

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1: GWAS analysis

The first stage of GWAS was divided into two steps: performed GWAS on the participants of UK Biobank and further conducted meta-GWAS using three cohorts (including UK Biobank). The GWAS of UK Biobank was performed on all TC patients and 1,031 TC cases by the newly released data (July, 2021). Then we match 5,155 controls without any cancers according to age (± 5 years old), sex, race, assessment center and year of enrollment, which were included in the next GWAS. Samples were genotyped using the UK Biobank Axiom array and UK BiLEVE Axiom Array. The released genotype data were imputed with the reference to the Haplotype Reference Consortium panel. Detailed genotyping and quality control (QC) procedures were described on the UK Biobank website (<http://biobank.ctsu.ox.ac.uk/>). Downstream QC procedures conducted for the next analysis: (1) samples or variants with call rate < 0.99 , (2) individuals with kinship coefficient > 0.0884 , (3) genotypic and phenotypic sex mismatch, (4) heterozygosity rate deviating more than three standard deviations from the mean and missingness of phenotypes or covariates, (5) missingness of phenotypes or covariates, (6) variants with minor allele frequency (MAF) < 0.01 , Hardy-Weinberg equilibrium $P_{(PHWE)} < 1.0 \times 10^{-6}$. After removing these samples and variants, we retained 6,121 samples (986 cases and 5,135 controls) and 6,562,992 SNPs for subsequent GWAS analysis. Then we conducted a fixed-effect Meta GWAS using summary data of UK Biobank (986 cases and 5,135 controls), the FinnGen Study including 321 TC and 96,178 controls and Italian residents based on 649 differentiated TC cases and 431 controls. (1) Hence, a total of 1956 TC cases and 101,924 controls were included in this meta-analysis. Relevant GWAS summary data could be found on the website (<https://gwas.mrcieu.ac.uk/datasets/ieu-a-1082/>; https://gwas.mrcieu.ac.uk/datasets/finn-a-C3_THYROID_GLAND/). Adjusted for age, BMI, year of enrollment, assessment center and the first five ancestry principal components (PCs). GWAS Manhattan

and Quantile-Quantile (QQ) plots were produced and checked for each variant. The genomic inflation factor was calculated by linkage disequilibrium score regression analysis (LDSC).

eMethods 2 The procedure of constructing other PRSs

Through searching GWAS-related studies of TC in PubMed, Ensemble, and MR-base platform, we included eight GWAS research and one PRS research of European related to TC (Supplementary table S2). Finally, four PRS were calculated: the PRS (PRS1) deprived of our Meta-GWAS analysis with $P < 5 \times 10^{-5}$, three secondary PRS deprived of our Meta-GWAS analysis with $P < 5 \times 10^{-6}$ (PRS2), published eight GWAS analyses (PRS3) and the PRS research of European (PRS4), respectively¹⁻⁹. All PRS were abstracted from autosome with $r^2 < 0.99$, $MAF \geq 0.01$ and $P < 5 \times 10^{-5}$. And we evaluated and selected the better PRS through the predictive power and the strength of association.

eAppendix. The result of GWAS analysis

In the GWAS of UK Biobank, we identified 223 genetic loci associated with TC risk of $P < 5 \times 10^{-8}$ on chromosomes 2 and 9, which were in extremely strong LD with rs965513 on chromosome 9 and rs6759952 on chromosome 2 (known SNP related with TC, $r^2 < 0.99$). The GWAS result was presented in Table S3, with the threshold $P < 5 \times 10^{-8}$. For replication, we conducted a GWAS meta-analysis using GWAS summary statistics from UK Biobank, the FinnGen Study and Italian residents. This meta-analysis was conducted using a fixed-effect inverse variance weighted method, and significant SNPs in three cohorts with $P < 5 \times 10^{-5}$ and Q (the Cochran's Q-test) > 0.05 were considered. There were 41 SNPs meeting the criteria, and two top SNPs (rs965513, *FOXO1* of chromosome 9, $P_{\text{meta}} = 5.60 \times 10^{-40}$); rs6759952, *DIRC3* of chromosome 2, $P_{\text{meta}} = 4.36 \times 10^{-11}$) independently associated with TC ($r^2 < 0.99$). Other SNPs with $P > 5 \times 10^{-8}$ and $P < 5 \times 10^{-5}$ were listed in Table S4. Manhattan and QQ plots are in eFigure 1, and the genomic inflation factor (λ) is 1.037.

eTable 1 Healthy lifestyle components		
Healthy lifestyle factors	Source and definition	Self-reported UK Biobank field code
1. Smoke	Never and previous	Favourable
	Current	Unfavourable
2. Total moderate-vigorous physical activity (min/wk):	>=150 minutes moderate activity per week or >= 75 minutes vigorous activity per week	Favourable
	Other	Unfavourable
3. Diet index	UK Biobank Food Frequency Questionnaire at baseline;	
	At least 4 of the following 7 food groups:	
	1. Fruits and Vegetables: >= 5 servings/day	
	2. Fish: >=3 servings/week	
	3. red meat Processed meats <=4 servings/week	
	4. Whole grains: >=5.5 servings/day	
	5. Refined grains <=2 servings/week	
	6. Sugar-sweetened beverages =0 servings/week	
	Adequate intake of >=3 dietary components	Favourable
	Adequate intake of <3 dietary components	Unfavourable
4. Moderate alcohol consumption	UK Biobank Touchscreen questionnaire at baseline; US Dietary guidelines for Americans 2015-2020 of up to 1 drink/day for women and up to 2 drinks/day for men.	
	Women: <14g/day 1 drink-equivalent	
	Men: <28g/day 2 drink-equivalent	
	Women>=14 1 drink-equivalent	Unfavourable
	Men>=28 2 drink-equivalent	
5. Be a Weight	BMI (kg/m ²)	
	18.5-24.9	Favourable
	25-29.9	Intermediate
	>=30 or <18.5	Unfavourable
	Waist circumference (cm(in))	
	Men: <94 (<37)	Favourable
	Women: <80 (<31.5)	
	Men: 94-<102 (37-<40)	Intermediate

	Women: 80-<88 (31.5-<35)	Unfavourable
	Men: ≥ 102 (≥ 40)	
	Women: ≥ 88 (≥ 35)	
	Weight	
	The sum score of BMI and waist circumference ≥ 4	Favourable
	The sum score of BMI and waist circumference < 4	Unfavourable
Lifestyle	3-5 favorable lifestyle factors	Favourable
	2 favorable lifestyle factors	Intermediate
	0-1 favorable lifestyle factors	Unfavourable

eTable 2 SNPs associated with thyroid cancer from PubMed, Ensemble, and MR-base platform

C H R	Position	SNP	MAF	Gene	P	PubMed ID
9	97793827	rs965513	0.34	<i>FOXE1</i>	2.00E-27	19198613
14	36180040	rs944289	0.42	<i>NKX2-1</i>	2.00E-09	19198613
14	36269155	rs116909374	0.04	<i>MBIP</i>	5.00E-11	22267200
2	217445617	rs966423	0.43	<i>DIRC3</i>	1.00E-09	22267200
8	32574851	rs2439302	0.47	<i>NRG1</i>	2.00E-09	22267200
9	97793827	rs965513	0.34	<i>FOXE1</i>	3.00E-10	23894154
2	217406996	rs6759952	0.44	<i>DIRC3</i>	6.00E-10	23894154
5	1279675	rs10069690	0.28	<i>TERT</i>	3.20E-07	23894154
7	110540965	rs10238549	0.32	<i>LOC105375451</i>	4.10E-06	23894154
9	136374886	rs10781500	0.39	<i>CARD9</i>	3.50E-05	23894154
3	158745312	rs7617304	0.22	<i>LOC100287290</i>	4.60E-05	23894154
20	39318791	rs7267944	0.19	<i>DHX35</i>	1.34E-08	25029422
9	97793827	rs965513	0.34	<i>FOXE1</i>	3.00E-23	25855579
9	97896036	rs7037324	0.22	<i>FOXE1</i>	1.00E-17	25855579
9	97865986	rs10122541	0.37	<i>FOXE1</i>	1.00E-17	25855579
9	97896036	rs7037324	0.37	<i>FOXE1</i>	1.00E-17	25855579
9	97775520	rs1588635	0.34	<i>PTCSC2</i>	2.00E-58	28195142
14	36269155	rs116909374	0.04	<i>MBIP</i>	1.00E-16	28195142
15	67163292	rs56062135	0.21	<i>SMAD3</i>	5.00E-09	28195142
5	1279675	rs10069690	0.28	<i>TERT</i>	3.00E-07	28195142
9	97772985	rs7030280	0.34	<i>PTCSC2</i>	5.00E-28	32887889
8	32575620	rs2466074	0.47	<i>NRG1</i>	5.00E-11	32887889
9	97886005	rs12002967	0.11	<i>FANCC</i>	3.00E-07	32887889
1	218449752	rs6697759	0.45	<i>RRP15</i>	4.00E-07	32887889
10	72033486	rs72806259	0.1	<i>Intergenic</i>	5.00E-07	32887889
4	112649292	rs76032629	0.03	<i>LARP7,</i> <i>MIR302A,</i> <i>MIR302B ,</i> <i>MIR302C,</i> <i>MIR302D,</i> <i>MIR367,</i> <i>MIR302CHG</i>	6.00E-07	32887889
4	156130312	rs555678255	0.1	<i>LOC102724785</i>	8.00E-07	32887889
11	20338417	rs74518511	0.03	<i>Intergenic</i>	9.00E-07	32887889
15	97673727	rs77166399	0.12	<i>LINC00923</i>	9.00E-07	32887889
9	97775520	rs1588635	0.34	<i>NR</i>	2.00E-58	33527407
16	79668474	rs16950982	0.35	<i>MAF</i>	4.70E-09	33527407
1	61142801	rs334729	0.04	<i>NFIA</i>	8.70E-08	33527407
19	22065515	rs10415826	0.2	<i>ZNF257</i>	8.70E-07	33527407

2	217427435	rs11693806	0.29	<i>DIRC3</i>	1.50E-24	32132206 *
14	36063370	rs368187	0.46	<i>LOC105370452</i>	5.10E-23	32132206 *
8	32575278	rs2466076	0.47	<i>NRG1</i>	1.50E-17	32132206 *
1	233276815	rs12129938	0.22	<i>PCNX2</i>	4.00E-11	32132206 *
10	103934543	rs7902587	0.09	<i>OBFC1</i>	5.40E-11	32132206 *
5	112150207	rs73227498	0.13	<i>EPB41L4A</i>	3.00E-10	32132206 *
15	67165147	rs2289261	0.37	<i>SMAD3</i>	3.10E-09	32132206 *
3	169800667	rs6793295	0.27	<i>LRRC34</i>	2.70E-08	32132206 *

CHR=chromosome; SNP=single nucleotide polymorphisms; MAF=minor allele frequency.

Note: the published literature (PMID: 32132206) was research on the relationship between polygenic risk score and thyroid cancer

eTable 3 Baseline Characteristics of six diet factors in the UK Biobank

Variable ^a	Overall (n=264,956)	Non incident TC (n= 264,533)	Incident TC (n=423)	P	
Total fruit and vegetables intake					
Unfavourable	196312 (74.09)	196012 (74.10)	300 (70.92)	0.15	
Favourable	68644 (25.91)	68521 (25.90)	123 (29.08)		
Fish intake					
Unfavourable	64922 (24.50)	64826 (24.51)	96 (22.70)	0.42	
Favourable	200034 (75.50)	199707 (75.49)	327 (77.30)		
Processed meat and red meat intake					
Unfavourable	190665 (71.96)	190381 (71.97)	284 (67.14)	0.03	
Favourable	74291 (28.04)	74152 (28.03)	139 (32.86)		
Whole grains intake					
Unfavourable	93786 (35.40)	93643 (35.40)	143 (33.81)	0.53	
Favourable	171170 (64.60)	170890 (64.60)	280 (66.19)		
Refine grains intake					
Unfavourable	137401 (51.86)	137195 (51.86)	206 (48.70)	0.21	
Favourable	127555 (48.14)	127338 (48.14)	217 (51.30)		
Sugar drinking intake					
Unfavourable	221086 (83.44)	220734 (83.44)	352 (83.22)	0.95	
Favourable	43870 (16.56)	43799 (16.56)	71 (16.78)		
^a Variables are numbers (percentages)					

eTable 4 Baseline characteristics between women and men

Variable ^a	Women (n=137,665)	Men (n=127,291)	P
Thyroid			<0.001
Case	302 (71.39)	121 (28.61)	
Control	137363 (99.78)	127170 (99.90)	
Age	57 (49, 62)	57 (49, 63)	0.003
Townsend deprivation index			<0.001
1 (least deprived)	30684 (22.29)	28219 (22.17)	
2-4	86362 (62.73)	78295 (61.51)	
5 (most deprived)	20619 (14.98)	20777 (16.32)	
Educational qualifications			<0.001
College or University degree	45640 (33.15)	45753 (35.94)	
Secondary Education	79005 (57.39)	64471 (50.65)	
Some professional qualifications	13020 (9.46)	17067 (13.41)	
Average total household income before tax			<0.001
Less than 18,000	24359 (17.73)	19451 (15.33)	
18,000 to 30,999	30605 (22.28)	27478 (21.65)	
31,000 to 51,999	51009 (37.13)	43099 (33.96)	
52,000 to 100,000	25000 (18.20)	29078 (22.91)	
Greater than 100,000	6398 (4.66)	7794 (6.14)	
Total fruit and vegetables intake			
Unfavourable	96592 (70.16)	99720 (78.34)	<0.001
Favourable	41073 (29.84)	27571 (21.66)	
Fish intake			
Unfavourable	31767 (23.08)	33155 (26.05)	<0.001
Favourable	105898 (76.92)	94136 (73.95)	
Processed meat and red meat intake			
Unfavourable	88013 (63.93)	102652 (80.64)	<0.001
Favourable	49652 (36.07)	24639 (19.36)	
Whole grains intake			
Unfavourable	43310 (31.46)	50476 (39.65)	<0.001
Favourable	94355 (68.54)	76815 (60.35)	
Refine grains intake			
Unfavourable	61852 (44.93)	75549 (59.35)	<0.001
Favourable	75813 (55.07)	51742 (40.65)	
Sugar drinking intake			
Unfavourable	115839 (84.15)	105247 (82.68)	<0.001
Favourable	21826 (15.85)	22044 (17.32)	
Diet index			<0.001
Unfavourable	53987 (39.22)	68932 (54.15)	
Favourable	83678 (60.78)	58359 (45.85)	
Total moderate-vigorous physical activity			<0.001
Unfavourable	65634 (47.68)	56736 (44.57)	

Favourable	72031 (52.32)	70555 (55.43)	
Weight			<0.001
Unfavourable	72920 (52.97)	73545 (57.78)	
Favourable	64745 (47.03)	53746 (42.22)	
Smoke intake			<0.001
Unfavourable	8333 (6.05)	12424 (9.76)	
Favourable	129332 (93.95)	114867 (90.24)	
Alcohol consumption			<0.001
Unfavourable	41153 (29.89)	40500 (31.82)	
Favourable	96512 (70.11)	86791 (68.18)	
Unweighted lifestyle			<0.001
Unfavourable	33621 (24.42)	41231 (32.39)	
Intermediate	45718 (33.21)	41969 (32.97)	
Favourable	58326 (42.37)	44091 (34.64)	
Weighted lifestyle			
Unfavourable	29989 (21.78)	59046 (46.39)	<0.001
Intermediate	55116 (40.04)	26799 (21.05)	
Favourable	52560 (38.18)	41446 (32.56)	
PRS			
T1	45595 (33.12)	42728 (33.57)	0.002
T2	46295 (33.63)	42019 (33.01)	
T3	45775 (33.25)	42544 (33.42)	

PRS=polygenic risk score; TC=thyroid cancer.

a Variable are numbers (percentages) except for age, which was presented as median and interquartile range

eTable 5 GWAS results of UK Biobank ($P < 5 \times 10^{-8}$)								
C H R	Position	SNP	Effect_ allele	Other_ allele	BETA	SE	P	LD
9	10055901 1	rs1329508 1	C	T	0.464	0.059	3.216E- 15	LD with rs965513
9	10055911 4	rs1329525 4	C	T	0.462	0.059	4.299E- 15	LD with rs965513
9	10067027 2	rs1561957	C	T	0.456	0.059	8.076E- 15	LD with rs965513
9	10056148 6	rs1081809 0	T	C	0.457	0.059	8.563E- 15	LD with rs965513
9	10054660 0	rs925489	T	C	0.452	0.058	1.049E- 14	LD with rs965513
9	10054893 4	rs7864322	T	C	0.452	0.058	1.091E- 14	LD with rs965513
9	10054901 3	rs7850258	G	A	0.452	0.058	1.091E- 14	LD with rs965513
9	10055490 7	rs4743131	G	C	0.451	0.058	1.166E- 14	LD with rs965513
9	10054217 6	rs1075992 7	G	A	0.450	0.058	1.289E- 14	LD with rs965513
9	10054762 7	rs4273946	C	G	0.450	0.058	1.298E- 14	LD with rs965513
9	10054797 2	rs7020976	C	T	0.450	0.058	1.321E- 14	LD with rs965513
9	10054814 4	rs7032019	A	G	0.451	0.059	1.322E- 14	LD with rs965513
9	10054486 8	rs7847663	T	C	0.450	0.058	1.339E- 14	LD with rs965513
9	10054604 0	rs4743130	T	C	0.450	0.058	1.339E- 14	LD with rs965513
9	10054621 9	rs1561962	T	C	0.450	0.058	1.339E- 14	LD with rs965513
9	10054639 1	rs925488	A	G	0.450	0.058	1.339E- 14	LD with rs965513
9	10053757 7	rs1098370 1	A	G	0.450	0.058	1.349E- 14	LD with rs965513
9	10053745 5	rs1098370 0	C	T	0.450	0.058	1.375E- 14	LD with rs965513
9	10053847 0	rs7028661	G	A	0.450	0.058	1.375E- 14	LD with rs965513

9	10054054 1	rs7021576	T	C	0.450	0.058	1.389E- 14	LD with rs965513
9	10054147 3	rs2401637	C	T	0.450	0.058	1.389E- 14	LD with rs965513
9	10055037 5	rs7030241	A	T	0.450	0.059	1.435E- 14	LD with rs965513
9	10055045 5	rs7027030	C	A	0.450	0.059	1.435E- 14	LD with rs965513
9	10053951 8	rs3605246 0	AT	A	0.450	0.059	1.467E- 14	LD with rs965513
9	10066353 5	rs1114920 99	GTTT CC	G	0.450	0.059	1.468E- 14	LD with rs965513
9	10053892 3	rs1081805 0	G	A	0.449	0.058	1.521E- 14	LD with rs965513
9	10055002 8	rs1443438	C	T	0.449	0.058	1.550E- 14	LD with rs965513
9	10055610 9	rs965513	G	A	0.449	0.059	1.592E- 14	
9	10053780 2	rs1588635	C	A	0.449	0.059	1.774E- 14	LD with rs965513
9	10055395 7	rs1098376 1	C	A	0.448	0.059	1.881E- 14	LD with rs965513
9	10065009 6	rs7866436	A	G	0.445	0.058	2.004E- 14	LD with rs965513
9	10055255 9	rs1073949 6	T	C	0.448	0.059	2.026E- 14	LD with rs965513
9	10053520 3	rs7030256	G	C	0.449	0.059	2.091E- 14	LD with rs965513
9	10053526 7	rs7030280	T	C	0.449	0.059	2.091E- 14	LD with rs965513
9	10066151 4	rs1135458 66	GTGA GGAA GGGA C	G	0.447	0.059	2.200E- 14	LD with rs965513
9	10066539 3	rs7044799	T	A	0.447	0.059	2.200E- 14	LD with rs965513
9	10065878 2	rs7587096 47	C	CTTA T	0.447	0.058	2.236E- 14	LD with rs965513
9	10066759 9	rs1561961	T	C	0.446	0.058	2.381E- 14	LD with rs965513
9	10058202 4	rs6478413	G	A	0.449	0.059	2.565E- 14	LD with rs965513
9	10064878 0	rs1081821 4	C	T	0.446	0.059	2.648E- 14	LD with rs965513

9	10066447 4	rs1098425 3	G	A	0.445	0.058	2.813E- 14	LD with rs965513
9	10058319 5	rs1443432	T	C	0.448	0.059	2.841E- 14	LD with rs965513
9	10066082 4	rs7022148	C	T	0.444	0.058	2.857E- 14	LD with rs965513
9	10066110 0	rs7034336	T	C	0.444	0.058	2.875E- 14	LD with rs965513
9	10066136 7	rs9775370	A	G	0.444	0.058	2.875E- 14	LD with rs965513
9	10066237 9	rs7027221	C	T	0.444	0.058	2.875E- 14	LD with rs965513
9	10066239 6	rs7038998	G	C	0.444	0.058	2.875E- 14	LD with rs965513
9	10066267 1	rs1073952 6	C	T	0.444	0.058	2.875E- 14	LD with rs965513
9	10066370 0	rs3824495	A	C	0.444	0.058	2.875E- 14	LD with rs965513
9	10066374 5	rs3808893	T	C	0.444	0.058	2.875E- 14	LD with rs965513
9	10066566 9	rs7031386	T	G	0.444	0.058	2.875E- 14	LD with rs965513
9	10066569 8	rs7048255	G	A	0.444	0.058	2.875E- 14	LD with rs965513
9	10066654 3	rs9299258	G	T	0.444	0.058	2.875E- 14	LD with rs965513
9	10065893 8	rs6478469	G	A	0.444	0.058	3.012E- 14	LD with rs965513
9	10066014 5	rs2870331 4	T	A	0.444	0.058	3.018E- 14	LD with rs965513
9	10066089 6	rs1098423 5	T	C	0.444	0.058	3.040E- 14	LD with rs965513
9	10066787 1	rs1145550 6	AT	A	0.445	0.059	3.044E- 14	LD with rs965513
9	10065640 2	rs7032086	G	T	0.444	0.058	3.062E- 14	LD with rs965513
9	10066028 4	rs1098423 0	T	C	0.444	0.058	3.062E- 14	LD with rs965513
9	10066197 2	rs1081824 1	G	A	0.444	0.058	3.160E- 14	LD with rs965513
9	10065271 1	rs1200652 2	C	G	0.443	0.058	3.268E- 14	LD with rs965513
9	10066438 2	rs6478471	G	A	0.443	0.058	3.305E- 14	LD with rs965513

9	10065258 2	rs1051225 5	A	G	0.443	0.058	3.311E- 14	LD with rs965513
9	10065275 5	rs1200476 2	G	A	0.443	0.058	3.311E- 14	LD with rs965513
9	10065312 8	rs1255087 2	A	G	0.443	0.058	3.311E- 14	LD with rs965513
9	10065382 1	rs7034249	T	C	0.443	0.058	3.311E- 14	LD with rs965513
9	10065409 3	rs7034648	A	C	0.443	0.058	3.311E- 14	LD with rs965513
9	10065645 9	rs7032114	G	T	0.443	0.058	3.311E- 14	LD with rs965513
9	10065711 9	rs1011521 6	G	T	0.443	0.058	3.311E- 14	LD with rs965513
9	10065772 0	rs7036589	T	A	0.443	0.058	3.311E- 14	LD with rs965513
9	10064863 1	rs1081821 3	C	T	0.444	0.059	3.432E- 14	LD with rs965513
9	10065831 8	rs7037324	G	A	0.442	0.058	3.643E- 14	LD with rs965513
9	10055697 2	rs1075994 4	G	A	0.443	0.059	3.867E- 14	LD with rs965513
9	10062982 7	rs4582663	G	T	0.438	0.059	8.244E- 14	LD with rs965513
9	10061414 0	rs3758249	C	T	0.433	0.058	9.782E- 14	LD with rs965513
9	10061747 9	rs1443434	T	G	0.433	0.058	9.796E- 14	LD with rs965513
9	10061065 2	rs7851552	A	C	0.433	0.058	1.014E- 13	LD with rs965513
9	10061075 9	rs7851660	A	C	0.433	0.058	1.014E- 13	LD with rs965513
9	10061123 3	rs1234830 4	C	T	0.433	0.058	1.014E- 13	LD with rs965513
9	10061227 0	rs894673	T	A	0.433	0.058	1.014E- 13	LD with rs965513
9	10061370 0	rs3758251	C	G	0.433	0.058	1.014E- 13	LD with rs965513
9	10061395 6	rs1004680 5	A	G	0.433	0.058	1.014E- 13	LD with rs965513
9	10061555 3	rs1330247 0	G	A	0.432	0.058	1.035E- 13	LD with rs965513
9	10061591 4	rs1867277	G	A	0.432	0.058	1.035E- 13	LD with rs965513

9	10061606 6	rs1867280	C	G	0.432	0.058	1.035E- 13	LD with rs965513
9	10061511 7	rs907577	T	C	0.432	0.058	1.057E- 13	LD with rs965513
9	10061594 9	rs1867278	A	C	0.432	0.058	1.057E- 13	LD with rs965513
9	10064177 1	rs7563968 39	C	CCAC CA	0.437	0.059	1.071E- 13	LD with rs965513
9	10061034 8	rs1081813 3	G	C	0.432	0.058	1.079E- 13	LD with rs965513
9	10061038 2	rs1234137 7	G	C	0.432	0.058	1.079E- 13	LD with rs965513
9	10058883 9	rs7848973	G	A	0.437	0.059	1.086E- 13	LD with rs965513
9	10058307 4	rs1012422 0	C	T	0.437	0.059	1.099E- 13	LD with rs965513
9	10061460 1	rs3758248	A	G	0.432	0.058	1.102E- 13	LD with rs965513
9	10061702 1	rs3021526	T	C	0.432	0.058	1.119E- 13	LD with rs965513
9	10060868 2	rs1234869 1	A	G	0.432	0.058	1.122E- 13	LD with rs965513
9	10060898 0	rs1328800 0	C	T	0.432	0.058	1.122E- 13	LD with rs965513
9	10060923 0	rs7873389	T	C	0.432	0.058	1.198E- 13	LD with rs965513
9	10064572 8	rs2120264	G	A	0.435	0.059	1.217E- 13	LD with rs965513
9	10063415 0	rs7528477 55	C	CAG	0.435	0.059	1.233E- 13	LD with rs965513
9	10066013 6	rs3532445 1	T	A	0.433	0.058	1.268E- 13	LD with rs965513
9	10063260 6	rs7868534	A	G	0.434	0.059	1.282E- 13	LD with rs965513
9	10059170 5	rs7033765	T	A	0.436	0.059	1.295E- 13	LD with rs965513
9	10063785 9	rs1012369 9	G	A	0.433	0.059	1.347E- 13	LD with rs965513
9	10063842 0	rs4743139	G	A	0.435	0.059	1.348E- 13	LD with rs965513
9	10063457 9	rs1955143	T	A	0.433	0.059	1.363E- 13	LD with rs965513
9	10063578 0	rs1075998 1	G	A	0.433	0.059	1.363E- 13	LD with rs965513

9	100636398	rs925487	T	C	0.433	0.059	1.363E-13	LD with rs965513
9	100647545	rs4255258	G	A	0.434	0.059	1.373E-13	LD with rs965513
9	100624259	rs12343182	C	G	0.433	0.059	1.401E-13	LD with rs965513
9	100626884	rs7860144	G	A	0.433	0.059	1.471E-13	LD with rs965513
9	100627562	rs13299924	T	C	0.433	0.059	1.471E-13	LD with rs965513
9	100628238	rs10120412	C	T	0.433	0.059	1.471E-13	LD with rs965513
9	100628268	rs10122541	A	G	0.433	0.059	1.471E-13	LD with rs965513
9	100628642	rs2417575	A	G	0.433	0.059	1.471E-13	LD with rs965513
9	100628707	rs2417576	T	C	0.433	0.059	1.471E-13	LD with rs965513
9	100631298	rs1443436	A	T	0.433	0.059	1.471E-13	LD with rs965513
9	100631662	rs7037175	C	G	0.433	0.059	1.471E-13	LD with rs965513
9	100631799	9:100631799_CCAA_A_C	C	CCAA A	0.433	0.059	1.471E-13	LD with rs965513
9	100633386	rs10818175	C	T	0.433	0.059	1.471E-13	LD with rs965513
9	100634589	rs1955144	G	A	0.433	0.059	1.471E-13	LD with rs965513
9	100634751	rs1955145	A	C	0.433	0.059	1.471E-13	LD with rs965513
9	100607497	rs6478437	G	A	0.430	0.058	1.578E-13	LD with rs965513
9	100607837	rs2401639	C	T	0.430	0.058	1.578E-13	LD with rs965513
9	100639065	rs12342417	A	G	0.432	0.059	1.619E-13	LD with rs965513
9	100639275	rs10984103	C	A	0.432	0.059	1.619E-13	LD with rs965513
9	100644939	rs4743142	A	G	0.432	0.059	1.629E-13	LD with rs965513
9	100604213	rs7040492	G	A	0.429	0.058	1.737E-13	LD with rs965513

9	100585506	rs4297160	A	G	0.433	0.059	1.786E-13	LD with rs965513
9	100623377	rs993501	A	G	0.431	0.059	1.839E-13	LD with rs965513
9	100624299	rs6478445	G	A	0.431	0.059	1.839E-13	LD with rs965513
9	100624622	rs10113884	T	C	0.431	0.059	1.839E-13	LD with rs965513
9	100642065	rs7044121	T	A	0.431	0.059	1.844E-13	LD with rs965513
9	100624770	rs10117642	C	T	0.431	0.059	1.931E-13	LD with rs965513
9	100624981	rs10119853	A	G	0.431	0.059	1.931E-13	LD with rs965513
9	100625193	rs10759975	C	T	0.431	0.059	1.931E-13	LD with rs965513
9	100630439	rs7847010	C	T	0.431	0.059	1.931E-13	LD with rs965513
9	100637681	rs13287360	G	A	0.431	0.059	1.931E-13	LD with rs965513
9	100640605	rs13286291	C	A	0.431	0.059	1.937E-13	LD with rs965513
9	100624602	rs10119760	C	G	0.430	0.059	1.985E-13	LD with rs965513
9	100640410	rs4592135	A	G	0.435	0.059	2.006E-13	LD with rs965513
9	100591463	rs7045138	T	C	0.432	0.059	2.040E-13	LD with rs965513
9	100599969	rs7049054	G	T	0.428	0.058	2.144E-13	LD with rs965513
9	100600241	rs7018683	C	T	0.428	0.058	2.144E-13	LD with rs965513
9	100600702	rs7860598	A	G	0.428	0.058	2.144E-13	LD with rs965513
9	100598568	rs4743134	A	C	0.427	0.058	2.200E-13	LD with rs965513
9	100599493	rs4743135	T	C	0.427	0.058	2.200E-13	LD with rs965513
9	100600635	rs7847126	C	A	0.427	0.058	2.200E-13	LD with rs965513
9	100610859	rs10638868	ACTC C	A	0.428	0.058	2.360E-13	LD with rs965513
9	100596439	rs7043885	T	C	0.427	0.058	2.410E-13	LD with rs965513

9	100603008	rs10818124	T	C	0.426	0.058	2.412E-13	LD with rs965513
9	100619090	rs202204950	T	TCTC	0.427	0.058	2.850E-13	LD with rs965513
9	100622189	rs907581	G	A	0.427	0.058	2.892E-13	LD with rs965513
9	100617583	rs1443435	C	T	0.424	0.058	3.067E-13	LD with rs965513
9	100596689	9:100596689_TA_T	T	TA	0.446	0.061	3.394E-13	LD with rs965513
9	100601771	rs7026669	C	T	0.439	0.060	3.736E-13	LD with rs965513
9	100606559	9:100606559_AAAA_T_A	A	AAAA T	0.437	0.060	5.064E-13	LD with rs965513
9	100606216	rs13295389	A	G	0.437	0.060	5.171E-13	LD with rs965513
9	100620077	rs35828132	ACCG G	A	0.420	0.058	6.287E-13	LD with rs965513
9	100582390	rs35061703	TAGA C	T	0.438	0.061	6.698E-13	LD with rs965513
9	100638602	rs577883824	G	GT	0.424	0.059	6.956E-13	LD with rs965513
9	100612185	rs894672	T	C	0.432	0.060	8.192E-13	LD with rs965513
9	100612774	rs7848950	C	T	0.432	0.060	8.192E-13	LD with rs965513
9	100614188	rs10983975	C	A	0.432	0.060	8.192E-13	LD with rs965513
9	100614296	rs4743138	G	A	0.432	0.060	8.192E-13	LD with rs965513
9	100615359	rs907576	T	C	0.432	0.060	8.192E-13	LD with rs965513
9	100615660	rs7849497	C	G	0.432	0.060	8.192E-13	LD with rs965513
9	100616041	rs1867279	C	T	0.432	0.060	8.192E-13	LD with rs965513
9	100616583	rs3021523	C	T	0.432	0.060	8.317E-13	LD with rs965513
9	100612807	rs1348386	G	A	0.431	0.060	8.724E-13	LD with rs965513
9	100617375	rs7046645	C	T	0.432	0.060	8.739E-13	LD with rs965513

9	10061971 9	rs1234719 1	T	C	0.417	0.058	8.775E- 13	LD with rs965513
9	10062041 2	rs4460498	C	T	0.417	0.058	9.043E- 13	LD with rs965513
9	10060618 8	rs7849834	C	T	0.431	0.060	1.049E- 12	LD with rs965513
9	10060603 6	rs7875783	G	A	0.429	0.060	1.222E- 12	LD with rs965513
9	10060543 3	rs7048394	C	T	0.429	0.060	1.229E- 12	LD with rs965513
9	10058142 7	rs7870871	C	T	0.429	0.060	1.270E- 12	LD with rs965513
9	10060600 4	rs7860651	T	C	0.428	0.060	1.388E- 12	LD with rs965513
9	10060393 5	rs7023267	A	G	0.428	0.060	1.465E- 12	LD with rs965513
9	10060030 8	rs7046186	G	A	0.427	0.061	1.748E- 12	LD with rs965513
9	10060071 2	rs7847259	G	A	0.427	0.061	1.748E- 12	LD with rs965513
9	10059523 8	rs7024345	G	A	0.427	0.061	1.760E- 12	LD with rs965513
9	10064484 5	9:1006448 45_TA_T	T	TA	0.429	0.061	1.778E- 12	LD with rs965513
9	10059270 5	rs1073951 3	T	C	0.427	0.061	1.930E- 12	LD with rs965513
9	10059826 1	rs1912996	T	G	0.426	0.061	2.000E- 12	LD with rs965513
9	10065812 3	rs7021160	A	C	0.425	0.061	2.129E- 12	LD with rs965513
9	10059203 0	rs6478423	T	C	0.426	0.061	2.187E- 12	LD with rs965513
9	10062073 0	rs973473	G	T	0.424	0.061	2.897E- 12	LD with rs965513
9	10062138 6	rs1912998	C	T	0.423	0.061	3.508E- 12	LD with rs965513
9	10059884 2	9:1005988 42_CT_C	C	CT	0.413	0.059	3.756E- 12	LD with rs965513
9	10062259 7	rs907580	C	T	0.421	0.061	4.069E- 12	LD with rs965513
9	10062272 3	rs907579	T	G	0.421	0.061	4.069E- 12	LD with rs965513
9	10062288 3	rs907578	G	A	0.421	0.061	4.069E- 12	LD with rs965513

9	100620326	rs1465965	T	C	0.421	0.061	4.335E-12	LD with rs965513
9	100621926	rs907582	C	T	0.420	0.061	4.772E-12	LD with rs965513
9	100608745	rs10759960	G	A	0.409	0.059	5.052E-12	LD with rs965513
9	100619733	rs925486	T	C	0.418	0.061	5.681E-12	LD with rs965513
9	100619561	rs925485	C	G	0.418	0.061	6.015E-12	LD with rs965513
9	100669073	rs723227	A	G	0.401	0.059	8.071E-12	LD with rs965513
9	100534823	rs7045465	T	A	0.391	0.058	1.768E-11	LD with rs965513
9	100534147	rs1877431	G	A	0.389	0.058	2.337E-11	LD with rs965513
9	100575888	rs7859751	A	G	0.398	0.060	2.364E-11	LD with rs965513
9	100574120	rs7870795	C	T	0.398	0.060	2.406E-11	LD with rs965513
9	100542706	rs6478395	C	T	-0.406	0.061	2.495E-11	LD with rs965513
9	100573925	rs7870540	C	T	0.397	0.060	3.016E-11	LD with rs965513
9	100532965	rs1533180	G	T	-0.396	0.061	1.118E-10	LD with rs965513
9	100533317	9:100533317_ACT_A	A	ACT	0.371	0.059	2.362E-10	LD with rs965513
9	100551908	rs7847449	C	A	-0.380	0.064	3.485E-09	LD with rs965513
9	100561147	rs1867281	A	G	-0.374	0.063	3.733E-09	LD with rs965513
9	100560368	rs10983796	T	C	-0.372	0.063	4.278E-09	LD with rs965513
9	100536542	rs62573974	C	T	-0.363	0.063	7.001E-09	LD with rs965513
9	100539696	rs10983705	G	C	-0.362	0.063	7.403E-09	LD with rs965513
9	100546486	rs754459513	TAA	T	-0.360	0.063	8.816E-09	LD with rs965513
9	100675976	rs2120262	A	C	0.337	0.059	8.829E-09	LD with rs965513

9	100543880	rs1877432	G	A	-0.360	0.063	9.588E-09	LD with rs965513
9	100536605	9:100536605_TGAA AAGTA_ T	TGAA AAGT A	T	-0.359	0.063	9.629E-09	LD with rs965513
9	100671393	rs10760011	C	A	0.332	0.058	1.326E-08	LD with rs965513
2	218296732	rs16857611	C	T	0.349	0.062	2.093E-08	LD with rs6759952
2	218296508	rs16857609	C	T	0.349	0.062	2.148E-08	LD with rs6759952
2	218296374	rs57481445	A	G	0.347	0.062	2.418E-08	LD with rs6759952
9	100670610	rs7042459	C	T	0.321	0.059	4.091E-08	LD with rs965513
2	218294217	rs12990503	G	C	0.341	0.062	4.252E-08	LD with rs6759952
2	218292141	rs3821098	C	T	0.340	0.062	4.521E-08	LD with rs6759952
2	218292158	rs11693806	G	C	0.340	0.062	4.521E-08	LD with rs6759952
CHR=chromosome; SNP=single nucleotide polymorphisms; MAF=minor allele frequency.								
Note: In the GWAS of UK Biobank, we identified 223 genetic loci associated with TC risk of $P < 5 \times 10^{-8}$ on chromosome 2 and 9, which were in extremely strong LD with rs965513 on chromosome 9 and rs6759952 on chromosome 2 (known SNP related with TC, $r^2=0.99$). The GWAS result was presented in Supplementary Table S3, with the threshold $P < 5 \times 10^{-8}$. For replication, we conducted a GWAS meta-analysis using GWAS summary statistics from UK Biobank, the FinnGen Study and Italian residents.								

eTable 6 Meta-GWAS results of three cohorts (n=1956)														
C H R	Posi tion	SNP	Effec t_alle le	Othe r_alle le	B E T A	S E	P	Q	R ²	N	I	M A F	Gene ^b	LD
18	648 465	rs11 8770 57	G	A	0. 26 1	0. 06 2	2.8 4E- 05	0. 36 41	0. 12 %	3	1. 0 3	0. 0 6	<i>C18orf5</i> 6, <i>CLUL1</i>	
9	100 726 574	rs47 4314 9	A	G	0. 26 2	0. 05 8	5.3 2E- 06	0. 70 87	0. 12 %	3	0	0. 0 6	<i>ANP32B</i> , <i>HEMGN</i>	LD with rs10512 256
6	139 151 784	rs11 1550 12	A	G	0. 17 3	0. 04 2	3.8 9E- 05	0. 88 62	0. 18 %	3	0	0. 2 8	<i>ECT2L</i>	
9	109 689 859	rs38 1454 0	C	T	0. 16 1	0. 03 9	4.5 3E- 05	0. 48 3	0. 19 %	3	0	0. 3 9	<i>MIR548</i> Q, <i>ZNF462</i>	
6	139 143 088	rs77 7317 7	G	A	0. 17 5	0. 04 2	3.2 8E- 05	0. 83 23	0. 19 %	3	0	0. 2 8	<i>ECT2L</i>	LD with rs11155 012
10	795 954 73	rs17 8179 7	A	G	- 0. 17 7	0. 04 3	3.9 6E- 05	0. 69 03	0. 19 %	3	0	0. 2 7	<i>DLG5</i>	
14	366 334 15	rs11 6914 8	T	C	0. 17 8	0. 04 3	4.2 6E- 05	0. 91 67	0. 19 %	3	0	0. 2 7	<i>LINC006</i> 09, <i>PTCSC3</i>	LD with rs19513 75
14	365 580 89	rs80 0761 7	G	A	0. 16 4	0. 04 0	3.6 8E- 05	0. 62 18	0. 19 %	3	0	0. 3 9	<i>LINC006</i> 09	LD with rs19513 75
19	926 468 1	rs81 1251 6	G	A	0. 20 0	0. 04 6	1.5 9E- 05	0. 51 66	0. 19 %	3	0	0. 2	<i>ZNF317</i>	
7	152 178 955	rs10 2358 93	G	A	0. 17 3	0. 04 2	3.6 7E- 05	0. 98 73	0. 19 %	3	0	0. 3 1	<i>LINC010</i> 03	
10	277 346 91	rs17 6819 69	C	T	- 0. 19 7	0. 04 6	1.7 2E- 05	0. 34 69	0. 20 %	3	5. 5 5	0. 2 2	<i>PTCHD3</i>	LD with rs24294 99
11	622 120 13	rs79 4214 3	T	G	- 0. 21 1	0. 05 1	4.0 2E- 05	0. 78 87	0. 21 %	3	0	0. 1 9	<i>AHNAK</i>	

1 4	365 207 75	rs19 5137 5	T	C	- 0. 16 9	0. 03 9	1.5 4E- 05	0. 39 41	0. 21 %	3	0	0. 4 2	<i>LOC105 370452</i>	
1 0	277 008 87	rs24 2949 9	A	G	0. 18 7	0. 04 3	1.1 0E- 05	0. 43 67	0. 21 %	3	0	0. 2 8	<i>PTCHD3</i>	
1 4	365 799 30	rs71 4514 5	G	A	0. 17 2	0. 04 0	1.4 4E- 05	0. 63 12	0. 21 %	3	0	0. 4	<i>LINC006 09</i>	LD with rs19513 75
1 0	277 043 60	rs79 1582 5	T	G	- 0. 21 2	0. 04 8	1.0 4E- 05	0. 47 55	0. 22 %	3	0	0. 2	<i>PTCHD3</i>	LD with rs24294 99
8	323 179 17	rs17 7162 95	A	C	0. 18 5	0. 04 0	3.8 4E- 06	0. 92 46	0. 23 %	3	0	0. 3 3	<i>NRG1, NRG1- IT3</i>	
1 4	365 642 42	rs11 6228 85	C	T	0. 17 8	0. 03 9	4.7 7E- 06	0. 64 24	0. 24 %	3	0	0. 4 3	<i>LINC006 09</i>	LD with rs19513 75
5	853 893 54	rs92 9345 6	G	A	0. 31 0	0. 07 1	1.1 3E- 05	0. 64 53	0. 24 %	3	0	0. 0 9	<i>intergeni c variant</i>	
2	218 292 652	rs14 7858 1	A	G	0. 23 6	0. 04 7	6.9 5E- 07	0. 73 48	0. 25 %	3	0	0. 1 8	<i>DIRC3</i>	LD with rs67599 52
1 8	674 320	rs37 4496 2	G	A	0. 32 0	0. 06 2	2.7 2E- 07	0. 83 05	0. 25 %	3	0	0. 0 9	<i>ENOSF1 , TYMS</i>	LD with rs11877 057
2	218 310 340	rs96 6423	T	C	- 0. 18 7	0. 03 8	1.0 5E- 06	0. 89 97	0. 26 %	3	0	0. 4 3	<i>DIRC3</i>	LD with rs67599 52
1 4	365 839 05	rs71 5076 8	T	G	0. 19 3	0. 04 0	1.1 7E- 06	0. 75 52	0. 27 %	3	0	0. 4	<i>LINC006 09</i>	LD with rs19513 75
9	100 686 815	rs10 5122 56	G	T	0. 26 9	0. 05 7	2.7 3E- 06	0. 68 22	0. 28 %	3	0	0. 1 5	<i>TRMO</i>	
5	111 463 837	rs27 982	C	T	- 0. 28 1	0. 05 4	2.1 8E- 07	0. 65 57	0. 30 %	3	0	0. 1 5	<i>EPB41L 4A</i>	

5	111 495 150	rs77 3033 4	G	A	- 0. 29 8	0. 05 8	2.7 8E- 07	0. 81 21	0. 30 %	3	0	0. 1 3	<i>EPB41L</i> <i>4A-AS1</i>	LD with rs27982
1 4	366 406 01	rs11 6915 1	A	G	0. 20 5	0. 03 9	1.9 0E- 07	0. 90 57	0. 31 %	3	0	0. 4 2	<i>PTCSC3</i>	LD with rs19513 75
9	100 742 253	rs78 5508 8	T	C	- 0. 20 9	0. 03 8	4.9 1E- 08	0. 42 37	0. 32 %	3	0	0. 4 1	<i>ANP32B</i>	LD with rs96551 3
2	218 277 119	rs12 4783 89	T	C	0. 35 3	0. 06 1	6.7 2E- 09	0. 78 09	0. 34 %	3	0	0. 1	<i>DIRC3</i>	LD with rs67599 52
9	100 664 194	rs70 4023 2	G	A	- 0. 25 9	0. 04 7	3.6 9E- 08	0. 40 67	0. 38 %	3	0	0. 2 5	<i>C9orf15</i> 6	LD with rs96551 3
2	218 305 064	rs67 1521 8	C	T	0. 25 2	0. 04 0	3.7 6E- 10	0. 99 %	0. 40 %	3	0	0. 3	<i>DIRC3</i>	LD with rs67599 52
5	111 480 534	rs17 1341 54	C	T	- 0. 31 9	0. 05 9	5.8 1E- 08	0. 71 68	0. 43 %	3	0	0. 1 7	<i>EPB41L</i> <i>4A-AS1</i>	LD with rs27982
2	218 271 719	rs67 5995 2	C	T	- 0. 25 3	0. 03 8	4.3 6E- 11	0. 33 97	0. 48 %	3	7. 3 7	0. 4 4	<i>DIRC3</i>	
2	218 304 106	rs26 1814 8	T	C	0. 27 8	0. 04 0	5.0 4E- 12	0. 89 24	0. 50 %	3	0	0. 3 1	<i>DIRC3</i>	LD with rs67599 52
9	100 666 931	rs65 86	T	C	- 0. 30 4	0. 04 0	2.4 5E- 14	0. 98 39	0. 66 %	3	0	0. 3 8	<i>C9orf15</i> 6	LD with rs96551 3
9	100 608 682	rs12 3486 91	A	G	- 0. 45 0	0. 03 9	2.6 1E- 31	0. 88 97	1. 48 %	3	0	0. 4 2	<i>FOXE1</i>	LD with rs96551 3
9	100 636 398	rs92 5487	T	C	- 0. 47 2	0. 03 9	7.5 2E- 34	0. 75 63	1. 55 %	3	0	0. 3 7	<i>FOXE1</i>	LD with rs96551 3

9	100 650 096	rs78 6643 6	A	G	- 0. 47 3	0. 03 9	3.3 0E- 34	0. 75	1. 56 %	3	0	0. 3 7	<i>C9orf15</i> 6	LD with rs96551 3
9	100 667 599	rs15 6196 1	T	C	- 0. 47 6	0. 03 9	1.6 3E- 34	0. 70 56	1. 58 %	3	0	0. 3 7	<i>C9orf15</i> 6	LD with rs96551 3
9	100 588 839	rs78 4897 3	G	A	- 0. 49 1	0. 03 9	5.8 5E- 37	0. 65 98	1. 74 %	3	0	0. 4 1	<i>FOXE1</i>	LD with rs96551 3
9	100 556 109	rs96 5513	G	A	- 0. 51 9	0. 03 9	5.6 0E- 40	0. 58 95	1. 80 %	3	0	0. 3 4	<i>FOXE1</i>	
CHR=chromosome; SNP=single nucleotide polymorphisms; MAF=minor allele frequency.														
Note: This meta-analysis was conducted using a fixed-effect inverse variance weighted method, and significant SNPs in three cohorts with $P < 5 \times 10^{-5}$ and Q (the Cochran's Q-test) > 0.05 were considered.														
a Quality control as following: MAF < 0.01 , LD ≥ 0.01 , Q (the Cochran's Q-test) > 0.05 , N=3														
b No relevant genes were found in the set upstream and downstream range of 100kb														

eTable 7 Genetic risk score selection					
PRS ^a	SNP	Effect allele	Beta ^a	P	Origin
PRS1 ^b	rs6759952	C	-0.253	4.36E-11	Meta-GWAS, P < 5E-5
	rs9293456	G	0.310	1.13E-05	Meta-GWAS, P < 5E-5
	rs27982	C	-0.281	2.18E-07	Meta-GWAS, P < 5E-5
	rs7773177	G	0.175	3.28E-05	Meta-GWAS, P < 5E-5
	rs10235893	G	0.173	3.67E-05	Meta-GWAS, P < 5E-5
	rs17716295	A	0.185	3.84E-06	Meta-GWAS, P < 5E-5
	rs965513	G	-0.519	5.60E-40	Meta-GWAS, P < 5E-5
	rs10512256	G	0.269	2.73E-06	Meta-GWAS, P < 5E-5
	rs3814540	C	0.161	4.53E-05	Meta-GWAS, P < 5E-5
	rs2429499	A	0.187	1.10E-05	Meta-GWAS, P < 5E-5
	rs1781797	A	-0.177	3.96E-05	Meta-GWAS, P < 5E-5
	rs7942143	T	-0.211	4.02E-05	Meta-GWAS, P < 5E-5
	rs1951375	T	-0.169	1.54E-05	Meta-GWAS, P < 5E-5
	rs11877057	G	0.261	2.84E-05	Meta-GWAS, P < 5E-5
	rs8112516	G	0.200	1.59E-05	Meta-GWAS, P < 5E-5
PRS2 ^b	rs6759952	C	-0.253	4.36E-11	Meta-GWAS, P < 5E-6
	rs27982	C	-0.281	2.18E-07	Meta-GWAS, P < 5E-6
	rs17716295	A	0.185	3.84E-06	Meta-GWAS, P < 5E-6
	rs965513	G	-0.519	5.60E-40	Meta-GWAS, P < 5E-6
	rs10512256	G	0.269	2.73E-06	Meta-GWAS, P < 5E-6
	rs11622885	C	0.178	4.77E-06	Meta-GWAS, P < 5E-6
	rs3744962	G	0.320	2.72E-07	Meta-GWAS, P < 5E-6
PRS3 ^b	rs10069690	T	0.182	3.20E-07	28195142
	rs10238549	C	0.239	4.10E-06	23894154
	rs10415826	T	0.199	8.70E-07	33527407
	rs10781500	C	0.207	3.50E-05	23894154
	rs116909374	T	0.593	5.00E-11	23894154
	rs12129938	A	0.278	4.00E-11	28195142
	rs16950982	G	0.199	4.70E-09	33527407
	rs2439302	G	0.307	2.00E-09	22267200
	rs334729	G	-0.635	8.70E-08	33527407
	rs368187	G	0.329	5.00E-23	28195142
	rs555678255	C	0.672	8.00E-07	32887889
	rs56062135	T	0.215	5.00E-09	28195142
	rs6759952	T	0.223	6.00E-10	23894154
	rs6793295	T	0.207	3.00E-08	28195142
	rs7030280	C	0.568	5.00E-28	32887889
	rs7267944	C	0.278	1.34E-08	25029422
	rs72806259	G	-0.398	5.00E-07	32887889
	rs73227498	A	0.315	3.00E-10	28195142

	rs74518511	C	-0.854	9.00E-07	32887889
	rs76032629	G	-0.519	6.00E-07	32887889
	rs7617304	T	0.223	4.60E-05	23894154
	rs77166399	G	-0.331	9.00E-07	32887889
	rs7902587	T	0.344	5.00E-11	28195142
PRS4 ^b	rs368187	G	0.329	5.10E-23	32132206
	rs12129938	A	0.278	4.00E-11	32132206
	rs11693806	C	0.358	1.50E-24	32132206
	rs6793295	T	0.207	2.70E-08	32132206
	rs73227498	A	0.315	3.00E-10	32132206
	rs2466076	G	0.278	1.50E-17	32132206
	rs1588635	A	0.525	2.00E-58	32132206
	rs2289261	C	0.207	3.10E-09	32132206
	rs7902587	T	0.344	5.40E-11	32132206
	rs116909374	T	0.593	1.10E-16	32132206
SNP=single nucleotide polymorphisms; PRS=polygenic risk score					
a The SNPs constructing PRS were performed quality control as following: MAF<0.01 and LD=0.01, and beta coefficient for effect size used as weight in PRS					
b PRS1 (P < 5E-6) and PRS2 (P < 5E-5) were derived from our meta-GWAS analysis; PRS3 was used SNPs from Table S2 and excluded LD (LD=0.01); and PRS4 is used for next analysis					

eTable 8 Association of different PRSs and risk of thyroid cancer

Characteristics	Model 1 ^a				Model 2 ^a			
	HR (95%CI)	P	P for trend	HR (95%CI) ^b	HR (95%CI)	P	P for trend	HR (95%CI) ^b
Weighted PRS2 (7 SNPs)			2.61 E-14	2.05 (1.46, 2.9)			1.37 E-13	2.33 (1.93, 2.82)
T1	Referenc e				Referenc e			
T2	1.84 (0.57, 5.94)	0.31			1.31 (0.99, 1.73)	0.06		
T3	2.55 (0.81, 7.99)	0.11			2.41 (1.88, 3.08)	3.36 E-12		
Unweighted PRS2 (7 SNPs)			0.08	1.01 (0.93, 1.1)			0.15	1.05 (0.99, 1.12)
T1	Referenc e				Referenc e			
T2	1.03 (0.75, 1.43)	0.84			1.04 (0.83, 1.29)	0.76		
T3	1.03 (0.72, 1.49)	0.86			1.22 (0.93, 1.6)	0.15		
Weighted PRS3 (23 SNPs)			1.36 E-12	1.66 (1.42, 1.96)			1.93 E-11	1.95 (1.68, 2.26)
T1	Referenc e				Referenc e			
T2	1.81 (1.02, 3.2)	0.04			1.47 (1.11, 1.95)	0.01		
T3	2.8 (1.65, 4.77)	1.44 E-04			2.68 (2.07, 3.47)	6.69 E-14		
Unweighted PRS3 (23 SNPs)			7.45 E-08	1.03 (0.98, 1.08)			1.17 E-07	1.05 (1.01, 1.09)
T1	Referenc e				Referenc e			

T2	0.96 (0.65, 1.42)	0.85				1.1 (0.86, 1.4)	0.45		
T3	1.07 (0.75, 1.52)	0.73				1.31 (1.03, 1.66)	0.03		
Weighted PRS4 (10 SNPs)			4.35 E-17	1.77 (1.4, 2.24)				1.74 E-15	1.74 (1.56, 1.94)
T1	Referenc e					Referenc e			
T2	1.04 (0.59, 1.84)	0.89				1.4 (1.06, 1.84)	0.02		
T3	1.72 (1.03, 2.88)	0.04				2.28 (1.77, 2.94)	1.32 E-10		
Unweighted PRS4 (10 SNPs)			0.01	1.15 (1.06, 1.24)				0.03	1.18 (1.12, 1.24)
T1	Referenc e					Referenc e			
T2	1.75 (1.07, 2.87)	0.03				1.28 (0.99, 1.66)	0.06		
T3	1.88 (1.17, 3.02)	0.01				1.88 (1.47, 2.4)	4.42 E-07		

SNP=single nucleotide polymorphisms; PRS=polygenic risk score.

^a Model 1 was not adjustment, Model 2 was adjusted for age, sex, and genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax

^b PRS were performed as a continuous variable using logistic regression model

eTable 9 Baseline characteristics of thyroid cancer participants between FTC and PTC

Variable	FTC (n = 55)	PTC (n = 207)	P	
Age	57.44 (7.75)	56.59 (7.89)	0.48	
Sex			0.75	
Women	38 (69.09)	150 (72.46)		
Men	17 (30.91)	57 (27.54)		
Townsend deprivation index			0.67	
1 (least deprived)	9 (16.36)	38 (18.36)		
2-4	37 (67.27)	126 (60.87)		
5 (most deprived)	9 (16.36)	43 (20.77)		
Educational qualifications			0.06	
College or University degree	19 (34.55)	61 (29.47)		
Secondary Education	26 (47.27)	128 (61.84)		
Some professional qualifications	10 (18.18)	18 (8.70)		
Average total household income before tax			0.80	
Less than 18,000	9 (16.36)	38 (18.36)		
18,000 to 30,999	15 (27.27)	52 (25.12)		
31,000 to 51,999	21 (38.18)	87 (42.03)		
52,000 to 100,000	9 (16.36)	23 (11.11)		
Greater than 100,000	1 (1.82)	7 (3.38)		
Diet index			0.63	
Unfavourable	29 (52.73)	119 (57.49)		
Favourable	26 (47.27)	88 (42.51)		
Total moderate-vigorous physical activity			0.81	
Favourable	25 (45.45)	88 (42.51)		
Unfavourable	30 (54.55)	119 (57.49)		
Smoke intake			0.35	
Favourable	51 (92.73)	180 (86.96)		
Unfavourable	4 (7.27)	27 (13.04)		
Alcohol consumption			0.18	
Favourable	47 (85.45)	157 (75.85)		
Unfavourable	8 (14.55)	50 (24.15)		
Healthy weight			0.23	
Unfavourable	24 (43.64)	70 (33.82)		
Favourable	31 (56.36)	137 (66.18)		
Lifestyle			0.26	
Favourable	19 (34.55)	62 (29.95)		
Intermediate	23 (41.82)	72 (34.78)		
Unfavourable	13 (23.64)	73 (35.27)		
Weighted lifestyle			0.76	
Favourable	13 (23.64)	47 (22.71)		

Intermediate	21 (38.18)	70 (33.82)		
Unfavourable	21 (38.18)	90 (43.48)		
Weighted PRS1			0.82	
T1	9 (16.36)	29 (14.01)		
T2	19 (34.55)	67 (32.37)		
T3	27 (49.09)	111 (53.62)		

eTable 10 The additive interaction between lifestyle and PRS (RERI)^a

Characteristics	PRS T2		PRS T3	
	RERI	95%CI	RERI	95%CI
Weighted healthy lifestyle				
Favourable	Reference		Reference	
Intermediate	1.16	0.20,2.12	0.37	-0.81,1.54
Unfavourable	1.01	-0.03,2.06	1.90	0.44,3.35
Unweighted healthy lifestyle				
Favourable	Reference		Reference	
Intermediate	0.96	0.17,1.75	0.33	-0.67,1.33)
Unfavourable	-0.02	-1.02,0.98	0.72	-0.48,1.93)
Diet index				
Favourable	Reference		Reference	
Unfavourable	-0.46	-1.43,0.50	-0.76	-1.95,0.44
Total moderate-vigorous physical activity				
Favourable	Reference		Reference	
Unfavourable	0.48	-0.34,1.30	0.66	-0.32,1.63
Smoke intake				
Favourable	Reference		Reference	
Unfavourable	0.46	-1.11,2.03	2.79	0.45,5.12
Alcohol consumption				
Favourable	Reference		Reference	
Unfavourable	-0.77	-1.60,0.06	-0.59	-1.53,0.36
Healthy weight				
Favourable	Reference		Reference	
Unfavourable	0.51	-0.22,1.23	0.62	-0.28,1.52

PRS=polygenic risk score; RERI=relative excess risk.

^aadjusted for age, sex, and genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax.

eTable 11 Associations of lifestyle components with incident thyroid cancer according to PRS stratified analysis in the nested case-control design ^a								
Characteristics	PRS T1		PRS T2		PRS T3		<i>P</i> for interaction	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>		
Weighted lifestyle							0.14	
Favourable	Reference		Reference		Reference			
Intermediate	0.95 (0.33, 2.74)	0.92	2.50 (1.14, 5.47)	0.02	1.03 (0.63, 1.69)	0.90		
RERI _{intermediate/favorable}	Reference		1.16 (0.35, 1.97)		0.02 (-1.37, 1.41)			
Unfavourable	1.48 (0.46, 4.73)	0.51	2.67 (1.15, 6.20)	0.023	2.05 (1.21, 3.47)	0.01		
RERI Unfavourable/Favourable	Reference		0.15 (-0.69, 0.99)		1.08 (-0.12, 2.28)			
Unweighted lifestyle							0.28	
Favourable	Reference		Reference		Reference			
Intermediate	0.23 (0.07, 0.72)	0.012	2.21 (1.07, 4.54)	0.031	1.15 (0.70, 1.88)	0.58		
RERI intermediate/Favourable	Reference		1.63 (0.61, 2.65)		0.71 (-0.17, 1.59)			
Unfavourable	0.94 (0.35, 2.54)	0.90	2.38 (1.11, 5.08)	0.03	1.97 (1.18, 3.30)	0.01		
RERI Unfavourable/Favourable	Reference		0.15 (-0.69, 0.99)		1.08 (-0.12, 2.28)			
Diet index							0.45	
Favourable	Reference		Reference		Reference			
Unfavourable	1.40 (0.63, 3.11)	0.41	1.48 (0.84, 2.62)	0.18	0.99 (0.66, 1.49)	0.96		
RERI ^f			-0.56 (-1.66, 0.54)		-0.40 (-1.50, 0.70)			

Total moderate-vigorous physical activity							0.52
Favourable	Reference		Reference		Reference		
Unfavourable	0.90 (0.41, 1.99)	0.80	2.14 (1.20, 3.82)	0.010	1.51 (1.01, 2.25)	0.04	
RERI			0.95 (0.25, 1.65)		0.93 (-0.06, 1.91)		
Smoke intake							0.06
Favourable	Reference		Reference		Reference		
Unfavourable	0.65 (0.11, 3.94)	0.64	0.80 (0.29, 2.16)	0.657	2.43 (1.19, 4.97)	0.02	
RERI			-0.213 (-1.880, 1.454)		3.406 (0.547, 6.264)		
Alcohol consumption							0.60
Favourable	Reference		Reference		Reference		
Unfavourable	0.88 (0.38, 2.04)	0.76	0.73 (0.36, 1.48)	0.38	0.88 (0.55, 1.42)	0.60	
RERI			-0.547 (-1.353, 0.258)		-0.05 (-0.96, 0.85)		
Weight							0.36
Favourable	Reference		Reference		Reference		
Unfavourable	0.96 (0.42, 2.20)	0.92	1.72 (0.94, 3.15)	0.08	1.44 (0.94, 2.21)	0.10	
RERI			0.77 (0.14, 1.40)		0.66 (-0.31, 1.64)		
PRS=polygenic risk score; RERI=relative excess risk.							
^a adjusted for age, sex, and genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax							
Note: RERI was used favourable lifestyle and lowest PRS as reference, and described as beta (95% CI)							

eTable 12 Combined analysis of PRS and lifestyle components on the risk of thyroid cancer*							
Characteristics	PRS T1		PRS T2		PRS T3		
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	
Weighted healthy lifestyle							
Favourable	Reference		1.1 (0.61, 1.98)	0.76	2.63 (1.59, 4.35)	<0.001	
Intermediate	1.35 (0.77, 2.38)	0.30	2.62 (1.58, 4.32)	<0.001	3.35 (2.06, 5.46)	<0.001	
Unfavourable	1.44 (0.8, 2.6)	0.22	2.81 (1.69, 4.69)	<0.001	4.89 (3.03, 7.91)	<0.001	
Unweighted healthy lifestyle							
Favourable	Reference		1.41 (0.87, 2.28)	0.16	2.64 (1.71, 4.07)	<0.001	
Intermediate	0.78 (0.43, 1.41)	0.41	2.11 (1.33, 3.35)	0.00	2.72 (1.75, 4.23)	<0.001	
Unfavourable	1.45 (0.86, 2.47)	0.17	1.94 (1.19, 3.17)	0.01	3.76 (2.42, 5.84)	<0.001	
Diet index							
Favourable	Reference		2.02 (1.35, 3.04)	<0.001	3.56 (2.44, 5.2)	<0.001	
Unfavourable	1.5 (0.95, 2.38)	0.08	2.16 (1.41, 3.3)	<0.001	3.26 (2.18, 4.86)	<0.001	
Total moderate-vigorous physical activity							
Favourable	Reference		1.53 (1, 2.35)	0.05	2.82 (1.91, 4.16)	<0.001	
Unfavourable	1.33 (0.84, 2.1)	0.23	2.47 (1.65, 3.7)	<0.001	3.75 (2.55, 5.49)	<0.001	
Smoke intake							
Favourable	Reference		1.67 (1.24, 2.25)	<0.001	2.62 (1.98, 3.46)	<0.001	
Unfavourable	0.98 (0.4, 2.41)	0.96	2.15 (1.13, 4.08)	0.02	5.54 (3.55, 8.65)	<0.001	
Alcohol consumption							
Favourable	Reference		1.93 (1.39, 2.68)	<0.001	2.93 (2.15, 3.99)	<0.001	
Unfavourable	0.88 (0.53, 1.48)	0.63	0.97 (0.59, 1.6)	0.91	2.24 (1.52, 3.29)	<0.001	
Healthy weight							
Favourable	Reference		1.45 (0.91, 2.31)	0.12	2.6 (1.71, 3.96)	<0.001	

Unfavourable	1.15 (0.72, 1.83)	0.56	2.16 (1.42, 3.28)	<0.001	3.42 (2.3, 5.09)	<0.001
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PRS=polygenic risk score.

*adjusted for age, sex, genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax.

eTable 13 The sex-difference of associations between lifestyle components with incident thyroid cancer ^a						
Characteristics	Women				Men	
	HR (95%CI)	P	P for trend ^b		HR (95%CI)	P for trend ^b
Total fruit and vegetables intake			0.711			0.531
Favourable	Reference				Reference	
Unfavourable	0.93 (0.73, 1.19)	0.555			0.92 (0.6, 1.42)	0.720
Fish intake			0.989			0.976
Favourable	Reference				Reference	
Unfavourable	1.01 (0.77, 1.32)	0.959			0.86 (0.55, 1.35)	0.515
Processed meat and red meat intake			0.707			0.259
Favourable	Reference				Reference	
Unfavourable	0.89 (0.71, 1.13)	0.353			1.46 (0.88, 2.43)	0.142
Whole grains intake			0.221			0.393
Favourable	Reference				Reference	
Unfavourable	0.93 (0.72, 1.19)	0.572			0.95 (0.65, 1.38)	0.772
Refine grains intake			0.552			0.884
Favourable	Reference				Reference	
Unfavourable	0.96 (0.76, 1.2)	0.700			0.9 (0.62, 1.3)	0.571
Sugar drinking intake			0.272			0.981
Favourable	Reference				Reference	
Unfavourable	1.2 (0.87, 1.66)	0.272			1.01 (0.63, 1.59)	0.981
Diet index			0.586			0.861
Favourable	Reference				Reference	
Unfavourable	1 (0.79, 1.26)	0.987			1.1 (0.76, 1.6)	0.598
Total moderate-vigorous physical activity			NA			NA
Favourable	Reference				Reference	
Unfavourable	1.32 (1.05, 1.67)	0.016			1.66 (1.15, 2.39)	0.006
Smoke intake			NA			NA
Favourable	Reference				Reference	

Unfavourable	1.36 (0.89, 2.07)	0.158		2.17 (1.33, 3.54)	0.002	
Alcohol consumption			0.025			0.214
Favourable	Reference			Reference		
Unfavourable	0.68 (0.51, 0.9)	0.006		0.76 (0.5, 1.15)	0.189	
Weight			0.003			0.045
Favourable	Reference			Reference		
Unfavourable	1.37 (1.08, 1.75)	0.010		1.17 (0.8, 1.71)	0.418	
Unweighted lifestyle			0.151			0.036
Favourable	Reference			Reference		
Intermediate	1.17 (0.89, 1.53)	0.265		0.97 (0.61, 1.55)	0.893	
Unfavourable	1.3 (0.97, 1.73)	0.076		1.56 (1.01, 2.42)	0.046	
Weighted lifestyle			<0.001			<0.001
Favourable	Reference			Reference		
Intermediate	1.63 (1.22, 2.17)	0.001		1.19 (0.68, 2.08)	0.540	
Unfavourable	1.99 (1.45, 2.71)	<0.001		1.79 (1.15, 2.8)	0.010	
PRS			<0.001			<0.001
T1	Reference			Reference		
T2	1.62 (1.15, 2.27)	0.006		1.9 (1.11, 3.27)	0.020	
T3	2.82 (2.06, 3.86)	<0.001		2.83 (1.7, 4.71)	<0.001	

PRS=polygenic risk score.

^aP for trend were performed by using factors as continuous variable.

^badjusted for age, genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax, and women further adjusted for age at menarche, menopausal status, number of live births, ever taken oral contraceptive pill, and ever used hormone-replacement therapy (HRT)

eTable 14 Combined analysis of PRS and lifestyle components on the risk of thyroid cancer in women ^a							
Characteristics	PRS T1			PRS T2		PRS T3	
	HR (95%CI)	P		HR (95%CI)	P	HR (95%CI)	P
Weighted lifestyle							
Favourable	Reference			1.20 (0.59, 2.44)	0.61	2.93 (1.6, 5.36)	<0.001
Intermediate	1.61 (0.83, 3.09)	0.16		2.86 (1.57, 5.2)	<0.001	3.93 (2.2, 7.04)	<0.001
Unfavourable	1.67 (0.80, 3.51)	0.17		2.88 (1.51, 5.49)	0.001	5.63 (3.1, 10.2)	<0.001
Unweighted lifestyle							
Favourable	Reference			1.59 (0.91, 2.77)	0.10	2.73 (1.63, 4.54)	<0.001
Intermediate	1.00 (0.52, 1.93)	1.00		2.07 (1.19, 3.58)	0.01	3.12 (1.86, 5.24)	<0.001
Unfavourable	1.43 (0.75, 2.74)	0.28		1.73 (0.95, 3.17)	0.07	3.82 (2.25, 6.48)	<0.001
Diet index							
Favourable	Reference			2.03 (1.29, 3.20)	0.002	3.34 (2.18, 5.12)	<0.001
Unfavourable	1.45 (0.85, 2.49)	0.18		1.71 (1.03, 2.85)	0.04	3.31 (2.09, 5.23)	<0.001
Total moderate-vigorous physical activity							
Favourable	Reference			1.51 (0.91, 2.52)	0.11	2.97 (1.87, 4.71)	<0.001
Unfavourable	1.34 (0.78, 2.31)	0.28		2.26 (1.40, 3.66)	<0.001	3.62 (2.3, 5.71)	<0.001
Smoke intake							
Favourable	Reference			1.56 (1.1, 2.22)	0.01	2.62 (1.9, 3.62)	<0.001

Unfavourable	0.62 (0.16, 2.39)	0.48		1.74 (0.74, 4.06)	0.20		4.79 (2.72, 8.45)	<0.001
Alcohol consumption								
Favourable	Reference			1.68 (1.14, 2.46)	0.01		2.82 (1.98, 4.02)	<0.001
Unfavourable	0.71 (0.37, 1.36)	0.30		0.99 (0.56, 1.75)	0.98		2.01 (1.28, 3.18)	<0.001
Weight								
Favourable	Reference			1.54 (0.89, 2.66)	0.12		2.63 (1.59, 4.34)	<0.001
Unfavourable	1.27 (0.73, 2.2)	0.40		2.10 (1.27, 3.48)	0.003		3.73 (2.32, 6)	<0.001
PRS=polygenic risk score.								
^a adjusted for age, genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax, age at menarche, menopausal status, number of live births, ever taken oral contraceptive pill, and ever used hormone-replacement therapy (HRT).								

eTable 15 Combined analysis of PRS and lifestyle components on the risk of thyroid cancer in men^a

Characteristics	PRS T1			PRS T2			PRS T3	
	HR (95%CI)	P		HR (95%CI)	P		HR (95%CI)	P
Weighted lifestyle								
Favourable	Reference			0.9 (0.3, 2.68)	0.85		1.89 (0.76, 4.69)	0.17
Intermediate	0.64 (0.17, 2.49)	0.52		2.14 (0.81, 5.61)	0.12		1.8 (0.68, 4.77)	0.24
Unfavourable	1.03 (0.39, 2.7)	0.96		2.2 (0.94, 5.16)	0.07		3.61 (1.61, 8.13)	0.00
Unweighted lifestyle								
Favourable	Reference			1.03 (0.38, 2.73)	0.96		2.21 (0.97, 5.06)	0.06
Intermediate	0.26 (0.06, 1.24)	0.09		1.99 (0.84, 4.7)	0.12		1.9 (0.81, 4.46)	0.14
Unfavourable	1.37 (0.54, 3.49)	0.50		1.99 (0.84, 4.71)	0.12		3.39 (1.52, 7.57)	<0.001
Diet index								
Favourable	Reference			2.04 (0.83, 5.07)	0.12		4.22 (1.85, 9.6)	<0.001
Unfavourable	1.66 (0.66, 4.16)	0.28		3.02 (1.3, 7.02)	0.01		3.45 (1.5, 7.91)	<0.001
Total moderate-vigorous physical activity								
Favourable	Reference			1.65 (0.75, 3.63)	0.22		2.36 (1.13, 4.91)	0.02
Unfavourable	1.29 (0.54, 3.1)	0.57		2.75 (1.3, 5.83)	0.01		4.27 (2.11, 8.66)	<0.001
Smoke intake								
Favourable	Reference			1.95 (1.08, 3.49)	0.03		2.62 (1.5, 4.58)	<0.001
Unfavourable	1.83 (0.53, 6.25)	0.34		2.99 (1.1, 8.13)	0.03		7.27 (3.45, 15.31)	<0.001
Alcohol consumption								
Favourable	Reference			2.72 (1.4, 5.27)	<0.001		3.35 (1.76, 6.37)	<0.001
Unfavourable	1.44 (0.59, 3.53)	0.42		0.93 (0.33, 2.65)	0.89		2.95 (1.4, 6.2)	<0.001
Weight								
Favourable	Reference			1.14 (0.46, 2.79)	0.78		2.53 (1.17, 5.44)	0.02
Unfavourable	0.83 (0.35, 1.94)	0.61		2.1 (0.99, 4.47)	0.05		2.57 (1.23, 5.34)	0.01

	2.02)	69	4.46)		5.36)	
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PRS = polygenic risk score.

^aadjusted for age, genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax.

eTable 16 Baseline characteristics of participants of thyroid cancer in the UK biobank in the sensitivity analysis					
Variable ^a	Overall (n=378,267) ^b	Non incident TC (n=377,830)	Incident TC (n=437)	P	
Age, median (IQR), y	57.00 (50.00, 63.00)	57.00 (50.00, 63.00)	59.00 (51.00, 63.00)		
Sex, No. (%)				<0.001	
Women	195343 (51.64)	195031 (51.62)	312 (71.40)		
Men	182924 (48.36)	182799 (48.38)	125 (28.60)		
Townsend deprivation index, No. (%)				0.774	
1 (least deprived)	75662 (20.00)	75578 (20.00)	84 (19.22)		
2-4	226954 (60.00)	226694 (60.00)	260 (59.50)		
5 (most deprived)	75651 (20.00)	75558 (20.00)	93 (21.28)		
Educational qualifications, No. (%)				0.325	
College or University degree	127178 (33.62)	127036 (33.62)	142 (32.49)		
Secondary Education	207589 (54.88)	207336 (54.88)	253 (57.89)		
Some professional qualifications	43500 (11.50)	43458 (11.50)	42 (9.61)		
Average total household income before tax, No. (%)				0.001	
Less than 18,000	65654 (17.36)	65571 (17.35)	83 (18.99)		
18,000 to 30,999	82016 (21.68)	81916 (21.68)	100 (22.88)		
31,000 to 51,999	137864 (36.45)	137679 (36.44)	185 (42.33)		
52,000 to 100,000	73039 (19.31)	72982 (19.32)	57 (13.04)		
Greater than 100,000	19694 (5.21)	19682 (5.21)	12 (2.75)		
Total fruit and vegetables intake, No. (%)				0.089	
Favourable	99430 (26.29)	99299 (26.28)	131 (29.98)		
Unfavourable	278837 (73.71)	278531 (73.72)	306 (70.02)		
Fish intake				0.265	
Unfavourable	285188 (75.39)	284848 (75.39)	340 (77.80)		
Favourable	93079 (24.61)	92982 (24.61)	97 (22.20)		
Processed meat and red meat intake, No. (%)				0.034	
Favourable	106117 (28.05)	105974 (28.05)	143 (32.72)		
Unfavourable	272150 (71.95)	271856 (71.95)	294 (67.28)		
Whole grains intake, No. (%)				0.299	
Favourable	241574 (63.86)	241284 (63.86)	290 (66.36)		

Unfavourable	136693 (36.14)	136546 (36.14)	147 (33.64)		
Refine grains intake, No. (%)				0.13 2	
Favourable	180717 (47.77)	180492 (47.77)	225 (51.49)		
Unfavourable	197550 (52.23)	197338 (52.23)	212 (48.51)		
Diet index, No. (%)				0.13 8	
Favourable	201730 (53.33)	201481 (53.33)	249 (56.98)		
Unfavourable	176537 (46.67)	176349 (46.67)	188 (43.02)		
Total moderate-vigorous physical activity, No. (%)				0.00 5	
Favourable	193635 (51.19)	193441 (51.20)	194 (44.39)		
Unfavourable	184632 (48.81)	184389 (48.80)	243 (55.61)		
Smoke intake, No. (%)				0.75 7	
Favourable	340562 (90.03)	340171 (90.03)	391 (89.47)		
Unfavourable	37705 (9.97)	37659 (9.97)	46 (10.53)		
Alcohol consumption, No. (%)				<0.0 01	
Favourable	262079 (69.28)	261737 (69.27)	342 (78.26)		
Unfavourable	116188 (30.72)	116093 (30.73)	95 (21.74)		
Healthy weight, No. (%)				0.00 2	
Favourable	166414 (43.99)	166254 (44.00)	160 (36.61)		
Unfavourable	211853 (56.01)	211576 (56.00)	277 (63.39)		
Lifestyle, No. (%)				0.67 2	
Favourable	139334 (36.83)	139182 (36.84)	152 (34.78)		
Intermediate	124544 (32.92)	124396 (32.92)	148 (33.87)		
Unfavourable	114389 (30.24)	114252 (30.24)	137 (31.35)		
Weighted healthy lifestyle, No. (%)				<0.0 01	
Favourable	140033 (37.02)	139913 (37.03)	120 (27.46)		
Intermediate	127818 (33.79)	127654 (33.79)	164 (37.53)		
Unfavourable	110416 (29.19)	110263 (29.18)	153 (35.01)		
Weighted PRS1 (15 SNPs), No. (%)				<0.0 01	
T1	126116 (33.34)	126036 (33.36)	80 (18.31)		
T2	126062 (33.33)	125931 (33.33)	131 (29.98)		
T3	126089 (33.33)	125863 (33.31)	226 (51.72)		

^aVariable are numbers (percentages) except for age, which was presented as median and interquartile range.

^bThere were 378,267 participants included in the sensitivity analysis, we excluded: 1) non-European descent (n = 26,852); 2) suffering from cancer (n = 47,956); 3) missing lifestyle variable (n = 49430). Finally, we included 437 TC cases and 377,830 patients without TC.

eTable 17 Associations between healthy lifestyle and incident thyroid cancer in the sensitivity analysis^a

Characteristics	HR (95%CI)	<i>P</i>	<i>P</i> for trend ^b
Weighted healthy lifestyle			
Favourable	Reference		<0.001
Intermediate	1.39 (1.1, 1.76)	0.01	
Unfavourable	1.83 (1.44, 2.33)	<0.001	
Unweighted healthy lifestyle			
Favourable	Reference		0.08
Intermediate	1.13 (0.9, 1.42)	0.28	
Unfavourable	1.23 (0.97, 1.55)	0.08	
Total fruit and vegetables intake			
Favourable	Reference		0.93
Unfavourable	0.95 (0.77, 1.16)	0.59	
Fish intake			
Favourable	Reference		0.98
Unfavourable	0.93 (0.74, 1.17)	0.52	
Processed meat and red meat intake			
Favourable	Reference		0.65
Unfavourable	0.96 (0.78, 1.18)	0.70	
Whole grains intake			
Favourable	Reference		0.26
Unfavourable	0.97 (0.79, 1.19)	0.76	
Refine grains intake			
Favourable	Reference		0.99
Unfavourable	0.96 (0.79, 1.16)	0.67	
Sugar drinking intake			
Favourable	Reference		0.85
Unfavourable	1.03 (0.8, 1.32)	0.85	
Diet index			
Favourable	Reference		0.47
Unfavourable	1 (0.82, 1.21)	0.99	
Total moderate-vigorous physical activity			
Favourable	Reference		NA
Unfavourable	1.28 (1.06, 1.55)	0.01	
Smoke intake			
Favourable	Reference		NA
Unfavourable	1.15 (0.84, 1.57)	0.38	
Alcohol consumption			
Favourable	Reference		0.01
Unfavourable	0.67 (0.53, 0.84)	<0.001	
Healthy weight			

Favourable	Reference		NA
Unfavourable	1.37 (1.12, 1.66)	0.002	
Weighted PRS1 (15 SNPs) [£]			
T1	Reference		<0.001
T2	1.62 (1.23, 2.15)	<0.001	
T3	2.81 (2.18, 3.63)	<0.001	

^aAdjusted for age, sex, genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax.

^b*P* for trend were performed by using lifestyle factors as continuous variable.

eTable 18 Combined analysis of PRS and lifestyle components on the risk of thyroid cancer in the sensitivity analysis ^a								
Characteristics	PRS T1			PRS T2			PRS T3	
	HR (95%CI)	<i>P</i>		HR (95%CI)	<i>P</i>		HR (95%CI)	<i>P</i>
Weighted healthy lifestyle								
Favourable	Reference			1 (0.58, 1.73)	0.99		2.6 (1.65, 4.08)	<0.001
Intermediate	1.29 (0.77, 2.16)	0.33		2.21 (1.39, 3.52)	<0.001		2.91 (1.86, 4.55)	<0.001
Unfavourable	1.18 (0.66, 2.09)	0.58		2.62 (1.62, 4.22)	<0.001		4.63 (2.98, 7.2)	<0.001
Unweighted healthy lifestyle								
Favourable	Reference			1.4 (0.88, 2.24)	0.16		2.63 (1.73, 4.01)	<0.001
Intermediate	0.82 (0.47, 1.43)	0.47		1.95 (1.24, 3.07)	0.003		2.95 (1.93, 4.51)	<0.001
Unfavourable	1.32 (0.79, 2.2)	0.29		1.71 (1.06, 2.76)	0.03		3.18 (2.07, 4.89)	<0.001
Diet index								
Favourable	Reference			1.79 (1.22, 2.63)	0.003		3.36 (2.36, 4.78)	<0.001
Unfavourable	1.31 (0.84, 2.03)	0.23		1.91 (1.27, 2.86)	0.001		2.94 (2.02, 4.28)	<0.001
Total moderate-vigorous physical activity								
Favourable	Reference			1.47 (0.97, 2.23)	0.07		2.66 (1.83, 3.86)	<0.001
Unfavourable	1.16 (0.75, 1.79)	0.52		2.02 (1.37, 2.99)	<0.001		3.4 (2.37, 4.9)	<0.001
Smoke intake								
Favourable	Reference			1.67 (1.25, 2.24)	<0.001		2.73 (2.09, 3.58)	<0.001
Unfavourable	1.09 (0.53, 2.28)	0.81		1.33 (0.69, 2.59)	0.39		3.83 (2.46, 5.95)	<0.001
Alcohol consumption								
Favourable	Reference			1.87 (1.36, 2.57)	<0.001		3 (2.23, 4.03)	<0.001
Unfavourable	0.91 (0.56, 1.48)	0.70		0.9 (0.55, 1.47)	0.67		2.1 (1.44, 3.06)	<0.001
Healthy weight								

Favourable	Reference		1.26 (0.8, 1.99)	0.32		2.55 (1.71, 3.82)	<0.001
Unfavourable	1.12 (0.72, 1.75)	0.62	2.11 (1.41, 3.15)	<0.001		3.35 (2.29, 4.9)	<0.001

^aadjusted for age, sex, genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax.

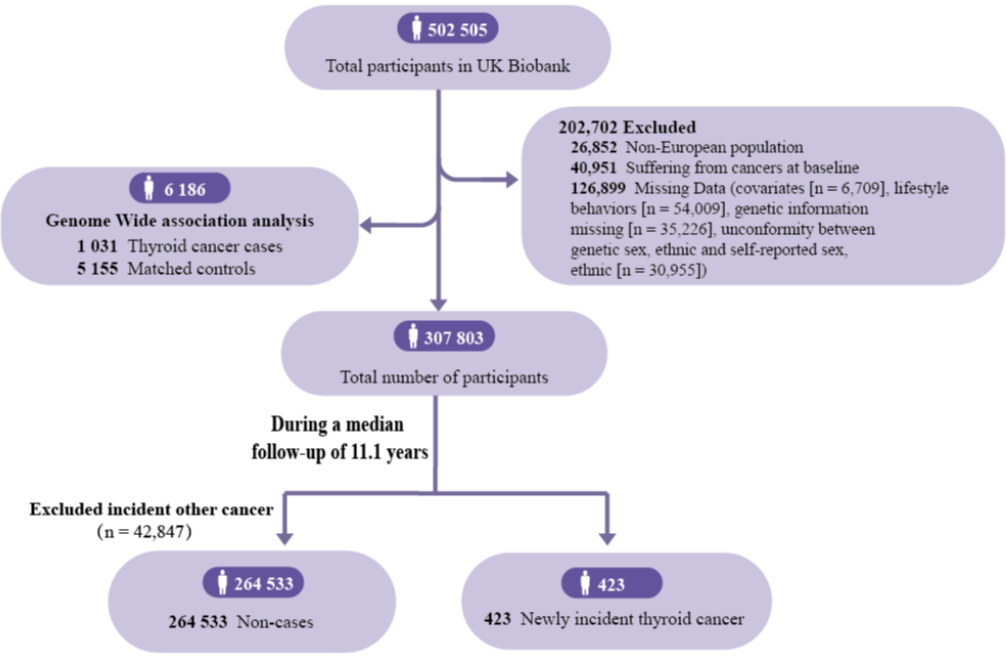
eTable 19 Associations between lifestyle component and incident thyroid cancer using competing risk analysis ^a		
Characteristics	HR (95%CI)	P
Diet index		
Favourable	Reference	
Unfavourable	0.98 (0.78, 1.23)	0.87
Total moderate-vigorous physical activity		
Favourable	Reference	
Unfavourable	1.42 (1.15, 1.77)	0.001
Smoke intake		
Favourable	Reference	
Unfavourable	1.30 (0.89, 1.90)	0.17
Alcohol consumption		
Favourable	Reference	
Unfavourable	0.72 (0.56, 0.92)	0.01
Healthy weight		
Favourable	Reference	
Unfavourable	1.32 (1.05, 1.66)	0.02
Unweighted healthy lifestyle		
Favourable	Reference	
Intermediate	1.20 (0.93, 1.56)	0.16
Unfavourable	1.30 (0.99, 1.70)	0.06
Weighted healthy lifestyle		
Favourable	Reference	
Intermediate	1.63 (1.23, 2.16)	<0.001
Unfavourable	1.91 (1.42, 2.56)	<0.001
Weighted PRS1 (15 SNPs)		
T1	Reference	
T2	1.77 (1.28, 2.43)	<0.001
T3	2.84 (2.11, 3.82)	<0.001
^a adjusted for age, sex, genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax.		

eTable 20 Combined analysis of PRS and lifestyle components on the risk of thyroid cancer using competing risk analysis ^a						
Characteristics	PRS T1		PRS T2		PRS T3	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Weighted healthy lifestyle						
Favourable	Reference		1.28 (0.64, 2.56)	0.49	3.08 (1.69, 5.61)	<0.001
Intermediate	1.71 (0.90, 3.25)	0.10	3.00 (1.65, 5.45)	<0.001	4.07 (2.29, 7.26)	<0.001
Unfavourable	1.57 (0.77, 3.20)	0.21	3.37 (1.84, 6.19)	<0.001	5.28 (2.95, 9.45)	<0.001
Unweighted healthy lifestyle						
Favourable	Reference		1.32 (0.76, 2.26)	0.32	2.63 (1.63, 4.24)	<0.001
Intermediate	0.70 (0.36, 1.38)	0.30	2.32 (1.41, 3.82)	<0.001	2.88 (1.77, 4.69)	<0.001
Unfavourable	1.41 (0.79, 2.54)	0.25	1.83 (1.06, 3.14)	0.03	3.22 (1.97, 5.28)	<0.001
Diet index						
Favourable	Reference		2.11 (1.34, 3.34)	0.001	3.70 (2.42, 5.65)	<0.001
Unfavourable	1.49 (0.88, 2.51)	0.13	2.18 (1.36, 3.49)	0.001	3.08 (1.95, 4.85)	<0.001
Total moderate-vigorous physical activity						
Favourable	Reference		1.39 (0.86, 2.26)	0.18	2.71 (1.76, 4.17)	<0.001
Unfavourable	1.19 (0.71, 2.00)	0.50	2.52 (1.63, 3.91)	<0.001	3.53 (2.31, 5.40)	<0.001
Smoke intake						
Favourable	Reference		1.76 (1.26, 2.45)	<0.001	2.74 (2.01, 3.74)	<0.001
Unfavourable	1.04 (0.37, 2.89)	0.94	1.90 (0.91, 3.99)	0.09	4.26 (2.50, 7.25)	<0.001
Alcohol consumption						
Favourable	Reference		2.00 (1.38, 2.90)	<0.001	3.01 (2.12, 4.28)	<0.001
Unfavourable	0.93 (0.53, 1.64)	0.81	1.10 (0.64, 1.87)	0.73	2.27 (1.47, 3.48)	<0.001
Healthy weight						

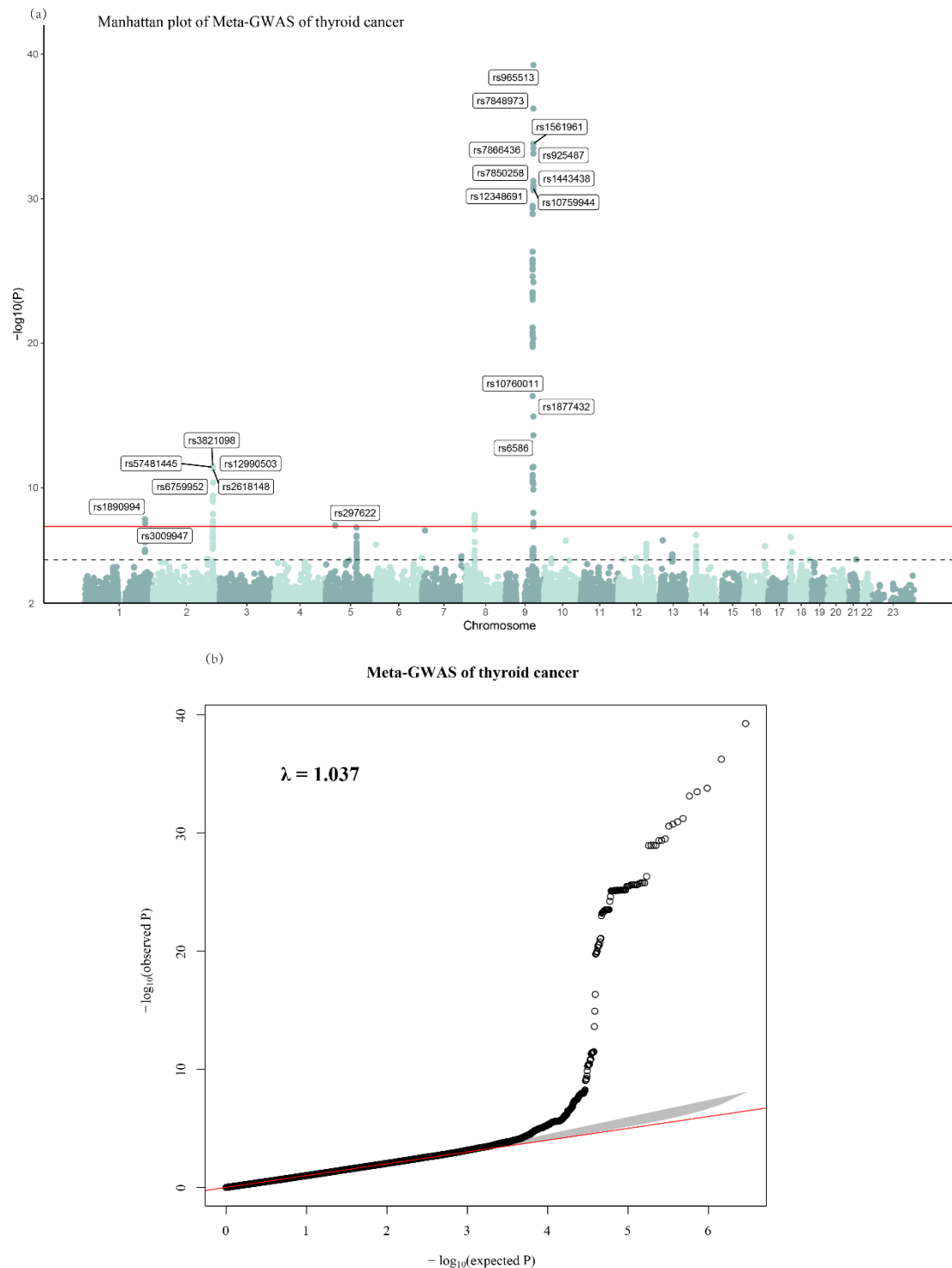
Favourable	Reference		1.63 (0.97, 2.73)	0.06	2.78 (1.73, 4.48)	<0.001
Unfavourable	1.25 (0.74, 2.12)	0.41	2.31 (1.43, 3.72)	<0.001	3.59 (2.28, 5.67)	<0.001

^aadjusted for age, sex, genetic composition, townsend deprivation index at recruitment, qualifications and average total household income before tax.

eFigure 1 Flow diagram for the Selection of TC cases in the UK biobank

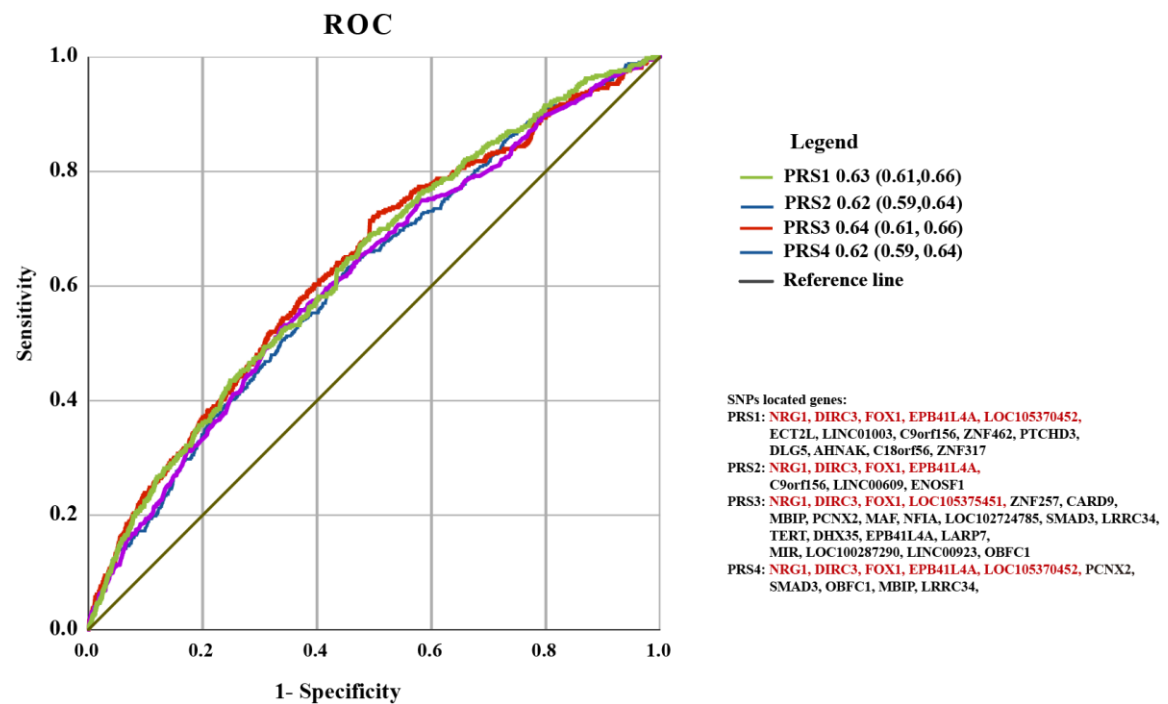


eFigure 2 Manhattan plot and QQ plot of Meta-GWAS of thyroid cancer



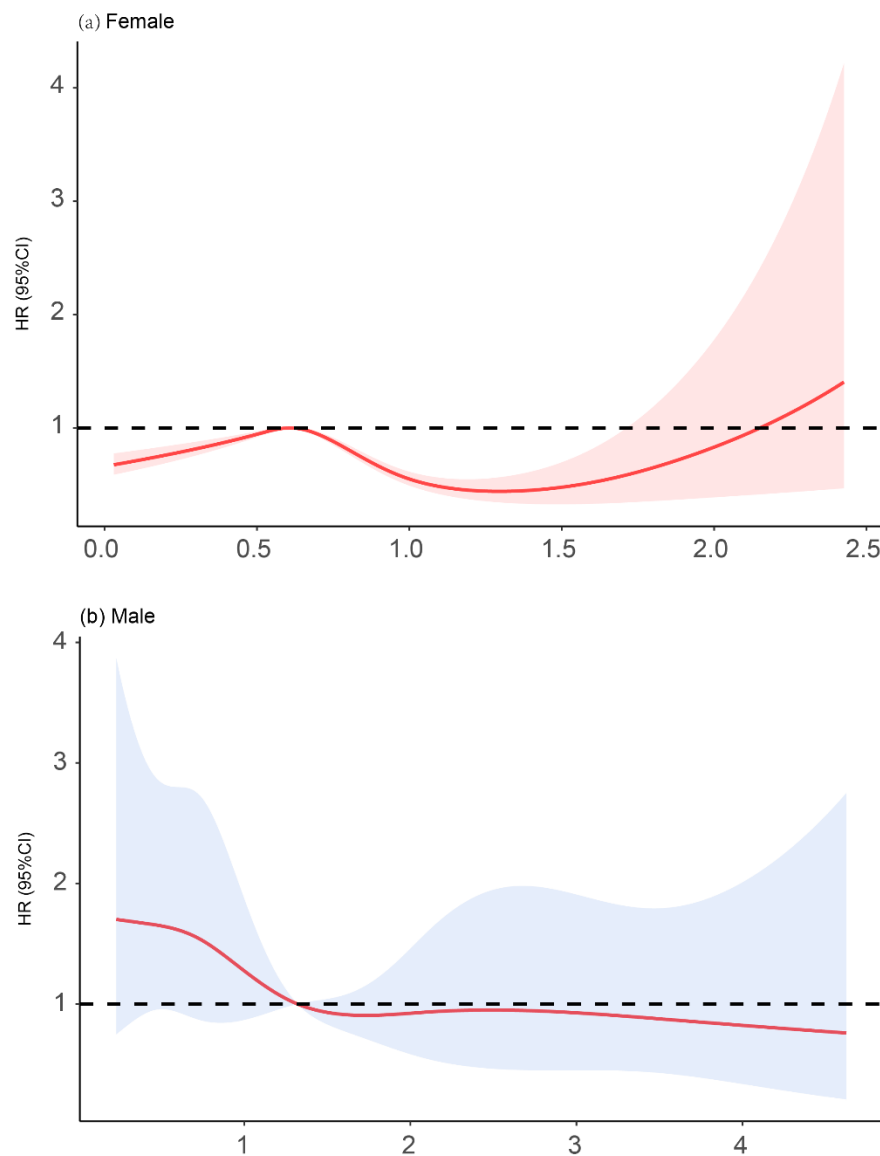
We plotted the Manhattan plot and QQ plot of Meta-GWAS of thyroid cancer. (a) Manhattan plot shows 6.5 million variants from Meta-GWAS of 1956 TC cases and 101,924 controls, the y-axis plots indicate $P < 1 \times 10^{-2}$; (b) QQ plot with $\lambda = 1.037$.

eFigure 3 ROC curve of genetic risk score



We compared the association between four PRS and TC. We obtained area under the ROC curves (AUC) of 0.63 (95%CI, 0.61 to 0.66) of PRS 1, 0.62 (95%CI, 0.59 to 0.64) of PRS 2, 0.64 (95%CI, 0.61 to 0.66) of PRS 3, and 0.62 (95%CI, 0.59 to 0.64) of PRS 4.

eFigure 4 Restricted cubic spline curve of drink score



We plotted the non-linear relationship between alcohol consumption and TC using restricted cubic spline (RCS) and adjusted for age, sex, the first five genetic principal components, educational qualifications, socioeconomic status, and the average total household income before tax. (a) The non-linear relationship between drink score and TC among 122,280 females (excluded those with drink score out of 5%-95%); (b) The non-linear relationship between drink score and TC among 111,538 males (excluded those with drink score out of 5%-95%).

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