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ORIGINAL ARTICLE

SGLT-2 inhibitors are beneficial in reducing the risk of thyroid cancer: findings from a Mendelian randomization study

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Abstract

Objective Previous studies have investigated the association between diabetes medications and thyroid cancer, but the results have not been conclusive. This study used a Mendelian randomization approach to investigate the causal relationship between diabetes medications and thyroid cancer (TC).

Methods Exposures were six major diabetes medications target, while outcomes were TC and its differentiated forms, including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Mendelian randomization was conducted using IVW, MR-Egger, and weighted median methods. Tests for heterogeneity, horizontal pleiotropy, and leave-one-out were also performed.

Results In European populations, SGLT2 inhibitors were significantly negatively associated with TC (OR 0.051, 95% CI 0.006–0.465, $P=0.0082$) as well as PTC (OR 0.034, 95% CI 0.003–0.411, $P=0.0079$), while no correlation was found with FTC. These findings remained consistent even after applying the Bonferroni correction.

Conclusions The evidence suggests that SGLT2 inhibitors could be potential therapeutic targets for TC, especially for PTC, in European populations. However, further large-scale randomized controlled trials are necessary to verify their ability to reduce the risk of and treat these types of cancer.

Keywords SGLT-2 inhibitors · Thyroid cancer · Diabetes medications · Mendelian randomization study

Introduction

Until 2022, thyroid cancer (TC) has become increasingly prevalent worldwide, with 586,000 reported cases, ranking it 9th in incidence [1]. TC, particularly papillary thyroid carcinoma (PTC), is experiencing a significant rise due to the widespread use and enhanced sensitivity of ultrasound and other diagnostic techniques [2]. In contrast, the global prevalence of diabetes is also on the rise. By 2019, there were already approximately 463 million adults with diabetes worldwide, with half of them remaining undiagnosed. Furthermore, projections indicate that by 2045, this number is expected to reach 700 million. Interestingly, TC and diabetes appear to be growing simultaneously [3].

In recent years, there has been increasing interest in exploring the potential of diabetes medications as cancer therapy [4, 5]. Several research studies support the repositioning of diabetes medications as potential anti-cancer agents. Type 2 diabetes is a known risk factor for the development of various cancers, including colorectal, liver, pancreatic, and TC [6, 7]. Additionally, hyperglycemia, hyperinsulinemia, and chronic inflammation may increase the risk of TC [8, 9]. It can be inferred that diabetic medications have an indirect therapeutic effect on cancer. It is important to note that this is an association and not necessarily a causal

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relationship. Secondly, TC cells have specialized metabolic pathways that may be sensitive to specific effects of diabetes [10]. The Warburg effect is considered a driver of cancer cell proliferation, which is dependent on glycolysis [11]. Some diabetic medications can inhibit glucose uptake by activating adenosine monophosphate-activated protein kinase(AMPK) or inhibiting glucose uptake [12].

While clinical studies and meta-analyses have provided evidence for the anticancer effects of diabetes medications [13, 14], traditional observational studies have inherent shortcomings, such as confounding factors and reverse causation, which have greatly hampered exploring the effects of diabetes medications on TC. Mendelian randomization is a powerful method for identifying causal associations by removing the influence of confounding factors. Like random assignment in randomized controlled trials, Mendelian randomization uses the random assignment of genetic variation at conception to reduce the effects of confounders. The genetic tool is non-modifiable, ensuring lifetime exposure and alleviating concerns about reverse causation [15, 16].

This study conducted Mendelian randomization (MR) analyses using summary-level statistics from published genome-wide association studies (GWAS) to assess the potential impact of diabetes medications on thyroid cancer.

Materials and methods

This study adhered to the guidelines of the Strengthening the Reporting of Observational Epidemiological Studies Using Mendelian Randomization (STROBE-MR) [17]. The study's flow chart is presented in Fig. 1.

Mendelian randomization design and selection of genetic instruments

Suitable targets for α-glucosidase inhibitors and dipeptidyl peptidase-IV are not yet available, so the following six classes of diabetes medications were selected for our study, including sulfonylureas, insulin/insulin analogs, glucagon-like peptide 1 analogs, thiazolidinediones, sodium-glucose cotransporter protein 2 (SGLT2) inhibitors, and metformin. Instrumental variables(IVs) for relevant diabetes medications were obtained by reference to previous literature [18–20]. The Genotype-Tissue Expression (GTEx) project characterizes the effects of genes on the transcriptome of human tissues and correlates these regulatory mechanisms with traits and diseases [21]. The eQTLGen Consortium conducted cis- and trans-expression quantitative trait loci (eQTL) analyses using blood-derived expression from 31,684 individuals. The aim was to gain insight into the initial stages of explaining complex phenotypes [22]. The study selected genetic variants associated with mRNA expression levels of diabetes drug genes from the eQTLGEN Consortium and GTEx. Then, it used glycated hemoglobin (HbA1c) from over 34,000 European populations without diabetes in the United Kingdom Biobank (UKB) to estimate the correlation between diabetes drug targets and HbA1c, from which single nucleotide polymorphisms (SNPs) were selected. The selected SNPs were associated with the entire region of HbA1c. The data were obtained from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/). The genetic co-localization approach was used to verify whether diabetes medications and HbA1c share the same causal variance. Bayesian modeling was used to estimate the posterior probabilities.

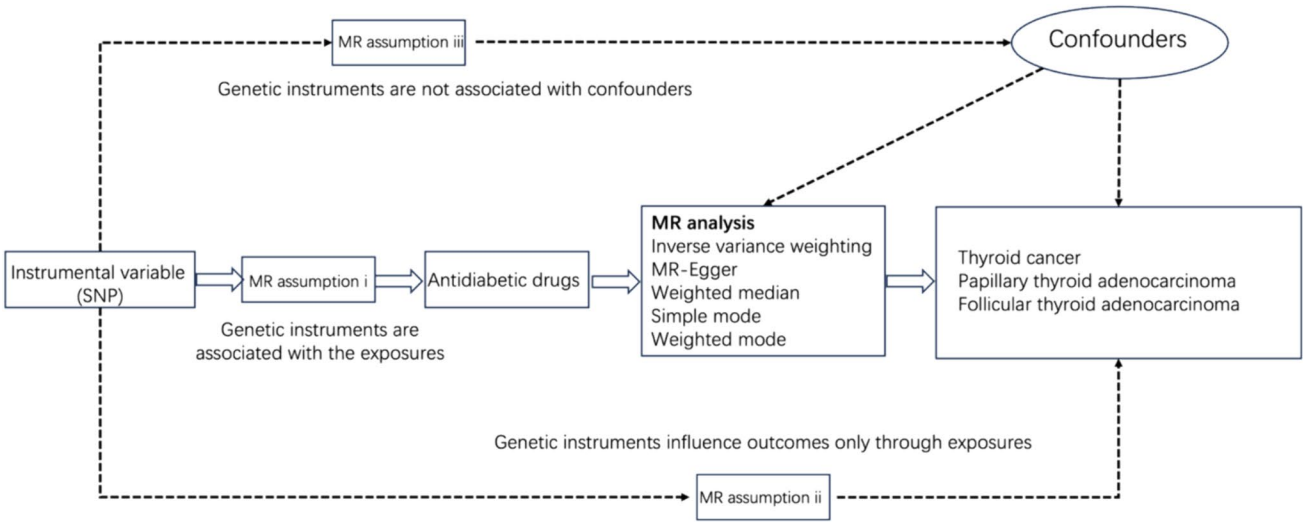

Fig. 1 Schematic representation of MR study design overview and assumptions

After validation, genetic variants closely associated with HbA1c were selected as genetic predictors for Mendelian randomization analysis [23].

Data sources for thyroid cancer

Studies have shown that diabetes medications can reduce the incidence of cancer, and we focus our study mainly on TC, of which differentiated thyroid cancer (DTC), is one of the most common TC, accounting for approximately 90% of cases, and based on the origin of the tumors, DTC mainly consists of PTC and follicular thyroid carcinoma (FTC), so we further explore the effects of diabetes medications on DTC potential effects. We obtained pooled data on genetic associations related to TC from the Finngen database. (https://www.finngen.fi/en) The Finngen database collects and analyzes genomic and health data from 500,000 Finnish biobank donors to understand disease progression and biological mechanisms. Online Resource 1 provided detailed information on the disease outcomes mentioned above.

Mendelian randomization analysis

The cores of mendelian randomization analysis are based on three assumptions [24]: (1) correlation, meaning that IVs are strongly associated with exposure; (2) exclusivity, meaning that IVs can only influence outcomes through exposure; and (3) independence, meaning that there are no confounders that influence the effect of exposure on outcomes. To satisfy the three hypotheses, we first set the genome-wide significance level at $P < 5*10^{-8}$. When we could not obtain enough SNPs for the analysis, we lowered the threshold to $5*10^{-6}$ and excluded SNPs with palindromic structures. Second, we used the standard parameter SNP ($r^2 < 0.001$, kb = 10,000 kb) to exclude the effect of linkage disequilibrium and ensure the independence of the included SNPs. Finally, we used PhenoScanner to remove the effects of confounders [25]. To ensure the robustness of the acquired IVs, we excluded SNPs with F < 10. F values greater than 10 indicate the absence of weak IVs [26].

To derive MR estimates, we used five MR methods, primarily relying on the random effects inverse variance weighting (IVW) method. The Wald Ratio method was used to estimate the causal effects for individual SNPs. IVW assumed that all instrumental variables (IVs) meet the validity criteria to obtain unbiased estimates with the highest statistical efficacy [27]. MR-Egger assumed that only more than half of the IVs are valid to obtain unbiased estimates [28]. Therefore, IVW was preferred when there was a conflict between the two. The heterogeneity of IVs was evaluated using the Cochran *Q*-test and MR-PRESSO [27, 29]. In cases where heterogeneity existed, MR-PRESSO removed the outliers and repeated the mendelian randomization analysis. Radial Mendelian randomization could be used to detect outliers more directly than traditional scatterplots. However, it might increase bias by removing all outliers and might not be able to identify the true model [30]. When MR-PRESSO and radial mendelian randomization produced contradictory results, MR-PRESSO would be given priority. The impact of individual IVs on mendelian randomization estimates was evaluated by removing them one by one [31]. The intercept of the MR-Egger test was used to assess horizontal pleiotropy, with a significance level of $P < 0.05$ indicating the presence of horizontal pleiotropy, and the distance of the intercept term from the value of 0 indicating the magnitude of horizontal pleiotropy [32].

Additionally, scatter plots were utilized to visually represent the effect size of each mendelian randomization method. Individual SNP estimates were displayed using forest plots. Funnel plots were employed to evaluate the balance of the distribution of individual SNP effects. The MR estimates were expressed as the ratio of ratios (OR), and for the glucose-lowering effects of diabetes medications (excluding metformin), all estimates were adjusted for each 1 mmol/L reduction in blood glucose. The study found that metformin had a HbA1c-lowering effect equivalent to a 6.75 mmol/mol (1.09%) reduction in HbA1c. To account for multiple tests, the Bonferroni correction was applied with a significance level *P* value < 0.017 (0.05/3).

All MR analyses were conducted using R version 4.3.1 (The R Foundation for Statistical Computing). Causal estimation was mainly conducted using the "TwoSampleMR" (version 0.5.7), "MRPRESSO" (version 1.0), "ggplot2" (version 3.4.3), "plyr" (version 1.8.8), and "phenoscanner" (version 1.0) packages.

Results

Only European population data were included in this study due to the sample overlap rate and bias caused by ethnic differences. Table 1 presented the IVW results of six diabetes drugs on TC. The results showed that SGLT2 inhibitors had a negative association with TC (OR 0.051, 95% CI 0.006–0.465, $P = 0.0082$). We conducted a subtype analysis of diabetic drugs and undifferentiated thyroid cancer, which included PTC and FTC. The results indicated that SGLT2 inhibitors were associated with a reduced risk of PTC (OR 0.034, 95% CI 0.003–0.411, $P = 0.0079$). However, there was no significant association between SGLT2 inhibitors and FTC (OR 9.7548, 95% CI 0.0052–17237.0628, $P = 0.5578$). The results remained unchanged after applying the Bonferroni correction. MR-Egger and weighted median, simple mode, and weighted mode could be used as complementary methods to IVW. Weighted median, simple mode, and weighted mode also indicated a negative correlation between

Table 1 IVW results of 6 diabetic drugs on thyroid cancer, papillary thyroid adenocarcinoma, and follicular thyroid adenocarcinoma

Exposure	Outcome	NSNP	OR	P
Sodium-glucose cotransporter 2 inhibitors	Thyroid cancer	6	0.051	0.0082
	Papillary thyroid adenocarcinoma	6	0.034	0.0079
	Follicular thyroid adenocarcinoma	6	9.447	0.5578
Metformin	Thyroid cancer	28	0.934	0.5839
	Papillary thyroid adenocarcinoma	29	0.879	0.3872
	Follicular thyroid adenocarcinoma	29	1.797	0.1598
Sulfonylureas	Thyroid cancer	5	23.654	0.1930
	Papillary thyroid adenocarcinoma	5	56.793	0.1678
	Follicular thyroid adenocarcinoma	5	0.013	0.4232
Thiazolidinediones	Thyroid cancer	2	9.058	0.5435
	Papillary thyroid adenocarcinoma	2	13.871	0.5230
	Follicular thyroid adenocarcinoma	2	317.239	0.6396
Insulin analogues	Thyroid cancer	2	1623.279	0.0870
	Papillary thyroid adenocarcinoma	2	667.354	0.1853
	Follicular thyroid adenocarcinoma	2	81.714	0.7871
Glucagon-like peptide-1 receptor agonists	Thyroid cancer	4	1.025	0.7614
	Papillary thyroid adenocarcinoma	4	1.002	0.9819
	Follicular thyroid adenocarcinoma	4	1.036	0.9226

SGLT2 inhibitors and TC, including PTC. However, MR-Egger showed a positive correlation between SGLT2 inhibitors and TC, including PTC (Online Resource 2). Additionally, both the Cochran Q test and MR-PRESSO indicated the lack of heterogeneity, while the MR-Egger test value of less than 0.05 suggested the absence of pleiotropy. (Online Resource 3) The Leave-one-out analysis showed that excluding a single SNP would have a significant impact on the final results. Additionally, radial mendelian randomization did not identify any outliers. These findings provided further evidence of the robustness of the mendelian randomization study. (Figs. 2, 3, 4, 5).

Additionally, the mendelian randomization results indicate that there is no correlation between sulfonylureas, insulin/insulin analogs, GLP-1 analogs, thiazolidinediones and metformin with TC, PTC, and FTC (Online Resource 2).

Discussion

The association between diabetes and cancers has been proposed, and diabetes medications have been suggested to affect cancer development. However, the causal relationship between the two has not been conclusively established. By using mendelian randomization study, the study eliminates the interference of confounding factors and helps to reveal the causal relationship between the two. Our study found that SGLT2 inhibitors significantly inhibit the development of TC, especially for PTC, at the genetic level. However, we did not find any causal relationship between other diabetes medications and TC or DTC.

Our study discussed the relationship between SGLT2 inhibitors and thyroid cancer and its classification at the genetic level, and there have been previous studies to support our findings from physiological and oncological perspectives. Studies have shown that diabetes medications can affect cancer development through DNA repair, the adenosine monophosphate-activated protein kinase pathway, immune function, apoptosis, and metabolism [33]. Cagliflozin, a representative SGLT2 inhibitor, has demonstrated various anticancer effects on different tumor cells in vitro. These effects include reducing the viability of thyroid cells and inhibiting the proliferation of thyroid cells [12, 34, 35]. Furthermore, a recent study indicates that cagliflozin may decrease TC cell viability or colony formation and modulate CXCL8 and CCL2, leading to a reduction in TC cell migration [36]. Previous studies have demonstrated that SGLT2 inhibitors can potentially impede the advancement of PTC by reducing the expression levels of cell cycle proteins D1 and D3 [12, 37, 38]. A study investigated the potential of SGLT2 inhibitors, cagliflozin and dagliflozin, in treating various cancers, including TC, through computerized and in vitro methods. The results suggest promising anticancer mechanisms for these inhibitors [39]. A cohort study recently published suggests that patients who take diabetes medications have a lower risk of developing certain malignancies, such as TC [40]. A meta-analysis conducted in 2022 on the effects of SGLT2 inhibitors on cancer incidence in patients with hyperglycemia revealed that SGLT2 inhibitors

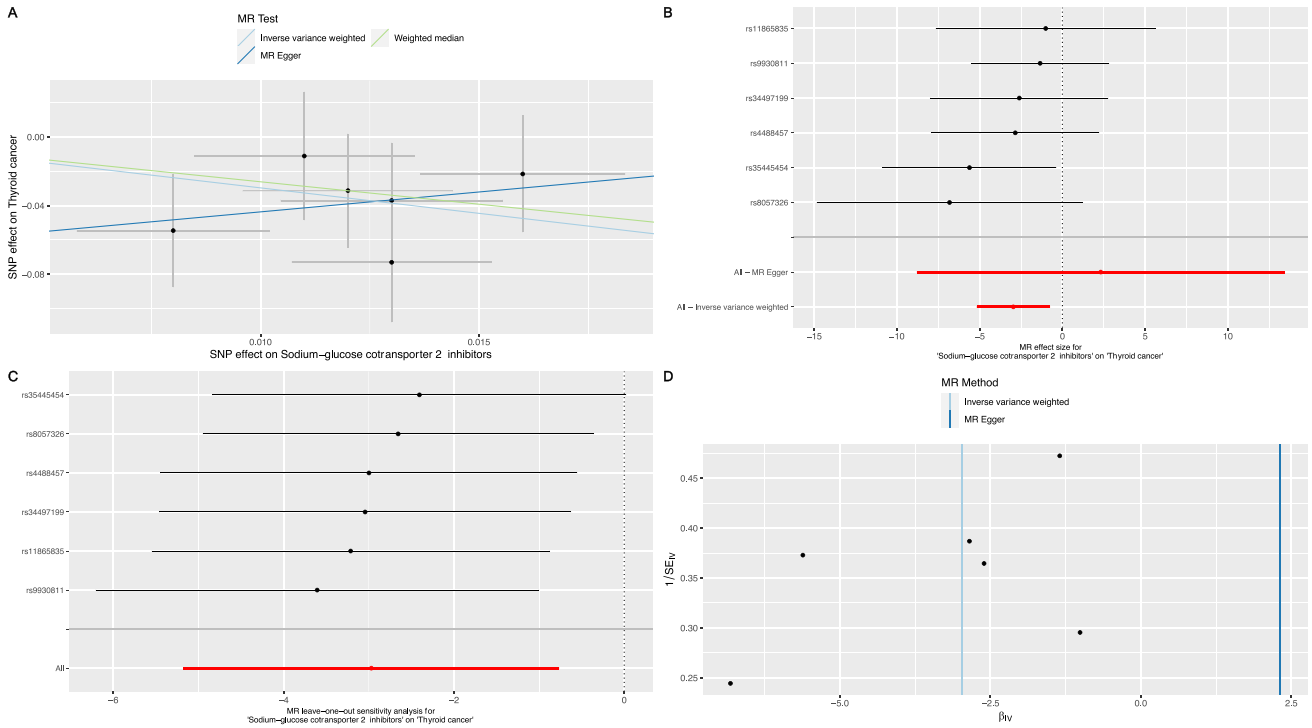

Fig. 2 Visualization of mendelian randomization analysis using Sodium-glucose cotransporter 2 inhibitors and thyroid cancer. **A** Scatterplot **B** Forest plot **C** Leave-one-out method **D** Funnel plot

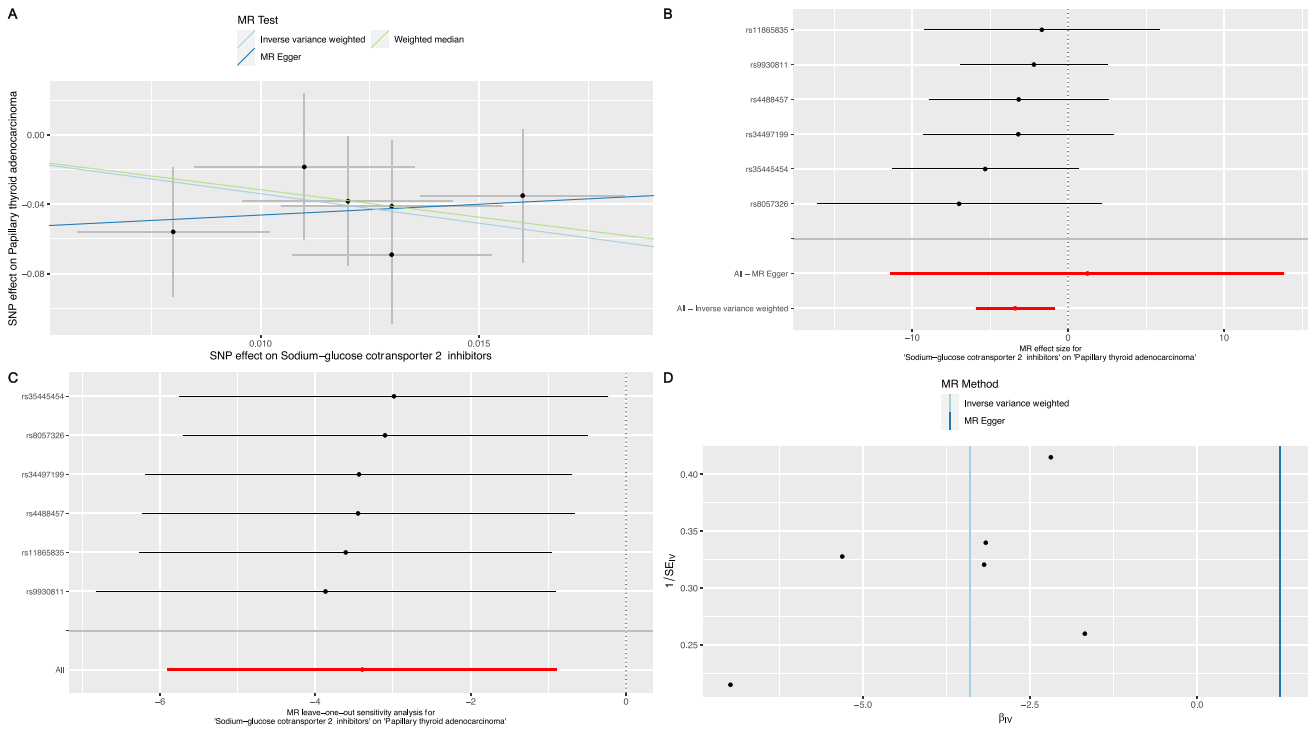

Fig. 3 Visualization of mendelian randomization analysis using Sodium-glucose cotransporter 2 inhibitors and papillary thyroid adenocarcinoma. **A** Scatterplot **B** Forest plot **C** Leave-one-out method **D** Funnel plot

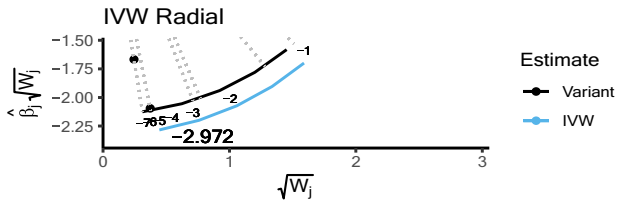

Fig. 4 Radial mendelian randomization plots displaying the relationship between Sodium-glucose cotransporter 2 inhibitors and thyroid cancer

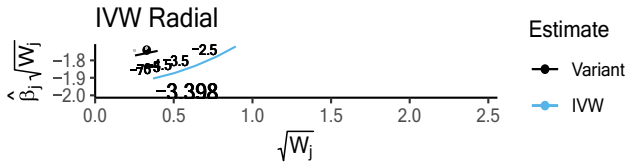

Fig. 5 Radial mendelian randomization plots displaying the relationship between Sodium-glucose cotransporter 2 inhibitors and papillary thyroid adenocarcinoma

significantly reduced cancer incidence [14]. However, a newer meta-analysis suggests that SGLT2 inhibitors do not affect cancer risk [41]. The conclusions' ambivalence may be influenced by various factors, such as the investigators, sample size, and bias of the included studies. This limitation hinders further exploration of the topic. Currently, there are fewer clinical observational studies on the relationship between SGLT2 inhibitors and TC, and more ex vivo and in vivo studies.

This study has several strengths. Firstly, it is the first study analyzing the relationship between diabetes medications targets and TC. Secondly, the sample size of the selected TC was over 300,000, which enhances the statistical validity of the findings and conclusions of the study. Moreover, the data used in our study were exclusively from individuals of European descent, thus avoiding any potential bias resulting from racial differences. Additionally, our research contributes to the repurposing of diabetes medications, which can significantly reduce the time and costs associated with developing new medications. It takes an average of nine years from drug discovery to entry into clinical trials, with a success rate of less than 10 percent [42], as well as the need to cross hurdles including financial and resource and intellectual property rights, compared with drug repositioning, which may take as little as three to four years [43]. Finally, sensitivity analyses were conducted using multiple methods, which enhanced the robustness of the results.

However, this study has several limitations. Firstly, it was conducted solely on a European population, which restricts the generalizability of the findings. Due to the limited availability of data, our study was restricted to investigating the relationship between TC and DTC. We were unable to explore the relationship with other undifferentiated thyroid cancers. Our finding did not observe an association between SGLT2 inhibitors and FTC, possibly due to the limited number of cases included in the study. Additionally, the SNPs of the diabetes medications targets we referenced have not been updated promptly as new study data become available, which may have had some impact on the results. Finally, the limited number of SNPs analyzed for thiazolidinedione and insulin analogs may introduce errors. To validate the results, a more comprehensive and updated GWAS database can be used to analyze the relationship between diabetes medications and thyroid cancer. Additionally, more randomized controlled trials are needed to explore the relationship between diabetes medications and TC, as well as other cancers, and to assess the safety and efficacy of their application.

Conclusion

The evidence suggests that SGLT2 inhibitors could be potential therapeutic targets for TC and PTC in European populations. However, further large-scale randomized controlled trials are necessary to verify their ability to reduce the risk of and treat these types of cancer.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00592-024-02344-8.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Lirong Zhang, Jiaqin Cai, Huiting Lin, Wenhua Wu, Congting Hu, Xinmiao Lin, Hong Sun and Xiaoxiao Wei. The first draft of the manuscript was written by Lirong Zhang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Information on the datasets covered in this manuscript can be found in https://gwas.mrcieu.ac.uk/ and r9.risteys.finngen.fi.

Declarations

Conflict of interest The authors declare there no conflict of interest.

Ethics approval This study's analysis is a secondary examination of publicly available data, not involving new human or animal research.

Informed consent For this type of retrospective study formal consent is not required.

References

1. Sung H, Ferlay J, Siegel RL et al (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209–249. https://doi.org/10.3322/caac.21660
2. Brito JP, Morris JC, Montori VM (2013) Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. BMJ 347:f4706. https://doi.org/10.1136/bmj.f4706
3. The Lancet Diabetes E (2021) World Diabetes Day 2021: a time of reckoning. Lancet Diabetes Endocrinol. vol 9, Issue (12) p 799. https://doi.org/10.1016/s2213-8587(21)00297-7
4. Shih JW, Wu ATH, Mokgautsi N et al (2024) Preclinical repurposing of sitagliptin as a drug candidate for colorectal Cancer by targeting CD24/CTNNB1/SOX4-centered signaling hub. Int J Mol Sci 25(1):609. https://doi.org/10.3390/ijms25010609
5. Wright EM, Ghezzi C, Loo DDF (2017) Novel and unexpected functions of SGLTs. Physiology 32(6):435–443. https://doi.org/10.1152/physiol.00021.2017
6. Ling S, Zaccardi F, Issa E et al (2023) Inequalities in cancer mortality trends in people with type 2 diabetes: 20 year population-based study in England. Diabetologia 66(4):657–673. https://doi.org/10.1007/s00125-022-05854-8
7. Yeo Y, Ma SH, Hwang Y et al (2014) Diabetes mellitus and risk of thyroid cancer: a meta-analysis. PLoS One. 9(6):e98135. https://doi.org/10.1371/journal.pone.0098135
8. Jee SH, Ohrr H, Sull JW et al (2005) Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293(2):194–202. https://doi.org/10.1001/jama.293.2.194
9. Giovannucci E, Harlan DM, Archer MC et al (2010) Diabetes and cancer: a consensus report. Diabetes Care 33(7):1674–1685. https://doi.org/10.2337/dc10-0666
10. Coelho RG, Fortunato RS, Carvalho DP (2018) Metabolic reprogramming in thyroid carcinoma. Front Oncol 8:82. https://doi.org/10.3389/fonc.2018.00082
11. Abdel-Wahab AF, Mahmoud W, Al-Harizy RM (2019) Targeting glucose metabolism to suppress cancer progression: prospective of anti-glycolytic cancer therapy. Pharmacol Res 150:104511. https://doi.org/10.1016/j.phrs.2019.104511
12. Wang Y, Yang L, Mao L et al (2022) SGLT2 inhibition restrains thyroid cancer growth via G1/S phase transition arrest and apoptosis mediated by DNA damage response signaling pathways. Cancer Cell Int 22(1):74. https://doi.org/10.1186/s12935-022-02496-z
13. Cui H, Wang Y, Yang S et al (2022) Antidiabetic medications and the risk of prostate cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Pharmacol Res 177:106094. https://doi.org/10.1016/j.phrs.2022.106094
14. Benedetti R, Benincasa G, Glass K et al (2022) Effects of novel SGLT2 inhibitors on cancer incidence in hyperglycemic patients: a meta-analysis of randomized clinical trials. Pharmacol Res 175:106039. https://doi.org/10.1016/j.phrs.2021.106039
15. Sekula P, Del Greco MF, Pattaro C et al (2016) Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol 27(11):3253–3265. https://doi.org/10.1681/asn.2016010098
16. Taylor AE, Davies NM, Ware JJ et al (2014) Mendelian randomization in health research: using appropriate genetic variants and avoiding biased estimates. Econ Hum Biol 13(100):99–106. https://doi.org/10.1016/j.ehb.2013.12.002
17. Skrivankova VW, Richmond RC, Woolf BAR et al (2021) Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. JAMA 326(16):1614–1621. https://doi.org/10.1001/jama.2021.18236
18. Tang B, Wang Y, Jiang X et al (2022) Genetic variation in targets of Antidiabetic drugs and Alzheimer disease risk: a Mendelian randomization study. Neurology 99(7):e650–e659. https://doi.org/10.1212/wnl.0000000000200771
19. Xu M, Zheng J, Hou T et al (2022) SGLT2 inhibition, choline metabolites, and cardiometabolic diseases: a mediation Mendelian randomization study. Diabetes Care 45(11):2718–2728. https://doi.org/10.2337/dc22-0323
20. Zheng J, Xu M, Walker V et al (2022) Evaluating the efficacy and mechanism of metformin targets on reducing Alzheimer's disease risk in the general population: a Mendelian randomisation study. Diabetologia 65(10):1664–1675. https://doi.org/10.1007/s00125-022-05743-0
21. Aguet F, Anand S et al (2020) The GTEx consortium atlas of genetic regulatory effects across human tissues. Science 369(6509):1318–1330. https://doi.org/10.1126/science.aaz1776
22. Võsa U, Claringbould A, Westra HJ et al (2021) Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat Genet 53(9):1300–1310. https://doi.org/10.1038/s41588-021-00913-z
23. Giambartolomei C, Vukcevic D, Schadt EE et al (2014) Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet. 10(5):e1004383. https://doi.org/10.1371/journal.pgen.1004383
24. König IR, Greco FMD (2018) Mendelian randomization: Progressing towards understanding causality. Ann Neurol 84(2):176–177. https://doi.org/10.1002/ana.25293
25. Kamat MA, Blackshaw JA, Young R et al (2019) PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics 35(22):4851–4853. https://doi.org/10.1093/bioinformatics/btz469
26. Burgess S, Thompson SG (2011) Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol 40(3):755–764. https://doi.org/10.1093/ije/dyr036
27. Burgess S, Butterworth A, Thompson SG (2013) Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 37(7):658–665. https://doi.org/10.1002/gepi.21758
28. Bowden J, Davey Smith G, Haycock PC et al (2016) Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 40(4):304–314. https://doi.org/10.1002/gepi.21965
29. Verbanck M, Chen CY, Neale B et al (2018) Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 50(5):693–698. https://doi.org/10.1038/s41588-018-0099-7
30. Bowden J, Spiller W, Del Greco MF et al (2018) Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the radial plot and radial regression. Int J Epidemiol 47(6):2100. https://doi.org/10.1093/ije/dyy265
31. Zheng J, Baird D, Borges MC et al (2017) Recent developments in Mendelian randomization studies. Curr Epidemiol Rep 4(4):330–345. https://doi.org/10.1007/s40471-017-0128-6
32. Bowden J, Davey Smith G, Burgess S (2015) Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 44(2):512–525. https://doi.org/10.1093/ije/dyv080
33. Pillai UJ, Ray A, Maan M et al (2023) Repurposing drugs targeting metabolic diseases for cancer therapeutics. Drug Discov Today 28(9):103684. https://doi.org/10.1016/j.drudis.2023.1036844
34. Yamamoto L, Yamashita S, Nomiyama T et al (2021) Sodium-glucose cotransporter 2 inhibitor canagliflozin attenuates lung

cancer cell proliferation in vitro. Diabetol Int 12(4):389–398. https://doi.org/10.1007/s13340-021-00494-6
35. Sabaa M, Sharawy MH, El-Sherbiny M et al (2022) Canagliflozin interrupts mTOR-mediated inflammatory signaling and attenuates DMBA-induced mammary cell carcinoma in rats. Biomed Pharmacother 155:113675. https://doi.org/10.1016/j.biopha.2022.113675
36. Coperchini F, Greco A, Croce L et al (2024) Canagliflozin reduces thyroid cancer cells migration in vitro by inhibiting CXCL8 and CCL2: An additional anti-tumor effect of the drug. Biomed Pharmacother 170:115974. https://doi.org/10.1016/j.biopha.2023.115974
37. Romitti M, Wajner SM, Ceolin L et al (2016) MAPK and SHH pathways modulate type 3 deiodinase expression in papillary thyroid carcinoma. Endocr Relat Cancer 23(3):135–146. https://doi.org/10.1530/erc-15-0162
38. Cai W, Shu LZ, Liu DJ et al (2023) Targeting cyclin D1 as a therapeutic approach for papillary thyroid carcinoma. Front Oncol 13:1145082. https://doi.org/10.3389/fonc.2023.1145082
39. Mohite P, Lokwani DK, Sakle NS (2024) Exploring the therapeutic potential of SGLT2 inhibitors in cancer treatment: integrating in silico and in vitro investigations. Naunyn Schmiedebergs Arch Pharmacol. https://doi.org/10.1007/s00210-024-03021-x
40. Bea S, Son H, Bae JH et al (2024) Risk of thyroid cancer associated with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: a population-based cohort study. Diabetes Obes Metab 26(1):108–117. https://doi.org/10.1111/dom.15292
41. Spiazzi BF, Naibo RA, Wayerbacher LF et al (2023) Sodium-glucose cotransporter-2 inhibitors and cancer outcomes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 198:110621. https://doi.org/10.1016/j.diabres.2023.110621
42. Sams-Dodd F (2005) Target-based drug discovery: Is something wrong? Drug Discov Today 10(2):139–147. https://doi.org/10.1016/s1359-6446(04)03316-1
43. Masuda T, Tsuruda Y, Matsumoto Y et al (2020) Drug repositioning in cancer: the current situation in Japan. Cancer Sci 111(4):1039–1046. https://doi.org/10.1111/cas.14318