• Mendelian Randomization •

Triglyceride-driven pathogenesis in thyroid-associated ophthalmopathy: a dual approach of clinical correlation and genetic causality

Jia-Min Cao, Hai-Yan Chen, Feng Zhang, Wei Xiong

Department of Ophthalmology, Third Xiangya Hospital, Central South University, Changsha 410013, Hunan Province, China

Correspondence to: Wei Xiong. Department of Ophthalmology, Third Xiangya Hospital, Central South University, Changsha 410013, Hunan Province, China. weixiong420@csu.edu.cn

Received: 2025-04-20 Accepted: 2025-10-17

Abstract

● **AIM:** To clarify the clinical correlations and causal relationships between lipid metabolism and the progression of thyroid-associated ophthalmopathy (TAO).

● **METHODS:** This case-control study retrieved clinical data from 2018 to 2023. A total of 2591 patients were enrolled, including 197 patients with TAO (case group) and 2394 patients with hyperthyroidism without TAO (control group). Serum lipid parameters, including triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and the HDL/total cholesterol ratio, as well as thyroid function markers, were compared between the two groups. Correlation analyses were performed to evaluate the associations between serum lipid levels and key ocular manifestations of TAO, including exophthalmos degree, clinical activity score, and disease severity. Furthermore, Mendelian randomization (MR) analysis was conducted using genome-wide association study (GWAS) datasets, with hyperthyroidism as the exposure variable and serum lipid parameters as the outcome variables, to infer the causal relationship between hyperthyroidism, lipid metabolism, and TAO progression.

● **RESULTS:** The TAO group consisted of 101 males and 96 females, while the hyperthyroidism group included 706 males and 1688 females. Compared with the control group, patients with TAO had significantly higher levels of triglycerides (1.83±1.21 *vs* 1.40±1.08 mmol/L, $P<0.01$), total cholesterol, LDL, and HDL. Correlation analysis showed that triglyceride levels were positively correlated with exophthalmos degree, whereas HDL levels were inversely correlated with exophthalmos degree. No significant associations were found between serum lipid levels and clinical activity score ($P>0.1$). MR analysis confirmed that hyperthyroidism exerted a causal effect in reducing serum triglycerides [inverse-variance weighting odds ratio (OR)=0.035, 95% confidence interval (CI): 0.01-0.12] and total cholesterol (OR=0.085, 95%CI: 0.02-0.34), with no evidence of horizontal pleiotropy (MR-PRESSO $P>0.05$).

● **CONCLUSION:** Elevated serum triglyceride levels are an independent risk factor for TAO severity, especially exophthalmos, and triglyceride metabolism is inversely regulated by thyroid function.

● **KEYWORDS:** thyroid-associated ophthalmopathy; lipid metabolism; triglyceride; Mendelian randomization; causal inference; exophthalmos

DOI:10.18240/ijo.2026.03.20

Citation: Cao JM, Chen HY, Zhang F, Xiong W. Triglyceride-driven pathogenesis in thyroid-associated ophthalmopathy: a dual approach of clinical correlation and genetic causality. *Int J Ophthalmol* 2026;19(3):582-589

INTRODUCTION

Thyroid-associated ophthalmopathy (TAO) is a multifactorial autoimmune disease closely related to systemic disease[1]. The risk factors of TAO include environmental, genetic, and societal factors[2]. These risk factors have some common pathogenesis in disease development. Dysfunction of the immune system induces abnormal levels of antibodies such as thyrotropin receptor (TSHR) and insulin-like growth factor 1 receptor (IGF-1R), which regulate downstream immune functions and trigger the progression of tissue edema, thus facilitating the development of an abnormal immune microenvironment, in addition to simulating transmitters and activating receptors[3]. Teprotumumab, an anti-IGF-1R antibody, has been proven to be an effective disease-controlling drug[4]. These activated signaling pathways drive higher levels of thyroid function, in turn promoting disease development. Thus, thyroid dysfunction is considered an important risk factor of TAO[5]. For example, higher free triiodothyronine (FT3) was identified in patients with TAO than in healthy controls, indicating its potential as a biomarker for diagnosis and prediction[6]. The guidelines from the European Group on Graves' Ophthalmopathy (EUGOGO) state the importance of controlling a higher level of thyroid function, as this is an important risk factor, and control can help to suppress disease development[7]. However, in clinical practice, patients with controlled thyroid function may still show disease development, illustrating the complex nature of TAO and the existence of other influencing factors.

Exophthalmos, a common manifestation of TAO, can result in symptoms such as changes in ocular structure and exposure to keratitis[8]. Both active and inactive stages of TAO can present with exophthalmos, though the underlying pathogenesis differs. In the active stage, a dysfunctional immune microenvironment causes tissue damage, which may manifest as orbital tissue edema, enlargement of extraocular muscles, and adipogenesis[9]. As inflammation subsides, edema decreases and extraocular muscles undergo fibrosis. However, adipogenesis continues[10]. The pathogenesis of adipogenesis is complex, involving abnormal lipid metabolism. When orbital fibroblasts differentiate into adipocytes, lipids—particularly triglycerides—accumulate within the cells. Oil-Red-O staining has confirmed adipogenesis in orbital fibroblasts[11]. Fibrocytes migrate from the circulatory system to orbital tissues, differentiate into fibroblasts, and their proliferation is influenced by circulating lipid levels[12]. Abnormal lipid levels have also been reported in TAO[13]. However, the relationship between lipid levels and thyroid function in TAO remains unclear, and whether lipids are a risk factor has not been definitively established.

Mendelian randomization (MR) is an epidemiological method used to detect causal relationships between exposure and outcome[14]. Compared to traditional randomized controlled trials, MR analysis faces fewer ethical constraints and can include larger sample sizes[15]. Unlike cross-sectional studies, MR provides stronger evidence for causality. The exposure and outcome datasets in MR studies are typically derived from genome-wide association studies (GWAS)[16]. Recent GWAS research has yielded numerous summary datasets that support the use of MR analysis. MR uses single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to represent exposure traits and infer causality based on three key assumptions[17].

In this study, blood lipid levels were compared between patients with TAO and those with hyperthyroidism using a case-control design. Associations between eye symptoms and blood lipid levels were examined to examine the role of lipids in disease development. MR analysis was then conducted to assess the causal relationship between thyroid function and blood lipid levels, aiming to inform potential therapeutic strategies for TAO.

PARTICIPANTS AND METHODS

Ethical Approval This study complied with the Declaration of Helsinki and approval was obtained from the IRB of the Third Xiangya Hospital of Central South University (ID: 23693). Written informed consent was collected from all study participants.

Data Collection Data were collected from the case records from 2018 to 2023 from the clinical data-sharing platform of Third Xiangya Hospital. The records of patients diagnosed with hyperthyroidism or TAO with available thyroid function and complete blood lipid test results were collected. The basic information extracted from the records included the time and frequency of hospitalization, age, gender, and diagnosis information. The patient's identifiable information has been obscured. The inspection data included results of thyroid function and complete blood lipid test. Thyroid function information, including FT3, free thyroxine (FT4), thyroglobulin (Tg), thyroid stimulating hormone (TSH), and antibodies to TSH receptor (TSHR), thrombopoietin (TPO), and Tg, was also collected. Further, complete blood lipid test results, including triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein levels and the ratio of high-density lipoprotein to total cholesterol, were collected. Ocular symptoms were also collected, including the degree of exophthalmos, severity, and clinical activity score, which were identified by the criteria from EUGOGO[7].

Data Preprocessing After obtaining data, data integrity was tested. Case records with any incomplete data were excluded. For patients records with multiple hospitalizations, only the first hospitalization was used. For patients with multiple results from the same examination in a single hospitalization, only the first examination result was retained. Among these records, the diagnosis information was used as the main grouping criteria. Patients diagnosed with TAO were classified into the TAO group, while other patients diagnosed with hyperthyroidism without TAO were classified into the hyperthyroidism group. The data used to detect the relationships between eye symptoms and the level of blood lipids was predominantly extracted from the TAO group. Figure 1 presents a flow chart of patient enrollment and the study process.

Data Analysis Gender and age information for patients in the TAO group and the hyperthyroidism group was counted respectively. Information on thyroid function and complete blood lipid test results are described as the Mean±standard deviation (SD). The triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein levels and the ratio of high-density lipoprotein to total cholesterol were compared between the groups using unpaired *t*-tests. The results are

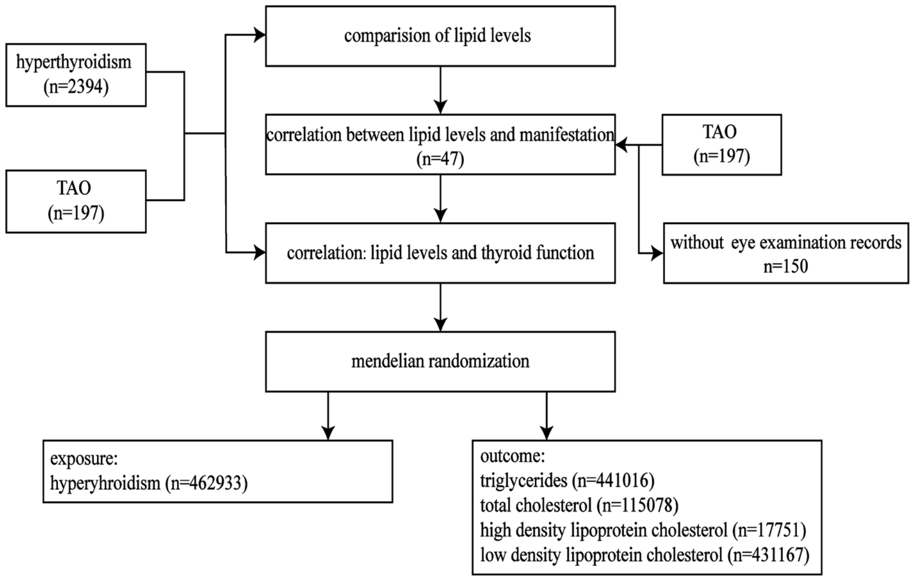

Figure 1 Design of the research TAO: Thyroid-associated ophthalmopathy.

shown using a scatter plot. To establish the relationship between the level of blood lipid and eye symptoms, a simple linear regression analysis was conducted between the degree of exophthalmos and the level of blood lipid, respectively. An unpaired *t*-test was used to detect the correlation between clinic activity score (CAS) and the level of blood lipids by comparing the levels of blood lipid of patients in the active (CAS<3) and inactive (CAS≥3) disease stages. One-way ANOVA was used to detect the correlation between disease severity and blood lipid levels by comparing the level of blood lipids of patients with different severity levels of disease. Moreover, to test the relationships between thyroid function and levels of blood lipids, correlation analysis was conducted between FT4 and triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein, and the ratio of high-density lipoprotein to total cholesterol. All analyses were conducted using GraphPad Prism 9.1.2, and significance was set as $P<0.05$.

Mendelian Randomization Mendelian randomization (MR) analysis was conducted using R language. The assumptions included in this study were as follows: hyperthyroidism had a direct regularity effect on the level of blood lipid, and causal effect existed between them. In this process, there were no confounders and horizontal pleiotropy existed. GWAS summary dataset was downloaded from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/), of which the GWAS ID included ukb-b-20289, ieu-b-111, met-d-Total_C, ebi-a-GCST008035, ebi-a-GCST90002412. Hyperthyroidism was set as the exposure and the blood lipid level was set as the outcome. After setting $P<5e^{-8}$, IVs were extracted, and another parameter was set as the default parameter in TwoSampleMR. package. To test whether weak instrumental variable bias existed, F statistics were calculated using the following formula: $F=R^2(n-k-1)/k(1-R^2)$; where R^2 was the exposure variance explained by SNPs, n was the sample size and k was the number of IVs[18].

Five methods were used to conduct Mendelian randomization analysis: inverse-variance weighting (IVW), weighted median method, weighted mode method, MR-Egger, and simple mode weighted[19-22]. To conduct the sensitivity analysis, the heterogeneity analysis was used to evaluate the compatibility of instrumental variables through Cochran's Q statistics. If Q_pval<0.05, a random effect model was used to test the causal effect. MR-PRESSO was used to detect the existence and effect of horizontal pleiotropy. Leave-one-out analysis was conducted to identify whether the potential outliers existed through IVW. The threshold of significance was set as 0.05.

RESULTS

Demographic Characteristics Through searching the case record platform and controlling data quality, 2591 patients were included in this study, comprising 197 TAO and 2394 hyperthyroidism cases. The hyperthyroidism group comprised a greater number of female than male patients, whereas the TAO group comprised a greater number of males recorded than female patients. In both groups, the children and the elderly comprised only a small portion of the population. Information on lipid levels and thyroid function is provided in Table 1. Among the TAO group, 150 cases lacked eye symptom data; the remaining 47 TAO patients with complete eye symptom data were used to analyze the relationships between lipid levels and eye symptoms (Figure 1).

Patients with TAO Show Higher Levels of Blood Lipids Blood lipid levels were compared between groups, the results showed that the TAO group had higher levels of triglyceride, total cholesterol, low-density lipoprotein, and high-density lipoprotein; however, a lower ratio of high-density lipoprotein

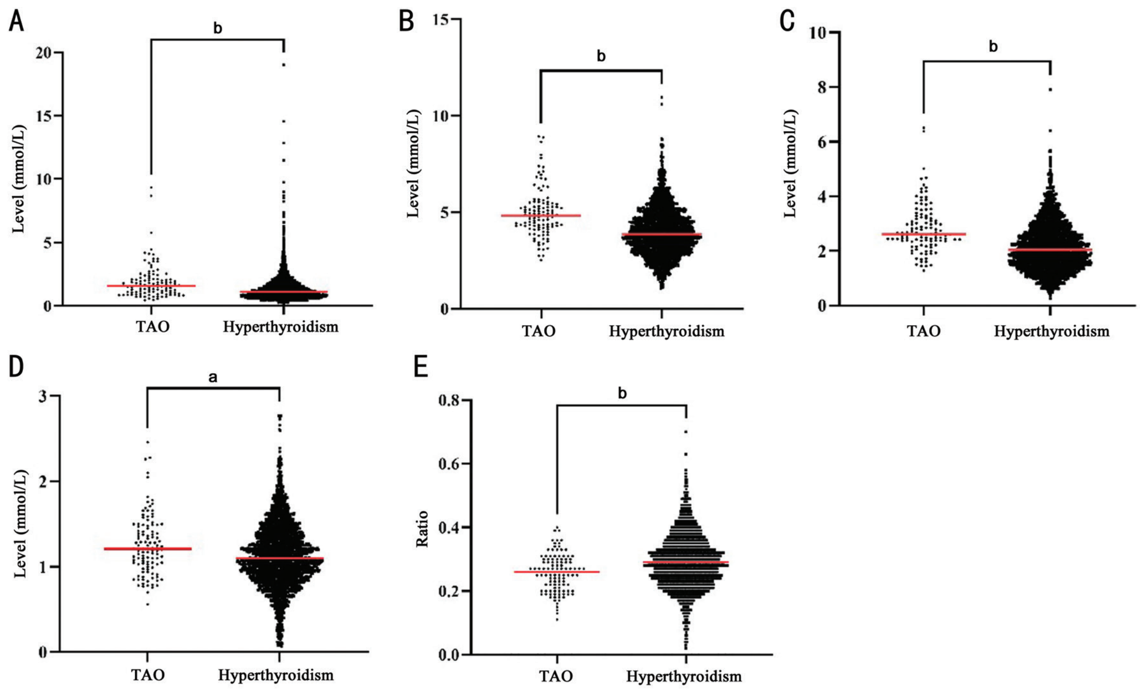

Figure 2 Comparison of blood lipid levels between TAO and hyperthyroidism groups A: Levels of triglyceride; B: Total cholesterol; C: Low-density lipoprotein; D: High-density lipoprotein; E: The high density lipoprotein to total cholesterol ratio. TAO: Thyroid-associated ophthalmopathy. [a]$P<0.001$; [b]$P<0.0001$.

to total cholesterol (Figure 2). In addition, more patients in the TAO group had pathological levels of triglyceride (44.64% *vs* 24.39%), total cholesterol (15.18% *vs* 4.76%), and low-density lipoprotein (8.70% *vs* 2.07%) compared to the hyperthyroidism group. Conversely, fewer patients in the TAO group had pathological levels of high-density lipoprotein (67.86% *vs* 77.81%) and the ratio of high-density lipoprotein to total cholesterol (4.46% *vs* 7.52%).

Blood Lipid Levels are Related to Ocular Symptoms To further explore the relationships between blood lipid levels and eye symptoms, data from 47 TAO patients (94 eyes) were analyzed. Three indicators of TAO—CAS, severity, and degree of exophthalmos—were assessed for their associations with triglyceride, total cholesterol, low-density lipoprotein, high-density lipoprotein, and the ratio of high-density lipoprotein to total cholesterol. The results showed that the degree of exophthalmos was positively associated with triglyceride levels, but negatively associated with high-density lipoprotein and low-density lipoprotein (Figure 3A-3C). No significant relationships were found between the degree of exophthalmos and total cholesterol or the ratio of high-density lipoprotein to total cholesterol (results not shown).

According to the severity classification from EUGOGO, TAO patients with different severity levels had different lipid profiles, with mild TAO patients showing higher levels of low-density lipoprotein (Figure 3D). The relationships between CAS and lipid levels were also examined; however, no significant associations were observed. To exclude the effect of edema on the analysis, 35 case records with CAS≥3 were excluded, and 12 case records (24 eyes) with CAS<3 were retained. In this subset, the degree of exophthalmos remained positively associated with triglyceride levels and negatively associated with both high-density lipoprotein and the ratio of high-density lipoprotein to total cholesterol, as shown in scatter plots (Figure 3E-3G).

Table 1 The demographic characteristics

Characteristics	TAO (*n*=197)	hyperthyroidism (*n*=2394)
Gender		
Male	101	706
Female	96	1688
Age, y		
<18	1	35
18–60	174	1807
>60	22	552
Thyroid function		
FT3 (pmol/L)	5.56±3.24	7.67±8.29
FT4 (pmol/L)	18.46±9.33	21.16±21.98
TSH (μIU/mL)	3.14±8.99	1.51±6.82
Tg (ng/mL)	70.86±114.81	65.84±119.12
TRAb (IU/L)	8.38±9.99	7.96±10.71
TPOAb (IU/mL)	165.84±1058.19	207.65±262.41
TgAb (IU/mL)	278.70±809.28	438.34±904.71

TAO: Thyroid-associated ophthalmopathy; FT3: Free triiodothyronine; FT4: Free thyroxine; TSH: Thyroid stimulating hormone; Tg: THYROGLOBULIN; TRAb: Antibodies to TSH receptor (TSHR); TPOAb: Antibodies to thrombopoietin (TPO); TgAb: Antibodies to Tg.

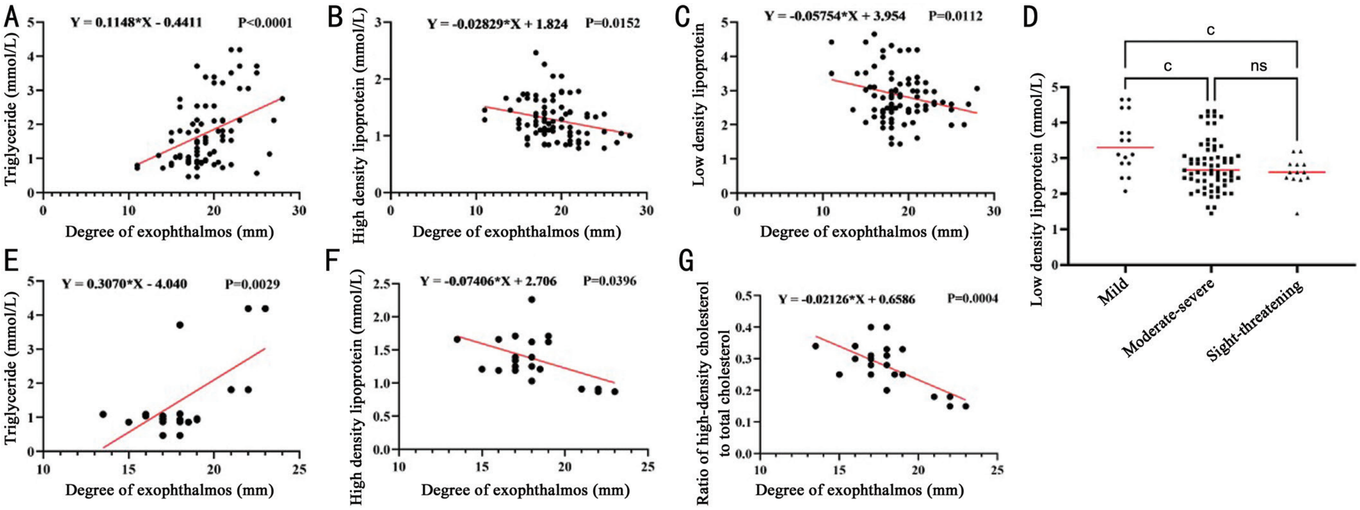

Figure 3 Relationships between eye symptoms and blood lipid levels The relationship between the degree of exophthalmos and lipid levels (A-C), the association between these verity and low-density lipoprotein (D), and in the subgroup analysis of inactive TAO patients (CAS<3), the relationship between TAO exophthalmometry and lipid levels (E-G). ^{c}P<0.01.

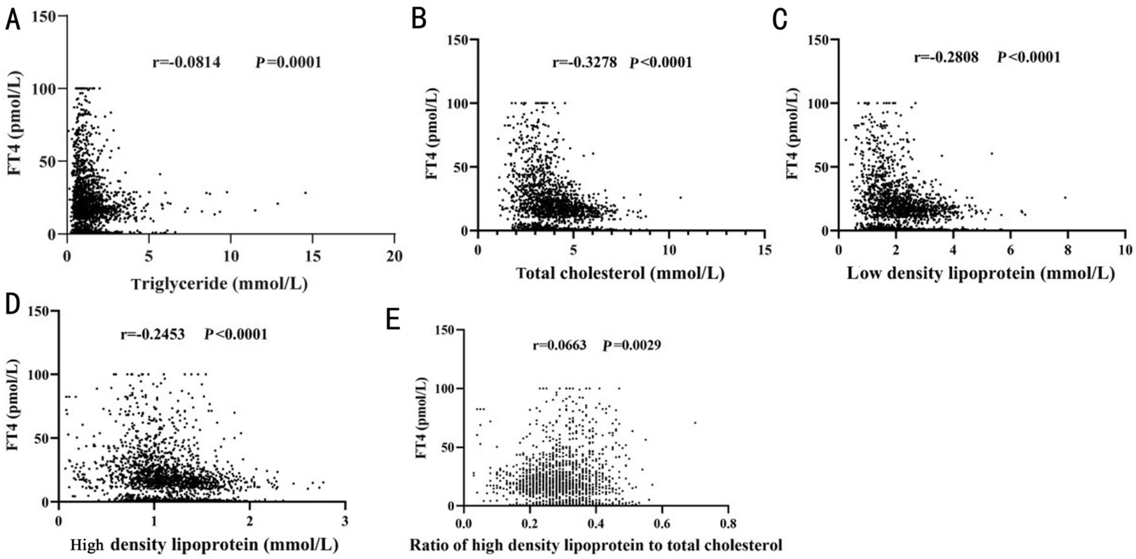

Figure 4 Relationships between FT4 and blood lipid levels A: Levels of triglyceride; B: Total cholesterol; C: Low-density lipoprotein; D: High-density lipoprotein; E: The high density lipoprotein to total cholesterol ratio. FT4: Free thyroxine.

Thyroid Function and Blood Lipid Levels are Negatively Correlated As FT4As is a key indicator of thyroid function, the relationships between FT4 and the level of blood lipids were analyzed. The results showed that triglyceride, total cholesterol, low-density lipoprotein, and high-density lipoprotein levels were all negatively correlated with FT4 (Figure 4A-4C). Additionally, the ratio of high-density lipoprotein to total cholesterol was also negatively related to FT4 levels (Figure 4D-4E).

Thyroid Function and Blood Lipid Levels Show Causal Effects In MR analysis, a total of 13 IVs were extracted, and the F-statistic was above 10, minimizing the risk of weak instrument bias. Using five MR methods, FT4 was shown to have a causal effect on triglyceride, total cholesterol, and low-density lipoprotein; however, not on high-density lipoprotein. After correcting for horizontal pleiotropy using MR-PRESSO, triglyceride and total cholesterol were confirmed to be negatively regulated by thyroid function (Figure 5A and 5D). The effects of individual SNPs on outcomes are shown in Figure 5B and 5E. The OR values for triglyceride and total cholesterol were 0.035 and 0.085, respectively, using the IVW method. Heterogeneity analysis revealed that IVs in the triglyceride dataset exhibited heterogeneity, while those in the total cholesterol dataset did not. The random effects model indicated the presence of a causal effect via IVW. Leave-one-out analysis showed no outliers in either the triglyceride or total cholesterol datasets (Figure 5C and 5F).

DISCUSSION

Although controlling thyroid function is considered an important part of the therapeutic strategy for patients with TAO, cannot be fully cured using anti-thyroid therapy alone, as other factors influence the pathogenesis of TAO. In this

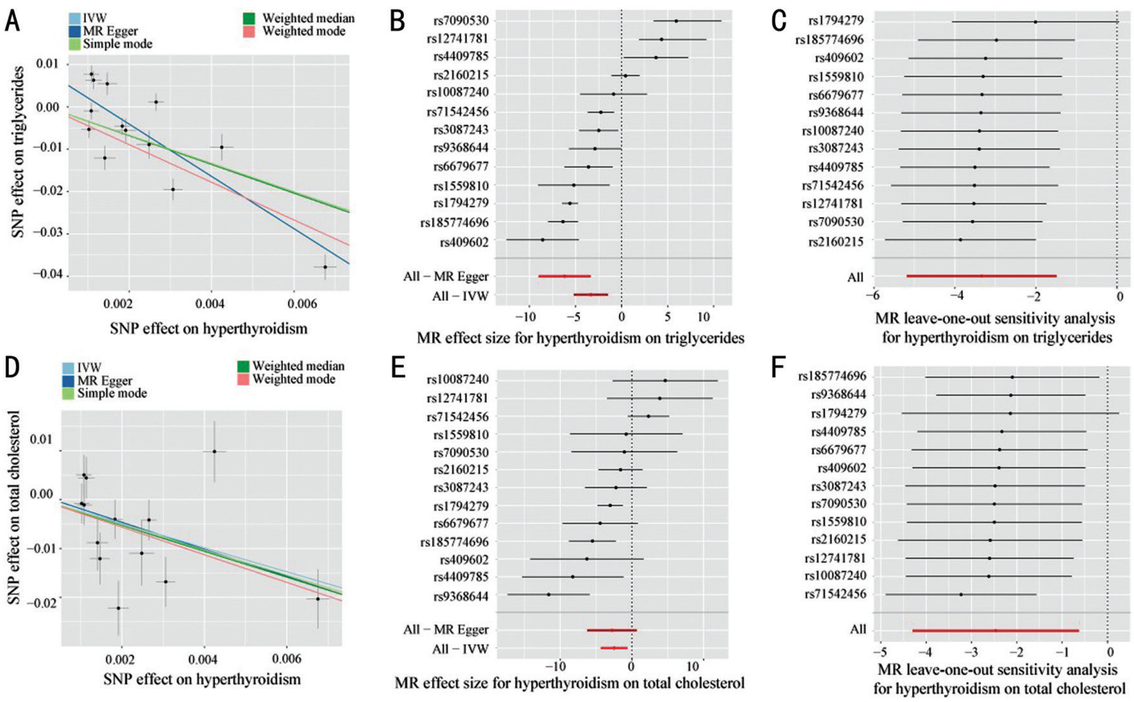

Figure 5 Causal effect between thyroid function and blood lipid levels Mendelian randomization methods demonstrate the negative effect of hyperthyroidism on triglyceride (A) and total cholesterol (D); effect of single SNPs on triglyceride (B) and total cholesterol (E); leave-one-out sensitivity analysis for triglyceride (C) and total cholesterol (F). MR: Mendelian randomization. SNPs: Single nucleotide polymorphisms; IVW: Inverse-variance weighting.

study, blood lipid levels were compared between the TAO and hyperthyroidism groups. A significant difference was observed: higher levels of triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein, and a lower ratio of high-density lipoprotein to total cholesterol were found in patients with TAO. These results suggest that lipids may play a role in facilitating the development of TAO. Therefore, the relationships between eye symptoms and lipid levels were further examined. The results showed that the degree of exophthalmos was positively related to triglyceride levels and negatively related to high-density lipoprotein. These findings indicate that lipid levels are associated with TAO development, as reflected in the ocular symptoms.

In this study, low-density lipoprotein levels were found to be negatively related to the degree of exophthalmos, and a negative relationship was also observed between TAO severity and low-density lipoprotein levels. However, no significant relationships were found between CAS and blood lipid levels. One possible explanation for this finding is that blood lipids may have less influence on the pathogenesis of edema. Since both the degree of exophthalmos and TAO severity are indicators of disease progression and reflect various pathogenic processes in orbital tissues, the effects of lipids might be confounded by factors such as edema. Edema often accompanies inflammation, which is the main pathological process during the active stage of TAO[23]. The lack of significant relationships between lipid levels and CAS further supports the idea that lipid levels may not be directly related to edema or inflammation. After excluding cases with CAS scores >3, analysis showed that exophthalmos was positively associated with triglyceride levels and negatively associated with high-density lipoprotein and the ratio of high-density lipoprotein to total cholesterol. This supports the notion that blood lipids may not be involved in edema.

This study also found negative correlations between FT4 levels and levels of triglycerides, total cholesterol, low-density lipoprotein, and high-density lipoprotein. While abnormal FT4 levels are considered a risk factor in TAO, the effects of FT4 on lipid metabolism remain unclear[24]. According to Lee, FT4 levels were positively correlated with triglycerides[25]. However, a single-center retrospective study found that low FT4 was associated with elevated blood lipid levels[26]. These contradictory findings highlight the complex regulatory interactions between thyroid function and lipid metabolism.

Previous studies have suggested that elevated serum cholesterol is a risk factor, and that low-density lipoprotein is positively associated with TAO[27]. Lanzolla found that serum cholesterol levels were higher in TAO patients compared to those without GO, whereas triglyceride and high-density lipoprotein cholesterol showed no significant associations with TAO[28]. Abnormal serum lipid levels mainly affect the process of adipogenesis. When fibroblasts are treated with PPAR-γ, orbital fibroblasts differentiate into adipocytes, during which lipids accumulate in these cells. Recent studies also suggest that serum lipids influence the immune system, increasing serum triglycerides and altering the phenotype of Th1 cells[29].

MR is used to detect causal effects between exposures and outcomes, and has been widely adopted as an independent analytical approach[30]. In this study, MR analysis demonstrated that hyperthyroidism negatively regulates triglyceride and total cholesterol levels. This finding not only aligns with the observed negative relationships in clinical data between TAO and hyperthyroidism but also confirms a regulatory relationship. It explains why, even when anti-thyroid drugs such as methimazole are used to control thyroid function in TAO patients, the disease may still progress—because elevated blood lipid levels, which are positively associated with exophthalmos severity, remain unaddressed.

There are several limitations in this study. A total of 2594 cases were included in the analysis[31]. However, after subgrouping, the sample sizes for specific comparisons—especially those examining relationships between blood lipid levels and eye symptoms—were still limited. Additionally, since the cases were obtained from a platform, detailed medical histories were unavailable, which may have influenced the results. For example, treatment regimens for TAO and hyperthyroidism differ: high-dose systemic glucocorticoids are first-line therapy for moderate-to-severe, active TAO, but not for hyperthyroidism. Moreover, as data were collected from a single research center, hospitalization bias may exist. Future studies should include data from multiple centers to improve generalizability.

This study suggests that elevated serum triglycerides independently contribute to the severity of TAO, particularly by exacerbating eyeball protrusion. By combining clinical cohort analysis with MR, we identified a bidirectional relationship between thyroid function and lipid metabolism: although hyperthyroidism is associated with decreased triglyceride and total cholesterol levels, paradoxically, TAO patients show significantly elevated lipid levels compared to non-TAO patients. This discrepancy suggests that lipid dysregulation in TAO may occur via thyroid-independent pathways, potentially involving orbital fibroblast adipogenesis or immune-metabolic interactions.

These findings support a dual-treatment strategy for managing TAO: 1) strict control of thyroid function to address systemic metabolic disturbances, 2) targeted lipid-lowering interventions (*e.g.*, beta-blockers or dietary modifications) to reduce local orbital lipid accumulation. Future multicenter studies are necessary to validate the effectiveness of combined thyroid and lipid regulation in preventing the progression of TAO, particularly in patients with refractory exophthalmos.

ACKNOWLEDGEMENTS

Availability of Data and Materials: The data in the study could be obtained by connecting the authors.

Foundations: Supported by the National Natural Science Foundation of China (No.82371104); the Natural Science Foundation of Hunan Province (No.2023JJ30851).

Conflicts of Interest: Cao JM, None; **Chen HY,** None; **Zhang F,** None; **Xiong W,** None.

REFERENCES

1 Bartalena L, Gallo D, Tanda ML, *et al*. Thyroid eye disease: epidemiology, natural history, and risk factors. *Ophthalmic Plast Reconstr Surg* 2023;39(6S).

2 Cao JM, Su YH, Chen ZK, *et al*. The risk factors for Graves' ophthalmopathy. *Graefes Arch Clin Exp Ophthalmol* 2022;260(4):1043-1054.

3 Cui XJ, Wang FT, Liu C. A review of TSHR- and IGF-1R-related pathogenesis and treatment of Graves' orbitopathy. *Front Immunol* 2023;14:1062045.

4 Toro-Tobon D, Rachmasari KN, Bradley EA, *et al*. Medical therapy in patients with moderate to severe, steroid-resistant, thyroid eye disease. *Thyroid* 2023;33(10):1237-1244.

5 Shen FY, Liu J, Fang LF, *et al*. Development and application of animal models to study thyroid-associated ophthalmopathy. *Exp Eye Res* 2023;230:109436.

6 Zhao SD, Shi SS, Yang WC, *et al*. RhoA with associated TRAb or FT3 in the diagnosis and prediction of Graves' ophthalmopathy. *Dis Markers* 2022;2022:8323946.

7 Bartalena L, Kahaly GJ, Baldeschi L, *et al*. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol* 2021;185(4).

8 Bartalena L, Piantanida E, Gallo D, *et al*. Management of Graves' hyperthyroidism: present and future. *Expert Rev Endocrinol Metab* 2022;17(2):153-166.

9 Yu CY, Ford RL, Wester ST, *et al*. Update on thyroid eye disease: Regional variations in prevalence, diagnosis, and management. *Indian J Ophthalmol* 2022;70(7):2335-2345.

10 Smith TJ. Controversies surrounding IGF-I receptor involvement in thyroid-associated ophthalmopathy. *Thyroid* 2025;35(3):232-244.

11 Byeon HJ, Choi SH, Kikkawa DO, *et al*. Therapeutic role of histone deacetylase inhibition in an *in vitro* model of Graves' orbitopathy. *Mol Med Rep* 2024;30(6):218.

12 Lin LC, Liu ZY, Mao S, *et al*. Epigenetic regulation of extracellular matrix mechanotransduction in cardiac fibrosis. *Biochem Pharmacol* 2025;242(Pt 2):117325.

13 Stasiak M, Zawadzka-Starczewska K, Tymoniuk B, *et al*. Associations between lipid profiles and Graves' orbitopathy can be HLA-dependent. *Genes* 2023;14(6):1209.

14 Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: a review. *Res Synth Methods* 2019;10(4):486-496.

15 Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. *JAMA* 2017;318(19):1925.

16 Ference BA, Holmes MV, Smith GD. Using Mendelian randomization to improve the design of randomized trials. *Cold Spring Harb Perspect Med* 2021;11(7):a040980.

17 Boehm FJ, Zhou X. Statistical methods for Mendelian randomization in genome-wide association studies: a review. *Comput Struct Biotechnol J* 2022;20:2338-2351.

18 Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *Int J Epidemiol* 2011;40(3):740-752.

19 Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol* 2013;37(7):658-665.

20 Bowden J, Davey Smith G, Haycock PC, *et al*. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted Median estimator. *Genet Epidemiol* 2016;40(4):304-314.

21 Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization *via* the zero modal pleiotropy assumption. *Int J Epidemiol* 2017;46(6):1985-1998.

22 Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015;44(2):512-525.

23 Łacheta D, Miśkiewicz P, Głuszko A, *et al*. Immunological aspects of Graves' ophthalmopathy. *Biomed Res Int* 2019;2019:7453260.

24 Tarboush F, Alsultan M, Alourfi Z. The correlation of lipid profile with subclinical and overt hypothyroidism: a cross-sectional study from Syria. *Medicine* 2023;102(37):e34959.

25 Lee YW, Yang TT, Lin YY, *et al*. Elevated free thyroxine levels might alter the effect of the lipid profile on insulin resistance in type 2 diabetes mellitus. *Diagnostics* (*Basel*) 2023;13(16):2656.

26 Xu YY, Zhao YQ, Xu XQ, *et al*. Serum lipid profile in relation to free thyroxine and the effect of levothyroxine treatment on lipids in patients with isolated hypothyroxinemia during pregnancy: a single-center retrospective study. *Lipids Health Dis* 2022;21(1):142.

27 Ye XZ, Huang SS, Liu J, *et al*. High serum cholesterol: a novel risk factor for thyroid associated ophthalmopathy? *Zhonghua Nei Ke Za Zhi* 2019;58(11):823-825.

28 Lanzolla G, Sabini E, Profilo MA, *et al*. Relationship between serum cholesterol and Graves' orbitopathy (GO): a confirmatory study. *J Endocrinol Invest* 2018;41(12):1417-1423.

29 Fang SJ, Zhang S, Huang YZ, *et al*. Evidence for associations between Th1/Th17 "hybrid" phenotype and altered lipometabolism in very severe Graves orbitopathy. *J Clin Endocrinol Metab* 2020;105(6):1851-1867.

30 Lawlor DA, Harbord RM, Sterne JA, *et al*. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med* 2008;27(8):1133-1163.

31 Liu K, Fu Y, Li T, *et al*. Clinical efficacy of thyroid-stimulating immunoglobulin detection for diagnosing Graves' disease and predictors of responsiveness to methimazole. *Clin Biochem* 2021;97:34-40.