

Supplementary Table 1. Summary statistics for cortisol-associated SNPs using as instrumental variables

SNP	Chr	nearby gene	EAF	Position	EA	OA	Beta	SE	P	F-statistic
rs11621961	14	SERPINA6	0.36	94769476	T	C	-0.08	0.01	4.0×10^{-8}	30.2
rs12589136	14	SERPINA6	0.22	94793686	T	G	0.10	0.01	3.3×10^{-12}	48.6
rs2749527	14	SERPINA1	0.49	94827068	T	C	-0.08	0.01	5.2×10^{-11}	43.2

Abbreviations: SNP, single-nucleotide polymorphism; Chr, chromosome; EAF, effect allele frequency; EA, effect allele; OA, other allele; SE, standard error; P, p value; GWAS, genome-wide association study.

Instrumental variables were selected from CORNET consortium (Bolton JL, et al. **PLOS Genetics**. 2014; 10(7): e10004474.

Supplementary Table 2. Data sources used for the MR analysis

	Traits	Sample size	Population	Consortium or cohort study (Link URL)
Exposure	Plasma cortisol	12,597	European	CORNET(28) (https://datashare.is.ed.ac.uk/handle/10283/2787)*
Outcome	Grip strength	461,026	European	UK Biobank (MRC IEU) (29) (https://doi.org/10.5523/bris.2fahpksont1zi26xosyamqo8rr)*
	WBLM	454,850		
	ALM	450,243	European	Pei YF, et al. (30)*
Using for multivariable MR and MR-BMA analyses	Fasting glucose	58,074	European	MAGIC (31) (https://magicinvestigators.org)*
	Fasting insulin	51,750		
	HOMA-IR	37,037		
	BMI	461,460	European	UK Biobank (MRC IEU) (29) (https://doi.org/10.5523/bris.2fahpksont1zi26xosyamqo8rr)*
	Waist circumference	462,166	Mixed	GLGC (32) (http://csg.sph.umich.edu/willer/public/lipids2013/)*
	Triglycerides	177,861		
	HDL cholesterol	187,167		
Testosterone	312,102			
Outcome for sex stratified analysis	Grip strength Men	166,424	European	UK Biobank (Neale Lab) (33) (http://www.nealelab.is/uk-biobank)
	Grip strength Women	193,280		
	WBLM Men	163,815		
	WBLM Women	190,993		
	ALM Men	205,513	European	Pei YF, et al. (30)*
	ALM Women	244,730		

*, Summary results were obtained through the MR-Base platform (database version v3.0.0 -2020-09-02) (34).

Abbreviations: MR, Mendelian randomization; BMA, Bayesian model averaging; CORNET, Cortisol Network; WBLM, whole body lean mass; ALM, appendicular lean mass; BMI, body mass index; MRC-IEU, MRC Integrative Epidemiology Unit; HOMA-IR, homeostasis model assessment for insulin resistance; MAGIC, the Meta-Analyses of Glucose and Insulin-related traits Consortium; HDL cholesterol, high density lipoprotein cholesterol; GLGC, The Global Lipids Genetics

Supplementary Table 3. Summary statistics for association of instrumental variables with muscle strength and mass

SNP	EA	OA	Grip strength			WBLM			ALM		
			Beta	SE	P	Beta	SE	P	Beta	SE	P
rs11621961	T	C	0.0023	0.0015	0.13	0.0034	0.0013	0.0069	0.0042	0.0020	0.033
rs12589136	T	G	-0.0032	0.0018	0.082	-0.0024	0.0015	0.11	-0.0016	0.0023	0.50
rs2749527	T	C	0.0027	0.0015	0.068	0.0025	0.0012	0.045	0.0024	0.0019	0.20

Abbreviations: SNP, single-nucleotide polymorphism; EA, effect allele; OA, other allele; WBLM, whole body lean mass; ALM, appendicular lean mass; SE, standard error, P, p value.

Supplementary Table 4.

Summary statistics for association of instrumental variables with muscle strength and mass in men and women

SNP	EA	OA	Grip strength						WBLM					
			MEN			Women			MEN			Women		
			Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P
rs11621961	T	C	7×10^{-4}	0.003	0.85	0.002	0.003	0.47	-3×10^{-4}	0.004	0.94	0.012	0.003	4×10^{-4}
rs12589136	T	G	-0.004	0.004	0.37	-0.004	0.004	0.23	-0.002	0.004	0.61	-0.004	0.004	0.26
rs2749527	T	C	0.002	0.003	0.66	0.007	0.003	0.01	-0.001	0.003	0.71	0.008	0.003	0.01
SNP	EA	OA	ALM											
			MEN			Women								
			Beta	SE	Beta	SE	Beta	SE						
rs11621961	T	C	5×10^{-4}	0.003	0.72	0.007	0.003	0.02						
rs12589136	T	G	-0.002	0.004	0.60	-0.001	0.003	0.73						
rs2749527	T	C	6×10^{-5}	0.003	0.79	0.004	0.003	0.07						

Abbreviations: SNP, single-nucleotide polymorphism; WBLM, whole body lean mass; ALM; appendicular lean mass; EA, effect allele; OA, other allele; SE, standard error, P, p value

Supplementary Table 5. Summary statistics for association of instrumental variables with traits using for multivariable MR

SNP	EA	OA	Fasting glucose			Fasting insulin			HOMA-IR		
			Beta	SE	P	Beta	SE	P	Beta	SE	P
rs11621961	T	C	-0.0016	0.0035	0.64	0.0024	0.0035	0.50	0.001	0.0046	0.76
rs12589136	T	G	3×10^{-4}	0.0038	0.93	6×10^{-4}	0.0038	0.88	0.024	0.0048	0.62
rs2749527	T	C	-9×10^{-4}	0.0031	0.78	-0.0015	0.0032	0.64	0.001	0.0040	0.86
SNP	EA	OA	BMI			Waist circumference			Triglycerides		
			Beta	SE	P	Beta	SE	P	Beta	SE	P
rs11621961	T	C	-0.0014	0.0020	0.50	-2×10^{-5}	0.0018	0.99	-0.008	0.0051	0.28
rs12589136	T	G	-0.0024	0.0024	0.33	-0.003	0.0022	0.80	0.003	0.0057	0.89
rs2749527	T	C	-0.0013	0.0019	0.50	5×10^{-4}	0.0018	0.42	7×10^{-4}	0.0046	0.62

SNP	EA	OA	HDL cholesterol			Testosterone		
			Beta	SE	P	Beta	SE	P
rs11621961	T	C	0.0072	0.0053	0.18	0.01	0.01	0.10
rs12589136	T	G	0.0011	0.0058	0.66	-0.01	0.01	0.55
rs2749527	T	C	0.0001	0.0048	0.93	0.01	0.01	0.55

Abbreviations: SNP, single-nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error, P, p value; HOMA-IR, homeostasis model assessment for insulin resistance; BMI, Body mass index; HDL cholesterol, high density lipoprotein cholesterol.

Supplementary Table 6. The functional grades of RegulomeDB

Category	Description
Likely to affect binding and linked to expression of a gene target	
1a	eQTL + TF binding + matched TF motif + matched DNase footprint + DNase peak
1b	eQTL + TF binding + any motif + DNase footprint + DNase peak
1c	eQTL + TF binding + matched TF motif + DNase peak
1d	eQTL + TF binding + any motif + DNase peak
1e	eQTL + TF binding + matched TF motif
1f	eQTL + TF binding/DNase peak
Likely to affect binding	
2a	TF binding + matched TF motif + matched DNase footprint + DNase peak
2b	TF binding + any motif + DNase footprint + DNase peak
2c	TF binding + matched TF motif + DNase peak
Less likely to affect binding	
3a	TF binding + any motif + DNase peak
3b	TF binding + matched TF motif
Minimal binding evidence	
4	TF binding + DNase peak
5	TF binding or DNase peak
6	Motif hit
7	No evidence

Abbreviations: SNP, single-nucleotide polymorphism; eQTL, expression quantitative trait loci; TF, transcription factor

This table was based on Boyle AP, et al. **Genome. Res.** 2012;22(9):1790-1797.

Supplementary Table 7. The 15 core chromatin states

Category	Description
1	active TSS
2	flanking active TSS
3	transcription at gene 5' and 3'
4	strong transcription
5	weak transcription
6	genic enhancers
7	enhancers
8	zinc finger genes and repeats
9	heterochromatic
10	bivalent/poised TSS
11	flanking bivalent/ poised TSS/enhancer
12	bivalent enhancer
13	repressed polycomb
14	weak repressed polycomb
15	quiescent/low

Abbreviations: TSS, transcription start site

The chromatin state represents the accessibility of genomic regions (every 200 bp) with 15 categorical states predicted by a hidden Markov model based on 5 chromatin marks for 127 epigenomes in the Roadmap Epigenomics Project (Kundaje A, et al. **Nature**. 2015;518(7539):317-30).

Supplementary Table 8. MR analysis for association of cortisol with muscle strength and mass

Method	Grip strength			WBLM			ALM		
	Estimate	95%CI	P	Estimate	95%CI	P	Estimate	95%CI	P
IVW	-0.031	-0.052 – -0.011	0.003	-0.032	-0.050 – -0.015	-3×10^{-4}	-0.031	-0.058 – -0.004	0.023
Cochran's Q	0.014		0.993	0.973		0.615	1.324		0.516
Weighted-median	-0.031	-0.056 – -0.006	0.015	-0.029	-0.051 – -0.007	0.009	-0.027	-0.059 – -0.004	0.017
MR-Egger	-0.028	-0.195 – 0.138	0.794	0.029	-0.111 – 0.169	0.754	0.079	-0.133 – 0.291	0.599
MR-Egger intercept	-3×10^{-4}		0.978	-0.0053		0.546	-0.0096		0.492

Abbreviations: MR, Mendelian randomization; WBLM, whole body lean mass; ALM, appendicular lean mass; 95%CI, 95% confidence interval; P, p value; IVW, inverse variance weighted

Supplementary Table 9. MR analysis for association of cortisol with muscle strength and mass in men and women

Method	Grip strength (Men)			WBLM (Men)			ALM (Men)		
	Estimate	95%CI	P	Estimate	95%CI	P	Estimate	95%CI	P
IVW	-0.022	-0.069 – 0.025	0.366	-0.001	-0.050 – 0.047	0.957	-0.009	-0.049 – 0.031	0.658
Cochran’s Q	0.216		0.898	0.399		0.819	0.145		0.930
Weighted-median	-0.020	-0.074 – 0.034	0.474	-0.003	-0.055 – 0.060	0.927	-0.007	-0.053 – 0.039	0.766
MR-Egger	-0.109	-0.483 – 0.265	0.670	-0.108	-0.491 – 0.275	0.679	-0.063	-0.381 – 0.256	0.766
MR-Egger intercept	0.008		0.725	0.009		0.680	0.005		0.795

Method	Grip strength (Women)			WBLM (Women)			ALM (Women)		
	Estimate	95%CI	P	Estimate	95%CI	P	Estimate	95%CI	P
IVW	-0.056	-0.099 – -0.013	0.011	-0.092	-0.152 – -0.032	0.003	-0.050	-0.095 – -0.004	0.003
Cochran's Q	1.450		0.484	3.570		0.168	3.163		0.206
Weighted-median	-0.044	-0.101 – 0.012	0.120	-0.084	-0.143 – -0.024	0.006	-0.045	-0.092 – 0.001	0.055
MR-Egger	-0.021	-0.425 – 0.384	0.936	0.233	-0.123 – 0.590	0.422	0.198	-0.089 – 0.485	0.406
MR-Egger intercept	-0.003		0.892	-0.028		0.323	-0.021		0.338

Abbreviations: MR, Mendelian randomization; WBLM, whole body lean mass; ALM, appendicular lean mass; 95%CI, 95% confidence interval; P, p value; IVW, inverse variance weighted

Supplementary Table 10. Functional annotation of GWAS for cortisol

Candidate SNP	Category/r ²	Nearest gene	Position	RegulomeDB score	MinChrState
rs11629326*	0.907089	SERPINA6	intergenic	2a	2
rs113375097	0.935226	SERPINA2P	intergenic	2b	5
rs59036614	0.808907	SERPINA2P	ncRNA_intronic	2b	5
rs4283161	0.93615	SERPINA2P	intergenic	3a	5
rs12589136	Top lead SNP/ Ind. Sig. SNP	SERPINA6	intergenic	4	5
rs4905188	0.941277	SERPINA2P	intergenic	4	5
rs35854995	0.941277	SERPINA2P	intergenic	4	5
rs8015996	1	SERPINA6	intronic	5	4
rs7161521	1	SERPINA6	intronic	5	2
rs11627377	0.624475	SERPINA2P	intergenic	5	5
rs56872560	0.930127	SERPINA2P	intergenic	5	5
rs58776570	0.941277	SERPINA2P	intergenic	5	5
rs4990242	0.691819	SERPINA2P	intergenic	5	5

rs4905191	0.941277	SERPINA2P	intergenic	5	5
rs67994395	0.745165	SERPINA2P	downstream	5	5
rs12588394	Ind. Sig. SNP	SERPINA2P	downstream	5	5
rs56045385	1	SERPINA2P	downstream	5	5
rs3762130	0.924488	SERPINA2P	intergenic	5	5
rs1243173	0.784151	SERPINA2P	intergenic	5	5
rs4905194	0.899235	SERPINA2P	intergenic	5	5
rs11850226	0.725354	SERPINA6	intronic	6	2
rs4905187	1	SERPINA6	intergenic	6	5
rs60271218	0.935226	SERPINA2P	intergenic	6	5
rs2749529	0.821813	SERPINA2P	intergenic	6	5
rs7145181	0.941277	SERPINA2P	intergenic	6	5
rs61981775	0.995957	SERPINA2P	downstream	6	5
rs34362280	0.745536	SERPINA2P	ncRNA_intronic	6	5
rs11621961	lead SNP/ Ind. Sig. SNP	SERPINA6	intergenic	7	4
rs11629171	Ind. Sig. SNP	SERPINA6	intronic	7	5
rs6575415	1	SERPINA6	intergenic	7	5
rs9989237	0.993988	SERPINA6	intergenic	7	5

rs4491436	1	SERPINA6	intergenic	7	5
rs55980335	0.941277	SERPINA2P	intergenic	7	5
rs58622098	0.941277	SERPINA2P	intergenic	7	5
rs3790035	1	SERPINA6	intronic	NA	5
rs5810669	0.659618	SERPINA6	intronic	NA	5
rs76983957	0.879498	SERPINA6	intronic	NA	2
rs562958467	0.879498	SERPINA6	intronic	NA	2
rs1956179	0.659618	SERPINA6	intronic	NA	2
rs941599	1	SERPINA6	intronic	NA	1
rs2281518*	1	SERPINA6	intronic	NA	1
rs3830907	0.682951	SERPINA6	intronic	NA	1
rs2281517	1	SERPINA6	upstream	NA	1
rs552388817	0.963693	SERPINA6	intergenic	NA	5
rs564417713	0.963693	SERPINA6	intergenic	NA	5
14:94792771:GTT:GTTT	0.963693	SERPINA6	intergenic	NA	5
14:94792771:GTT:GTTTT	0.963693	SERPINA6	intergenic	NA	5
rs718187	1	SERPINA6	intergenic	NA	5

rs2749539	0.64434	SERPINA6	intergenic	NA	5
rs909287*	0.917589	SERPINA6	intergenic	NA	2
14:94808984:A:ATGGCAGCATGTTG	0.907089	SERPINA6	intergenic	NA	2
rs2736889	0.737938	SERPINA6	intergenic	NA	2
rs941598	0.735782	SERPINA2P	intergenic	NA	5
rs2736883	0.747182	SERPINA2P	intergenic	NA	5
rs1956174	0.917589	SERPINA2P	intergenic	NA	5
rs2749530	0.812275	SERPINA2P	intergenic	NA	5
rs11323398	0.795548	SERPINA2P	intergenic	NA	5
rs2736899	0.808907	SERPINA2P	intergenic	NA	5
rs551235702	0.759959	SERPINA2P	intergenic	NA	5
rs2736898	1	SERPINA2P	intergenic	NA	5
rs35329919	0.808907	SERPINA2P	intergenic	NA	5
rs2013150	0.808907	SERPINA2P	intergenic	NA	5
rs2749527	Ind. Sig. SNP	SERPINA2P	intergenic	NA	7
rs2736890	0.745536	SERPINA2P	intergenic	NA	7
rs67599794	1	SERPINA2P	intergenic	NA	5

rs33955450	0.98787	SERPINA2P	downstream	NA	1
rs138849755	0.995957	SERPINA2P	downstream	NA	5
rs3819333	0.947368	SERPINA2P	ncRNA_intronic	NA	5
rs941595	0.936655	SERPINA2P	ncRNA_intronic	NA	5
rs1950652	0.924488	SERPINA2P	intergenic	NA	5
rs3762132	0.787486	SERPINA2P	intergenic	NA	5
rs3762127	0.911817	SERPINA2P	intergenic	NA	5
rs3748319	0.917414	SERPINA2P	intergenic	NA	5
rs941594	0.983812	SERPINA2P	intergenic	NA	5
rs2010983	0.784151	SERPINA2P	intergenic	NA	5
rs1243172	0.987871	SERPINA2P	intergenic	NA	5
rs1243171	0.787486	SERPINA2P	intergenic	NA	5
rs1243170	0.936345	SERPINA2P	intergenic	NA	5

Abbreviations: SNP, single-nucleotide polymorphism; GWAS, genome-wide association study; minChrState, minimum chromatin state

All candidate SNPs were located on chromosome 14. *, rs11629326, rs909287, and rs2281518 were located within the regulatory regions for muscle tissues by 15-core chromatin state

Supplementary Table 11. Mapped genes of candidate SNPs for cortisol

Symbol	Chr	start	end	posMap SNPs	eqtlMap SNPs	Eqtl MapminQ	ciMap	ci MapminQ	IndSigSNPs
OTUB2	14	99492675	94515276	0	0	-	Yes	4e-11	rs11621961;rs11629171; rs12589136;rs2749527
DDX24	14	94517266	94547591	0	4	1e-05	No	-	rs11629171;rs11621961
ASB2	14	94400499	94443137	0	0	-	Yes	1e-07	rs12589136;rs12588394
TCL1A	14	96176304	96180533	0	0	-	Yes	2e-07	rs11621961;rs11629171; rs12589136;rs2749527
IFI27L2	14	94594116	94596590	0	28	0	No	-	rs12589136;rs12588394; rs2749527;rs11629171
PPP4R4	14	94612465	94746072	0	75	0	No	-	rs12589136;rs12588394; rs11629171;rs2749527;rs11621961
SERPINA10	14	94749650	94746072	1	0	-	No	-	rs11621961
IFI27L1	14	94547628	94570192	0	30	0	No	-	rs12589136;rs12588394; rs11621961;rs2749527

SERPINA12	14	94953611	94984181	0	0	-	Yes	1e-17	rs11621961;rs11629171; rs12589136;rs2749527;rs12588394
CLMN	14	95648277	95786243	0	24	0.02	No	-	rs12589136;rs12588394
SERPINA9	14	94929054	94946026	0	11	0.003	No	-	rs12589136
SERPINA6	14	94770585	94789731	21	63	9e-08	No	-	rs11621961;rs11629171; rs12589136;rs2749527;rs12588394
SERPINA11	14	94908801	94919127	0	2	0.049	No	-	rs2749527
SERPINA1	14	94843084	94857030	12	74	0	Yes	6e-14	rs12589136;rs12588394; rs2749527;rs11629171;rs11621961

Abbreviations: SNP, single-nucleotide polymorphism; GWAS, genome-wide association study; minChrState, minimum chromatin state. eQTL, expression quantitative trait loci; FDR, false discovery rate; All mapped genes were protein-coding. posMapSNPs: The number of SNPs mapped to gene based on positional mapping. eqtlMapSNPs: The number of SNPs mapped to the gene based on eQTL mapping. eQTLMapminQ: The minimum eQTL FDR of mapped SNPs. ciMap, “Yes” if the gene is mapped by chromatin interaction mapping. ciMapminQ, The minimum ci FDR of mapped SNPs, IndSigSNPs, rsID of the all independent significant SNPs of mapped SNPs.