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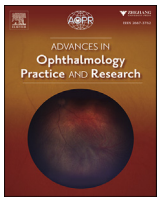

Full Length Article

Causal association between non-thyroidal autoimmune diseases and Graves' ophthalmopathy: A mendelian randomization study

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ABSTRACT

Purpose: This Mendelian randomization (MR) analysis study aimed to investigate the genetic causal relationship between non-thyroidal autoimmune diseases (ADs) and Graves' ophthalmopathy (GO).

Materials: Single nucleotide polymorphisms (SNPs) associated with inflammatory bowel disease (IBD), multiple sclerosis (MS), psoriasis vulgaris (PV), type 1 diabetes (T1D), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) were obtained from the IEU Open genome-wide association studies (GWAS) database, GWAS data for GO were obtained from the FinnGen database. Bidirectional MR analysis was conducted using inverse variance weighted (IVW) method, weighted median (WM) method and MR-Egger test. Cochran's Q statistic was used to assess the heterogeneity between SNP estimates. MR-Egger regression was used to evaluate horizontal pleiotropy and MR pleiotropy residual sum and outlier (MR-PRESSO) test was used to detect the outliers.

Results: For non-thyroidal ADs, the forward MR results using the IVM method showed that T1D (OR = 1.259, 95% CI 1.026–1.5465; $P = 0.028$) and SLE (OR = 1.807, 95%CI 1.229–2.655; $P = 0.003$) were correlated with the risk of GO at the genetic level, while there was no evidence showing that IBD, MS, PV and RA were correlated with GO. In the reverse MR study, there was a significant increase in the risk of developing T1D in GO (OR = 1.135, 95%CI 1.018–1.265; $P = 0.022$), but pleiotropy and heterogeneity existed.

Conclusions: In the European population, there is strong genetic evidence that patients with T1D and SLE have a higher risk of developing GO, whereas the effect of GO on ADs is unclear.

1. Introduction

Graves' ophthalmopathy (GO), also known as thyroid-associated ophthalmopathy and thyroid eye disease, is an autoimmune inflammatory disease related to thyroid diseases such as Graves' disease (GD), causing hyperthyroidism, and Hashimoto's disease, causing hypothyroidism. A small proportion of patients can be euthyroid (approximately 5%).[1] It is an organ-specific disorder caused by immunological imbalance of the thyroid gland. The antibodies produced by T and B cells, mainly thyroid receptor antibodies and insulin like growth factor antibodies attack orbital soft tissue such as orbital fat and extraocular muscle.[2] The symptoms of GO mainly include eyelid retraction, redness of the eye, and exophthalmos in severe cases, there might be optic nerve damage caused by the impression of soft tissue. GO changes the appearance and visual function of patients, which causes mental burden and affects their quality of life. Although it is believed to be associated with abnormal immune response, the pathogenesis of GO has not yet been fully elucidated.

Expect for GO, there are also other autoimmune diseases (ADs) such as systemic lupus erythematosus (SLE), type 1 diabetes (T1D), and inflammatory bowel disease (IBD), which cause lifelong recurrent symptoms and bring socio-economic burden for both the patients and society. Owing to shared genetic or environmental factors, ADs tend to cluster among individuals. It has been reported that non-thyroidal ADs may be related to some thyroid disease such as thyroditis.[3–5] However, most of the studies were observational cohort studies that only reported the prevalence and the underlying genetic association between those non-thyroidal autoimmune diseases remains unclear.

With the advantage of minimizing residual confounding factors, Mendelian randomization (MR) has been used to assess the potential causal association between exposure factors and outcomes.[6] This approach uses independent single-nucleotide polymorphisms (SNPs) extracted from genome-wide association studies (GWASs) to evaluate the

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impact of exposure. Since genetic makeup is determined randomly at an early stage of life, MR can eliminate acquired factors such as lifestyle and environment. Several studies have focused on the causal relationships between autoimmune diseases and GD,[7–9] suggesting potential links between non-thyroidal autoimmune diseases and GO. In this study, we aimed to reveal the possible relationship between other immune-related diseases and GO, and to explore more on the complex causes of GO.

2. Materials and methods

2.1. MR study design

We used the public GWAS summary data for the analysis. IBD, multiple sclerosis (MS), psoriasis vulgaris (PV), rheumatoid arthritis (RA), SLE, and T1D were included in this study based on the previously published studies. Bidirectional MR analysis was conducted to assess the causal association between these ADs and GO. Fig. 1 shows a schematic flow chart of the study. The MR analysis meets three main assumptions: (1) correlation assumption: the included instrumental variables (IVs) must be closely related to exposure (non-thyroidal autoimmune diseases); (2) independence assumption: IVs are independent of the confounding factors of non-thyroidal autoimmune diseases and GO; and (3) exclusion assumption: IVs only affect GO via non-thyroidal autoimmune diseases. Only GWASs obtained from the European population were used to minimize the bias caused by ethnic variety.

2.2. Data sources of non-thyroidal ADs and GO

The GWAS data for 6 non-thyroidal ADs were procured from the Integrative Epidemiology Unit (IEU) Open GWAS database (https://gwas.mrcieu.ac.uk/). The summary data for GO were obtained from the FinnGen database (www.finngen.fi/en/, version: R9), with the endpoint name "E4_GRAVES_OPHT_STRICT". Details of the data sources were shown in Table 1.

2.3. Genetic instrument selection

The SNPs were selected based on the MR assumptions mentioned above: (1) each selected SNP was associated with non-thyroidal ADs at a genome-wide significance threshold of $P < 5 \times 10^{-8}$, and if the number of included SNPs was insufficient for subsequent MR analysis, the threshold value was set to $P < 5 \times 10^{-6}$; (2) the linkage disequilibrium analysis clumped the SNPs further ($r^2 < 0.001$ and clumping distance = 10000 kb); (3) The *F*-statistics were used to assess the weak instrumental variable bias to ensure that there was a robust correlation between IVs and exposure ($F > 10$ deemed to be valid).

2.4. Statistical analysis

Statistical analysis was performed using the R software (version 4.3.1). The "Two SampleMR" package (version 0.6.0) was used for the MR analysis. Three MR methods were used to evaluate the causal relationship between non-thyroidal ADs and GO: the variance weighted (IVW) method,[10] weighted median (WM)[11] method and MR-Egger test.[12] The IVM method was selected as the primary approach due to its ability to provide precise effect estimates under the assumption of no horizontal pleiotropy, as it calculates the Wald ratio for each SNP, ensuring optimal statistical power in this context. To enhance robustness, we supplemented IVM with the WM and MR-Egger methods. The WM approach offers greater resilience in causal effect estimation, performing reliably even if up to 50% of the IVs are invalid. Meanwhile, MR-Egger provides an intercept test to detect horizontal pleiotropy and remains applicable even when all IVs are invalid. Odds ratios (OR) and 95% confidence intervals (CI) were used to determine effect size.

Cochran's Q statistic was used to assess the heterogeneity between SNP estimates. A random-effects model was used if heterogeneity was present ($P < 0.05$). Otherwise, the fixed-effects model was used. We used the MR-Egger regression to evaluate horizontal pleiotropy. MR pleiotropy residual sum and outlier (MR-PRESSO) test was used to confirm the

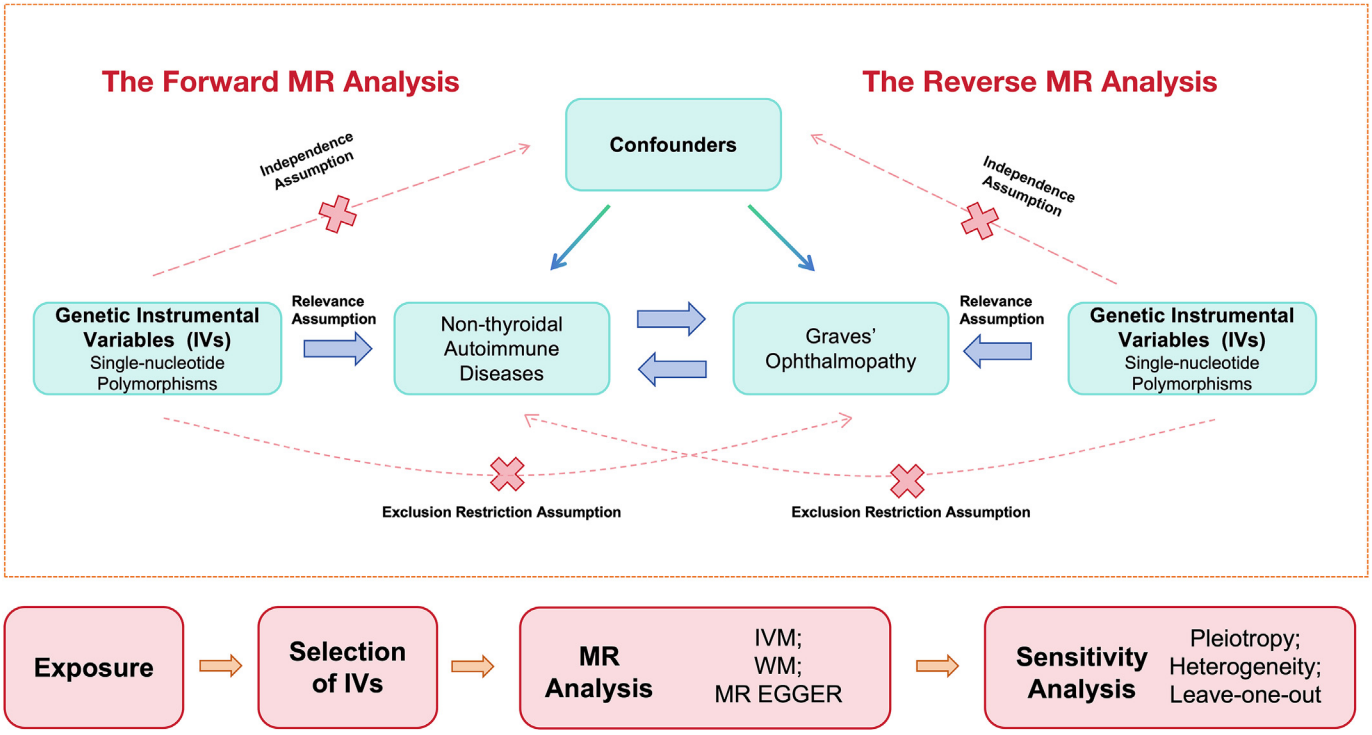

Fig. 1. Overview of the Mendelian randomization (MR) study and three assumptions it meets.

Table 1
Sources and characteristics of diseases.

Exposure	GWAS-ID or FinnGen endpoint name	Sample size	Number of SNPs	Year
Inflammatory bowel disease	ieu-a-292	75000	14378	2012
Multiple sclerosis	ieu-a-1025	38589	156632	2013
Psoriasis vulgaris	ebi-a-GCST90018907	483174	24191364	2021
Type 1 diabetes	ebi-a-GCST90018925	457695	24182422	2021
Systemic lupus erythematosus	ebi-a-GCST90018917	482911	24198877	2021
Rheumatoid arthritis	ebi-a-GCST90018910	417256	24175266	2021
Graves' ophthalmopathy	E4_GRAVES_OPHT_STRICT	377277	20170236	2023

results and detect the outliers. After removing the outliers, we re-conducted the MR analysis. Finally, leave-one-out analysis was employed to assess the influence of individual SNP.

Since all data were obtained from publicly shared databases, no additional ethical approval was required for this study.

3. Results

3.1. The forward MR analyses

Under a threshold of $P < 5 \times 10^{-8}$, 144 IVs for IBD, 49 for MS, 15 for PV, 25 for RA, 5 for SLE and 18 for T1D were strongly correlated with these exposures. All the F-statistics of the IVs were larger than 10, ranging from 45.52 to 179.09, indicating that there was no weak instrumental bias, and the SNPs had adequate validity. We employed the MR-PRESSO method and found outlier SNPs, including rs11889341, rs35139284, rs6679677, rs7731626 for RA and rs13204736, rs6679677, rs9273363 for T1D. A subsequent MR analysis was done after removing these outliers. We then re-ran the MR-PRESSO test. Global p values for IBD, MS, PV, RA, SLE and T1D were 0.013, <0.001, 0.142, 0.069, 0.132, and 0.336, respectively.

The IVM method showed that in European populations, there was a significant increase in the risk of developing GO in SLE (OR = 1.807, 95% CI 1.229–2.655; $P = 0.003$) and T1D (OR = 1.259, 95%CI 1.026–1.5465; $P = 0.028$) patients. There is insufficient evidence to show that the other four ADs are associated with GO. (Fig. 2). The SNPs included in the MR analysis are listed in Supplementary Table 1.

In the MR-Egger regression, Except for RA ($P = 0.016$), all other IVs had p values larger than 0.05, indicating that there was no significant horizontal pleiotropy for the five diseases and GO. Cochrane's Q test showed that there was no heterogeneity between PV and GO ($P = 0.088$), RA and GO ($P = 0.089$), or T1D and GO ($P = 0.377$), whereas for the other three ADs with GO, heterogeneity existed. The random effects IVM was used for the MR analysis (Table 2). The leave-one-out analysis of the IVs is shown in Fig. 3. Visualized scatter plots for the three MR methods on the IVs are shown in Fig. 4.

3.2. The reverse MR analyses

Due to the removal of linkage disequilibrium, only one SNP for the exposure factor GO met the criteria of $r^2 < 0.001$ and a distance of 10000 kb. Therefore, we adjusted the threshold for strong association from $P < 5 \times 10^{-8}$ to $P < 5 \times 10^{-6}$ and proceeded with the subsequent analysis. F-statistics was 29.56 for GO as the exposure. After removing outliers detected by MR-PRESSO test (rs1794283, rs6931627, rs72880049 for PV, rs72880049 for RA, rs1794283 for SLE and rs142033332, rs1794283, rs28377838, rs296492, rs68090711, rs7321862 for T1D), the MR analysis was re-conducted. 8 IVs for PV, 10 IVs for RA, 10 IVs for SLE and 5 IVs for T1D were included in the MR analysis (Supplementary Table 2). The IVM method showed that in European populations, there was a significant increase in the risk of developing T1D in GO (OR = 1.135, 95%CI 1.018–1.265; $P = 0.022$). There is insufficient evidence to show that other ADs are associated with GO. (Fig. 5). However, the

Table 2
The results of sensitivity analysis.

Exposure	Heterogeneity P	MR-Egger intercept	Pleiotropy P
Inflammatory bowel disease	0.009	−0.014	0.452
Multiple sclerosis	0.001	0.015	0.586
Psoriasis vulgaris	0.088	0.073	0.063
Type 1 diabetes	0.377	0.060	0.149
Systemic lupus erythematosus	<0.001	0.073	0.900
Rheumatoid arthritis	0.089	0.119	0.016

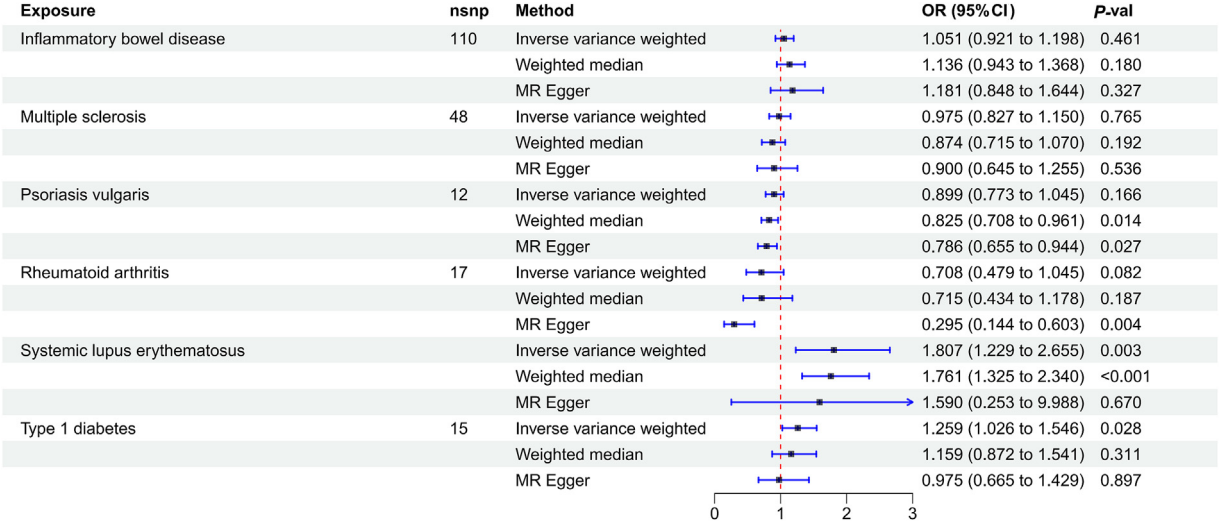

Fig. 2. Mendelian randomization estimates from instrument variants for on Graves' ophthalmopathy risk of non-thyroidal autoimmune diseases.

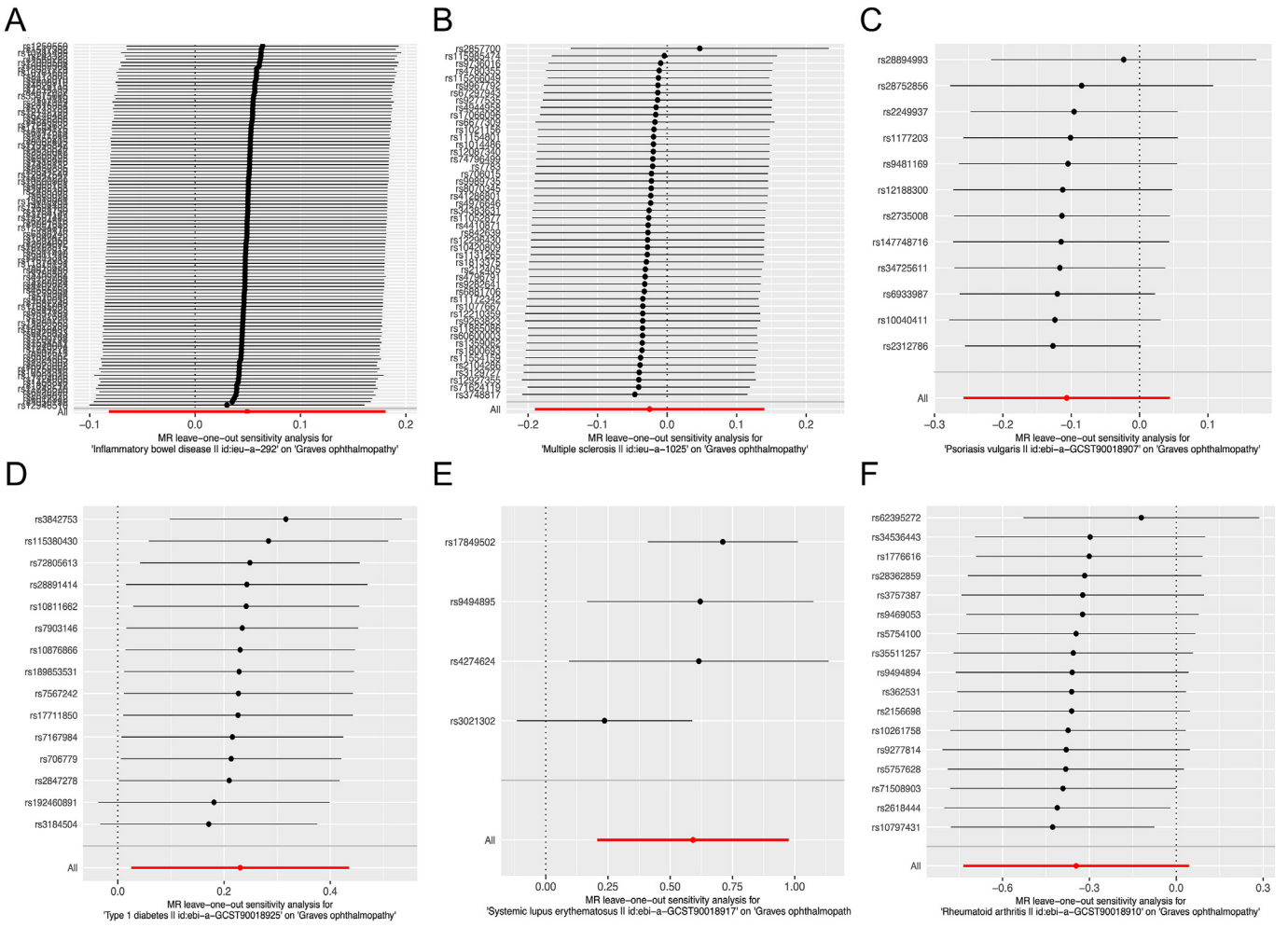

Fig. 3. Leave-one-out plots showing the causal association between non-thyroidal autoimmune diseases and Graves' ophthalmopathy (GO). (A) Inflammatory bowel disease on GO; (B) Multiple sclerosis on GO; (C) Psoriasis vulgaris on GO; (D) Type 1 diabetes on GO; (E) Systemic lupus erythematosus on GO; (F) Rheumatoid arthritis on GO.

Cochrane's Q test showed that there was heterogeneity between T1D and GO ($P = 0.010$) and global p of new MR-PRESSO test for T1D was 0.043, suggesting that the result was not robust.

4. Discussion

In this study, we conducted a bidirectional MR analysis of the association between non-thyroidal ADs and GO in the European population. MR investigation suggested that SLE and T1D were significantly correlated with GO. This study helps explore the underlying mechanisms of GO.

Although the pathogenesis of T1D is not fully understood, it is believed to be a complicated process involving genetics, immune system, and environment. In T1D, the pancreatic β cells are attacked due to T-cell regulated immune response.[13] In the preclinical stage of T1D, autoantibodies are produced against the secretion of insulin and C-peptide, and subsequently, T1D can develop and lead to clinical manifestations. A pediatric cohort study in Taiwan, China reported that approximately 26% of the study cohort was positive for thyroid autoantibodies and was dominated by females (59.9%).[14] The prevalence of autoimmune thyroid disease (AITD) was ranges from 5% to 23% in different studies.[14–17] Moreover, existing data have shown that about 30% of the T1D patients develop AITD after a few years of follow-up.[18–20] Although the pathogenesis of GD and T1D differs, it is believed that there are genetic links between them, which can be proven by epidemiological evidence (clustering in families).

SLE affects different organs and tissues, such as the skin, brain, and kidney and mainly affects women of childbearing age. It is believed to be influenced by deficiency of single or multiple genes, environment, and female hormones.[21] It has been reported that patients with SLE have a higher possibility of developing hypothyroidism or hyperthyroidism than normal control group. Thyroid peroxidase and thyroglobulin antibodies have also been detected in some patients with SLE.[22] In contrast, patients with AITD have a higher risk of developing SLE,[23] which further indicates a possible link between GO and SLE.

HLA alleles, especially HLA class II, are believed to contribute to the co-existence of autoimmune diseases. HLA class II molecules are produced in the endoplasmic reticulum and are recognized by the receptors on the surface of $CD4^+$ T cells. HLA II molecules present peptides to $CD4^+$ T cells and induce immune response. HLA antigens DQ2, cytotoxic T-lymphocyte- associated antigen (CTLA4), protein tyrosine phosphatase non-receptor type 22 (PTPN22), and so on were believed to be confer susceptibility to T1D, SLE and ATID.[20,24] PTPN22 is a strong susceptibility gene that is shared by ADs. Previous studies have found that it is strongly related to ADs with targeted tissues such as T1D, SLE and GD.[25] In addition, epigenetic mechanisms might also contribute to the etiology of the co-occurrence of the diseases.[26] The B-cell receptor repertoire has been found to show a distinct skewing for ADs, which may also explain the coexistence of the ADs.[27]

Although GO is one of the manifestations of GD, a large series report

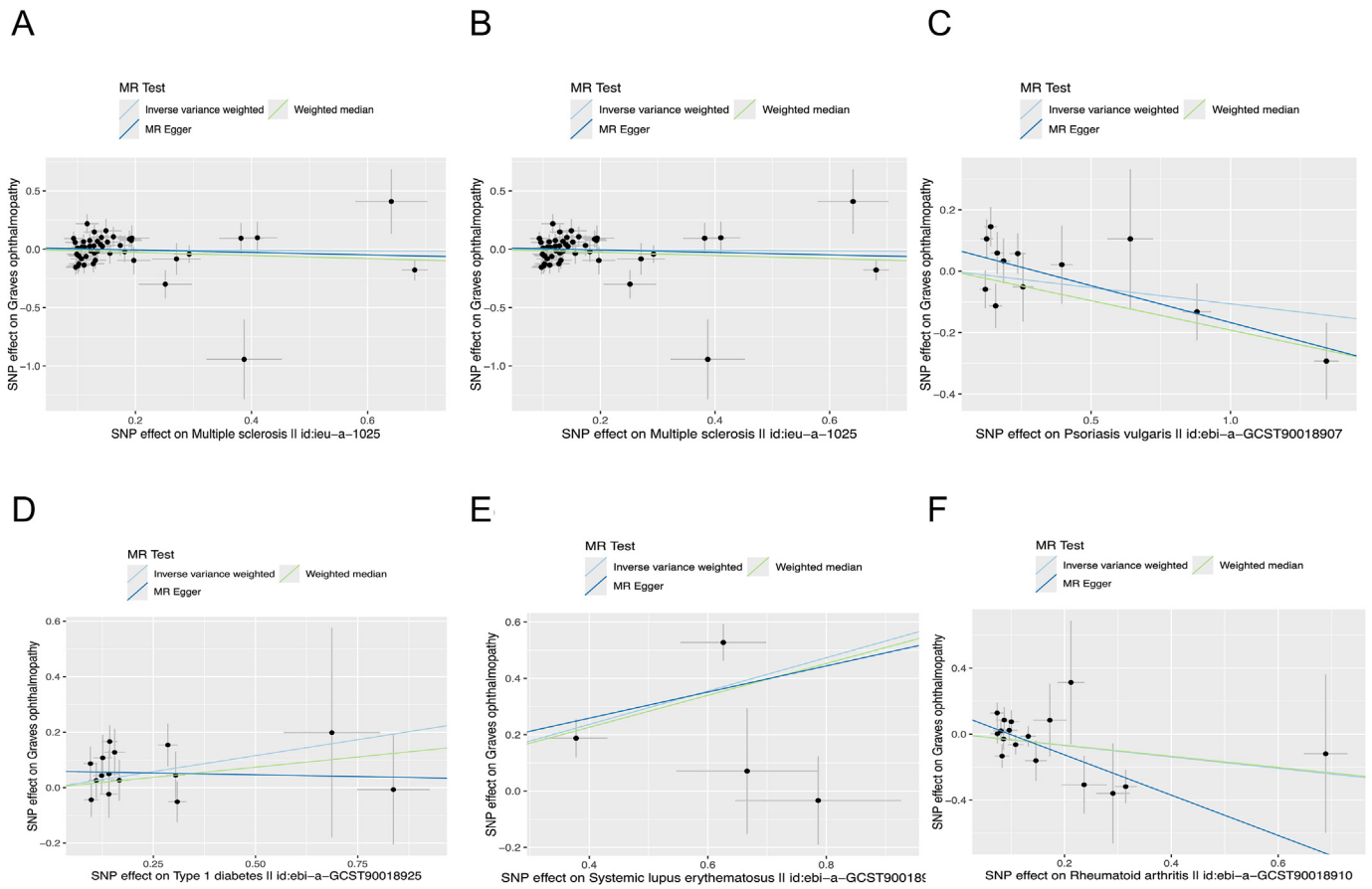

Fig. 4. Scatter plots showing the SNP effect of each non-thyroidal autoimmune disease on Graves' ophthalmopathy (GO). (A) Inflammatory bowel disease on GO; (B) Multiple sclerosis on GO; (C) Psoriasis vulgaris on GO; (D) Type 1 diabetes on GO; (E) Systemic lupus erythematosus on GO; (F) Rheumatoid arthritis on GO.

Outcome	nsnp	method	OR (95%CI)	*P*-val
Psoriasis vulgaris	8	Inverse variance weighted	0.975 (0.921 to 1.032)	0.376
		Weighted median	0.985 (0.914 to 1.061)	0.687
		MR Egger	1.006 (0.879 to 1.151)	0.933
Rheumatoid arthritis	10	Inverse variance weighted	0.993 (0.947 to 1.041)	0.778
		Weighted median	1.005 (0.959 to 1.053)	0.825
		MR Egger	0.965 (0.859 to 1.083)	0.558
Systemic lupus erythematosus	10	Inverse variance weighted	1.039 (0.911 to 1.184)	0.571
		Weighted median	0.978 (0.829 to 1.153)	0.789
		MR Egger	1.059 (0.714 to 1.571)	0.782
Type 1 diabetes	5	Inverse variance weighted	1.135 (1.018 to 1.265)	0.022
		Weighted median	1.040 (0.947 to 1.141)	0.416
		MR Egger	1.000 (0.787 to 1.270)	0.999

Fig. 5. The reverse mendelian randomization analysis: forest plots for the estimated causal effects between non-thyroidal autoimmune diseases and Graves' ophthalmopathy using different methods.

found that patients with GO have other ADs more frequently (18.9%) than GD patients (15.6%).[28] One possible explanation could be that patients who develop GO may have stronger immune response.

In our study, we also found that the link between GO and other AD, including IBD, MS, PV, and RA could not be established. MS was also proven to be unrelated to GD in another MR study, and our study further proved that for GO, the MR results were negative as well.[29] Although some studies have reported a correlation between GD and IBD and, RA on SNP level,[7,9] and some have reported coexisting GD and PV,[30] we did not find convincing evidence to prove that GO is linked to these diseases. GO and GD are not completely identical; some GO patients may have normal thyroid function or hypothyroidism without accompanying GD, and not all cases of GD involve orbital involvement. These findings indicate that GD patients with orbital involvement may have similar but different genetic backgrounds compared to those who do not develop eye disease.

Two-sample MR revealed that genetically, patients with GO may have higher risk of getting T1D, but the result was not robust because there existed heterogeneity and pleiotropy, indicating that causal relationship

between GO and non-thyroidal ADs might be unidirectional. Ferrari et al. reported opposite conclusion that compare to control group, patients with GD have higher risk of getting other ADs including T1D, SLE, RA, MS and PV, and the distribution of these ADs are similar in GO patients.[28] We believe that one possible reason for this discrepancy is the difference in sample size. Although Ferrari et al.'s study included 1069 healthy controls, the proportion of patients with autoimmune diseases was very low; for example, only one participant had T1D, and none had SLE, which may have influenced the results.

The main strength of this study is that we used the MR method to explore the causal relationship between GO and non-thyroidal autoimmune diseases. However, this study has some limitations. First, this study only focused on the European population. Some studies suggested that there might be a genetic link between ADs and GD in Asian group.[31–33] However, although a part of GO develops from GD, there is limited GWAS data available for GO, particularly for Asian populations, the results of our study should be validated for different ethnic groups in the future. Second, although we used GWAS data from the FinnGen database for GO and for other ADs, the IEU Open GWAS database was chosen, there was a possibility that there might be overlapping individuals in these databases.

5. Conclusions

In conclusion, we found that in the European population, there is strong genetic evidence that patients with T1D and SLE have a higher risk of developing GO. The relationship between GD and some ADs has been reported previously, but we found that although GO, usually occur in patients with GD, it has distinct MR results for some ADs such as IBD and RA, which indicates that for GD patients, those with eye involvement may have different genetic backgrounds. This study offers new insights into treatment and targeted interventions by considering the patient's genetic background. However, genetic liability or predisposition does not imply a direct causal connection. Further investigation through observational studies or laboratory research is needed to validate the links between GO and other autoimmune diseases.

Study approval

Not Applicable.

Author contributions

LM: Data curation, Formal analysis, Investigation, Software, Methodology, Visualization, Writing - original draft; XJ: Formal analysis, Investigation, Writing - review and editing; ZH: Writing - review and editing, Supervision; DL: Conceptualization, Funding acquisition, Project administration, Supervision. Writing - review and editing, All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

MR	Mendelian randomization
ADs	autoimmune diseases
GO	Graves' ophthalmopathy
SNP	single nucleotide polymorphisms
IBD	inflammatory bowel disease
MS	multiple sclerosis
PV	psoriasis vulgaris
T1D	type 1 diabetes
SLE	systemic lupus erythematosus
RA	rheumatoid arthritis
GWAS	genome-wide association studies
IVW	inverse variance weighted
WM	weighted median

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2024.11.004.

References

1. Kumari R, Chandra Saha B. Advances in the management of thyroid eye diseases: an overview. *Int Ophthalmol*. 2018;38(5):2247–2255. https://doi.org/10.1007/s10792-017-0694-0.
2. Naik VM, Naik MN, Goldberg RA, Smith TJ, Douglas RS. Immunopathogenesis of thyroid eye disease: emerging paradigms. *Surv Ophthalmol*. 2010;55(3):215–226. https://doi.org/10.1016/j.survophthal.2009.06.009.
3. Keovilayhong S, Mulliez A, Feral L, et al. Epidemiology of myasthenia gravis in France: incidence, prevalence, and comorbidities based on national healthcare insurance claims data. Rev Neurol (Paris). Published online April 5, 2024:S0035-3787(24)00485-5. doi:10.1016/j.neurol.2024.02.392.
4. Tomer Y, Menconi F. Type 1 diabetes and autoimmune thyroiditis: the genetic connection. *Thyroid Off J Am Thyroid Assoc*. 2009;19(2):99–102. https://doi.org/10.1089/thy.2008.1565.
5. Leal Rato M, Santos M, de Sá J, Ferreira J. Comorbid autoimmune disorders in people with multiple sclerosis: a retrospective cohort study. *J Neuroimmunol*. 2023;385:578226. https://doi.org/10.1016/j.jneuroim.2023.578226.
6. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in Epidemiology using mendelian randomization: the STROBE-MR statement. *JAMA*. 2021;326(16):1614–1621. https://doi.org/10.1001/jama.2021.18236.
7. Wu D, Xian W, Hong S, Liu B, Xiao H, Li Y. Graves' disease and rheumatoid arthritis: a bidirectional mendelian randomization study. *Front Endocrinol*. 2021;12:702482. https://doi.org/10.3389/fendo.2021.702482.
8. Xian W, Liu B, Li J, et al. Graves' disease and systemic lupus erythematosus: a Mendelian randomization study. *Front Immunol*. 2024;15:1273358. https://doi.org/10.3389/fimmu.2024.1273358.
9. Xian W, Wu D, Liu B, et al. Graves disease and inflammatory bowel disease: a bidirectional mendelian randomization. *J Clin Endocrinol Metab*. 2023;108(5):1075–1083. https://doi.org/10.1210/clinem/dgac683.
10. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698. https://doi.org/10.1038/s41588-018-0099-7.
11. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. https://doi.org/10.1002/gepi.21965.
12. 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. https://doi.org/10.1093/ije/dyv080.
13. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet Lond Engl*. 2018;391:2449–2462. https://doi.org/10.1016/S0140-6736(18)31320-5, 10138.
14. Wang LT, Huang CY, Lin CH, et al. Graves disease is more prevalent than Hashimoto disease in children and adolescents with type 1 diabetes. *Front Endocrinol*. 2023;13. https://doi.org/10.3389/fendo.2022.1083690.
15. Chikuba N, Akazawa S, Yamaguchi Y, et al. Type 1 (insulin-dependent) diabetes mellitus with coexisting autoimmune thyroid disease in Japan. *Intern Med Tokyo Jpn*. 1992;31(9):1076–1080. https://doi.org/10.2169/internalmedicine.31.1076.
16. Prinz N, Tittel SR, Bachran R, et al. Characteristics of patients with type 1 diabetes and additional autoimmune disease in the DPV registry. *J Clin Endocrinol Metab*. 2021;106(9):e3381–e3389. https://doi.org/10.1210/clinem/dgab376.
17. Hwang GB, Yoon JS, Park KJ, Lee HS, Hwang JS. Prevalence of autoimmune thyroiditis in patients with type 1 diabetes: a long-term follow-up study. *Ann Pediatr Endocrinol Metab*. 2018;23(1):33–37. https://doi.org/10.6065/apem.2018.23.1.33.

18. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. *J Clin Endocrinol Metab*. 2003;88(7):2983–2992. https://doi.org/10.1210/jc.2002-021845.
19. Sharma H, Sahlot R, Purwar N, et al. Co-existence of type 1 diabetes and other autoimmune ailments in subjects with autoimmune thyroid disorders. *Diabetes Metabol Syndr*. 2022;16(2):102405. https://doi.org/10.1016/j.dsx.2022.102405.
20. Frommer L, Kahaly GJ. Type 1 diabetes and autoimmune thyroid disease—the genetic link. *Front Endocrinol*. 2021;12:618213. https://doi.org/10.3389/fendo.2021.618213.
21. Tsokos George C. Systemic lupus erythematosus. *N Engl J Med*. 2011;365(22):2110–2121. https://doi.org/10.1056/NEJMra1100359.
22. Athanassiou L, Kostoglou-Athanassiou I, Kaiafa G, et al. Thyroid disease and systemic lupus erythematosus. *Medicina*. 2023;59(11):1911. https://doi.org/10.3390/medicina59111911.
23. Sohn SY, Ahn JY, Lee MK, et al. Risk of non-thyroidal autoimmune diseases in patients with Graves' disease: a nationwide retrospective cohort study. Rheumatol Oxf Engl. Published online January 5, 2024:kead708. doi:10.1093/rheumatology/kead708.
24. Hasham A, Tomer Y. Genetic and epigenetic mechanisms in thyroid autoimmunity. *Immunol Res*. 2012;54(1-3):204–213. https://doi.org/10.1007/s12026-012-8302-x.
25. Zheng J, Ibrahim S, Petersen F, Yu X. Meta-analysis reveals an association of PTPN22 C1858T with autoimmune diseases, which depends on the localization of the affected tissue. *Gene Immun*. 2012;13(8):641–652. https://doi.org/10.1038/gene.2012.46.
26. Barberis M, Rojas López A. Metabolic imbalance driving immune cell phenotype switching in autoimmune disorders: tipping the balance of T- and B-cell interactions. *Clin Transl Med*. 2024;14(3):e1626. https://doi.org/10.1002/ctm2.1626.
27. Wang Q, Feng D, Jia S, Lu Q, Zhao M. B-cell receptor repertoire: recent Advances in autoimmune diseases. *Clin Rev Allergy Immunol*. 2024;66(1):76–98. https://doi.org/10.1007/s12016-024-08984-6.
28. Ferrari SM, Fallahi P, Ruffilli I, et al. The association of other autoimmune diseases in patients with Graves' disease (with or without ophthalmopathy): review of the literature and report of a large series. *Autoimmun Rev*. 2019;18(3):287–292. https://doi.org/10.1016/j.autrev.2018.10.001.
29. Han Z, Han P, Wang F, et al. Negative causal exploration of systemic sclerosis: a Mendelian randomization analysis. *Sci Rep*. 2024;14(1):5200. https://doi.org/10.1038/s41598-024-55808-w.
30. Qureshi NK, Bansal SK. Autoimmune thyroid disease and psoriasis vulgaris after COVID-19 in a male teenager. *Case Rep Pediatr*. 2021;2021:7584729. https://doi.org/10.1155/2021/7584729.
31. Su T, Gan Y, Ma S, et al. Graves' disease and the risk of five autoimmune diseases: a Mendelian randomization and colocalization study. *Diabetes Metabol Syndr*. 2024;18(5):103023. https://doi.org/10.1016/j.dsx.2024.103023.
32. Kajita R, Takahashi H, Yoshino S, et al. Characteristics of human leukocyte antigen class II genes in Japanese patients with type 1 diabetes and autoimmune thyroid disease. *Tohoku J Exp Med*. 2024;263(2):133–139. https://doi.org/10.1620/tjem.2024.J027.
33. Wang T, Zhang Y, Chen X, et al. The potential causal association between systemic lupus erythematosus and endocrine and metabolic disorders in the East Asian population: a bidirectional two-sample Mendelian randomization study. *Lupus*. 2024;33(3):223–231. https://doi.org/10.1177/09612033241227276.