						Pleiotropy test		
	MR-Egger			IVW			MR-Egger		
	Q	Q_df	Q_pval	Q	Q_df	Q_pval	Intercept	SE	*P*
CRC	13.91	6	0.03	14.55	7	0.04	−2.11E−04	4.00E−04	0.617
Small intestine	5.17	6	0.52	7.01	7	0.43	−6.88E−05	4.93E−05	0.224
Gastric	16.18	6	0.01	29.42	7	0.01	−5.89E−02	2.66E−02	0.686
Liver	6.57	5	0.25	7.49	6	0.28	−0.116	0.138	0.439
Esophagus	5.82	6	0.44	6.09	7	0.52	5.12E−05	9.69E−05	0.616
Pancreas	17.17	6	0.01	17.24	7	0.02	0.009	0.059	0.873

exceeded this requirement: the insulin use dataset (ukb-a-153) comprised 337,159 samples, and the CRC dataset (ieu-b-4965) included 377,673 samples. These substantial sample sizes provide ample statistical power to identify associations between insulin use and CRC risk.

IVs selection and evaluation

We initially identified SNPs significantly linked to insulin use as instrumental variables (IVs) from the IEU Open GWAS database, adhering to a stringent criterion of $p<5\times10^{-8}$ for significance. To mitigate linkage disequilibrium and ensure IV independence, we applied parameters $r^2<0.001$ and kb>10,000 kb. Furthermore, we utilized the MR-PRESSO method to detect and exclude outliers and palindromic sequences, thereby bolstering the study's reliability. The F-statistic for each SNP was calculated using the formula $F=\beta^2 exposure/SE^2 exposure$, with those below a threshold of 10, indicating weak instruments, being excluded to prevent bias. By rigorously applying these criteria, we enhanced the reliability of our MR study, with the selected SNPs detailed in Table 2.

Mendelian randomization analyses

To increase the reliability of our study, we used five different MR methods to investigate the causal relationship between insulin use and digestive cancers. Our primary method was Inverse Variance Weighting (IVW), which uses a linear regression model to estimate causal effects under the assumption that all SNPs are valid IVs that influence cancer outcomes solely through insulin use, with no horizontal pleiotropy. Given the potential for pleiotropy to bias results, we complemented IVW with four additional MR methods. The weighted median method provides a robust causal effect estimate by predicting the effect of each SNP on exposure and outcome, and assigning weights based on the variance of these predictions. The MR-Egger method accounts for possible heterogeneity among IVs, provides a corrected causal effect estimate, and detects pleiotropy through its intercept; a value close to zero indicates minimal pleiotropy, while deviations indicate its presence. The results of these tests for heterogeneity and pleiotropy are shown in Table 3. We also used simple and weighted models to strengthen our MR results. By using MR methods with different assumptions, rather than relying on IVW alone, we improved the stability and reliability of our causal inferences between insulin use and digestive system tumours. This comprehensive approach deepens our understanding of how insulin use in people with diabetes might affect the risk of digestive system tumours.

Sensitivity analysis

To ensure the robustness and consistency of the results of our Mendelian randomisation study, and to identify potential biases, we implemented a number of quality control measures. First, we meticulously cleaned each dataset, removing missing data, outliers and erroneous records to improve data quality and analytical precision. Heterogeneity among genetic variants was assessed using Cochran's Q test, with a P value of less than 0.05 indicating significant variation among SNPs serving as IVs. We also used the MR Egger intercept and MR-PRESSO to detect horizontal pleiotropy in SNPs. The MR

Egger intercept, which is designed to detect pleiotropy, approaches zero with a lower probability of pleiotropy. Conversely, the MR-PRESSO method was instrumental in identifying and removing outliers and pleiotropic SNPs that could bias our results by examining the correlation between genetic variants and excluding those that unduly influence the MR results. We also used the MR Egger intercept and MR-PRESSO to detect horizontal pleiotropy in SNPs. The MR Egger intercept, which is designed to detect pleiotropy, approaches zero as the probability of pleiotropy decreases. Conversely, the MR-PRESSO method was instrumental in identifying and removing outliers and pleiotropic SNPs that could bias our results by examining the correlation between genetic variants and excluding those that unduly influence the MR results. For our two-sample Mendelian randomisation analysis, we used the R programming environment (version 4.3.3), R Studio (version 3.6.1), and the Two Sample MR package (version 0.5.11), with P values less than 0.05 considered statistically significant.

Results

Characteristics and results of selected SNP

To enhance the validity of our SNP selection, we adhered to stringent criteria. We identified SNPs associated with insulin use at a genome-wide significance level $P<5\times10^{-8}$) and excluded those not meeting the linkage disequilibrium threshold of $r^2<0.01$. The remaining SNPs served as our initial instrumental variables. We then calculated the F-statistic using the formula F = β^2exposure/SE^2exposure, where F-values greater than 10 indicated sufficient statistical power to mitigate bias from the instrumental variables. The formula for calculating R^2 is $2\times(1\text{-EAF})\times EAF\times\left(\frac{\beta}{SE\times\sqrt{N}}\right)^2$, considering the sample size (N), minor allele frequency (MAF), effect size (β), and standard error (SE) from the exposure GWAS study. Data for these calculations were sourced from the original literature or comprehensive GWAS summary files. Furthermore, to account for potential confounding factors, we utilized the PhenoScanner V2 database to identify SNPs related to digestive system tumor risk factors, including smoking, alcohol consumption, inflammatory bowel disease, low fiber diet, and BMI. These SNPs, which could affect outcomes through alternative pathways, were excluded to maintain the integrity of our Mendelian randomization assumptions. After thorough screening, we selected a total of 47 SNPs as our final instrumental variables, with specific details presented in Table 2.

Causal associations of insulin use with CRC and other digestive system cancers

In our Mendelian randomization study, we investigated the causal associations between insulin use and CRC, as well as other cancers of the digestive system. A total of eight SNPs were rigorously selected as IVs to fulfil the three main hypotheses of the MR study, details of which are given in Table 2.

For CRC, the IVW approach showed a significant association with insulin use (OR=1.1037, 95%CI=1.0183–1.1962, $P=0.016$), suggesting an increased risk of CRC in diabetic patients using insulin. This finding was corroborated by additional MR methods, all indicating a positive association, as detailed in Table 4 and visualised in Fig. 2. To ensure the reliability of our findings, we used MR-PRESSO ($p=0.36$) and MR Egger intercept to detect pleiotropy and found no evidence of it, supporting the robustness of our results. Cochran's Q test suggested that our study had some heterogeneity, which indicated that there were differences in the prediction effect size of single SNPs on the outcome, but this did not affect the reliability of the final results. The leave-one-out method further confirmed the stability and reliability of our results, as shown in Fig. 3.

To extend our investigation to other digestive cancers, we applied the same stringent criteria for SNP selection and used IVW as the primary method of analysis, supplemented by four other methods. The results, shown in Table 4, indicated no significant causal association between insulin use and cancers of the stomach, small intestine, liver, oesophagus or pancreas, except for CRC. Heterogeneity and pleiotropy tests using Cochran's Q test and MR-PRESSO confirmed the stability of these findings, as shown in Fig. 4.

In conclusion, our study suggests a positive association between insulin use and the risk of CRC, with no significant associations found for other cancers of the digestive system.

Discussion

In the present study, a two-sample Mendelian randomization approach was employed, utilising data from the OPEN GWAS database, to investigate the potential causal relationship between insulin use and digestive system tumours.The findings suggest a notable association between insulin use and an elevated risk of CRC; however, they do not provide unequivocal evidence of causality for other types of digestive system cancers.

The rapid progression of the global economy and the development of technological innovations have precipitated profound lifestyle modifications, resulting in a proliferation of sugar-rich diets and, consequently, a marked escalation in the prevalence of diabetes [21]. This condition has become a critical global public health

Table 4 MR results of the causal relationship between insulin and digestive system tumors

Outcomes	Methods	Nsnp	β	Se	OR(95%CI)	*P*-value	FDR-corrected *P*-value
Colorectal	MR Egger	8	0.141	0.091	1.151 (1.018, 1.295)	0.173	0.216
	Weighted median	8	0.115	0.034	1.122 (1.048, 1.201)	0.001	0.005
	Inverse variance weighted	8	0.099	0.041	1.104 (1.018, 1.199)	0.016	0.027
	Simple mode	8	0.070	0.063	1.073 (0.933, 1.234)	0.313	0.313
	Weighted mode	8	0.120	0.036	1.128 (1.044, 1.216)	0.011	0.027
Gastric	MR Egger	8	5.279	5.889	183.668 (0.238, ∞)	0.405	0.405
	Weighted median	8	-3.899	2.383	0.020 (0.000, 1.461)	0.102	0.273
	Inverse variance weighted	8	-5.971	3.726	0.002 (0.000, 0.154)	0.109	0.273
	Simple mode	8	-7.608	8.329	0.000 (0.000, 0.004)	0.391	0.405
	Weighted mode	8	-2.781	2.254	0.057 (0.010, 0.328)	0.257	0.405
Esophagus	MR Egger	8	-0.013	0.022	0.987 (0.956, 1.019)	0.566	0.963
	Weighted median	8	0.001	0.013	1.001 (0.978, 1.024)	0.963	0.963
	Inverse variance weighted	8	-0.003	0.011	0.997 (0.976, 1.018)	0.765	0.963
	Simple mode	8	0.008	0.021	1.008 (0.976, 1.041)	0.697	0.963
	Weighted mode	8	0.003	0.015	1.003 (0.971, 1.036)	0.852	0.963
Small intestine	MR Egger	8	0.020	0.011	1.020 (0.998, 1.042)	0.120	0.200
	Weighted median	8	0.014	0.007	1.014 (1.000, 1.029)	0.025	0.125
	Inverse variance weighted	8	0.007	0.005	1.007 (0.997, 1.018)	0.193	0.241
	Simple mode	8	0.013	0.012	1.013 (0.989, 1.037)	0.364	0.364
	Weighted mode	8	0.014	0.007	1.014 (0.999, 1.029)	0.098	0.200
Pancreas	MR Egger	8	7.290	13.817	1404.892 (0.588, ∞)	0.617	0.771
	Weighted median	8	12.709	4.959	351154.189 (20.905, ∞)	0.010	0.050
	Inverse variance weighted	8	9.307	6.125	9542.088 (6.311, ∞)	0.129	0.215
	Simple mode	8	1.305	11.988	3.689 (0.029, ∞)	0.916	0.916
	Weighted mode	8	13.178	4.974	559101.526 (15.903, ∞)	0.033	0.083
Liver	MR Egger	7	38.987	40.531	4959.511 (0.436, ∞)	0.380	0.602
	Weighted median	7	12.975	16.644	435.582 (0.291, ∞)	0.436	0.602
	Inverse variance weighted	7	7.042	13.492	1131.526 (0.772, ∞)	0.602	0.602
	Simple mode	7	16.422	26.170	14590647.135 (0.053, ∞)	0.553	0.602
	Weighted mode	7	13.254	21.230	559101.526 (2.236, ∞)	0.555	0.602

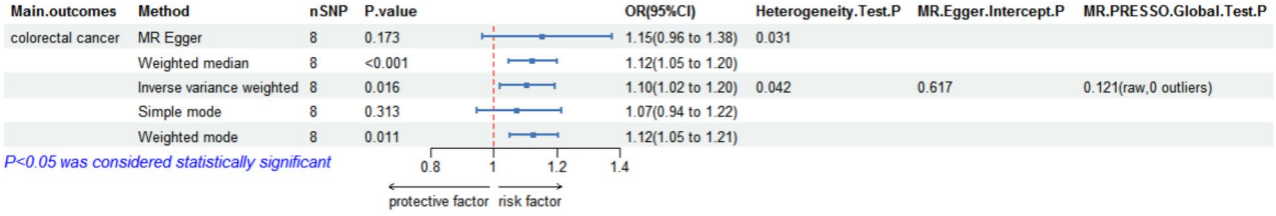

Fig. 2 Results of MR analysis of the causal association between insulin use and colorectal cancer

issue due to its high incidence and costly treatments, significantly threatening public health [22]. Data indicates that in 2017, the global prevalence of diabetes was approximately 425 million, a figure that climbed to 9.3% in 2019. Projections indicate that by 2045, the number of affected individuals will rise to 629 million, representing a 50% increase from 2017 [23]. Diabetes mellitus, a prevalent endocrine disorder, is primarily classified into type 1 (T1D) and type 2 (T2D), with T2D constituting approximately 90% of all diabetes cases [24]. T1D, which frequently manifests in adolescence, is typified by an autoimmune attack on the pancreatic β-cells, resulting in inadequate insulin production to satisfy the body's metabolic requirements. T2D, prevalent among middle-aged and elderly individuals, is typically linked to impaired β-cell function, necessitating the use of exogenous insulin for nearly all diabetic patients. The American Diabetes Association's glycemic control guidelines and numerous cohort studies [25–27] suggest that the initiation of insulin therapy early in the course of the disease can reduce the risk of microangiopathy. Consequently, the reliance

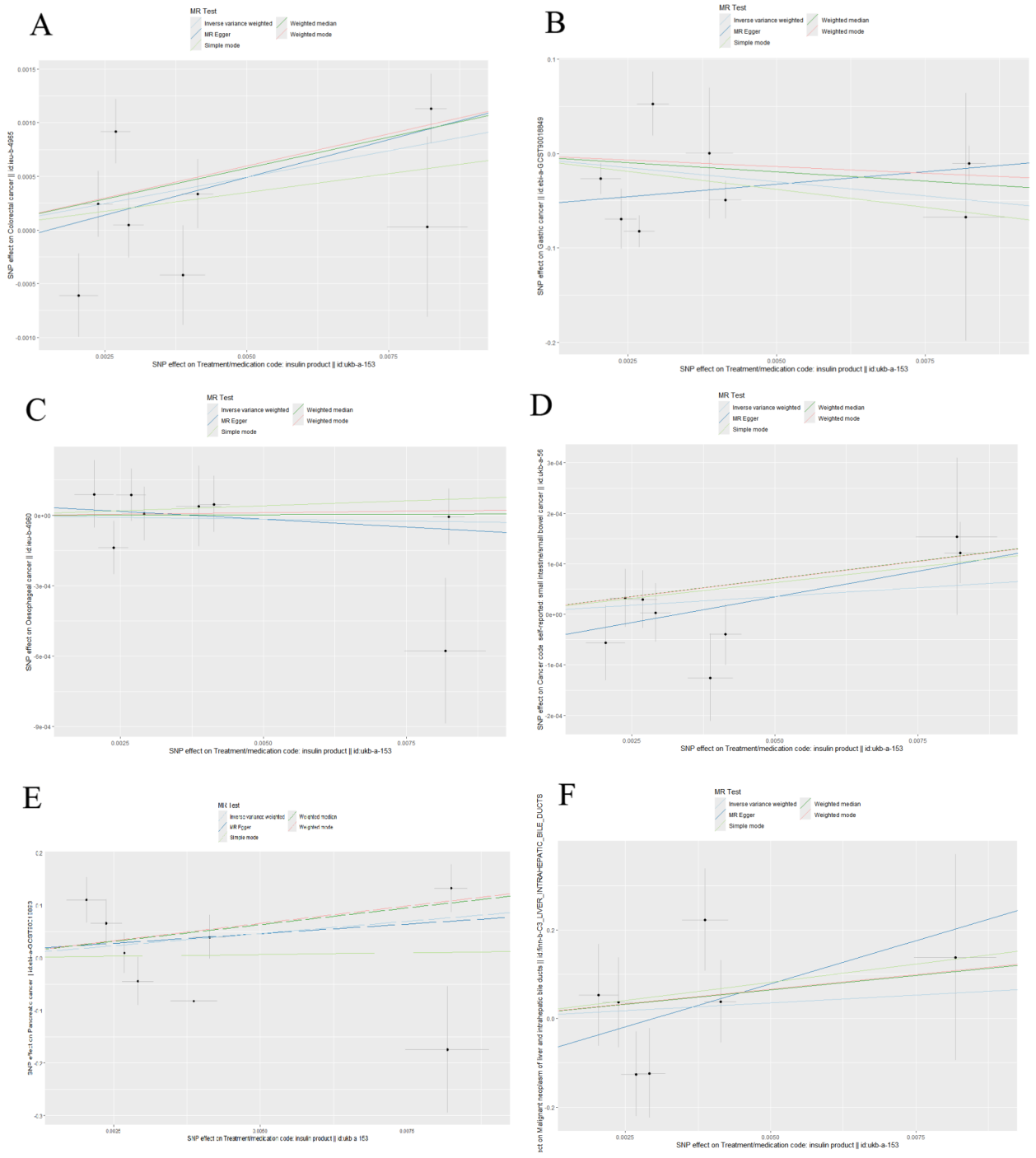

Fig. 3 Scatter plot of MR Results of the association between insulin use and digestive system tumors. (**A**): Colorectal cancer; (**B**): Gastric cancer; (**C**): esophagus cancer; (**D**): Small intestine cancer; (**E**): Pancreatic cancer; (**F**): Malignant neoplasm of liver and intrahepatic bile ducts

on exogenous insulin in diabetes treatment is growing, reflecting an upward trend in global insulin usage.

The question of whether the use of insulin elevates the risk of cancer has proven to be a complex and long-standing enigma within the medical research community. Given the prevalence of diabetes and its management through insulin therapy, elucidating the causal link between insulin and cancer is of paramount importance. Two primary mechanisms have been proposed to explain the potential role of insulin in tumour growth. Firstly, insulin's interaction with the insulin receptor or the IGF receptor [28, 29]. Secondly, insulin's facilitation of IGF-1

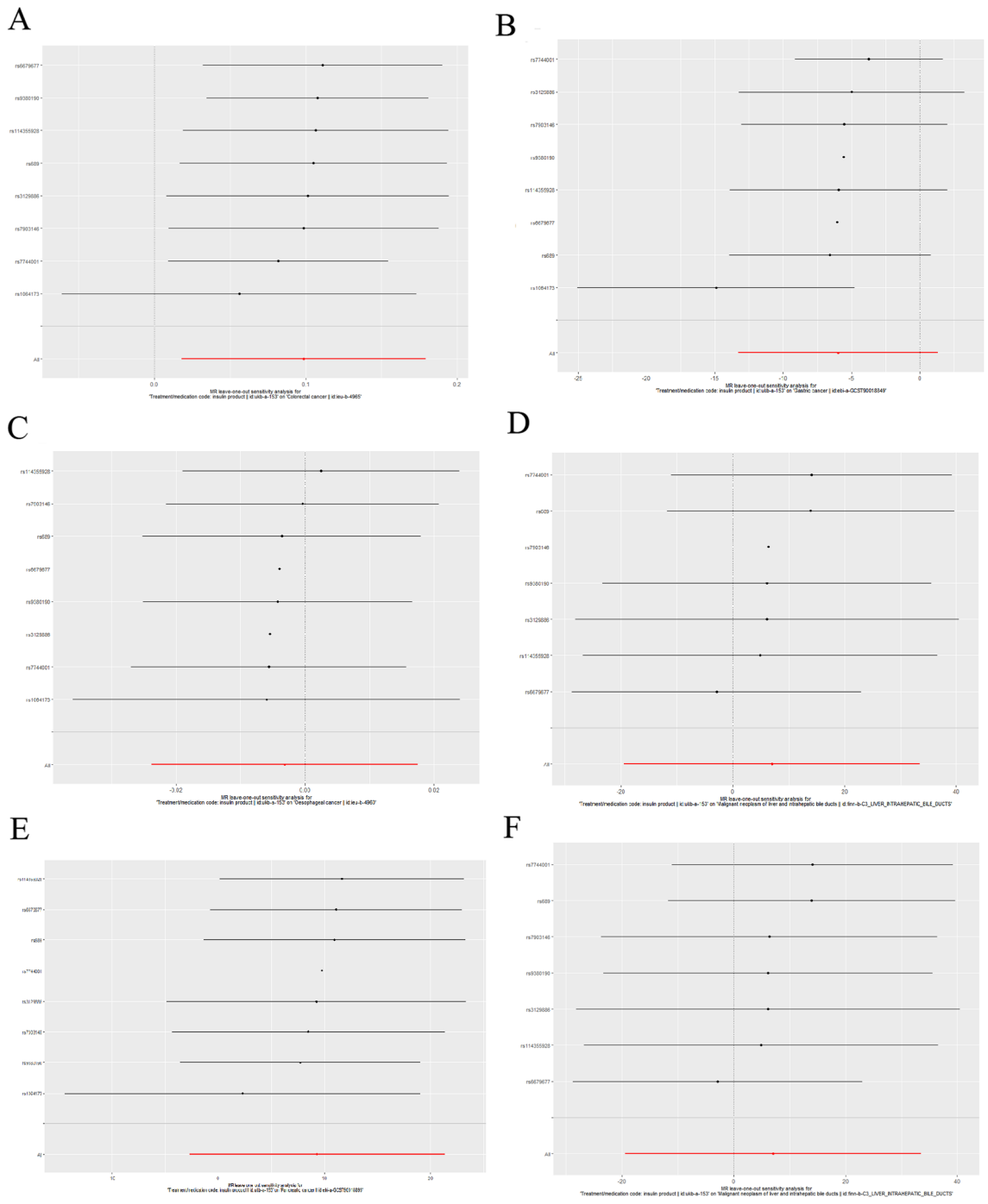

Fig. 4 Leave-one-out plot of MR results of the association between insulin use and digestive system tumors. (**A**): Colorectal cancer; (**B**): Gastric cancer; (**C**): Esophagus cancer; (**D**): Small intestine cancer; (**E**): Pancreatic cancer; (**F**): Malignant neoplasm of liver and intrahepatic bile ducts

binding to the IGF receptor by suppressing IGF-binding proteins. This interaction establishes a network among IGF family members and other growth factors, influencing cellular processes such as proliferation, differentiation, apoptosis, and transformation [30], with IGF family members being particularly implicated in cancer progression and metastasis [31, 32]. However, the intricate pathways connecting insulin use and cancer are not yet fully understood, necessitating speculation based on epidemiological and animal studies [8–13, 33, 34]. While cohort studies and animal experiments suggest a potential increase in cancer risk associated with insulin, these findings often do not align with clinical practice [35]. The potential causes of this discrepancy include factors such

as small sample sizes, population diversity, inconsistent follow-up periods, and variations in dietary habits, which may all contribute to biases in the outcomes.

The findings of this study indicate a positive correlation between insulin use and CRC, yet no significant causal link was identified between insulin use and other gastrointestinal malignancies. In essence, while insulin use may mitigate the risk of microangiopathy and enhance survival rates in diabetic patients, it appears to potentially elevate the risk of CRC in this population. In a study conducted by Chang CH et al. [36], 108,920 patients from the Taiwan National Health Insurance claims database were enrolled, with 8,194 cancer patients constituting the experimental group and 32,776 diabetic patients serving as the control group. The study revealed that the use of any insulin was associated with an increased risk of cancer (OR=1.97, 95%CI 1.85–2.09). Furthermore, the significant association between insulin use and an elevated risk of liver, colorectal, lung, stomach, and pancreatic cancers is at odds with the MR findings. This discrepancy may be attributed to the previously mentioned confounding factors, including the geographical location of the study (conducted in Taiwan, China, involving an Asian population) and the racial composition of the cohort (compared to our MR study, which focused on a European cohort). Furthermore, the subtropical climate and distinct dietary habits of Taiwan may contribute to the observed discrepancies in results when compared to Europe.

In the study conducted by Gu Y et al. [37], 98 patients in the insulin-using group developed cancer, compared to 170 patients in the non-insulin-using group. The respective cancer incidence rates were 0.786% and 0.743%. The study's findings indicated no significant difference in cancer risk between the two groups (RR=1.20, 95%CI 0.89–1.62, P=0.228). It is noteworthy that the use of insulin not only increased the mortality risk among users (RR=1.89, 95% CI 1.47–2.43, P<0.0001) but was also significantly associated with an elevated risk of death in cancer patients (RR=2.16, 95% CI 1.39–3.35, P=0.001). These findings emphasise the necessity of formulating a range of personalised treatment strategies for cancer patients to improve their prognosis.

It is imperative to emphasise the contentious nature of insulin's impact on hepatocellular carcinoma (HCC). While a number of studies have indicated a significant link between insulin use and liver cancer risk [36, 38], the present research did not establish a causal connection. The observed discrepancy can be attributed to two factors. Firstly, the data, sourced from a European database, may be subject to regional and ethnic variances, resulting in inconsistent findings. Secondly, as Yin J et al. [39] have demonstrated, chronic hepatitis B or C infection significantly increases the risk of liver cancer among insulin users (OR=1.27, 95%CI 1.04–1.55). However, the Global Burden of Hepatitis reports for 2009 and 2019 indicate that hepatitis B incidence in Europeans is notably lower than in Asians [40, 41]. The absence of genetic data on insulin users in Asia prevents further exploration of this relationship. Consequently, it is recommended that individuals who use insulin and have chronic viral hepatitis undergo regular liver function checks.

In the present study, the False Discovery Rate (FDR) correction was employed in order to address the issue of multiple comparisons. This approach has been demonstrated to enhance the identification of authentic genetic associations, whilst concomitantly managing the false positive rate. The employment of FDR correction enabled a more precise evaluation of the association between insulin use and the risk of developing digestive tumours. This approach serves to minimise false positives arising from multiple testing, thereby enhancing the confidence in the genetic associations that have been identified. While FDR does elevate the statistical significance threshold, it ensures the robustness of our findings. This approach empowers us to interpret our results with greater assurance by ruling out associations attributable to chance. While FDR correction is effective for controlling false positives, it may falter with small samples or weak effects. However, given the study's substantial sample size, FDR correction effectively manages false positives, enhancing the study's reliability and validity.

Limitations

The present study is not without limitations. First, the decision to focus exclusively on genetic data from European populations to reduce the impact of population stratification may have limited the generalisability of the findings. Secondly, the aggregation of data from GWAS without individual-level details precluded consideration of potential confounders such as age, weight, sex and medication regimens, which may have influenced the results, particularly given that diabetes treatments extend beyond insulin. Furthermore, the lack of GWAS data on insulin use in Asia, a region with high rates of gastrointestinal cancers, suggests that more comprehensive data and clinical trials are needed to validate our findings. The fact that both the small bowel cancer GWAS data and the insulin use dataset came from the same research groups deviates from the ideal two-sample MR design. Interpretation of the results for small bowel cancer should be undertaken with caution. Finally, future research needs to address the potential accuracy and completeness limitations of this study's data, which were derived from public databases and not peer-reviewed, through measures such as data validation, peer review and collaborative sharing.

Conclusion

In conclusion, our TSMR analysis suggests a positive causal association between insulin use and the risk of colorectal cancer. This finding has implications for CRC prevention in diabetic patients undergoing insulin therapy, emphasising the need for regular endoscopy and tumour marker testing. However, to increase the reliability of our MR findings, we need additional comprehensive GWAS data with larger sample sizes. In addition, more clinical trials and basic research are needed to elucidate the biological mechanisms underlying the association between insulin use and cancer.

Abbreviations

MR	Mendelian randomization
SNPs	Single nucleotide polymorphisms
IVs	Instrumental variables
CRC	Colorectal cancer
GWAS	Genome-wide association study
HCC	Hepatocellular carcinoma
FDR	False discovery rate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13452-1.

Supplementary Material 1

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Author contributions

Conception/design: CDZ, JL, LW, MY, and CZ. Document retrieval: CDZ, JL, YM, LW, and GS. Collection and/or assembly of the data: JL, YM, LW, and GS. Data analysis and interpretation: CDZ, JL, YM, LW, GS, CH, and YX. Manuscript writing: CDZ, JL, YM, LW, GZ, CH, and YX. Final approval of the manuscript: CDZ, JL, YM, LW, GS, CH, and YX.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All studies were approved by their respective review boards, and all patients and volunteers in the studies gave informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and Mortality Worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.
2. Wang Y, Huang Y, Chase RC, et al. Global Burden of Digestive diseases: a systematic analysis of the Global Burden of diseases Study, 1990 to 2019. Gastroenterology. 2023;165(3):773–e78315. https://doi.org/10.1053/j.gastro.2023.05.050.
3. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: Update 2021. Gastroenterology. 2022;162(2):621–44. https://doi.org/10.1053/j.gastro.2021.10.017.
4. Delgado-Aros S, Locke GR 3rd, Camilleri M, et al. Obesity is associated with increased risk of gastrointestinal symptoms: a population-based study. Am J Gastroenterol. 2004;99(9):1801–6. https://doi.org/10.1111/j.1572-0241.2004.30887.x.
5. Olsen J, Kronborg O. Coffee, tobacco and alcohol as risk factors for cancer and adenoma of the large intestine. Int J Epidemiol. 1993;22(3):398–402. https://doi.org/10.1093/ije/22.3.398.
6. Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ, et al. Helicobacter pylori seropositivity as a risk factor for pancreatic cancer. J Natl Cancer Inst. 2001;93(12):937–41. https://doi.org/10.1093/jnci/93.12.937.
7. Sarkar S, Heyward J, Alexander GC, Kalyani RR. Trends in insulin types and devices used by adults with type 2 diabetes in the United States, 2016 to 2020. JAMA Netw Open. 2021;4(10):e2128782. Published 2021 Oct 1. https://doi.org/10.1001/jamanetworkopen.2021.28782
8. Colmers IN, Bowker SL, Tjosvold LA, Johnson JA. Insulin use and cancer risk in patients with type 2 diabetes: a systematic review and meta-analysis of observational studies. Diabetes Metab. 2012;38(6):485–506. https://doi.org/10.1016/j.diabet.2012.08.011.
9. Chen CH, Lin CL, Hsu CY, Kao CH. Insulin enhances and metformin reduces risk of colorectal carcinoma in type-2 diabetes. QJM. 2020;113(3):194–200. https://doi.org/10.1093/qjmed/hcz253.
10. Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology. 2004;127(4):1044–50. https://doi.org/10.1053/j.gastro.2004.07.011.
11. Campbell PT, Deka A, Jacobs EJ, et al. Prospective study reveals associations between colorectal cancer and type 2 diabetes mellitus or insulin use in men. Gastroenterology. 2010;139(4):1138–46. https://doi.org/10.1053/j.gastro.2010.06.072.
12. But A, De Bruin ML, Bazelier MT, et al. Cancer risk among insulin users: comparing analogues with human insulin in the CARING five-country cohort study. Diabetologia. 2017;60(9):1691–703. https://doi.org/10.1007/s00125-017-4312-5.
13. Pradhan R, Yin H, Yu OHY, Azoulay L. The Use of Long-Acting insulin analogs and the risk of Colorectal Cancer among patients with type 2 diabetes: a Population-based Cohort Study. Drug Saf. 2020;43(2):103–10. https://doi.org/10.1007/s40264-019-00892-5.
14. Smith GD, Ebrahim S. Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003;32(1):1–22. https://doi.org/10.1093/ije/dyg070.
15. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet. 2014;23(R1):R89–98. https://doi.org/10.1093/hmg/ddu328.
16. Lawlor DA, Commentary. Two-sample mendelian randomization: opportunities and challenges. Int J Epidemiol. 2016;45(3):908–15. https://doi.org/10.1093/ije/dyw127.
17. Bu WJ, Song L, Zhao DY, Guo B, Liu J. Insulin therapy and the risk of colorectal cancer in patients with type 2 diabetes: a meta-analysis of observational studies. Br J Clin Pharmacol. 2014;78(2):301–9. https://doi.org/10.1111/bcp.12350. PMID: 25099257; PMCID: PMC4137822.1.69.
18. Wang L, Cai S, Teng Z, Zhao X, Chen X, Bai X. Insulin therapy contributes to the increased risk of colorectal cancer in diabetes patients: a meta-analysis. Diagn Pathol. 2013;8:180. https://doi.org/10.1186/1746-1596-8-180. PMID: 24175949; PMCID: PMC4228484.1.61.
19. Yin S, Bai H, Jing D. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients: a systemic review and meta-analysis. Diagn Pathol. 2014;9:91. https://doi.org/10.1186/1746-1596-9-91. PMID: 24885616; PMCID: PMC4107999.
20. Sun A, Liu R, Sun G. Insulin therapy and risk of colorectal cancer: an updated meta-analysis of epidemiological studies. Curr Med Res Opin. 2014;30(3):423 – 30. https://doi.org/10.1185/03007995.2013.858622IF2.4 Q1. Epub 2013 Nov 6. PMID: 24156655.

21. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the global burden of disease study 2021 [published correction appears in Lancet. 2023;402(10408):1132]. Lancet. 2023;402(10397):203–34. https://doi.org/10.1016/S0140-6736(23)01301-6.
22. Xie J, Wang M, Long Z, et al. Global burden of type 2 diabetes in adolescents and young adults, 1990–2019: systematic analysis of the global burden of Disease Study 2019. BMJ. 2022;379:e072385. https://doi.org/10.1136/bmj-2022-072385. Published 2022 Dec 7.
23. Standl E, Khunti K, Hansen TB, Schnell O. The global epidemics of diabetes in the 21st century: current situation and perspectives. Eur J Prev Cardiol. 2019;26(2suppl):7–14. https://doi.org/10.1177/2047487319881021.
24. Kaul K, Tarr JM, Ahmad SI, Kohner EM, Chibber R. Introduction to diabetes mellitus. Adv Exp Med Biol. 2012;771:1–11. https://doi.org/10.1007/978-1-4614-5441-0_1.
25. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28(2):103–17. https://doi.org/10.1016/0168-8227(95)01064-k.
26. Franklin VL, Khan F, Kennedy G, Belch JJ, Greene SA. Intensive insulin therapy improves endothelial function and microvascular reactivity in young people with type 1 diabetes. Diabetologia. 2008;51(2):353–60. https://doi.org/10.1007/s00125-007-0870-2.
27. Intensive blood-glucose control. With sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK prospective diabetes study (UKPDS) Group [published correction appears in Lancet 1999;354(9178):602]. Lancet. 1998;352(9131):837–53.
28. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst. 2002;94(13):972–80. https://doi.org/10.1093/jnci/94.13.972.
29. Gallagher EJ, Alikhani N, Tobin-Hess A, et al. Insulin receptor phosphorylation by endogenous insulin or the insulin analog AspB10 promotes mammary tumor growth independent of the IGF-I receptor. Diabetes. 2013;62(10):3553–60. https://doi.org/10.2337/db13-0249.
30. Kasprzak A. Autophagy and the insulin-like growth factor (IGF) system in Colonic cells: implications for colorectal neoplasia. Int J Mol Sci. 2023;24(4):3665. https://doi.org/10.3390/ijms24043665. Published 2023 Feb 11.
31. LeRoith D, Baserga R, Helman L, Roberts CT Jr. Insulin-like growth factors and cancer. Ann Intern Med. 1995;122(1):54–9. https://doi.org/10.7326/0003-4819-122-1-199501010-00009.
32. Baciuchka M, Remacle-Bonnet M, Garrouste F, Favre R, Sastre B, Pommier G. Insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) proteolysis in patients with colorectal cancer: possible association with the metastatic potential of the tumor. Int J Cancer. 1998;79(5):460–7. https://doi.org/10.1002/(sici)1097-0215(19981023)79:5%3C460::aid-ijc3%3E3.0.co;2-z.
33. Tseng CH. Human insulin therapy is associated with an increased risk of lung cancer: a population-based retrospective cohort study. Front Endocrinol (Lausanne). 2019;10:443. https://doi.org/10.3389/fendo.2019.00443. Published 2019 Jul 11.
34. Chung YW, Han DS, Park KH, Eun CS, Yoo KS, Park CK. Insulin therapy and colorectal adenoma risk among patients with type 2 diabetes mellitus: a case-control study in Korea. Dis Colon Rectum. 2008;51(5):593–7. https://doi.org/10.1007/s10350-007-9184-1.
35. Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. Cancer Epidemiol Biomarkers Prev. 1996;5(12):1013–5.
36. Chang CH, Lin JW, Wu LC, Lai MS, Chuang LM. Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2012;97(7):E1170–5. https://doi.org/10.1210/jc.2012-1162.
37. Gu Y, Wang C, Zheng Y, et al. Cancer incidence and mortality in patients with type 2 diabetes treated with human insulin: a cohort study in Shanghai. PLoS ONE. 2013;8(1):e53411. https://doi.org/10.1371/journal.pone.0053411.
38. Yin J, Freedman ND, Liu Y, et al. Associations between serum glucose, insulin, insulin resistance and the risk of incident primary liver cancer or chronic liver disease mortality: a nested case-control study. Br J Cancer. 2023;128(2):275–84. https://doi.org/10.1038/s41416-022-02042-8.
39. Chiang CH, Kuo CS, Lin WW, Su JH, Chen JD, Huang KC. Chronic viral hepatitis signifies the association of premixed insulin analogues with liver cancer risks: a nationwide population-based study. Int J Environ Res Public Health. 2019;16(12):2097. https://doi.org/10.3390/ijerph16122097. Published 2019 Jun 13.
40. Collaborators GBD2019HB. Global, regional, and national burden of hepatitis B, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet Gastroenterol Hepatol. 2022;7(9):796–829. https://doi.org/10.1016/S2468-1253(22)00124-8.
41. Hsu YC, Huang DQ, Nguyen MH. Global burden of hepatitis B virus: current status, missed opportunities and a call for action. Nat Rev Gastroenterol Hepatol. 2023;20(8):524–37. https://doi.org/10.1038/s41575-023-00760-9.

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