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Thyroid Dysfunction and Oral Lichen Planus: Evidence From Two-Sample Mendelian Randomization Analysis

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ABSTRACT

Introduction and aims: Epidemiological studies have shown that the association between thyroid dysfunction (TD) and oral lichen planus (OLP) is controversial, and the causal relationship remains ill-defined. This study aims to investigate their probable mutual causality using bidirectional Mendelian randomization (MR) analyses.

Methods: We extracted genetic instruments for OLP and 10 phenotypes of TD from the genome-wide association studies database. The inverse variance weighted method was primarily used to evaluate the bidirectional causal relationship between TD and OLP. The results' robustness was verified by sensitivity analysis (Cochran's Q test, MR-Egger intercept, and leave-one-out test). Bonferroni correction threshold (0.05/10) was applied to determine significant differences.

Results: Forward MR analysis indicated that Hashimoto's thyroiditis (HT) was suggestively linked to a higher likelihood of developing OLP (P = .0077), while hypothyroidism significantly increased the risk of OLP occurrence (P = .0002). The reverse MR study found that OLP was suggestively related to the occurrence of hyperthyroidism (P = .0126) and thyroid cancer (P = .0244). Furthermore, OLP was found to significantly increase the risk of HT ($P = 3.47 \times 10^{-8}$), Graves' disease ($P = 1.03 \times 10^{-5}$), hypothyroidism ($P = 1.08 \times 10^{-8}$), and elevated thyroid-stimulating hormone levels ($P = 1.99 \times 10^{-6}$). No major pleiotropy or heterogeneity was detected ($P > .05$).

Conclusion: These findings suggest that hypothyroidism significantly increases the risk of OLP, while OLP may contribute to the development of autoimmune thyroid disorders, particularly HT, Graves' disease, hypothyroidism, and thyroid-stimulating hormone. These findings highlight the complex interaction between endocrine and immune systems, emphasizing the need for further research into shared molecular pathways and potential clinical implications.

Clinical Relevance: This study provides a genetic foundation for understanding the relationship between TD and OLP, which aids early screening and diagnosis and informs therapy development.

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Abbreviations: CI, Confidence intervals; FT3, Free triiodothyronine; FT4, Free thyroxine; GD, Graves' disease; GWAS, Genome-wide association studies; HT, Hashimoto's thyroiditis; IFN-γ, interferon-gamma; IVs, Instrumental variables; IVW, Inverse variance weighted; LD, Linkage disequilibrium; MR, Mendelian randomization; OLP, Oral lichen planus; OR, Odds ratio; SNPs, Single nucleotide polymorphisms; TC, Thyroid cancer; TD, Thyroid dysfunction; T3, triiodothyronine; T4, thyroxine; Th1, T helper 1; Th2, T helper 2; TNF-α, tumour necrosis factor-alpha; TPOAb, Thyroid peroxidase antibodies; TSH, Thyroid-stimulating hormone; Treg, regulatory T-cell

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Introduction

Oral lichen planus (OLP) refers to an inflammatory and immune-related condition that has an adverse effect on the oral mucosa.[1] The disease demonstrates a predilection for middle-aged women and affects an estimated 0.5% to 2.0% of the global population, though its aetiology and pathogenic mechanisms remain to be elucidated.[2] OLP exhibits diverse clinical manifestations, such as erosive, reticular, and atrophic forms,[3] and can result in severe discomfort, including pain, burning sensations, and mucosal sensitivity. Although OLP is generally considered benign, the erosive form carries a risk of transforming into oral squamous cell carcinoma and requires regular monitoring.[4] Although various treatments have been developed for controlling OLP symptoms,[5] OLP remains a chronic condition that is susceptible to relapse, with an uncertain long-term prognosis. Many factors, such as psychological stress, viral infections (including hepatitis C virus), and immune system disorders, may significantly contribute to the development of the disease.[6] Furthermore, emerging evidence suggests that systemic conditions, particularly endocrine disorders such as thyroid dysfunction (TD), along with metabolic disorders like hypertension and diabetes, can perform certain functions in the development and progression of OLP.[7–9] Among which, TD has attracted growing attention due to its potential association with autoimmune disorders.

Thyroid disease is a prevalent endocrine disorder that presents various health risks and has a high incidence, underscoring its importance as a pivotal concern in global public health. Accumulating evidence has denoted a possible connection between TD and OLP. Siponen et al[10] observed a heightened incidence of OLP in people exhibiting hypothyroidism and found a strong association between the two conditions. In contrast, there does not exist a significant correlation between hypothyroidism and OLP from the outcomes of a case-control study performed in China; instead, Hashimoto's thyroiditis (HT) and thyroid nodules were closely linked to OLP.[11] These conflicting findings underscore the complexity of the relationship between thyroid disease and OLP, which is frequently confounded by various factors and the likelihood of reverse causation. Gaining a clearer understanding of this relationship is crucial for the targeted treatment strategies' development.

To resolve these issues, forward and reverse Mendelian randomization (MR) analysis utilizing broad-range genome-wide association studies (GWAS) data is conducted to reveal the possible causal connection of TD and OLP. Unlike the previous observational studies, MR studies exhibit reduced susceptibility to potential social and environmental confounding factors, as well as reverse causality. MR utilizes genetic variants with the characteristic of being greatly and exclusively connected with the exposure and thus specifically selected as instrumental variables (IVs).[12] The finding could establish a theoretical basis for understanding the mechanistic connection between these two conditions.

Materials and methods

Experimental design

The 10 thyroid-related phenotypes were analysed, including HT, Graves' disease (GD), hypothyroidism, hyperthyroidism, thyroid nodules, thyroid cancer (TC), thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), and thyroid peroxidase antibodies (TPOAb) levels. In order to identify whether TD promotes the occurrence of OLP, a forward MR analysis was operated where TD served as the exposure and OLP served as what came out. Alternatively, throughout the reverse MR analysis, we examined OLP as the exposure to assess the possible effects on TD. For clarity, we also provide a flow chart outlining the study design (Figure 1A). It is essential that our IVs satisfy the following core assumptions in our MR model: (1) they are tightly relevant to the exposure; (2) they exhibit no association with confounding factors that affect the exposure and the outcome altogether; (3) the exposure is the only influencing pathway of IVs (Figure 1B).[13]

All analyses utilized publicly available summary statistics, which negated the need for additional ethical approval or informed consent. The STROBE-MR guidelines (Supplementary Table S1) were followed in the conduct of this study, ensuring methodological rigour and scientific validity.[14]

Data collection

Data on exposure and outcomes were provided by the GWAS database. All of the data was collected from individuals of European descent, which mitigates potential biases associated with ethnic heterogeneity. Data on HT and TC were extracted from the IEU OpenGWAS repository using the IDs (ebi-a-GCST90018855, ieu-a-1082), which consolidates data from multiple GWAS.[15,16] Information on GD, hypothyroidism, hyperthyroidism, and thyroid nodules was obtained from the FinnGen consortium.[17] Data on TSH, FT4, FT3, and TPOAb levels were extracted from the ThyroidOmics Consortium.[18,19] Data on OLP were sourced from the FinnGen consortium, comprising 6411 case samples and 405,770 control samples, with 21,306,348 single nucleotide polymorphisms (SNPs) (Table 1).[17]

Criteria for SNP selection

We selected SNPs related to the exposure of interest using a significance threshold of $P < 5 \times 10^{-8}$. Subsequently, independent SNPs were clustered into linkage disequilibrium criterion of r^2 less than 0.001 and a physical distance greater than 10,000 kb in the 1000 Genomes reference panel.[20] SNPs were utilized with an effect allele frequency >0.01 and eliminated those with an *F*-statistic <10 (a measure of SNP strength as IVs) to keep away from weak instrument bias.[21] The detailed information regarding the F-calculated processes is shown in the Supplementary Equation S1.

To fulfil assumptions 2 and 3, we utilized the NHGRI-EBI GWAS Catalog as the primary source for gene-phenotype association data[22] and excluded SNPs that might be influenced by confounding variables affecting study outcomes. Next, the exposure and outcome data were synchronized, and the SNPs that were incompatible or palindromic were excluded. In parallel, we implemented the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) test and MR-radial models to identify and remove outliers.[23,24] After this

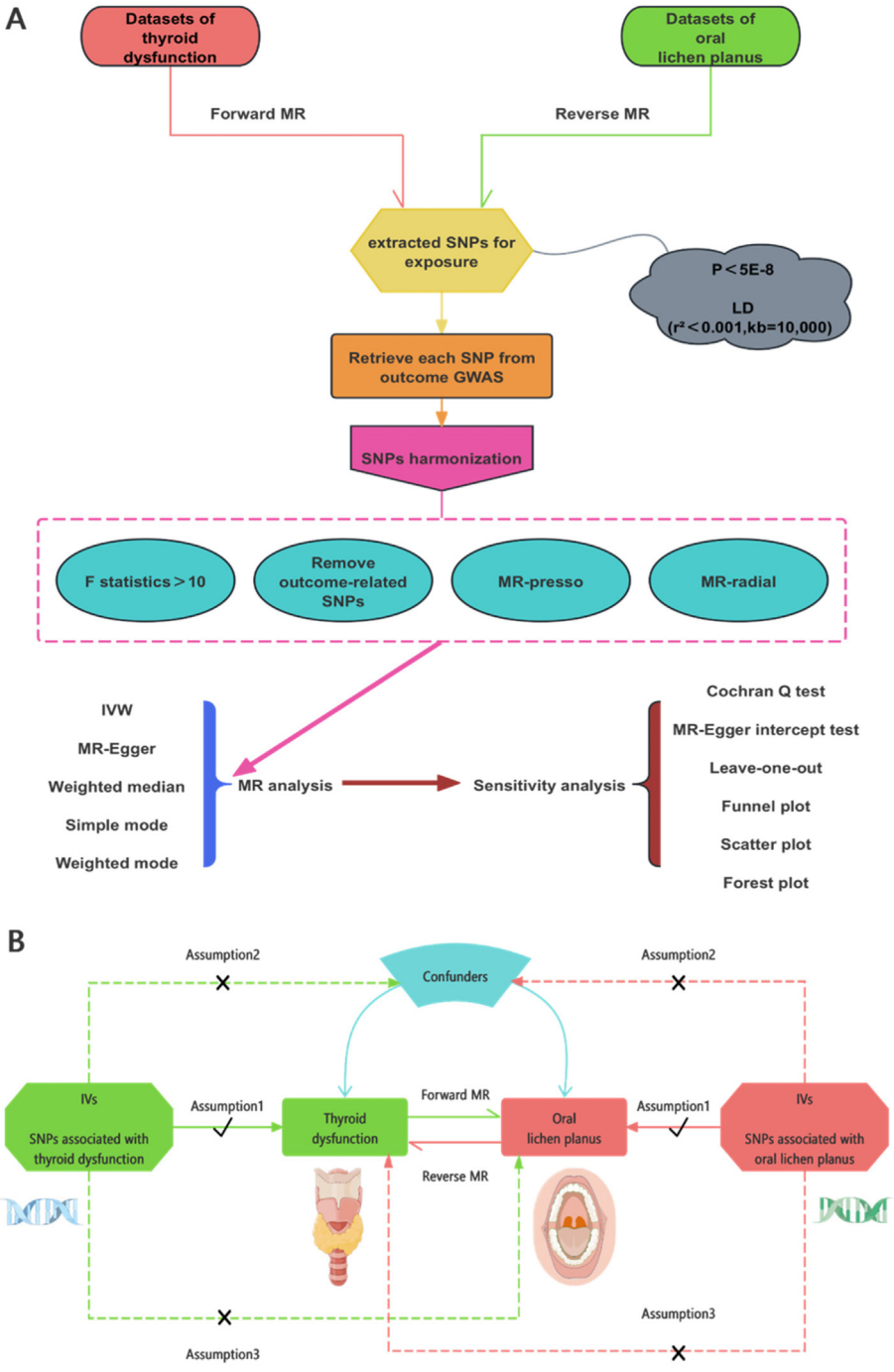

Fig. 1 – (A) Flowchart of the study design. (B) Three core assumptions of MR analysis (By Figdraw). GWAS, genome-wide association study; IV, instrumental variable; IVW, inverse variance weighted; LD, linkage disequilibrium; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

exclusion process, we reanalysed the data using the remaining SNPs.

Statistical analysis

MR analysis was conducted in R program (version 4.4.0) using TwoSampleMR (version 0.5.7) and MR-PRESSO (version 1.0), with a Bonferroni-corrected threshold of $P < .005$ ($\alpha = 0.05/10$) to adjust for multiple testing.[25] Here, $P < .005$ was thought to suggest a significant association, but $.005 < P < .05$ was regarded as an implication of a possible link.

To testify to the causal effects of TD with OLP, five different MR methods were selected, including inverse variance weighted (IVW), MR-Egger, weighted median, simple mode, and weighted mode analyses.[26–29] Under certain conditions, literature has demonstrated that the IVW method yields superior performance compared to other approaches. This method excludes the intercept term in the regression model

Table 1 – Detailed description of data sources.

Exposure/outcome	GWAS ID	Data source	Sample size	Total SNPs	Population	Y	Web sources
HT	ebi-a-GCST90018855	IEU open database	395,640	24,146,037	European	2021	https://gwas.mrcieu.ac.uk/
GD	finngen_R10_E4_GRAVES_STRICT	FinnGen	412,181	21,306,349	European	2023	https://www.finngen.fi/fi
Hypothyroidism	finngen_R10_E4_HYTHY_AI_STRICT	FinnGen	344,168	21,304,850	European	2023	https://www.finngen.fi/fi
Hyperthyroidism	finngen_R10_AUTOIMMUNE_HYPERTHYROIDISM	FinnGen	307,166	21,303,541	European	2023	https://www.finngen.fi/fi
Thyroid nodule	finngen_R10_E4_NONTOXIC_THYROID	FinnGen	412,181	21,306,349	European	2023	https://www.finngen.fi/fi
TC	ieu-a-1082	IEU open database	1080	572,028	European	2013	https://gwas.mrcieu.ac.uk/
TSH	—	ThyroidOmics Consortium	271,040	7987,299	European	2024	https://transfer.sysepi.medizin.uni-greifswald.de/thyroidomics/
FT4	—	ThyroidOmics Consortium	119,120	7815,339	European	2024	https://transfer.sysepi.medizin.uni-greifswald.de/thyroidomics/
FT3	—	ThyroidOmics Consortium	59,061	7905,033	European	2024	https://transfer.sysepi.medizin.uni-greifswald.de/thyroidomics/
TPOAb levels	—	ThyroidOmics Consortium	12,353	2425,174	European	2014	https://transfer.sysepi.medizin.uni-greifswald.de/thyroidomics/
OLP	finngen_R10_K11_LICHEN_PLANUS_WIDE	FinnGen	412,181	21,306,348	European	2023	https://www.finngen.fi/fi

FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; GWAS ID, genome-wide association study identity; HT, Hashimoto's thyroiditis; OLP, oral lichen planus; SNP, single nucleotide polymorphism; TC, thyroid cancer; TPOAb, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

and instead uses the inverse of the outcome variance as a weighting during model fitting.[28] As such, in situations without pleiotropy and independent of heterogeneity, the primary approach for MR analysis became the IVW method, with four additional methods serving as supporting strategies. When heterogeneity appeared, a random-effects IVW model was applied. Additionally, the MR-Egger method was utilized for the purpose of analysis where pleiotropy was found to be present.

To strengthen the reliability of our results, we conducted sensitivity analysis. Firstly, the MR-Egger method was employed to examine horizontal pleiotropy, which involves weighted linear regression with an unconstrained intercept.[30] The intercept stands for the mean pleiotropic effect of genetic variation (the average direct impact of variation on the outcome). When the intercept deviates from 0 (P value of the intercept <.05), it indicates the presence of horizontal pleiotropy. Secondly, Cochran's Q test is employed to investigate heterogeneity (the smaller the P value, the higher the heterogeneity).[26] Thirdly, a leave-one-out analysis is conducted, where each SNP is sequentially removed to assess the stability and reliability of the obtained results.[31] Finally, scatter plots are used to visually assess the directional consistency of different MR methods; funnel plots are introduced to evaluate the presence of heterogeneity among SNPs; forest plots are built to display individual effect estimates and confidence intervals (CI) for each SNP in relation to exposure and outcome.

Results

IVs selection

In the forward MR analysis, we selected IVs according to predetermined stringent criteria. All SNPs demonstrated robust instrumental strength (F-statistic >10). Finally, we identified valid IVs for TD: HT (3 SNPs), GD (11 SNPs), hypothyroidism (116 SNPs), hyperthyroidism (6 SNPs), thyroid nodules (6 SNPs), TC (323 SNPs), TSH (149 SNPs), FT4 (53 SNPs), FT3 (6 SNPs), and TPOAb (7 SNPs). In the reverse analyses, the same selection criteria were applied to identify the corresponding SNPs. Complete genetic variant data are provided in Supplementary Tables S2 to S21.

Causal effect of TD on OLP

The IVW method revealed a positive causal correlation between HT and OLP (odds ratio [OR] = 1.2887, 95% CI: 1.0694-1.5530, P = .0077), which was supported by the weighted median method (OR = 1.2522, 95% CI: 1.0080-1.5554, P = .0421). Similarly, a positive causal connection was identified between hypothyroidism and OLP (OR = 1.1041, 95% CI: 1.0473-1.1639, P = .0002). This outcome was consistent across multiple MR methods, including the weighted median (OR = 1.2522, 95% CI: 1.0080-1.5554, P = .0421), MR-Egger (OR = 1.1648, 95% CI: 1.0255-1.3229, P = .0206), and weighted mode (OR = 1.2312, 95% CI: 1.0690-1.4179, P = .0047). In contrast, no statistically significant causal relationships were noticed between GD, hyperthyroidism, thyroid nodules, TC,

TSH, FT4, FT3, TPOAb levels, and the risk of OLP, all *P* values >.05 (Figure 2). The Bonferroni correction (0.05/10) found a robust causal relationship was confirmed between hypothyroidism and OLP, while a potential causal link between HT and OLP was identified.

Several sensitivity analyses were conducted to assess potential heterogeneity and horizontal pleiotropy. The Cochran's Q test for both the IVW and MR-Egger approaches indicated no significant heterogeneity among the IVs. Moreover, the MR-Egger intercept showed $P > .05$, suggesting the absence of horizontal pleiotropy (Table 2). The leave-one-out analysis demonstrated that no SNP exhibits a disproportionate impact on the overall causal estimate (Supplementary Figure S1). Furthermore, the funnel plot displayed a roughly symmetrical distribution of causal estimates, indicating minimal bias from potential confounders (Supplementary Figure S2). The

Exposure	Method	Snps	OR (95% CI)	P value
HT	MR Egger	3	1.619 (0.423 – 6.188)	0.6096
	Weighted median	3	1.252 (1.008 – 1.555)	0.0421
	Inverse variance weighted	3	1.289 (1.069 – 1.553)	0.0077
	Simple mode	3	1.192 (0.913 – 1.558)	0.3262
	Weighted mode	3	1.227 (0.943 – 1.596)	0.2677
GD	MR Egger	11	1.038 (0.919 – 1.172)	0.5637
	Weighted median	11	1.024 (0.962 – 1.090)	0.4562
	Inverse variance weighted	11	1.004 (0.949 – 1.061)	0.9011
	Simple mode	11	1.005 (0.889 – 1.136)	0.9410
	Weighted mode	11	1.033 (0.963 – 1.108)	0.3841
Autoimmune hypothyroidism	MR Egger	116	1.165 (1.026 – 1.323)	0.0206
	Weighted median	116	1.129 (1.039 – 1.226)	0.0040
	Inverse variance weighted	116	1.104 (1.047 – 1.164)	0.0002
	Simple mode	116	1.137 (0.904 – 1.430)	0.2748
	Weighted mode	116	1.231 (1.069 – 1.418)	0.0047
Autoimmune hyperthyroidism	MR Egger	6	0.992 (0.843 – 1.168)	0.9306
	Weighted median	6	1.030 (0.966 – 1.100)	0.3656
	Inverse variance weighted	6	1.028 (0.956 – 1.106)	0.4595
	Simple mode	6	0.983 (0.877 – 1.100)	0.7728
	Weighted mode	6	1.023 (0.952 – 1.098)	0.5651
Thyroid nodule	MR Egger	6	0.992 (0.843 – 1.168)	0.9306
	Weighted median	6	1.030 (0.966 – 1.100)	0.3656
	Inverse variance weighted	6	1.028 (0.956 – 1.106)	0.4595
	Simple mode	6	0.983 (0.877 – 1.100)	0.7728
	Weighted mode	6	1.023 (0.952 – 1.098)	0.5651
TC	MR Egger	323	1.001 (0.998 – 1.004)	0.3571
	Weighted median	323	1.000 (0.998 – 1.002)	0.9662
	Inverse variance weighted	323	1.001 (0.999 – 1.002)	0.3985
	Simple mode	323	0.999 (0.994 – 1.004)	0.7346
	Weighted mode	323	1.000 (0.997 – 1.003)	0.8992
TSH	MR Egger	149	0.927 (0.810 – 1.062)	0.2769
	Weighted median	149	1.013 (0.901 – 1.139)	0.8264
	Inverse variance weighted	149	1.020 (0.943 – 1.102)	0.6256
	Simple mode	149	0.947 (0.757 – 1.186)	0.6374
	Weighted mode	149	0.965 (0.846 – 1.101)	0.5972
FT4	MR Egger	53	0.988 (0.773 – 1.261)	0.9203
	Weighted median	53	0.973 (0.790 – 1.197)	0.7929
	Inverse variance weighted	53	0.995 (0.878 – 1.127)	0.9384
	Simple mode	53	1.199 (0.812 – 1.770)	0.3667
	Weighted mode	53	0.984 (0.808 – 1.198)	0.8705
FT3	MR Egger	6	1.555 (0.442 – 5.477)	0.5296
	Weighted median	6	1.121 (0.801 – 1.569)	0.5047
	Inverse variance weighted	6	1.106 (0.840 – 1.455)	0.4735
	Simple mode	6	1.128 (0.706 – 1.802)	0.6369
	Weighted mode	6	1.184 (0.783 – 1.790)	0.4594
TPOAb levels	MR Egger	7	1.071 (0.442 – 2.599)	0.8846
	Weighted median	7	0.854 (0.513 – 1.423)	0.5448
	Inverse variance weighted	7	0.840 (0.564 – 1.253)	0.3934
	Simple mode	7	0.586 (0.240 – 1.429)	0.2843
	Weighted mode	7	0.858 (0.434 – 1.697)	0.6753

Fig. 2 – The forest plot illustrates the causal effects of thyroid dysfunction (TD) on oral lichen planus (OLP). 95% CI, 95% confidence intervals; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; HT, Hashimoto's thyroiditis; OR, odds ratio; SNP, single nucleotide polymorphism; TC, thyroid cancer; TPOAb, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

Table 2 – Horizontal pleiotropy and heterogeneity testing in Mendelian randomization (MR) analysis of the association between thyroid dysfunction (TD) and oral lichen planus (OLP).

Exposure	Outcome	Horizontal pleiotropy test		Heterogeneity test			
		MR Egger		MR Egger		IVW	
		Egger intercept	*P* value	Cochran's Q	*P* value	Cochran's Q	*P* value
HT	OLP	−0.029	.792	2.104	.147	2.346	.309
GD		−0.010	.553	14.109	.118	14.705	.143
Autoimmune hypothyroidism		−0.004	.367	91.803	.937	92.622	.938
Autoimmune hyperthyroidism		0.015	.652	10.018	.040	10.611	.060
Thyroid nodule		0.006	.477	30.775	.852	31.290	.863
TC		−0.001	.595	229.338	1.000	229.621	1.000
TSH		0.005	.095	100.309	.999	103.126	.998
FT4		0.000	.944	47.107	.629	47.112	.666
FT3		−0.021	.615	1.142	.888	1.438	.920
TPOAb levels		−0.020	.568	6.006	.306	6.455	.374
OLP	HT	0.033	.225	6.048	.534	7.818	.451
	GD	0.005	.917	2.242	.691	2.254	.813
	Autoimmune hypothyroidism	0.000	.985	0.690	.876	0.690	.953
	Autoimmune hyperthyroidism	−0.010	.864	6.558	.364	6.593	.472
	Thyroid nodule	−0.006	.496	8.634	.567	9.134	.610
	TC	−0.466	.350	0.638	.727	2.104	.551
	TSH	−0.001	.874	2.639	.620	2.667	.751
	FT4	0.002	.775	6.460	.596	6.547	.684
	FT3	0.006	.440	8.780	.361	9.506	.392
	TPOAb levels	0.048	.380	0.496	.481	2.658	.265

FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; HT, Hashimoto's thyroiditis; IVW, inverse variance weighted; MR, Mendelian randomization; OLP, oral lichen plan; TC, thyroid cancer; TPOAb, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

scatter plots showed consistent directionality among various MR methods, while the forest plot further confirmed the robustness and consistency of the result (Supplementary Figures S3 and S4).

Causal effect of OLP on TD

We initiated a reverse MR analysis to investigate whether OLP causally impacts TD, using a methodology similar to the forward MR analysis. The IVW results indicated a positive causal relationship between OLP and several thyroid phenotypes: HT (OR = 1.2816, 95% CI: 1.1735-1.3997, $P = 3.47 \times 10^{-8}$), GD (OR = 1.4924, 95% CI: 1.2492-1.7829, $P = 1.03 \times 10^{-5}$), hypothyroidism (OR = 1.1623, 95% CI: 1.1039-1.2238, $P = 1.08 \times 10^{-8}$), hyperthyroidism (OR = 1.2794, 95% CI: 1.0542-1.5526, $P = .0126$), TC (OR = 2.3500, 95% CI: 1.1168-4.9449, $P = .0244$), and TSH levels (OR = 1.0540, 95% CI: 1.0314-1.0770, $P = 1.99 \times 10^{-6}$). To enhance the robustness of the above result, we utilized four additional MR strategies: weighted median, simple mode, weighted mode, and MR-Egger. Among the weighted median, simple mode, and weighted mode methods, all confirmed the associations between OLP and HT, GD, hypothyroidism, and TSH levels. The weighted median method also demonstrated an association between OLP and hyperthyroidism. Although these four MR methods failed to indicate a significant association between OLP and TC, the results of all methods consistently showed the same directionality. Furthermore, no causal relationships were identified between OLP and thyroid nodules, FT4, FT3, or TPOAb levels, all *P* values >.05 (Figure 3). After the application of the Bonferroni correction (0.05/10), we established a strong causal relationship between OLP and HT, GD, hypothyroidism, and TSH levels. Furthermore, a possible causal connection was observed between OLP and hyperthyroidism, as well as TC.

Both Cochran's Q test and the MR-Egger intercept indicated that we did not observe any heterogeneity or horizontal pleiotropy (Table 2), which was supported by the leave-one-out analysis (Supplementary Figure S5). Scatter plots demonstrated consistent directionality across various MR methods, while funnel plots exhibited symmetrical distributions, suggesting minimal bias (Supplementary Figures S6 and S7). Furthermore, the forest plot illustrated the causal effects of each SNP on both OLP and TD (Supplementary Figure S8). Consequently, the results derived from the IVW method are considered reliable.

Discussion

The present study represents the first MR analysis to investigate the bidirectional causal relationship between TD and OLP. After Bonferroni correction, the forward MR analysis found a significant causal effect of hypothyroidism on the development of OLP, with a suggestive association between HT and OLP. OLP had no appreciable correlation with other thyroid phenotypes, including GD, hyperthyroidism, thyroid nodules, TC, FT4, FT3, TSH, and TPOAb. Conversely, reverse MR analysis revealed significant causal effects of OLP on various thyroid conditions, including HT, GD, hypothyroidism, and TSH levels, suggesting potential causal relationships with hyperthyroidism and TC. However, no significant effects were observed between OLP and other thyroid phenotypes

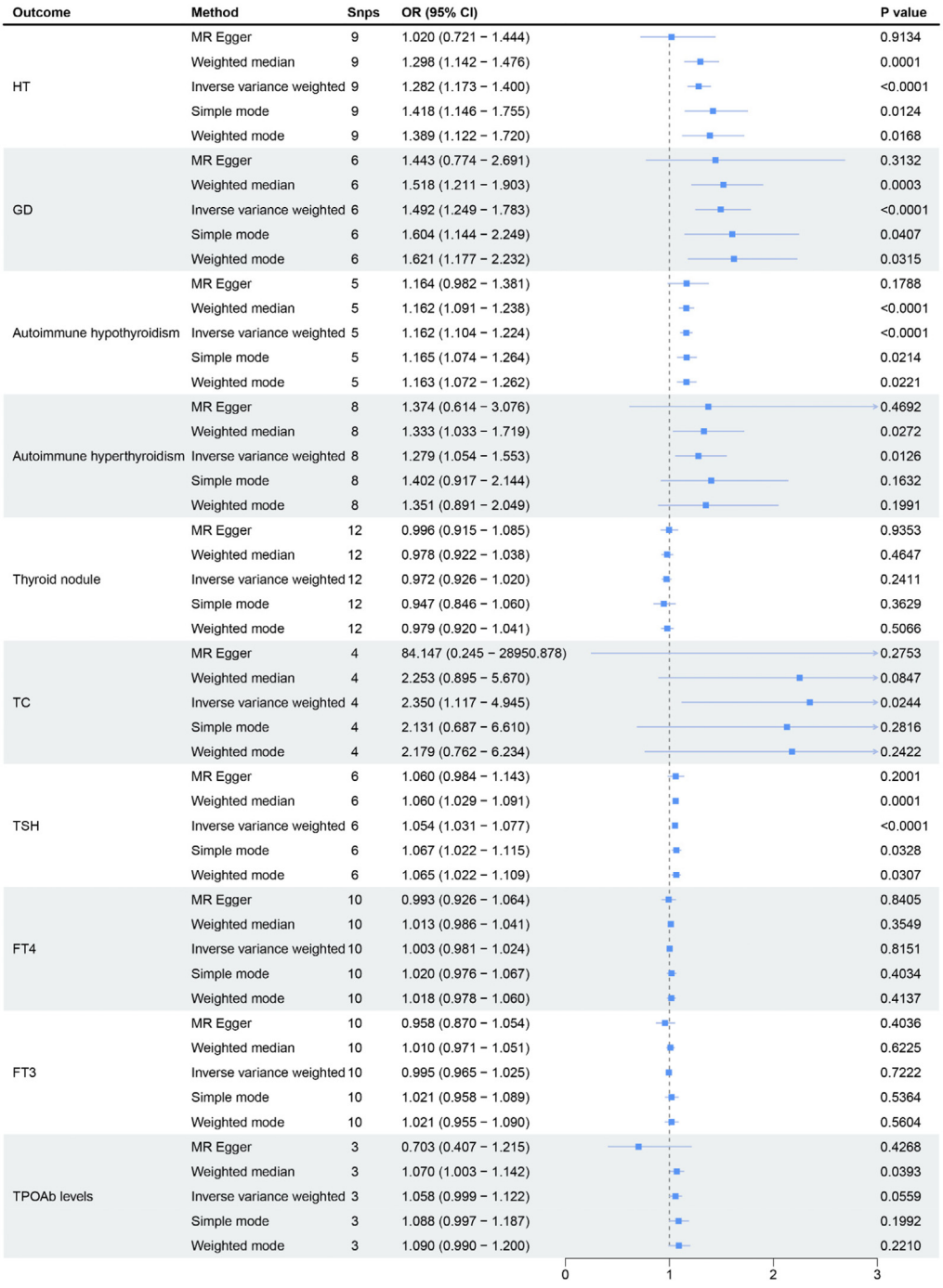

Fig. 3 – The forest plot illustrates the causal effects of oral lichen planus (OLP) on thyroid dysfunction (TD). 95% CI, 95% confidence intervals; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; HT, Hashimoto's thyroiditis; OR, odds ratio; SNP, single nucleotide polymorphism; TC, thyroid cancer; TPOAb, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

(thyroid nodules, FT4, FT3, and TPOAb). Notably, sensitivity analyses confirmed the robustness of these findings.

Comparison with previous studies

Previous epidemiologic studies have reported inconsistent results regarding the association between TD and OLP. For example, Lavaee et al[32] conducted a retrospective study of 523 patients with OLP and found no significant association between hypothyroidism and OLP, a finding that has been replicated in other retrospective studies.[11,33] In contrast, studies by Garcia-Pola et al[34] and Piloni et al[35] showed that individuals with OLP have a higher predisposition to hypothyroidism, with HT being a significant risk factor for OLP. Other studies[36–38] have shown similar associations of OLP with both hypothyroidism and HT. In addition, studies have

shown that low FT4 levels, TPOAb levels, and thyroid nodules are strongly associated with OLP.[11,39,40] The discrepancies between research findings may be due to differences in study design, data sources, and diagnostic criteria. Especially, our study used MR analysis and GWAS data to lower the inherent reverse causation and confusing factor likelihood in observational investigations. Moreover, ethnic and genetic distinctions could help to explain the noted variations, especially as our investigation was carried out just in European people.

Potential biological mechanisms linking TD and OLP

The observed bidirectional causal relationship between TD and OLP may be explained by multiple biological pathways, including immune dysregulation, thyroid hormone fluctuations, inflammatory responses, and genetic susceptibility.

Autoimmune mechanisms and immune dysregulation

Abnormal immune responses are a common feature of TD and OLP. OLP is a T-cell-mediated chronic inflammatory illness mostly driven by T helper 1 (Th1) responses,[41] while HT and GD are autoimmune thyroid diseases mediated by Th1 and T helper 2 (Th2) immunological pathways, respectively.[42] Particularly in HT, the activation of Th1 pathways in TD releases proinflammatory cytokines including interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α), which can increase cytotoxic T-cell activity and cause epithelial damage in distant tissues including the oral mucosa.[43]

One possible mechanism linking TD and OLP is systemic autoimmune spillover. The breakdown of immunological tolerance in TD may extend beyond of the thyroid gland and cause immune-mediated damage to other tissues including the oral epithelium.[44,45] Increased TPOAb and thyroglobulin antibodies may deregulate the systemic immune system and aggravate the inflammatory reaction in the oral mucosa.[36,38]

On the contrary, persistent immunological activation in OLP may upregulate systemic inflammatory mediators, hence changing thyroid function and maybe raising vulnerability to autoimmune thyroid disorders.[46] IFN-γ and TNF-α accompany the invasion of $CD8^+$ cytotoxic T cells into OLP lesions and their consequent death of basal keratinocytes.[47] These cytokines can affect the activity of antigen-presenting cells and cause a proinflammatory condition that might lead to thyroid autoimmunity.[47]

Influence of thyroid hormone imbalances on mucosal immunity

Thyroid hormones, particularly triiodothyronine (T3) and thyroxine (T4), are critical in regulating immune function and maintaining epithelial homeostasis.[48] Hypothyroidism is associated with a reduction in T3 and T4 levels, which can impair the function of innate and adaptive immune cells.[48] This hormonal deficiency may impair oral keratinocyte proliferation and compromise epithelial integrity, increasing susceptibility to chronic inflammatory diseases such as OLP.[49]

Additionally influencing the balance of pro- and anti-inflammatory cytokines are thyroid hormones. Often in a hypothyroid state, there is a shift towards a proinflammatory milieu marked by rising production of IFN-γ, TNF-α, and interleukin-6.[50] However, these cytokines are precisely associated with the pathogenesis of OLP, suggesting that thyroid hormone dysregulation may be one of the causative factors of OLP.[51] Furthermore, demonstrated to be detrimental to regulatory T-cell (Treg) activity are low thyroid hormone levels, hence aggravating immunological dysregulation in OLP.[52]

Hyperthyroidism might affect OLP by means of metabolic changes and higher systemic inflammation. Excess thyroid hormones have been linked to the pathophysiology of OLP by increasing the generation of reactive oxygen species and hence regulating oxidative stress pathways.[52] Furthermore, linked to hyperthyroidism is higher expression of adhesion molecules and chemokines, which can help lymphocyte penetration into the oral mucosa and stimulate OLP formation.[53]

Chronic inflammation and cytokine imbalance

Both TD and OLP are marked by chronic inflammation, which perhaps may be a fundamental mechanism connecting the two disorders. HT is linked to ongoing inflammatory activity in the thyroid gland, which raises proinflammatory cytokine levels generally.[54] Commonly found in HT, elevated TNF-α and interleukin-6 have been demonstrated to cause mucosal inflammation and epithelial barrier breakdown in OLP.[55]

Important in influencing apoptosis and cell survival routes in the oral epithelium are inflammatory cytokines. Enhanced TNF-α signalling in OLP stimulates keratinocyte death by means of NF-κB and JNK pathway activation.[56] In HT, too, chronic inflammation is linked to higher NF-κB activation, implying that shared inflammatory pathways might be the foundation for both disorders.[57]

Role of lifestyle and environmental factors

Genetic factors may make some people more susceptible to TD and OLP by modulating immune and inflammatory responses. Variations in immune-related genes, especially in the HLA region, are strongly associated with the development of these two diseases.[58] The HLA-DR and HLA-DQ genes, which are closely associated with HT and GD, have also been implicated as risk factors for OLP, suggesting that we may share the same genetic susceptibility.[59]

Between TD and OLP, epigenetic changes could be rather essential. T-cell differentiation and cytokine generation are regulated by DNA methylation and histone changes of immune-related genes, therefore affecting one's vulnerability to these disorders.[60] Furthermore, influencing our epigenetic profile and so modulating the immune response and changing the risk of disease are various environmental elements, such as chronic stress, viral infections, and smoking.[61,62]

Clinical implications and management strategies

According to our MR results, patients with TD – especially those with hypothyroidism – should have regular oral exams to help to identify OLP early on and enable treatment. Likewise, patients with OLP may be likely to develop TD, particularly HT, GD, hypothyroidism, and raised TSH levels. These results emphasize the need for systematic thyroid function screening for those diagnosed with OLP. OLP mostly affects middle-aged women, a demographic also at high risk for TD; hence, dual screening approaches may help to improve general patient outcomes and early detection.

Study strengths and limitations

This study has several strengths that enhance its reliability and scientific impact. The use of MR provides a robust framework for causal inference, minimizing confounding and reverse causation inherent in observational studies. By using genetic variants as IVs, our study strengthens the evidence for a bidirectional causal relationship between TD and OLP. The bidirectional MR design provides a comprehensive perspective on their interactions, while multiple sensitivity analyses confirm the robustness of our findings. The use of strong IVs (*F*-statistic >10) ensures reliability, and the exclusive inclusion of European GWAS data minimizes population stratification bias, thereby enhancing internal validity.

However, this study also has some limitations. Although MR reduces the influence of confounding factors, it cannot completely exclude the possibility of horizontal pleiotropy, in which genetic variants affect outcomes through pathways independent of exposure. Although sensitivity analyses showed no significant pleiotropy, residual effects cannot be completely ruled out. Another limitation is the generalizability of our findings, as the study was conducted exclusively in European populations. Given the genetic and environmental differences between ethnic groups, future studies should validate these findings in more diverse populations. Furthermore, although MR establishes causality at the genetic level, it does not provide direct mechanistic insights at the molecular level. Future research should integrate transcriptomics, proteomics, and metabolomics to elucidate the biological pathways underlying the observed associations. Despite these limitations, this study provides novel insights into the shared pathophysiology of TD and OLP and highlights the need for integrated screening and management strategies in clinical practice.

Conclusions

This study provides strong genetic evidence of a bidirectional causal relationship between TD and OLP. Hypothyroidism was found to significantly increase the risk of OLP, and HT may be a potential causative factor for it. Additionally, our reverse studies indicated OLP greatly raises the risk of HT, GD, hypothyroidism, and TSH; it may also be a potential risk factor for hyperthyroidism and TC. These findings highlight the interplay between systemic thyroid disorders and oral inflammation, emphasizing the need for further research into shared immunological and endocrine mechanisms to improve clinical management.

Conflict of 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 article.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.identj.2025.02.028.

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