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The causal relationship between thyroid dysfunction and carpal tunnel syndrome

A Mendelian randomization study

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Abstract

Mendelian randomization was used to investigate the causal relationship between thyroid dysfunction (including hypothyroidism and hyperthyroidism) and carpal tunnel syndrome. Genetic loci independently associated with hypothyroidism and hyperthyroidism were selected as instrumental variables from pooled data from genome-wide association studies. Inverse variance weighting (IVW) was used to analyze the causal effect, supplemented by weighted median and MR-Egger. Heterogeneity test, pleiotropy testing and leave-one-out analysis were used to analyze the sensitivity test to explore the robustness of the results. Both hypothyroidism and hyperthyroidism increase the risk of carpal tunnel syndrome (hypothyroidism: IVW, OR = 1.04, 95% CI = 1.01–1.08, P = .017; hyperthyroidism: IVW, OR = 1.08, 95% CI = 1.05–1.12, P = 9.218E-06, no pleiotropy was found in both tests. Patients with thyroid dysfunction have an increased risk of carpal tunnel syndrome.

Abbreviations: CTS = carpal tunnel syndrome, GWAS = genome-wide association studies, IVW = inverse variance weighting, MR = Mendelian randomization, SNPs = single nucleotide polymorphisms, WME = weighted median.

Keywords: carpal tunnel syndrome, hyperthyroidism, hypothyroidism, mendelian randomization, thyroid dysfunction

1. Introduction

Carpal tunnel syndrome (CTS) is a series of symptoms and signs caused by compression of the median nerve in the carpal tunnel.[1] Typical symptoms include numbness and pain in the three and a half fingers of the radial side, decreased grip strength of the affected hand, and thumb abduction and weakness in the opposite palm. Long-term patients with the disease may appear the great thenar atrophy, the affected finger sensation and other symptoms, causing great trouble to the daily life of patients. The diagnosis can be combined with nerve conduction examination, ultrasound, and electromyography.[2] With a prevalence of about 1% to 5%,[3] CTS is one of the most common musculoskeletal disorders in most countries.[4] Studies have found that thyroid hormone has a significant effect on musculoskeletal,[5–7] and thyroid diseases are closely related to gynecologic infertility, cardiovascular, neurological and musculoskeletal diseases.[8–11] Traditional studies believe that CTS is related to thyroid dysfunction.[12,13] However, traditional observational studies often have problems such as too small sample size and difficulty in avoiding the interference of reverse causality and confounding factors.[14] Therefore, it is necessary to further clarify the causal relationship between them, so as to provide a theoretical basis for clinical treatment and prevention.

Mendelian randomization (MR) is a research method to study the causal relationship between exposure factors and outcomes.[15] By using single nucleotide polymorphisms (SNPs) strongly associated with exposure as an instrumental variable, it relies on genes being equally and randomly assigned to offspring during meiosis.[16] Genes are not easily affected by other factors, which can effectively minimize confounding factors and reverse causality.[17] There are no studies using MR To further investigate the causal relationship between thyroid dysfunction and carpal tunnel syndrome. Therefore, we conducted this MR study to provide important evidence for the causal role of thyroid dysfunction in causing carpal tunnel syndrome.

2. Data and methods

2.1. Data sources

In this study, hypothyroidism and hyperthyroidism were selected as exposures and carpal tunnel syndrome as outcomes. Hypothyroidism and thyroid function hyperfunction and carpal tunnel syndrome genome-wide association studies (GWAS) summary data are from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk). The data are all from Europe.

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The datasets generated during and/or analyzed during the current study are publicly available.

The data for this study were obtained from the original study, so moral review and informed consent were not required. We used the data are from IEU Open GWAS project, you can find it from the website (https://gwas.mrcieu.ac.uk).

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Hypothyroidism (ebi-a-GCST90018862) contained 24,138,872 SNPs with a sample size of 410141. Hyperthyroidism (ebi-a-GCST90018860) included 24,189,279 SNPs with a sample size of 460,499; carpal tunnel syndrome (ebi-a-GCST90018813) contained 24,181,062 SNPs with a sample size of 480,201, as shown in Table 1. The data for this study were obtained from the original study, so moral review and informed consent were not required.

2.2. Filtering conditions of tool variables

To be an effective tool for causal reasoning in MR Studies, genetic variation must satisfy 3 core assumptions: (1) genetic variation is directly related to exposure; (2) genetic variation is not associated with confounding factors; (3) genetic variation affects outcomes only through exposure.[18] SNPs related to hypothyroidism and hyperthyroidism were selected as instrumental variables with $P < 5 \times 10^{-8}$ as the condition (instrumental variable).[19] Secondly, in order to eliminate linkage imbalance, kb = 10,000 and $r^2 < 0.001$ were used as screening conditions to ensure that individual SNPS were independent of each other.[20] Finally, the *F*-value of each SNP was calculated, SNPs with $F > 10$ were screened, and weak instrumental variables were excluded.[21]

2.3. Mendelian randomization analysis

Statistical analyses were performed using the "TwoSampleMR" software package in R (version 4.3.2).[22] The causal relationship between exposure (hypothyroidism, hyperthyroidism) and outcome (carpal tunnel syndrome) was analyzed using 3 MR analyses: inverse variance weighted (IVW), weighted median (WME), and MR-Egger.[23] Cochran *Q* value was used to verify the existence of heterogeneity,[24] and the MR-Egger intercept method was used to verify horizontal pleiotropy.[25] Finally, leave-one-out analysis was conducted to evaluate whether a single SNP affected the causal relationship between exposure and outcome. The leave-one-out method refers to whether the analysis results are robust after each SNP is eliminated one by one.[26]

3. Results

Through the Mendelian randomization analysis of hypothyroidism, hyperthyroidism, and CTS, there is a positive causal relationship between thyroid dysfunction and CTS.

3.1. Tool variables

SNPs closely related to hypothyroidism and hyperthyroidism were screened according to $P < 5 \times 10^{-8}$, $r^2 < 0.001$, kb = 10,000, $F > 10$ and other conditions. Data that intersected with SNPs were screened from the aggregated GWAS data of carpal tunnel syndrome, and SNPs directly related to the outcome indicators were excluded, leaving 76 and 13 SNPs (Table 2). We will use this as the instrumental variable of this study.

3.2. Causal relationship between hypothyroidism, hyperthyroidism, and carpal tunnel syndrome

According to the results of MR analysis, IVW method shows that hypothyroidism can increase the incidence of CTS (IVW, OR = 1.04, 95% CI = 1.01–1.08, *P* = .017). Although the results of WME and MR-Egger are not statistically significant (MR-Egger: OR = 1.08, 95% CI = 1.00–1.16, *P* = .062; WME: OR = 1.03, 95% CI = 0.98–1.09, *P* = .198), the direction of IVW, MR-Egger and WME results is consistent, and the results are reliable, indicating that hypothyroidism can increase the incidence of CTS. Hyperthyroidism has a positive causal relationship with CTS: IVW (OR = 1.08, 95% CI = 1.05–1.12, *P* = 9.218E-04), MR-Egger (OR = 1.17, 95% CI = 1.08–1.26, *P* = 2.445E-03), WME (OR = 1.09, 95% CI = 1.04–1.14, *P* = 6.874E-04), IVW, MR-Egger and WME results showed the same direction. The results are shown in Table 3.

3.3. Sensitivity analysis

Cochran *Q* test of MR-Egger and IVW showed hypothyroidism–carpal tunnel syndrome (MR-Egger: *P* = 2.476E-04; IVW: *P* = 2.472E-04). Heterogeneity existed in the results, but this study adopted a random effects model for analysis to minimize the influence of heterogeneity.[27] Therefore, although heterogeneity exists, it does not affect the validity of the results. Hyperthyroidism–carpal tunnel syndrome: MR-Egger *P* = .555; IVW *P* = .268, indicating no heterogeneity in hyperthyroidism–carpal tunnel syndrome results (Table 3 and Fig. 1). The MR-Egger regression method was used to test horizontal pleiotropy, and *P* = .385 for hypothyroidism–carpal tunnel syndrome and *P* = .057 for hyperthyroidism–carpal tunnel syndrome, both with *P* values > .05, the results showed that neither of them had horizontal pleiotropy (Table 3 and Fig. 2). The leave-one-out method was used to analyze the data of the 2 groups, and no SNPs were found to have a strong impact on the results, and the results were relatively robust (Fig. 3).

4. Discussions

At present, there are no studies to analyze the causal relationship between thyroid dysfunction and CTS from a genetic perspective. This MR study fills this gap and reveals the relationship between hyperthyroidism, hypothyroidism, and CTS, respectively.

CTS is one of the most common diseases, affecting about 3% of American adults,[28] and it is estimated that the economic cost of treating CTS in the United States exceeds $2 billion per year,[29] accounting for a considerable share of healthcare and compensation costs.[30] Thyroid dysfunction is closely related to CTS. It is believed that hypothyroidism is one of the risk factors for CTS,[31,32] and its mechanism may be related to the deposition of mucinous substances or mucopolysaccharides on the median nerve.[33] The treatment of CTS is mainly divided into surgical treatment and nonsurgical treatment, both of which have clinical benefits.[34] Although surgical decompression has certain complications,[35] it has a significant therapeutic effect on CTS, but

Table 1

Brief information on GWAS data for hyperthyroidism, hypothyroidism, and carpal tunnel syndrome.

Trait	ID	Number of SNPs	Sample size	Population	Sex	Release date
Hypothyroidism	ebi-a-GCST90018862	24,138,872	410,141	European	Males and females	2021
Hyperthyroidism	ebi-a-GCST90018860	24,189,279	460,499	European	Males and females	2021
Carpal tunnel syndrome	ebi-a-GCST90018813	24,181,062	480,201	European	Males and females	2021

Table 2

Information on the final screening of SNPs from GWAS data.

			Hyperthyroidism–carpal tunnel syndrome					
	SNP	EA	OA	Beta	Eaf	SE	*P*	*F*
1	rs1794280	T	A	0.5463	0.098516	0.0391	2.29E-44	195.2122
2	rs2160215	C	T	0.2483	0.425594	0.0226	3.82E-28	120.7076
3	rs28375776	G	C	-0.2432	0.127029	0.0407	2.25E-09	35.70561
4	rs2856821	C	T	-0.1879	0.196264	0.0274	7.69E-12	47.02735
5	rs3087243	A	G	-0.2038	0.380249	0.0224	7.94E-20	82.77714
6	rs385863	G	C	0.1335	0.505395	0.0214	4.09E-10	38.91644
7	rs4338740	C	T	0.1844	0.207075	0.0264	2.87E-12	48.7879
8	rs58722186	T	C	0.1359	0.302235	0.0233	5.23E-09	34.01929
9	rs604912	G	A	0.1198	0.538777	0.0217	3.15E-08	30.47841
10	rs6131010	G	A	0.1306	0.712807	0.0237	3.60E-08	30.36601
11	rs6679677	A	C	0.2936	0.111921	0.0379	8.79E-15	60.01113
12	rs758778	C	T	0.3072	0.203646	0.0348	1.02E-18	77.92594
13	rs9258222	A	G	-0.2367	0.086896	0.0418	1.44E-08	32.0658
			Hypothyroidism–carpal tunnel syndrome					
	SNP	EA	OA	Beta	Eaf	SE	*P*	*F*
1	rs10075764	G	A	-0.057	0.302413	0.0104	4.26E-08	30.03868
2	rs10126000	A	C	-0.0683	0.688692	0.0104	5.13E-11	43.12932
3	rs10424978	A	C	-0.0775	0.624328	0.0102	2.77E-14	57.72992
4	rs1065386	C	G	-0.1183	0.480463	0.0125	3.93E-21	89.56686
5	rs1079418	G	A	-0.0657	0.262374	0.011	2.14E-09	35.6733
6	rs10917477	G	A	0.064	0.386901	0.01	1.75E-10	40.9598
7	rs11171710	A	G	-0.0698	0.443916	0.01	3.19E-12	48.72016
8	rs11406335	TG	T	-0.057	0.417169	0.0103	3.44E-08	30.62479
9	rs11406335	TG	T	-0.057	0.417169	0.0103	3.44E-08	30.62479
10	rs11420448	GT	G	0.1533	0.046701	0.0275	2.39E-08	31.07541
11	rs114285740	C	G	0.1669	0.027378	0.0301	3.06E-08	30.74522
12	rs11675342	T	C	0.0906	0.387729	0.01	1.40E-19	82.0832
13	rs11875260	G	A	0.0751	0.172925	0.0135	2.54E-08	30.94641
14	rs12117927	A	C	0.0627	0.476541	0.0105	2.29E-09	35.65779
15	rs12379417	A	G	0.0583	0.317559	0.0103	1.51E-08	32.03764
16	rs12582330	T	G	-0.061	0.624365	0.0109	2.05E-08	31.31876
17	rs12593201	A	G	0.0905	0.325432	0.0112	7.69E-16	65.29185
18	rs12984428	A	G	-0.0659	0.35604	0.0102	1.11E-10	41.74153
19	rs13090803	T	G	0.0829	0.190624	0.0128	9.00E-11	41.94566
20	rs13109179	A	G	0.0647	0.461895	0.01	9.42E-11	41.8607
21	rs1364450	C	A	0.0886	0.126235	0.0139	1.97E-10	40.62896
22	rs141232332	G	GTTT	0.2243	0.451125	0.0127	4.48E-70	311.9241
23	rs142997491	G	A	0.2385	0.013564	0.0412	7.02E-09	33.51045
24	rs1432806	G	A	0.0583	0.338619	0.0105	2.89E-08	30.82878
25	rs1479565	A	G	0.0975	0.498866	0.0101	7.53E-22	93.18894
26	rs1534430	T	C	-0.086	0.428394	0.0101	1.44E-17	72.50234
27	rs187707293	A	T	0.2419	0.013386	0.044	3.99E-08	30.22486
28	rs2111485	G	A	0.0813	0.479023	0.0102	1.43E-15	63.52997
29	rs2114702	A	T	0.07	0.26671	0.0111	3.00E-10	39.76931
30	rs2234167	A	G	0.0825	0.102013	0.015	3.75E-08	30.24985
31	rs2247314	C	T	-0.086	0.376495	0.0104	1.06E-16	68.37984
32	rs229528	T	C	0.0903	0.496016	0.01	2.31E-19	81.5405
33	rs2412976	G	C	0.0637	0.478888	0.0103	5.47E-10	38.24743
34	rs2445608	A	G	-0.0593	0.430366	0.0101	3.79E-09	34.47184
35	rs244685	G	T	-0.0858	0.79915	0.0132	7.06E-11	42.24979
36	rs28418426	C	T	0.1877	0.501169	0.0133	2.21E-45	199.1696
37	rs2921053	C	G	-0.0599	0.589616	0.0101	3.36E-09	35.17295
38	rs2988277	T	C	0.0593	0.287022	0.0106	2.49E-08	31.29648
39	rs307558	A	G	-0.0688	0.742625	0.0119	8.01E-09	33.42573
40	rs3087243	A	G	-0.1466	0.386088	0.0102	4.77E-47	206.5692
41	rs3118469	T	A	0.0803	0.295174	0.0106	3.82E-14	57.38749
42	rs3184504	C	T	-0.1734	0.668513	0.0102	7.50E-65	288.9986
43	rs34536443	C	G	-0.1863	0.044028	0.0263	1.46E-12	50.17786
44	rs3775291	T	C	-0.0649	0.287788	0.0108	1.65E-09	36.11102
45	rs434294	G	A	-0.0683	0.322802	0.0109	3.36E-10	39.26325
46	rs4409785	C	T	0.1069	0.142566	0.0133	8.04E-16	64.6026
47	rs4529854	T	C	-0.0768	0.723438	0.0107	6.56E-13	51.51726
48	rs4835534	C	T	-0.1421	0.156356	0.0132	7.06E-27	115.8879
49	rs5912815	G	T	-0.0511	0.576761	0.0084	1.05E-09	37.00676
50	rs61759532	T	C	0.0905	0.188941	0.0122	1.42E-13	55.02694
51	rs61877856	T	C	-0.0658	0.197495	0.0115	1.14E-08	32.73814

(*Continued*)

Table 2

(*Continued*)

			Hypothyroidism–carpal tunnel syndrome					
	SNP	**EA**	**OA**	**Beta**	**Eaf**	**SE**	***P***	***F***
52	rs6679677	A	C	0.3637	0.108444	0.0159	2.39E-115	523.2271
53	rs6908626	T	G	0.1441	0.17075	0.0141	2.04E-24	104.445
54	rs7030280	T	C	0.2075	0.745664	0.0108	1.02E-82	369.1361
55	rs71508903	T	C	0.0934	0.210816	0.0125	9.34E-14	55.83051
56	rs7223956	C	T	-0.0902	0.897005	0.0144	4.27E-10	39.23611
57	rs73192661	T	C	-0.1061	0.428858	0.01	4.05E-26	112.5716
58	rs736374	A	G	0.0832	0.375103	0.0103	6.00E-16	65.24843
59	rs7441808	G	A	0.0766	0.21091	0.0111	5.17E-12	47.6222
60	rs7488011	T	C	0.1052	0.356485	0.0111	2.52E-21	89.82214
61	rs7574865	G	T	-0.1321	0.74252	0.0117	1.67E-29	127.477
62	rs7742626	C	T	0.0686	0.267343	0.0116	3.41E-09	34.97278
63	rs78765971	G	GAC	0.2444	0.146942	0.0162	1.68E-51	227.599
64	rs79490353	C	T	0.2006	0.024115	0.0349	8.82E-09	33.03763
65	rs7990020	C	A	0.0577	0.453482	0.0101	9.97E-09	32.63674
66	rs853305	C	T	-0.0802	0.718894	0.0111	4.40E-13	52.20362
67	rs881858	A	G	0.0665	0.747899	0.0108	8.46E-10	37.91348
68	rs911760	A	C	0.0879	0.212143	0.0125	1.95E-12	49.44878
69	rs926103	C	T	-0.0678	0.697985	0.0104	7.65E-11	42.50016
70	rs9264277	C	T	-0.0862	0.645071	0.0111	9.03E-15	60.30682
71	rs9271365	G	T	0.2484	0.443466	0.0105	4.91E-123	559.6577
72	rs9273371	T	C	0.0791	0.193385	0.014	1.65E-08	31.92234
73	rs9277559	C	T	-0.133	0.331026	0.012	1.86E-28	122.8397
74	rs9497965	T	C	0.0827	0.409035	0.0102	3.71E-16	65.7368
75	rs9511151	A	G	-0.0976	0.279567	0.0106	3.08E-20	84.77851
76	rs9902341	T	C	0.0801	0.172257	0.0129	4.68E-10	38.55525

EA = effect allele, Eaf = effect allele frequency, GWAS = genome-wide association studies, IVW = inverse variance weighting, OA = other allele, SE = standard error, SNPs = single nucleotide polymorphisms.

Table 3

MR regression results and sensitivity analysis results.

Exposure	**Method**	**nSNP**	**OR 95%CI**	***P***	**Horizontal pleiotropy *P***	**Cochran´s *Q* *P***
Hypothyroidism	IVW	13	1.04 (1.01–1.08)	0.017		2.47E-04
	MR-Egger	13	1.08 (1.00–1.16)	0.063	0.385	2.48E-04
	Weighted median	13	1.03 (0.98–1.09)	0.198		
Hyperthyroidism	IVW	75	1.08 (1.05–1.12)	9.22E-06		0.268
	MR-Egger	75	1.17 (1.08–1.26)	2.45E-03	0.057	0.555
	Weighted median	75	1.09 (1.04–1.14)	6.87E-04		

CI = confidence interval, IVW = inverse variance weighting, OR = odds ratios, SNP = single nucleotide polymorphisms.

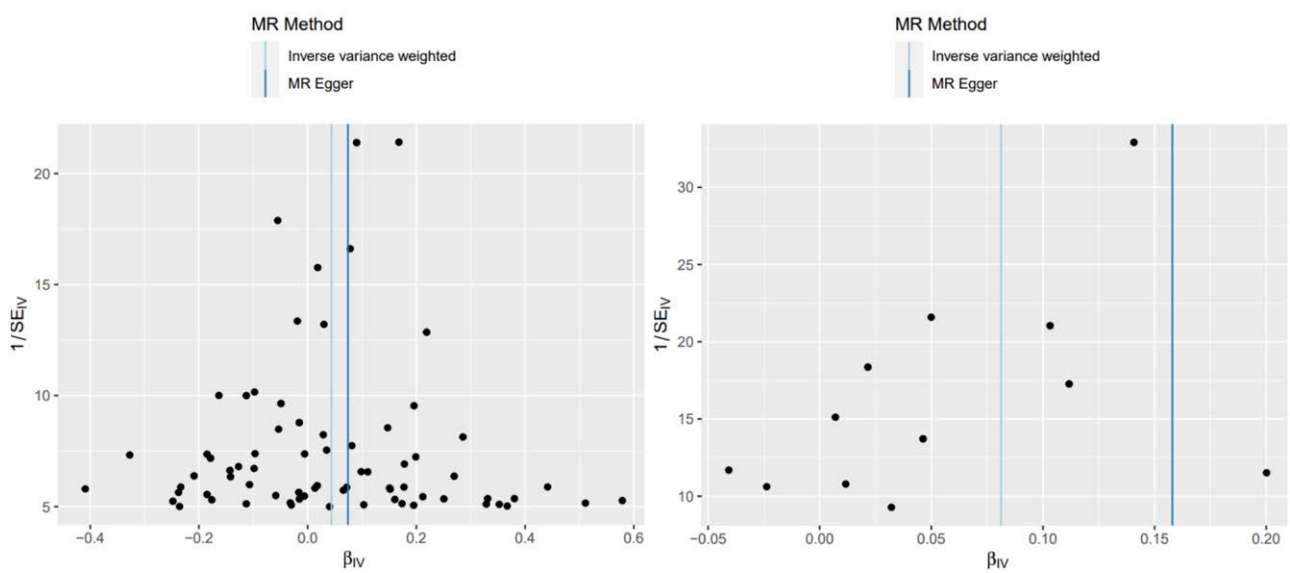

Figure 1. Illustration of heterogeneity test results, hypothyroidism–carpal tunnel syndrome on the left, hyperthyroidism–carpal tunnel syndrome on the right.

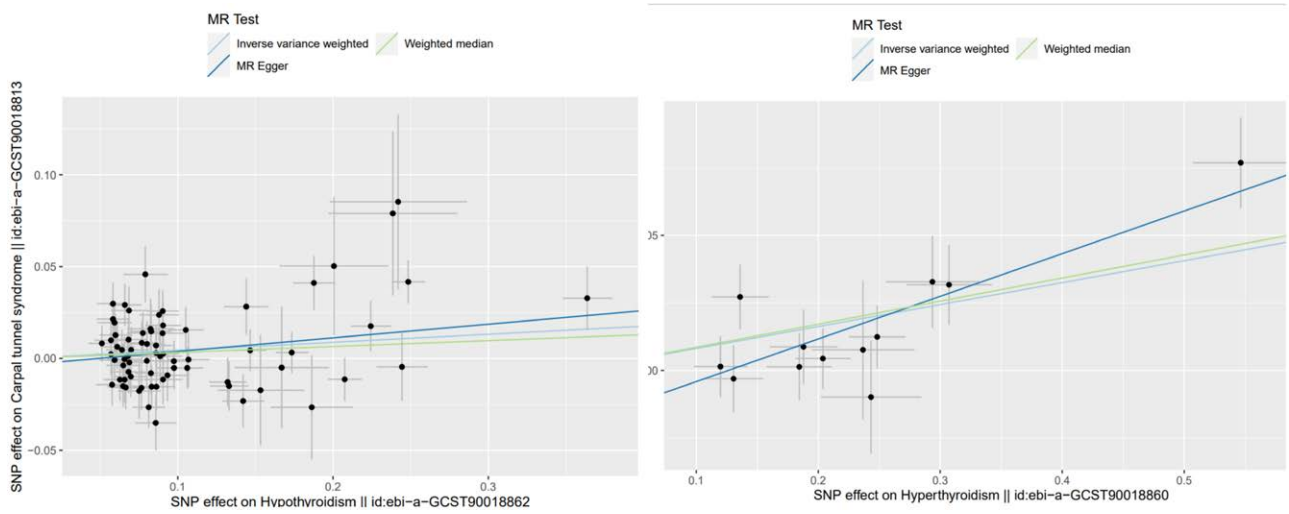

Figure 2. Illustration of the horizontal pleiotropy test results, hypothyroidism–carpal tunnel syndrome on the left and hyperthyroidism–carpal tunnel syndrome on the right.

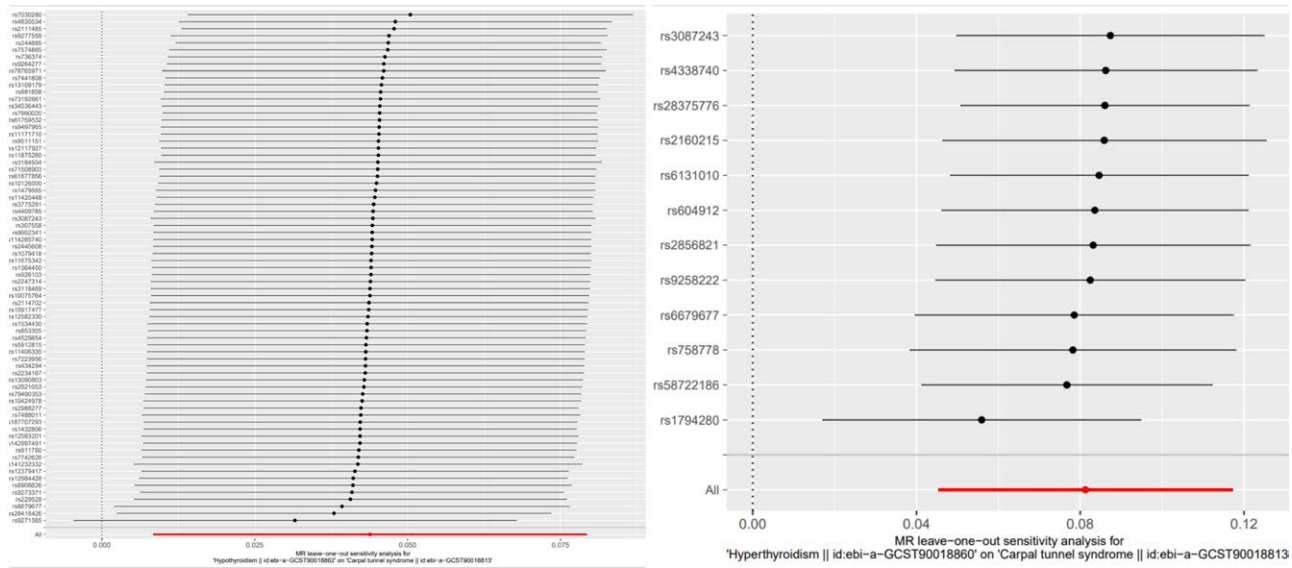

Figure 3. Illustration of the results of the leave-one-out method, hypothyroidism–carpal tunnel syndrome on the left and hyperthyroidism–carpal tunnel syndrome on the right.

there is a risk of recurrence if the release is incomplete.[28] Some patients have certain concerns about surgical treatment due to various reasons. There are many conservative treatment options, including oral medication, splint fixation, ultrasound therapy, and drug injection and so on. However, studies have also shown that conservative treatment is effective for about 82% of patients, but the vast majority of them will have relapse.[36] Therefore, it is very meaningful to search for the cause of disease and to screen and prevent it.

The results of this study showed that compared with the general population, the risk of carpal tunnel syndrome was 1.04 times higher in patients with hypothyroidism and 1.08 times higher in patients with hyperthyroidism (IVW, OR = 1.04, 95% CI = 1.01–1.08; IVW, OR = 1.08, 95% CI = 1.05–1.12). In the general population, 4.6% have hypothyroidism and 1.3% have hyperthyroidism.[37] It can be seen that the incidence of thyroid dysfunction is high in the population, and it is necessary to actively prevent carpal tunnel syndrome in patients with thyroid dysfunction. In addition, previous studies have shown that thyroid dysfunction is significantly related to musculoskeletal diseases such as carpal tunnel syndrome, adhesive joint capsitis and trigger finger.[38] However, this study avoids the interference of traditional research[14] and confirms that patients with thyroid dysfunction are more prone to carpal tunnel syndrome from a genetic perspective.

At the same time, the study has some limitations. First, because all the data came from populations of European descent, it is not known whether the results apply to other populations. Secondly, due to the limitations of current conditions, the sample size of the data used is still small, and the study on reverse causality cannot be carried out. In the future, relevant studies can be conducted when the database is further expanded. Finally, gender dimorphism exists in thyroid dysfunction, which is more common in women than in men.[39] However, the MR study was not stratified by sex, so the conclusion will be affected to some extent.

5. Conclusion

Through the analysis and discussion of genetic data, this MR study found that the prevalence of carpal tunnel syndrome was higher in patients with hypothyroidism, suggesting that active control of hypothyroidism could reduce the occurrence of carpal tunnel syndrome.

Author contributions

Conceptualization: Fan Zhang.
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Writing – original draft: Fan Zhang, Rongrong Cui, Liang Yin.
Writing – review & editing: Fan Zhang, Rongrong Cui, Liang Yin, Rongxiu Bi, Shilu Wang.

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