Observational Study

Medicine

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Assessment of causal association between autoimmune thyroiditis and thyroid cancer

A Mendelian randomization study

Qihong Zhang, MD[a], Xiabin Lan, MD, PhD[b,*]

Abstract

Currently, the precise interplay between autoimmune thyroiditis, particularly Hashimoto thyroiditis, and thyroid cancer remains ambiguous. While certain observational studies suggest autoimmune thyroiditis (including Hashimoto thyroiditis) as a predisposing factor for thyroid cancer. Nevertheless, it is still uncertain whether autoimmune thyroiditis is independently associated with thyroid cancer. We employed Mendelian randomization (MR) study methodology, a genetic analysis approach, to evaluate the causal impact of autoimmune thyroiditis on the occurrence of thyroid cancer. We obtained and synthesized statistical data by utilizing public available genome-wide association studies (GWAS). Our study utilized GWAS summary statistics datasets associated with autoimmune thyroiditis (including Hashimoto thyroiditis) as the exposure data source and selected GWAS summary statistics datasets related to thyroid cancer as the outcome data source. Single nucleotide polymorphisms closely associated with autoimmune thyroiditis were chosen as instrumental variables. We conducted 2-sample MR analyses to elucidate the causal association between autoimmune thyroiditis and thyroid cancer. The inverse variance-weighted (IVW) method was employed as the primary methodology, supplemented by additional MR methods including MR-Egger regression, weighted median, simple mode, and weighted mode analyses, to bolster the robustness of our findings. The MR analysis conducted using the IVW method did not confirm a causal relationship between autoimmune thyroiditis and thyroid cancer (odds ratio [OR] = 0.8554, 95% confidence interval [CI]: 0.7193 to 1.0172, $P = .0772$; OR = 0.8477, 95% CI: 0.7159 to 1.0039, $P = .0555$; and OR = 1.1324, 95% CI: 0.9342 to 1.3725, $P = .2052$, from 3 eligible dataset analyses, respectively). Additionally, MR analysis did not observe a causal association between Hashimoto thyroiditis and thyroid cancer (OR = 1.0449, 95% CI: 0.9400 to 1.1615, $P = .4155$; and OR = 0.9897, 95% CI: 0.8174 to 1.1984, $P = .9159$, from 2 eligible dataset analyses, respectively). Consistency in results across alternative MR methods was observed. This study employing MR methodology indicates the absence of significant causal relationship between exposure to autoimmune thyroiditis (including Hashimoto thyroiditis) and thyroid cancer. Further validation through larger-scale studies with increased sample sizes is warranted in future investigations.

Abbreviations: CI = confidence interval, EA = effect allele, EAF = effect allele frequency, GWAS = genome-wide association studies, IVs = instrumental variables, IVW = inverse-variance weighted, MR = Mendelian randomization, OA = other allele, OR = odds ratio, SE = standard error, SNPs = single nucleotide polymorphisms.

Keywords: autoimmune thyroiditis, causal relationship, Hashimoto thyroiditis, Mendelian randomization study, thyroid cancer

1. Introduction

Thyroid cancer stands as the most common endocrine malignancy. In Europe, there are approximately 3500 new cases each year.[1] In the United States, the incidence of thyroid cancer is 15.7 cases per 100,000 population annually.[2] Globally, an estimated 567,233 new instances of thyroid cancer and 41,071 deaths occur each year.[3] The incidence of thyroid cancer has exhibited a marked increase across most regions worldwide over the past few decades. The risk of thyroid cancer appears to be influenced by factors such as race, radiation exposure, and gender.[4]

Autoimmune thyroiditis ranks among the most prevalent autoimmune diseases, with Graves' disease and Hashimoto thyroiditis being the most common forms.[5,6] However, there are also other forms of autoimmune destructive thyroiditis, including silent and postpartum thyroiditis. Autoimmune thyroiditis affects approximately 5% of the population, constituting one of the highest prevalence rates among autoimmune

The authors have no conflict of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

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How to cite this article: Zhang Q, Lan X. Assessment of causal association between autoimmune thyroiditis and thyroid cancer: A Mendelian randomization study. Medicine 2025;104:9(e41633).

Received: 3 June 2024 / Received in final form: 31 January 2025 / Accepted: 4 February 2025

http://dx.doi.org/10.1097/MD.0000000000041633

diseases. Dysfunction of the immune system prompts immune attacks against the thyroid gland, predominantly manifesting as hypothyroidism.[7]

The association between autoimmune thyroiditis and thyroid cancer was initially proposed by Dailey,[8] yet the relationship between autoimmune thyroiditis and thyroid cancer has remained ambiguous, particularly concerning Hashimoto thyroiditis. Previous observational studies assessing the relationship between autoimmune thyroiditis and thyroid cancer indicated that autoimmune thyroiditis may serve as a potential risk factor for thyroid cancer. However, conflicting evidence suggested that autoimmune thyroiditis may have a protective role in tumor progression.[9–11] Hence, elucidating the causal relationship between autoimmune thyroiditis and thyroid cancer holds significant practical implications for mitigating thyroid cancer incidence.

To clarify the direction and strength of the association between autoimmune thyroiditis and thyroid cancer, we employed Mendelian randomization (MR) study methodology. MR is a robust genetic epidemiological tool that utilizes genetic polymorphisms as instrumental variables (IVs) to minimize biases caused by confounding or reverse causation, thus analyzing genetic variations associated with exposure to evaluate the causal relationship between exposure and disease outcomes.[12] By applying this method to unravel the causal relationship between autoimmune thyroiditis and thyroid cancer, we aim to provide novel insights for reducing thyroid cancer incidence.

2. Methods and materials

2.1. Ethical approval

This study based on publicly accessible summary-level data. Ethical clearance was obtained from the relevant Institutional Review Boards for all studies included in the analysis.

2.2. Research methodology

MR is a method for assessing the impact of exposures on disease development. IVs are leveraged as genetic variants. Compared to standard multivariate regression methods, MR analysis has demonstrated to be more robust to measurement error, confounding factors, and reverse causation, thereby enabling more precise causal inferences.[13,14]

This method employs genetic variation as IVs in epidemiological research to mimic randomized controlled trials,[15] where alleles are randomly allocated at conception. Consequently, it is less susceptible to be influenced by confounding or reverse causation. MR is more robust in handling confounding factors, whether environmental or lifestyle factors, as well as reverse causation, and has found widespread application in examining the causal effects of exposure factors on disease.[16,17]

In our study, a 2-sample MR design was adopted to scrutinize the causal relationship between autoimmune thyroiditis (including Hashimoto thyroiditis) and thyroid cancer. The inverse variance-weighted (IVW) method was utilized for assessing causal effects and evaluate pleiotropy, supplemented by MR-Egger regression

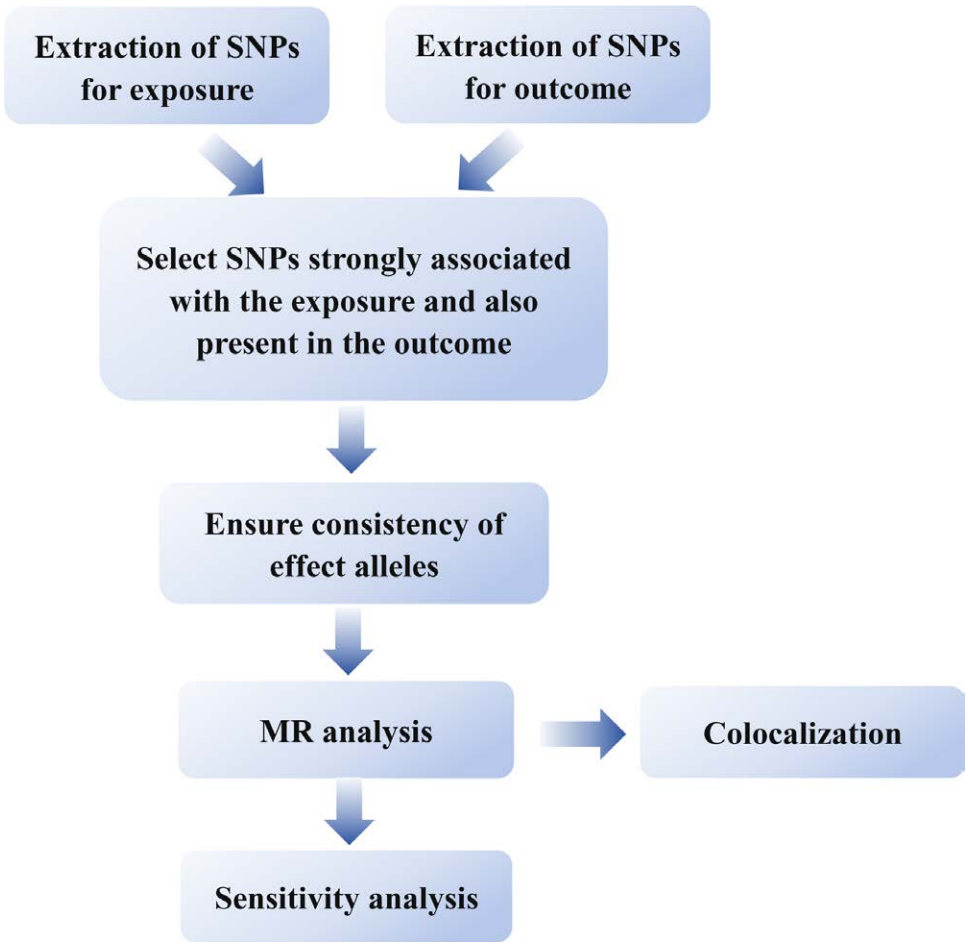

Figure 1. Research framework overview of Mendelian randomization analysis. SNPs = single nucleotide polymorphisms.

analysis to assess pleiotropy effects (The research framework overview of MR analysis is shown in Figure 1).

2.3. Data sources

In this study, we selected summary statistics data from genome-wide association studies (GWAS) pertaining to autoimmune thyroiditis (including Hashimoto thyroiditis) as the exposure data source,[18] which we obtained from the FinnGen database.[19] The data for thyroid cancer was derived from a European cohort with thyroid cancer patients selected from the GWAS Catalog database as the outcome data source. These 2 population cohorts exhibit dissimilar clinical and demographic characteristics (such as age, gender, race, education, etc.), but they possess genetic comparability owing to common European ancestry. Therefore, we consider them to share similar genetic characteristics. Notably, there is no sample overlap between the exposure and outcome datasets. Regarding the acquisition of Hashimoto thyroiditis data, we only identified data from East Asian populations in the GWAS Catalog database.

3. Selection of genetic IVs

When conducting MR analysis, 3 fundamental assumptions need to be considered: The relevance assumption: genetic variants must be strongly associated with the exposure factor. The independence assumption: genetic variants must not be correlated with any potential confounding factors. The exclusion restriction assumption: genetic variants can only affect the outcome through the exposure factor and not directly associated with the outcome[20] (Fig. 2).

We employed a series of criteria to filter IVs: in order to ensure an adequate number of IVs, single nucleotide polymorphisms (SNPs) with a significance level of P value $< 5 \times 10^{-6}$ and F statistics ≥ 10 (F statistics = beta^2/se^2) were selected from the entire genome, ensuring a strong correlation between IVs and the exposure factor. Subsequently, the selected IVs needed to pass an independence test. To examine the independence and linkage disequilibrium effects of these variables, we set the linkage disequilibrium parameter r^2 to 0.001 and the genetic distance to 10,000 kb. Finally, to ensure consistency between the SNP's impact on exposure and its effect on outcomes, we removed palindromic SNPs (e.g., those with A/T or G/C alleles). The selection of these IVs ensured the reliability of our study results.

In our investigation, we identified 1026 SNPs significantly associated with the exposure factor by filtering for a P value $< 5 \times 10^{-6}$. Subsequently, we conducted linkage disequilibrium analysis using the ld_clump function in the R package "ieugwasr," setting the r^2 and kb parameters to 0.001 and 10,000, respectively, to remove highly correlated variables and ensure that IVs do not interfere with each other. This process yielded 7 IVs significantly associated with the exposure factor and mutually independent. Finally, we filtered for IVs with an F value >10, which is typically considered sufficiently significant for IV selection. Then, we comprehensively searched for thyroid cancer risk factors from previously published literature.[21] Based on the MR assumptions mentioned earlier, we excluded SNPs associated with thyroid cancer risk factors by searching SNP information on the PhenoScanner website (https://pmc.ncbi.nlm.nih.gov/articles/PMC6853652/).[22] Ultimately, we selected 7 genetic IVs for causal inference analysis (Table S1, Supplemental Digital Content, http://links.lww.com/MD/O422).

Furthermore, in the study investigating the causal relationship between Hashimoto thyroiditis and thyroid cancer risk, there was insufficient data on Hashimoto thyroiditis and thyroid cancer. If the original P value threshold ($P < 5 \times 10^{-6}$) was applied for screening the exposure data, an insufficient number of SNPs would be selected as IVs. Therefore, we relaxed the P value threshold to $<1 \times 10^{-5}$ in our study. Eventually, we extracted 18 IVs from the exposure factor data for causal inference analysis (Table S2, Supplemental Digital Content, http://links.lww.com/MD/O422).

4. MR analysis

We utilized the genetic instruments obtained from the aforementioned data and conducted 2-sample MR analysis using the inverse variance weighted (IVW), MR-Egger, weighted median, simple mode, and weighted mode methods to estimate the impact of the exposure factor on outcome data. In terms of algorithmic principles, the IVW method integrates the Wald ratio of each SNP's causal effect through meta-analysis to generate the most precise estimates. Therefore, the results of the aforementioned IVs primarily rely on the IVW method, with the other 4 methods serving as supplementary approaches.

5. Sensitivity analysis

For sensitivity analysis, various statistical methods were applied. We first conducted MR pleiotropy residual sum and outlier (MR-PRESSO) tests to detect horizontal pleiotropy

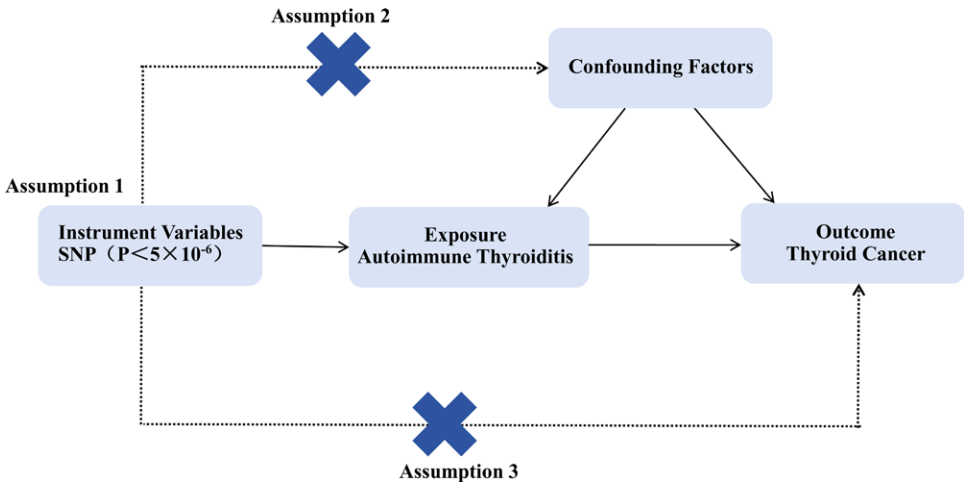

Figure 2. Assumptions of Mendelian randomization study design between autoimmune thyroiditis (including Hashimoto thyroiditis) and thyroid cancer.

($P < .05$) and remove outlier SNPs. Additionally, horizontal pleiotropy was assessed through the intercept of the MR-Egger method. Subsequently, Cochran Q test (heterogeneity test) was employed to analyze heterogeneity among IVs. Based on the degree of heterogeneity, further analysis was conducted using a fixed-effect model or a random-effect model (IVW calculation using a fixed-effect model when $Q > 0.05$ and a random-effect model when $Q < 0.05$). Leave-one-out analysis was also performed to detect whether the significant association between the exposure factor and outcome was driven by individual SNP, implying the deletion of different SNPs for MR analysis in each iteration. All analyses, including sensitivity analysis and MR analysis, were conducted using the R package TwoSampleMR.

6. Co-localization analysis

After identifying the exposure-outcome pairs with causal relationships, gene co-localization analysis was performed to identify potential shared genetic mechanisms: Each IV identified from the MR was used as a lead SNP, and SNPs within 500 kb window upstream and downstream were selected for co-localization analysis. A threshold of 0.75 was utilized to determine the evidence of co-localization.[23–25]

7. Results

The data for autoimmune thyroiditis were obtained from the FinnGen database (https://www.finngen.fi/en) (ID: finngen_R9_E4_THYROIDITAUTOIM) GWAS summary-level data, serving as the exposure data, which encompassed 321,192 samples and 20,168,706 detected SNPs. The data for thyroid cancer were sourced from the GWAS Catalog database (ID: GCST008371, GCST90041865, and GCST90041919, Table 1).

Regarding Hashimoto thyroiditis, data were sourced from the GWAS Catalog database, specifically selecting the Hashimoto thyroiditis (ID: GCST90018635) GWAS summary-level data of East Asian populations as the exposure data. It comprises 173,193 samples and 12,456,977 detected SNPs. The data for thyroid cancer were obtained from the GWAS Catalog database (ID: GCST90018709 and GCST90246033, Table 2).

7.1. MR analysis of the association between exposure to autoimmune thyroiditis and thyroid cancer risk

After excluding palindromic sequences and unmatched SNPs, 7 IVs were included for 2-sample MR analysis (Table S1, Supplemental Digital Content, http://links.lww.com/MD/O422). The IVW model results indicate no significant causal relationship between the exposure factor and outcome indicators (Fig. 3; Tables 3, 4, and 5).

The data on autoimmune thyroiditis (ID: finngen_R9_E4_THYROIDITAUTOIM) and thyroid cancer (ID: GCST008371) were subjected to MR analysis. The results obtained through the IVW method indicated that exposure to autoimmune thyroiditis did not confer an increased risk of developing thyroid cancer (odds ratio (OR) = 0.8554, 95% confidence interval (CI): 0.7193 to 1.0172, $P = .0772$). Additionally, analyses employing the MR-Egger, Simple mode, Weighted median, and Weighted mode methods yielded more conservative estimates, which did not reach

Table 1

Details of exposure (autoimmune thyroiditis) and outcome (thyroid cancer) data.

Type	Trait	ID	Population	Sample_size	nSNP
Exposure	Autoimmune thyroiditis	finngen_R9_E4_THYROIDITAUTOIM	EUR	321,192	20,168,706
Outcome	Thyroid cancer	GCST008371	EUR	407,757	28,338,944
Outcome	Thyroid cancer (PheCode 193)	GCST90041865	EUR	456,348	11,796,992
Outcome	Cancer code, self-reported: thyroid cancer (UKB data field 20001_1065)	GCST90041919	EUR	456,276	11,796,984

Table 2

Details of exposure (Hashimoto thyroiditis) and outcome (thyroid cancer) data.

Type	Trait	ID	Population	Sample_size	nSNP
Exposure	Hashimoto thyroiditis	GCST90018635	EAS	173,193	12,456,977
outcome	Thyroid cancer	GCST90018709	EAS	178,723	12,457,950
outcome	ICD10C73: Malignant neoplasm of thyroid gland	GCST90246033	EAS	75,862	6886,564

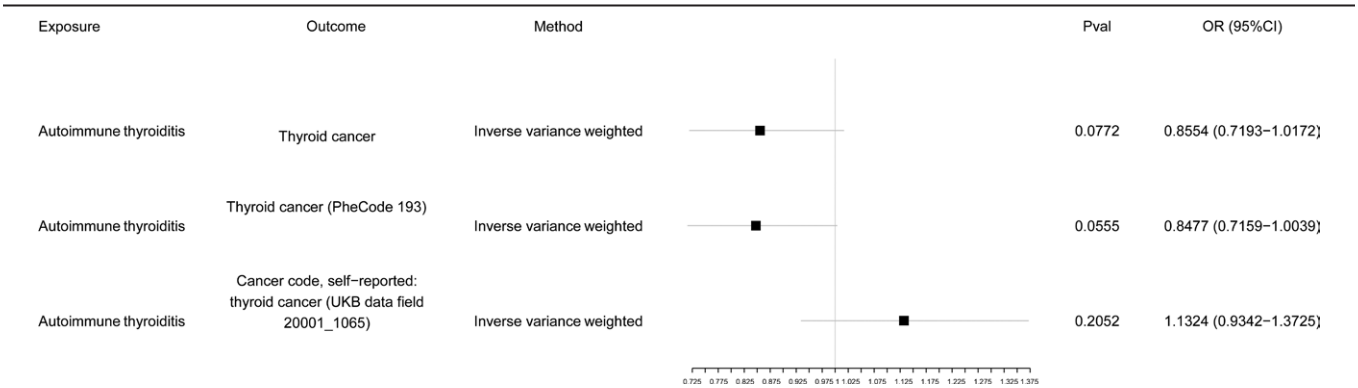

Figure 3. Forest plot of Mendelian randomization analysis between autoimmune thyroiditis and thyroid cancer. CI = confidence intervals, OR = odds ratios.

Table 3

MR analysis results of autoimmune thyroiditis (ID: finngen_R9_E4_THYROIDITAUTOIM) and thyroid cancer (ID: GCST008371).

nSNP	Method	*P* value	OR (95% CI)
7	Inverse variance weighted	.0772	0.8554 (0.7193~1.0172)
7	MR Egger	.5458	1.3518 (0.5429~3.3661)
7	Simple mode	.2479	0.8051 (0.5776~1.1222)
7	Weighted median	.0624	0.8059 (0.6422~1.0113)
7	Weighted mode	.1525	0.7799 (0.5792~1.0501)

CI = confidence intervals, OR = odds ratios.

Table 4

MR analysis results of autoimmune thyroiditis (ID: finngen_R9_E4_THYROIDITAUTOIM) and thyroid cancer (ID: GCST90041865).

nSNP	Method	*P* value	OR (95%CI)
7	Inverse variance weighted	.0555	0.8477 (0.7159–1.0039)
7	MR Egger	.6781	1.2221 (0.5004–2.9844)
7	Simple mode	.1817	0.7546 (0.5236–1.0874)
7	Weighted median	.0433	0.7932 (0.6335–0.9931)
7	Weighted mode	.1106	0.7421 (0.5429–1.0144)

CI = confidence intervals, OR = odds ratios.

statistical significance (MR-Egger: OR = 1.3518, 95% CI: 0.5429 to 3.3661, *P* = .5458; Simple mode: OR = 0.8051, 95% CI: 0.5776 to 1.1222, *P* = .2479; Weighted median: OR = 0.8059, 95% CI: 0.6422 to 1.0113, *P* = .0624; Weighted mode: OR = 0.7799, 95% CI: 0.5792 to 1.0501, *P* = .1525; Table 3).

The MR analysis was conducted on data for autoimmune thyroiditis (ID: finngen_R9_E4_THYROIDITAUTOIM) and thyroid cancer (ID: GCST90041865). The IVW method results suggested that exposure to autoimmune thyroiditis did not significantly increase the risk of thyroid cancer (OR = 0.8477, 95% CI: 0.7159 to 1.0039, *P* = .0555). And analyses using alternative MR methods including MR-Egger, simple mode, weighted median, and weighted mode methods produced more conservative estimates that did not reach statistical significance (MR-Egger: OR = 1.2221, 95% CI: 0.5004 to 2.9844, *P* = .6781; simple mode: OR = 0.7546, 95% CI: 0.5236 to 1.0874, *P* = .1817; weighted median: OR = 0.7932, 95% CI: 0.6335 to 0.9931, *P* = .0433; weighted mode: OR = 0.7421, 95% CI: 0.5429 to 1.0144, *P* = .1106; Table 4).

Data on autoimmune thyroiditis (ID: finngen_R9_E4_THYROIDITAUTOIM) and thyroid cancer (ID: GCST90041919) were subjected to MR analysis. The results from the IIVW method indicated that exposure to autoimmune thyroiditis did not significantly elevate the risk of developing thyroid cancer (OR = 1.1324, 95% CI: 0.9342 to 1.3725, *P* = .2052). Moreover, analyses using the MR-Egger, simple mode, weighted median, and weighted mode methods yielded more conservative estimates that did not reach statistical significance (MR-Egger: OR = 1.6549, 95% CI: 0.5734 to 4.7763, *P* = .3944; simple mode: OR = 1.0458, 95% CI: 0.7486 to 1.4609, *P* = .8019; weighted median: OR = 1.0273, 95% CI: 0.8289 to 1.2732, *P* = 1.0273; weighted mode: OR = 1.0376, 95% CI: 0.7746 to 1.3897, *P* = .8129; Table 5).

The aforementioned research findings suggest that, based on the MR analysis method, there is currently insufficient evidence to establish a robust and significant causal relationship between autoimmune thyroiditis and thyroid cancer.

7.2. MR analysis of the association between Hashimoto thyroiditis exposure and thyroid cancer risk

After excluding palindromic sequences and unmatched SNPs, a 2-sample MR analysis was conducted utilizing 18 IVs (Table S2, Supplemental Digital Content, http://links.lww.com/MD/O422). The results from the IVW model indicate the absence of a statistically significant causal relationship between the exposure factor and the outcome indicator (Fig. 4; Tables S3 and S4, Supplemental Digital Content, http://links.lww.com/MD/O422).

Hashimoto thyroiditis (ID: GCST90018635) and thyroid cancer (ID: GCST90018709) were subjected to MR analysis. The results from the IVW method indicated that exposure to Hashimoto thyroiditis did not increase the risk of developing thyroid cancer (OR = 1.0449, 95% CI: 0.9400 to 1.1615, *P* = .4155). Additionally, analyses employing the MR-Egger, simple mode, weighted median, and weighted mode approaches yielded more conservative estimations that did not reach statistical significance (MR-Egger: OR = 1.1701, 95% CI: 0.9670 to 1.4159, *P* = .1259; simple mode: OR = 1.0412, 95% CI: 0.8152 to 1.3297, *P* = .7505; weighted median: OR = 1.0523, 95% CI: 0.9129 to 1.2130, *P* = .4819; weighted mode: OR = 1.0533, 95% CI: 0.8377 to 1.3242, *P* = .6625) (Table S3, Supplemental Digital Content, http://links.lww.com/MD/O422).

Hashimoto thyroiditis (ID: GCST90018635) and Malignant neoplasm of thyroid gland (ID: GCST90246033) underwent MR analysis. The results from the IVW method indicated that exposure to Hashimoto thyroiditis did not increase the risk of developing thyroid cancer (OR = 0.9897, 95% CI: 0.8174 to 1.9071, *P* = .9159). Moreover, analyses employing the MR-Egger, simple mode, weighted median, and weighted mode approaches yielded more conservative estimates that did not reach statistical significance (MR-Egger: OR = 1.2301, 95% CI: 0.7934 to 1.9071, *P* = .3765; simple mode: OR = 1.1686, 95% CI: 0.7939 to 1.7201, *P* = .4463; weighted median: OR = 1.1438, 95% CI: 0.8830 to 1.4817, *P* = .3090; weighted mode: OR = 1.1731, 95% CI: 0.8408 to 1.6367, *P* = .3677) (Table S4, Supplemental Digital Content, http://links.lww.com/MD/O422).

The above study results imply that, according to MR analysis, there is currently insufficient evidence to establish a robust and significant causal relationship between autoimmune thyroiditis and thyroid cancer.

Table 5

MR analysis results of autoimmune thyroiditis (ID: finngen_R9_E4_THYROIDITAUTOIM) and thyroid cancer (ID: GCST90041919).

nSNP	Method	*P* value	OR (95% CI)
7	Inverse variance weighted	.2052	1.1324 (0.9342–1.3725)
7	MR Egger	.3944	1.6549 (0.5734–4.7763)
7	Simple mode	.8019	1.0458 (0.7486–1.4609)
7	Weighted median	.8057	1.0273 (0.8289–1.2732)
7	Weighted mode	.8129	1.0376 (0.7746–1.3897)

CI = confidence intervals, OR = odds ratios.

8. Discussion

Thyroid cancer is a malignancy with a complex etiology, influenced by genetic, environmental, and lifestyle factors.[26–28] Autoimmune thyroiditis(notably Hashimoto thyroiditis) has been extensively studied due to its potential association with thyroid cancer.[29–31] This MR study sought to elucidate the causal relationship between autoimmune thyroiditis and thyroid cancer. However, the results of this study do not decisively establish a consistent and significant causal link between autoimmune thyroiditis and thyroid cancer.

Autoimmune thyroiditis, also known as autoimmune thyroid disease, represents a chronic inflammatory condition characterized by the immune system's attacking on thyroid tissue.[7] It comprises mainly 2 subtypes: Hashimoto thyroiditis and Graves' disease.[32] Hashimoto thyroiditis is characterized by heightened levels of thyroperoxidase antibodies (TPOAb) and thyroglobulin antibodies

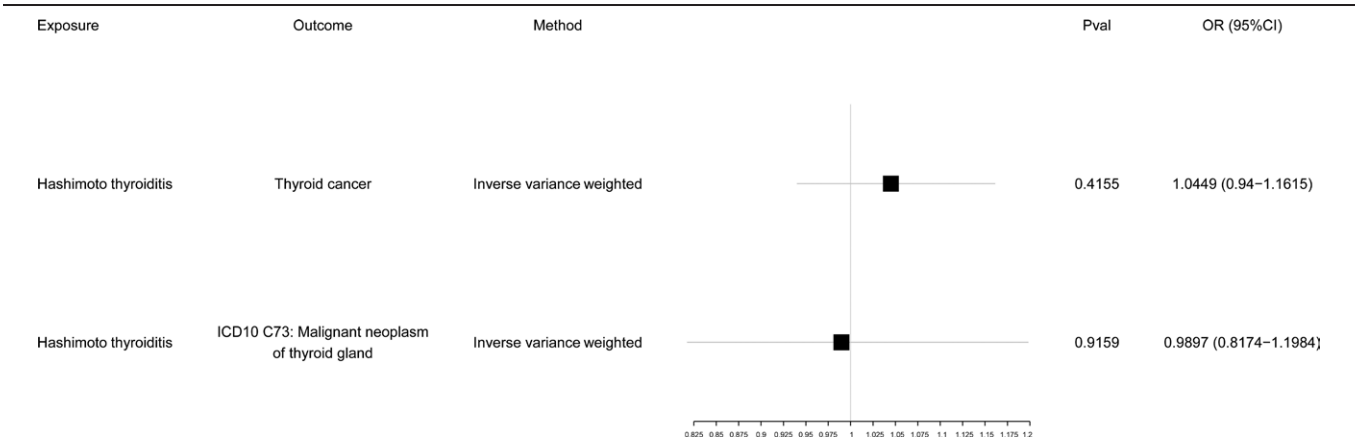

Figure 4. Forest plot of Mendelian randomization analysis between Hashimoto thyroiditis and thyroid. CI = confidence intervals, OR = odds ratios.

(TG-Ab),[33] whereas GD patients exhibit elevated levels of thyrotropin receptor antibodies (TR-Ab).[34,35] Hashimoto thyroiditis, a specific type of autoimmune thyroiditis, is categorized as chronic lymphocytic thyroiditis.[36,37] Currently, the incidence of these diseases is increasing. However, the precise etiology of autoimmune thyroiditis remains incompletely elucidated.[38–42] It is generally acknowledged that genetic, environmental, and immunoregulatory factors play pivotal roles in its pathogenesis[43–45]

Over the years, the relationship between autoimmune thyroiditis and thyroid cancer has garnered significant attention,[30] particularly contentious is the association between Hashimoto thyroiditis and thyroid cancer.[46] Previous studies, including clinical research and meta-analyses, have yielded heterogeneous results when exploring the relationship between autoimmune thyroiditis and thyroid cancer. Some studies have failed to establish a significant correlation between the 2,[47,48] while others have indicated a plausible biological link between autoimmune thyroiditis and thyroid cancer.[49,50] One possible explanation is that autoimmune thyroiditis represents a state of heightened immune system activity, precipitating chronic inflammation of thyroid tissue and potentially increasing the risk of thyroid cancer.[51,52] Furthermore, the inflammatory state of thyroiditis may promote the activity of carcinogenic factors such as DNA damage and cell proliferation.[53,54]

Previous observational studies have frequently concluded a positive association between autoimmune thyroiditis and thyroid cancer. For instance, some studies have indicated an elevated incidence of thyroid cancer among patients with autoimmune thyroiditis compared to the general population.[55,56] While these observational studies provide preliminary insights into disease associations, they highlight directions for further investigation. However, observational studies are inherently limited in design. The primary concern lies in their inability to effectively control for confounding factors such as lifestyle, genetic predisposition, and environmental influences, all of which may concurrently influence the onset of both thyroid cancer and autoimmune thyroiditis.[57,58] Moreover, reverse causality poses a common issue in observational studies, whereby it's challenging to ascertain whether autoimmune thyroiditis precipitates thyroid cancer or vice versa.[59,60]

MR study is a method that utilizes genetic diversity to study potential causal relationships, using genetic variants as IVs to assess causal relationships between exposure factors and disease outcomes.[16,17] In our study, we employed specific genetic variants as IVs to assess the causal association between autoimmune thyroiditis and thyroid cancer. These genetic variants are known to be associated with both diseases but are not affected by confounding factors. Our IVW analysis yielded null evidence of a causal link between autoimmune thyroiditis and thyroid cancer. Additionally, subsequent analyses within a 2-sample MR framework, including the weighted median, MR -Egger, and weighted mode methods,[61,62] all of which failed to uncover a causal effect between autoimmune thyroiditis and thyroid cancer at the genetic level. Moreover, our study did not substantiate a causal connection between Hashimoto thyroiditis and thyroid cancer, either. Plausible explanations for these findings are that the relationship between autoimmune thyroiditis and thyroid cancer may be more complex, involving multiple interacting common risk factors (such as lifestyle factors or environmental factors) rather than a direct biological causal relationship.[63,64] It is worth noting that inadequate sample size may lead to insufficient statistical power, hindering the detection of subtle effects. Additionally, although MR analysis can reduce the interference of confounding factors, it relies on the strong association between the selected genetic variants and the disease. If these variants are not strongly related to the disease, deviations from this criterion may yield negative results.

Despite the clinical coexistence of autoimmune thyroiditis and thyroid cancer, the MR analysis conducted in this study indicates that there is no direct causal link between the 2 conditions. This conclusion contributes novel evidence for the etiology of thyroid cancer, holding crucial implications for the development of targeted prevention and treatment strategies. Future research needs to further explore the biological mechanisms underlying autoimmune thyroiditis and thyroid cancer, elucidating their molecular and cellular interactions, which may reveal new biomarkers or therapeutic targets. Additionally, comprehensive analysis of additional potential factors, including environmental factors, lifestyle choices, and genetic backgrounds, are warranted to provide a more nuanced understanding of the complex relationship between these conditions.

In conclusion, the evidence presented in this study does not demonstrate a causal relationship between autoimmune thyroiditis (including Hashimoto thyroiditis) and thyroid cancer. This underscores the necessity for heightened awareness of the multifaceted and intricate nature of thyroid diseases in research endeavors. Furthermore, our findings serve as a catalyst for future studies, providing novel insights and directions to enhance our comprehension of thyroid diseases and advance the development of more effective treatment.

Acknowledgments

This work was supported by Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (2023RC138,2022PY005), and Zhejiang Provincial Natural Science Foundation of China under Grant No. LY24H160019.

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