Supplementary Material

Genetic Association of Finger Photoplethysmography-Derived Arterial Stiffness Index with Blood Pressure and Coronary Artery Disease

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Supplementary Results

Interrogation of non-coding loci from the ASI genome-wide association analysis

Since the lead variants occur within non-coding regions of the genome, we evaluated for evidence of chromatin conformational change to physically link variants with nearby coding regions. Further evaluation of chromatin contact and enhancers within human aorta primary tissues at these 5 loci was performed using the Hi-C Unifying Genomic Integrator(1) (**Supplementary Figure II**). Notably, the top variant region in the second *TEX41* intron most strongly contacts an aorta enhancer region at *ZEB2*, a gene which is also highly expressed in aorta(1). Additionally, the *COL4A2* intronic variant region physically interacts with *COL4A1* at an aorta enhancer, and both are expressed in aorta(1).

Interrogation of coding loci from the ASI genome-wide association analysis

Of all variants with moderate significance ($P<1x10^{-4}$), no predicted loss-of-function variants were identified; however, two missense variants predicted to be deleterious (via the MetaSVM *in silico* prediction score(2)) were identified. These predicted disruptive missense variants were within *HFE*, rs1800562 (+0.028 SD, $P=5.3x10^{-5}$, MAF=0.076), and within *NEFH*, rs149955255 (+0.135 SD, $P=5.9x10^{-5}$, MAF=0.0034) (**Supplementary Table VII**). Notably, polymorphisms in *HFE*, the gene implicated in hereditary hemochromatosis, are known to promote excessive iron accumulation, and have been associated with aortic stiffness(3) and endothelial dysfunction(4).

Supplementary Table I: Incident phenotype definitions

Please find details in the Major Resource Table.

Supplementary Table II: Sample filtration criteria

Criteria	N
Not White, British Ancestry **Submitted Gender != Inferred Gender** **Putative Sex Chromosome Aneuploidy** **Het Missing Outliers** **Non-Consented for Analysis**	80,155
≥ 2nd Degree Relatives	36,158
Prevalent Peripheral Vascular Disease	3511
Prevalent Aortic Valve Disease	1629
Prevalent Coronary Artery Disease	15,386
Total Unique Samples Filtered	127,043
Total Unique Samples Included	375,586

Supplementary Table III: Summary statistics for the pulse wave analysis phenotypes in UK Biobank (N=131,686).

Pulse wave analysis phenotypes	Median	Q1	Q3
Arterial Stiffness Index (m/s)	9	7	11
Reflection Index (unitless)	70	59	78
Shoulder Position (ms)	23	17	26
Notch Position (ms)	43	39	47
Peak Position (ms)	24	19	26
Pulse Rate (beats/min)	68	61	75

Supplementary Table IV: Univariate association of inverse-rank normalized stiffness index with clinical cardiovascular risk factors.

Covariate	Beta*	SE	P
Age	0.0243	3.34×10^{-04}	$<1 \times 10^{-300}$
Sex [Male]	0.399	5.38×10^{-03}	$<1 \times 10^{-300}$
BP Meds	0.340	8.91×10^{-03}	$<1 \times 10^{-300}$
Prevalent Hypertension	0.211	6.01×10^{-03}	1.38×10^{-269}
Ever smoked	0.183	5.41×10^{-03}	3.02×10^{-250}
Prevalent Hypercholesterolemia	0.199	7.96×10^{-03}	4.07×10^{-137}
Exercise ≥ 3x/wk	-0.160	9.29×10^{-03}	2.91×10^{-66}
Prevalent Diabetes	0.196	0.0127	9.12×10^{-54}
Alcohol ≥ 1x/mo	0.0550	5.98×10^{-03}	3.29×10^{-20}
>6 Tablespoons Veggies/day	-0.0635	0.0176	3.14×10^{-04}

*All continuous variables (except for Age) are in SD units

Supplementary Table V: Missense variants with moderate association with arterial stiffness (P<1x10^{-4}). The MetaSVM in-silico prediction from dbNSFP is denoted as T for "tolerated" versus "D" for "deleterious." Here, two deleterious missense variants are present. There were no variants with loss-of-function consequences and arterial stiffness P<1x10^{-4}.

v	rsID	Gene	MAF	P	Beta	SE	MetaSVM	hgvsp
08:23001988:A:G	["rs1133782"]	*TNFRSF10D*	0.40	1.36x10^{-06}	0.018	0.0038	T	p.Leu310Ser
22:42609148:T:C	["rs5758651"]	*TCF20*	0.21	1.58x10^{-06}	-0.022	0.0045	T	p.Ser722Gly
19:56719545:A:G	["rs117883767"]	*ZSCAN5C*	8.54x10^{-04}	2.38x10^{-05}	-0.287	0.0678	T	p.Asn244Ser
04:146063471:C:T	["rs151020153"]	*OTUD4*	4.60x10^{-03}	2.66x10^{-05}	0.121	0.0289	T	p.Val502Met
10:14974905:T:C	["rs12768894"]	*DCLRE1C*	0.18	2.75x10^{-05}	-0.020	0.0048	T	p.His243Arg
12:53442956:G:C	["rs12369033"]	*TENC1*	0.29	3.54x10^{-05}	-0.017	0.0041	T	p.Arg10Thr
06:26093141:G:A	["rs1800562"]	*HFE*	0.08	5.29x10^{-05}	0.028	0.0069	D	p.Cys282Tyr
22:29879534:C:A	["rs149955255"]	*NEFH*	3.40x10^{-03}	5.98x10^{-05}	0.135	0.0337	D	p.Arg352Ser
03:97311483:C:T	["rs4857276"]	*EPHA6*	5.15x10^{-03}	5.99x10^{-05}	0.109	0.0271	T	p.Ala805Val
19:49337577:C:T	["rs116979565"]	*HSD17B14*	9.94x10^{-03}	7.89x10^{-05}	0.073	0.0186	T	p.Ala56Thr
17:73487830:A:G	["rs35709918"]	*KIAA0195*	5.51x10^{-04}	8.20x10^{-05}	0.309	0.0785	T	p.Asn482Ser
08:39468128:A:T	["rs73605945"]	*ADAM18*	5.24x10^{-03}	8.39x10^{-05}	0.100	0.0255	T	p.Gln142Leu
19:5714234:C:T	["rs148374055"]	*LONP1*	8.85x10^{-04}	8.42x10^{-05}	0.244	0.0620	T	p.Ala160Thr
11:55563362:G:A	["rs145501127"]	*OR5D14*	3.06x10^{-03}	8.52x10^{-05}	-0.131	0.0333	T	p.Val111Met
03:12393125:C:G	["rs1801282"]	*PPARG*	0.12	8.95x10^{-05}	-0.022	0.0057	T	p.Pro12Ala
15:77471361:G:A	["rs117879553"]	*PEAK1*	2.00x10^{-03}	9.75x10^{-05}	-0.161	0.0412	T	p.Arg970Cys

Supplementary Table VI: Genome-wide association results from the UK Biobank (N= 131,686) for the six independent instrumental variants with $P<5x10^{-7}$ used for arterial stiffness index Mendelian randomization. Betas refer to the alternate allele and are in units of SD ASI per alternate allele.

Variant (chr:pos:ref:alt, hg19)	rsID	Gene	Consq	Known MI Locus Nearby	MAF	P	Beta	SE
02:145775399:T:C	["rs1006923"]	*TEX41*	intron_variant	*ZEB2*	0.32	$3.72x10^{-10}$	-0.025	0.0040
13:41185309:G:A	["rs7331212"]	*FOXO1*	intron_variant	*NA*	0.26	$9.26x10^{-09}$	-0.024	0.0042
19:658013:A:G	["rs1009628"]	*RNF126*	intron_variant	*NA*	0.15	$1.21x10^{-07}$	-0.027	0.0051
22:42654327:C:G	["rs17478227"]	*TCF20*	intron_variant	*NA*	0.20	$1.95x10^{-07}$	-0.024	0.0046
13:111015877:C:T	["rs872588"]	*COL4A2*	intron_variant	*COL4A1-COL4A2*	0.42	$2.34x10^{-07}$	-0.020	0.0038
02:145701992:C:T	["rs786250"]	*TEX41*	intron_variant	*ZEB2*	0.35	$4.78x10^{-07}$	0.019	0.0039

Supplementary Table VII: Sensitivity analysis of the ASI GRS to evaluate associations with potential environmental confounders using univariate logistic regression. Analyses were performed among individuals not in the ASI genome-wide association analyses using logistic regression. Odds ratio represents risk conferred by 1-SD increase in genetically-elevated ASI.

	OR	SE	P
SEX (MALE)	1.16	0.13	0.25
EVER SMOKING STATUS (0/1)	1.07	0.132	0.617
VEGETABLE INTAKE (>6TB)	1.09	0.239	0.73
ALCOHOL INTAKE (>1-3X/MO)	0.95	0.147	0.747
EXERCISE (>3X/WK)	1.21	0.45	0.68

Supplementary Table VIII: Results from association of phenotypic and genotypic ASI in the UKBB with A) blood pressure adjusted for medications, and B) raw blood pressure. A) Outcome refers to SBP+15 mmHg and DBP+10mmHg if on BP Meds. Estimate is provided in mmHg/SD of ASI mediated by exposure. B) Outcome is raw SBP and DBP, BP Meds are included as covariates in the adjusted models. In both A&B, HR is provided per SD of ASI mediated by the instrument. ASI=arterial stiffness index, GRS = genetic risk score

A)

Outcome	Instrument (SD)	Covariates*	Estimate	SE	P	N
SBP (mmHg)	ASI GRS	Unadjusted	6.37	1.43	8.13E-06	208897
		Adjusted Model 1	5.10	1.31	9.52E-05	
		Adjusted Model 2	4.63	1.29	3.37E-04	
	ASI phenotype	Unadjusted	2.96	0.06	<1e-300	137858
		Adjusted Model 1	0.83	0.05	6.44E-53	
		Adjusted Model 2	0.55	0.05	5.77E-24	
DBP (mmHg)	ASI GRS	Unadjusted	3.48	0.78	8.72E-06	208894
		Adjusted Model 1	3.13	0.75	3.26E-05	
		Adjusted Model 2	2.61	0.72	2.85E-04	
	ASI phenotype	Unadjusted	2.07	0.03	<1e-300	137862
		Adjusted Model 1	1.41	0.03	<1e-300	
		Adjusted Model 2	1.05	0.03	7.27E-272	

*Unadjusted model refers to a univariate model with no covariates.
Adjusted Model 1 uses age, sex, and smoking status as covariates.
Adjusted Model 2 uses age, sex, smoking status, heart rate, vegetable intake, alcohol intake, and exercise frequency, prevalent hypercholesterolemia, and prevalent diabetes as covariates.

B)

Outcome	Instrument [SD]	Covariates*	Estimate	SE	P	N
SBP (mmHg)	ASI GRS	Unadjusted	5.65	1.35	2.81E-05	208897
		Adjusted Model 1	4.48	1.26	3.78E-04	
		Adjusted Model 2	4.12	1.25	9.79E-04	
	ASI Phenotype	Unadjusted	2.50	0.05	<1e-300	137858
		Adjusted Model 1	0.85	0.05	3.08E-59	
		Adjusted Model 2	0.62	0.05	3.62E-32	
DBP (mmHg)	ASI GRS	Unadjusted	3.01	0.73	4.08E-05	208897
		Adjusted Model 1	2.73	0.72	1.45E-04	
		Adjusted Model 2	2.28	0.69	9.11E-04	
	ASI Phenotype	Unadjusted	1.77	0.03	<1e-300	137858
		Adjusted Model 1	1.42	0.03	<1e-300	
		Adjusted Model 2	1.10	0.03	<1e-300	

*Unadjusted model refers to a univariate model with no covariates.
Adjusted Model 1 uses BP Meds, age, sex, and smoking status as covariates.
Adjusted Model 2 uses BP Meds, age, sex, smoking status, heart rate, vegetable intake, alcohol intake, and exercise frequency, prevalent hypercholesterolemia, and prevalent diabetes as covariates.

Supplementary Table IX: Results from association of phenotypic and genotypic ASI in the UKBB with incident CAD using A) a more liberal phenotypic definition of CAD, and B) a more stringent phenotypic definition of CAD. A) liberal definition of CAD includes billing codes for heart attack, angina pectoris, unstable angina, myocardial infarction, coronary atherosclerosis, coronary artery revascularization, and other acute, subacute, and chronic forms of ischemic heart disease, or with self-reported angina, heart attack/myocardial infarction, coronary angioplasty +/- stent, or coronary artery bypass graft (CABG) surgery. B) stringent definition of CAD is the same as (A) but excludes billing codes for angina pectoris and unstable angina, and self-reported angina. HR is provided per SD of ASI mediated by the instrument. ASI=arterial stiffness index, GRS = genetic risk score

A)

Outcome	Exposure	Covariates*	HR	SE	P	Cases (N)	Controls (N)
CAD (Liberal definition)	ASI GRS	Unadjusted	1.30	0.36	0.47	7534	215527
		Adjusted Model 1	1.20	0.36	0.62		
		Adjusted Model 2	1.12	0.36	0.75		
	ASI Phenotype	Unadjusted	1.30	0.016	2.15E-58	3692	126615
		Adjusted Model 1	1.10	0.017	2.01E-08		
		Adjusted Model 2	1.08	0.019	7.24E-06		

B)

Outcome	Instrument (SD)	Covariates*	HR	SE	P	Cases (N)	Controls (N)
CAD (Stringent definition)	ASI GRS	Unadjusted	0.95	0.47	0.91	4404	223402
		Adjusted Model 1	0.87	0.47	0.76		
		Adjusted Model 2	0.81	0.47	0.66		
	ASI Phenotype	Unadjusted	1.34	0.022	2.08E-41	2027	131115
		Adjusted Model 1	1.10	0.024	3.45E-05		
		Adjusted Model 2	1.09	0.024	4.25E-04		

*Unadjusted model refers to a univariate model with no covariates.
Adjusted Model 1 uses age, sex, and smoking status as covariates.
Adjusted Model 2 uses age, sex, smoking status, heart rate, vegetable intake, alcohol intake, and exercise frequency, prevalent hypercholesterolemia, prevalent diabetes, and prevalent hypertension as covariates.

Supplementary Table X: Association of each of the 6 ASI genetic risk score variants with incident CAD in the UKBB. Reported hazard ratios refer to the ASI-raising allele. (Note: the liberal CAD definition is used here)

Variant	Nearest Gene	HR*	SE	P	Cases (N)	Controls (N)
rs7331212	FOXO1	0.99	0.02	0.69	7534	215527
rs872588	COL4A2	1.02	0.02	0.15		
rs1009628	RNF126	1.05	0.02	0.04		
rs17478227	TCF20	1.04	0.02	0.05		
rs786250	TEX41	0.97	0.02	0.12		
rs1006923	TEX41	0.97	0.02	0.08		

* Direction corresponds to increasing ASI effect allele

Supplementary Table XI: 2-Sample Mendelian randomization with coronary artery disease. 2-Sample MR analysis between stiffness index and coronary artery disease using arterial stiffness index genetic associations from 131,686 in the UK Biobank and coronary artery disease associations from 184,305 individuals in the Coronary Artery Disease Genetics Consortium (CARDIOGRAMplusC4D). Results from several different 2-sample MR methods are shown, the highlighted results from the penalized robust IVW method were reported in main text. MR=Mendelian randomization, IVW=inverse-variance weighted

Method	*Beta*	*SE*	*95% CI Lower*	*95% CI Upper*	*P-value*
Simple median	-0.679	0.338	-1.342	-0.017	0.045
Weighted median	-0.857	0.352	-1.547	-0.166	0.015
Penalized weighted median	-0.994	0.409	-1.796	-0.192	0.015
IVW	-0.757	0.434	-1.607	0.094	0.081
Penalized IVW	-0.571	0.408	-1.371	0.228	0.161
Robust IVW	-0.757	0.448	-1.635	0.122	0.091
Penalized robust IVW	-0.576	0.403	-1.366	0.214	0.153
MR-Egger	1.579	3.794	-5.857	9.015	0.677
(intercept)	-0.053	0.086	-0.221	0.115	0.535
Penalized MR-Egger	4.159	2.571	-0.879	9.197	0.106
(intercept)	-0.103	0.057	-0.215	0.008	0.069
Robust MR-Egger	1.969	4.659	-7.164	11.101	0.673
(intercept)	-0.061	0.091	-0.239	0.117	0.502

Supplementary Table XII: A list of known independent CAD loci and their discovery sources.

Chr	SNP	Reported Gene	Study Source	Paper
1	rs17114036	*PPAP2B*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
1	rs4845625	*IL6R*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
1	rs17464857	*MIA3*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
1	rs11206510	*PCSK9*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
1	rs602633	*SORT1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
2	rs1561198	*VAMP5-VAMP8-GGCX*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
2	rs2252641	*ZEB2-TEX41*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
2	rs6725887	*WDR12*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
2	rs1250229	*FN1*	CAD_ExmChip_Replication_EA	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f2
2	rs1801251	*KCNJ13-GIGYF2*	CAD_ExmChip_Replication_EA	https://www.ncbi.nlm.nih.gov/pubmed/28209224
2	rs515135	*APOB*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
2	rs6544713	*ABCG5-ABCG8*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
2	rs2972146	*LOC646736*	CAD_UKB_ExmChip_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f2
3	rs9818870	*MRAS*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
3	rs12493885	*ARHGEF26*	CAD_ExmChip_Replication_EA	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f2
3	rs17843797	*UMPS-ITGB5*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f3
3	rs748431	*FGD5*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f4
3	rs7623687	*RHOA*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f5
4	rs17087335	*REST-NOA1*	CAD_1KG_add_ALL	http://www.nature.com/ng/journal/v47/n10/full/ng.3396.html
4	rs1878406	*EDNRA*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
4	rs7692387	*GUCY1A3*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
4	rs10857147	*FGF5*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f2
4	rs7678555	*MAD2L1*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f2
5	rs273909	*SLC22A4-SLC22A5*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
5	rs1800449	*LOX*	CAD_ExmChip_Replication_EA	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f2
6	rs9369640	*PHACTR1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
6	rs3130683	*C2*	CAD_ExmChip_Replication_EA	https://www.ncbi.nlm.nih.gov/pubmed/28209224
6	rs10947789	*KCNK5*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
6	rs12190287	*TCF21*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
6	rs4252120	*PLG*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
6	rs12205331	*ANKS1A*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
6	rs3798220	*SLC22A3-LPAL2-LPA*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
7	rs2023938	*HDAC9*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
7	rs11556924	*ZC3HC1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
7	rs3918226	*NOS3*	CAD_1KG_add_ALL	http://www.nature.com/ng/journal/v47/n10/full/ng.3396.html
8	rs264	*LPL*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
8	rs2954029	*TRIB1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
9	rs1333049	*CDKN2BAS1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
9	rs111245230	*SVEP1*	CAD_ExmChip_Replication_EA	http://www.nejm.org/doi/full/10.1056/NEJMoa1507652
9	rs579459	*ABO*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
10	rs2505083	*KIAA1462*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
10	rs501120	*CXCL12*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
10	rs2246833	*LIPA*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
10	rs12413409	*CYP17A1-CNNM2-NT5C2*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
11	rs10840293	*SWAP70*	CAD_1KG_add_ALL	http://www.nature.com/ng/journal/v47/n10/full/ng.3396.html
11	rs11042937	*CTR9-MRVI1*	CAD_ExmChip_Replication_EA	https://www.ncbi.nlm.nih.gov/pubmed/28209224
11	rs974819	*PDGFD*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
11	rs9326246	*ZNF259-APOA5-APOA1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
12	rs11172113	*LRP1*	CAD_ExmChip_Replication_EA	https://www.ncbi.nlm.nih.gov/pubmed/28209224
12	rs11830157	*KSR2*	CAD_1KG_rec_ALL	http://www.nature.com/ng/journal/v47/n10/full/ng.3396.html
12	rs3184504	*SH2B3*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
12	rs11057830	*SCARB1*	CAD_ExmChip_Replication_EA	https://www.ncbi.nlm.nih.gov/pubmed/28209224
12	rs11057401	*CCDC92*	CAD_UKB_ExmChip_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html #f2

12	rs10841443	*RP11-664H17.1*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html#f2
12	rs1169288	*HNF1A*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html#f2
13	rs9319428	*FLT1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
13	rs4773144	*COL4A1-COL4A2*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
14	rs2895811	*HHIPL1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
15	rs17293632	*SMAD3*	CAD_ExmChip_Replication_EA	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4589895/
15	rs7173743	*ADAMTS7*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
15	rs8042271	*MFGE8-ABHD2*	CAD_1KG_add_ALL	http://www.nature.com/ng/journal/v47/n10/full/ng.3396.html
15	rs17514846	*FURIN-FES*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
16	rs247616	*CETP-HERPUD1*	CAD_ExmChip_Replication_EA	https://www.ncbi.nlm.nih.gov/pubmed/28209224
16	rs3851738	*BCAR1-CFDP1-TMEM170A*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html#f2
16	rs7500448	*CDH13*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html#f2
17	rs2281727	*SMG6*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
17	rs12936587	*RAI1-PEMT-RASD1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
17	rs15563	*UBE2Z*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
17	rs7212798	*BCAS3*	CAD_1KG_add_ALL	http://www.nature.com/ng/journal/v47/n10/full/ng.3396.html
18	rs663129	*PMAIP1-MC4R*	CAD_1KG_add_ALL	http://www.nature.com/ng/journal/v47/n10/full/ng.3396.html
19	rs12976411	*ZNF507-LOC400684*	CAD_1KG_rec_ALL	http://www.nature.com/ng/journal/v47/n10/full/ng.3396.html
19	rs116843064	*ANGPTL4*	CAD_ExmChip_Replication_EA	http://www.nejm.org/doi/full/10.1056/NEJMoa1507652
19	rs1122608	*LDLR*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
19	rs2075650	*ApoE-ApoC1*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
19	rs8108632	*TGFB1*	CAD_UKB_1KG_add_ALL	http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3914.html#f2
21	rs9982601	*KCNE2*	CAD_CARDIOgRAMplusC4D_fisher_ALL	http://www.nature.com/ng/journal/v45/n1/full/ng.2480.html
22	rs180803	*POM121L9P-ADORA2A*	CAD_1KG_add_ALL	http://www.nature.com/ng/journal/v47/n10/full/ng.3396.html

Supplementary Table XIII: Comparing variant-level effects between ASI and CAD. ASI variant-level summary statistics are from the UK Biobank association, CAD summary statistics refer to the CARDIOGRAMplusC4D consortium results with 1000 Genomes Phase 1(5) imputation provided in the "cad.add.160614.website.txt.gz" file downloaded from http://www.cardiogramplusc4d.org/data-downloads/. The 77 variants listed here are the ones identified from **Supplementary Table 9** above. ASI = arterial stiffness index, CAD = coronary artery disease

CAD Locus	*rsID*	*ASI-raising allele*	*ASI Beta*	*ASI SE*	*ASI P*	*CAD Beta*	*CAD SE*	*CAD P*
ZEB2-TEX41	rs2252641	T	0.0167	0.0037	6.68E-06	-0.033	0.010	5.16E-04
PHACTR1	rs9349379	A	0.0153	0.0038	4.49E-05	-0.132	0.010	1.81E-42
ABO	rs600038* (rs579459 proxy)	T	0.0177	0.0045	8.82E-05	-0.074	0.011	7.15E-11
CYP17A1-CNNM2-NT5C2	rs12413409	G	0.0231	0.0069	0.000794	0.075	0.014	1.07E-07
SH2B3	rs3184504	T	0.0116	0.0037	0.00163	0.064	0.011	1.03E-09
LRP1	rs11172113	T	0.0103	0.0037	0.00613	-0.041	0.010	1.71E-05
FGF5	rs10857147	T	0.0111	0.0041	0.00626	0.055	0.011	5.83E-07
WDR12	rs6725887	T	0.0148	0.0055	0.00706	-0.133	0.015	9.51E-18
MRAS	rs9818870	C	0.0131	0.0051	0.00971	-0.065	0.014	2.21E-06
ZC3HC1	rs11556924	C	0.0096	0.0038	0.011	0.073	0.011	5.34E-11
PMAIP1-MC4R	rs663129	A	0.0109	0.0043	0.012	0.058	0.011	3.20E-08
FURIN-FES	rs17514846	A	0.0089	0.0037	0.0164	0.051	0.010	3.10E-07
BCAR1-CFDP1-TMEM170A	rs3851738	G	0.0090	0.0038	0.0171	-0.045	0.010	1.88E-06
IL6R	rs4845625	T	0.0087	0.0037	0.0194	0.051	0.009	3.93E-08
ApoE-ApoC1	rs2075650	A	0.0120	0.0053	0.0229	-0.071	0.015	1.61E-06
SMG6	rs2281727	A	0.0082	0.0039	0.034	-0.047	0.010	7.11E-07
LOC646736	rs2972146	T	0.0081	0.0039	0.0346	0.039	0.010	1.38E-04
ARHGEF26	rs12493885	G	0.0097	0.0052	0.0616	-0.066	0.016	2.43E-05
UMPS-ITGB5	rs17843797	T	0.0095	0.0055	0.0829	-0.064	0.014	2.43E-06
CCDC92	rs11057401	T	0.0067	0.0040	0.0893	0.027	0.010	8.31E-03
EDNRA	rs1878406	T	0.0090	0.0053	0.0907	0.060	0.012	1.24E-06
KIAA1462	rs2505083	C	0.0061	0.0037	0.101	0.061	0.010	1.57E-10
TRIB1	rs2954029	A	0.0060	0.0037	0.106	0.044	0.009	2.61E-06
LIPA	rs2246833	C	0.0060	0.0039	0.12	-0.065	0.010	1.33E-11
ABCG5-ABCG8	rs6544713	T	0.0058	0.0039	0.139	0.051	0.010	8.88E-07
RP11-664H17.1	rs10841443	G	0.0058	0.0039	0.142	0.051	0.010	5.81E-07
LPL	rs264	G	0.0078	0.0053	0.143	0.058	0.013	1.06E-05
CDKN2BAS1	rs1333049	C	0.0053	0.0037	0.148	0.193	0.009	3.86E-93
LDLR	rs1122608	T	0.0060	0.0042	0.155	-0.073	0.011	2.73E-11
REST-NOA1	rs17087335	G	0.0066	0.0047	0.166	-0.061	0.011	4.59E-08
PPAP2B	rs17114036	G	0.0088	0.0064	0.166	-0.123	0.017	2.22E-13
ANGPTL4	rs116843064	G	0.0181	0.0134	0.175	0.141	0.043	1.04E-03
SVEP1	rs111245230	C	0.0126	0.0101	0.21	0.054	0.027	4.56E-02
GUCY1A3	rs7692387	G	0.0057	0.0047	0.233	0.068	0.012	7.35E-09
SCARB1	rs11057830	A	0.0060	0.0053	0.259	0.046	0.013	6.85E-04
MAD2L1	rs7678555	C	0.0046	0.0041	0.262	0.054	0.011	3.26E-07
UBE2Z	rs15563	A	0.0040	0.0037	0.284	-0.040	0.009	1.83E-05
FLT1	rs9319428	G	0.0043	0.0040	0.288	-0.040	0.010	7.13E-05
NOS3	rs3918226	C	0.0073	0.0069	0.29	-0.133	0.022	1.69E-09
VAMP5-VAMP8-GGCX	rs1561198	C	0.0038	0.0037	0.3	-0.058	0.009	6.37E-10
PCSK9	rs11206510	C	0.0046	0.0047	0.326	-0.075	0.013	2.34E-08
MIA3	rs17464857	G	0.0047	0.0051	0.358	-0.057	0.014	4.18E-05
KCNJ13-GIGYF2	rs1801251	G	0.0035	0.0038	0.367	-0.039	0.010	1.06E-04
HNF1A	rs1169288	C	0.0035	0.0040	0.381	0.047	0.010	1.98E-06
C2	rs3130683	T	0.0045	0.0052	0.383	0.049	0.017	4.15E-03
RHOA	rs7623687	A	0.0041	0.0053	0.434	0.070	0.014	5.22E-07
LOX	rs1800449	T	0.0039	0.0049	0.435	0.045	0.012	3.06E-04
SLC22A3-LPAL2-LPA	rs3798220	T	0.0101	0.0137	0.464	-0.350	0.060	4.66E-09
SORT1	rs602633	G	0.0032	0.0045	0.472	0.096	0.012	6.97E-17
ANKS1A	rs12205331	C	0.0032	0.0044	0.475	0.026	0.013	4.21E-02
APOB	rs515135	T	0.0033	0.0048	0.497	-0.067	0.012	3.09E-08
SWAP70	rs10840293	A	0.0022	0.0037	0.551	0.055	0.010	1.28E-08
BCAS3	rs2120222* (rs7212798 proxy)	C	0.0028	0.0052	0.588	0.070	0.014	1.92E-07

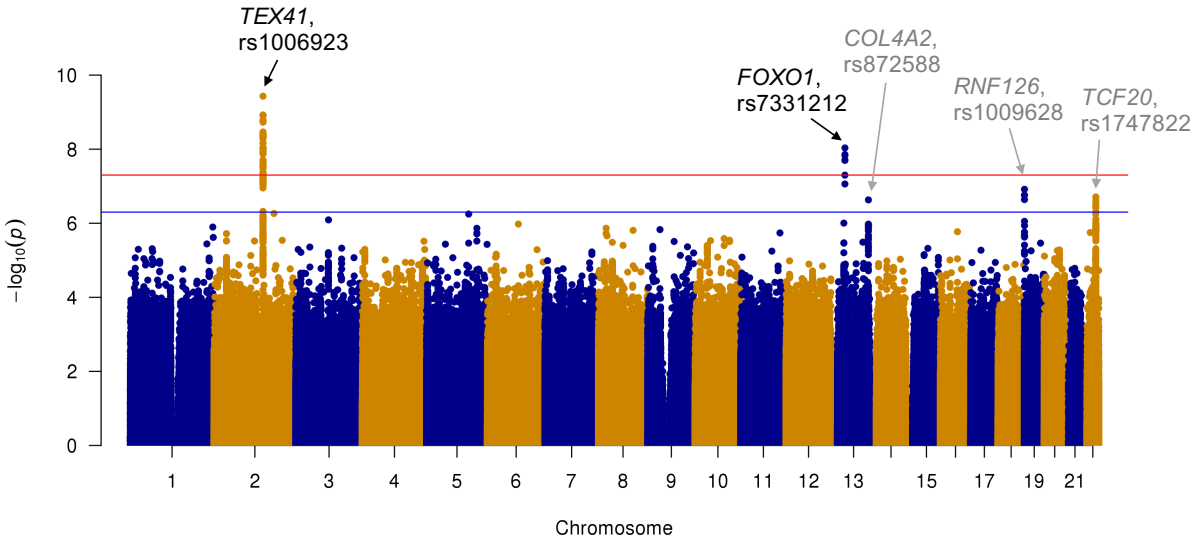
HDAC9	rs2023938	C	0.0030	0.0062	0.626	0.059	0.015	1.36E-04
FGD5	rs748431	G	0.0017	0.0038	0.649	0.049	0.009	2.14E-07
RAI1-PEMT-RASD1	rs12936587	A	0.0016	0.0037	0.67	-0.033	0.010	8.24E-04
CXCL12	rs501120	T	0.0023	0.0055	0.672	0.079	0.012	1.39E-11
ZNF507-LOC400684	rs12976411	T	0.0040	0.0097	0.678	-0.048	0.018	9.12E-03
COL4A1-COL4A2	rs4773144	A	0.0015	0.0037	0.692	-0.052	0.010	3.87E-07
MFGE8-ABHD2	rs8042271	A	0.0039	0.0100	0.699	-0.097	0.018	3.68E-08
SMAD3	rs17293632	T	0.0017	0.0043	0.7	-0.070	0.012	5.72E-09
CTR9-MRVI1	rs11042937	T	0.0014	0.0037	0.706	0.012	0.010	2.19E-01
CDH13	rs7500448	G	0.0016	0.0043	0.707	-0.055	0.012	2.11E-06
MFGE8-ABHD2	rs56015348* (rs8042271 proxy)	A	0.0033	0.0100	0.742	-0.092	0.018	4.39E-07
PLG	rs4252120	T	0.0012	0.0040	0.777	0.033	0.011	3.32E-03
KCNE2	rs9982601	C	0.0014	0.0055	0.793	-0.110	0.015	1.33E-13
CETP-HERPUD1	rs247616	C	0.0009	0.0039	0.816	0.031	0.010	2.36E-03
SLC22A4-SLC22A5	rs273909	G	0.0013	0.0057	0.821	0.056	0.015	1.24E-04
KSR2	rs11830157	G	0.0008	0.0038	0.825	0.035	0.010	3.88E-04
TGFB1	rs1989457* (rs8108632 proxy)	C	0.0008	0.0038	0.833	-0.045	0.010	3.15E-06
HHIPL1	rs2895811	T	0.0007	0.0037	0.841	-0.041	0.010	1.86E-05
ADAMTS7	rs7173743	C	0.0007	0.0037	0.841	-0.076	0.009	5.55E-16
TCF21	rs12190287	C	0.0007	0.0038	0.846	0.058	0.018	1.07E-03
POM121L9P-ADORA2A	rs5760368* (rs180803 proxy)	C	0.0022	0.0173	0.898	-0.134	0.024	2.48E-08
KCNK5	rs10947789	C	0.0002	0.0043	0.96	-0.053	0.011	1.63E-06
ZNF259-APOA5-APOA1	rs9326246	C	0.0003	0.0074	0.969	0.046	0.015	2.46E-03
PDGFD	rs974819	T	0.0001	0.0041	0.986	0.063	0.010	2.44E-10

Supplementary Table XIV: Evaluating the reverse association, of CAD influencing ASI, using 2-sample Mendelian randomization, using the variant-level statistics from Supplementary Table 10 across 77 CAD GWAS variants.

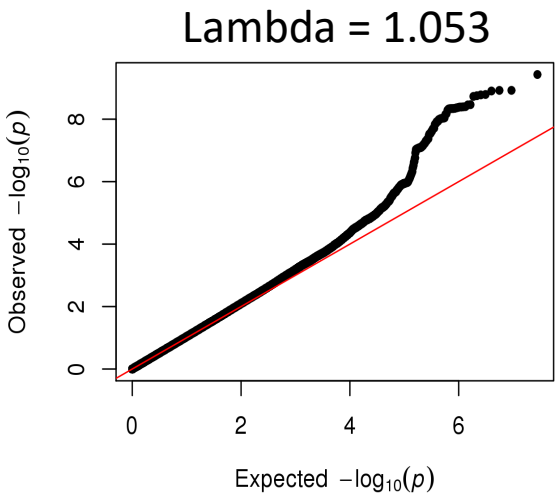
Method	*Estimate*	*Std Error*	*Lower 95% CI*	*Upper 95% CI*	*P-value*
Simple median	0.006	0.015	-0.022	0.035	0.67
Weighted median	-0.003	0.013	-0.029	0.023	0.829
Penalized weighted median	0.023	0.014	-0.004	0.051	0.091
IVW	-0.006	0.012	-0.03	0.018	0.637
Penalized IVW	0.008	0.01	-0.012	0.028	0.423
Robust IVW	0	0.016	-0.031	0.03	0.989
Penalized robust IVW	0.008	0.011	-0.014	0.03	0.469
MR-Egger	-0.028	0.027	-0.081	0.025	0.299
(intercept)	0.002	0.002	-0.002	0.005	0.354
Penalized MR-Egger	-0.02	0.022	-0.064	0.024	0.376
(intercept)	0.002	0.001	-0.001	0.005	0.234
Robust MR-Egger	-0.03	0.045	-0.119	0.059	0.507
(intercept)	0.002	0.002	-0.003	0.007	0.386

Supplementary Figure I: Manhattan and quantile-quantile plot of genome-wide association statistics for arterial stiffness index. A) Manhattan plot labeling loci achieving $P<5x10^{-7}$. B) Quantile-quantile plot shows no significant genomic inflation (Lambda < 1.10).

A.

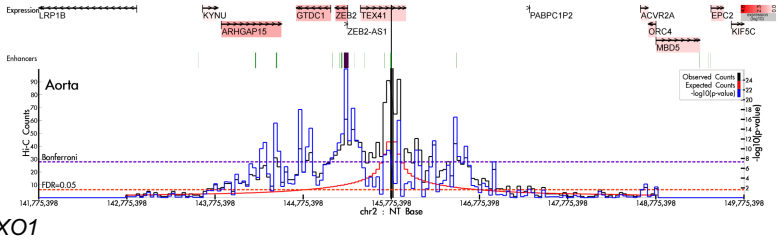


B.

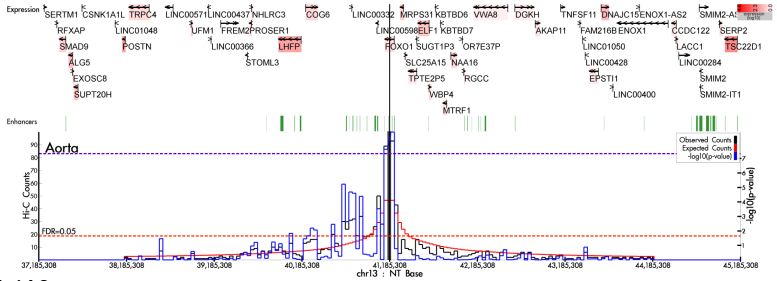


Supplementary Figure II: Chromatin contact points and aorta enhancers at top arterial stiffness index loci. The HUGIn platform (http://yunliweb.its.unc.edu/HUGIn/#plots) was used to visualize chromatin contact points at top arterial stiffness index loci. The panel of genes on the top indicate expression level in aorta with intensity of red color. Below this is an indication of aorta enhancer regions. The black vertical line in the center of each plot is aligned to the top variant at that locus. The probability of physical chromatin contact between each top variant and regions around it is indicated via the blue waveforms, which are estimated by taking into account the observed (black) versus expected (red) chromatin contact counts at each region around the top variant.

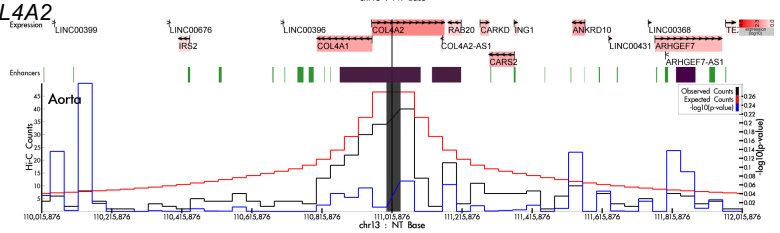
A. *TEX41*



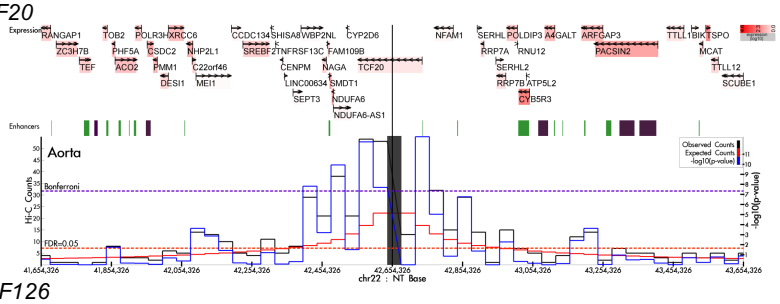
B. *FOXO1*



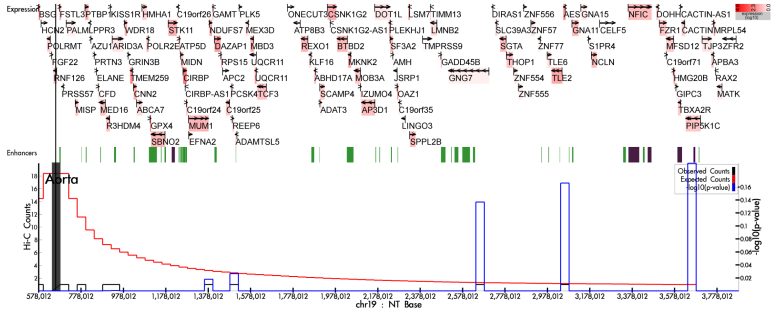
C. *COL4A2*



D. *TCF20*

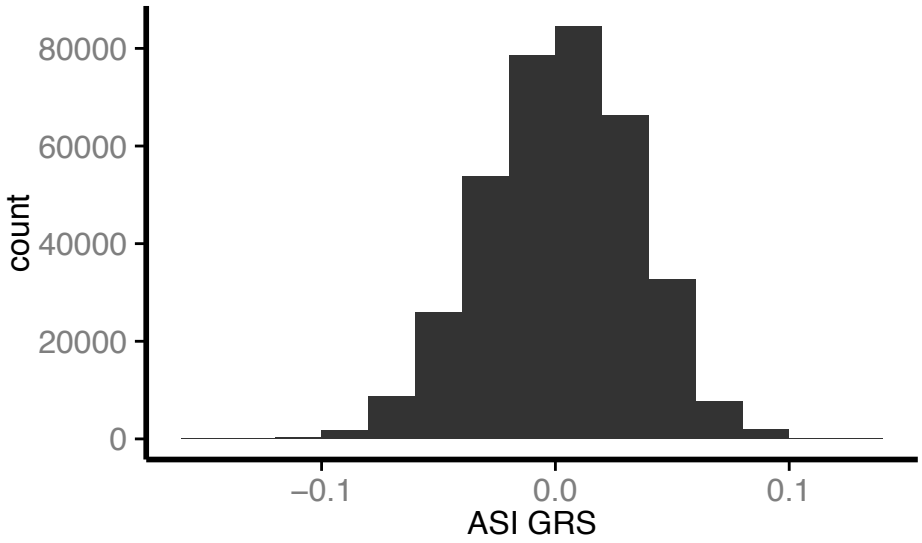


E. *RNF126*

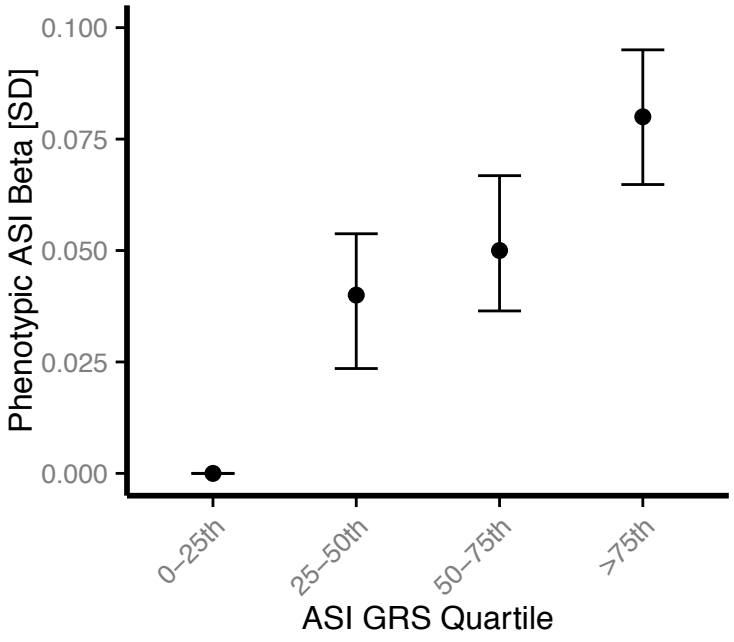


Supplementary Figure III: Arterial stiffness genetic risk score histogram and association with arterial stiffness index phenotype. A. Histogram of the arterial stiffness index raw genetic risk score (GRS) prior to inverse-rank normalization and adjustment, B. Association of quartiles of the adjusted, inverse-rank normalized arterial stiffness genetic risk score with the inverse-rank normalized arterial stiffness phenotype in SD (F-statistic: 138, $P=8x10^{-32}$).

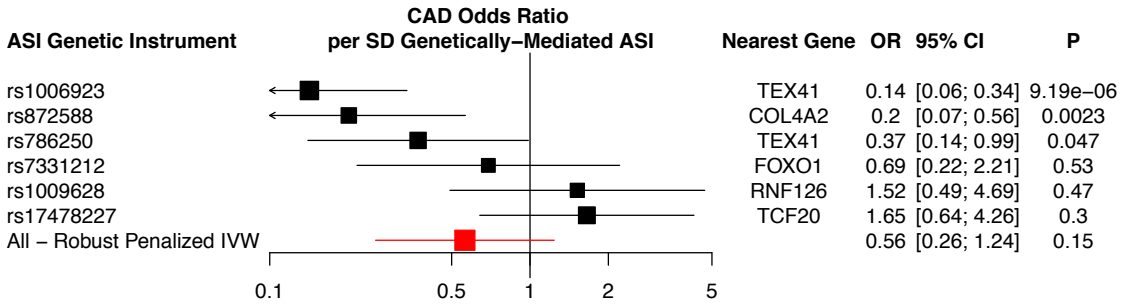
A.



B.



Supplementary Figure IV: Association of ASI genetic instruments, individually and combined, with prevalent CAD in 184,305 individuals (60,810 prevalent cases) from the CARDIOGRAMplusC4D cohort using 2-sample Mendelian Randomization. Variant-level odds ratios are reported as CAD effect normalized to the ASI effect. The combined ASI genetic risk score effect is provided from the robust, penalized inverse-variance weighted 2-sample MR method. ASI = Arterial stiffness index, CAD = coronary artery disease.



References

1. Martin JS, Xu Z, Reiner AP et al. HUGIn: Hi-C Unifying Genomic Interrogator. Bioinformatics 2017;33:3793-3795.
2. Dong C, Wei P, Jian X et al. Comparison and integration of deleteriousness prediction methods for nonsynonymous SNVs in whole exome sequencing studies. Hum Mol Genet 2015;24:2125-37.
3. Valenti L, Maloberti A, Signorini S et al. Iron Stores, Hepcidin, and Aortic Stiffness in Individuals with Hypertension. PLoS One 2015;10:e0134635.
4. Gaenzer H, Marschang P, Sturm W et al. Association between increased iron stores and impaired endothelial function in patients with hereditary hemochromatosis. J Am Coll Cardiol 2002;40:2189-94.
5. Nikpay M, Goel A, Won HH et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015;47:1121-1130.