

Supplemental Material

Table S1. Baseline characteristics of participants included in genetic analyses in UK Biobank, by sex

	Men	Women	All
Number of participants	154,069 (46.4)	177,895 (53.6)	331,964
Demographic factors			
Age, y	57.1 (8.1)	56.7 (7.9)	56.9 (8.0)
Socioeconomic deprivation tertile			
1 (least deprived)	51,471 (33.4)	59,182 (33.3)	110,653 (33.3)
2	50,691 (32.9)	59,957 (33.7)	110,648 (33.3)
3 (most deprived)	51,907 (33.7)	58,756 (33.0)	110,663 (33.3)
Education, university/college, %	51,136 (33.2)	53,821 (30.3)	104,957 (31.6)
Lifestyle factors			
Current smoking, %	18,152 (11.8)	15,349 (8.6)	33,501 (10.1)
Current drinking, %	146,425 (95)	163,666 (92)	310,091 (93.4)
Postmenopausal (yes in women), %	-	109,747 (61.7)	109,747 (33.1)
Physical activity, MET-h/week	30.9 (13.7, 63.0)	29.1 (13.5, 57.0)	29.8 (13.6, 59.6)
Family history of diseases, N (%)			
Family history of CVD	108,377 (70.3)	135,939 (76.4)	244,316 (73.6)
Family history of diabetes	29,523 (19.2)	37,572 (21.1)	67,095 (20.2)
Medical history, N (%)			
Use of antihypertensive drugs	38,221 (24.8)	30,956 (17.4)	69,177 (20.8)
Use of cholesterol-lowering drugs	35,434 (23)	22,323 (12.5)	57,757 (17.4)
Baseline coronary artery disease	12,553 (8.1)	5,517 (3.1)	18,070 (5.4)
Baseline ischemic stroke	594 (0.4)	259 (0.1)	853 (0.3)
Baseline heart failure	1,194 (0.8)	383 (0.2)	1,577 (0.5)
Baseline type 2 diabetes	9,051 (5.9)	5,059 (2.8)	14,110 (4.3)
Clinical measurements			
BMI, kg/m ²	27.8 (4.2)	27.0 (5.1)	27.4 (4.7)
WC, cm	97.0 (11.3)	84.6 (12.5)	90.3 (13.5)
WHR	0.93 (0.89, 0.98)	0.81 (0.77, 0.86)	0.87 (0.80, 0.94)
SBP, mm Hg	141.3 (17.4)	135.6 (19.2)	138.3 (18.6)
DBP, mm Hg	84.2 (10.0)	80.7 (9.9)	82.3 (10.1)
Random glucose, mmol/L	4.96 (4.61, 5.36)	4.92 (4.60, 5.28)	4.93 (4.60, 5.32)
Hba1c, %	5.37 (5.14, 5.62)	5.36 (5.14, 5.59)	5.37 (5.14, 5.60)
Hemoglobin, mg/dL	15.0 (14.4, 15.7)	13.6 (13.0, 14.1)	14.2 (13.4, 15.1)
HDL, mmol/L	1.28 (0.31)	1.60 (0.38)	1.45 (0.38)
LDL, mmol/L	3.49 (0.86)	3.64 (0.87)	3.57 (0.87)
TG, mmol/L	1.70 (1.19, 2.45)	1.35 (0.97, 1.91)	1.50 (1.06, 2.16)
TC, mmol/L	5.50 (1.13)	5.90 (1.13)	5.71 (1.14)
CRP, mg/L	1.27 (0.66, 2.52)	1.37 (0.65, 2.95)	1.32 (0.66, 2.74)

Values are exhibited as numbers (percentages) for categorical variables and means (SDs)/medians (IQRs) for continuous variables.

BMI=body mass index; CRP=C reactive protein; CVD=cardiovascular disease; DBP=diastolic blood pressure; Hba1c=hemoglobin A1c; HDL=high density lipoprotein cholesterol; IQR=interquartile range; LDL=low density lipoprotein cholesterol; MET=metabolic equivalent of task; WC=waist circumference; WHR=waist-to-hip ratio; SBP=systolic blood pressure; SD=standard deviation; TC=total cholesterol; TG=triglycerides.

Table S2. Codes used in the UK Biobank study to identify cardiometabolic diseases

Disease	ICD9	ICD10	Non-cancer illness code, self-reported (20002)	Diseases diagnosed by doctor (6150, 2443)	Medication (6153, 6177)
CAD	410-414	I20-I25	1074, 1075	1, 2 (6150)	
HF	428	I50	1076		
IS	433-434	I63	1583		
T2D	25000, 25010, 25020, 25090	E11			

Abbreviations: CAD=coronary artery disease; HF=heart failure; ICD=International Classification of Disease; IS=ischemic stroke; T2D=type 2 diabetes.

Table S3. Variants associated with hemoglobin

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
1	1	3318769	C	G	PRDM16	0.64	-0.02	0.0022	13.84				
2	1	3684954	C	A						0.24	0.03	0.0042	13.71
3	1	3691528	A	G	SMIM1	0.23	0.03	0.0026	36.70				
4	1	10483167	G	A	PGD	0.14	0.02	0.0033	10.35				
5	1	12661421	G	C	DHRS3	0.33	0.02	0.0023	11.90				
6	1	15814186	C	T	CELA2B	0.53	0.02	0.0021	13.18				
7	1	16370178	A	AGCTC T	CLCNKB,RP11- 5P18.10	0.40	0.02	0.0022	26.19				
8	1	17409382	T	C	PADI2	0.58	0.02	0.0022	14.52				
9	1	20757820	T	C	LINC01141	0.12	-0.02	0.0033	9.57				
10	1	22700351	A	G		0.18	0.02	0.0028	17.27				
11	1	25022314	G	A		0.25	0.02	0.0025	13.66				

12	1	26183738	AT	A	AUNIP	0.54	0.02	0.0021	11.73				
13	1	29486128	C	T	SRSF4	0.05	0.03	0.0047	12.31				
14	1	31594199	C	CAAA		0.11	0.02	0.0035	10.58				
15	1	40421617	TG	T	MFSD2A	0.26	-0.02	0.0024	15.61				
16	1	43761651	C	T		0.62	-0.02	0.0022	19.09				
17	1	45984852	ATGT	A	PRDX1	0.23	0.02	0.0025	14.08				
18	1	46073489	G	A	NASP					0.47	-0.03	0.0035	12.58
19	1	46497500	T	A	MAST2	0.44	-0.03	0.0021	38.71				
20	1	47953054	T	C	RP4-666O22.3	0.61	-0.01	0.0022	9.60				
21	1	48022107	C	T		0.10	-0.03	0.0036	18.59				
22	1	48116939	TAA	T		0.40	0.02	0.0022	12.32				
23	1	53328394	C	G	ZYG11A	0.62	0.02	0.0022	14.95				
24	1	66077590	T	G	LEPR	0.20	0.02	0.0027	12.00				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
25	1	79452106	C	T	ELTD1	0.12	0.02	0.0033	8.27				
26	1	88641063	A	G		0.42	0.01	0.0022	9.91				
27	1	89363264	C	T		0.36	0.01	0.0022	9.16				
28	1	120267505	C	G	PHGDH	0.32	-0.02	0.0023	12.04				
29	1	147287992	A	T		0.16	0.03	0.0029	18.68				
30	1	151750433	T	C	TDRKH	0.32	0.01	0.0023	8.85				
31	1	154976518	A	G	ZBTB7B	0.03	-0.07	0.0064	28.66				
32	1	155178782	A	T	MTX1	0.60	0.03	0.0022	51.65	0.60	0.03	0.0036	18.23
33	1	155261636	C	T	PKLR	0.00	-0.25	0.0318	13.85				
34	1	155261709	G	A	PKLR	0.00	-0.18	0.0202	17.80				
35	1	158530416	C	T	OR6P1	0.25	-0.02	0.0025	12.71				
36	1	161515326	C	T	FCGR3A	0.12	0.03	0.0033	23.89				
37	1	161623025	G	C	FCGR2B					0.13	0.04	0.0055	10.38

38	1	161644811	C	T	FCGR2B	0.19	-0.02	0.0028	14.96				
39	1	172140548	C	T	DNM3					0.42	-0.02	0.0036	8.38
40	1	172167226	T	C	DNM3	0.31	-0.02	0.0023	18.53				
41	1	172415351	GA	G	C1orf105	0.50	-0.01	0.0021	9.58				
42	1	173813197	G	A	DARS2	0.24	-0.02	0.0025	10.40				
43	1	182997286	CCT	C	LAMC1	0.44	0.01	0.0022	9.30				
44	1	199010721	C	T	RP11-16L9.4	0.72	-0.02	0.0024	22.80				
45	1	200034969	A	G	NR5A2	0.27	0.01	0.0024	8.50				
46	1	203660781	A	G	ATP2B4					0.90	-0.04	0.0059	10.22
47	1	203667409	T	C	ATP2B4	0.90	-0.04	0.0036	30.50				
48	1	204220232	T	C	PLEKHA6	0.53	0.01	0.0021	9.76				
49	1	211104853	T	C	KCNH1	0.69	0.01	0.0023	9.06				
50	1	212402580	G	A	RP11-15I11.3	0.41	-0.01	0.0022	10.93				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
51	1	213039546	C	T	FLVCR1	0.75	0.02	0.0024	12.14				
52	1	213966887	T	C	RP11-323I1.1	0.27	0.03	0.0024	25.95	0.27	0.02	0.0041	8.77
53	1	214176380	T	C	PROX1	0.26	0.04	0.0024	60.61				
54	1	214177423	G	A	PROX1					0.26	0.03	0.0040	17.26
55	1	217034049	C	T	ESRRG	0.20	0.02	0.0027	14.08				
56	1	217472265	G	A		0.15	0.03	0.0030	22.65				
57	1	230301811	T	G	GALNT2	0.61	-0.02	0.0022	11.48				
58	1	231114595	C	T	TTC13	0.40	-0.01	0.0022	10.79				
59	1	231470772	A	G	EXOC8					0.63	0.03	0.0037	12.40
60	1	231495316	A	G	EGLN1,SPRTN	0.63	0.03	0.0022	35.93				
61	1	231558054	G	C	EGLN1					0.02	0.13	0.0125	23.73
62	1	231562228	A	G	EGLN1	0.02	0.12	0.0076	54.59				
63	1	248039451	C	T	TRIM58	0.33	0.02	0.0022	26.27	0.34	0.02	0.0037	8.98

64	2	12104445	T	C	AC096559.1	0.79	-0.02	0.0026	9.57				
65	2	12930330	G	T		0.31	0.02	0.0023	15.29				
66	2	21286057	T	C		0.82	-0.02	0.0028	9.20				
67	2	23897725	G	A	KLHL29	0.10	0.03	0.0035	17.00	0.10	0.04	0.0059	9.75
68	2	25578588	C	G		0.08	0.03	0.0039	15.70				
69	2	25950158	CT	C	AC010150.2	0.31	0.02	0.0023	14.93				
70	2	27779565	T	A	AC109829.1	0.18	0.02	0.0028	16.82				
71	2	28941262	C	T	AC097724.3	0.65	-0.01	0.0022	9.66				
72	2	39743876	T	C	AC007246.3	0.51	0.01	0.0021	10.16				
73	2	42285575	T	A	PKDCC	0.20	0.02	0.0027	9.54				
74	2	43429058	G	T	THADA	0.47	-0.02	0.0021	20.07				
75	2	44014301	A	G	DYNC2L11	0.07	0.03	0.0041	10.98				
76	2	45886261	G	C	PRKCE	0.29	0.01	0.0023	8.10				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
77	2	46005646	G	C	PRKCE	0.80	-0.02	0.0026	10.43				
78	2	46225778	T	C	PRKCE	0.45	-0.01	0.0021	11.58				
79	2	46293826	C	T	PRKCE	0.01	-0.12	0.0099	34.46	0.01	-0.13	0.0163	14.52
80	2	46309262	C	G	PRKCE	0.35	-0.03	0.0022	33.94				
81	2	46352326	C	G	PRKCE	0.18	-0.02	0.0028	18.12	0.18	-0.03	0.0046	8.77
82	2	46353166	A	G	PRKCE					0.34	-0.07	0.0037	84.86
83	2	46360907	G	C	PRKCE	0.34	-0.07	0.0023	240.15				
84	2	46363699	T	C	PRKCE	0.13	0.05	0.0032	53.27				
85	2	46558432	A	G	EPAS1	0.46	0.02	0.0021	13.61				
86	2	47030363	A	G		0.48	0.02	0.0021	22.52	0.48	0.02	0.0036	10.35
87	2	54007171	A	C	ASB3,GPR75-ASB3	0.33	0.02	0.0023	13.54				
88	2	66752251	A	G	MEIS1	0.61	0.02	0.0022	11.41				
89	2	69813458	T	C	AAK1	0.13	0.02	0.0032	10.05				

90	2	100775920	C	A		0.36	-0.01	0.0022	10.11				
91	2	112247747	T	A	MIR4435-1HG	0.13	-0.02	0.0033	11.46				
92	2	113965200	A	T	PSD4					0.22	0.04	0.0043	16.84
93	2	113972945	A	G	PAX8-AS1	0.21	0.03	0.0026	32.81				
94	2	120848049	C	T	EPB41L5	0.05	0.04	0.0050	16.62				
95	2	121988884	G	A	TFCP2L1	0.14	0.03	0.0031	22.77				
96	2	121995638	G	C	TFCP2L1					0.14	0.03	0.0051	10.85
97	2	135283654	C	T	TMEM163	0.34	-0.01	0.0023	10.15				
98	2	144352423	C	T	ARHGAP15,RP11-570L15.1	0.22	0.02	0.0026	8.42				
99	2	145664860	C	CA	TEX41	0.23	0.03	0.0025	28.73				
100	2	145783282	G	A	TEX41					0.75	-0.02	0.0041	8.88
101	2	160957824	C	G	ITGB6	0.24	-0.02	0.0025	10.37				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
102	2	165528876	C	T	COBLL1	0.39	-0.02	0.0022	18.22				
103	2	176974104	G	T	HOXD11	0.64	0.03	0.0023	27.44				
104	2	177779131	A	T		0.55	-0.01	0.0021	8.12				
105	2	204357497	CT	C	RAPH1	0.69	-0.01	0.0023	8.65				
106	2	208003579	A	T	KLF7	0.68	-0.02	0.0023	15.93	0.68	-0.02	0.0038	10.02
107	2	208632817	G	A	FZD5	0.08	-0.03	0.0040	10.81				
108	2	219555573	C	A	STK36	0.45	-0.02	0.0021	21.55				
109	2	219557738	G	A	STK36					0.45	-0.02	0.0036	10.74
110	2	227111435	TTA	T		0.65	0.02	0.0022	13.39				
111	2	239069196	C	T	FAM132B	0.44	0.02	0.0021	12.13				
112	2	242644728	C	T	ING5	0.46	0.01	0.0021	10.02				
113	3	12368233	A	T	PPARG					0.25	-0.03	0.0042	8.84
114	3	12379351	A	G	PPARG	0.21	-0.03	0.0026	32.81				

115	3	12737066	GGTT	G		0.47	-0.02	0.0022	11.77				
116	3	14929509	C	CA	FGD5	0.66	-0.02	0.0022	15.81				
117	3	23395310	ATT	A	UBE2E2	0.25	0.02	0.0025	11.46				
118	3	25053482	G	A	AC133680.1	0.65	-0.01	0.0022	8.80				
119	3	30181399	A	AG	AC137674.2	0.40	0.02	0.0023	11.59				
120	3	37987856	C	A	CTDSPL	0.10	0.04	0.0036	22.81				
121	3	41882697	G	A	ULK4	0.12	0.02	0.0035	11.24				
122	3	46979013	G	C	CCDC12	0.68	-0.01	0.0024	8.16				
123	3	52567617	A	G	NT5DC2	0.54	-0.02	0.0023	20.99	0.54	-0.02	0.0036	8.20
124	3	56744261	A	AAAAA AC						0.31	-0.03	0.0039	15.46
125	3	56780003	C	T	ARHGEF3	0.31	-0.03	0.0023	33.58				
126	3	58405636	TTAAG	T	PXK	0.37	-0.02	0.0022	22.20				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
127	3	58456811	C	T						0.37	-0.02	0.0037	8.65
128	3	66881402	G	C		0.11	0.02	0.0033	11.30				
129	3	69841880	C	A	MITF	0.42	0.02	0.0022	27.15	0.42	0.02	0.0036	9.38
130	3	70061377	G	C	RP11-460N16.1	0.00	-0.11	0.0175	10.21				
131	3	72396329	G	A		0.24	0.02	0.0025	9.64				
132	3	121628658	AT	A	SLC15A2	0.48	-0.02	0.0021	14.56				
133	3	132198815	G	GTTATT	DNAJC13	0.11	-0.03	0.0035	12.52				
134	3	141092050	G	T	ZBTB38	0.41	0.02	0.0022	12.02				
135	3	143845892	T	C		0.31	0.01	0.0023	8.42				
136	3	169098791	C	T	MECOM	0.44	-0.02	0.0021	18.57				
137	3	172276502	A	C	RP11-408H1.3	0.01	-0.07	0.0104	11.13				
138	3	187641417	T	C		0.54	0.01	0.0023	8.68				
139	3	193799549	C	T		0.26	-0.02	0.0024	10.04				

140	3	194506202	ACT	A	AC090505.6					0.60	0.02	0.0037	9.61
141	3	194506427	G	A	AC090505.6	0.58	0.02	0.0022	17.24				
142	3	194676805	G	A						0.50	-0.02	0.0035	9.31
143	3	194681297	G	A		0.50	-0.02	0.0021	19.97				
144	3	195751397	T	A	TFRC	0.58	0.02	0.0022	11.51				
145	3	196176998	GGT	G	AC117490.2	0.76	0.01	0.0025	8.32				
146	4	23737865	A	G	RP11-380P13.1	0.05	0.05	0.0050	21.04				
147	4	23888619	A	G	PPARGC1A	0.49	-0.01	0.0021	8.83				
148	4	48590606	C	T	FRYL	0.50	-0.01	0.0021	10.93				
149	4	55335501	T	C		0.35	0.02	0.0022	24.52				
150	4	55408875	A	T		0.25	-0.04	0.0025	70.86	0.25	-0.03	0.0041	15.68
151	4	77373079	C	T	SHROOM3	0.50	0.03	0.0021	35.60	0.50	0.02	0.0035	11.61
152	4	79344554	C	T	FRAS1	0.03	0.04	0.0062	9.38				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
153	4	81181072	A	T		0.29	0.02	0.0024	21.38				
154	4	87984331	A	G	AFF1	0.38	0.03	0.0022	48.54				
155	4	88030261	G	T	AFF1					0.59	-0.03	0.0036	17.00
156	4	89742244	C	T	FAM13A	0.46	0.02	0.0021	12.00				
157	4	103188709	C	T	SLC39A8	0.07	0.05	0.0041	34.18	0.08	0.05	0.0067	12.23
158	4	115519825	G	A	UGT8	0.87	0.03	0.0032	14.61				
159	4	115569030	T	G	UGT8					0.18	-0.03	0.0046	8.86
160	4	124765262	AAC	A	LINC01091	0.11	-0.02	0.0034	10.07				
161	4	146445680	T	C	SMAD1	0.58	0.01	0.0022	9.56				
162	4	148976981	A	G	ARHGAP10	0.60	-0.02	0.0022	15.11				
163	4	157836033	G	GGGAA AGTCT	PDGFC	0.59	-0.01	0.0022	8.96				
164	4	187977377	C	T	RP11-696F12.1	0.23	-0.01	0.0025	8.26				

165	5	448291	C	A	EXOC3	0.41	0.02	0.0022	16.18				
166	5	457261	C	A	EXOC3					0.31	0.02	0.0039	8.29
167	5	946453	C	G	RP11-661C8.2	0.00	-0.10	0.0162	8.51				
168	5	1115115	C	T	SLC12A7	0.59	-0.02	0.0022	11.53				
169	5	34507508	T	G		0.47	-0.02	0.0022	12.10				
170	5	34507785	T	C						0.47	-0.03	0.0036	11.50
171	5	34660677	A	G	RAI14	0.46	-0.02	0.0021	14.15				
172	5	38869035	G	T	OSMR	0.13	-0.03	0.0032	14.81				
173	5	40620582	C	T						0.88	-0.03	0.0055	8.10
174	5	40623128	C	T		0.88	-0.02	0.0033	12.09				
175	5	52221748	T	C	ITGA1	0.06	-0.03	0.0046	10.52				
176	5	55807370	C	T	AC022431.2	0.75	0.02	0.0024	16.54				
177	5	72144005	C	T	TNPO1	0.92	0.03	0.0039	17.07				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
178	5	76479833	T	C		0.13	0.03	0.0032	17.25	0.13	0.04	0.0053	11.60
179	5	88110363	C	T	MEF2C	0.76	-0.02	0.0025	10.55				
180	5	111357751	A	AC	NREP-AS1	0.06	-0.03	0.0045	12.03				
181	5	125843369	C	T		0.44	0.01	0.0021	8.62				
182	5	127249136	A	G	CTC-228N24.1	0.18	-0.02	0.0028	12.28				
183	5	137000719	T	C	KLHL3	0.19	0.02	0.0027	10.85				
184	5	142622669	A	G		0.33	-0.02	0.0023	11.21				
185	5	147886011	G	A	HTR4	0.42	-0.01	0.0022	8.93				
186	5	154027482	GT	G		0.14	0.03	0.0031	18.93				
187	5	159559407	G	A	AC008706.1	0.01	-0.12	0.0148	14.29				
188	5	176784512	G	A	RGS14	0.26	0.03	0.0024	30.25				
189	5	176798040	T	G	RGS14					0.33	0.02	0.0038	8.88
190	6	1740921	A	AT	GMDS	0.44	0.02	0.0022	12.17				

191	6	2050791	A	G	GMDS	0.54	-0.03	0.0021	32.87	0.54	-0.03	0.0036	14.13
192	6	2522808	A	G		0.77	-0.02	0.0025	9.54				
193	6	7222093	G	T	RREB1	0.44	0.02	0.0022	21.20				
194	6	7229619	G	A	RREB1	0.30	0.03	0.0023	30.55	0.30	0.03	0.0039	10.67
195	6	12288422	A	G	EDN1	0.75	-0.02	0.0025	14.67				
196	6	13508443	A	T		0.69	-0.01	0.0023	9.44				
197	6	16288192	G	A	GMPR					0.38	-0.02	0.0037	9.52
198	6	16289908	G	GTC	GMPR	0.38	-0.02	0.0022	20.03				
199	6	22130601	C	T	CASC15	0.46	0.02	0.0021	19.42				
200	6	25712496	C	A		0.01	0.06	0.0090	9.12				
201	6	26072992	C	T						0.08	0.18	0.0067	161.97
202	6	26091179	C	G	HFE					0.15	0.11	0.0049	102.70
203	6	26093141	G	A	HFE	0.08	0.19	0.0040	489.62				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
204	6	26104632	T	G	HIST1H1T,HIST1H4C	0.85	-0.11	0.0030	290.88				
205	6	29821606	A	T	MICF	0.08	0.03	0.0040	11.81				
206	6	29916885	T	C	HLA-A					0.29	0.03	0.0040	14.93
207	6	30138645	G	A	TRIM15	0.09	0.03	0.0037	11.89				
208	6	31113113	C	A	CCHCR1	0.08	0.04	0.0040	17.87				
209	6	31242083	G	C	HLA-C, USP8P1					0.14	-0.03	0.0051	10.31
210	6	31407331	G	C	HCP5	0.66	-0.04	0.0022	70.71				
211	6	32174048	A	G	NOTCH4	0.07	-0.04	0.0041	20.64				
212	6	32559007	A	T	HLA-DRB1	0.25	-0.05	0.0025	83.37				
213	6	32623434	T	C	HLA-DQB1-AS1					0.35	-0.05	0.0039	31.98
214	6	34168059	T	TA		0.05	0.04	0.0051	12.22				
215	6	36207598	A	G	PNPLA1	0.37	-0.01	0.0022	9.46				
216	6	36555803	A	AT		0.18	-0.02	0.0028	10.23				

217	6	37027232	C	T		0.51	-0.02	0.0021	24.16				
218	6	39146230	T	C		0.22	-0.02	0.0026	10.82				
219	6	43230103	GGT	G	TTBK1	0.14	-0.02	0.0031	14.99				
220	6	43730644	A	T		0.16	0.03	0.0029	30.44				
221	6	43731651	G	T						0.06	-0.07	0.0077	18.60
222	6	43737486	C	T	VEGFA	0.50	-0.03	0.0021	55.47				
223	6	43742626	T	C	VEGFA					0.50	-0.03	0.0035	19.84
224	6	43757896	C	A	VEGFA	0.48	0.02	0.0021	20.24				
225	6	43801654	C	T		0.16	-0.04	0.0029	33.94				
226	6	43801905	CT	C						0.84	0.04	0.0049	12.53
227	6	43804808	G	C		0.69	0.04	0.0023	60.02				
228	6	43809802	T	C						0.31	-0.04	0.0038	20.34
229	6	43868986	A	G		0.45	-0.02	0.0022	20.72				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
230	6	43941137	T	C		0.05	-0.07	0.0050	42.60	0.05	-0.06	0.0083	14.14
231	6	44030011	A	G	RP5-1120P11.1	0.88	0.07	0.0035	83.99	0.89	0.07	0.0060	30.33
232	6	50791584	CACAA	C	TFAP2B	0.36	0.02	0.0023	14.49				
233	6	51838263	A	G	PKHD1	0.48	0.01	0.0022	10.80				
234	6	52656169	T	G	GSTA1	0.57	0.02	0.0022	27.94				
235	6	52725521	T	C	RP11-392A23.4					0.53	0.02	0.0036	8.32
236	6	125622737	T	G	HDDC2	0.18	0.02	0.0028	16.34				
237	6	126223944	G	A	NCOA7	0.48	0.01	0.0021	11.27				
238	6	126703390	T	A		0.44	-0.02	0.0022	20.45				
239	6	127446610	G	C	RSPO3	0.49	0.03	0.0021	34.91				
240	6	127448249	C	G	RSPO3					0.52	0.02	0.0036	11.31
241	6	130378833	T	C	L3MBTL3	0.68	0.02	0.0023	23.77				
242	6	134241797	C	T		0.77	-0.02	0.0026	11.72				

243	6	135405122	A	C	HBS1L	0.50	-0.01	0.0021	10.05				
244	6	135411228	T	C	HBS1L					0.26	-0.05	0.0041	33.54
245	6	135418635	C	T	HBS1L	0.26	-0.05	0.0024	104.04				
246	6	139835689	C	T		0.59	-0.02	0.0022	14.53				
247	6	142814991	C	T		0.03	-0.04	0.0061	9.39				
248	6	143142313	A	C	HIVEP2	0.35	0.01	0.0023	8.42				
249	6	163941243	T	G	QKI	0.03	-0.04	0.0067	9.90				
250	6	166074760	C	G	PDE10A	0.72	-0.02	0.0024	10.36				
251	6	166162335	T	C	PDE10A	0.63	-0.01	0.0022	10.54				
252	7	671593	C	CA	PRKAR1B	0.59	0.02	0.0022	27.27	0.59	0.03	0.0037	11.35
253	7	1286567	G	T		0.69	-0.04	0.0024	54.88	0.69	-0.03	0.0039	13.16
254	7	6749758	G	A	PMS2CL,ZNF12	0.11	0.02	0.0035	11.76	0.11	0.04	0.0058	9.35
255	7	25420102	G	C		0.09	-0.03	0.0038	12.30				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
256	7	50436828	T	A	IKZF1	0.37	-0.01	0.0022	8.58				
257	7	80303700	AGCACAAAT AAAGCACT	A	CD36	0.14	0.02	0.0032	10.30				
258	7	91773213	T	C	LRRD1,CTB-161K23.1	0.48	-0.02	0.0021	17.86				
259	7	99923063	C	T	PMS2P1					0.01	-0.15	0.0211	12.62
260	7	99953124	C	T	PILRB	0.01	-0.15	0.0127	31.93				
261	7	100083971	G	A	NYAP1					0.01	-0.28	0.0228	35.15
262	7	100218631	C	T	TFR2	0.03	0.05	0.0062	13.24				
263	7	100226902	C	T	TFR2	0.00	0.16	0.0175	19.06				
264	7	100228655	G	T	TFR2	0.01	0.10	0.0134	13.88				
265	7	100239422	G	A	TFR2	0.01	0.17	0.0145	32.52	0.00	0.24	0.0285	15.78
266	7	100275444	G	A	GNB2					0.01	-0.18	0.0252	11.77
267	7	100298904	T	C	POP7	0.29	0.03	0.0023	36.67	0.29	0.03	0.0039	13.60

268	7	100306920	G	A	POP7	0.02	-0.05	0.0074	10.14				
269	7	100309180	A	G	POP7	0.01	-0.31	0.0130	124.61				
270	7	100314474	C	T	EPO	0.01	-0.13	0.0116	30.36	0.01	-0.12	0.0191	9.99
271	7	100319633	G	A	EPO	0.01	-0.29	0.0146	87.32				
272	7	101231632	G	A		0.33	-0.02	0.0023	10.98				
273	7	129048940	A	C	AHCYL2	0.27	0.02	0.0024	13.81				
274	7	129663496	C	T	ZC3HC1	0.39	-0.02	0.0022	14.31				
275	7	134369310	A	G	AC009276.4					0.00	-0.18	0.0311	8.44
276	7	134659326	A	G	CALD1	0.64	-0.02	0.0022	11.54				
277	7	150502468	AT	A	TMEM176B	0.11	-0.03	0.0034	15.45				
278	7	150755173	T	G	CDK5	0.25	0.02	0.0024	14.15				
279	7	150952770	G	A	SMARCD3	0.11	-0.02	0.0034	9.62				
280	7	151411494	G	T	PRKAG2					0.28	-0.06	0.0040	58.56

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
281	7	151414329	T	C	PRKAG2	0.29	-0.07	0.0024	185.08				
282	8	9184231	G	A	RP11-115J16.1	0.91	-0.03	0.0037	16.67				
283	8	12897602	C	T	RNU6-842P	0.60	0.01	0.0022	8.73				
284	8	23372787	T	TTTTG						0.14	0.03	0.0052	8.12
285	8	23377161	C	T		0.14	0.02	0.0031	10.04				
286	8	32432796	G	T	NRG1	0.55	0.01	0.0021	10.79				
287	8	40045119	C	T		0.56	-0.02	0.0022	14.77				
288	8	41540828	T	C	ANK1	0.02	0.05	0.0072	12.98				
289	8	42399667	C	T	SMIM19	0.59	0.03	0.0022	34.29				
290	8	42455206	T	C						0.59	0.03	0.0036	11.50
291	8	48864284	GGAAA	G	PRKDC	0.90	-0.02	0.0035	10.00				
292	8	61175880	TA	T	CA8	0.42	0.01	0.0022	9.92				
293	8	76493714	A	T		0.19	-0.02	0.0027	11.09				

294	8	81376290	C	CTGT		0.30	-0.02	0.0023	14.10				
295	8	95935164	C	A	NDUF6					0.47	-0.02	0.0036	8.19
296	8	95992473	C	A	NDUF6	0.48	-0.02	0.0021	30.56				
297	8	116495909	T	A	TRPS1					0.23	0.03	0.0042	11.52
298	8	116557955	C	G	TRPS1	0.55	0.02	0.0021	19.18				
299	8	116667539	G	T	TRPS1	0.28	0.02	0.0024	11.97				
300	8	128971861	C	T	PVT1					0.34	-0.03	0.0037	13.61
301	8	128972721	A	G	PVT1	0.34	-0.02	0.0022	19.17				
302	8	129060804	G	A	PVT1	0.34	0.02	0.0022	12.98				
303	9	2622134	C	T	VLDLR	0.38	0.02	0.0023	25.16				
304	9	2622146	ACGGCGGC GG	A	VLDLR					0.39	0.03	0.0038	10.66
305	9	4118111	G	T	GLIS3	0.60	-0.02	0.0022	27.09	0.60	-0.02	0.0037	10.36

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
306	9	6370088	A	G		0.95	0.04	0.0048	16.27				
307	9	13976285	G	A		0.30	-0.04	0.0023	50.24				
308	9	13980152	G	A						0.36	-0.03	0.0037	16.98
309	9	20551460	C	G	MLLT3	0.21	-0.02	0.0026	9.38				
310	9	32418353	C	T	ACO1	0.00	0.23	0.0297	14.43				
311	9	32425676	T	G	ACO1	0.36	0.02	0.0022	19.83				
312	9	32455262	T	C	ACO1, DDX58					0.30	-0.02	0.0039	8.77
313	9	33116941	G	C	B4GALT1	0.19	-0.02	0.0027	10.03				
314	9	92226172	C	G	GADD45G	0.47	-0.01	0.0022	8.63				
315	9	93801208	G	A		0.24	0.02	0.0025	11.53				
316	9	107761370	TA	T		0.21	0.02	0.0027	9.95				
317	9	114824708	T	C	SUSD1	0.30	-0.02	0.0023	11.48				
318	9	114897899	T	C	SUSD1	0.22	-0.02	0.0026	15.43				

319	9	116349209	G	C	RP11-168K11.2,RGS3	0.15	-0.03	0.0030	20.18				
320	9	130622946	T	C		0.83	-0.04	0.0028	41.47				
321	9	130628524	T	A	AK1, MIR4672, RP11-203J24.9					0.12	0.05	0.0056	17.72
322	9	131841887	C	T	DOLPP1	0.72	0.02	0.0024	10.34				
323	9	136128000	G	C	RP11-430N14.4, ABO					0.06	0.08	0.0073	24.65
324	9	136131188	C	T	ABO	0.06	0.08	0.0044	74.03				
325	9	136141504	G	A	ABO	0.13	0.03	0.0032	15.35				
326	9	136141870	C	T	ABO	0.18	-0.08	0.0028	208.23				
327	9	136149709	AC	A	ABO					0.18	-0.08	0.0047	70.47
328	9	136825333	G	A	VAV2					0.67	-0.02	0.0038	9.44
329	10	3245548	T	C		0.44	0.01	0.0021	9.28				
330	10	3791224	G	T	RP11-184A2.3	0.50	0.02	0.0022	12.69				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
331	10	5254821	C	G	AKR1C4	0.15	0.02	0.0030	11.47				
332	10	13557945	G	C	BEND7	0.33	0.02	0.0023	11.92				
333	10	13737768	C	T	FRMD4A	0.46	0.02	0.0022	13.40				
334	10	36461955	CT	C		0.50	0.01	0.0021	11.04				
335	10	44858681	C	A	CXCL12	0.28	0.02	0.0024	18.13				
336	10	45406608	T	C	RP11-285G1.2,TMEM72-AS1	0.58	-0.02	0.0022	10.83				
337	10	48411796	G	T	GDF2	0.12	-0.03	0.0033	14.05				
338	10	60272708	T	C	BICC1	0.46	0.02	0.0021	14.75				
339	10	61469090	C	T	SLC16A9	0.77	0.01	0.0025	8.32				
340	10	71007973	CT	C	HKDC1	0.58	0.03	0.0022	35.50				
341	10	71094504	T	C	HK1	0.11	0.15	0.0034	414.07	0.11	0.15	0.0057	155.91
342	10	77293109	A	G		0.71	0.02	0.0024	11.13				

343	10	77932816	T	TA	C10orf11	0.24	0.02	0.0025	13.93
344	10	82141337	G	A		0.13	-0.02	0.0031	8.85
345	10	88925529	T	A	FAM35A	0.85	0.02	0.0030	12.53
346	10	90296467	A	T	RNLS	0.32	0.01	0.0023	9.31
347	10	96999873	G	A	PDLIM1	0.32	0.01	0.0023	8.93
348	10	104670832	C	A	RP11-724N1.1	0.34	-0.02	0.0023	11.21
349	10	114708510	C	T	TCF7L2	0.29	0.01	0.0024	8.76
350	11	1689409	G	A	AP006285.7	0.17	-0.02	0.0029	9.02
351	11	2190591	C	G	TH	0.20	0.02	0.0027	11.28
352	11	2325427	T	C	TSPAN32	0.02	0.05	0.0078	9.74
353	11	3944329	CA	C	STIM1	0.54	0.01	0.0022	8.64
354	11	6667353	A	G	DCHS1	0.62	-0.01	0.0022	9.56
355	11	8742865	TC	T	ST5	0.45	-0.03	0.0022	37.86

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
356	11	8862530	G	A	ST5					0.45	-0.03	0.0036	16.56
357	11	8866146	A	AAAT	ST5	0.24	0.03	0.0025	33.15				
358	11	10178437	T	C	RP11-748C4.1, SBF2					0.24	-0.05	0.0041	31.55
359	11	10195282	G	T	SBF2	0.24	-0.05	0.0025	75.14				
360	11	10249664	CTGTT	C	SBF2					0.05	-0.09	0.0086	22.99
361	11	10279241	A	G	SBF2	0.06	-0.06	0.0045	41.08				
362	11	10405200	C	A	AMPD3	0.01	0.09	0.0153	8.51				
363	11	10508903	G	T	AMPD3	0.01	-0.09	0.0112	13.89				
364	11	10679441	T	C	MRVI1	0.67	0.02	0.0023	17.46				
365	11	13335926	C	T	ARNTL	0.38	0.02	0.0022	14.70				
366	11	16259405	C	T	SOX6	0.54	0.01	0.0021	8.42				
367	11	27677583	C	A	BDNF	0.20	0.02	0.0027	9.40				
368	11	30749090	T	C		0.45	0.02	0.0021	28.62				

			GTTCCCGCT											
369	11	30749171	CTGTAACCTTA	G		0.04	-0.07	0.0055	37.39					
			TCAAC											
370	11	30903442	T	A	DCDC1					0.80	0.03	0.0045	9.80	
371	11	47380593	G	A	SPI1	0.59	0.02	0.0022	13.78					
372	11	61549025	G	A	MYRF, TMEM258					0.35	0.03	0.0037	13.51	
373	11	61581764	T	C	FADS1	0.31	0.03	0.0023	40.87					
374	11	74039147	C	T	PGM2L1,RP11-632K5.3	0.51	0.01	0.0021	8.40					
375	11	75455021	C	A	RN7SL786P	0.16	0.02	0.0029	13.01					
376	11	75531695	C	T	UVRAG					0.11	0.04	0.0058	9.35	
377	11	95795807	C	T	MAML2	0.23	-0.02	0.0026	9.25					
378	11	111202478	A	G		0.51	0.02	0.0021	14.79					

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
379	11	118298252	T	C	ATP5L	0.22	-0.02	0.0026	10.91				
380	12	2520453	C	A	CACNA1C					0.37	0.03	0.0037	11.67
381	12	2522077	C	T	CACNA1C	0.37	0.03	0.0022	37.25				
382	12	4330068	TTC	T		0.21	-0.02	0.0026	16.25				
383	12	11803303	G	C	ETV6	0.04	-0.04	0.0056	10.02				
384	12	13046211	C	T	GPRC5A					0.15	-0.03	0.0049	8.10
385	12	13050341	ATGAGAAGA CC	A	GPRC5A	0.15	-0.03	0.0030	25.96				
386	12	15307775	T	TA	RERG,RERG-AS1	0.34	-0.02	0.0023	10.73				
387	12	21710749	T	C	GYS2	0.80	0.02	0.0027	11.33				
388	12	46199589	T	C	ARID2	0.51	0.02	0.0021	11.78				
389	12	48403839	T	A	RP1-228P16.3	0.62	0.03	0.0022	53.27				
390	12	48496565	G	C	SENP1	0.09	0.03	0.0037	12.90				

391	12	48512285	C	A	PFKM	0.81	-0.05	0.0027	67.50	0.81	-0.05	0.0045	26.00
392	12	48736303	C	A	ZNF641					0.43	0.04	0.0036	28.12
393	12	52318378	A	T	ACVRL1	0.11	0.02	0.0034	10.41				
394	12	54749111	A	AGT	RP11-753H16.3,RP11-753H16.5	0.39	0.01	0.0023	8.67				
395	12	57807114	T	C	R3HDM2	0.76	-0.02	0.0025	19.12				
396	12	64901246	A	G	RP11-439H13.2	0.56	0.01	0.0022	9.41				
397	12	91144040	T	G		0.28	0.02	0.0024	10.69				
398	12	109036359	A	C	CORO1C,RP11-689B22.2	0.39	0.01	0.0022	8.40				
399	12	110294902	T	C	GLTP	0.23	-0.02	0.0025	14.07				
400	12	111884608	T	C	SH2B3	0.52	-0.07	0.0021	222.87	0.52	-0.06	0.0035	74.01
401	12	111885310	G	A	SH2B3	0.00	0.21	0.0239	17.57				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
402	12	112037526	A	G	RP11-686G8.2	0.78	0.06	0.0026	117.46				
403	12	115366182	T	C		0.41	0.02	0.0022	12.80				
404	12	117588433	TG	T	FBXO21	0.43	-0.02	0.0022	12.27				
405	12	121454622	C	T	C12orf43					0.30	0.02	0.0039	9.22
406	12	121471337	G	A	OASL	0.28	0.03	0.0024	25.31				
407	12	133112394	CGT	C	FBRSL1	0.23	0.02	0.0025	13.04				
408	13	29230581	A	G	POMP	0.35	-0.02	0.0022	24.94				
409	13	29239630	T	C	POMP					0.61	0.02	0.0037	9.44
410	13	33723244	C	T	STARD13	0.29	0.02	0.0024	13.24				
411	13	51165494	C	T	DLEU1	0.53	-0.02	0.0021	13.47				
412	13	51386889	C	T	DLEU7,DLEU7-AS1	0.57	0.01	0.0022	10.23				
413	13	71714717	G	T	LINC00348	0.60	0.01	0.0022	9.49				
414	13	78447373	T	A		0.78	-0.02	0.0026	9.42				

415	13	110424933	A	AG	IRS2	0.06	0.03	0.0048	9.61				
416	13	114551993	T	C	GAS6	0.33	0.02	0.0023	21.61				
417	14	21542766	A	G	ARHGEF40	0.17	-0.02	0.0029	16.67				
418	14	24808961	T	G	RIPK3	0.05	0.03	0.0051	8.35				
419	14	24881986	T	C	NYNRIN	0.48	0.01	0.0021	9.63				
420	14	34646269	C	T	EGLN3	0.68	0.02	0.0023	18.35				
421	14	34724550	T	C	EGLN3	0.38	0.01	0.0022	10.39				
422	14	36099366	C	T	RALGAPA1	0.09	-0.03	0.0038	15.67				
423	14	50655357	G	C	SOS2	0.01	0.07	0.0102	9.67				
424	14	50923249	C	T	MAP4K5	0.07	-0.03	0.0042	12.10				
425	14	64703593	G	T	ESR2	0.48	-0.03	0.0021	30.83	0.48	-0.02	0.0035	11.28
426	14	65506975	A	G	CHURC1- FNTB,MAX,FNTB	0.14	0.03	0.0031	17.27				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
427	14	65892694	CA	C	FUT8	0.21	-0.02	0.0026	12.17				
428	14	69264564	C	CT	ZFP36L1	0.71	0.02	0.0024	10.54				
429	14	73884540	A	G	NUMB	0.48	0.02	0.0021	12.44				
			CGCTCCTCT										
430	14	74208345	GCAGGCTTC	C	ELMSAN1	0.01	0.10	0.0132	13.22				
			CGCA										
431	14	74218569	C	T	ELMSAN1					0.01	0.13	0.0217	8.74
432	14	76624547	T	G	GPATCH2L	0.53	0.02	0.0021	13.18				
433	14	86119802	C	T		0.27	0.01	0.0024	8.12				
434	14	99698931	C	A	BCL11B	0.51	0.02	0.0021	12.00				
435	14	102987884	T	C		0.64	0.01	0.0022	9.75				
436	14	104194278	C	T	ZFYVE21	0.59	-0.01	0.0022	9.50				
437	15	33324280	C	T	FMN1	0.18	0.02	0.0028	13.50				

438	15	41190639	T	G	VPS18	0.06	-0.03	0.0045	9.24				
439	15	42768198	C	T	ZNF106	0.75	0.02	0.0025	16.97				
440	15	43726625	A	C	TP53BP1	0.03	-0.10	0.0068	43.84				
441	15	44028047	C	T	CATSPER2P1					0.02	-0.09	0.0119	14.16
442	15	51085374	T	C		0.15	0.02	0.0030	9.44				
443	15	57719138	G	C	CGNL1	0.25	-0.02	0.0025	10.64				
444	15	58680178	T	C	ALDH1A2	0.36	-0.02	0.0022	15.30				
445	15	58723939	G	A	LIPC,ALDH1A2	0.22	-0.02	0.0026	18.55				
446	15	58727325	A	G	RP11-355N15.1					0.79	0.03	0.0044	8.17
447	15	60945980	A	AT	RORA	0.37	-0.02	0.0022	14.37				
448	15	63359093	CT	C	TPM1	0.80	-0.02	0.0027	10.51				
449	15	66020908	A	G	RAB11A,DENND4A	0.25	-0.02	0.0025	15.27				
450	15	66049600	TG	T	DENND4A, RAB11A					0.44	-0.02	0.0036	8.32

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
451	15	66921963	G	C	RP11-321F6.1	0.37	0.02	0.0022	11.54				
452	15	66943404	C	G	RP11-321F6.1	0.81	0.02	0.0027	16.87				
453	15	66944221	T	TA	RP11-321F6.1					0.56	-0.02	0.0036	9.06
454	15	66999615	C	CT	SMAD6	0.24	0.02	0.0025	13.16				
455	15	67166007	C	A		0.01	0.07	0.0102	11.54				
456	15	68581390	T	C	FEM1B	0.34	-0.01	0.0023	8.72				
457	15	72108307	G	T	NR2E3	0.23	-0.02	0.0025	16.11				
458	15	75448181	C	T		0.67	-0.02	0.0023	16.24				
459	15	76123209	T	G		0.20	-0.03	0.0027	26.81				
460	15	76277092	T	C	NRG4	0.55	-0.03	0.0021	33.92				
461	15	76298132	A	G	NRG4	0.51	-0.04	0.0021	62.17				
462	15	76298744	A	G	NRG4					0.51	-0.04	0.0036	23.58
463	15	78230929	A	G	RP11-114H24.4	0.71	-0.02	0.0024	10.58				

464	15	78537238	C	CGGGG TGCGG	ACSBG1	0.39	-0.02	0.0022	25.64				
465	15	86160268	A	G	AKAP13	0.24	0.02	0.0025	9.32				
466	15	95696202	C	T		0.06	0.03	0.0045	8.36				
467	15	99284074	C	T	IGF1R	0.64	0.01	0.0022	8.73				
468	16	157592	CAA	C	NPRL3	0.62	-0.02	0.0023	21.47				
469	16	204126	A	G	HBM,HBZ	0.20	0.02	0.0029	9.52				
470	16	215106	C	A	HBZP1	0.11	-0.03	0.0036	19.84				
471	16	232396	AGAGT	A	HBA1,HBQ1,LA16c- OS12.2,Y_RNA	0.00	-0.41	0.0393	24.51				
472	16	249022	C	T	LUC7L					0.07	0.05	0.0071	11.16
473	16	250184	G	A	LUC7L					0.00	-0.31	0.0492	9.37
474	16	2086421	C	T	SLC9A3R2	0.01	-0.12	0.0129	19.74				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
475	16	4676660	G	A	MGRN1	0.82	0.02	0.0027	10.76				
476	16	16259596	G	A	ABCC6	0.03	0.05	0.0066	14.88				
477	16	30103160	C	A	TBX6	0.40	0.02	0.0022	23.00				
478	16	51170026	G	T	SALL1	0.05	-0.04	0.0052	12.36				
479	16	51187951	GA	G	SALL1	0.65	-0.02	0.0023	15.85				
480	16	52581047	C	G	TOX3	0.21	-0.02	0.0026	9.02				
481	16	57344314	AT	A		0.79	0.02	0.0028	8.76				
482	16	67829763	TAAAC	T	RANBP10					0.07	0.05	0.0071	10.71
483	16	67940350	A	G	PSKH1	0.12	0.04	0.0033	27.14				
484	16	69693035	T	A	NFAT5	0.32	0.01	0.0023	8.17				
485	16	72079657	C	T	TXNL4B	0.19	-0.02	0.0027	12.48				
486	16	72144174	T	C	DHX38	0.18	-0.02	0.0028	17.20				
487	16	79199414	A	T	WVOX	0.42	-0.02	0.0022	12.18				

488	16	86356582	G	A		0.09	-0.04	0.0038	23.94				
489	16	87869313	T	C	SLC7A5	0.29	0.02	0.0024	10.80				
490	16	88777073	G	C	CTU2	0.01	-0.08	0.0101	14.62				
491	16	88782050	G	A	PIEZO1	0.01	0.11	0.0111	21.23				
492	16	88784654	G	C	PIEZO1	0.00	0.29	0.0281	23.88				
493	16	88798519	AG	A	PIEZO1, RP5- 1142A6.2					0.01	0.15	0.0249	8.36
494	16	88800295	C	T	RP5-1142A6.2,PIEZO1	0.21	0.02	0.0026	20.09				
495	16	88856084	C	G	PIEZO1	0.58	-0.05	0.0022	99.76				
496	16	88858646	T	G						0.58	-0.05	0.0037	43.31
497	16	89698070	C	T	DPEP1	0.44	0.03	0.0022	30.95				
498	16	89734349	T	C	SPATA33					0.42	0.02	0.0036	8.94
499	17	7106378	G	A	DLG4	0.01	0.12	0.0159	12.85				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
500	17	7366619	T	C	ZBTB4	0.13	-0.03	0.0032	18.87				
501	17	7732351	T	A	DNAH2	0.58	-0.02	0.0022	25.61				
502	17	7737331	C	T	DNAH2					0.57	-0.02	0.0036	9.80
503	17	8161149	C	T	PFAS					0.50	-0.02	0.0035	9.96
504	17	8216468	T	C	ARHGEF15	0.50	0.02	0.0021	22.32				
505	17	14822052	G	A		0.74	0.02	0.0025	11.22				
506	17	17007351	A	AG	MPRIP	0.74	-0.02	0.0024	10.58				
507	17	19914399	T	A	SPECC1	0.53	0.01	0.0021	8.69				
508	17	27152869	T	C	FAM222B	0.28	0.02	0.0024	16.95				
509	17	28164263	G	C	SSH2	0.49	-0.01	0.0021	8.24				
510	17	35851177	A	C	DUSP14	0.64	-0.01	0.0022	10.41				
511	17	36172155	C	T		0.72	0.01	0.0024	8.55				
512	17	37784464	C	G	PPP1R1B	0.72	-0.02	0.0024	17.55				

513	17	42329004	A	C	SLC4A1	0.70	-0.03	0.0023	28.35	0.70	-0.02	0.0039	9.32
514	17	42338248	A	G	SLC4A1,AC003043.1	0.11	0.03	0.0034	23.22				
515	17	43811072	A	G	CRHR1, RP11- 105N13.4, RP11- 293E1.1					0.23	0.04	0.0041	25.50
516	17	44332351	A	G	RP11-259G18.3	0.23	0.05	0.0025	79.52				
517	17	44906949	T	C	WNT3	0.77	-0.03	0.0026	34.34	0.77	-0.03	0.0042	15.19
518	17	46683800	C	T	HOXB3,HOXB6	0.16	-0.02	0.0029	15.56				
519	17	47047596	A	G	GIP	0.41	-0.01	0.0022	9.41				
520	17	53364788	C	A	HLF	0.60	-0.01	0.0022	9.76				
521	17	57821430	G	A	VMP1					0.30	-0.02	0.0039	8.96
522	17	57866165	T	TAA	VMP1	0.22	-0.03	0.0026	31.04				
523	17	59242914	T	G	BCAS3	0.82	0.03	0.0028	23.68				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
524	17	59448945	A	G	BCAS3, RP11- 332H18.5					0.83	-0.03	0.0048	10.20
525	17	59456589	C	T	BCAS3	0.83	-0.04	0.0028	38.80				
526	17	61880270	C	CA	DDX42	0.58	-0.02	0.0022	18.12				
527	17	67081278	A	G	ABCA6	0.02	0.09	0.0072	35.90	0.02	0.10	0.0120	15.73
528	17	76124810	A	AG	TMC6	0.22	0.02	0.0026	15.77				
529	17	76406170	T	C	PGS1	0.58	-0.01	0.0022	9.04				
530	17	80189895	C	T	SLC16A3	0.25	-0.01	0.0025	8.63				
531	17	81049741	G	A	METRNL	0.71	0.02	0.0024	12.28				
532	18	11997350	A	G	IMPA2	0.26	-0.01	0.0024	8.21				
533	18	12546603	G	C	SPIRE1	0.09	-0.02	0.0038	9.96				
534	18	12857002	G	T	PTPN2	0.55	-0.02	0.0021	14.08				
535	18	42811727	T	C	SLC14A2	0.19	0.02	0.0027	13.31				

536	18	43085920	A	G	RP11-749H17.1,SLC14A2	0.90	0.03	0.0036	11.90				
537	18	43845880	CTT	C	C18orf25	0.55	-0.02	0.0021	14.93				
538	18	46207268	G	A	CTIF,RP11-426J5.2	0.03	-0.05	0.0061	15.06				
539	18	46343221	C	T	CTIF	0.88	-0.02	0.0033	12.97				
540	18	46460903	C	G	SMAD7	0.52	-0.02	0.0021	21.01				
541	18	46463136	A	G	SMAD7					0.45	-0.02	0.0036	9.04
542	18	55313997	C	T	ATP8B1	0.12	-0.02	0.0032	12.27				
543	19	807442	G	C	PTBP1	0.60	0.03	0.0022	40.24	0.60	0.03	0.0036	13.31
544	19	808586	C	G	PTBP1	0.14	0.04	0.0031	30.57				
545	19	1244900	A	G	MIDN	0.47	0.01	0.0021	8.83				
546	19	1435771	G	A	RPS15	0.50	0.02	0.0021	12.18				
547	19	2161321	T	C	AP3D1					0.47	0.03	0.0036	13.49

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
548	19	2164351	T	A	AP3D1	0.40	0.03	0.0022	47.96				
549	19	4426164	CT	C	CHAF1A	0.71	0.02	0.0024	24.48				
550	19	4498154	G	A	HDGFRP2	0.56	0.03	0.0022	40.38				
551	19	4502201	T	C	HDGFRP2					0.57	0.03	0.0036	12.49
552	19	13128861	G	A	NFIX	0.05	-0.03	0.0049	9.03				
553	19	19379549	C	T	TM6SF2	0.07	0.03	0.0041	14.29				
554	19	32593682	T	C	AC011518.1	0.65	-0.02	0.0022	11.64				
555	19	33231028	C	G	TDRD12	0.16	-0.03	0.0031	20.01				
556	19	33754548	C	T		0.08	0.04	0.0039	23.03				
557	19	35947661	A	T	FFAR2	0.29	-0.02	0.0024	10.45				
558	19	35947890	G	A						0.28	-0.03	0.0040	10.06
559	19	41132022	C	G	LTBP4	0.17	0.02	0.0028	17.06				
560	19	41297106	G	C	RAB4B-EGLN2,RAB4B	0.16	-0.02	0.0029	9.65				

561	19	41305065	G	A	RAB4B-EGLN2,EGLN2	0.02	0.08	0.0088	17.55				
562	19	41305138	G	T	EGLN2	0.02	-0.12	0.0073	59.44	0.02	-0.10	0.0124	15.40
563	19	41306650	C	T	EGLN2	0.02	-0.10	0.0087	27.56	0.02	-0.09	0.0144	9.02
564	19	41307024	G	A	EGLN2	0.00	0.29	0.0343	16.24				
565	19	41324078	G	A	CTC-490E21.12					0.31	0.03	0.0039	10.30
566	19	44268325	C	G	KCNN4	0.22	0.03	0.0026	24.64				
567	19	44278781	G	A	KCNN4					0.23	0.03	0.0043	8.42
568	19	45715976	A	G	EXOC3L2	0.34	0.02	0.0023	23.62				
569	19	45766729	G	A	MARK4	0.26	0.02	0.0024	17.58				
570	19	46219958	CA	C	FBXO46	0.45	-0.02	0.0022	11.42				
571	19	46878629	G	A	PPP5C	0.31	-0.02	0.0023	10.47				
572	19	47572987	T	C	ZC3H4					0.72	-0.02	0.0040	9.46
573	19	47623080	C	CT	SAE1	0.70	-0.03	0.0024	26.27				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
574	19	50017538	G	C	FCGRT	0.01	0.09	0.0114	13.89				
575	19	50035161	C	T	RCN3	0.01	0.07	0.0109	8.71				
576	19	50051561	T	TTTGG	RCN3					0.20	0.03	0.0045	10.95
577	19	50090422	C	CT	NOSIP,PRRG2	0.22	0.03	0.0026	21.63				
578	19	51003387	CAGAG	C		0.02	0.06	0.0080	12.75				
579	20	4142839	G	A	SMOX	0.40	0.01	0.0022	9.03				
580	20	10974785	C	G	RP11-103J8.1	0.52	0.01	0.0021	8.52				
581	20	11177055	G	A		0.05	0.03	0.0050	11.45				
582	20	25294041	A	G	ABHD12	0.14	-0.02	0.0031	9.91				
583	20	39678289	C	T	TOP1	0.55	0.01	0.0021	10.95				
584	20	39797465	T	C	PLCG1					0.55	0.02	0.0036	8.11
585	20	43042364	C	T	HNF4A	0.03	0.07	0.0061	31.50				
586	20	49101590	T	C		0.55	0.02	0.0021	22.68				

587	20	55918934	T	G	SPO11	0.01	0.10	0.0146	10.54				
588	20	56119516	C	A						0.60	0.02	0.0036	9.13
589	20	56137834	A	G	PCK1	0.51	0.02	0.0021	26.58				
590	20	57237670	G	A	STX16-NPEPL1,STX16	0.38	0.01	0.0022	9.52				
591	20	61030580	A	T		0.71	-0.02	0.0024	13.20				
592	20	61037490	G	A	GATA5	0.93	0.03	0.0042	15.12				
593	20	62483993	A	G		0.70	-0.02	0.0024	9.60				
594	21	16339172	G	C	NRIP1	0.10	-0.03	0.0035	12.97				
595	21	16576783	G	A		0.34	-0.03	0.0023	41.35				
596	21	16578159	A	C						0.34	-0.03	0.0038	15.91
597	21	16785688	G	C						0.28	-0.03	0.0040	11.88
598	21	16794755	A	G		0.30	-0.03	0.0023	32.55				
599	21	35346855	TA	T	LINC00649					0.57	-0.03	0.0036	13.13

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
600	21	35347960	C	T	LINC00649	0.58	-0.02	0.0022	27.18				
601	21	35356706	G	A		0.15	-0.04	0.0030	35.10				
602	21	35356814	G	T		0.66	0.02	0.0023	18.69				
603	21	36450841	C	T	RUNX1	0.14	0.02	0.0030	13.84				
604	21	37834258	T	C	AP000695.6,CLDN14,A P000695.4	0.76	0.03	0.0025	38.51	0.77	0.03	0.0043	12.98
605	21	38055216	C	T		0.22	-0.03	0.0026	33.20				
606	21	38071988	A	G	SIM2	0.22	0.03	0.0026	22.65				
607	21	38072356	G	C	SIM2, AP000697.6					0.28	-0.03	0.0041	10.82
608	21	38168446	T	C	HLCS	0.08	-0.02	0.0038	10.18				
609	21	39868927	T	C	ERG	0.85	0.02	0.0030	11.53				
610	21	40466570	G	A						0.27	0.02	0.0040	8.68
611	21	40466744	G	A		0.27	0.02	0.0024	12.74				

612	21	44139647	A	AG	PDE9A	0.59	-0.02	0.0022	11.56				
613	21	45746102	T	C	PFKL	0.01	-0.06	0.0098	9.63				
614	22	21929566	A	T	UBE2L3	0.16	-0.02	0.0031	10.82				
615	22	29203314	C	T	CTA-292E10.6	0.19	-0.03	0.0027	23.96	0.18	-0.03	0.0046	10.33
616	22	30371350	A	G	MTMR3	0.25	-0.02	0.0025	15.38				
617	22	36762634	T	C	MYH9	0.68	-0.02	0.0023	14.25				
618	22	37462936	A	G	TMPRSS6	0.56	0.10	0.0022	481.33	0.56	0.10	0.0036	168.25
619	22	37469593	C	T	TMPRSS6	0.00	-0.57	0.0758	13.19				
620	22	37471290	G	A	TMPRSS6	0.12	-0.07	0.0032	113.22				
621	22	37506410	T	C	TMPRSS6	0.43	-0.04	0.0022	83.22				
622	22	37508424	G	C	TMPRSS6					0.43	-0.04	0.0036	34.22
623	22	38603571	CCAGTAGCT GGGACTA	C	MAFF	0.54	0.01	0.0021	9.33				

No	Chr	BP	REF	ALT	Gene	Statistics for Hgb2020				Statistics for Hgb2016			
						ALF	BETA	SE	logP	ALF	BETA	SE	logP
624	22	39009135	A	T	FAM227A	0.27	-0.02	0.0024	12.28				
625	22	39527935	C	T	CBX7	0.60	-0.02	0.0022	12.79				
626	22	43114551	G	A	A4GALT	0.47	0.03	0.0021	38.08				
627	22	43115576	T	C	A4GALT					0.59	0.03	0.0036	17.16
628	22	44324727	C	G	PNPLA3	0.22	0.03	0.0026	38.25				
629	22	44324730	C	T	PNPLA3					0.22	0.03	0.0043	11.52
630	22	45999938	T	A	CTA-941F9.9, FBLN1					0.46	-0.03	0.0036	12.90
631	22	46004023	C	T	CTA-941F9.9	0.45	-0.03	0.0022	38.47				
632	22	46309893	C	G		0.34	0.02	0.0022	27.63				
633	22	46372968	C	T	WNT7B	0.32	0.03	0.0023	45.14				
634	22	46376384	A	G	WNT7B, CR536603.1					0.68	-0.03	0.0038	15.38

ALF= alternative allele frequency; ALT=alternative allele; BP=base-pair position; CHR: chromosome number; REF=reference allele; SE=standard error.

Table S4. SNP-based heritability estimates of iron biomarkers using the GWAS summary statistics

Biomarkers	n	h_g^2 (SE)
Transferrin saturation	131,471	0.043 (0.009)
Serum iron	163,511	0.036 (0.008)
Serum ferritin	246,139	0.062 (0.006)
Total iron binding capacity	135,430	0.078 (0.037)
Hemoglobin (2016)	173,480	0.137 (0.011)
Hemoglobin (2020)	563,085	0.160 (0.011)

h_g^2 , SNP heritability.

Table S5. Variants associated with ferritin, serum iron, total iron binding capacity, and transferrin saturation in the meta-analysis

Phenotype	Position (hg38)	rs-name	Minor allele	Major allele	Predicted causal gene	Closest gene	Consequence	Effect in SD (95% CI)	<i>P</i>	MAF (%)
Ferritin	chr1:22257509	rs75965181	A	T	<i>WNT4</i>	<i>WNT4</i>	intergenic	-0.12 (-0.14, -0.097)	3.70×10 ⁻²⁶	2.14
Ferritin	chr1:115671658	rs10801913	A	G	<i>VANGL1</i>	<i>VANGL1</i>	intron	0.024 (0.016, 0.031)	2.63×10 ⁻¹⁰	30.7
Ferritin	chr1:169549811	rs6025	T	C	<i>F5</i>	<i>F5</i>	missense	0.15 (0.12, 0.17)	6.93×10 ⁻³⁷	2.79
Ferritin	chr1:220115348	rs551459670	A	G	<i>IARS2</i>	<i>IARS2</i>	intron	0.14 (0.1, 0.18)	1.28×10 ⁻¹³	1.1
Ferritin	chr2:27508073	rs1260326	T	C	<i>GCKR</i>	<i>GCKR</i>	missense	0.025 (0.018, 0.032)	1.48×10 ⁻¹²	36.8
Ferritin	chr2:28948938	rs6757653	T	C	<i>WDR43</i>	<i>WDR43</i>	downstream	0.032 (0.024, 0.039)	9.34×10 ⁻¹⁶	27.4
Ferritin	chr2:215435759	rs1250259	T	A	<i>FN1</i>	<i>FN1</i>	missense	-0.024 (-0.032, -0.017)	1.84×10 ⁻¹⁰	28.8
Ferritin	chr3:52502023	rs762752083	T	G	<i>STAB1</i>	<i>STAB1</i>	stop gained	0.35 (0.26, 0.44)	3.19×10 ⁻¹⁴	0.24
Ferritin	chr3:52502709	rs750717575	A	G	<i>STAB1</i>	<i>STAB1</i>	missense	0.24 (0.16, 0.32)	2.18×10 ⁻⁸	0.27
Ferritin	chr3:52505379	rs745795585	A	G	<i>STAB1</i>	<i>STAB1</i>	missense	0.29 (0.23, 0.35)	2.60×10 ⁻¹⁹	0.47
Ferritin	chr3:52693659	rs34216132	C	G	<i>STAB1</i>	<i>GNL3</i>	missense	0.17 (0.11, 0.22)	3.50×10 ⁻⁹	0.333
Ferritin	chr3:134222476	rs1131262	T	C	<i>RYK</i>	<i>RYK</i>	missense	-0.032 (-0.042, -0.021)	6.66×10 ⁻⁹	11.2
Ferritin	chr6:43813355	rs36184164	G	T	<i>VEGFA</i>	<i>VEGFA</i>	intergenic	0.036 (0.025, 0.046)	6.46×10 ⁻¹²	12.6
Ferritin	chr7:30472178	rs2529440	T	C	<i>NOD1</i>	<i>NOD1</i>	intron	-0.035 (-0.041, -0.028)	4.60×10 ⁻²³	44.6
Ferritin	chr8:10711019	rs4841429	G	A	<i>RP1L1</i>	<i>RP1L1</i>	intergenic	0.06 (0.048, 0.073)	8.21×10 ⁻²¹	7.86
Ferritin	chr8:23520397	rs13253974	A	G	<i>SLC25A37</i>	<i>SLC25A37</i>	intergenic	0.024 (0.017, 0.032)	2.51×10 ⁻¹¹	32.3
Ferritin	chr8:125478730	rs2954029	T	A	<i>TRIB1</i>	<i>TRIB1</i>	intergenic	-0.024 (-0.031, -0.018)	1.42×10 ⁻¹²	47.9

Phenotype	Position (hg38)	rs-name	Minor allele	Major allele	Predicted causal gene	Closest gene	Consequence	Effect in SD (95% CI)	P	MAF (%)
Ferritin	chr9:33117967	rs7865362	T	C	<i>B4GALT1</i>	<i>B4GALT1</i>	intron	0.025 (0.018, 0.032)	1.03×10 ⁻¹¹	36
Ferritin	chr10:69334748	rs17476364	C	T	<i>HK1</i>	<i>HK1</i>	intron	0.043 (0.032, 0.054)	3.57×10 ⁻¹⁴	10.8
Ferritin	chr11:2211323	rs12419620	G	T	<i>TH</i>	<i>TH</i>	intergenic	-0.031 (-0.04, -0.022)	3.43×10 ⁻¹¹	16.1
Ferritin	chr11:47738526	rs12807014	C	T	<i>FNBP4</i>	<i>FNBP4</i>	intron	-0.029 (-0.036, -0.021)	2.72×10 ⁻¹³	27.4
Ferritin	chr11:60393365	rs4938939	A	G	<i>MS4A7</i>	<i>MS4A7</i>	upstream	0.022 (0.015, 0.03)	3.01×10 ⁻⁹	29.3
Ferritin	chr12:50983028	-	3.5 kb del	-	<i>SLC11A2</i>	<i>SLC11A2</i>	large deletion	-0.16 (-0.19, -0.13)	1.46×10 ⁻²⁴	0.68
Ferritin	chr14:33941686	rs996347	C	T	<i>EGLN3</i>	<i>EGLN3</i>	intron	0.049 (0.042, 0.056)	2.99×10 ⁻⁴¹	35.5
Ferritin	chr15:45106240	rs57659670	C	T	<i>DUOX2</i>	<i>DUOX2</i>	missense	-0.14 (-0.16, -0.13)	1.05×10 ⁻¹¹³	7.53
Ferritin	chr15:65624189	rs3743171	T	A	<i>DPP8</i>	<i>SLC24A1</i>	missense	-0.024 (-0.032, -0.015)	2.92×10 ⁻⁸	19.1
Ferritin	chr16:325782	rs9921222	C	T	<i>AXIN1</i>	<i>AXIN1</i>	intron	0.025 (0.018, 0.032)	1.09×10 ⁻¹²	49.2
Ferritin	chr16:4752385	rs3747602	G	T	<i>ZNF500</i>	<i>ZNF500</i>	synonymous	0.021 (0.014, 0.028)	2.47×10 ⁻⁹	36.8
Ferritin	chr17:7116978	rs535064984	C	T	<i>ASGR1</i>	<i>ASGR1</i>	downstream	0.23 (0.18, 0.28)	3.61×10 ⁻¹⁹	0.58
Ferritin	chr17:9890100	rs55789050	T	A	<i>GLP2R</i>	<i>GLP2R</i>	3_prime_UTR	-0.027 (-0.034, -0.02)	6.07×10 ⁻¹⁴	33.3
Ferritin	chr17:74942005	rs1542752	T	C	<i>OTOP3</i>	<i>OTOP3</i>	missense	0.034 (0.025, 0.044)	1.44×10 ⁻¹²	15.3
Ferritin	chr19:5840608	rs708686	T	C	<i>FUT6</i>	<i>FUT6</i>	upstream	-0.031 (-0.039, -0.023)	1.96×10 ⁻¹⁴	25.8
Ferritin	chr19:18467063	rs4808802	C	G	<i>ELL</i>	<i>ELL</i>	intron	0.028 (0.019, 0.036)	3.42×10 ⁻¹¹	21.8
Ferritin	chr19:48703417	rs601338	G	A	<i>FUT2</i>	<i>FUT2</i>	stop gained	0.028 (0.021, 0.035)	7.04×10 ⁻¹⁶	48.4
Ferritin	chr19:49046859	rs143041401	A	G	<i>FTL</i>	<i>CGB8</i>	downstream	0.11 (0.078, 0.13)	4.03×10 ⁻¹⁴	1.61

Phenotype	Position (hg38)	rs-name	Minor allele	Major allele	Predicted causal gene	Closest gene	Consequence	Effect in SD (95% CI)	P	MAF (%)
Ferritin	chr20:40495768	rs6029148	A	G	<i>MAFB</i>	<i>MAFB</i>	intergenic	0.046 (0.033, 0.058)	5.56×10 ⁻¹²	7.1
Ferritin	chr2:189553964	rs12693541	C	T	<i>SLC40A1</i>	<i>SLC40A1</i>	intergenic	0.079 (0.069, 0.09)	2.21×10 ⁻⁴⁸	11.9
Ferritin	chr6:26090951	rs1799945	G	C	<i>HFE</i>	<i>HFE</i>	missense	0.059 (0.049, 0.069)	1.51×10 ⁻³¹	13.7
Ferritin	chr6:26092913	rs1800562	A	G	<i>HFE</i>	<i>HFE</i>	missense	0.13 (0.12, 0.15)	1.85×10 ⁻⁸⁴	6.77
Ferritin	chr9:133264504	-	G	GAAACTGCC	<i>ABO</i>	<i>ABO</i>	intron	-0.062 (-0.071, -0.052)	2.48×10 ⁻³⁷	23.1
Ferritin	chr17:58358748	rs34523089	T	C	<i>MTMR4</i>	<i>RNF43</i>	missense	0.069 (0.059, 0.078)	3.16×10 ⁻⁴⁸	16.1
Ferritin	chr22:37066896	rs855791	A	G	<i>TMPRSS6</i>	<i>TMPRSS6</i>	missense	-0.044 (-0.051, -0.038)	6.14×10 ⁻³⁷	43.1
Iron	chr1:65671556	rs35945185	A	G	<i>LEPR</i>	<i>LEPR</i>	intergenic	0.031 (0.023, 0.039)	1.54×10 ⁻¹³	36.5
Iron	chr1:154454494	rs2228145	C	A	<i>IL6R</i>	<i>IL6R</i>	missense	0.026 (0.018, 0.034)	8.42×10 ⁻¹¹	40.7
Iron	chr2:238160555	rs13007705	T	C	<i>ERFE</i>	<i>ERFE</i>	intron	0.029 (0.021, 0.037)	2.01×10 ⁻¹²	42.5
Iron	chr3:66376605	rs7630745	C	T	<i>LRIG1</i>	<i>LRIG1</i>	downstream	0.025 (0.017, 0.033)	2.09×10 ⁻⁹	35.8
Iron	chr6:135081201	rs9399136	C	T	<i>MYB</i>	<i>HBS1L</i>	intergenic	0.057 (0.049, 0.066)	1.08×10 ⁻³⁶	25.9
Iron	chr7:50360747	rs12718598	C	T	<i>IKZF1</i>	<i>IKZF1</i>	intron	0.027 (0.019, 0.034)	3.69×10 ⁻¹¹	46.3
Iron	chr15:45106240	rs57659670	C	T	<i>DUOX2</i>	<i>DUOX2</i>	missense	-0.042 (-0.056, -0.028)	1.08×10 ⁻⁸	7.53
Iron	chr17:69253570	rs77262773	T	C	<i>ABCA5</i>	<i>ABCA5</i>	splice_region	0.081 (0.055, 0.11)	9.54×10 ⁻¹⁰	2.61
Iron	chr19:35456759	rs2005682	T	A	<i>HAMP</i>	<i>FFAR2</i>	downstream	-0.029 (-0.037, -0.02)	2.37×10 ⁻¹¹	30.5
Iron	chr3:133757906	rs748587164	A	T	<i>TF</i>	<i>TF</i>	stop gained	-0.52 (-0.66, -0.39)	7.12×10 ⁻¹⁴	0.12
Iron	chr3:133779897	rs4854760	G	A	<i>RAB6B</i>	<i>TF</i>	upstream	0.053 (0.044, 0.062)	5.67×10 ⁻³³	31.3

Phenotype	Position (hg38)	rs-name	Minor allele	Major allele	Predicted causal gene	Closest gene	Consequence	Effect in SD (95% CI)	P	MAF (%)
Iron	chr6:26090951	rs1799945	G	C	<i>HFE</i>	<i>HFE</i>	missense	0.17 (0.16, 0.18)	1.26×10 ⁻¹⁸⁷	13.7
Iron	chr6:26092913	rs1800562	A	G	<i>HFE</i>	<i>HFE</i>	missense	0.27 (0.26, 0.29)	3.66×10 ⁻²⁷⁶	6.77
Iron	chr7:100638347	rs7385804	C	A	<i>TFR2</i>	<i>TFR2</i>	upstream	-0.057 (-0.065, -0.049)	9.42×10 ⁻⁴³	37.1
Iron	chr22:37066896	rs855791	A	G	<i>TMPRSS6</i>	<i>TMPRSS6</i>	missense	-0.17 (-0.18, -0.16)	1.00×10 ⁻³⁰⁰	43.1
Iron	chr22:37074634	rs773570300	T	TG	<i>TMPRSS6</i>	<i>TMPRSS6</i>	frameshift	-0.76 (-0.88, -0.65)	7.00×10 ⁻⁴⁰	0.16
TIBC	chr1:169549811	rs6025	T	C	<i>F5</i>	<i>F5</i>	missense	-0.093 (-0.13, -0.061)	1.76×10 ⁻⁸	2.79
TIBC	chr4:3450618	rs59950280	A	G	<i>HGFAC</i>	<i>HGFAC</i>	downstream	0.033 (0.023, 0.043)	5.87×10 ⁻¹¹	33.5
TIBC	chr6:135081201	rs9399136	C	T	<i>MYB</i>	<i>HBS1L</i>	intergenic	-0.033 (-0.044, -0.023)	2.65×10 ⁻¹⁰	25.9
TIBC	chr14:94380925	rs17580	A	T	<i>SERPINA1</i>	<i>SERPINA1</i>	missense	0.076 (0.053, 0.099)	1.19×10 ⁻¹⁰	3.79
TIBC	chr15:45106240	rs57659670	C	T	<i>DUOX2</i>	<i>DUOX2</i>	missense	0.077 (0.06, 0.094)	3.67×10 ⁻¹⁹	7.53
TIBC	chr19:49587947	rs112727702	T	G	<i>PRRG2</i>	<i>PRRG2</i>	upstream	0.043 (0.032, 0.054)	2.08×10 ⁻¹⁴	23.2
TIBC	chr20:17615510	rs1132274	A	C	<i>RRBP1</i>	<i>RRBP1</i>	missense	0.036 (0.023, 0.048)	1.93×10 ⁻⁸	16.8
TIBC	chr2:189553964	rs12693541	C	T	<i>SLC40A1</i>	<i>SLC40A1</i>	intergenic	-0.048 (-0.063, -0.034)	2.53×10 ⁻¹¹	11.9
TIBC	chr3:133757906	rs748587164	A	T	<i>TF</i>	<i>TF</i>	stop gained	-2.3 (-2.5, -2.1)	4.28×10 ⁻¹⁴⁸	0.12
TIBC	chr3:133779897	rs4854760	G	A	<i>RAB6B</i>	<i>TF</i>	upstream	0.34 (0.33, 0.36)	1.00×10 ⁻³⁰⁰	31.3
TIBC	chr3:196073940	rs3817672	C	T	<i>TFRC</i>	<i>TFRC</i>	missense	-0.031 (-0.04, -0.022)	6.32×10 ⁻¹¹	44
TIBC	chr6:26090951	rs1799945	G	C	<i>HFE</i>	<i>HFE</i>	missense	-0.12 (-0.13, -0.1)	4.29×10 ⁻⁶⁶	13.7
TIBC	chr6:26092913	rs1800562	A	G	<i>HFE</i>	<i>HFE</i>	missense	-0.45 (-0.47, -0.43)	1.00×10 ⁻³⁰⁰	6.77

Phenotype	Position (hg38)	rs-name	Minor allele	Major allele	Predicted causal gene	Closest gene	Consequence	Effect in SD (95% CI)	P	MAF (%)
TIBC	chr8:18415790	rs1495743	G	C	<i>NAT2</i>	<i>NAT2</i>	intergenic	-0.043 (-0.055, -0.032)	9.00×10 ⁻¹⁴	21.4
TIBC	chr11:61802358	rs174546	T	C	<i>FADS1</i>	<i>FADS1</i>	3_prime_UTR	0.046 (0.037, 0.056)	6.62×10 ⁻²²	35.4
TIBC	chr22:37066896	rs855791	A	G	<i>TMPRSS6</i>	<i>TMPRSS6</i>	missense	0.026 (0.017, 0.035)	2.88×10 ⁻⁸	43.1
TSAT	chr2:238160555	rs13007705	T	C	<i>ERFE</i>	<i>ERFE</i>	intron	0.033 (0.024, 0.042)	1.10×10 ⁻¹²	42.5
TSAT	chr6:135081201	rs9399136	C	T	<i>MYB</i>	<i>HBS1L</i>	intergenic	0.067 (0.057, 0.077)	5.32×10 ⁻³⁹	25.9
TSAT	chr15:45106240	rs57659670	C	T	<i>DUOX2</i>	<i>DUOX2</i>	missense	-0.058 (-0.074, -0.041)	5.73×10 ⁻¹²	7.53
TSAT	chr19:35456759	rs2005682	T	A	<i>HAMP</i>	<i>FFAR2</i>	downstream	-0.032 (-0.042, -0.022)	6.25×10 ⁻¹¹	30.5
TSAT	chr3:133757906	rs748587164	A	T	<i>TF</i>	<i>TF</i>	stop gained	0.72 (0.55, 0.88)	1.58×10 ⁻¹⁷	0.12
TSAT	chr3:133779897	rs4854760	G	A	<i>RAB6B</i>	<i>TF</i>	upstream	-0.096 (-0.11, -0.086)	9.95×10 ⁻⁸³	31.3
TSAT	chr3:196073940	rs3817672	C	T	<i>TFRC</i>	<i>TFRC</i>	missense	0.026 (0.017, 0.034)	2.29×10 ⁻⁸	44
TSAT	chr6:26090951	rs1799945	G	C	<i>HFE</i>	<i>HFE</i>	missense	0.21 (0.2, 0.23)	6.10×10 ⁻²²⁹	13.7
TSAT	chr6:26092913	rs1800562	A	G	<i>HFE</i>	<i>HFE</i>	missense	0.45 (0.42, 0.47)	1.00×10 ⁻³⁰⁰	6.77
TSAT	chr7:100638347	rs7385804	C	A	<i>TFR2</i>	<i>TFR2</i>	upstream	-0.062 (-0.071, -0.053)	2.87×10 ⁻³⁹	37.1
TSAT	chr22:37066896	rs855791	A	G	<i>TMPRSS6</i>	<i>TMPRSS6</i>	missense	-0.17 (-0.18, -0.16)	1.00×10 ⁻³⁰⁰	43.1
TSAT	chr22:37074634	rs773570300	T	TG	<i>TMPRSS6</i>	<i>TMPRSS6</i>	frameshift	-0.78 (-0.91, -0.65)	6.66×10 ⁻³¹	0.16

Effects are measured in standard deviations (SD) and are always shown for the minor allele. Missing data are denoted by "-". CI=confidence interval; MAF=minor allele frequency; SD= standard deviation;

TIBC=total iron binding capacity; TSAT=transferrin saturation.

Table S6. Characteristics of the publically available datasets used for Mendelian randomization analyses

Consortium	Phenotype	Year	PMID	Cases/Controls *	Source
CARDIoGRAMplusC4D	Coronary artery disease	2022	36474045	181,522/984,168	https://www.ebi.ac.uk/gwas/

Multiple consortia [†]	Heart failure	2022	36376295	115,150/1,550,331	https://www.ebi.ac.uk/gwas/
GIGASTROKE	Ischemic stroke	2022	36180795	62,100/1,234,808	https://www.ebi.ac.uk/gwas/
DIAMANTE	Type 2 diabetes	2022	35551307	80,154/853,816	http://www.diagram-consortium.org/
GIANT	Body-mass index (kg/m ²)	2019	30239722	806,834	
	Waist circumference (cm)	2015	25673412	210,088	http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium
	Waist-to-hip ratio	2019	30239722	697,734	
	Hip circumference (cm)	2015	25673412	210,088	
	Height (cm)	2018	30124842	693,529	
GLGC	HDL-cholesterol (mmol/L)	2021		1,320,016	
	LDL-cholesterol (mmol/L)	2021		1,320,016	
	Total cholesterol (mmol/L)	2021	34887591	1,320,016	http://lipidgenetics.org/
	Triglycerides (mmol/L)	2021		1,320,016	
	Non-HDL (mmol/L)	2021		1,320,016	
UK Biobank	C reactive protein (mg/L)	2021	33462484	318,271	https://doi.org/10.35092/yhjc.12355382
	Liver fat (%)	2021		32,858	
	Liver iron (mg/g)	2021	34128465	32,858	https://www.ebi.ac.uk/gwas/
	Liver volume (L)	2021		32,860	
	Pancreas iron (mg/g)	2021		25,617	
CKDGen	eGFR _{crea} (ml/min/1.73m ²)	2021	34272381	1,201,909	http://ckdgen.imbi.uni-freiburg.de/
MAGIC	Fasting glucose (mmol/L)	2021		281,416	
	Fasting insulin (mmol/L)	2021	34059833	281,416	https://magicinvestigators.org/
	2h glucose	2021		281,416	
	Hemoglobin A1c (%)	2021		281,416	
SSGAC	Educational attainment (years)	2018	30038396	1,131,881	https://www.thessgac.org/data
EGG	Birth weight (kg)	2019	31043758	298,142	http://egg-consortium.org/

*Cases/controls for binary phenotypes and numbers of participants for quantitative traits. [†]GWAS summary statistics for HF were obtained from a combination of HERMES, Penn Medicine Biobank, eMERGE, Mount Sinai BioMe, Geisinger DiscovEHR, FinnGen, and the Global Biobank Meta-analysis Initiative. Abbreviations: CARDIoGRAMplusC4D=Coronary Artery Disease Genome wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics consortium; EGG=Early Growth Genetics; GIANT=Genetic Investigation of Anthropometric Traits; MAGIC=Meta-Analyses of Glucose and Insulin-related traits Consortium; SSGAC= Social Science Genetic Association Consortium.

Table S7. Casual associations of hemoglobin with risk of cardiometabolic diseases in UK Biobank using semiparametric methods to assess nonlinear exposure-outcome relationships for Mendelian randomization

Outcome	Quartile	localized average causal effect		P for non-linearity tests			Heterogeneity tests	
		Estimate (95%CI)	P	Fractional polynomial	Quadratic test	Cochran's Qtest	Cochran's Qtest	P for trend
Coronary artery diseases (n=39,818/280,311)				0.724	0.703	0.853	0.00	8.8×10 ⁻¹⁷
	1	1.03 (0.96, 1.11)	0.398					
	2	1.03 (0.95, 1.11)	0.532					
	3	1.07 (0.99, 1.16)	0.080					
	4	1.04 (0.97, 1.12)	0.281					
	Total	1.04 (1.00, 1.08)	0.038					
Heart failure (n=10,717/280,311)				0.888	0.793	0.221	0.00	2.3×10 ⁻¹⁶
	1	1.01 (0.90, 1.13)	0.914					
	2	1.11 (0.96, 1.28)	0.171					
	3	1.16 (1.00, 1.35)	0.054					
	4	0.96 (0.83, 1.10)	0.530					
	Total	1.04 (0.97, 1.11)	0.264					
Ischemic stroke (n=5,646/280,311)				0.879	0.783	0.866	0.00	2.5×10 ⁻¹⁵
	1	1.03 (0.87, 1.22)	0.753					

	2	0.92 (0.76, 1.12)	0.394					
	3	0.99 (0.82, 1.20)	0.918					
	4	0.98 (0.82, 1.17)	0.819					
	Total	0.98 (0.90, 1.08)	0.698					
Type 2 diabetes (n=24,790/303,807)				0.276	0.177	0.065	0.00	5.4×10 ⁻¹⁶
	1	1.02 (0.94, 1.11)	0.577					
	2	1.22 (1.10, 1.34)	7.2×10 ⁻⁵					
	3	1.13 (1.03, 1.25)	0.011					
	4	1.13 (1.04, 1.23)	5.4×10 ⁻³					
	Total	1.12 (1.07, 1.17)	1.3×10 ⁻⁶					

Odds ratios from Mendelian randomization represents the estimates for effect of a 1 unit increase of the hemoglobin-increasing genetic risk scores (GRS-Hgb), which equivalent to 1 SD increase in levels of hemoglobin, on outcome of interest after adjusting for age, sex, center, genotyping array, and genetic principal components (the first 10PCs).

Table S8. Mendelian randomization estimates of a 1-SD higher plasma levels of hemoglobin on risk of CAD, HF, IS and T2D using different MR methods

Outcome	Method	Hemoglobin		
		SNP	OR (95%CI)	P
Coronary artery disease (n=181,522/984,168)				
	Inverse variance weighted	137	1.00 (0.94, 1.06)	0.987
	Weighted median	137	0.95 (0.90, 1.00)	0.068
	Weighted mode	137	0.92 (0.86, 0.97)	0.004
	MR Egger	137	0.93 (0.82, 1.06)	0.269
	Egger intercept		0.00 (-0.00, 0.01)	0.203
Heart failure (n=115,150/1,550,331)				
	Inverse variance weighted	123	0.98 (0.94, 1.03)	0.454
	Weighted median	123	0.99 (0.93, 1.04)	0.666
	Weighted mode	123	0.99 (0.92, 1.06)	0.689
	MR Egger	123	1.07 (0.96, 1.18)	0.216
	Egger intercept		-0.00 (-0.01, 0.00)	0.069
Ischemic stroke (n=62,100/1,234,808)				
	Inverse variance weighted	108	1.10 (1.04, 1.16)	0.002
	Weighted median	108	1.05 (0.97, 1.13)	0.212
	Weighted mode	108	1.02 (0.95, 1.11)	0.557
	MR Egger	108	1.17 (1.04, 1.32)	0.008
	Egger intercept		-0.00 (-0.01, 0.00)	0.195
Type 2 diabetes (n=80,154/853,816)				
	Inverse variance weighted	110	1.07 (0.98, 1.16)	0.160
	Weighted median	110	1.01 (0.93, 1.10)	0.817
	Weighted mode	110	1.14 (1.02, 1.28)	0.021
	MR Egger	110	1.01 (0.85, 1.20)	0.934
	Egger intercept		0.00 (-0.00, 0.01)	0.470

Odds ratios represents the estimates for effect of a 1 SD increase in levels of hemoglobin on outcome of interest. Mendelian randomization was implemented through "TwoSampleMR" package in R-version 3.6.3. CAD=coronary artery disease; HF= heart failure; IS= Ischemic stroke; MR=Mendelian randomization; T2D=type 2 diabetes.

Table S9. Causal associations of hemoglobin with risk of cardiometabolic diseases in males of UK Biobank using semiparametric methods to assess nonlinear exposure-outcome relationships for Mendelian randomization

Outcome	Quartile	localized average causal effect		<i>P</i> for non-linearity tests			Heterogeneity tests	
		Estimate (95%CI)	<i>P</i>	Fractional polynomial	Quadratic test	Cochran's Qtest	Cochran's Qtest	<i>P</i> for trend
Coronary artery diseases (n=26,330/121,291)				0.798	0.793	0.123	2.1×10 ⁻⁵	0.004
	1	1.05 (0.97, 1.15)	0.239					
	2	1.07 (0.97, 1.17)	0.190					
	3	1.20 (1.09, 1.32)	1.6×10 ⁻⁴					
	4	1.04 (0.95, 1.14)	0.404					
	Total	1.08 (1.04, 1.13)	5.6×10 ⁻⁴					
Heart failure (n=7,064/121,291)				0.935	0.933	0.181	1.2×10 ⁻⁵	2.1×10 ⁻³
	1	1.00 (0.87, 1.14)	0.949					
	2	1.06 (0.89, 1.27)	0.482					
	3	1.23 (1.03, 1.47)	0.023					
	4	0.95 (0.81, 1.13)	0.573					
	Total	1.04 (0.96, 1.13)	0.317					
Ischemic stroke (n=3,532/121,291)				0.966	0.959	0.793	7.2×10 ⁻⁶	8.6×10 ⁻⁴
	1	1.07 (0.86, 1.31)	0.552					
	2	0.98 (0.78, 1.25)	0.897					

	3	1.16 (0.92, 1.47)	0.221					
	4	1.02 (0.82, 1.27)	0.853					
	Total	1.05 (0.94, 1.18)	0.357					
Type 2 diabetes (n=15,176/137,218)				0.768	0.753	0.874	2.3×10 ⁻⁶	4.8×10 ⁻⁵
	1	1.07 (0.97, 1.19)	0.191					
	2	1.15 (1.02, 1.29)	0.026					
	3	1.11 (0.98, 1.24)	0.094					
	4	1.10 (0.99, 1.23)	0.084					
	Total	1.10 (1.04, 1.17)	5.4×10 ⁻⁴					

Odds ratios from Mendelian randomization represents the estimates for effect of a 1 unit increase of the hemoglobin-increasing genetic risk scores (GRS-Hgb), which equivalent to 1 SD increase in levels of hemoglobin, on outcome of interest after adjusting for age, center, genotyping array, and genetic principal components (the first 10 PCs).

Table S10. Causal associations of hemoglobin with risk of cardiometabolic diseases in females of UK Biobank using semiparametric methods to assess nonlinear exposure-outcome relationships for Mendelian randomization

Outcome	Quartile	localized average causal effect		P for non-linearity tests			Heterogeneity tests	
		Estimate (95%CI)	P	Fractional polynomial	Quadratic test	Cochran's Qtest	Cochran's Qtest	P for trend
Coronary artery diseases (n=13,488/159,020)				0.504	0.237	0.369	0.00	6.6×10 ⁻¹⁵
	1	0.95 (0.84, 1.07)	0.405					
	2	0.89 (0.78, 1.01)	0.070					
	3	0.96 (0.84, 1.10)	0.568					

4	1.04 (0.92, 1.18)	0.505					
Total	0.96 (0.90, 1.02)	0.225					
Heart failure (n=3,653/159,020)			0.855	0.820	0.542	0.00	2.9×10^{-15}
1	1.04 (0.84, 1.29)	0.729					
2	1.13 (0.88, 1.44)	0.335					
3	0.87 (0.67, 1.13)	0.300					
4	1.05 (0.84, 1.33)	0.658					
Total	1.03 (0.91, 1.15)	0.660					
Ischemic stroke (n=2,114/159,020)			0.813	0.735	0.426	0.00	4.2×10^{-15}
1	0.93 (0.69, 1.25)	0.647					
2	0.69 (0.50, 0.95)	0.024					
3	0.83 (0.60, 1.14)	0.251					
4	0.97 (0.73, 1.30)	0.837					
Total	0.86 (0.74, 1.01)	0.060					
Type 2 diabetes (n=9,614/166,589)			0.212	0.027	0.030	0.00	8.5×10^{-15}
1	0.94 (0.82, 1.09)	0.422					
2	1.26 (1.07, 1.48)	4.6×10^{-3}					
3	1.12 (0.96, 1.31)	0.166					
4	1.22 (1.06, 1.39)	4.3×10^{-3}					

Total 1.13 (1.05, 1.22) 7.6×10⁻⁴

Odds ratios from Mendelian randomization represents the estimates for effect of a 1 unit increase of the hemoglobin-increasing genetic risk scores (GRS-Hgb), which equivalent to 1 SD increase in levels of hemoglobin, on outcome of interest after adjusting for age, center, genotyping array, and genetic principal components (the first 10PCs).

Table S11. Causal effects of a 1-SD higher hemoglobin level on transferrin saturation, serum iron, ferritin, and total iron binding capacity

MR method	Transferrin Saturation		Serum iron		Serum ferritin		Total iron binding capacity	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Inverse variance weighted	0.23 (0.12, 0.35)	8.3×10⁻⁵	0.20 (0.11, 0.30)	4.5×10⁻⁵	0.12 (0.06, 0.17)	7.3×10⁻⁵	-0.04 (-0.10, 0.02)	0.158
Weighted median	0.04 (-0.01, 0.09)	0.101	0.05 (0.00, 0.09)	0.033	-0.01 (-0.05, 0.03)	0.685	-0.01 (-0.06, 0.04)	0.605
Weighted mode	0.05 (-0.03, 0.13)	0.244	0.04 (-0.02, 0.09)	0.182	-0.08 (-0.15, -0.01)	0.018	-0.03 (-0.13, 0.08)	0.648
MR Egger	0.62 (0.41, 0.84)	8.9×10⁻⁸	0.54 (0.37, 0.72)	6.5×10⁻⁹	0.29 (0.19, 0.40)	1.2×10⁻⁷	-0.13 (-0.24, -0.02)	0.024
Egger intercept	-0.02 (-0.03, -0.01)	6.6×10⁻⁵	-0.02 (-0.02, -0.01)	1.0×10⁻⁵	-0.01 (-0.01, -0.00)	1.1×10⁻⁴	0.00 (-0.00, 0.01)	0.072

Estimates represent the effect of a 1 SD increase in levels of hemoglobin on transferrin saturation, serum iron, log-transformed serum ferritin, and total iron binding capacity respectively. Mendelian randomization was implemented through "TwoSampleMR" package in R-version 3.6.3. CI=confidence interval; SD=standard deviation.

Table S12. Mendelian randomization estimates of a 1-SD higher in levels of iron biomarkers on risk of other cardiometabolic diseases

Outcome	Method	Transferrin Saturation			Serum iron			Serum ferritin			Total iron binding capacity		
		SNP	OR (95%CI)	P	SNP	OR (95%CI)	P	SNP	OR (95%CI)	P	SNP	OR (95%CI)	P
Any stroke (n=73,652/1,234,808)													
	Inverse variance weighted	10	1.03 (0.96, 1.11)	0.404	13	1.05 (0.96, 1.15)	0.246	32	0.93 (0.82, 1.05)	0.246	14	1.00 (0.94, 1.05)	0.878
	Weighted median	10	1.03 (0.97, 1.09)	0.348	13	1.06 (0.97, 1.15)	0.213	32	0.97 (0.84, 1.10)	0.610	14	1.00 (0.96, 1.04)	0.979
	Weighted mode	10	1.03 (0.97, 1.09)	0.409	13	1.06 (0.98, 1.15)	0.203	32	1.00 (0.67, 1.48)	0.993	14	1.00 (0.97, 1.03)	0.977
	MR Egger	10	1.08 (0.96, 1.20)	0.224	13	1.07 (0.94, 1.23)	0.324	32	0.89 (0.69, 1.15)	0.382	14	1.00 (0.92, 1.08)	0.932
	Egger intercept		-0.01 (-0.02, 0.01)	0.336		-0.00 (-0.01, 0.01)	0.716		0.00 (-0.01, 0.01)	0.716		-0.00 (-0.01, 0.01)	0.964

Cardioembolic stroke (n=10,804/1,234,808)

Inverse variance weighted	9	1.03 (0.86, 1.23)	0.739	11	1.02 (0.82, 1.27)	0.832	29	1.00 (0.77, 1.29)	0.980	12	0.96 (0.85, 1.08)	0.467
Weighted median	9	1.03 (0.86, 1.25)	0.738	11	1.01 (0.78, 1.31)	0.940	29	1.18 (0.85, 1.62)	0.326	12	0.99 (0.90, 1.08)	0.804
Weighted mode	9	1.04 (0.82, 1.31)	0.767	11	0.85 (0.59, 1.21)	0.383	29	1.46 (0.93, 2.28)	0.108	12	0.98 (0.90, 1.07)	0.693
MR Egger	9	1.04 (0.78, 1.37)	0.813	11	0.97 (0.69, 1.36)	0.856	29	1.28 (0.68, 2.41)	0.450	12	1.02 (0.88, 1.17)	0.817
Egger intercept		-0.00 (-0.03, 0.03)	0.962		0.01 (-0.02, 0.03)	0.676		-0.01 (-0.03, 0.01)	0.401		-0.01 (-0.04, 0.01)	0.212

Large artery stroke (n=6,399/1,234,808)

Inverse variance weighted	7	1.07 (0.75, 1.54)	0.703	9	1.26 (0.78, 2.01)	0.343	27	0.96 (0.68, 1.37)	0.835	9	1.06 (0.82, 1.36)	0.655
Weighted median	7	1.35 (0.90, 2.04)	0.148	9	1.63 (1.04, 2.54)	0.034	27	0.79 (0.50, 1.26)	0.322	9	1.09 (0.96, 1.23)	0.204
Weighted mode	7	1.57 (0.82, 3.00)	0.219	9	1.75 (1.07, 2.87)	0.055	27	0.74 (0.43, 1.27)	0.280	9	1.11 (0.97, 1.26)	0.178
MR Egger	7	1.08 (0.51, 2.27)	0.852	9	2.19 (0.96, 5.00)	0.105	27	0.88 (0.34, 2.26)	0.788	9	1.12 (0.80, 1.57)	0.526
Egger intercept		-0.00 (-0.05, 0.05)	0.990		-0.03 (-0.07, 0.01)	0.165		0.00 (-0.03, 0.04)	0.834		-0.01 (-0.06, 0.04)	0.610

Small vessel stroke (n=6,811/1,234,808)

Inverse variance weighted	5	0.93 (0.69, 1.26)	0.648	7	1.09 (0.75, 1.61)	0.644	24	0.85 (0.57, 1.27)	0.430	7	1.03 (0.87, 1.23)	0.702
Weighted median	5	0.85 (0.60, 1.21)	0.377	7	0.96 (0.59, 1.55)	0.860	24	0.70 (0.44, 1.10)	0.118	7	1.05 (0.92, 1.18)	0.478
Weighted mode	5	0.85 (0.60, 1.20)	0.417	7	0.88 (0.50, 1.56)	0.675	24	0.63 (0.33, 1.21)	0.182	7	1.04 (0.92, 1.17)	0.563
MR Egger	5	0.54 (0.25, 1.20)	0.227	7	0.52 (0.17, 1.60)	0.306	24	0.85 (0.28, 2.53)	0.766	7	1.03 (0.81, 1.32)	0.807
Egger intercept		0.04 (-0.01, 0.09)	0.243		0.03 (-0.01, 0.08)	0.226		0.00 (-0.04, 0.04)	0.989		0.00 (-0.04, 0.04)	0.983

Odds ratios represents the estimates for effect of 1 SD increase in levels of transferrin saturation, serum iron, log-transformed serum ferritin, and total iron binding capacity respectively, on outcomes of interest. Mendelian randomization was implemented through "TwoSampleMR" package in R-version 3.6.3.

Table S13. Mendelian randomization estimates of a 1-SD higher plasma levels of iron biomarkers on risk of CAD, HF, IS, and T2D using different MR methods

Outcome	Method	Transferrin Saturation			Serum iron			Serum ferritin			Total iron binding capacity		
		SNP	OR (95%CI)	P	SNP	OR (95%CI)	P	SNP	OR (95%CI)	P	SNP	OR (95%CI)	P
Coronary artery disease (n=71,602/261,418)													
	Inverse variance weighted	10	0.93 (0.88, 0.98)	7.9×10⁻³	14	0.91 (0.83, 0.99)	0.033	36	0.86 (0.77, 0.96)	6.4×10⁻³	15	1.04 (0.96, 1.12)	0.379
	Weighted median	10	0.95 (0.91, 0.98)	5.8×10⁻³	14	0.91 (0.86, 0.95)	1.2×10⁻⁴	36	0.91 (0.84, 0.99)	0.029	15	1.03 (1.00, 1.05)	0.070
	Weighted mode	10	0.94 (0.91, 0.97)	6.0×10⁻³	14	0.92 (0.88, 0.95)	8.5×10⁻⁴	36	0.97 (0.88, 1.08)	0.601	15	1.02 (1.00, 1.05)	0.088
	MR Egger	10	0.94 (0.87, 1.02)	0.198	14	0.95 (0.83, 1.08)	0.432	36	0.92 (0.75, 1.12)	0.409	15	0.99 (0.90, 1.09)	0.887

Egger intercept		-0.00 (-0.01, 0.01)	0.660		-0.00 (-0.02, 0.01)	0.404		-0.00 (-0.01, 0.01)	0.482		0.01 (-0.00, 0.02)	0.181
Heart failure (n=115,150/1,550,331)												
Inverse variance weighted	10	0.98 (0.95, 1.01)	0.168	14	0.98 (0.94, 1.02)	0.333	33	0.96 (0.90, 1.02)	0.191	15	1.01 (0.99, 1.04)	0.342
Weighted median	10	0.97 (0.93, 1.01)	0.106	14	0.96 (0.91, 1.01)	0.152	33	1.01 (0.93, 1.09)	0.856	15	1.02 (0.99, 1.05)	0.185
Weighted mode	10	0.97 (0.93, 1.01)	0.169	14	0.97 (0.93, 1.02)	0.276	33	0.98 (0.89, 1.07)	0.615	15	1.02 (0.99, 1.04)	0.261
MR Egger	10	0.98 (0.94, 1.03)	0.472	14	0.98 (0.92, 1.04)	0.506	33	0.97 (0.85, 1.10)	0.603	15	1.02 (0.98, 1.06)	0.316
Egger intercept		-0.00 (-0.01, 0.00)	0.811		0.00 (-0.00, 0.01)	0.963		-0.00 (-0.01, 0.00)	0.860		-0.00 (-0.01, 0.00)	0.620
Ischemic stroke (n=62,100/1,234,808)												
Inverse variance weighted	10	1.02 (0.95, 1.11)	0.557	13	1.04 (0.94, 1.14)	0.427	32	0.91 (0.80, 1.04)	0.171	13	0.99 (0.94, 1.05)	0.811
Weighted median	10	1.01 (0.95, 1.08)	0.683	13	1.03 (0.95, 1.13)	0.458	32	0.90 (0.78, 1.04)	0.157	13	1.00 (0.96, 1.04)	0.944
Weighted mode	10	1.02 (0.95, 1.09)	0.676	13	1.03 (0.94, 1.13)	0.495	32	0.89 (0.69, 1.15)	0.398	13	1.00 (0.96, 1.04)	0.836
MR Egger	10	1.07 (0.95, 1.20)	0.308	13	1.07 (0.92, 1.23)	0.393	32	0.88 (0.67, 1.14)	0.336	13	1.00 (0.92, 1.08)	0.952
Egger intercept		-0.01 (-0.02, 0.01)	0.373		-0.00 (-0.01, 0.01)	0.627		0.00 (-0.01, 0.01)	0.722		-0.00 (-0.01, 0.01)	0.853
Type 2 diabetes (n=80,154/853,816)												
Inverse variance weighted	10	1.07 (1.01, 1.13)	0.015	13	1.05 (0.97, 1.15)	0.238	32	1.04 (0.88, 1.23)	0.625	13	0.95 (0.90, 1.01)	0.127
Weighted median	10	1.09 (1.04, 1.14)	3.0×10⁻⁴	13	1.06 (0.99, 1.14)	0.098	32	1.22 (1.09, 1.37)	4.3×10⁻⁴	13	0.96 (0.92, 1.00)	0.038
Weighted mode	10	1.09 (1.04, 1.14)	4.4×10⁻³	13	1.07 (1.02, 1.13)	0.022	32	1.23 (1.09, 1.37)	1.4×10⁻³	13	0.96 (0.93, 0.99)	0.041
MR Egger	10	1.10 (1.02, 1.19)	0.046	13	1.14 (1.02, 1.28)	0.041	32	1.37 (1.01, 1.85)	0.053	13	0.96 (0.88, 1.04)	0.293
Egger intercept		-0.00 (-0.01, 0.01)	0.366		-0.01 (-0.02, 0.00)	0.078		-0.01 (-0.03, -0.00)	0.049		-0.00 (-0.01, 0.01)	0.944

Odds ratios represents the estimates for effect of 1 SD increase in levels of transferrin saturation, serum iron, log-transformed serum ferritin, and total iron binding capacity respectively, on outcomes of interest. Mendelian randomization was implemented through "TwoSampleMR" package in R-version 3.6.3.

Table S14. Sensitivity analyses of Mendelian randomization estimates of a 1-SD higher plasma levels of iron biomarkers on CAD, HF, IS, and T2D using variants after excluding LDL-C related variant HFE (p. Cys282Tyr)-rs1800562

Outcome	Method	Transferrin Saturation			Serum iron			Serum ferritin			Total iron binding capacity		
		SNP	OR (95%CI)	P	SNP	OR (95%CI)	P	SNP	OR (95%CI)	P	SNP	OR (95%CI)	P
Coronary artery disease (n=71,602/261,418)													
	Inverse variance weighted	9	0.92 (0.86, 0.99)	0.026	13	0.91 (0.82, 1.01)	0.068	35	0.87 (0.77, 0.97)	0.013	14	1.03 (0.94, 1.13)	0.571
	Weighted median	9	0.95 (0.90, 1.00)	0.051	13	0.93 (0.88, 0.98)	4.9×10⁻³	35	0.99 (0.91, 1.08)	0.824	14	1.01 (0.98, 1.04)	0.371
	Weighted mode	9	0.94 (0.89, 0.98)	0.025	13	0.92 (0.87, 0.96)	3.6×10⁻³	35	1.00 (0.91, 1.09)	0.945	14	1.01 (0.98, 1.05)	0.370

MR Egger	9	0.94 (0.83, 1.06)	0.338	13	0.96 (0.81, 1.13)	0.613	35	0.94 (0.75, 1.18)	0.591	14	0.97 (0.87, 1.09)	0.641
Egger intercept		-0.00 (-0.01, 0.01)	0.799		-0.01 (-0.02, 0.01)	0.406		-0.00 (-0.01, 0.01)	0.418		0.01 (-0.00, 0.02)	0.159
Heart failure (n=115,150/1,550,331)												
Inverse variance weighted	9	0.98 (0.94, 1.02)	0.394	13	0.99 (0.95, 1.03)	0.620	32	0.96 (0.90, 1.03)	0.281	14	1.01 (0.98, 1.04)	0.606
Weighted median	9	0.98 (0.93, 1.03)	0.409	13	0.98 (0.93, 1.04)	0.478	32	1.01 (0.94, 1.10)	0.748	14	1.01 (0.98, 1.04)	0.403
Weighted mode	9	0.97 (0.93, 1.02)	0.305	13	0.98 (0.93, 1.04)	0.570	32	1.00 (0.90, 1.11)	0.951	14	1.01 (0.98, 1.04)	0.412
MR Egger	9	1.00 (0.93, 1.07)	0.945	13	0.99 (0.93, 1.07)	0.879	32	0.98 (0.85, 1.13)	0.824	14	1.01 (0.97, 1.06)	0.545
Egger intercept		-0.00 (-0.01, 0.00)	0.608		-0.00 (-0.01, 0.00)	0.837		-0.00 (-0.01, 0.00)	0.723		-0.00 (-0.01, 0.00)	0.715
Ischemic stroke (n=62,100/1,234,808)												
Inverse variance weighted	9	1.02 (0.92, 1.14)	0.652	12	1.04 (0.93, 1.16)	0.499	31	0.90 (0.79, 1.03)	0.131	12	1.00 (0.93, 1.07)	0.915
Weighted median	9	1.00 (0.91, 1.09)	0.943	12	1.01 (0.91, 1.12)	0.830	31	0.89 (0.76, 1.03)	0.120	12	1.00 (0.96, 1.05)	0.874
Weighted mode	9	1.03 (0.93, 1.13)	0.601	12	1.04 (0.93, 1.15)	0.534	31	0.81 (0.64, 1.03)	0.092	12	1.00 (0.96, 1.04)	0.961
MR Egger	9	1.11 (0.93, 1.33)	0.294	12	1.08 (0.90, 1.29)	0.437	31	0.83 (0.62, 1.11)	0.217	12	1.00 (0.91, 1.10)	0.952
Egger intercept		-0.01 (-0.03, 0.01)	0.320		-0.00 (-0.02, 0.01)	0.622		0.00 (-0.01, 0.02)	0.530		-0.00 (-0.01, 0.01)	0.826
Type 2 diabetes (n=80,154/853,816)												
Inverse variance weighted	9	1.05 (0.98, 1.12)	0.207	12	1.02 (0.93, 1.12)	0.721	31	1.01 (0.84, 1.20)	0.938	12	0.97 (0.90, 1.04)	0.440
Weighted median	9	1.05 (0.98, 1.12)	0.187	12	1.03 (0.96, 1.10)	0.455	31	1.13 (1.01, 1.27)	0.039	12	0.98 (0.95, 1.02)	0.324
Weighted mode	9	1.03 (0.97, 1.09)	0.345	12	1.03 (0.97, 1.10)	0.323	31	1.17 (1.03, 1.34)	0.024	12	0.98 (0.94, 1.02)	0.354
MR Egger	9	1.08 (0.95, 1.22)	0.291	12	1.10 (0.96, 1.27)	0.195	31	1.31 (0.93, 1.86)	0.136	12	0.98 (0.89, 1.08)	0.702
Egger intercept		-0.00 (-0.02, 0.01)	0.611		-0.01 (-0.02, 0.00)	0.164		-0.01 (-0.03, 0.00)	0.096		-0.00 (-0.01, 0.01)	0.779

Odds ratios represents the estimates for effect of 1 SD increase in levels of transferrin saturation, serum iron, log-transformed serum ferritin, and total iron binding capacity respectively, on outcomes of interest. Mendelian randomization was implemented through "TwoSampleMR" package in R-version 3.6.3.

Table S15. Sensitivity analysis of Mendelian randomization estimates of a 1-SD higher plasma levels of iron biomarkers on CAD, HF, IS, and T2D using four variants that are associated with systemic iron status [DUOX2 (p. His678Arg)-rs57659670, HFE (p. Cys282Tyr)-rs1800562, TMPRSS6 (p. Val749Ala)-rs855791, HFE (p. H63D)-rs1799945]

Outcome	Method	Transferrin Saturation		Serum iron		Serum ferritin		Total iron binding capacity	
		OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Coronary artery disease (n=71,602/261,418)									
	Inverse variance weighted	0.94 (0.90, 0.97)	1.1×10⁻³	0.92 (0.88, 0.95)	2.2×10⁻⁵	0.88 (0.74, 1.05)	0.166	1.06 (0.97, 1.16)	0.180
	Weighted median	0.94 (0.90, 0.98)	2.8×10⁻³	0.91 (0.86, 0.95)	5.6×10⁻⁵	0.92 (0.82, 1.04)	0.191	1.06 (1.01, 1.10)	0.012

Weighted mode	0.94 (0.91, 0.98)	0.062	0.91 (0.86, 0.95)	0.028	0.96 (0.86, 1.08)	0.556	1.06 (1.01, 1.10)	0.092
MR Egger	0.95 (0.86, 1.05)	0.429	0.89 (0.77, 1.02)	0.229	1.09 (0.81, 1.46)	0.631	1.02 (0.92, 1.12)	0.779
Egger intercept	-0.00 (-0.03, 0.02)	0.797	0.01 (-0.02, 0.03)	0.670	-0.02 (-0.04, 0.00)	0.255	0.01 (-0.00, 0.03)	0.278
Heart failure (n=115,150/1,550,331)								
Inverse variance weighted	0.98 (0.95, 1.02)	0.374	0.98 (0.93, 1.03)	0.376	0.98 (0.88, 1.09)	0.681	1.02 (0.97, 1.08)	0.500
Weighted median	0.97 (0.93, 1.01)	0.129	0.96 (0.92, 1.01)	0.127	0.97 (0.87, 1.08)	0.561	1.02 (0.97, 1.07)	0.427
Weighted mode	0.97 (0.93, 1.01)	0.244	0.96 (0.92, 1.01)	0.204	0.98 (0.87, 1.11)	0.789	1.03 (0.98, 1.08)	0.372
MR Egger	0.97 (0.88, 1.07)	0.581	0.94 (0.81, 1.09)	0.500	1.01 (0.79, 1.30)	0.924	1.01 (0.93, 1.10)	0.766
Egger intercept	0.00 (-0.02, 0.02)	0.763	0.01 (-0.02, 0.03)	0.622	-0.00 (-0.02, 0.02)	0.780	0.00 (-0.01, 0.01)	0.883
Ischemic stroke (n=62,100/1,234,808)								
Inverse variance weighted	1.04 (0.91, 1.19)	0.531	1.05 (0.89, 1.25)	0.551	0.95 (0.65, 1.40)	0.807	0.96 (0.80, 1.15)	0.660
Weighted median	1.02 (0.95, 1.10)	0.581	1.02 (0.93, 1.12)	0.622	0.95 (0.74, 1.23)	0.695	0.95 (0.88, 1.03)	0.212
Weighted mode	1.02 (0.96, 1.09)	0.548	1.03 (0.94, 1.12)	0.594	0.83 (0.67, 1.04)	0.201	0.96 (0.88, 1.06)	0.475
MR Egger	1.16 (0.84, 1.60)	0.471	1.36 (0.83, 2.24)	0.347	0.70 (0.30, 1.63)	0.498	0.95 (0.71, 1.27)	0.774
Egger intercept	-0.03 (-0.10, 0.05)	0.557	-0.05 (-0.13, 0.04)	0.395	0.03 (-0.04, 0.10)	0.503	0.00 (-0.05, 0.05)	0.945
Type 2 diabetes (n=80,154/853,816)								
Inverse variance weighted	1.08 (1.00, 1.16)	0.050	1.08 (0.97, 1.21)	0.142	1.27 (1.13, 1.43)	9.4×10⁻⁵	0.89 (0.83, 0.96)	1.3×10⁻³
Weighted median	1.09 (1.04, 1.15)	9.2×10⁻⁴	1.09 (1.03, 1.17)	6.7×10⁻³	1.30 (1.15, 1.48)	4.2×10⁻⁵	0.90 (0.85, 0.95)	1.6×10⁻⁴
Weighted mode	1.09 (1.04, 1.14)	0.030	1.08 (1.01, 1.15)	0.114	1.32 (1.13, 1.53)	0.039	0.90 (0.85, 0.96)	0.041
MR Egger	1.07 (0.88, 1.29)	0.570	1.01 (0.70, 1.46)	0.975	1.43 (1.12, 1.82)	0.102	0.91 (0.82, 1.00)	0.203
Egger intercept	0.00 (-0.04, 0.04)	0.946	0.01 (-0.05, 0.08)	0.719	-0.01 (-0.03, 0.01)	0.393	-0.00 (-0.02, 0.01)	0.643

Odds ratios represents the estimates for effect of 1 SD increase in levels of transferrin saturation, serum iron, log-transformed serum ferritin, and total iron binding capacity respectively, on outcomes of interest. Mendelian randomization was implemented through "TwoSampleMR" package in R-version 3.6.3.

Table S16. Causal effects of a 1-SD higher plasma levels of iron biomarkers on selected cardiometabolic risk factors

Risk factor	N	Transferrin Saturation			Serum iron			Serum ferritin			Total iron binding capacity		
		SNP	Estimates (95%CI)	P	SNP	Estimates (95%CI)	P	SNP	Estimates (95%CI)	P	SNP	Estimates (95%CI)	P
Education	1,131,881	10	0.01 (-0.00, 0.03)	0.146	14	0.01 (-0.01, 0.03)	0.268	35	-0.00 (-0.03, 0.03)	0.836	15	-0.01 (-0.02, 0.01)	0.229
Ever smoker	518,633	10	1.00 (0.99, 1.01)	0.889	14	1.00 (0.99, 1.02)	0.694	35	1.00 (0.97, 1.03)	0.941	15	1.00 (0.99, 1.01)	0.901

Anthropometric measurements

BMI (kg/m ²)	806,834	10	-0.01 (-0.02, 0.01)	0.21	14	-0.01 (-0.03, 0.01)	0.434	35	0.01 (-0.04, 0.05)	0.737	15	0.01 (-0.00, 0.02)	0.299
WC (cm)	210,088	10	0.02 (0.00, 0.04)	0.039	13	0.03 (-0.00, 0.05)	0.05	27	0.03 (-0.05, 0.10)	0.504	13	-0.01 (-0.03, 0.01)	0.252
WHR	697,734	10	0.00 (-0.01, 0.01)	0.341	14	0.00 (-0.02, 0.02)	0.926	35	0.00 (-0.04, 0.05)	0.865	15	-0.00 (-0.02, 0.01)	0.496
HIP (cm)	210,088	10	0.02 (-0.00, 0.05)	0.053	13	0.03 (0.00, 0.06)	0.029	27	0.06 (-0.03, 0.14)	0.195	12	-0.01 (-0.03, 0.01)	0.426
Height (cm)	693,529	10	0.04 (0.01, 0.07)	0.002	13	0.04 (0.01, 0.08)	0.016	27	0.02 (-0.08, 0.11)	0.719	14	-0.03 (-0.06, 0.00)	0.074
Birth weight (kg)	298,142	10	0.01 (-0.01, 0.03)	0.505	14	0.01 (-0.03, 0.05)	0.634	35	-0.00 (-0.05, 0.04)	0.9	15	-0.01 (-0.02, 0.01)	0.384

Glycaemic traits

FG (mmol/L)	281,416	10	-0.00 (-0.02, 0.01)	0.443	14	-0.01 (-0.03, 0.01)	0.381	36	-0.01 (-0.07, 0.05)	0.666	15	-0.00 (-0.03, 0.02)	0.8
FI (mmol/L)	281,416	10	-0.01 (-0.02, 0.00)	0.075	14	-0.01 (-0.03, 0.00)	0.063	36	-0.05 (-0.10, 0.00)	0.056	15	0.00 (-0.01, 0.02)	0.406
2h glucose	281,416	10	0.03 (-0.02, 0.09)	0.251	14	0.05 (-0.03, 0.13)	0.194	36	0.15 (0.03, 0.27)	0.015	15	-0.00 (-0.05, 0.05)	0.985
Hba1c (%)	281,416	10	-0.10 (-0.13, -0.07)	1.9×10⁻⁹	14	-0.13 (-0.16, -0.09)	2.1×10⁻¹⁰	36	-0.13 (-0.23, -0.03)	0.008	15	0.04 (0.00, 0.09)	0.047

Blood lipids

HDL (mmol/L)	1,320,016	10	0.00 (-0.02, 0.03)	0.988	14	-0.01 (-0.04, 0.03)	0.729	37	-0.03 (-0.07, 0.01)	0.148	15	-0.02 (-0.08, 0.04)	0.477
LDL (mmol/L)	1,320,016	10	-0.09 (-0.14, -0.04)	2.4×10⁻⁴	14	-0.10 (-0.19, -0.01)	0.026	37	-0.16 (-0.29, -0.02)	0.020	15	0.04 (-0.05, 0.12)	0.391
TC (mmol/L)	1,320,016	10	-0.07 (-0.12, -0.02)	5.9×10⁻³	14	-0.08 (-0.16, -0.00)	0.042	37	-0.12 (-0.26, 0.03)	0.126	15	0.02 (-0.06, 0.11)	0.604
TG (mmol/L)	1,320,016	10	0.03 (0.01, 0.04)	5.8×10⁻⁴	14	0.03 (0.01, 0.06)	0.010	37	0.10 (-0.08, 0.28)	0.264	15	0.00 (-0.08, 0.08)	0.957
Non-HDL (mmol/L)	1,320,016	10	-0.07 (-0.12, -0.03)	2.2×10⁻³	14	-0.08 (-0.16, -0.01)	0.028	37	-0.11 (-0.26, 0.04)	0.156	15	0.03 (-0.05, 0.11)	0.459

Blood pressure

SBP (mm Hg)	757,601	10	0.58 (-0.15, 1.30)	0.118	14	0.68 (-0.16, 1.51)	0.113	31	-0.23 (-1.58, 1.11)	0.734	15	-0.22 (-0.80, 0.35)	0.449
DBP (mm Hg)	757,601	10	0.62 (0.09, 1.16)	0.022	14	0.72 (0.12, 1.31)	0.019	32	0.27 (-0.58, 1.12)	0.537	15	-0.32 (-0.75, 0.10)	0.138
PP (mm Hg)	757,601	10	-0.05 (-0.43, 0.34)	0.819	14	-0.04 (-0.55, 0.47)	0.871	31	-0.51 (-1.20, 0.17)	0.143	15	0.09 (-0.20, 0.37)	0.558
Imaging													
Liver fat	32,858	10	0.01 (-0.03, 0.06)	0.554	14	0.02 (-0.05, 0.08)	0.577	33	0.04 (-0.06, 0.15)	0.409	15	0.01 (-0.02, 0.05)	0.477
Liver iron	32,858	10	0.87 (0.61, 1.12)	3.5×10⁻¹¹	14	0.99 (0.60, 1.38)	4.8×10⁻⁷	33	0.99 (0.50, 1.49)	8.8×10⁻⁵	15	-0.51 (-0.83, -0.19)	0.002
Liver volume	32,860	10	0.04 (-0.00, 0.07)	0.07	14	0.04 (-0.04, 0.12)	0.37	33	0.13 (-0.01, 0.27)	0.064	15	-0.02 (-0.07, 0.04)	0.534
Pancreas iron	25,617	10	-0.02 (-0.07, 0.03)	0.462	14	-0.03 (-0.09, 0.03)	0.36	33	-0.09 (-0.18, -0.01)	0.03	15	0.01 (-0.03, 0.05)	0.66
Other risk factors													
eGFR	1,201,909	10	0.01 (0.00, 0.01)	0.021	14	0.01 (0.00, 0.01)	0.028	33	0.01 (0.00, 0.02)	0.024	15	-0.00 (-0.01, 0.00)	0.157
CRP	318,271	10	0.05 (0.02, 0.08)	2.4×10⁻⁴	14	-0.01 (-0.32, 0.30)	0.964	31	0.08 (-0.06, 0.22)	0.247	14	-0.02 (-0.06, 0.01)	0.214

Effect estimates were expressed as odds ratio (95%CI) otherwise as beta (95%CI) represents the estimates for effect of a 1 SD increase in levels of transferrin saturation, serum iron, log-transformed serum ferritin, and total iron binding capacity on outcomes of interest. Mendelian randomization was implemented through “TwoSampleMR” package in R-version 3.6.3 and the estimates were calculated from inverse weighted variance method. BMI=Body-mass index; CI=confidence interval; CRP=C reactive protein; DBP=diastolic blood pressure; FG=Fasting glucose; FI=Fasting insulin; Hba1c=hemoglobin A1c; HDL=high density lipoprotein cholesterol; HIP=Hip circumference; LDL=low density lipoprotein cholesterol; PP=pulse pressure; SBP=systolic blood pressure; TC=Total cholesterol; TG=Triglycerides; WC=Waist circumference; WHR=Waist-to-hip ratio.

Table S17. Sensitivity analysis of Mendelian randomization estimates of a 1-SD higher plasma levels of iron biomarkers on selected cardiometabolic risk factors by limiting variants not associated with LDL-C

Risk factor	N	Transferrin Saturation			Serum iron			Serum ferritin			Total iron binding capacity		
		SNP	Estimates (95%CI)	P	SNP	Estimates (95%CI)	P	SNP	Estimates (95%CI)	P	SNP	Estimates (95%CI)	P
Education	1,131,881	9	0.02 (0.01, 0.04)	0.001	13	0.02 (-0.00, 0.04)	0.097	34	-0.00 (-0.03, 0.03)	0.978	14	-0.01 (-0.03, 0.00)	0.06

Ever smoker	518,633	9	1.00 (0.99, 1.01)	0.976	13	1.00 (0.98, 1.02)	0.749	34	1.00 (0.97, 1.03)	0.991	14	1.00 (0.99, 1.01)	0.761
Anthropometric measurements													
BMI (kg/m ²)	806,834	9	0.00 (-0.01, 0.02)	0.793	13	0.00 (-0.02, 0.03)	0.914	34	0.02 (-0.03, 0.07)	0.381	14	-0.00 (-0.01, 0.01)	0.532
WC (cm)	210,088	9	0.03 (0.01, 0.06)	0.013	12	0.03 (0.00, 0.06)	0.035	26	0.03 (-0.06, 0.11)	0.51	12	-0.02 (-0.05, 0.01)	0.218
WHR	697,734	9	0.00 (-0.01, 0.02)	0.65	13	-0.00 (-0.02, 0.02)	0.76	34	0.00 (-0.05, 0.05)	0.966	14	-0.00 (-0.02, 0.01)	0.68
HIP (cm)	210,088	9	0.03 (0.00, 0.06)	0.035	12	0.04 (0.00, 0.07)	0.026	26	0.06 (-0.03, 0.16)	0.202	11	-0.01 (-0.04, 0.02)	0.517
Height (cm)	693,529	9	0.01 (-0.01, 0.04)	0.273	12	0.01 (-0.01, 0.04)	0.36	26	-0.03 (-0.12, 0.07)	0.581	13	-0.01 (-0.05, 0.03)	0.556
Birth weight (kg)	298,142	9	0.00 (-0.02, 0.03)	0.804	13	0.01 (-0.04, 0.05)	0.794	34	-0.01 (-0.06, 0.04)	0.736	14	-0.01 (-0.02, 0.01)	0.597
Glycaemic traits													
FG (mmol/L)	281,416	9	-0.01 (-0.02, 0.00)	0.179	13	-0.01 (-0.03, 0.01)	0.245	35	-0.02 (-0.08, 0.05)	0.609	14	-0.00 (-0.03, 0.03)	0.858
FI (mmol/L)	281,416	9	-0.01 (-0.03, 0.00)	0.052	13	-0.02 (-0.03, 0.00)	0.059	35	-0.05 (-0.11, 0.00)	0.051	14	0.01 (-0.01, 0.02)	0.463
2h glucose	281,416	9	0.02 (-0.05, 0.09)	0.616	13	0.04 (-0.05, 0.13)	0.389	35	0.14 (0.02, 0.27)	0.028	14	0.02 (-0.04, 0.08)	0.47
Hba1c (%)	281,416	9	-0.11 (-0.15, -0.07)	8.0×10⁻⁷	13	-0.12 (-0.17, -0.08)	2.2×10⁻⁷	35	-0.11 (-0.21, -0.01)	0.035	14	0.03 (-0.02, 0.08)	0.267
Blood lipids													
HDL (mmol/L)	1,320,016	9	0.00 (-0.03, 0.04)	0.932	13	-0.01 (-0.05, 0.03)	0.733	36	-0.03 (-0.07, 0.01)	0.139	14	-0.03 (-0.10, 0.04)	0.402
LDL (mmol/L)	1,320,016	9	-0.06 (-0.12, -0.00)	0.043	13	-0.06 (-0.16, 0.03)	0.201	36	-0.12 (-0.26, 0.01)	0.077	14	-0.00 (-0.09, 0.09)	0.950
TC (mmol/L)	1,320,016	9	-0.04 (-0.11, 0.02)	0.186	13	-0.05 (-0.14, 0.04)	0.272	36	-0.09 (-0.24, 0.07)	0.282	14	-0.01 (-0.11, 0.08)	0.779
TG (mmol/L)	1,320,016	9	0.04 (0.02, 0.06)	4.8×10⁻⁴	13	0.04 (0.01, 0.07)	0.022	36	0.11 (-0.08, 0.29)	0.272	14	0.01 (-0.09, 0.11)	0.850
Non-HDL (mmol/L)	1,320,016	9	-0.04 (-0.10, 0.01)	0.130	13	-0.05 (-0.13, 0.03)	0.230	36	-0.08 (-0.24, 0.08)	0.334	14	-0.00 (-0.09, 0.09)	0.924
Blood pressure													
SBP (mm Hg)	757,601	9	0.57 (-0.44, 1.58)	0.271	13	0.58 (-0.43, 1.58)	0.26	30	-0.54 (-1.97, 0.88)	0.454	14	-0.07 (-0.76, 0.63)	0.845

DBP (mm Hg)	757,601	9	0.46 (-0.27, 1.19)	0.216	13	0.49 (-0.19, 1.16)	0.158	31	-0.09 (-0.94, 0.75)	0.828	14	-0.10 (-0.58, 0.38)	0.675
PP (mm Hg)	757,601	9	0.11 (-0.41, 0.63)	0.68	13	0.09 (-0.51, 0.68)	0.781	30	-0.46 (-1.21, 0.28)	0.22	14	0.02 (-0.33, 0.36)	0.929
Imaging													
Liver fat	32,858	9	0.00 (-0.06, 0.06)	0.964	13	0.01 (-0.07, 0.09)	0.829	32	0.04 (-0.08, 0.15)	0.52	14	0.03 (-0.01, 0.07)	0.156
Liver iron	32,858	9	0.55 (0.39, 0.72)	3.2×10⁻¹¹	13	0.59 (0.41, 0.78)	2.2×10⁻¹⁰	32	0.52 (0.25, 0.79)	1.6×10⁻⁴	14	-0.17 (-0.40, 0.06)	0.155
Liver volume	32,860	9	0.04 (-0.01, 0.09)	0.121	13	0.03 (-0.06, 0.13)	0.512	32	0.14 (-0.01, 0.29)	0.077	14	-0.01 (-0.07, 0.05)	0.744
Pancreas iron	25,617	9	-0.01 (-0.08, 0.05)	0.646	13	-0.03 (-0.11, 0.05)	0.48	32	-0.10 (-0.19, -0.01)	0.036	14	0.00 (-0.04, 0.05)	0.895
Other risk factors													
eGFR	1,201,909	9	0.01 (-0.00, 0.01)	0.104	13	0.01 (-0.00, 0.01)	0.134	32	0.01 (-0.00, 0.02)	0.061	14	-0.00 (-0.01, 0.00)	0.483
CRP	318,271	9	0.04 (0.00, 0.08)	0.035	13	-0.05 (-0.43, 0.33)	0.797	30	0.06 (-0.09, 0.21)	0.418	13	-0.00 (-0.05, 0.04)	0.848

Effect estimates were expressed as odds ratio (95%CI) otherwise as beta (95%CI) represents the estimates for effect of a 1 SD increase in levels of transferrin saturation, serum iron, log-transformed serum ferritin, and total iron binding capacity on outcomes of interest. Mendelian randomization was implemented through "TwoSampleMR" package in R-version 3.6.3 and the estimates were calculated from inverse weighted variance method. BMI=Body-mass index; CI=confidence interval; CRP=C reactive protein; DBP=diastolic blood pressure; FG=Fasting glucose; FI=Fasting insulin; Hba1c=hemoglobin A1c; HDL=high density lipoprotein cholesterol; HIP=Hip circumference; LDL=low density lipoprotein cholesterol; PP=pulse pressure; SBP=systolic blood pressure; TC=Total cholesterol; TG=Triglycerides; WC=Waist circumference; WHR=Waist-to-hip ratio.

Table S18. Sensitivity analyses of Mendelian randomization estimates of a 1-SD higher plasma levels of iron biomarkers on selected cardiometabolic risk factors by using four variants that associated with systemic iron status [DUOX2 (p. His678Arg)-rs57659670, HFE (p. Cys282Tyr)-rs1800562, TMPRSS6 (p. Val749Ala)-rs855791, HFE (p. H63D)-rs1799945]

Risk factor	N	Transferrin Saturation		Serum iron		Serum ferritin		Total iron binding capacity	
		Estimates (95%CI)	P	Estimates (95%CI)	P	Estimates (95%CI)	P	Estimates (95%CI)	P
Education	1,131,881	0.01 (-0.01, 0.03)	0.389	0.02 (-0.01, 0.04)	0.199	0.01 (-0.06, 0.07)	0.824	0.00 (-0.03, 0.03)	0.996
Ever smoker	518,633	1.00 (0.99, 1.01)	0.773	1.00 (0.99, 1.02)	0.737	1.01 (0.98, 1.05)	0.477	1.00 (0.98, 1.01)	0.833

Anthropometric measurements

BMI (kg/m ²)	806,834	-0.01 (-0.03, 0.01)	0.329	-0.01 (-0.03, 0.02)	0.541	-0.01 (-0.07, 0.05)	0.676	0.02 (-0.00, 0.04)	0.055
WC (cm)	210,088	0.02 (0.00, 0.05)	0.04	0.03 (0.01, 0.06)	0.021	0.07 (-0.01, 0.15)	0.081	-0.02 (-0.06, 0.03)	0.441
WHR	697,734	0.00 (-0.01, 0.02)	0.383	0.01 (-0.01, 0.02)	0.455	0.01 (-0.02, 0.04)	0.689	-0.01 (-0.02, 0.01)	0.339
HIP (cm)	210,088	0.03 (0.00, 0.06)	0.029	0.04 (0.01, 0.07)	0.005	0.10 (-0.00, 0.19)	0.051	-0.02 (-0.08, 0.04)	0.477
Height (cm)	693,529	0.04 (0.01, 0.08)	0.026	0.05 (-0.01, 0.11)	0.121	0.08 (-0.07, 0.24)	0.288	-0.07 (-0.10, -0.03)	1.3×10⁻⁴
Birth weight (kg)	298,142	0.00 (-0.01, 0.02)	0.525	0.01 (-0.01, 0.03)	0.58	0.01 (-0.03, 0.06)	0.491	-0.01 (-0.03, 0.01)	0.452

Glycemic traits

FG (mmol/L)	281,416	-0.00 (-0.02, 0.01)	0.633	-0.00 (-0.02, 0.01)	0.611	-0.01 (-0.06, 0.03)	0.616	0.00 (-0.02, 0.02)	0.772
FI (mmol/L)	281,416	-0.01 (-0.02, 0.00)	0.056	-0.02 (-0.03, -0.00)	0.044	-0.03 (-0.07, 0.00)	0.091	0.01 (-0.01, 0.03)	0.272
2h glucose	281,416	0.04 (-0.01, 0.09)	0.108	0.05 (-0.01, 0.12)	0.11	0.14 (-0.00, 0.29)	0.057	-0.05 (-0.12, 0.02)	0.152
Hba1c (%)	281,416	-0.10 (-0.12, -0.08)	5.4×10⁻²⁶	-0.13 (-0.15, -0.10)	2.7×10⁻²⁹	-0.22 (-0.42, -0.02)	0.032	0.11 (0.01, 0.20)	0.024

Blood lipids

HDL (mmol/L)	1,320,016	0.00 (-0.01, 0.01)	0.648	0.00 (-0.01, 0.02)	0.436	0.00 (-0.02, 0.03)	0.887	0.00 (-0.01, 0.01)	0.800
LDL (mmol/L)	1,320,016	-0.10 (-0.13, -0.06)	6.3×10⁻⁷	-0.11 (-0.19, -0.04)	3.9×10⁻³	-0.20 (-0.41, 0.00)	0.055	0.13 (0.09, 0.17)	5.1×10⁻¹²
TC (mmol/L)	1,320,016	-0.08 (-0.12, -0.04)	1.8×10⁻⁴	-0.09 (-0.16, -0.01)	0.020	-0.16 (-0.34, 0.02)	0.082	0.11 (0.08, 0.13)	7.8×10⁻¹⁷
TG (mmol/L)	1,320,016	0.03 (0.01, 0.05)	2.2×10⁻³	0.04 (0.02, 0.07)	4.6×10⁻⁵	0.09 (0.02, 0.15)	0.011	-0.03 (-0.08, 0.01)	0.178
Non-HDL (mmol/L)	1,320,016	-0.08 (-0.12, -0.04)	2.7×10⁻⁴	-0.09 (-0.16, -0.01)	0.022	-0.16 (-0.35, 0.03)	0.107	0.11 (0.08, 0.14)	2.9×10⁻¹³

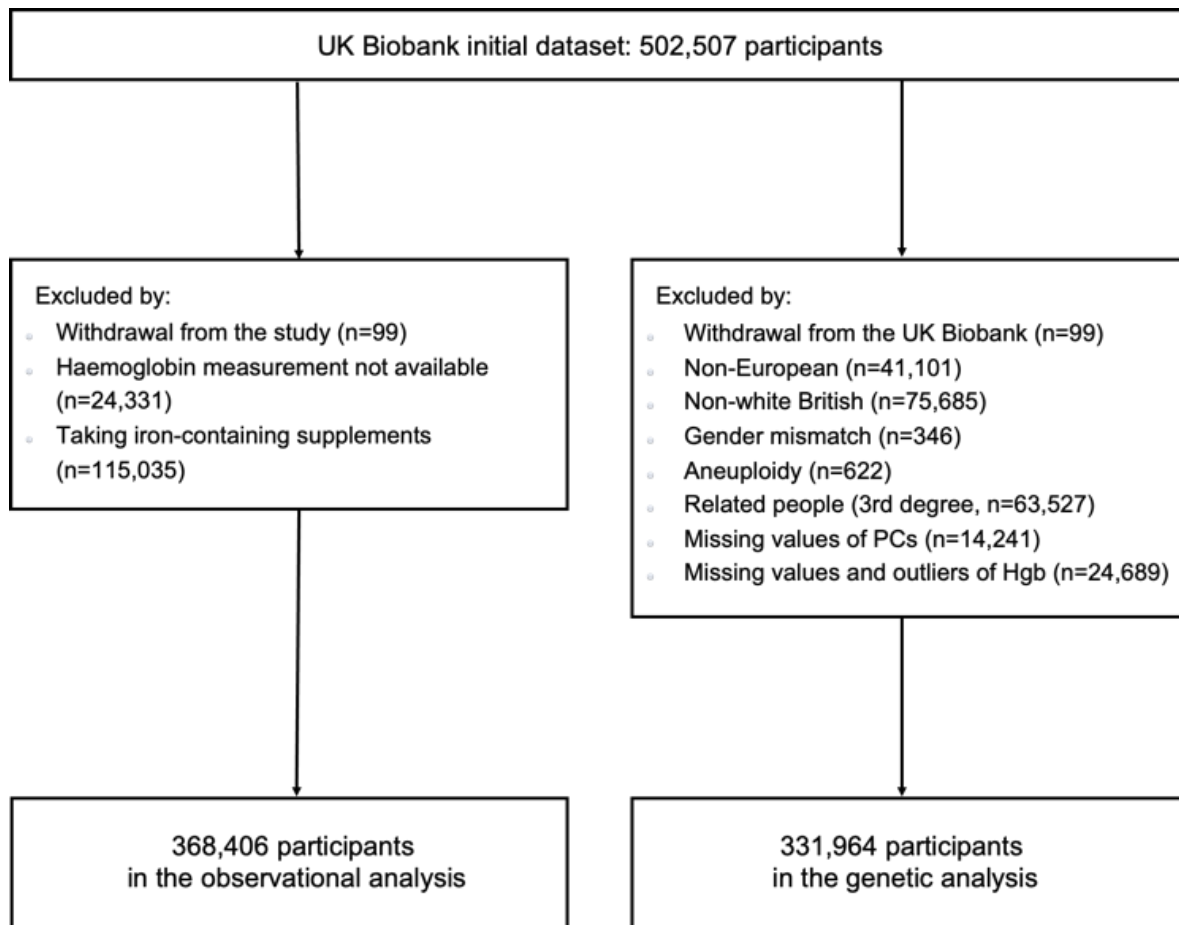
Blood pressure

SBP (mm Hg)	757,601	0.71 (-0.52, 1.94)	0.257	0.81 (-0.84, 2.46)	0.337	1.36 (-2.38, 5.10)	0.476	-0.96 (-2.54, 0.62)	0.232
DBP (mm Hg)	757,601	0.83 (0.13, 1.54)	0.021	0.98 (-0.06, 2.02)	0.064	1.79 (-0.73, 4.31)	0.163	-1.08 (-2.00, -0.17)	0.02

PP (mm Hg)	757,601	-0.12 (-0.65, 0.41)	0.658	-0.16 (-0.84, 0.52)	0.638	-0.45 (-1.87, 0.97)	0.537	0.13 (-0.57, 0.83)	0.713
Imaging									
Liver fat	32,858	0.02 (-0.02, 0.07)	0.33	0.03 (-0.03, 0.08)	0.405	0.05 (-0.08, 0.17)	0.449	-0.03 (-0.09, 0.03)	0.272
Liver iron	32,858	0.97 (0.61, 1.33)	1.3×10⁻⁷	1.14 (0.39, 1.90)	0.003	2.17 (0.18, 4.17)	0.033	-1.28 (-1.59, -0.98)	2.8×10⁻¹⁶
Liver volume	32,860	0.04 (-0.01, 0.09)	0.092	0.05 (-0.01, 0.12)	0.12	0.13 (0.02, 0.25)	0.022	-0.05 (-0.12, 0.01)	0.129
Pancreas iron	25,617	-0.03 (-0.08, 0.02)	0.304	-0.04 (-0.10, 0.03)	0.301	-0.08 (-0.22, 0.06)	0.279	0.03 (-0.04, 0.10)	0.383
Other risk factors									
eGFR	1,201,909	0.01 (-0.00, 0.01)	0.083	0.01 (-0.00, 0.02)	0.118	0.02 (0.01, 0.03)	1.7×10⁻⁵	-0.01 (-0.02, 0.00)	0.078
CRP	318,271	0.07 (0.05, 0.08)	1.3×10⁻¹⁹	0.08 (0.06, 0.11)	2.3×10⁻¹⁰	0.16 (0.06, 0.25)	0.001	-0.08 (-0.12, -0.03)	6.4×10⁻⁴

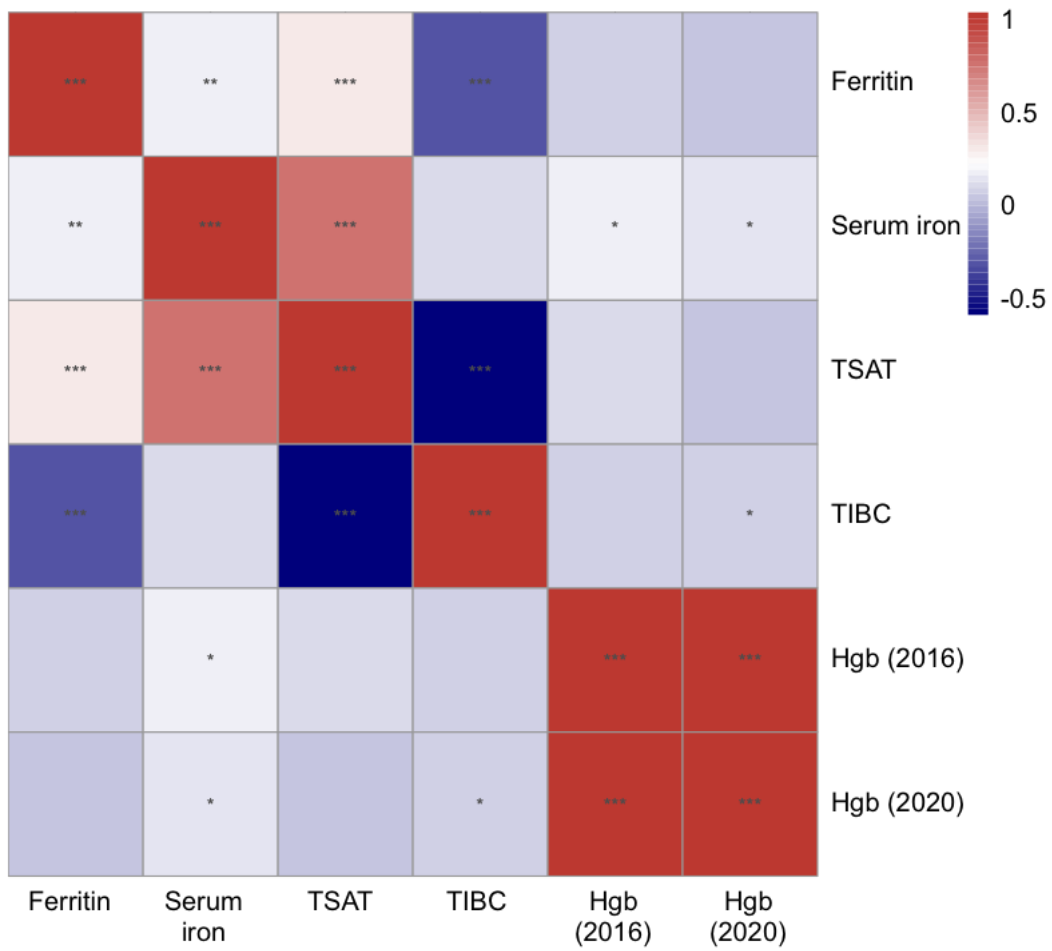
Effect estimates were expressed as odds ratio (95%CI) otherwise as beta (95%CI) represents the estimates for effect of a 1 SD increase in levels of transferrin saturation, serum iron, log-transformed serum ferritin, and total iron binding capacity on outcomes of interest. Mendelian randomization was implemented through "TwoSampleMR" package in R-version 3.6.3 and the estimates were calculated from inverse weighted variance method. BMI=Body-mass index; CI=confidence interval; CRP=C reactive protein; DBP=diastolic blood pressure; FG=Fasting glucose; FI=Fasting insulin; Hba1c=hemoglobin A1c; HDL=high density lipoprotein cholesterol; HIP=Hip circumference; LDL=low density lipoprotein cholesterol; PP=pulse pressure; SBP=systolic blood pressure; TC=Total cholesterol; TG=Triglycerides; WC=Waist circumference; WHR=Waist-to-hip ratio.

Figure S1. Flow diagram of participants in UK Biobank



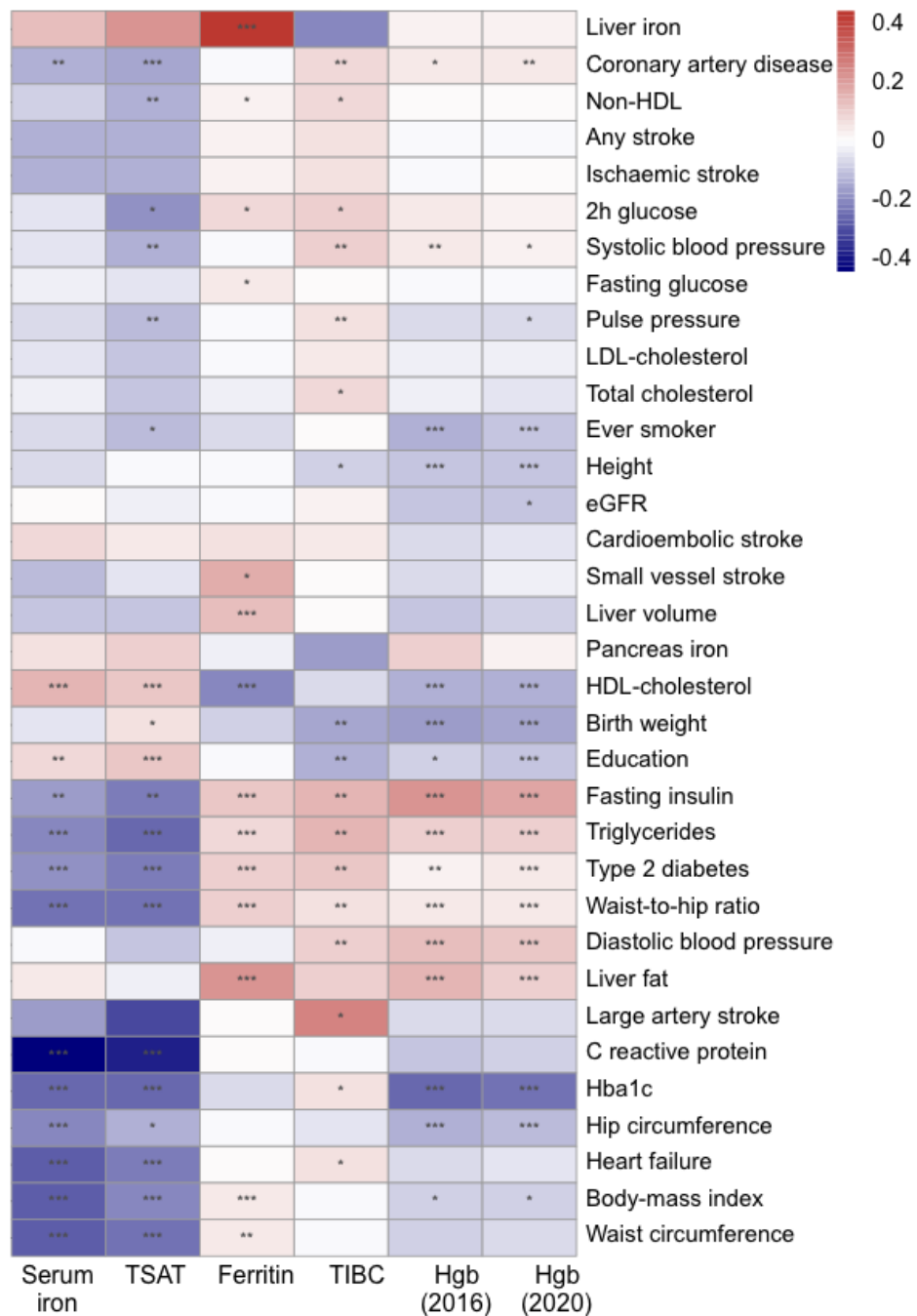
Abbreviations: Hgb=hemoglobin; PC=principal component.

Figure S2. Genetic correlations between iron biomarkers and hemoglobin



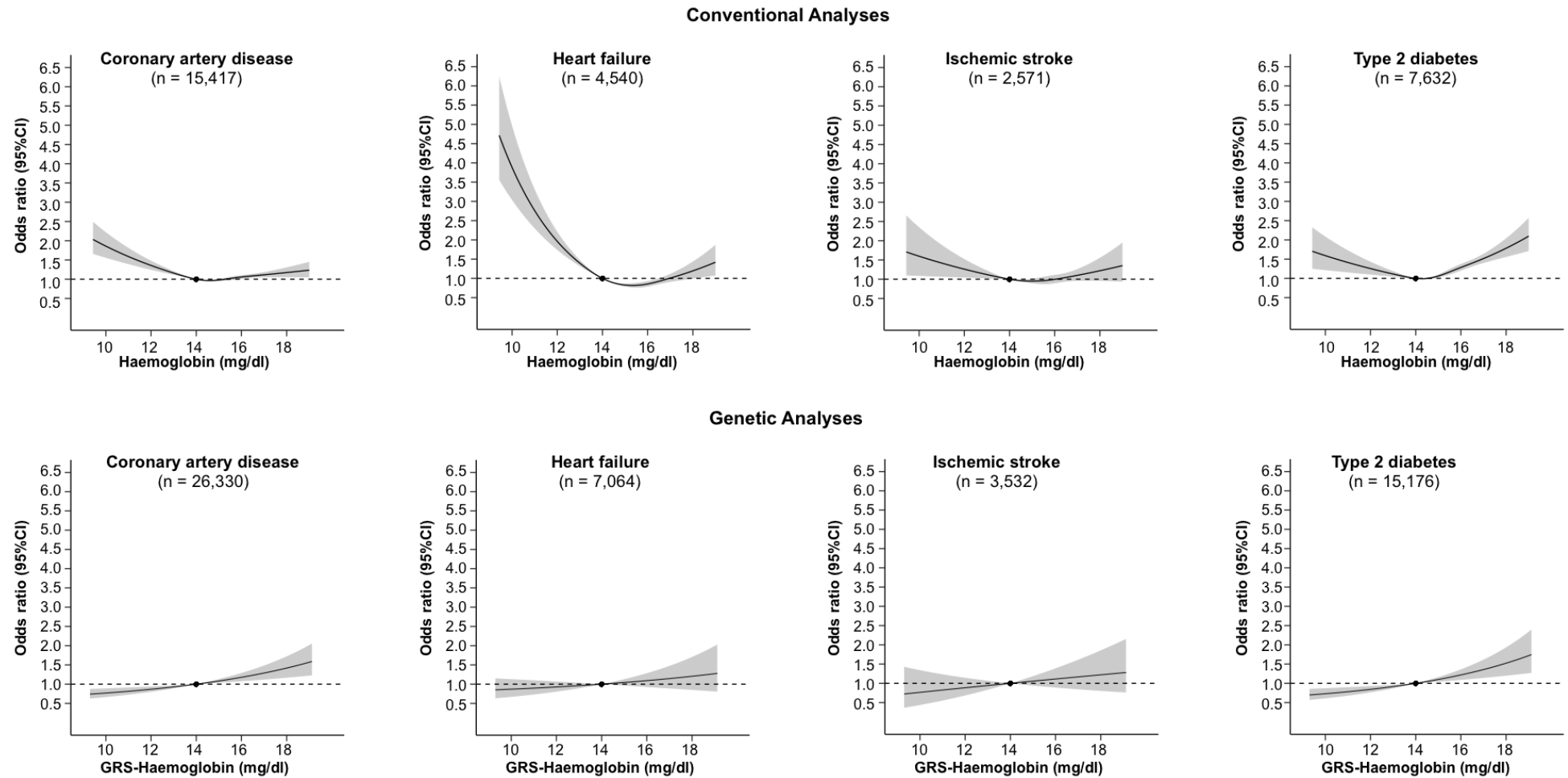
Genetic correlation was performed in LDSC (Version-1.0.1), and significant associations were indicated by the * symbol (*: $0.01 < p \leq 0.05$, **: $0.001 < p \leq 0.01$, ***: $p \leq 0.001$). Hgb=hemoglobin; TIBC=total iron binding capacity; TSAT=transferrin saturation.

Figure S3. Genetic correlations of iron biomarkers and hemoglobin with different phenotypes collected from GWAS consortia



Genetic correlation was performed in LDSC (Version-1.0.1), and significant associations were indicated by the * symbol (*: $0.01 < p \leq 0.05$, **: $0.001 < p \leq 0.01$, ***: $p \leq 0.001$). Hgb=hemoglobin; TIBC=total iron binding capacity; TSAT=transferrin saturation; eGFR=estimated glomerular filtration rate.

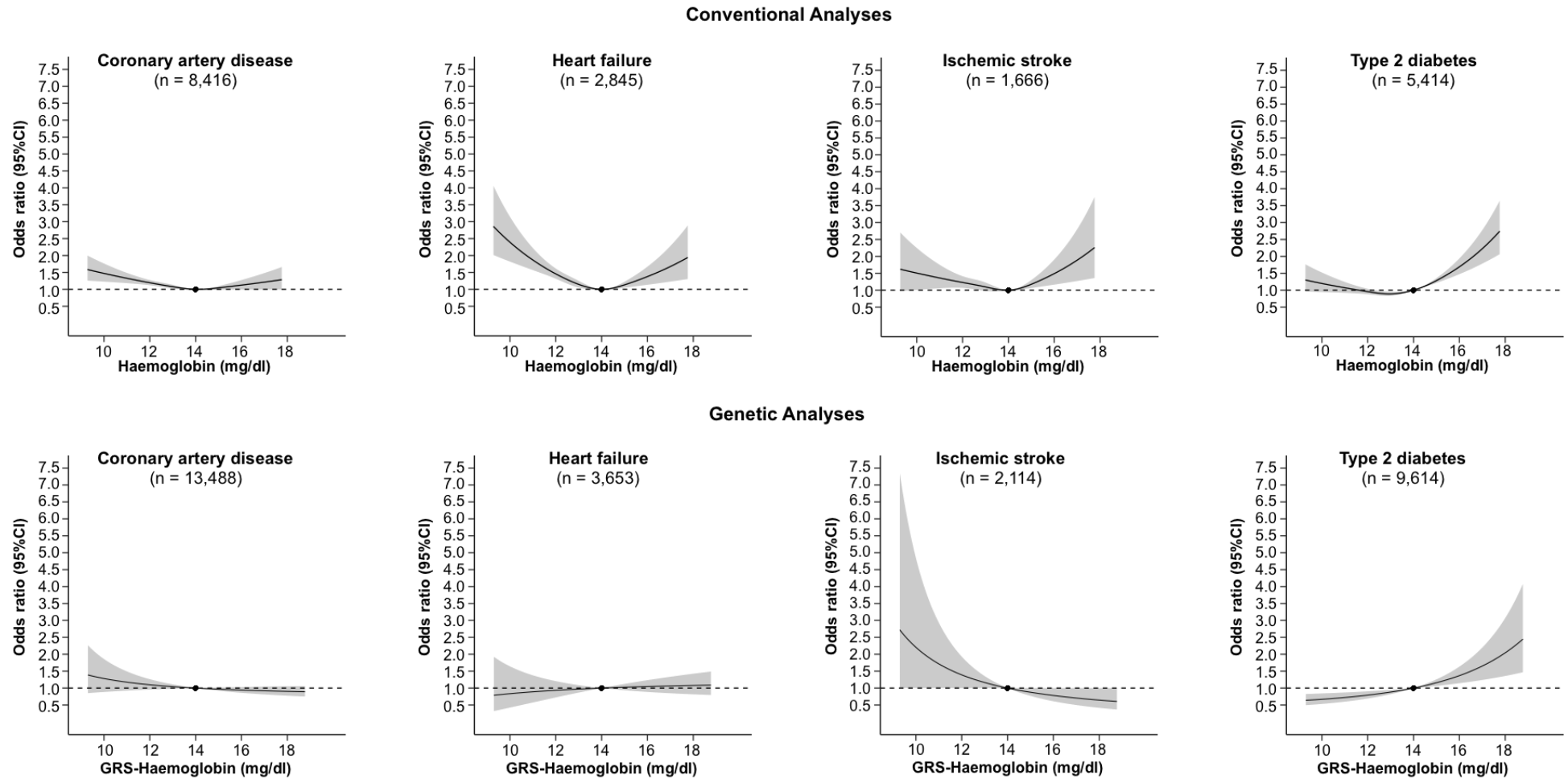
Figure S4. Associations of hemoglobin with coronary artery disease, heart failure, ischemic stroke, and type 2 diabetes in males of UK Biobank



Associations for hemoglobin with coronary artery disease, heart failure, ischemic stroke, and type 2 diabetes were obtained from conventional analyses and non-linear Mendelian randomization using the fractional polynomial method on data of UK Biobank. We used multivariable logistic regression in observational analysis to estimate the risk of incident cardiometabolic diseases among individuals by levels of hemoglobin after adjusting sociodemographic factors (age, ethnicity, and education), socioeconomic status (Townsend deprivation index), family history of CVD or diabetes, smoking status, alcohol intake,

physical activity, BMI, baseline diabetes, medication use (antihypertensive or cholesterol-lowering drugs), SBP, and triglycerides where appropriate. Odds ratios from Mendelian randomization represents the estimates for effect of a 1 unit increase of the hemoglobin-increasing genetic risk scores (GRS-Hgb), which equivalent to 1 SD increase in levels of hemoglobin, on outcome of interest after adjusting age, center, genotyping array, and genetic principal components (the first 10 PCs). BMI=Body-mass index; CVD=cardiovascular disease; GRS=genetic risk score; SBP=systolic blood pressure.

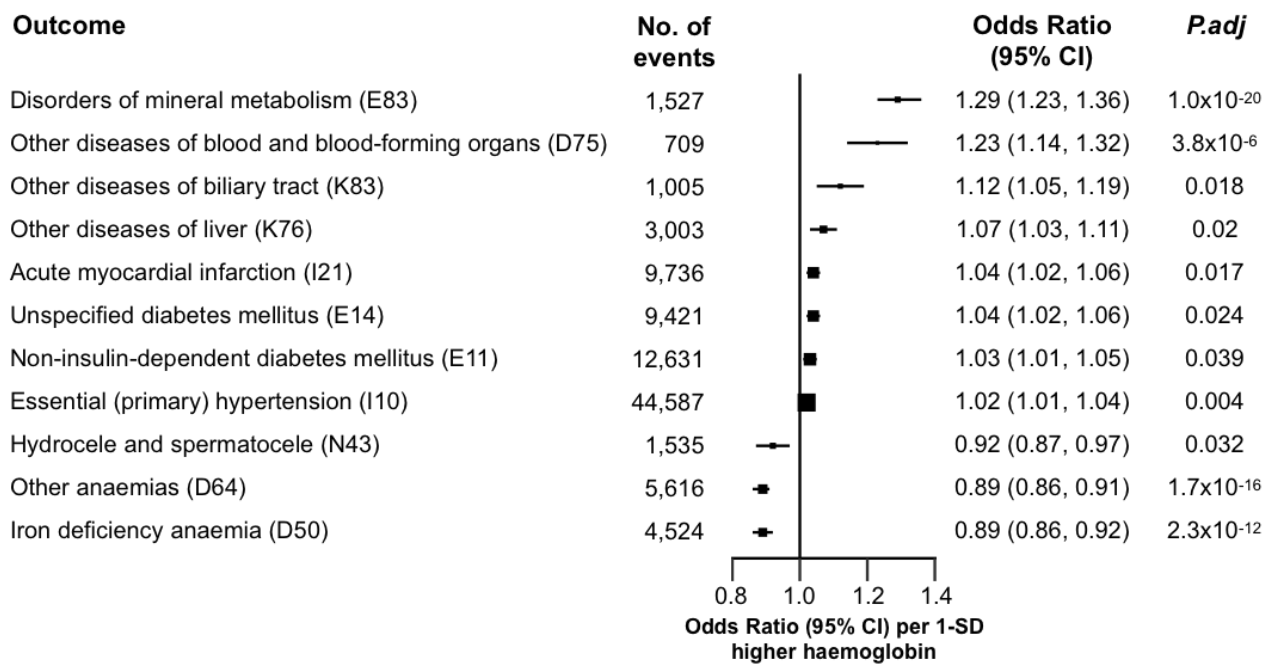
Figure S5. Associations of hemoglobin with coronary artery disease, heart failure, ischemic stroke, and type 2 diabetes in females of UK Biobank



Associations for hemoglobin with coronary artery disease, heart failure, ischemic stroke, and type 2 diabetes were obtained from conventional analyses and non-linear Mendelian randomization using the fractional polynomial method on data of UK Biobank. We used multivariable logistic regression in observational analysis to estimate the risk of incident cardiometabolic diseases among individuals by levels of hemoglobin after adjusting sociodemographic factors (age, ethnicity, and education), socioeconomic status (Townsend deprivation index), family history of CVD or diabetes, smoking status, alcohol intake,

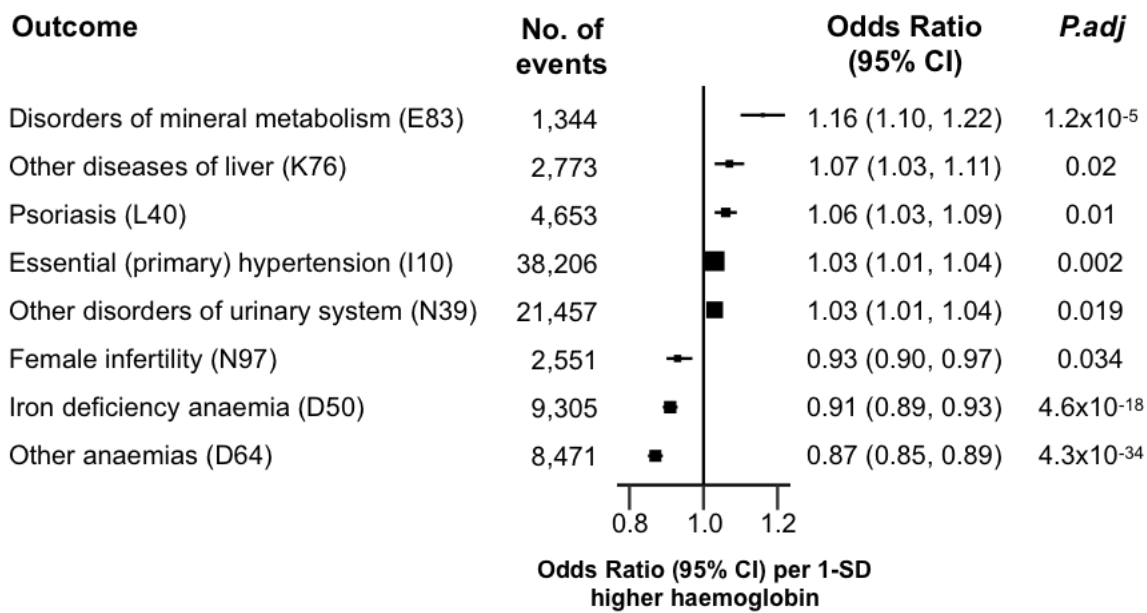
physical activity, BMI, baseline diabetes, medication use (antihypertensive or cholesterol-lowering drugs), SBP, and triglycerides where appropriate. Odds ratios from Mendelian randomization represents the estimates for effect of a 1 unit increase of the hemoglobin-increasing genetic risk scores (GRS-Hgb), which equivalent to 1 SD increase in levels of hemoglobin, on outcome of interest after adjusting age, center, genotyping array, and genetic principal components (the first 10 PCs). BMI=Body-mass index; CVD=cardiovascular disease; GRS=genetic risk score; SBP=systolic blood pressure.

Figure S6. Associations of a polygenic risk score for hemoglobin with different disease outcomes in males in UK Biobank



Odds ratios obtained from PheWAS represent the estimates for effect of a 1 unit increase of the hemoglobin-increasing genetic risk scores (GRS-Hgb), which equivalent to 1 SD increase in levels of hemoglobin, on outcome of interest after adjusting age, center, genotyping array, and genetic principal components (the first 10 PCs). We included events that were more than 500 cases in our analyses (319 diseases) and showed the associations that survived after correction for multiple testing. ICD-10 codes were also shown in the parentheses for each outcome above. Error bars represent 95% confidence intervals. All statistical tests were two-sided, following a correction for multiple testing using a strategy controlling for the false discovery rate. CI=confidence interval; GRS=genetic risk score; ICD=International Classification of Diseases; PC=principal component; PheWAS=phenome-wide association studies; SD=standard deviation.

Figure S7. Associations of a polygenic risk score for hemoglobin with different disease outcomes in females in UK Biobank



Odds ratios obtained from PheWAS represent the estimates for effect of a 1 unit increase of the hemoglobin-increasing genetic risk scores (GRS-Hgb), which equivalent to 1 SD increase in levels of hemoglobin, on outcome of interest after adjusting age, center, genotyping array, and genetic principal components (the first 10 PCs). We included events that involved more than 500 cases in our analysis (376 diseases) and showed the associations that survived after correction for the multiple testing. ICD-10 codes were also shown in the parentheses for each outcome above. Error bars represent 95% confidence intervals. All statistical tests were two-sided, following a correction for multiple testing using a strategy controlling for the false discovery rate. CI=confidence interval; GRS=genetic risk score; ICD=International Classification of Diseases; PC=principal component; PheWAS=phenome-wide association studies; SD=standard deviation.