

Thyroid function, sex hormones and sexual function: a Mendelian randomization study

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Table S1. Summary-level instrument-TSH associations

Exposure	Nearest gene	SNP	EA	OA	Chr	Beta	SE	P value	Sample size	F	Type of AITD
TSH	CAPZB	rs10917469	A	G	1	0.111	0.009	4.00E-39	51018	152	/
TSH	CAPZB	rs12089835	T	C	1	0.073	0.007	1.30E-28	51018	109	/
TSH	CAPZB	rs74804879	T	C	1	0.050	0.007	1.20E-14	51018	51	/
TSH	VAV3	rs17020122	T	C	1	0.104	0.011	5.30E-20	51018	89	/
TSH	NFIA	rs334725	A	G	1	0.174	0.015	2.40E-32	51018	135	/
TSH	DIRC3	rs6724073	T	C	2	0.051	0.008	1.30E-10	52047	41	/
TSH	IGFBP5	rs16856540	C	T	2	0.055	0.008	7.80E-11	52047	47	/
TSH	IGFBP5	rs13015993	A	G	2	0.082	0.007	4.50E-32	52047	137	/
TSH	IGF2BP2	rs13100823	C	T	3	0.041	0.007	6.80E-10	54288	34	/
TSH	TM4SF4	rs28502438	T	C	3	0.034	0.006	3.70E-08	54288	32	/
TSH	SYN2	rs1663070	C	T	3	0.046	0.007	3.50E-11	54288	43	/
TSH	HES1	rs59381142	G	A	3	0.058	0.008	1.70E-14	52048	53	/
TSH	NR3C2	rs11732089	T	C	4	0.115	0.008	1.70E-51	52047	207	/
TSH	NR3C2	rs6535624	A	G	4	0.042	0.006	1.60E-11	52047	49	/
TSH	PDE8B	rs1119208	T	C	5	0.046	0.006	6.60E-13	53074	59	/
TSH	PDE8B	rs113974964	C	T	5	0.124	0.015	2.10E-17	53074	68	/
TSH	PDE8B	rs139149784	A	G	5	0.156	0.029	5.00E-08	49018	29	/
TSH	PDE8B	rs139424329	G	A	5	0.200	0.032	5.10E-10	45981	39	/
TSH	PDE8B	rs182873197	C	T	5	0.080	0.014	1.70E-08	53074	33	/
TSH	PDE8B	rs2127387	A	G	5	0.144	0.006	1.10E-117	53074	576	/
TSH	PDE8B	rs7702192	A	C	5	0.070	0.006	2.60E-30	53074	136	/
TSH	PDE8B	rs62362610	C	G	5	0.073	0.012	7.70E-10	53074	37	/
TSH	VEGFA	rs744103	A	T	6	0.092	0.007	6.70E-41	54288	173	/
TSH	VEGFA	rs9381266	T	C	6	0.073	0.007	1.80E-25	54288	109	/

TSH	PDE10A	rs1079418	A	G	6	0.101	0.007	8.20E-53	52424	208	/
TSH	PDE10A	rs73022105	T	C	6	0.105	0.016	1.20E-11	52424	43	/
TSH	PSORS1C1	rs1265091	T	C	6	0.057	0.009	3.20E-11	47651	40	/
TSH	SASH1	rs9497965	T	C	6	0.044	0.006	9.80E-13	54288	54	/
TSH	SULF1	rs10957494	G	A	8	0.040	0.007	1.10E-09	54288	33	/
TSH	TG	rs118039499	A	C	8	0.184	0.024	2.00E-14	48736	59	/
TSH	TG	rs2739067	G	A	8	0.042	0.006	2.40E-11	54288	49	/
TSH	SLC25A37	rs56009477	A	G	8	0.052	0.008	3.70E-10	54288	42	/
TSH	NRG1	rs2439301	G	A	8	0.059	0.008	8.20E-15	54288	54	/
TSH	GLIS3	rs10814915	T	C	9	0.042	0.006	5.10E-12	54288	49	/
TSH	ABO	rs8176645	A	T	9	0.052	0.006	3.90E-16	54288	75	/
TSH	C9orf92	rs9298749	C	A	9	0.039	0.006	8.80E-10	54288	42	/
TSH	GATA3	rs11255790	C	T	10	0.041	0.007	6.80E-10	54288	34	/
TSH	NKX2-3	rs200574439	C	A	10	0.047	0.006	3.70E-13	54288	61	/
TSH	PTEN	rs4933466	A	G	10	0.040	0.006	5.10E-10	54288	44	/
TSH	PRDM11	rs12284404	G	A	11	0.067	0.007	2.50E-22	54288	92	/
TSH	CADM1	rs4445669	C	T	11	0.040	0.006	5.80E-11	54288	44	/
TSH	SPATA13	rs7329958	C	T	13	0.044	0.007	1.10E-11	54288	40	/
TSH	TSHR	rs11159482	T	C	14	0.085	0.013	6.30E-11	54288	43	/
TSH	TSHR	rs59334515	C	T	14	0.054	0.007	1.10E-13	54288	60	/
TSH	TSHR	rs12893151	C	A	14	0.062	0.008	1.00E-15	54288	60	/
TSH	ITPK1	rs8015085	A	G	14	0.067	0.008	2.40E-18	54288	70	/
TSH	MBIP	rs398745	C	A	14	0.052	0.006	4.00E-17	54288	75	/
TSH	MBIP	rs2254613	G	T	14	0.035	0.006	3.40E-08	54288	34	/
TSH	FGF7	rs17477923	T	C	15	0.083	0.007	2.60E-33	54288	141	/
TSH	FGF7	rs11639111	T	C	15	0.045	0.006	3.60E-13	54288	56	/

TSH	DET1	rs13329353	T	C	15	0.061	0.007	5.20E-21	54288	76	/
TSH	MIR365A	rs30227	C	T	16	0.047	0.006	7.60E-14	54288	61	/
TSH	ADCY9	rs1045476	A	G	16	0.049	0.008	2.40E-09	54288	38	/
TSH	MAF	rs17767491	A	G	16	0.088	0.007	3.40E-42	54288	158	/
TSH	BCAS3	rs1157994	G	A	17	0.090	0.016	5.30E-09	50232	32	/
TSH	NSF	rs77819282	A	G	17	0.045	0.007	1.10E-09	54288	41	/
TSH	SOX9	rs963384	T	C	17	0.035	0.006	2.80E-08	54288	34	/
TSH	SOX9	rs1042673	G	A	17	0.055	0.006	3.60E-19	54288	84	/
TSH	INSR	rs4804413	T	C	19	0.053	0.006	8.60E-18	51942	78	/
TSH	FOXA2	rs1203944	C	T	20	0.051	0.007	2.40E-12	54288	53	/
TSH	PRKX	rs12390237	G	A	X	0.046	0.007	1.70E-11	36501	43	/
TSH(AITD)	CAPZB	rs10917469	A	G	1	0.111	0.009	4.00E-39	51018	152	GD
TSH(AITD)	VAV3	rs17020122	T	C	1	0.104	0.011	5.30E-20	51018	89	HT, TPOAb
TSH(AITD)	DIRC3	rs6724073	T	C	2	0.051	0.008	1.30E-10	52047	41	TPOAb
TSH(AITD)	IGFBP5	rs16856540	C	T	2	0.055	0.008	7.80E-11	52047	47	GD
TSH(AITD)	IGFBP5	rs13015993	A	G	2	0.082	0.007	4.50E-32	52047	137	GD
TSH(AITD)	IGF2BP2	rs13100823	C	T	3	0.041	0.007	6.80E-10	54288	34	GD
TSH(AITD)	SYN2	rs1663070	C	T	3	0.046	0.007	3.50E-11	54288	43	GD
TSH(AITD)	NR3C2	rs6535624	A	G	4	0.042	0.006	1.60E-11	52047	49	TPOAb
TSH(AITD)	PDE8B	rs139424329	G	A	5	0.200	0.032	5.10E-10	45981	39	HT
TSH(AITD)	PSORS1C1	rs1265091	T	C	6	0.057	0.009	3.20E-11	47651	40	GD
TSH(AITD)	SASH1	rs9497965	T	C	6	0.044	0.006	9.80E-13	54288	54	GD
TSH(AITD)	SPATA13	rs7329958	C	T	13	0.044	0.007	1.10E-11	54288	40	TPOAb
TSH(AITD)	TSHR	rs59334515	C	T	14	0.054	0.007	1.10E-13	54288	60	GD
TSH(AITD)	FGF7	rs17477923	T	C	15	0.083	0.007	2.60E-33	54288	141	TPOAb
TSH(AITD)	MAF	rs17767491	A	G	16	0.088	0.007	3.40E-42	54288	158	TPOAb, GD

TSH(no AITD)	CAPZB	rs12089835	T	C	1	0.073	0.007	1.30E-28	51018	109	/
TSH(no AITD)	CAPZB	rs74804879	T	C	1	0.050	0.007	1.20E-14	51018	51	/
TSH(no AITD)	NFIA	rs334725	A	G	1	0.174	0.015	2.40E-32	51018	135	/
TSH(no AITD)	TM4SF4	rs28502438	T	C	3	0.034	0.006	3.70E-08	54288	32	/
TSH(no AITD)	HES1	rs59381142	G	A	3	0.058	0.008	1.70E-14	52048	53	/
TSH(no AITD)	NR3C2	rs11732089	T	C	4	0.115	0.008	1.70E-51	52047	207	/
TSH(no AITD)	PDE8B	rs1119208	T	C	5	0.046	0.006	6.60E-13	53074	59	/
TSH(no AITD)	PDE8B	rs113974964	C	T	5	0.124	0.015	2.10E-17	53074	68	/
TSH(no AITD)	PDE8B	rs139149784	A	G	5	0.156	0.029	5.00E-08	49018	29	/
TSH(no AITD)	PDE8B	rs182873197	C	T	5	0.080	0.014	1.70E-08	53074	33	/
TSH(no AITD)	PDE8B	rs2127387	A	G	5	0.144	0.006	1.10E-117	53074	576	/
TSH(no AITD)	PDE8B	rs7702192	A	C	5	0.070	0.006	2.60E-30	53074	136	/
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TSH(no AITD)	VEGFA	rs744103	A	T	6	0.092	0.007	6.70E-41	54288	173	/
TSH(no AITD)	VEGFA	rs9381266	T	C	6	0.073	0.007	1.80E-25	54288	109	/
TSH(no AITD)	PDE10A	rs1079418	A	G	6	0.101	0.007	8.20E-53	52424	208	/
TSH(no AITD)	PDE10A	rs73022105	T	C	6	0.105	0.016	1.20E-11	52424	43	/
TSH(no AITD)	SULF1	rs10957494	G	A	8	0.040	0.007	1.10E-09	54288	33	/
TSH(no AITD)	TG	rs118039499	A	C	8	0.184	0.024	2.00E-14	48736	59	/
TSH(no AITD)	TG	rs2739067	G	A	8	0.042	0.006	2.40E-11	54288	49	/
TSH(no AITD)	SLC25A37	rs56009477	A	G	8	0.052	0.008	3.70E-10	54288	42	/
TSH(no AITD)	NRG1	rs2439301	G	A	8	0.059	0.008	8.20E-15	54288	54	/
TSH(no AITD)	GLIS3	rs10814915	T	C	9	0.042	0.006	5.10E-12	54288	49	/
TSH(no AITD)	ABO	rs8176645	A	T	9	0.052	0.006	3.90E-16	54288	75	/
TSH(no AITD)	C9orf92	rs9298749	C	A	9	0.039	0.006	8.80E-10	54288	42	/
TSH(no AITD)	GATA3	rs11255790	C	T	10	0.041	0.007	6.80E-10	54288	34	/

TSH(no AITD)	NKX2-3	rs200574439	C	A	10	0.047	0.006	3.70E-13	54288	61	/
TSH(no AITD)	PTEN	rs4933466	A	G	10	0.040	0.006	5.10E-10	54288	44	/
TSH(no AITD)	PRDM11	rs12284404	G	A	11	0.067	0.007	2.50E-22	54288	92	/
TSH(no AITD)	CADM1	rs4445669	C	T	11	0.040	0.006	5.80E-11	54288	44	/
TSH(no AITD)	TSHR	rs11159482	T	C	14	0.085	0.013	6.30E-11	54288	43	/
TSH(no AITD)	TSHR	rs12893151	C	A	14	0.062	0.008	1.00E-15	54288	60	/
TSH(no AITD)	ITPK1	rs8015085	A	G	14	0.067	0.008	2.40E-18	54288	70	/
TSH(no AITD)	MBIP	rs398745	C	A	14	0.052	0.006	4.00E-17	54288	75	/
TSH(no AITD)	MBIP	rs2254613	G	T	14	0.035	0.006	3.40E-08	54288	34	/
TSH(no AITD)	FGF7	rs11639111	T	C	15	0.045	0.006	3.60E-13	54288	56	/
TSH(no AITD)	DET1	rs13329353	T	C	15	0.061	0.007	5.20E-21	54288	76	/
TSH(no AITD)	MIR365A	rs30227	C	T	16	0.047	0.006	7.60E-14	54288	61	/
TSH(no AITD)	ADCY9	rs1045476	A	G	16	0.049	0.008	2.40E-09	54288	38	/
TSH(no AITD)	BCAS3	rs1157994	G	A	17	0.090	0.016	5.30E-09	50232	32	/
TSH(no AITD)	NSF	rs77819282	A	G	17	0.045	0.007	1.10E-09	54288	41	/
TSH(no AITD)	SOX9	rs963384	T	C	17	0.035	0.006	2.80E-08	54288	34	/
TSH(no AITD)	SOX9	rs1042673	G	A	17	0.055	0.006	3.60E-19	54288	84	/
TSH(no AITD)	INSR	rs4804413	T	C	19	0.053	0.006	8.60E-18	51942	78	/
TSH(no AITD)	FOXA2	rs1203944	C	T	20	0.051	0.007	2.40E-12	54288	53	/
TSH(no AITD)	PRKX	rs12390237	G	A	X	0.046	0.007	1.70E-11	36501	43	/

SNP, single nucleotide polymorphism; EA: effect allele; OA: other allele; Chr: chromosome; Beta: beta-coefficient; SE, standard error; F: strength of instrument; TSH, thyroid stimulating hormone; AITD: autoimmune thyroid disease. GD: Graves' disease. HT: Hashimoto's thyroiditis. TPOAb: thyroid peroxidase antibodies.

Table S2. Summary-level instrument-FT4 associations

Exposure	Nearest gene	SNP	EA	OA	Chr	Beta	SE	P value	Sample size	F
FT4	DIO1	rs12033572	C	G	1	0.115	0.017	1.40E-11	49269	46
FT4	DIO1	rs145019385	T	C	1	0.181	0.032	1.10E-08	42463	32
FT4	DIO1	rs2235544	A	C	1	0.139	0.007	4.20E-101	49269	394
FT4	DIO1	rs954878	G	A	1	0.058	0.007	4.80E-19	49269	69
FT4	ACMSD	rs4954192	C	T	2	0.041	0.007	8.40E-09	44902	34
FT4	SOX2-OT	rs6785807	G	A	3	0.059	0.009	2.50E-10	49269	43
FT4	AADAT	rs6854291	A	G	4	0.117	0.011	1.30E-24	47314	113
FT4	ID4	rs10946313	T	C	6	0.046	0.007	2.30E-11	49269	43
FT4	SLC17A4	rs137964359	C	T	6	0.200	0.032	2.10E-10	49269	39
FT4	SLC17A4	rs9356988	G	A	6	0.051	0.007	3.60E-12	49269	53
FT4	LOC728012	rs17185536	T	C	6	0.073	0.008	1.90E-19	49269	83
FT4	CA8	rs67583169	C	G	8	0.061	0.01	1.00E-10	49269	37
FT4	GLIS3	rs10119187	T	C	9	0.050	0.009	4.10E-09	49269	31
FT4	NEK6	rs10818937	C	T	9	0.048	0.007	1.30E-11	49269	47
FT4	FOXE1	rs10739496	T	C	9	0.078	0.007	4.20E-30	49269	124
FT4	FOXE1	rs10984606	G	T	9	0.040	0.007	1.20E-09	49269	33
FT4	QSOX2	rs55679545	A	G	9	0.044	0.008	8.40E-09	49269	30
FT4	LHX3	rs7860634	A	G	9	0.104	0.008	7.70E-44	44811	169
FT4	FNBP4	rs11039355	C	T	11	0.039	0.007	3.50E-08	49269	31
FT4	SLCO1B1	rs4149056	C	T	12	0.051	0.009	1.30E-08	49269	32
FT4	DIO3OS	rs11626434	C	G	14	0.058	0.007	4.10E-17	49269	69
FT4	DIO3OS	rs12323871	C	T	14	0.047	0.008	1.40E-08	49269	35
FT4	DIO2	rs150816132	G	A	14	0.220	0.04	3.50E-08	38640	30
FT4	DIO2	rs225014	T	C	14	0.054	0.007	1.80E-15	49269	60

FT4	DIO2	rs978055	A	T	14	0.038	0.007	1.10E-08	49269	29
FT4	USP3	rs12907106	G	C	15	0.041	0.007	3.70E-08	49269	34
FT4	SNX29	rs8063103	G	C	16	0.052	0.009	1.60E-08	49269	33
FT4	NCOR1	rs11078333	A	T	17	0.051	0.007	9.90E-13	49269	53
FT4	SLC25A52	rs1080094	G	A	18	0.042	0.007	4.10E-10	49269	36
FT4	SLC25A52	rs113107469	T	C	18	0.200	0.022	1.10E-19	49269	83
FT4	MC4R	rs56069042	A	G	18	0.106	0.019	1.20E-08	49269	31
FT4_within	DIO1	rs12033572	C	G	1	0.115	0.017	1.40E-11	49269	46
FT4_within	DIO1	rs145019385	T	C	1	0.181	0.032	1.10E-08	42463	32
FT4_within	DIO1	rs2235544	A	C	1	0.139	0.007	4.20E-101	49269	394
FT4_within	DIO1	rs954878	G	A	1	0.058	0.007	4.80E-19	49269	69
FT4_within	DIO2	rs150816132	G	A	14	0.220	0.04	3.50E-08	38640	30
FT4_within	DIO2	rs225014	T	C	14	0.054	0.007	1.80E-15	49269	60
FT4_within	DIO2	rs978055	A	T	14	0.038	0.007	1.10E-08	49269	29
FT4_outside	ACMSD	rs4954192	C	T	2	0.041	0.007	8.40E-09	44902	34
FT4_outside	SOX2-OT	rs6785807	G	A	3	0.059	0.009	2.50E-10	49269	43
FT4_outside	AADAT	rs6854291	A	G	4	0.117	0.011	1.30E-24	47314	113
FT4_outside	ID4	rs10946313	T	C	6	0.046	0.007	2.30E-11	49269	43
FT4_outside	SLC17A4	rs137964359	C	T	6	0.200	0.032	2.10E-10	49269	39
FT4_outside	SLC17A4	rs9356988	G	A	6	0.051	0.007	3.60E-12	49269	53
FT4_outside	LOC728012	rs17185536	T	C	6	0.073	0.008	1.90E-19	49269	83
FT4_outside	CA8	rs67583169	C	G	8	0.061	0.01	1.00E-10	49269	37
FT4_outside	GLIS3	rs10119187	T	C	9	0.050	0.009	4.10E-09	49269	31
FT4_outside	NEK6	rs10818937	C	T	9	0.048	0.007	1.30E-11	49269	47
FT4_outside	FOXE1	rs10739496	T	C	9	0.078	0.007	4.20E-30	49269	124
FT4_outside	FOXE1	rs10984606	G	T	9	0.040	0.007	1.20E-09	49269	33

FT4_outside	QSOX2	rs55679545	A	G	9	0.044	0.008	8.40E-09	49269	30
FT4_outside	LHX3	rs7860634	A	G	9	0.104	0.008	7.70E-44	44811	169
FT4_outside	FNBP4	rs11039355	C	T	11	0.039	0.007	3.50E-08	49269	31
FT4_outside	SLCO1B1	rs4149056	C	T	12	0.051	0.009	1.30E-08	49269	32
FT4_outside	DIO3OS	rs11626434	C	G	14	0.058	0.007	4.10E-17	49269	69
FT4_outside	DIO3OS	rs12323871	C	T	14	0.047	0.008	1.40E-08	49269	35
FT4_outside	USP3	rs12907106	G	C	15	0.041	0.007	3.70E-08	49269	34
FT4_outside	SNX29	rs8063103	G	C	16	0.052	0.009	1.60E-08	49269	33
FT4_outside	NCOR1	rs11078333	A	T	17	0.051	0.007	9.90E-13	49269	53
FT4_outside	SLC25A52	rs1080094	G	A	18	0.042	0.007	4.10E-10	49269	36
FT4_outside	SLC25A52	rs113107469	T	C	18	0.200	0.022	1.10E-19	49269	83
FT4_outside	MC4R	rs56069042	A	G	18	0.106	0.019	1.20E-08	49269	31

SNP, single nucleotide polymorphism; EA: effect allele; OA: other allele; Chr: chromosome; Beta: beta-coefficient; SE, standard error; F: strength of instrument; FT4, free thyroxine.

Table S3. Summary-level instrument-hypo and hyperthyroidism associations

Exposure	Nearest gene	SNP	EA	OA	Chr	Beta	SE	P value	Sample size	F
hypo	CAPZB	rs75491569	C	T	1	0.238	0.037	8.70E-08	53241	41
hypo	VAV3	rs78495697	T	C	1	0.316	0.041	2.60E-11	53241	59
hypo	TPO	rs11675342	T	C	2	0.160	0.025	1.50E-07	53241	41
hypo	PDE8B	rs1382879	C	T	5	0.153	0.026	2.10E-06	48969	35
hypo	PDE10A	rs2983514	A	G	6	0.154	0.027	1.60E-05	51313	33
hypo	FOXE1	rs7032019	A	G	9	0.248	0.027	5.55E-17	53241	84
hypo	ATXN2	rs597808	A	G	12	0.180	0.026	3.50E-09	53241	48
hypo	FMNL1	rs12449792	T	C	17	0.157	0.028	2.40E-05	46314	31
hyper	CAPZB	rs12138950	C	A	1	0.258	0.042	5.50E-10	51668	38
hyper	PDE8B	rs2046045	T	G	5	0.329	0.034	4.40E-22	50420	94
hyper	PDE10A	rs2983514	G	A	6	0.199	0.032	5.20E-10	49745	39
hyper	VEGFA	rs66760320	T	C	6	0.192	0.035	4.40E-08	51668	30
hyper	FOXE1	rs925488	A	G	9	0.190	0.033	1.10E-08	48508	33
hyper	PRDM11	rs11038357	A	T	11	0.235	0.035	3.10E-11	48508	45
hyper	FGF7	rs17477923	C	T	15	0.245	0.034	6.10E-13	48508	52
hyper	SOX9	rs8077245	T	G	17	0.205	0.033	5.00E-10	48508	39

SNP, single nucleotide polymorphism; EA: effect allele; OA: other allele; Chr: chromosome; Beta: beta-coefficient; SE, standard error; F: strength of instrument; Hypo, hypothyroidism; Hyper, hyperthyroidism.

S4. Sensitivity analyses of mendelian randomization for the association of thyroid function with CSVD using adverse approaches

Exposure	MR-PRESSO		MR-Egger		Weighted Median		Weighted mode	
	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
WMH								
TSH	0.017(-0.030, 0.063)	0.48	-0.085(-0.212, 0.042)	0.2	-0.020(-0.096, 0.055)	0.6	-0.011(-0.102, 0.080)	0.82
TSH(AITD)	-0.027(-0.165, 0.110)	0.7	-0.345(-0.727, 0.038)	0.11	-0.061(-0.198, 0.076)	0.38	-0.077(-0.237, 0.082)	0.36
TSH(no AITD)	0.024(-0.026, 0.073)	0.35	-0.017(-0.157, 0.123)	0.81	0.002(-0.079, 0.084)	0.95	-0.007(-0.102, 0.089)	0.89
FT4	-0.056(-0.147, 0.036)	0.24	0.098(-0.095, 0.291)	0.33	0.006(-0.096, 0.107)	0.91	-0.003(-0.103, 0.098)	0.96
FT4(within)	-	-	-0.161(-0.457, 0.135)	0.48	0.020(-0.111, 0.151)	0.76	0.014(-0.132, 0.159)	0.87
FT4(outside)	-0.100(-0.210, 0.010)	0.09	0.169(-0.106, 0.443)	0.25	-0.019(-0.145, 0.106)	0.77	-0.033(-0.202, 0.136)	0.71
Hypothyroidism	-0.016(-0.075, 0.043)	0.61	0.286(0.865, 0.678)	0.1	0.213(0.966, 0.914)	0.02	0.252(0.957, 0.893)	0.03
Hyperthyroidism	0.008(-0.011, 0.026)	0.45	0.533(1.058, 0.899)	0.22	0.461(1.016, 0.974)	0.06	0.523(1.019, 0.965)	0.07
MD								
TSH	0.292(0.062, 0.523)	0.02	0.264(-0.341, 0.869)	0.4	0.226(-0.118, 0.569)	0.2	0.303(-0.163, 0.768)	0.21
TSH(AITD)	0.407(-0.096, 0.910)	0.14	0.307(-1.287, 1.900)	0.71	0.365(-0.253, 0.982)	0.25	-0.031(-1.018, 0.956)	0.95
TSH(no AITD)	0.222(-0.039, 0.483)	0.1	0.252(-0.411, 0.915)	0.46	0.200(-0.175, 0.576)	0.3	0.330(-0.139, 0.798)	0.18
FT4	-0.316(-0.682, 0.050)	0.1	-0.126(-1.041, 0.789)	0.79	-0.203(-0.680, 0.274)	0.4	-0.161(-0.609, 0.287)	0.49
FT4(within)	-	-	0.224(-1.099, 1.547)	0.8	-0.154(-0.702, 0.394)	0.58	-0.148(-0.750, 0.454)	0.68
FT4(outside)	-0.383(-0.853, 0.086)	0.13	-0.307(-1.757, 1.143)	0.69	-0.312(-0.885, 0.261)	0.29	-0.074(-0.738, 0.589)	0.83
Hypothyroidism	0.137(-0.084, 0.358)	0.26	0.596(0.765, 0.299)	0.67	0.183(1.165, 0.931)	0.38	0.775(1.045, 0.783)	0.33
Hyperthyroidism	-0.101(-0.217, 0.014)	0.14	0.681(1.179, 0.570)	0.89	0.335(0.910, 0.751)	0.1	0.585(0.935, 0.745)	0.16
FA								
TSH	-0.236(-0.507, 0.035)	0.1	-0.057(-0.783, 0.668)	0.88	-0.150(-0.501, 0.200)	0.4	0.013(-0.496, 0.522)	0.96
TSH(AITD)	-0.526(-1.020, -0.031)	0.06	-0.660(-2.225, 0.905)	0.43	-0.673(-1.275, -0.070)	0.03	-0.799(-1.687, 0.089)	0.11
TSH(no AITD)	-0.087(-0.398, 0.225)	0.59	0.046(-0.763, 0.855)	0.91	0.052(-0.354, 0.458)	0.8	0.0004(-0.522, 0.523)	0.99

FT4	0.630(0.350, 0.909)	<0.001	0.214(-0.496, 0.923)	0.56	0.361(-0.064, 0.787)	0.1	0.391(-0.106, 0.887)	0.14
FT4(within)	-	-	0.329(-0.965, 1.624)	0.71	0.297(-0.246, 0.840)	0.28	0.342(-0.259, 0.944)	0.38
FT4(outside)	0.796(0.461, 1.131)	<0.001	0.429(-0.595, 1.453)	0.43	0.519(-0.019, 1.058)	0.06	0.516(-0.152, 1.184)	0.15
Hypothyroidism	-0.045(-0.239, 0.149)	0.66	0.676(0.824, 0.346)	0.67	0.721(0.956, 0.745)	0.2	0.435(1.189, 0.789)	0.58
Hyperthyroidism	0.091(-0.073, 0.254)	0.32	0.408(0.715, 0.351)	0.38	0.475(1.076, 0.881)	0.27	0.941(0.990, 0.767)	0.25

CI, confidence interval; MR, Mendelian randomization; SNP, single nucleotide polymorphism; TSH, thyroid stimulating hormone; FT4, free thyroxine; AITD, autoimmune thyroid disease; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

S5. Sensitivity analyses of mendelian randomization for the association of thyroid function with CSVD using multivariable inverse-variance weighted approach

Exposure	MVMR adjusted for SBP*		MVMR adjusted for DBP*	
	β (95% CI)	P Value	β (95% CI)	P Value
WMH				
TSH	0.025(-0.022, 0.071)	0.64	0.012(-0.038, 0.062)	0.64
TSH(AITD)	-0.069(-0.183, 0.045)	0.50	-0.055(-0.214, 0.105)	0.50
TSH(no AITD)	0.039(-0.013, 0.090)	0.38	0.024(-0.030, 0.077)	0.38
FT4	0.002(-0.086, 0.089)	0.68	-0.018(-0.102, 0.067)	0.68
FT4(within)	0.142(-0.007, 0.291)	<0.001	0.089(0.051, 0.128)	<0.001
FT4(outside)	0.001(-0.121, 0.123)	0.42	-0.043(-0.147, 0.061)	0.42
Hypothyroidism	-0.013(-0.093, 0.067)	0.70	-0.016(-0.100, 0.068)	0.70
Hyperthyroidism	0.007(-0.018, 0.032)	0.77	0.003(-0.018, 0.024)	0.77
MD				
TSH	0.324(0.087, 0.561)	0.007	0.278(0.026, 0.529)	0.03
TSH(AITD)	0.277(-0.180, 0.734)	0.23	0.413(-0.185, 1.010)	0.18
TSH(no AITD)	0.267(-0.016, 0.550)	0.06	0.201(-0.081, 0.484)	0.16
FT4	-0.285(-0.705, 0.135)	0.18	-0.229(-0.618, 0.160)	0.25
FT4(within)	-0.351(-0.791, 0.089)	0.12	-0.279(-0.305, -0.253)	<0.001
FT4(outside)	-0.435(-1.050, 0.180)	0.17	-0.298(-0.823, 0.227)	0.27
Hypothyroidism	0.218(-0.050, 0.486)	0.11	0.230(-0.058, 0.517)	0.12
Hyperthyroidism	-0.124(-0.259, 0.011)	0.07	-0.129(-0.268, 0.010)	0.07
FA				
TSH	-0.239(-0.523, 0.045)	0.10	-0.162(-0.459, 0.136)	0.29
TSH(AITD)	-0.509(-1.046, 0.027)	0.06	-0.574(-1.157, 0.010)	0.054
TSH(no AITD)	-0.105(-0.441, 0.231)	0.54	-0.004(-0.347, 0.340)	0.98

FT4	0.549(0.256, 0.841)	<0.001	0.537(0.246, 0.827)	<0.001
FT4(within)	0.166(-0.306, 0.637)	0.49	0.292(-0.074, 0.659)	0.12
FT4(outside)	0.776(0.384, 1.169)	<0.001	0.699(0.327, 1.071)	<0.001
Hypothyroidism	-0.139(-0.349, 0.070)	0.19	-0.148(-0.369, 0.074)	0.19
Hyperthyroidism	0.175(0.050, 0.300)	0.006	0.099(-0.060, 0.258)	0.22

CI, confidence interval; MR, Mendelian randomization; SNP, single nucleotide polymorphism; TSH, thyroid stimulating hormone; FT4, free thyroxine; AITD, autoimmune thyroid disease; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy; SBP, systolic blood pressure; DBP, diastolic blood pressure.

* Summary-level data for SBP and DBP were obtained from Evangelou Eet al, Nat Genet 2018, PMID: 30224653.

S6. Mendelian randomization pleiotropy and heterogeneity analyses for the association of thyroid function with CSVD

Phenotypes	Egger Intercept		Cochran's Q statistic in IVW	
	Intercept (95% CI)	P Value	Q Value	P Value
WMH				
TSH	0.01(-0.001,0.02)	0.09	36.41	0.63
TSH(AITD)	0.02(-0.003,0.05)	0.12	23.28	0.02
TSH(no AITD)	0.003(-0.006,0.01)	0.51	24.74	0.78
FT4	-0.01(-0.02,0.01)	0.24	24.76	0.1
FT4(within)	0.02(-0.01,0.06)	0.38	2.17	0.34
FT4(outside)	-0.01(-0.03,0.003)	0.13	21.58	0.09
Hypothyroidism	0.03(-0.02,0.07)	0.32	16.42	0.02
Hyperthyroidism	-0.01(-0.05,0.03)	0.58	1.92	0.86
MD				
TSH	0.003(-0.04,0.04)	0.87	44.17	0.3
TSH(AITD)	0.01(-0.10,0.11)	0.9	15.57	0.16
TSH(no AITD)	-0.001(-0.04,0.04)	0.97	33.89	0.33
FT4	-0.01(-0.08,0.06)	0.78	25.6	0.08
FT4(within)	-0.05(-0.19,0.10)	0.64	0.49	0.78
FT4(outside)	0.002(-0.09,0.10)	0.97	25	0.03
Hypothyroidism	0.08(-0.10,0.26)	0.42	11.58	0.12
Hyperthyroidism	-0.07(-0.24,0.10)	0.46	2.77	0.74
FA				
TSH	-0.01(-0.06,0.04)	0.63	66.72	0.01
TSH(AITD)	0.01(-0.10,0.11)	0.86	15.71	0.15
TSH(no AITD)	-0.01(-0.06,0.05)	0.78	52.81	0.01
FT4	0.03(-0.03,0.08)	0.33	12.26	0.78

FT4(within)	2.17(-1.75,6.09)	0.34	0.39	0.82
FT4(outside)	0.02(-0.05,0.08)	0.59	10.31	0.74
Hypothyroidism	0.03(-0.14,0.20)	0.74	9.3	0.23
Hyperthyroidism	0.11(-0.05,0.28)	0.26	5.55	0.35

IVW, inverse-variance weighted; CI, confidence interval; TSH, thyroid stimulating hormone; FT4, free thyroxine; AITD, autoimmune thyroid disease; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

Figure S1. Scatter plots for MR analyses of the associations of stratified TSH levels with the risk of cerebral small vessel disease

Scatter plots for MR analyses of the associations of TSH associated with AITD with WMH (A), MD (B), and FA(C), and the associations of TSH not associated with AITD with WMH (D), MD (E), and FA(F), respectively.

The color line indicates the estimate of effect using different MR methods. Circles indicate marginal genetic associations with thyroid function and risk of outcome for each variant. Error bars indicate 95% CIs.

MR, Mendelian randomization; SNP, single-nucleotide polymorphism; CI, confidence interval; TSH, Thyroid-stimulating hormone; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy; AITD, autoimmune thyroid disease.

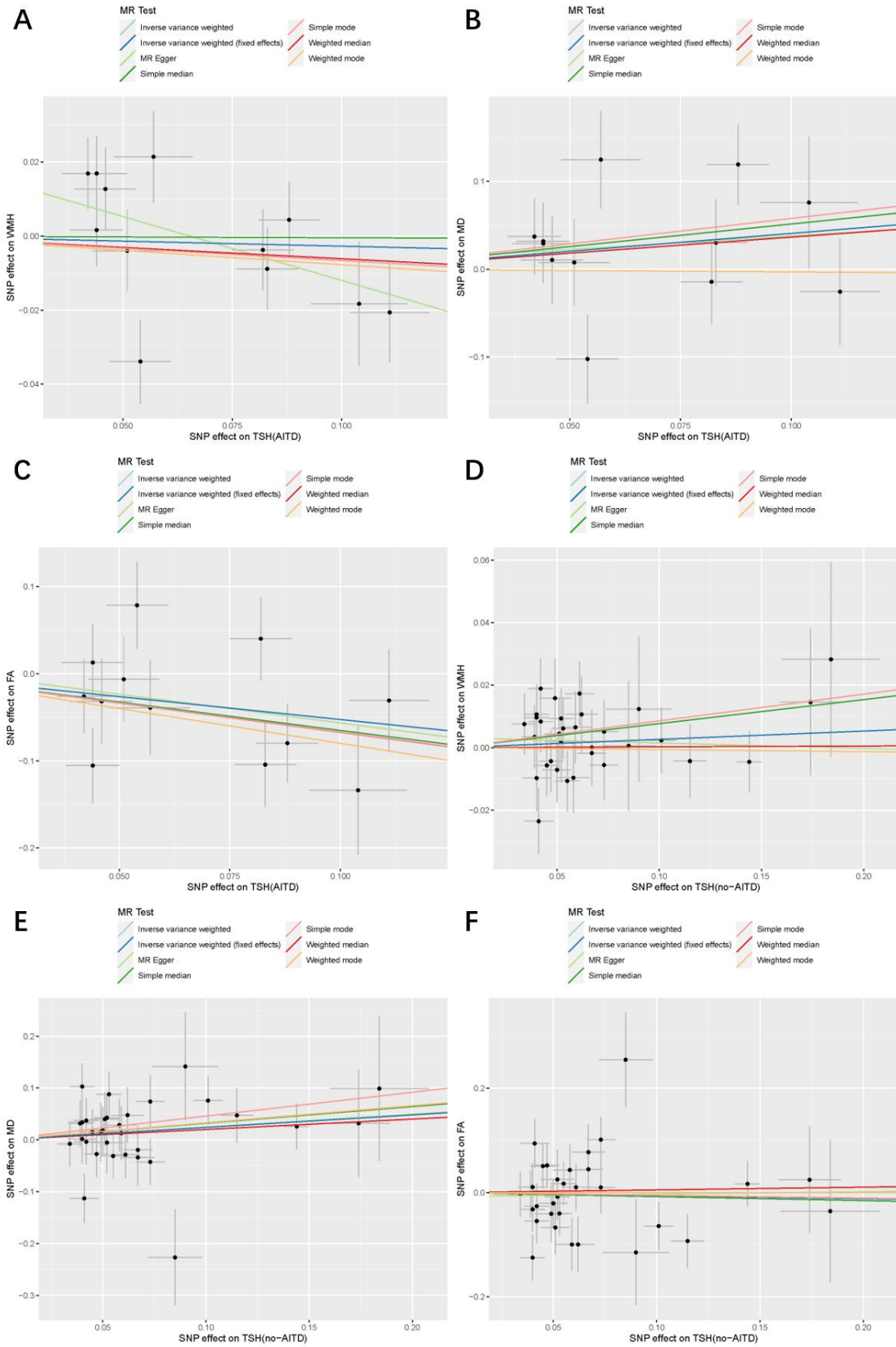


Figure S2. Scatter plots for MR analyses of the associations of stratified FT4 levels with the risk of cerebral small vessel disease

Scatter plots for MR analyses of the associations of FT4 within DIO1 and DIO2 with WMH (A), MD (B), and FA(C), and the associations of FT4 outside DIO1 and DIO2 with WMH (D), MD (E), and FA(F), respectively.

The color line indicates the estimate of effect using different MR methods. Circles indicate marginal genetic associations with thyroid function and risk of outcome for each variant. Error bars indicate 95% CIs.

MR, Mendelian randomization; SNP, single-nucleotide polymorphism; CI, confidence interval; FT4, Free tetraiodo-thyronine; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

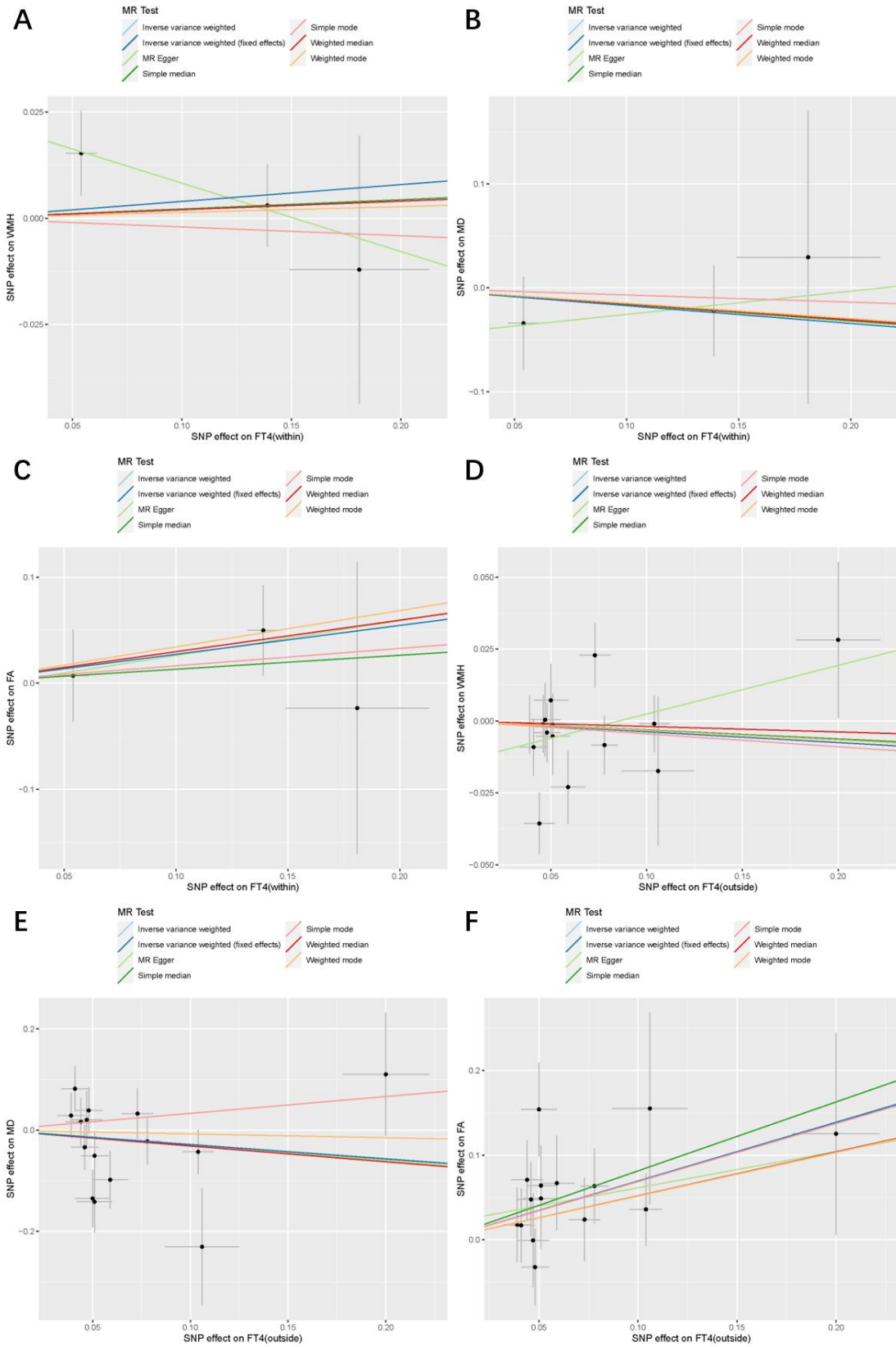


Figure S3. Scatter plots for MR analyses of the associations of hypo and hyperthyroidism with the risk of cerebral small vessel disease

Scatter plots for MR analyses of the associations of hypothyroidism with WMH (A), MD (B), and FA(C), and the associations of hyperthyroidism with WMH (D), MD (E), and FA(F), respectively.

The color line indicates the estimate of effect using different MR methods. Circles indicate marginal genetic associations with thyroid function and risk of outcome for each variant. Error bars indicate 95% CIs.

MR, Mendelian randomization; SNP, single-nucleotide polymorphism; CI, confidence interval; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

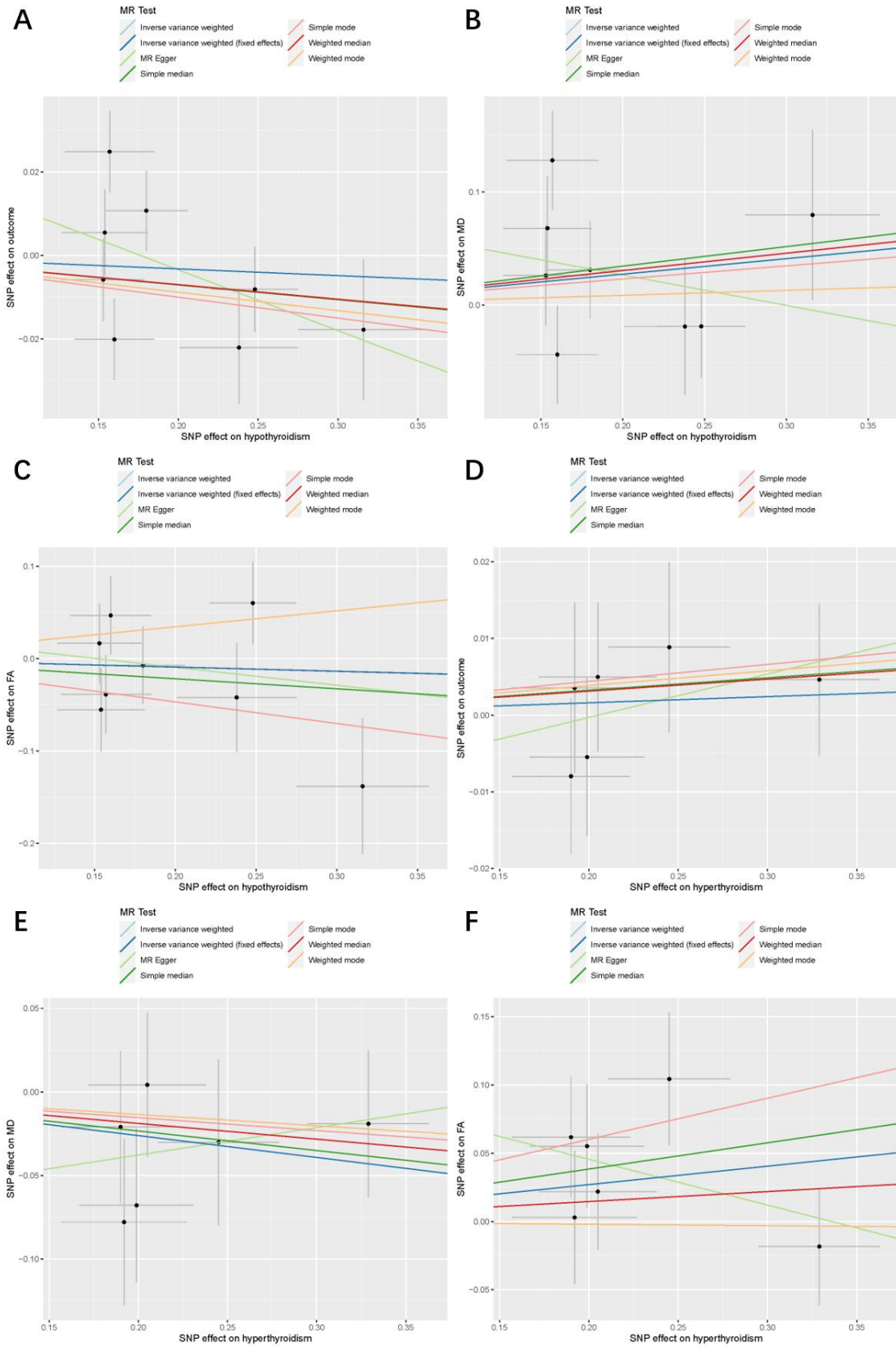


Figure S4. MR leave-one-out sensitivity analysis for the associations of thyroid function with the risk of cerebral small vessel disease

MR leave-one-out sensitivity analysis for the associations of TSH with WMH (A), MD (B), and FA(C), and the associations of FT4 with WMH (D), MD (E), and FA(F), respectively.

Circles indicate MR estimates for telomere length on MD using IVW method if the SNP was omitted. The bars indicate the CI of MR estimates.

MR, Mendelian randomization; IVW, inverse-variance weighted; SNP, single-nucleotide polymorphism; CI, confidence interval; TSH, Thyroid-stimulating hormone; FT4, Free tetraiodo-thyronine; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

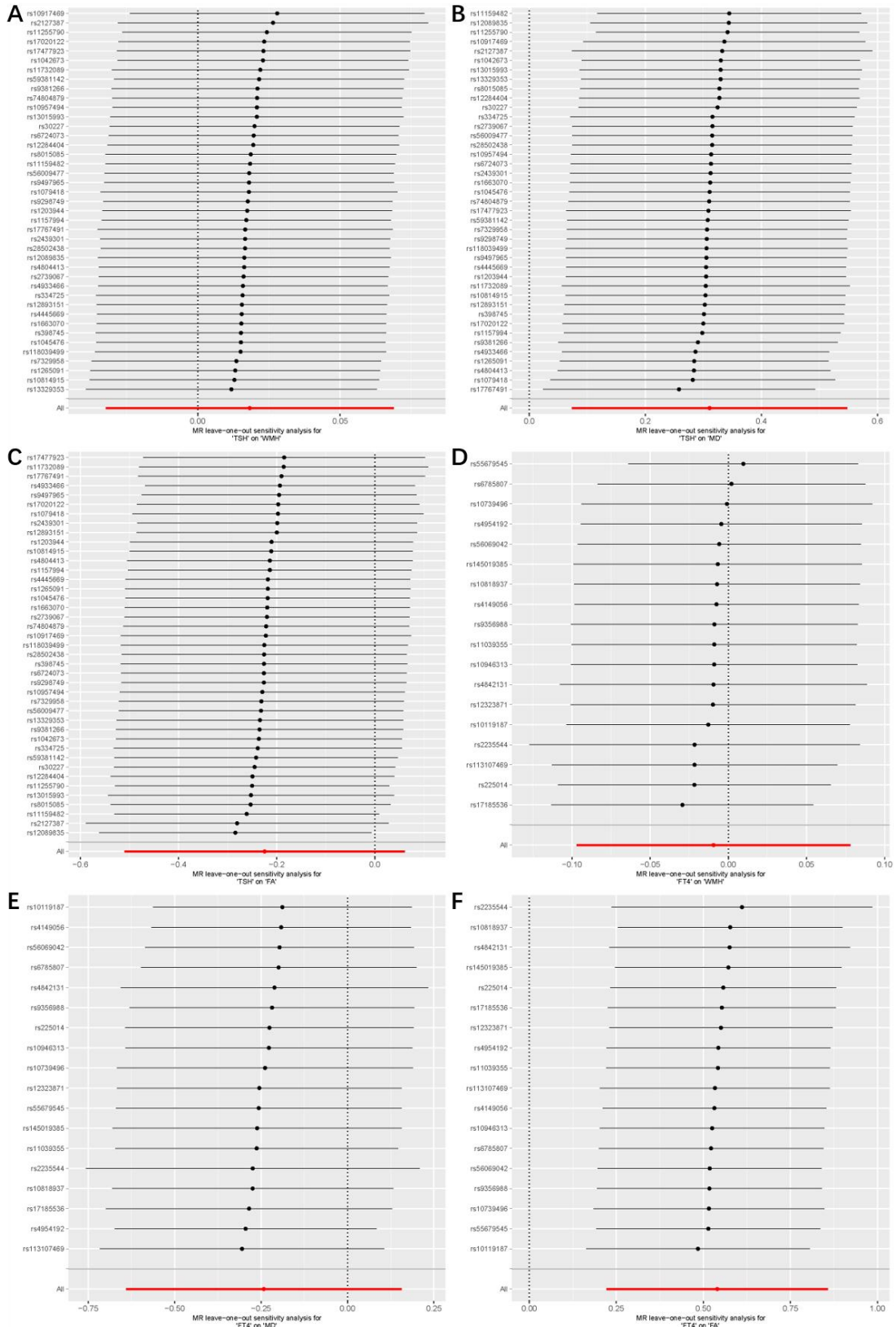


Figure S5. MR leave-one-out sensitivity analysis for the associations of stratified TSH levels with the risk of cerebral small vessel disease

MR leave-one-out sensitivity analysis for the associations of TSH associated with AITD with WMH (A), MD (B), and FA(C), and the associations of TSH not associated with AITD with WMH (D), MD (E), and FA(F), respectively.

Circles indicate MR estimates for telomere length on MD using IVW method if the SNP was omitted. The bars indicate the CI of MR estimates.

MR, Mendelian randomization; IVW, inverse-variance weighted; SNP, single-nucleotide polymorphism; CI, confidence interval; TSH, Thyroid-stimulating hormone; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

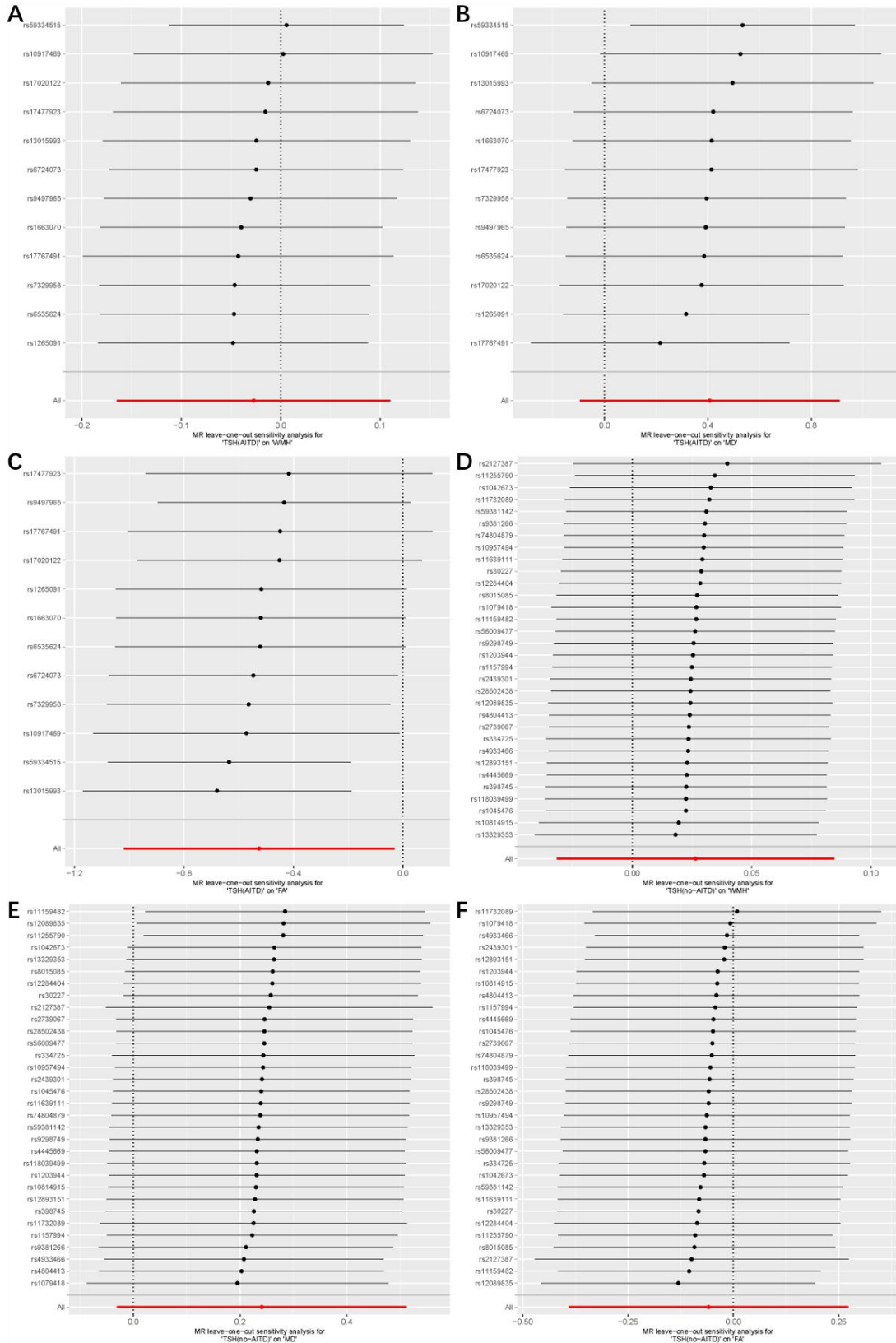


Figure S6. MR leave-one-out sensitivity analysis for the associations of stratified FT4 levels with the risk of cerebral small vessel disease

MR leave-one-out sensitivity analysis for the associations of FT4 within DIO1 and DIO2 with WMH (A), MD (B), and FA(C), and the associations of FT4 outside DIO1 and DIO2 with WMH (D), MD (E), and FA(F), respectively.

Circles indicate MR estimates for telomere length on MD using IVW method if the SNP was omitted. The bars indicate the CI of MR estimates.

MR, Mendelian randomization; IVW, inverse-variance weighted; SNP, single-nucleotide polymorphism; CI, confidence interval; FT4, Free tetraiodo-thyronine; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

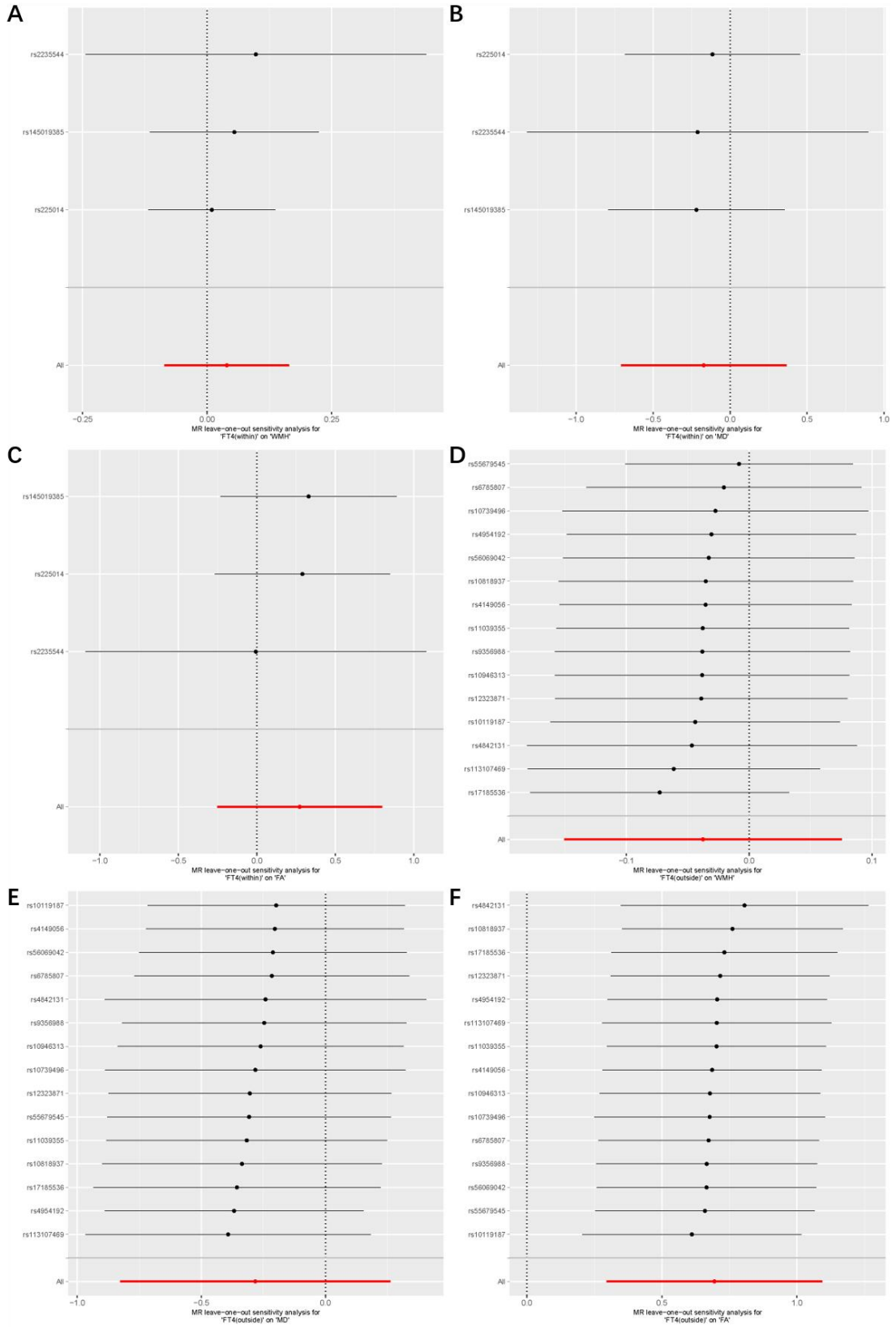


Figure S7. MR leave-one-out sensitivity analysis for the associations of hypo and hyperthyroidism with the risk of cerebral small vessel disease

MR leave-one-out sensitivity analysis for the associations of hypothyroidism with WMH (A), MD (B), and FA(C), and the associations of hyperthyroidism with WMH (D), MD (E), and FA(F), respectively.

Circles indicate MR estimates for telomere length on MD using IVW method if the SNP was omitted. The bars indicate the CI of MR estimates.

MR, Mendelian randomization; IVW, inverse-variance weighted; SNP, single-nucleotide polymorphism; CI, confidence interval; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

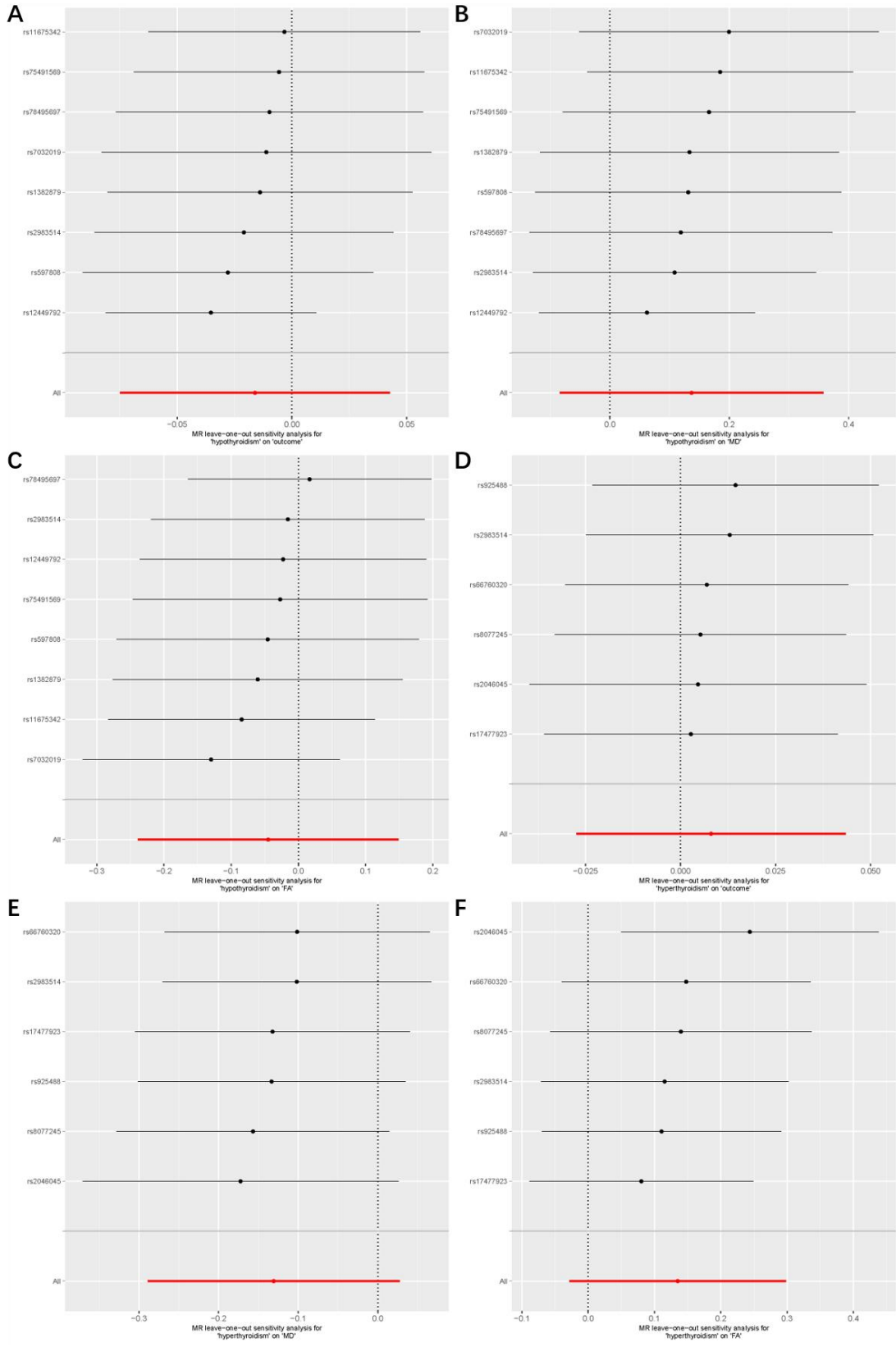


Figure S8. Funnel plots for MR analyses of the associations of thyroid function with the risk of cerebral small vessel disease

Funnel plots for MR analyses of the associations of TSH with WMH (A), MD (B), and FA(C), and the associations of FT4 with WMH (D), MD (E), and FA(F), respectively.

Funnel plot evaluated the presence of possible heterogeneity across the estimates, which indicates the potential pleiotropic effects. The figure presents the observed causal effect of each SNP by dot, and the averaged causal effect of all combined SNPs using IVW (light blue line) and MR-Egger (dark blue line) method on x-axis. Y axis presents the inverse standard error of the estimated causal effect for each of SNP.

MR, Mendelian randomization; IVW, inverse-variance weighted; SNP, single-nucleotide polymorphism; TSH, Thyroid-stimulating hormone; FT4, Free tetraiodo-thyronine; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

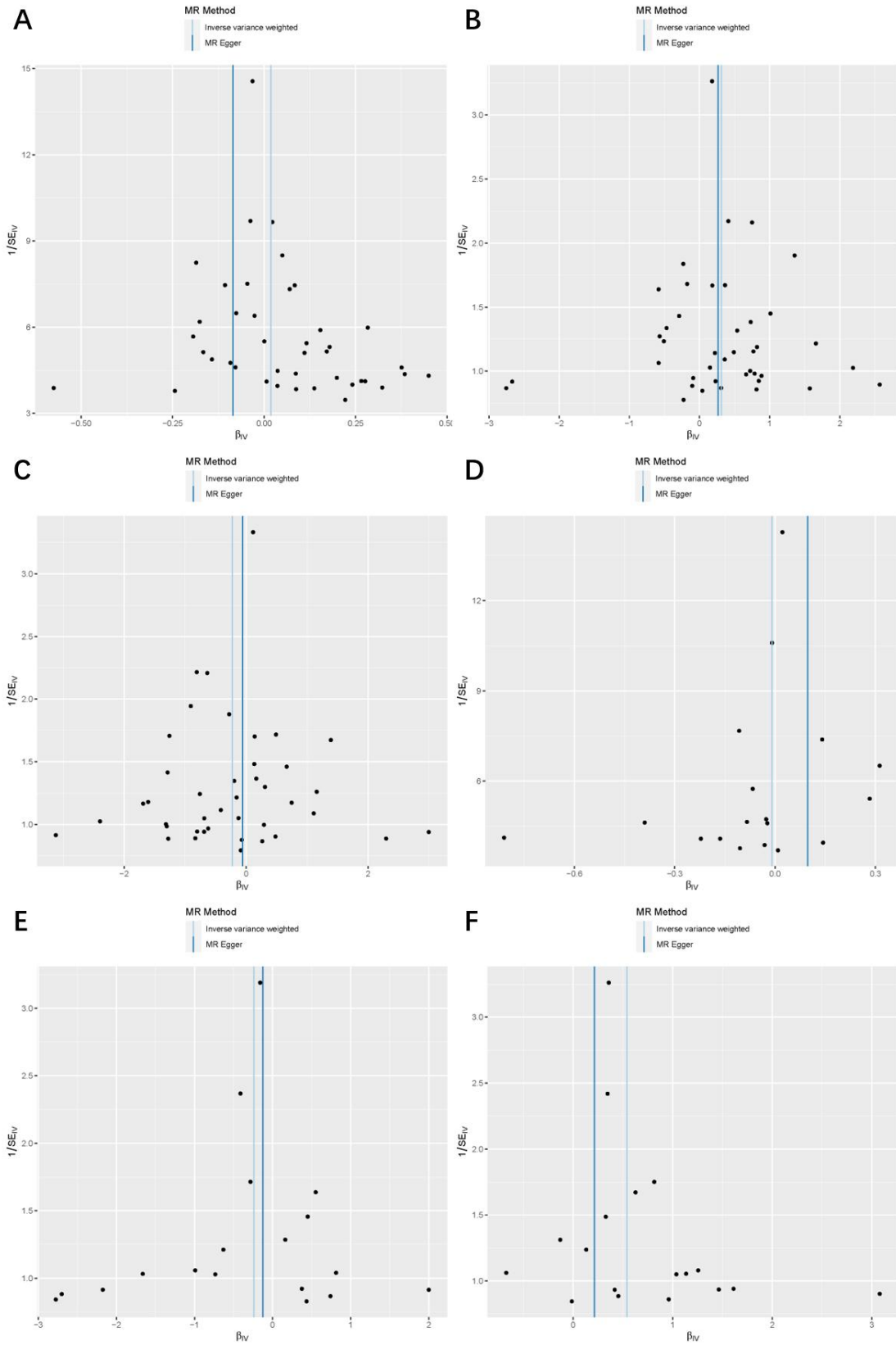


Figure S9. Funnel plots for MR analyses of the associations of stratified TSH levels with the risk of cerebral small vessel disease

Funnel plots for MR analyses of the associations of TSH associated with AITD with WMH (A), MD (B), and FA(C), and the associations of TSH not associated with AITD with WMH (D), MD (E), and FA(F), respectively.

Funnel plot evaluated the presence of possible heterogeneity across the estimates, which indicates the potential pleiotropic effects. The figure presents the observed causal effect of each SNP by dot, and the averaged causal effect of all combined SNPs using IVW (light blue line) and MR-Egger (dark blue line) method on x-axis. Y axis presents the inverse standard error of the estimated causal effect for each of SNP.

MR, Mendelian randomization; IVW, inverse-variance weighted; SNP, single-nucleotide polymorphism; TSH, Thyroid-stimulating hormone; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy; AITD, autoimmune thyroid disease.

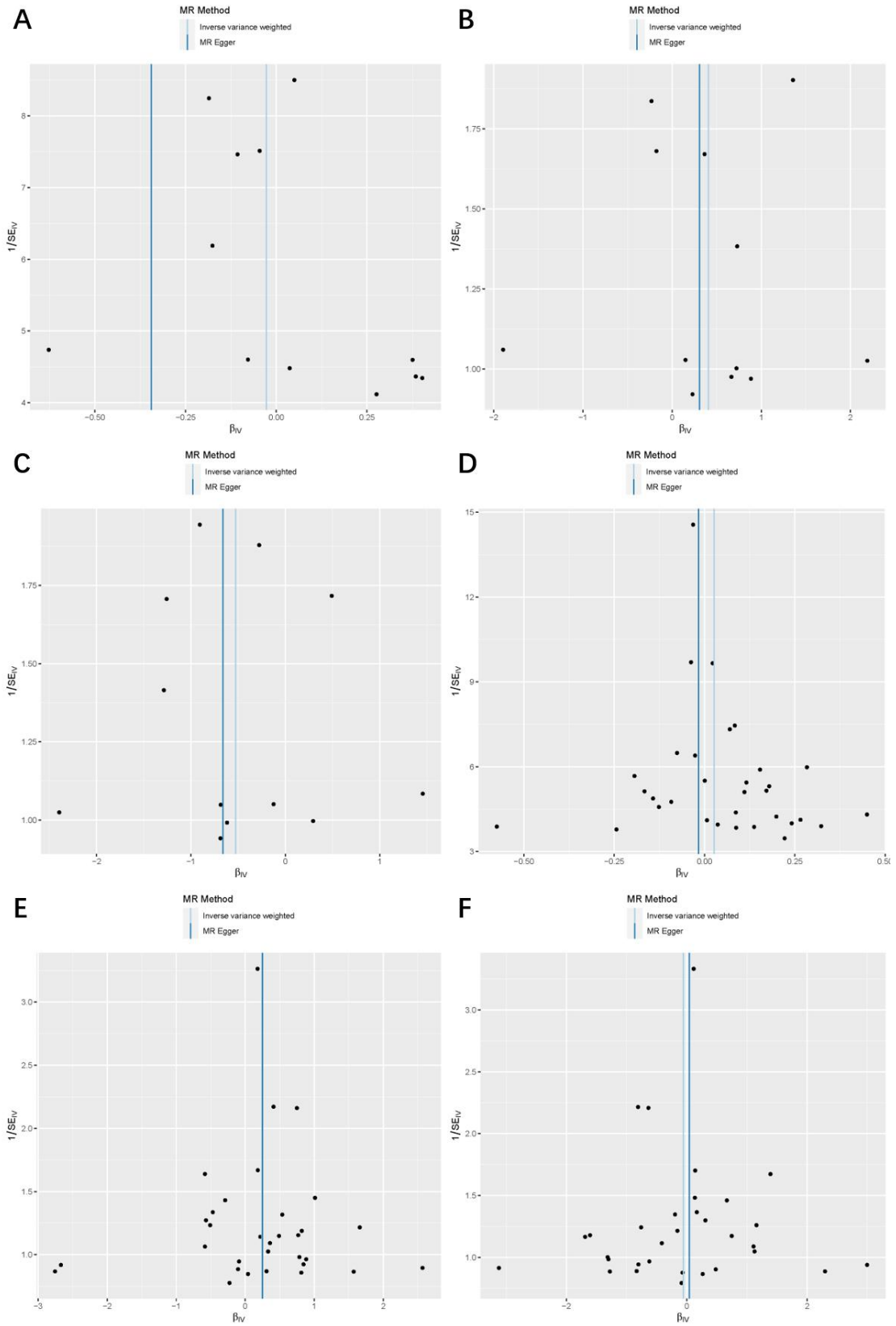


Figure S10. Funnel plots for MR analyses of the associations of stratified FT4 levels with the risk of cerebral small vessel disease

Funnel plots for MR analyses of the associations of FT4 within DIO1 and DIO2 with WMH (A), MD (B), and FA(C), and the associations of FT4 outside DIO1 and DIO2 with WMH (D), MD (E), and FA(F), respectively.

Funnel plot evaluated the presence of possible heterogeneity across the estimates, which indicates the potential pleiotropic effects. The figure presents the observed causal effect of each SNP by dot, and the averaged causal effect of all combined SNPs using IVW (light blue line) and MR-Egger (dark blue line) method on x-axis. Y axis presents the inverse standard error of the estimated causal effect for each of SNP.

MR, Mendelian randomization; IVW, inverse-variance weighted; SNP, single-nucleotide polymorphism; FT4, Free tetraiodo-thyronine; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

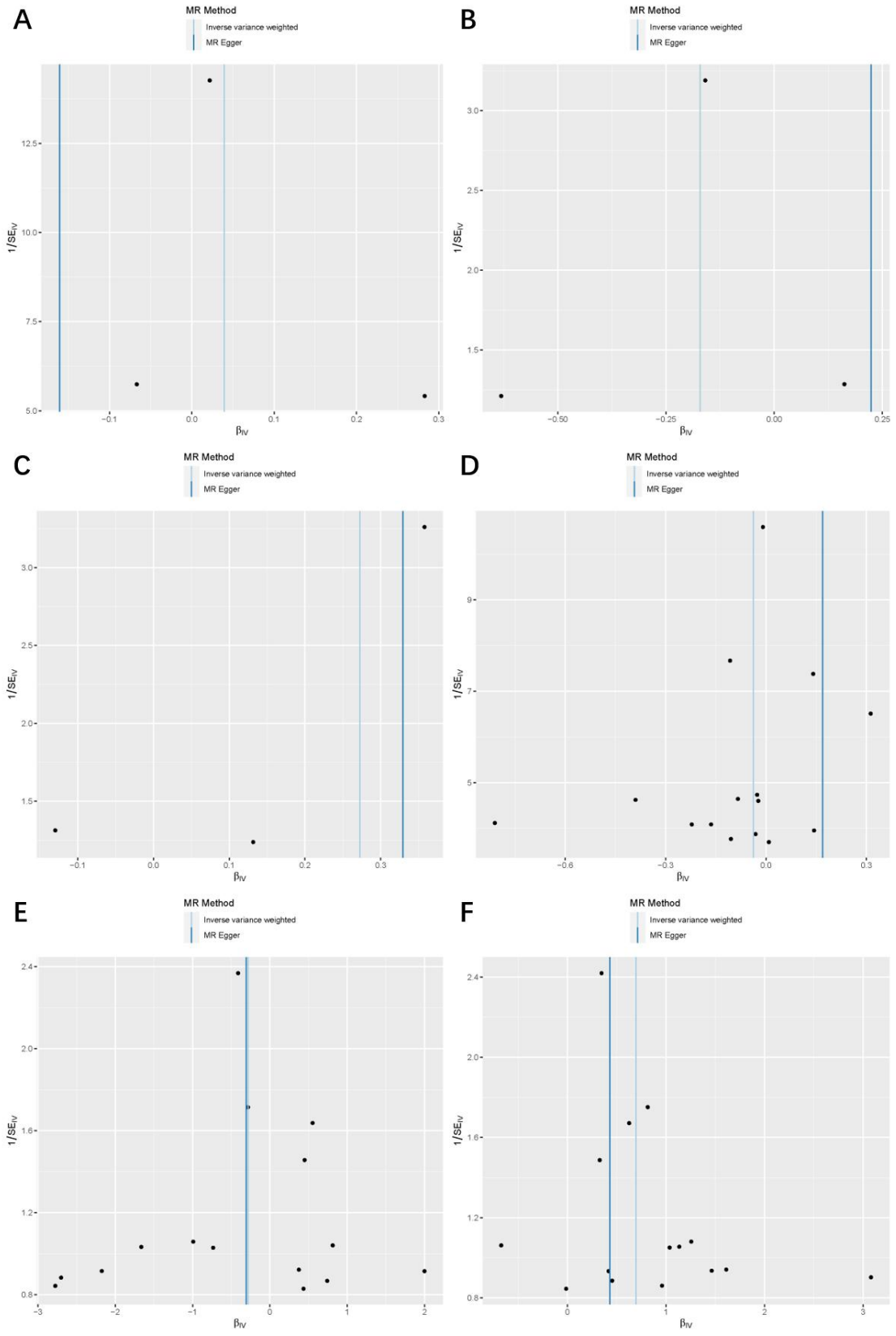


Figure S11. Funnel plots for MR analyses of the associations of hypo and hyperthyroidism with the risk of cerebral small vessel disease

Funnel plots for MR analyses of the associations of hypothyroidism with WMH (A), MD (B), and FA(C), and the associations of hyperthyroidism with WMH (D), MD (E), and FA(F), respectively.

Funnel plot evaluated the presence of possible heterogeneity across the estimates, which indicates the potential pleiotropic effects. The figure presents the observed causal effect of each SNP by dot, and the averaged causal effect of all combined SNPs using IVW (light blue line) and MR-Egger (dark blue line) method on x-axis. Y axis presents the inverse standard error of the estimated causal effect for each of SNP.

MR, Mendelian randomization; IVW, inverse-variance weighted; SNP, single-nucleotide polymorphism; WMH, white matter hyperintensity; MD, mean diffusivity; FA, fractional anisotropy.

