

**Table S1** Information about the selected databases

GWAS ID	Names of exposures and outcomes	Composition	Source
finn-b-E4_GOITRENOD	Nontoxic single thyroid nodule	1,121 cases; 187,684 controls; European	IEU OpenGWAS project (mrcieu.ac.uk)
ukb-b-20289	Non-cancer illness code, self-reported: hyperthyroidism/thyrotoxicosis	3,545 cases; 459,388 controls; European	IEU OpenGWAS project (mrcieu.ac.uk)
GCST90018855	Hashimoto's thyroiditis GCST90018855_buildGRCh37.tsv.gz	395,640 European. 173,193 East Asian	GWAS Catalog (ebi.ac.uk)
GCST90161832	Thyroid stimulating hormone measurement GCST90161832_buildGRCh37.tsv.gz	2,935 Greater Middle Eastern (Middle Eastern, North African or Persian)	GWAS Catalog (ebi.ac.uk)
GCST90043622	Nontoxic goiter, multinodular goiter GCST90043622_buildGRCh37.tsv.gz	456,348 European	GWAS Catalog (ebi.ac.uk)
ukb-b-19732	Non-cancer illness code, self-reported: hypothyroidism/myxedema	462,933 European	IEU OpenGWAS project (mrcieu.ac.uk)
finn-b-CD2_BENIGN_THYROID	Benign neoplasm of thyroid gland	456,348 European	IEU OpenGWAS project (mrcieu.ac.uk)
GCST90018929	Thyroid carcinoma GCST90018929_buildGRCh37.tsv.gz	491,974 European. 178,723 East Asian	GWAS Catalog (ebi.ac.uk)
GCST90018847	Graves' disease GCST90018847_buildGRCh37.tsv.gz	458,620 European. 175,465 East Asian	GWAS Catalog (ebi.ac.uk)
GCST90014441	Autoimmune thyroid disease GCST90014441_buildGRCh37.tsv	324,681 European	GWAS Catalog (ebi.ac.uk)

GWAS, genome-wide association studies; IEU, Integrative Epidemiology Unit.

**Table S2** Information on the selected SNPs

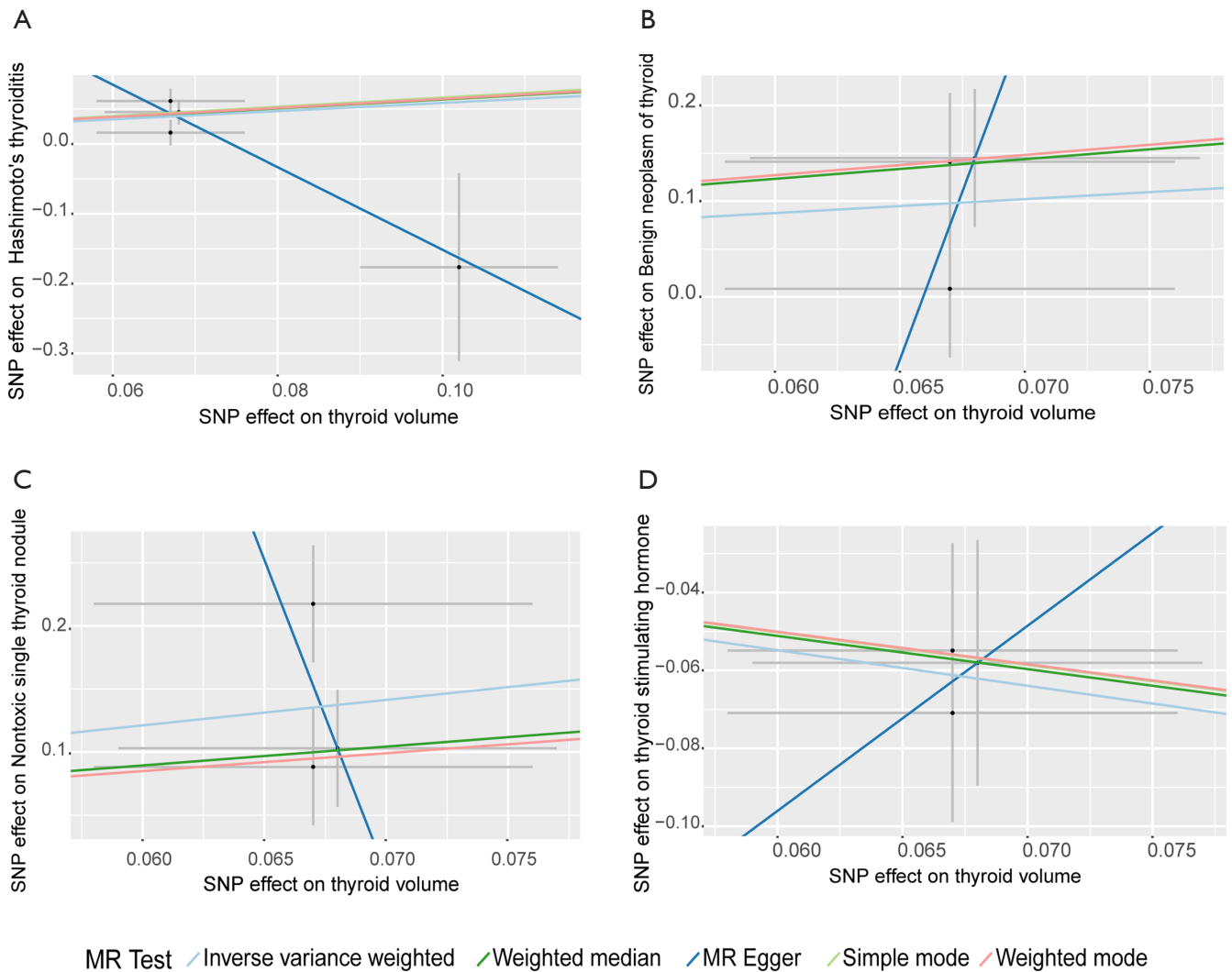
Locus	Chr.	Position	Lead SNP	Effect	SE	Allele 1	Allele 2	EAF	R2	F-statistic
1	1	19711702	rs12138950	-0.102	1.20E-02	A	C	0.847	0.01450148	18.0441064
2	15	47522589	rs4338740	-0.067	9.00E-03	T	C	0.738	0.01116114	13.8408294
3	16	78302049	rs17767419	0.068	9.00E-03	T	C	0.321	0.01149294	14.2570717
4	1	19638105	rs12045440	0.067	9.00E-03	T	G	0.664	0.01116114	13.8408294

SNP, single nucleotide polymorphism; Chr., chromosome; SE, standard error; EAF, effect allele frequencies.

**Table S3** Five MR methods estimate the causal effect of thyroid volume on thyroid disease and TSH

Thyroid disease and TSH	Inverse variance weighted				Weighted median				MR-Egger				Simple mode				Weighted mode			
	OR (95% CI)	$\beta$	SE	P value	OR (95% CI)	$\beta$	SE	P value	OR (95% CI)	$\beta$	SE	P value	OR (95% CI)	$\beta$	SE	P value	OR (95% CI)	$\beta$	SE	P value
Non-toxic single thyroid nodules	7.536 (2.280, 24.911)	2.020	0.610	P<0.001	4.442 (1.430, 13.795)	1.491	0.578	0.009	2.577×10 <sup>-22</sup> (1.490×10 <sup>-117</sup> , 4.460×10 <sup>73</sup> )	-49.710	111.884	0.73	4.122 (0.988, 17.192)	1.416	0.729	0.19	4.122 (1.126, 15.083)	1.416	0.662	0.17
Hyperthyroidism	1.011 (1.008, 1.014)	0.011	0.001	P<0.001	1.010 (1.007, 1.014)	0.010	0.002	P<0.001	1.007 (0.991, 1.023)	0.007	0.008	0.48	1.010 (1.005, 1.015)	0.010	0.003	0.04	1.010 (1.005, 1.015)	0.010	0.002	0.03
Hypothyroidism	0.981 (0.959, 1.003)	-0.020	0.011	0.08	0.988 (0.978, 0.998)	-0.012	0.005	0.02	0.944 (0.815, 1.093)	-0.058	0.075	0.52	0.998 (0.974, 1.022)	-0.002	0.012	0.86	0.997 (0.983, 1.012)	-0.003	0.007	0.74
Hashimoto's thyroiditis	1.800 (1.167, 2.778)	0.588	0.221	0.008	1.891 (1.281, 2.793)	0.637	0.199	0.001	0.003 (1.272×10 <sup>-7</sup> , 57.788)	-5.911	5.085	0.37	1.943 (1.243, 3.038)	0.664	0.228	0.06	1.908 (1.272, 2.860)	0.646	0.207	0.052
Non-toxic multinodular goiter	121.541 (23.323, 633.378)	4.800	0.842	P<0.001	55.152 (14.515, 209.562)	4.010	0.681	P<0.001	179.800 (0.001, 2.501×10 <sup>7</sup> )	5.192	6.042	0.48	43.681 (7.590, 251.396)	3.777	0.893	0.02	43.681 (10.090, 189.104)	3.777	0.748	0.02
Benign neoplasm	4.300 (1.170, 15.802)	1.459	0.664	0.03	7.809 (1.667, 36.578)	2.055	0.788	0.009	3.072×10 <sup>30</sup> (1.364×10 <sup>-68</sup> , 6.919×10 <sup>128</sup> )	70.200	115.543	0.65	8.323 (1.100, 62.955)	2.119	1.032	0.18	8.323 (1.085, 63.864)	2.119	1.040	0.18
Graves' disease	0.136 (0.065, 0.282)	-1.998	0.374	P<0.001	0.117 (0.060, 0.225)	-2.149	0.336	P<0.001	0.000 (1.489×10 <sup>-7</sup> , 0.938)	-7.892	3.994	0.19	0.112 (0.041, 0.300)	-2.193	0.505	0.02	0.134 (0.066, 0.275)	-2.008	0.366	0.01
Thyroid carcinoma	0.401 (0.208, 0.772)	-0.915	0.334	0.006	0.397 (0.188, 0.838)	-0.924	0.381	0.02	2.654 (0.018, 389.841)	0.976	2.546	0.74	0.657 (0.203, 2.129)	-0.420	0.600	0.53	0.265 (0.078, 0.897)	-1.329	0.622	0.12
Autoimmune thyroid disease	1.045 (1.022, 1.069)	0.044	0.011	P<0.001	1.037 (1.010, 1.065)	0.036	0.013	0.007	1.010 (0.901, 1.133)	0.010	0.059	0.88	1.038 (1.000, 1.076)	0.037	0.019	0.14	1.037 (1.005, 1.070)	0.037	0.016	0.11
TSH	0.401 (0.247, 0.652)	-0.913	0.248	P<0.001	0.426 (0.237, 0.767)	-0.852	0.300	0.004	115.729 (2.855×10 <sup>-30</sup> , 4.691×10 <sup>33</sup> )	4.751	37.132	0.92	0.433 (0.219, 0.855)	-0.837	0.347	0.14	0.434 (0.220, 0.858)	-0.834	0.348	0.14

MR, Mendelian randomization; TSH, thyroid stimulating hormone; OR, odds ratio; CI, confidence interval; SE, standard error.



**Figure S1** A scatter plot showing genetically predicted thyroid volume on thyroid diseases. Inverse variance-weighted, weighted-median, MR-Egger, simple mode, and weighted-mode slopes represent the results from these regression analyses. (A) A scatter plot showing the effects of SNPs on thyroid volume and Hashimoto's thyroiditis. (B) A scatter plot showing the effects of SNPs on thyroid volume and benign thyroid neoplasms. (C) A scatter plot showing the effects of SNPs on thyroid volume and non-toxic single thyroid nodules. (D) A scatter plot showing the effects of SNPs on thyroid volume and thyroid stimulating hormone. SNP, single nucleotide polymorphism; MR, Mendelian randomization.

**Table S4** Testing for genetic pleiotropy

Thyroid disease and TSH	MR-Egger		
	Intercept	SE	P value
Non-toxic single thyroid nodules	3.483	7.534	0.724
Hyperthyroidism	0.000	0.001	0.676
Hypothyroidism	0.003	0.006	0.655
Hashimoto's thyroiditis	0.440	0.344	0.329
Non-toxic multinodular goiter	-0.029	0.446	0.954
Benign neoplasm	-4.629	7.780	0.658
Graves' disease	0.405	0.273	0.277
Thyroid carcinoma	-0.135	0.180	0.532
Autoimmune thyroid disease	0.003	0.005	0.614
TSH	-0.381	2.498	0.904

TSH, thyroid stimulating hormone; MR, Mendelian randomization; SE, standard error.