Original Article

Causal effects of thyroid volume change on thyroid disease: a Mendelian randomization study

Huiming Yuan[1,2,3,4#], Dalang Fang[5,6#], Congjun Wang[2,3,4,7], Kaitian Zheng[1,2,3,4], Moon Young Oh[8], Ye Wang[2,3,4,9], Junqiang Chen[1,2,3,4]

[1]Department of Gastrointestinal Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, China; [2]Guangxi Key Laboratory of Enhanced Recovery after Surgery for Gastrointestinal Cancer, Nanning, China; [3]Guangxi Clinical Research Center for Enhanced Recovery after Surgery, Nanning, China; [4]Guangxi Zhuang Autonomous Region Engineering Research Center for Artificial Intelligence Analysis of Multimodal Tumor Images, Nanning, China; [5]Department of Gland Surgery, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China; [6]Key Laboratory of Tumor Molecular Pathology of Baise, Baise, China; [7]Department of Pediatric Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, China; [8]Department of Surgery, Seoul National University College of Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea; [9]Department of Internet Hospital Operation, The First Affiliated Hospital of Guangxi Medical University, Nanning, China

Contributions: (I) Conception and design: Y Wang, J Chen, H Yuan, D Fang; (II) Administrative support: J Chen, Y Wang; (III) Provision of study materials or patients: C Wang, D Fang; (IV) Collection and assembly of data: K Zheng, H Yuan; (V) Data analysis and interpretation: Y Wang, H Yuan, MY Oh; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Ye Wang, MD. Guangxi Key Laboratory of Enhanced Recovery after Surgery for Gastrointestinal Cancer, Nanning, China; Guangxi Clinical Research Center for Enhanced Recovery after Surgery, Nanning, China; Guangxi Zhuang Autonomous Region Engineering Research Center for Artificial Intelligence Analysis of Multimodal Tumor Images, Nanning, China; Department of Internet Hospital Operation, The First Affiliated Hospital of Guangxi Medical University, No. 6 Shuangyong Road, Nanning 530021, China. Email: wangye@sr.gxmu.edu.cn; Junqiang Chen, MD. Department of Gastrointestinal Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, China; Guangxi Key Laboratory of Enhanced Recovery after Surgery for Gastrointestinal Cancer, Nanning, China; Guangxi Clinical Research Center for Enhanced Recovery after Surgery, Nanning, China; Guangxi Zhuang Autonomous Region Engineering Research Center for Artificial Intelligence Analysis of Multimodal Tumor Images, No. 22 Shuangyong Road, Nanning 530021, China. Email: chenjunqiang@gxmu.edu.cn.

Background: Observational studies have suggested an association between thyroid volume changes and thyroid disease, but the causal relationship and direction of these effects remain unclear. This study employs a two-sample Mendelian randomization (MR) approach to assess the effect of thyroid volume on clinically common benign and malignant thyroid diseases.

Methods: Summary data from genome-wide association studies (GWAS) were utilized for secondary data analysis to investigate the link between thyroid volume and disease. Gene loci strongly associated with thyroid volume were selected as the instrumental variables. Five complementary two-sample MR methods were used to evaluate the causal effect of thyroid volume on thyroid diseases and thyroid stimulating hormone (TSH).

Results: Thyroid volume was found to be significantly associated with autoimmune thyroid disease [odds ratio (OR) =1.045; 95% confidence interval (CI): 1.022–1.069; P<0.001], Hashimoto's thyroiditis (OR =1.800; 95% CI: 1.167–2.778; P=0.008), Graves' disease (OR =0.136; 95% CI: 0.065–0.282; P<0.001), hyperthyroidism (OR =1.011; 95% CI: 1.008–1.014; P<0.001), multinodular goiters (OR =121.541; 95% CI: 23.323–633.378; P<0.001), non-toxic single thyroid nodules (OR =7.536; 95% CI: 2.280–24.911; P<0.001), benign thyroid neoplasms (OR =4.300; 95% CI: 1.170–15.802; P=0.03), and TSH levels (OR =0.401; 95% CI: 0.247–0.652; P<0.001). Thyroid volume was negatively associated with thyroid carcinomas (OR =0.401; 95% CI: 0.208–0.772; P=0.006; β =–0.915).

Conclusions: Our study found that there is a causal relationship between thyroid volume and some thyroid

diseases, and that increased thyroid volume levels exert protective effects on thyroid carcinoma. Monitoring thyroid volume may be of value in the prevention of clinical thyroid diseases.

Keywords: Thyroid volume; thyroid disease; thyroid carcinoma; Mendelian randomization (MR); causal relationship

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Introduction

The thyroid gland plays an essential role in the body's endocrine system, and thyroid disorders are among the most prevalent endocrine diseases worldwide (1-3). Functional changes in the thyroid gland can cause diseases such as hypothyroidism, hyperthyroidism, and thyroiditis (4,5), whereas changes in its size and structure manifests as benign nodules, diffuse goiters, malignant tumors (4,5). In recent years, the incidence of thyroid carcinoma has been increasing, making it the most common type of endocrine tumor (6,7). Although the prognosis of patients with thyroid carcinoma is generally favorable, current treatments remain ineffective in improving outcomes for those with locally advanced or recurrent metastatic thyroid carcinoma (8). A recent survey of 78,470 patients administered in 31 Chinese provinces, municipalities, and autonomous regions reported that the prevalence of thyroid diseases among adults aged over 18 years is as high as 50%. Specifically, the prevalence of abnormal thyroid function was 15.17%, positive thyroid autoantibodies 14.19%, thyroid nodules 20.43%, and goiters 1.17% (9).

In addition to well-established factors for thyroid disease, such as age, gender, smoking, stress, iodine deficiency or excess, genetics, autoimmunity, and ionizing radiation (10-15), there is emerging evidence of a potential association between thyroid volume and the diagnosis, treatment, and prognosis of some thyroid diseases (16). Therefore, further research and the identification of other pathogenic factors could provide new insights into the prevention and management of thyroid diseases, including malignant thyroid tumors.

In our previous non-genetic observational study, we reported a possible correlation between thyroid size and thyroid disease (17,18). However, study limitations related to the sample size, reverse causality, confounding factors, and bias hindered our ability to conduct a causality analysis. To overcome these limitations, we sought to apply a genetic epidemiological technique to investigate the relationship between thyroid volume and thyroid disease.

Mendelian randomization (MR), first introduced by Katan in his investigation of whether low serum cholesterol levels directly increase cancer risk (19), uses genetic variants as instrumental variables to assess causality, similar to randomized controlled trials. This approach reduces

Highlight box

Key findings

- Using Mendelian randomization (MR), we identified a significant causal relationship between thyroid volume and multiple thyroid diseases. Notably, an increased thyroid volume appears to exert a protective effect against thyroid carcinoma. Monitoring thyroid volume may be valuable in the prevention of clinical thyroid diseases. These findings may introduce new indicators and concepts for the prevention and treatment of thyroid carcinoma.

What is known and what is new?

- Several factors, including age, sex, smoking, stress, iodine levels, genetics, autoimmunity, and ionizing radiation, are known to contribute to thyroid disease. Non-genetic observational studies have reported a possible correlation between thyroid size and thyroid disease.
- In this study, we analyzed the causal relationship between thyroid volume and clinically common thyroid conditions. Notably, thyroid volume was significantly associated with autoimmune thyroid disease, Hashimoto's thyroiditis, Graves' disease, hyperthyroidism, multinodular goiters, non-toxic single thyroid nodules, benign thyroid neoplasms, thyroid carcinomas, and thyroid stimulating hormone (TSH) levels.

What is the implication, and what should change now?

- We conducted a comprehensive study and found that there is a causal relationship between thyroid volume and some thyroid diseases, and that thyroid volume is negatively correlated with thyroid carcinoma. Further research on the mechanisms underlying these associations is necessary, and it may provide new insights into the prevention and treatment of thyroid diseases, including malignant thyroid tumors.

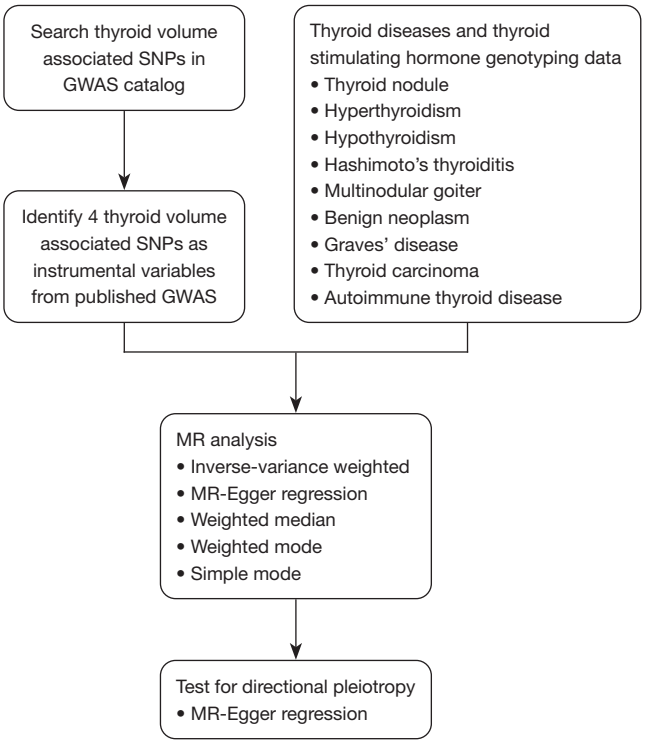

Figure 1 Study design flowchart. SNPs, single nucleotide polymorphisms; GWAS, genome-wide association studies; MR, Mendelian randomization.

confounding bias through random assignment. In the present study, we used a bidirectional design to examine the relationship between thyroid volume and thyroid disease. MR leverages the random assortment of genetic variants during gamete formation, which mimics the random allocation process in a population and theoretically eliminates the effects of confounders (20,21). Since genetic variation precedes environmental exposure, confounding, and disease outcomes, MR also addresses reverse causality (22,23). This method has become widely utilized in causality studies involving genome-wide association studies (GWAS) data. However, any MR analysis must satisfy three core assumptions: (I) association: genetic variants should exhibit a close correlation with exposure factors; (II) independence: genetic variants are independent of confounding factors affecting the "exposure-outcome" association; and (III) exclusivity: the impact of genetic variants on the outcome is solely mediated by exposure factors (24,25). Provided the above assumptions are met, the analysis can effectively assess the relationship between exposure and outcomes based on pooled data.

Given these premises, we employed a two-sample MR method with single nucleotide polymorphism (SNP) as the instrumental variable and GWAS summary data to investigate the genetic causality between thyroid volume and thyroid disease at the genetic level. We present this article in accordance with the STROBE-MR reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-441/rc).

Methods

Aggregate data resources

Thyroid volume

The analytical process used in this study is summarized in *Figure 1*. GWAS summary statistics for thyroid volume were obtained from Teumer *et al.* (26). In their research, GWAS analyses were performed using data from the Study of Health in Pomerania (SHIP—0/3,620 people) in West Pomerania, and the Cooperative Health Research in the Augsburg Region (KORA F4—1,290 people). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Thyroid disease

We obtained nine publicly available thyroid disease datasets from the GWAS, including non-toxic single thyroid nodules, hyperthyroidism, hypothyroidism, Hashimoto's thyroiditis, autoimmune thyroid disease, Graves' disease, multinodular goiters, benign neoplasms, and thyroid carcinomas. Summary statistics for non-toxic single thyroid nodules were obtained from a GWAS of 1,121 European ancestry patients and 187,684 European ancestry controls (finn-b-E4_GOITRENOD). Summary statistics for hyperthyroidism were obtained from a GWAS meta-analysis of 3,545 European ancestry patients and 459,388 European ancestry controls (ukb-b-20289). Summary statistics for hypothyroidism were obtained from a GWAS meta-analysis of 22,687 European ancestry patients and 440,246 controls (ukb-b-19732). Summary statistics for Hashimoto's thyroiditis were obtained from a GWAS meta-analysis of 15,654 European ancestry patients, 379,986 European ancestry controls, 537 East Asian ancestry controls, and 172,656 East Asian ancestry controls (27). Summary statistics for non-toxic multinodular goiters were obtained from the discovery phase of a GWAS meta-analysis of 587 European ancestry patients and 455,761 controls (28). Pooled statistics for benign neoplasms were obtained from

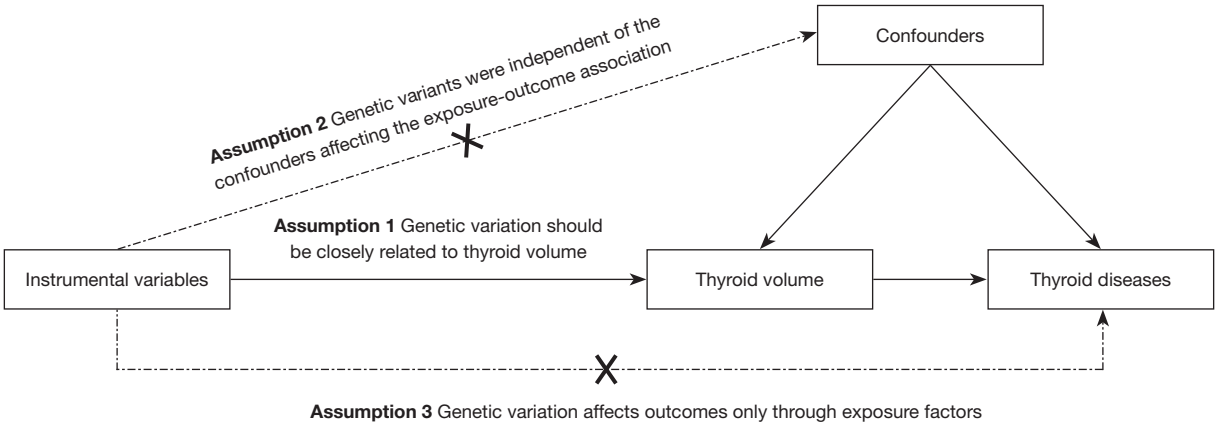

Figure 2 Schematic representation of the Mendelian randomization model and assumptions. Solid lines indicate the presence of an association and dashed lines indicate the absence of an association.

a GWAS meta-analysis of 455 European ancestry patients (finn-b-CD2_BENIGN_THYROID) and 218,337 controls. Summary statistics for Graves' disease were obtained from a GWAS meta-analysis of 1,678 European ancestry patients, 456,942 European ancestry controls, 2,809 East Asian ancestry patients, and 172,656 East Asian ancestry controls (27). Summary statistics for thyroid carcinoma were obtained from a GWAS meta-analysis of 1,054 European ancestry patients, 490,920 European ancestry controls, 361 East Asian ancestry patients, and 178,362 East Asian ancestry controls (28). Finally, summary statistics for autoimmune thyroid disease were obtained from a GWAS meta-analysis of 607 European ancestry patients and 324,074 controls (29).

Thyroid stimulating hormone (TSH)

Summary statistics for TSH levels were obtained from GWAS, including the statistics for 2,935 Qatari ancestry patients (30). Detailed information of the datasets is provided in Table S1.

Tool selection

In the GWAS of thyroid volume by Teumer *et al.*, all SNPs with allele frequencies <0.01 were eliminated (26). The meta-analysis accounted for factors such as age, sex, body surface area, and smoking status. The relationship between natural log-transformed thyroid volume (mL) and "thyroid volume" was assessed using a linear additive model. A Hardy-Weinberg equilibrium was present for all the SNPs linked to thyroid volumes of interest in the GWASs (P>0.05). SNPs strongly correlated with thyroid volume level were continued to be selected as instrumental variables from GWAS data [$P<5\times10^{-8}$ and minor allele frequency (MAF) >0.01]. The lead SNPs of these four loci were further analyzed using a multiple linear regression model to verify their independence for "thyroid volume", and the correlations remained significant and essentially unchanged, showing the statistical independence of these four SNPs. Four loci were recognized as having genome-wide significance for "thyroid volume".

Statistical analysis

The MR analysis followed three basic assumptions (*Figure 2*). Five complementary two-sample MR methods were employed: inverse variance weighting (IVW), the MR-Egger, weighted-median (WM), weighted-mode, and simple mode methods, to assess the causal effects of thyroid volume on thyroid disease and TSH levels. A multiplicative random effects model was used to infer causality in the IVW regression. If either of the SNPs exhibited horizontal pleiotropy, the IVW results may be biased. To mitigate this, the other four MR methods were used to complement and reinforce reliability. The MR-Egger method used the slope coefficient of the Egger regression to assess the causal effect, providing more robust estimates of causal effects, especially when the validity of instrumental variables was questioned (31). The WM method, due to the robustness to extreme values and reliance on the statistical properties of the median, can effectively prevent up to 50% of invalid instrumental variables (32). The weighted-mode method,

under more relaxed assumptions, provides consistent estimates with reduced bias and lower type I error rate (33). Statistical analysis was performed used two-sample MR (version 0.5.5) from the R package (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Determine tool variables and result selection

Four SNPs were selected as instrumental variables for thyroid volume. Details of the four SNPs are provided in Table S2. The F-statistics values of all the SNPs were >10, with statistically significant P values, indicating that the instrumental variables were not weakly biased.

MR analysis

The MR analysis revealed correlations between thyroid volume and benign thyroid disease. Based on the IVW method of analysis, thyroid volume was significantly correlated with autoimmune thyroid disease [odds ratio (OR) =1.045; 95% confidence interval (CI): 1.022–1.069; P<0.001], Hashimoto's thyroiditis (OR =1.800; 95% CI: 1.167–2.778; P=0.008), Graves' disease (OR =0.136; 95% CI: 0.065–0.282; P<0.001), hyperthyroidism (OR =1.011; 95% CI: 1.008–1.014; P<0.001), multinodular goiters (OR =121.541; 95% CI: 23.323–633.378; P<0.001), non-toxic single thyroid nodules (OR =7.536; 95% CI: 2.280–24.911; P<0.001), and benign thyroid neoplasms (OR =4.300; 95% CI: 1.170–15.802; P=0.03). A causal relationship was found between thyroid volume and TSH levels (OR =0.401; 95% CI: 0.247–0.652; P<0.001) (Table S3). However, no MR correlation was found between thyroid volume and hypothyroidism (OR =0.981; 95% CI: 0.959–1.003; P=0.08) (Table S3). These results suggest that thyroid volume may not be causally related to hypothyroidism, but may be causally related to other benign diseases (Figure S1). For Graves' disease, thyroid volume appears to act as a protective factor, whereas for benign diseases, it serves a risk factor (*Figure 3*).

Additionally, the IVW results revealed a significant causal relationship between thyroid volume and thyroid carcinoma (OR =0.401; 95% CI: 0.208–0.772; P=0.006) (Table S3). The WM method also produced similar results (OR =0.397; 95% CI: 0.188–0.838; P=0.02), suggesting a strong causal link between increased thyroid volume and reduced risk of thyroid carcinoma (*Figure 4*). The IVW and WM β values of –0.915 and –0.924, respectively, indicated that larger thyroid volume is associated with a lower risk of thyroid carcinoma (Table S3).

Reliability evaluation

In the assessment for genetic pleiotropy, the MR-Egger regression analysis revealed a near-zero intercept for the relationship between thyroid volume and thyroid carcinoma, suggesting that genetic pleiotropy did not significantly influence the causal estimates. Similar results were observed in the MR-Egger regression analysis for thyroid volume and other thyroid disorders, with no evidence of pleiotropy, indicating that the MR estimates are highly reliable (Table S4).

Discussion

The thyroid gland, an essential organ, is subject to various disease states. Various factors can interact with the morphology and volume of the thyroid gland (34,35). Thyroid volume plays an important role in the diagnosis of thyroid diseases, the determination of curative effect, and conduction of epidemiological studies. The wide range of thyroid volumes in normal adults indicates individual differences in thyroid volume (36). Environmental factors, such as iodine intake, also affect thyroid volume, as seen in populations with different iodine consumption levels (37).

In this study, we identified a causal relationship between thyroid volume and thyroid disease using a two-sample MR analysis. We observed that thyroid volume is causally related to TSH levels and several benign thyroid disorders, including thyroid nodules and goiters. Thyroid volume appears to be a risk factor for these benign thyroid disorders, but serves as a protective factor for Graves' disease. In addition, our findings suggest that an increase in thyroid size is associated with a reduced risk of thyroid carcinoma, indicating a protective role of larger thyroid volumes against malignancy.

A multifactorial analysis has previously shown that TSH levels, thyroid volume, and female gender are all independent risk factors for the development of thyroid nodules (38). Our findings also revealed a negative correlation between thyroid volume and TSH levels, suggesting that larger thyroid volumes are associated with lower TSH levels. This may indicate that as thyroid volume increases, TSH secretion tends to be within a lower range.

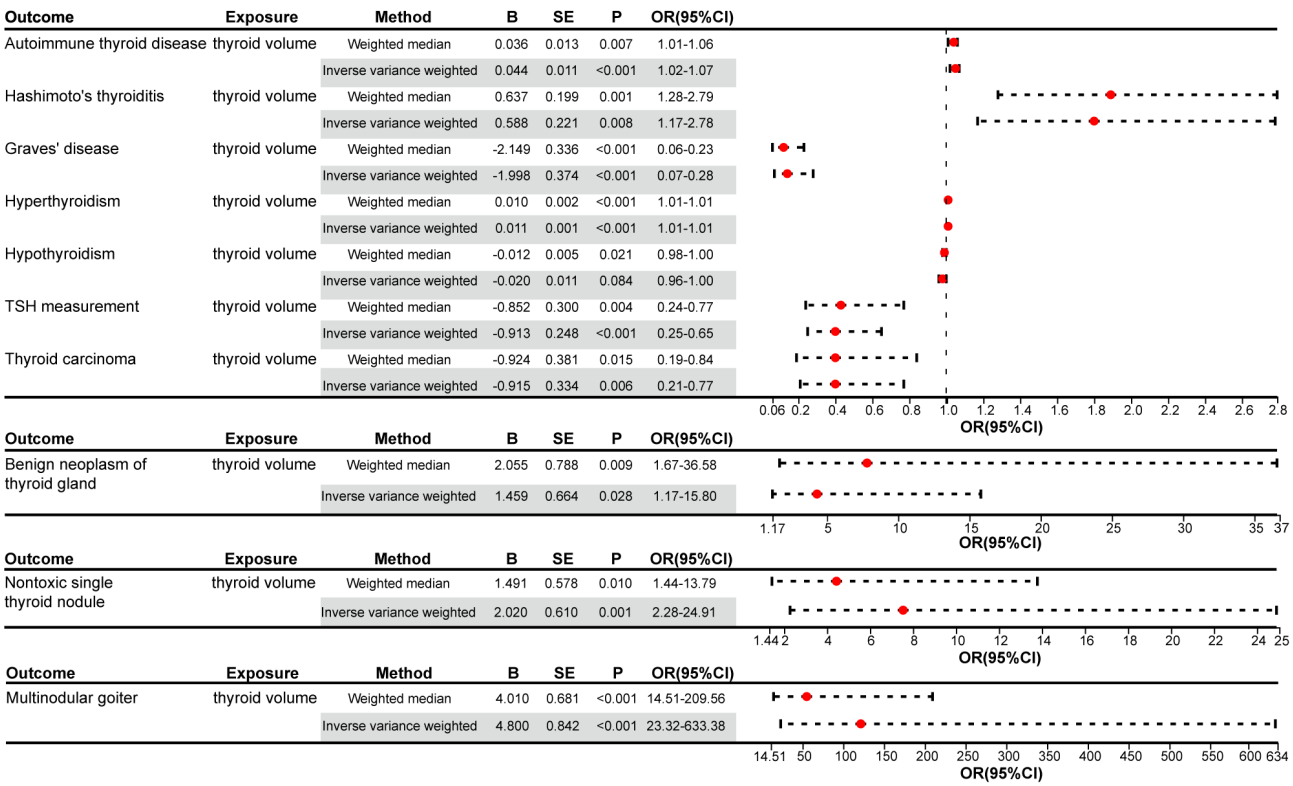

Figure 3 Forest plot showing the ORs and 95% CIs for the effect of thyroid volume on thyroid diseases using two-sample Mendelian randomization. SE, standard error; OR, odds ratio; CI, confidence interval.

There is conflicting evidence regarding whether TSH influences thyroid growth. One study observed a significant correlation between serum TSH and thyroid volume (39). However, a study has found no such correlation between serum TSH and thyroid volume (40). It is possible that TSH does not directly affect thyroid tissue but plays a role in thyroid enlargement under certain conditions, such as when thyroid hormone secretion increases due to autonomous thyroid function or when thyroid mass increases. Alternately, the presence of thyroid-stimulating antibodies could explain the lower TSH levels in larger thyroid glands.

For some benign thyroid gland diseases, our observations showed that the larger the volume of the thyroid gland, the greater the risk of developing thyroid nodules and goiters, reinforcing the idea that thyroid volume is a risk factor for these conditions. Thyroid follicles, the functional units of the gland, determine the gland's size based on their number, the size of colloid-filled follicles, and the activity of the thyrocytes. This structural dependence could explain the link between thyroid volume and benign thyroid disorders (41).

Previous research has identified thyroid volume as an independent risk factor for thyroid nodules, with a positive correlation between nodule size and thyroid volume (38). Our findings align with this perspective. It might be that several extrinsic and intrinsic factors, such as iodine environment, body mass index, body surface area, and family genetics, influenced the thyroid size in the European population in the GWAS summary statistics. Iodine deficiency, a high body mass index, and a high body surface area can cause an increase in thyroid size, and are associated with the occurrence and development of thyroid nodules and goiters (42). The marked hypothyroidism of progressive autoimmune thyroiditis is accompanied by thyroid retraction. Although the underlying mechanism of retraction is unknown, it is most likely triggered by apoptosis-induced thyroid cell death (43). Coincidentally, the main progression of Hashimoto's thyroiditis is accompanied by an increase in apoptosis (44,45).

Brčić *et al.* identified two genome-wide significant loci associated with thyroid volume in patients with

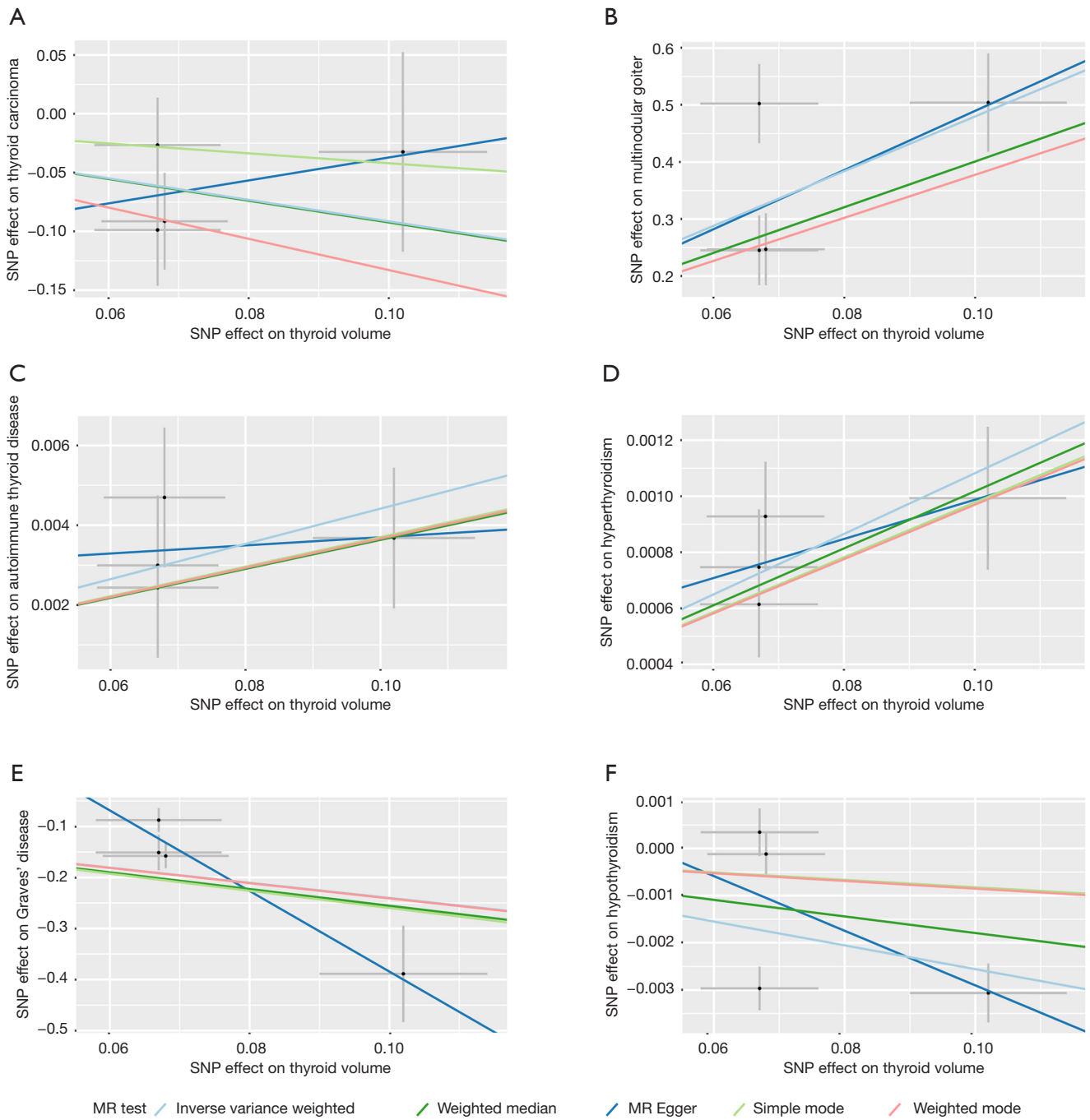

Figure 4 A scatter plot showing genetically predicted thyroid volume on thyroid diseases. Inverse variance-weighted, weighted-median, MR-Egger, simple mode, and weighted-mode slopes represent the results from these regression analyses. (A) A scatter plot showing the effects of SNPs on thyroid volume and thyroid carcinoma. (B) A scatter plot showing the effects of SNPs on thyroid volume and multinodular goiter. (C) A scatter plot showing the effects of SNPs on thyroid volume and autoimmune thyroid disease. (D) A scatter plot showing the effects of SNPs on thyroid volume and hyperthyroidism. (E) A scatter plot showing the effects of SNPs on thyroid volume and Graves' disease. (F) A scatter plot showing the effects of SNPs on thyroid volume and hypothyroidism. SNP, single nucleotide polymorphism; MR, Mendelian randomization.

Hashimoto's thyroiditis (41). One is located in the anti-apoptotic transcription factor (*AATF*), and the other near the chromatin remodeling *SMARCA2*. Notably, the major allele T of *AATF* variant rs7212416 had a negative effect on thyroid volume. *AATF* has anti-apoptotic effects, and the decreased activity of *AATF* in the thyroid gland of patients with Hashimoto's thyroiditis may be due to decreased expression or ubiquitin-dependent degradation, leading to increased apoptotic activity (46). It may be that *AATF* activity and the extent of apoptosis are affected by potential genetic variants (41). Further, the effect of this SNP on thyroid volume may be stimulated by the underlying pathological state of Hashimoto's thyroiditis (47). In Hashimoto's thyroiditis, autoimmune damage mainly involves autoimmune system abnormalities, as well as related apoptotic effects and gene variants. The apoptosis of thyroid cells and the imbalance of apoptosis of immune cells will lead to the injury of thyroid tissue (48). In addition, certain cytokine genes and thyroid-specific antigen gene variants may affect inflammatory response and immune regulation, such as interleukin-6 (IL-6) and transforming growth factor-β (TGF-β), in the specific case of Hashimoto's thyroiditis, damage mechanisms strike the thyroid gland (48,49). However, some patients with Hashimoto's thyroiditis have been observed to have a goiter on one side and an atrophied thyroid gland on the other side (50).

One study noted that in patients with new-onset Graves' disease, reduced vitamin D levels and changing vitamin D status were significantly associated with thyroid volume, and that the thyroid volume was markedly larger in such patients. Interestingly, reduced vitamin D levels in female patients have been found to be significantly correlated with thyroid volume (51). However, no clear causal relationship has been established between changes in thyroid volume and thyroid function, particularly in hypothyroidism.

A German GWAS reported that four loci were associated with thyroid volume and the risk of goiters. Among them, two independent loci were identified as being associated with the risk of goiters in the *CAPZB* region of chromosome 1p36; the leading SNP rs12138950 was most strongly associated with both phenotypes and was located in the upstream region of *CAPZB*, and the leading SNP rs12045440 was located in intron 1 of the *CAPZB* gene (52), which is the same SNP that we screened as an instrumental variable. In addition, the leading SNP rs4338740, located on chromosome 15q21, is located within the second intron of *FGF7*, which belongs to the family of fibroblast growth factors, is involved in the regulation of thyroid volume, and also influences the development of tumors (26). Our study identified thyroid enlargement as a protective factor against thyroid malignancy, consistent with the findings of Duran *et al.* (53). We hypothesize that genetic variants influencing thyroid volume might also affect tumor susceptibility.

This study used public databases to save time and costs. The datasets predominantly comprised European populations with little heterogeneity. However, this study had some limitations. First, the study re-analyzed GWAS meta-analysis data without stratifying patients by sex, limiting our ability to identify gender-specific genetic loci. Second, the two-sample MR approach allowed us to assess linear relationships between exposure and outcome but did not permit non-linear analyses. Third, the study predominantly focused on European populations, so further validation in Chinese or other ethnic groups is required. Finally, although MR can infer causal associations, it cannot explain the underlying mechanisms, which warrants further exploration.

Conclusions

In conclusion, the present study used MR to explore the causal relationships between thyroid volume and multiple thyroid disorders. An increased thyroid volume may reduce the risk of thyroid carcinoma, offering new insights for the prevention and treatment of thyroid diseases. Further research is needed to investigate the possible mechanisms underlying these associations.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-441/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-441/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-441/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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