

Supplemental Material

Appendix

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Data S1.

Biological effects of the HFE and TMPRSS6 proteins on systemic iron status

The biological effects of the HFE and TMPRSS6 proteins on iron status are diverse and complex. HFE is a membrane protein which is thought to regulate iron uptake through competitive inhibition of the TRF1 transferrin receptor.¹ When transferrin saturation (and thus systemic iron status) is high, the HFE protein is free to bind to a protein complex including TFR2, which potentiates expression of the iron transport regulator hepcidin.² Hepcidin inhibits the gut enterocyte and macrophage iron export protein ferroportin, which is usually involved in the uptake and release of iron into the hepatic portal system.^{3, 4} As a result, iron absorption is reduced by hepcidin. In contrast, TMPRSS6 is a transmembrane serine protease which may inhibit hepcidin production during systemic iron depletion, thus increasing iron uptake.⁵

Table S1. Cohort demographics and covariates for the Genetics of Iron Status Consortium GWAS meta-analysis, adapted from Benjamin et al. 2014.⁶

Cohort	Study	Discovery/Replication	References (PMID)	n	Sex	Mean age +/- SD (years)	Population	Covariates	Exclusion criteria
Australia-Adult	QIMR Berghofer Adult	Discovery	19820699; 21151130; 20802479	3432	M	47.5 +/- 12.3	European	Age, 5 PCs	
				5716	F	46.0 +/- 12.8			
Australia-Adolescent	QIMR Berghofer Adolescent	Discovery	17539372	1230	M	14.6 +/- 2.0	European	Age, 5 PCs	
				1314	F	14.9 +/- 2.3			
Estonia (original)	Estonian Genome Project	Discovery	24518929	440	M	37.3 +/- 15.4	European	Age, sex, 5 PCs	
				453	F	37.5 +/- 15.7			
Val Borbera	Val Borbera Study	Discovery	19847309	733	M	54.4 +/- 18.4	European	Age, 5 PCs	
				926	F	54.8 +/- 18.7			
NBS	Nikmegen Biomedical Study	Discovery	16254196; 18794855	889	M	66.3 +/- 7.1	European		
				902	F	56.6 +/- 10.8			
Cambridge	UK Blood Services (UKBS) Common Controls panel	Discovery	17554300	1198	M	45.1 +/- 11.9	European		
				1221	F	42.1 +/- 12.7			
Micros/EURAC	Micros/EURAC	Discovery	17550581	528	M	45.5 +/- 15.8	European		
				690	F	46.0 +/- 16.7			
ERF/Rotterdam	ERF/Rotterdam	Discovery	15054401; 16877869	342	M	54.6 +/- 14.1	European	Age	
				529	F	52.8 +/- 15.1			
KORA F3	Kooperative Gesundheitsforschung in der Region Augsburg	Discovery	16032513; 16032514	809	M	63.0 +/- 10.1	European	Age	
				825	F	62.1 +/- 10.1			
KORA F4	Kooperative Gesundheitsforschung in der Region Augsburg	Discovery	16032513; 16032514	882	M	61.2 +/- 8.9	European	Age	
				927	F	60.6 +/- 8.8			
BHS	Busselton Health Study	Discovery	19643935	397	M	54.0 +/- 15.4	European		
				480	F	55.5 +/- 14.9			
Estonia (replication)	Estonian Genome Project	Replication	24518929	547	M	54.4 +/- 16.1	European	Age, sex, 5 PCs	
				470	F	53.4 +/- 15.9			
InCHIANTI	InCHIANTI study	Replication	19880490	536	M	67.1 +/- 15.3	European	Age, sex, centre	
				670	F	69.1 +/- 15.6			
SardiNIA	SardiNIA study on aging	Replication	16934002	2051	M	43.7 +/- 18.1	European	Age, age-squared, sex	
				2643	F	43.1 +/- 17.3			

CoLAUS	Cohorte Lausanne	Replication	18366642	2550	M	52.9 +/- 10.8	European	Age, sex, first 5 ancestry PCs	
				2869	F	52.9 +/- 10.8			
PREVEND	Prevention of Renal and Vascular Endstage Disease	Replication	Website: http://www.prevend.org/index.php	1875	M	50.9 +/- 12.8	European	Age, sex, first 5 PCs	
				1769	F	48.2 +/- 12.0			
FENLAND	Fenland Study	Replication	21248185	615	M	44.5 +/- 7.4	European	Age, sex, 4 PCs	Psychosis; diabetes; illness with a prognosis <1 year; requiring walking aids
				787	F	45.4 +/- 7.2			Psychosis; pregnancy; lactation; diabetes; illness with a prognosis <1 year; requiring walking aids
INTERACT (cases)	InterAct (cases)	Replication	21717116	2087	M	54.7 +/- 8.0	European	Age, sex, centre, 5 PCs	
				2251	F	55.6 +/- 8.3			
INTERACT (subcohort)	InterAct (controls)	Replication	21717116	1816	M	52.2 +/- 9.2	European	Age, sex, centre, 5 PCs	
				3140	F	51.7 +/- 9.6			

Table S2. Association estimates for SNPs associated with biomarkers of iron status at genome-wide significance identified from the Genetics of Iron Status Consortium GWAS meta-analysis.⁶

SNP	Corresponding gene	E A	EAF	Iron			Transferrin			Transferring Saturation			Log ₁₀ Ferritin		
				Estimate	Standard Error	p value	Estimate	Standard Error	p value	Estimate	Standard Error	p value	Estimate	Standard Error	p value
rs744653	<i>WDR75-SLC40A1</i>	T	0.854	0.004	0.010	0.702	0.068	0.010	1.35×10^{-11}	-0.028	0.011	0.008	-0.089	0.010	8.37×10^{-19}
rs8177240	<i>TF</i>	T	0.669	-0.066	0.007	6.65×10^{-20}	-0.380	0.007	8.43×10^{-610}	0.100	0.008	7.24×10^{-38}	0.021	0.007	0.004
rs9990333**	<i>TFRC</i>	T	0.460	0.017	0.007	0.014	-0.051	0.007	1.95×10^{-13}	0.039	0.007	7.28×10^{-8}	0.001	0.007	0.878
rs1800562*	<i>HFE (C282Y)</i>	A	0.067	0.328	0.016	2.72×10^{-97}	-0.479	0.016	8.90×10^{-196}	0.577	0.016	2.19×10^{-270}	0.204	0.016	1.54×10^{-38}
rs1799945*	<i>HFE (H63D)</i>	C	0.850	-0.189	0.010	1.10×10^{-81}	0.114	0.010	9.36×10^{-30}	-0.231	0.010	5.13×10^{-109}	-0.065	0.010	1.71×10^{-10}
rs7385804**	<i>TFR2</i>	A	0.621	0.064	0.007	1.36×10^{-18}	-0.003	0.007	0.728	0.054	0.008	6.07×10^{-12}	0.015	0.007	0.039
rs4921915	<i>NAT2</i>	A	0.782	0.004	0.009	0.633	0.079	0.009	7.05×10^{-19}	-0.026	0.009	0.004	0.001	0.009	0.886
rs651007	<i>ABO</i>	T	0.202	-0.004	0.009	0.611	-0.001	0.009	0.916	-0.006	0.009	0.498	-0.050	0.009	1.31×10^{-8}
rs6486121	<i>ARNTL</i>	T	0.631	-0.009	0.007	0.202	-0.046	0.007	3.89×10^{-10}	0.015	0.008	0.048	0.006	0.007	0.424
rs174577	<i>FADS2</i>	A	0.330	0.001	0.007	0.878	0.062	0.007	2.28×10^{-17}	-0.025	0.008	0.002	-0.012	0.007	0.098
rs411988**	<i>TEX14</i>	A	0.564	-0.002	0.007	0.770	0.014	0.007	0.052	-0.012	0.007	0.115	-0.044	0.007	1.59×10^{-10}
rs855791*	<i>TMPRSS6 (V736A)</i>	A	0.446	-0.181	0.007	1.32×10^{-139}	0.044	0.007	1.98×10^{-9}	-0.190	0.008	6.41×10^{-137}	-0.055	0.007	1.38×10^{-14}

EA, effect allele; EAF, effect allele frequency

* SNPs used in the main MR analyses

**SNPs used in the MR sensitivity analyses

Table S3. Cohort demographics and covariates for the International Network against Thrombosis (INVENT) Collaboration GWAS meta-analysis.⁷

Cohort	Discovery/Replication	Design	References (PMID)	Sex	n	Cases (n)	Control (n)	Mean age +/- SD (years)	Population	Venous thromboembolism (%)	Pulmonary embolism (%)	Covariates	Inclusion criteria	Exclusion criteria
Atherosclerosis Risk in Communities study	Discovery	Cohort	2646917	M	3857	241	8646	54.2 +/- 5.7	United States (4 US communities)	100	41	Age, sex, center and 3 first PCs	45-64 years old	Prior VTE
				F	5030									
Cardiovascular Health Study	Discovery	Cohort	8275211; 1669507	M	1238	95	3024	72.3 +/- 5.4	United States (4 US communities)	100	29	Age, gender and site	65+ years old	Prior VTE; CVD
				F	1881									
Early-Onset Venous Thrombosis	Discovery	Case-control	19278955	M	622	411	1228	36 +/- 9 (cases); 50 +/- 6 (controls)	France	100	35	4 first PCs	European VTE onset <50 years old	Prior VTE; surgery; hospitalisation; cancer; autoimmunity; oral contraceptive pill; pregnancy; post-partum; strong genetic risk for VTE
				F	1017									
Genetics In Familial Thrombosis	Discovery	Case-control	23742623	M	1070	434	1850	42 +/- 8.1 (cases); 59 +/- 6.7 (controls)	The Netherlands	65	33	Family structure	First VTE <46 years; sibling(s) with confirmed	Prior VTE
				F	1214									
Heart and Vascular Health	Discovery	Case-control	7637142	M	677	858	1744	66.0 +/- 10.7	United States (Washington State)	100	52	Age, sex, index year, hypertension status and 5 PCs	18-89 years old	Prior VTE
				F	1925									
MARseille THrombosis Association study	Discovery	Case-control	22443383	M	871	1542	1110	40.94 +/- 15.70 (cases); 68.07 +/- 2.24 (controls)	France	100	21	4 first PCs	European; first VTE	Prior VTE; surgery; hospitalisation; cancer; autoimmunity; oral contraceptive pill; pregnancy; post-partum; strong genetic risk for VTE
				F	1781									

Mayo GWAS of VTE	Discovery	Case-control	22672568	M	1257	1264	1301	54.96 +/- 16.03	United States (Rochester, Minnesota)	100	49	Age, sex, stroke/MI and state of residence	18+ years old	Malignancy-related VTE; active cancer; autoimmunity; rheumatologic disease; prior bone marrow transplant; prior liver transplant; vasculitis; vascular anomaly; mechanical cause of thrombosis, e.g. pacemaker or CVC
				F	1308									
Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis	Discovery	Case-control	15701913	M	1096	1289	1049	48.19 +/- 12.84 (cases); 76.16 +/- 5.35 (controls)	The Netherlands	100	NA	Age and 4 PCs	18-70 years old	Prior VTE; cancer
				F	1242									
Nurses Health Study, Nurses Health Study II and Health Professional Follow-Up Study	Discovery	Case-control	7612801	M	1891	409	4844	58.3 +/- 9.9	United States (11 US states)	49	20	4PCs and study site	NHS: women 30-55 years old; NHSII women 25-42 years old; HPFS: men 40-75 years old	Prior pulmonary embolism
				F	3362									
Nurses Health Study, Nurses Health Study II and Health Professional Follow-Up Study	Discovery	Case-control	7612801	M	1537	426	5720	61.9 +/- 8.9	United States (11 US states)	49	27	4PCs and study site	NHS: women 30-55 years old; NHSII women 25-42 years old; HPFS: men 40-75 years old	Prior pulmonary embolism
				F	4610									
Women's Genome Health Study	Discovery	Cohort	18070814	M	0	538	22116	54.2 +/- 7.1	United States	100	44	Age and 1 PC	Women; 45+ years old, no prior CVD; no prior cancer	Prior VTE; prior cancer
				F	22654									
Etude des Déterminants/Interaction de la Thrombose veineuse	Replication	Case-control	16634748	M	1085	1179	1179	65.5 +/- 17.6	France (West)	100	57	Age and sex		Prior VTE
				F	1273									
Etude des Facteurs de Risque de	Replication	Case-control	21980494	M	498	607	607	52.3 +/- 19.1	France (Center)	100	71	Age and sex	18+ years old	Prior VTE; cancer (active or

thrombose Veineuse				F	716									less than 5 years ago); short life expectancy
MARseille THrombosis Association study 2012	Replication	Case-control	22443383	M	951	1223	801	49.5 +/- 14.9	France (South East)	100	34	Age and sex	European; first VTE	Prior VTE; surgery; hospitalisati on; cancer; autoimmunit y; oral contraceptiv e pill; pregnancy; post-partum; strong genetic risk for VTE
				F	1073									

Table S4. Cohort demographics and covariates for the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium GWAS meta-analysis.⁸

Cohort	Discovery/Replication	Design	References (PMID)	Sex	N	Population	Parameter measured	clMT (n)	Carotid plaque cases and controls (n)	Carotid plaques cases (n)	Mean age +/- SD (years)	Covariates	Exclusion criteria
AGES	Discovery	Cohort	17351290	M	1297	Icelandic	clMT, Plaque	3068	3053	2043	76.4 +/- 5.4	Age, sex	
				F	1771								
ARIC	Discovery	Cohort	9180252	M	4067	4 US communities; 45-64 years old	clMT, Plaque	8663	8857	1626	54.3 +/- 5.7	Age, sex, region, 10 PCs	
				F	4596								
ASPS	Discovery	Cohort	7800110; 10408549	M	127	Austrian; 45-85 years old	clMT	303			65.5 +/- 11.0	Age, sex	Previous stroke; previous TIA; neuropsychiatric disease, including dementia; abnormal neurology on examination
				F	176								
ASPS-FAM	Discovery	Cohort	7800110; 10408549	M	334	Austrian	Plaque		773	490	65.9 +/- 8.0	Age, sex	Previous stroke; previous TIA; neuropsychiatric disease, including dementia; abnormal neurology on examination
				F	439								
CAPS	Discovery	Cohort	12006917	M	443	German	clMT				48.9 +/- 13.3	Age, sex, 4 PCs	
				F	443								
CHS	Discovery	Cohort	1669507	M	1975	US communities; over 65 years old	clMT, Plaque	3239	3125	2069	72.3 +/- 5.4	Age, sex, clinic	
				F	1265								
DHS	Discovery	Cohort	21409311	M	25	US		915			61.4 +/- 9.5	Age, sex, 2 PCs	
				F	112								
ERF	Discovery	Cohort	15845033	M	1214	Netherlands	clMT, Plaque	2270	2443	1218	48.7 +/- 14.4	Age, sex, family structure	
				F	1507								
FHS	Discovery	Cohort	5921755; 474565; 17372189	M	1403	US community	clMT, Plaque	3004	3008	530	58.5 +/- 9.7	Age, sex, 10 PCs	
				F	1601								
3C-Dijon	Discovery	Cohort	14598854; 18063810	M	937	French; over 65 years old	clMT, Plaque	2518	2473	1218	72.6 +/- 4.0	Age, sex, 4 PCs	Aged over 80 years; carotid artery surgery; no genome-wide genetic information
				F	1581								

LBC1936	Discovery	Cohort	22253310	M	396	Scottish	cIMT, Plaque	759	759	220	72.8 +/- 0.8	Age, sex, 4 PCs	
				F	363								
MESA	Discovery	Cohort	12397006	M	1198	6 US communities	cIMT, Plaque	2500	2492	393	62.6 +/- 10.3	Age, sex, site, 4 PCs	
				F	1309								
NEO	Discovery	Cohort	23576214	M	2726	Dutch; 45-65 years old	cIMT	5675			56.0 +/- 5.9	Age, sex, 4 PCs	
				F	2949								
NESDA	Discovery	Cohort	18763692; 19065144; 21745125	M	204	European; 18-65 years old	cIMT, Plaque	572	572	86	44.7 +/- 12.2	Age, sex	Non-fluent Dutch speaker; psychiatric condition
				F	368								
ORCADES	Discovery	Cross-sectional	18760389	M	1128	Scottish archipelago	cIMT	1914			53.7 +/- 14.9	Age, sex, 3 PCs	
				F	763								
RS I	Discovery	Cohort	19728115	M	1978	Dutch; over 55 years old	cIMT, Plaque	4946	4910	2920	69.0 +/- 8.8		
				F	2968								
RS II	Discovery	Cohort	19728115	M	901			1980	2016	1509	64.7 +/- 7.9		
				F	1079								
SHIP	Discovery	Cohort	11565448; 20167617	M	1781	German; 20-79 years old	cIMT, Plaque	3619	3666	1989	53.3 +/- 13.7	Age, sex	Non-German citizenship; resident outside of study area
				F	1838								
SHIP-TREND	Discovery	Cohort	11565448; 20167617	M	432			983	985	338	50.1 +/- 13.7	Age, sex	Non-German citizenship; resident outside of study area
				F	551								
ALSPAC	Discovery	Cohort	22507743; 22507742	M	0	UK	cIMT	3200			47.9 +/- 4.5	Age, 10 PCs	
				F	3200								
YFS	Discovery	Cross-sectional	18263651	M	909	Finnish	cIMT, Plaque	2015	2013	48	37.7 +/- 5.0		
				F	1106								
BRHS	Discovery	Cohort	12540690	M	889	UK	cIMT	889			78.7 +/- 4.8	Age, sex	
				F	0								
EAS	Discovery	Cohort	12540690	M	353	Edinburgh, UK; 55-74 years old		731			69.8 +/- 5.6	Age, sex	Terminal illness; severe psychiatric disease
				F	378								
ET2DS	Discovery	Cohort	19077235	M	445	UK		868			68.9 +/- 4.2	Age, sex	Non-diabetic; unable to complete examinations
				F	423								
IMPROVE	Discovery	Cohort	19952003	M	1636		cIMT	3389			64.5 +/- 1.9		

				F	1753	5 European countries						Age, sex, 3 PCs	
LIFE-Adult	Discovery	Cohort	26362881	M	1531	German	cIMT, Plaque	3208	4534	2726	59.1 +/- 11.9	Age, sex	
				F	1677								
LIFE-Heart	Discovery	Cohort	26362881	M	1240			1924	2755	2117	62.5 +/- 11.0	Age, sex	Myocardial infarction
				F	684								
MDC	Discovery	Cohort	8429286	M	1050	Swedish	cIMT	2142			57.4 +/- 6.0	Age, sex	Mental incapacity; non-fluent Swedish speaker
				F	1093								
MRC1946	Discovery	Cohort	16204333	M	603	UK	cIMT	1258			63.3 +/- 1.1	Age, sex	
				F	655								
NBS	Discovery	Cohort	28082374	M	268	Dutch	cIMT	549			57.8 +/- 5.2	Age, sex	
				F	281								
PIVUS	Discovery	Cohort	www.medsci.uu.se/PIVUS	M	482	Uppsala County, Sweden	cIMT	964			70.2 +/- 0.2	Age, sex	
				F	482								
WHII	Discovery	Cohort	1674771	M	1699	UK	cIMT	2177			60.8 +/- 5.9	Age, sex	
				F	508								

Table S5. SNP-iron association estimates obtained from the Genetics of Iron Status Consortium GWAS meta-analysis.⁶

SNP-iron status associations (n=48 972)

SNP	EA	EAF	Iron				Transferrin Saturation				Log ₁₀ Ferritin				Transferrin			
			R ²	F	E	SE	R ²	F	E	SE	R ²	F	E	SE	R ²	F	E	SE
rs1800562	A	0.07	1.3	668	0.33	0.016	4.2	2127	0.58	0.016	0.5	256	0.2	0.016	2.9	1446	-0.479	0.016
rs1799945	G	0.15	0.9	450	0.19	0.010	1.4	676	0.23	0.010	0.1	53	0.07	0.010	0.3	163	-0.114	0.010
rs855791	G	0.55	1.6	806	0.18	0.007	1.8	889	0.19	0.008	0.1	73	0.06	0.007	0.1	47	-0.044	0.007

SNP indicates single nucleotide polymorphism, EA, effect allele, EAF, effect allele frequency F, F statistic, E, Estimate, SE, standard error, R², percentage of the iron marker variation explained by the SNP

Table S6. MR estimates and statistical sensitivity analyses.

Outcome	Exposure	Method	Estimate	95% CI	P-value
Carotid intima-media thickness (units are millimeter change)	Iron	Main IVW MR	0.00	-0.01-0.01	0.90
		Sensitivity IVW MR	0.00	-0.01-0.01	0.70
		MR-Egger	0.00	-0.01-0.02	0.61
		MR-Egger intercept	0.00	0.00-0.00	0.28
		Weighted median	0.00	-0.02-0.01	0.58
	MR-PRESSO	0.00	-0.01-0.01	0.76	
	Ferritin	Main IVW MR	0.01	-0.02-0.03	0.58
		Sensitivity IVW MR	0.00	-0.02-0.02	0.92
		MR-Egger	0.02	-0.01-0.05	0.25
		MR-Egger intercept	0.00	0.00-0.00	0.11
		Weighted median	0.00	-0.03-0.03	0.97
	MR-PRESSO	0.00	-0.03-0.03	0.96	
	Transferrin saturation	Main IVW MR	0.00	-0.01-0.01	0.75
		Sensitivity IVW MR	0.00	-0.01-0.01	0.88
		MR-Egger	0.01	-0.01-0.02	0.26
		MR-Egger intercept	0.00	0.00-0.00	0.11
		Weighted median	0.01	-0.01-0.02	0.11
	MR-PRESSO	0.00	-0.01-0.01	0.92	
	Transferrin	Main IVW MR	-0.01	-0.02-0.01	0.32
		Sensitivity IVW MR	-0.01	-0.02-0.01	0.33
MR-Egger		-0.01	-0.03-0.00	0.07	
MR-Egger intercept		0.00	0.00-0.00	0.05	
Weighted median		-0.01	-0.02-0.00	0.11	
MR-PRESSO	-0.01	-0.02-0.01	0.45		
Carotid plaque (units are odds ratio)	Iron	Main IVW MR	0.85	0.73-0.99	0.04
		Sensitivity IVW MR	0.84	0.72-0.97	0.02
		MR-Egger	0.86	0.70-1.06	0.17
		MR-Egger intercept	-0.01	-0.03-0.02	0.69
		Weighted median	0.85	0.72-1.01	0.06
	MR-PRESSO	0.84	0.75-0.94	0.03	
	Ferritin	Main IVW MR	0.72	0.51-1.01	0.06
		Sensitivity IVW MR	0.70	0.51-0.97	0.03
		MR-Egger	0.75	0.49-1.17	0.21
		MR-Egger intercept	-0.01	-0.03-0.02	0.61
		Weighted median	0.73	0.51-1.04	0.08
	MR-PRESSO	0.70	0.54-0.90	0.04	
	Transferrin saturation	Main IVW MR	0.89	0.80-1.00	0.05
		Sensitivity IVW MR	0.89	0.80-0.99	0.04
		MR-Egger	0.92	0.80-1.06	0.25
		MR-Egger intercept	-0.01	-0.04-0.02	0.49
		Weighted median	0.89	0.79-1.00	0.06
	MR-PRESSO	0.89	0.81-0.98	0.06	
	Transferrin	Main IVW MR	1.15	0.97-1.35	0.11
		Sensitivity IVW MR	1.13	0.96-1.33	0.15
MR-Egger		1.06	0.87-1.29	0.57	
MR-Egger intercept		0.02	-0.01-0.04	0.20	
Weighted median		1.13	0.95-1.33	0.17	
MR-PRESSO	1.13	0.94-1.35	0.24		
Venous thromboembolism (units are odds ratio)	Iron	Main IVW MR	1.37	1.14-1.66	1.0x10 ⁻³
		Sensitivity IVW MR	1.36	1.13-1.64	9.0x10 ⁻⁴
		MR-Egger	1.32	1.04-1.68	0.02
		MR-Egger intercept	0.00	-0.03-0.03	0.92
		Weighted median	1.37	1.12-1.67	2.0x10 ⁻³
	MR-PRESSO	1.34	1.18-1.52	0.01	
	Ferritin	Main IVW MR	1.92	1.28-2.88	1.7x10 ⁻³
		Sensitivity IVW MR	1.83	1.26-2.66	1.6x10 ⁻³
		MR-Egger	1.76	1.09-2.85	0.02
		MR-Egger intercept	0.00	-0.03-0.03	0.87
		Weighted median	1.80	1.19-2.73	0.01
	MR-PRESSO	1.81	1.40-2.35	0.01	
	Transferrin saturation	Main IVW MR	1.25	1.09-1.43	1.1x10 ⁻³
		Sensitivity IVW MR	1.25	1.10-1.43	8.0x10 ⁻⁴
		MR-Egger	1.23	1.04-1.45	0.01
		MR-Egger intercept	0.00	-0.03-0.03	0.81
		Weighted median	1.25	1.09-1.43	2.0x10 ⁻³
	MR-PRESSO	1.24	1.16-1.34	4.4x10 ⁻³	
	Transferrin	Main IVW MR	0.76	0.63-0.92	0.01
		Sensitivity IVW MR	0.76	0.63-0.92	3.9x10 ⁻³
MR-Egger		0.79	0.65-0.98	0.03	
MR-Egger intercept		-0.01	-0.04-0.01	0.35	
Weighted median		0.78	0.65-0.95	0.01	
MR-PRESSO	0.76	0.64-0.90	0.03		

cIMT represents carotid intima-media thickness; IVW, inverse-variance weighted; MR, Mendelian randomization; SD, standard deviation; and OR, odds ratio.

Table S7. The minimum and maximum true causal effects required to achieve 80% statistical power for the main IVW MR analysis.

Exposure (units are standard deviation change)	Exposure variance explained by instruments (%)	Outcome	Number of participants	Proportion of outcome participants that are cases (%)	Detectable effect at 80% power
Serum iron	3.8	Carotid intima-media thickness (units are millimeter change)	71,128	Not applicable	<-0.01 or >0.01
Ferritin	0.7				<-0.02 or >0.02
Transferrin saturation	7.4				<-0.01 or >0.01
Transferrin saturation	3.3				<-0.01 or >0.01
Serum iron	3.8	Carotid plaque (units are odds ratio)	48,434	44.5	<0.88 or >1.44
Ferritin	0.7				<0.73 or >1.35
Transferrin saturation	7.4				<0.91 or >1.10
Transferrin saturation	3.3				<0.87 or >1.15
Serum iron	3.8	Venous thromboembolism (units are odds ratio)	60,139	12.5	<0.83 or >1.18
Ferritin	0.7				<0.61 or >1.43
Transferrin saturation	7.4				<0.88 or >1.13
Transferrin saturation	3.3				<0.81 or >1.21

Supplemental References:

1. Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, Dormishian F, Domingo R, Jr., Ellis MC, Fullan A, Hinton LM, Jones NL, Kimmel BE, Kronmal GS, Lauer P, Lee VK, Loeb DB, Mapa FA, McClelland E, Meyer NC, Mintier GA, Moeller N, Moore T, Morikang E, Prass CE, Quintana L, Starnes SM, Schatzman RC, Brunke KJ, Drayna DT, Risch NJ, Bacon BR and Wolff RK. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nature Genetics*. 1996;13:399-408.
2. Gao J, Chen J, Kramer M, Tsukamoto H, Zhang AS and Enns CA. Interaction of the hereditary hemochromatosis protein HFE with transferrin receptor 2 is required for transferrin-induced hepcidin expression. *Cell Metabolism*. 2009;9:217-27.
3. Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T and Kaplan J. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004;306:2090-2093.
4. Nemeth E and Ganz T. Regulation of iron metabolism by hepcidin. *Annual Review of Nutrition*. 2006;26:323-42.
5. Zhao N, Nizzi CP, Anderson SA, Wang J, Ueno A, Tsukamoto H, Eisenstein RS, Enns CA and Zhang AS. Low intracellular iron increases the stability of matriptase-2. *The Journal of Biological Chemistry*. 2015;290:4432-46.
6. Benyamin B, Esko T, Ried JS, Radhakrishnan A, Vermeulen SH, Traglia M, Gögele M, Anderson D, Broer L, Podmore C, Luan J, Kutalik Z, Sanna S, van der Meer P, Tanaka T, Wang F, Westra HJ, Franke L, Mihailov E, Milani L, Hälldin J, Häldin J, Winkelmann J, Meitinger T, Thiery J, Peters A, Waldenberger M, Rendon A, Jolley J, Sambrook J, Kiemeny LA, Sweep FC, Sala CF, Schwienbacher C, Pichler I, Hui J, Demirkan A, Isaacs A, Amin N, Steri M, Waeber G, Verweij N, Powell JE, Nyholt DR, Heath AC, Madden PA, Visscher PM, Wright MJ, Montgomery GW, Martin NG, Hernandez D, Bandinelli S, van der Harst P, Uda M, Vollenweider P, Scott RA, Langenberg C, Wareham NJ, van Duijn C, Beilby J, Pramstaller PP, Hicks AA, Ouwehand WH, Oexle K, Gieger C, Metspalu A, Camaschella C, Toniolo D, Swinkels DW, Whitfield JB and Consortium I. Novel loci affecting iron homeostasis and their effects in individuals at risk for hemochromatosis. *Nature Communications*. 2014;5:4926.
7. Germain M, Chasman DI, de Haan H, Tang W, Lindstrom S, Weng LC, de Andrade M, de Visser MC, Wiggins KL, Suchon P, Saut N, Smadja DM, Le Gal G, van Hylckama Vlieg A, Di Narzo A, Hao K, Nelson CP, Rocanin-Arjo A, Folkersen L, Monajemi R, Rose LM, Brody JA, Slagboom E, Aissi D, Gagnon F, Deleuze JF, Deloukas P, Tzourio C, Dartigues JF, Berr C, Taylor KD, Civelek M, Eriksson P, Cardiogenics C, Psaty BM, Houwing-Duitermaat J, Goodall AH, Cambien F, Kraft P, Amouyel P, Samani NJ, Basu S, Ridker PM, Rosendaal FR, Kabrhel C, Folsom AR, Heit J, Reitsma PH, Tregouet DA, Smith NL and Morange PE. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. *American Journal of Human Genetics*. 2015;96:532-42.
8. Franceschini N, Giambartolomei C, de Vries PS, Finan C, Bis JC, Huntley RP, Loring RC, Tajuddin SM, Winkler TW, Graff M, Kavousi M, Dale C, Smith AV, Hofer E, van Leeuwen EM, Nolte IM, Lu L, Scholz M, Sargurupremraj M, Pitkanen N, Franzen O, Joshi PK, Noordam R, Marioni RE, Hwang SJ, Musani SK, Schminke U, Palmas W, Isaacs A, Correa A, Zonderman AB, Hofman A, Teumer A, Cox AJ, Uitterlinden AG, Wong A, Smit AJ, Newman AB, Britton A, Ruusalepp A, Sennblad B, Hedblad B, Pasaniuc B, Penninx BW, Langefeld CD, Wassel CL, Tzourio C, Fava C, Baldassarre D, O'Leary DH, Teupser D, Kuh D, Tremoli E, Mannarino E, Grossi E, Boerwinkle E, Schadt EE, Ingelsson E, Veglia F, Rivadeneira F, Beutner F, Chauhan G, Heiss G, Snieder H, Campbell H, Volzke H, Markus HS, Deary IJ, Jukema JW, de Graaf J, Price J, Pott J, Hopewell JC, Liang J, Thiery J, Engmann J, Gertow K, Rice K, Taylor KD, Dhana K, Kiemeny L, Lind L, Raffield LM, Launer LJ, Holdt LM, Dorr M, Dichgans M, Traylor M, Sitzer M, Kumari M, Kivimaki M, Nalls MA, Melander O, Raitakari O, Franco OH, Rueda-Ochoa OL, Roussos P, Whincup PH, Amouyel P, Giral P, Anugu P, Wong Q, Malik R, Rauramaa R, Burkhardt R, Hardy R,

Schmidt R, de Mutsert R, Morris RW, Strawbridge RJ, Wannamethee SG, Hagg S, Shah S, McLachlan S, Trompet S, Seshadri S, Kurl S, Heckbert SR, Ring S, Harris TB, Lehtimäki T, Galesloot TE, Shah T, de Faire U, Plagnol V, Rosamond WD, Post W, Zhu X, Zhang X, Guo X, Saba Y, Consortium M, Dehghan A, Seldenrijk A, Morrison AC, Hamsten A, Psaty BM, van Duijn CM, Lawlor DA, Mook-Kanamori DO, Bowden DW, Schmidt H, Wilson JF, Wilson JG, Rotter JI, Wardlaw JM, Deanfield J, Halcox J, Lytikäinen LP, Loeffler M, Evans MK, Debette S, Humphries SE, Volker U, Gudnason V, Hingorani AD, Björkegren JLM, Casas JP and O'Donnell CJ. GWAS and colocalization analyses implicate carotid intima-media thickness and carotid plaque loci in cardiovascular outcomes. *Nature Communications*. 2018;9:5141.