Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure

Supplementary Information

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Supplementary Figures

Supplementary Figure 1 Quantile-Quantile plots and Manhattan plots of overall association results for pulse pressure (a,c) and mean arterial pressure (b,d). Quantile-Quantile plots show $-\log_{10}(P)$ of association results. λ_{GC} before genomic control was 1.08 and 1.12. Manhattan plots show $-\log_{10}(P)$ of association tests ordered by chromosome and position.

a)



Stage 1 Pulse Pressure λ =1.08

Stage 1 Mean Arterial Pressure λ =1.12





Pulse Pressure



Mean Arterial Pressure



Supplementary Figure 2 Forest plots of the stage 1 meta-analysis for the 8 SNPs at the novel PP and/or MAP loci. Each of the SNPs included in the figure showed genome-wide significant association (P<5x10⁻⁸) with PP, MAP or both in data from stages 1 and 2 combined. The contributing effect from each study is shown by a blue square, with confidence intervals indicated by horizontal lines. The contributing weight of each study to the meta-analysis is indicated by the size of the square. The combined meta-analysis estimate in the stage 1 data is shown at the bottom of each graph. M: male subset, F: female subset.



Forest plot for PP rs11222084

Cohorts

Forest plot for PP rs871606 Forest plot for PP rs2071518 TwinsUK F SUVIMAX M SUVIMAX F SHIP M SHIP F RSI PROCARDIS M PROCARDIS M PROCARDIS M DRCARDIS NTR NEDHS TwinsUK F SUVIMAX M SUVIMAX F SHIP M SHIP NSPHS NFBC1966 M NFBC1966 M NFBC1966 M NESDA F NESDA M MiGen controls F MiGen controls F MiGen S3 M KORA S3 M Colaus F CONTIS F CROATIS F CROATIS F COATIS M DGI contris F CROATIS M DGI contris F CROATIS M BHS C TIDGC M BS8C TIDGC F ASPS ARIC AGES NSPHS NFBC1966 M NFBC1966 M NESDA F MESDA F ME Cohorts + Summary Summary -15 -10 -5 0 5 10 -8 -6 -4 -2 0 2 4 6 Effects Effects

8



Cohorts

9



Cohorts

10

Supplementary Figure 3 Expression levels of 6 genes in the novel PP-associated regions and 4 genes in the novel MAPassociated regions measured in aorta tissue samples from 4 individuals

Further details are given in the Supplementary Note.

Cumulative (n=4) wiggle plots for a) PP and b) MAP associated gene transcripts are shown. *PIK3CG* expression was below the filtering threshold and is therefore not shown. *red:* total reads per base. *blue:* RefSeq intronic -and exonic regions. *black:* Human mRNAs. *grey:* Spliced ESTs.

c) As positive controls, expression levels of 4 genes (Epidermal growth factor receptor (*EGFR*), actin alpha 2 (*ACTA2*), collagen type IV alpha 1 (*COL4A1*) and elastin (*ELN*)) expected to be expressed in aortic tissue were measured in the aorta samples described in the Supplementary Note. Relative number of reads for each positive control gene transcript is presented as the log10 of the sum (n=4) of reads per kilo base per million.

d) Relative number of reads for 6 PP and 4 MAP -associated gene transcripts are presented as the sum (n=4) of reads per kilo base per million (RpkM). *PIK3CG* expression was below the filtering threshold and was set to 0. *GRB14* -and *ADRB1* transcripts were covered by reads located at only one or aberrant exonic -or intronic region and were therefore regarded as not expressed.

a)



b)





c)



MAP Sum (N=4) reads/Kb/Million (RpKM)



Supplementary Figure 4 Region plots of SNP association with *ADRB1* and *ZNF589* transcript expression. Statistical significance of each SNP is shown on the $-\log_{10}$ scale as a function of chromosome position (NCBI build 36). The correlations (r^2) of each of the surrounding SNPs to SNP rs319684 are shown by the shade indicated in the key. Gene locations and orientation are indicated below the plot. Fine –scale recombination rate is shown in blue.

a) Region plot of SNP association with *ADRB1* transcript expression in brain and blood (PFC; pre-frontal cortex, VC; visual cortex). SNP rs2782980 is associated with MAP in this study. The *P* value of association of rs2782980 with *ADRB1* is shown. The top eSNP for *ADRB1* expression in brain or blood is rs740746 which has $r^2=0.125$ with rs2782980 and shows association with MAP in our stage 1 analysis (*P*=8.9x10⁻⁶). The second most associated SNP is rs10787516 which has $r^2=0.092$ and shows association with MAP in our stage 1 analysis (*P*=5.0x10⁻⁶).

b) Region plot of SNP association with *ZNF589* transcript expression in monocytes. SNP rs319684 is the best available proxy in this database for the MAP-associated SNP at the *MAP4* locus rs319690 (r^2 =0.74). The *P* value of association of rs319684 with *ZNF589* expression is shown. The top eSNP for *ZNF589* expression in the region is rs1045482 which has r^2 =0.354 with rs319684. SNP rs6787599 which is in strong linkage disequilibrium with rs1045482 (r^2 =1) shows association with MAP in our stage 1 analysis (*P*=6.1x10⁻⁴).





Supplementary Tables

Supplementary Table 1: Sample population characteristics and genotyping platform details for each study.

A) Sample population characteristics. Stage 1: Age, Gene/Environment Susceptibility –Reykjavik (AGES) , Atherosclerosis Risk in Communities Study (ARIC), Austrian Stroke Prevention Study (ASPS), British 1958 Birth Cohort - Type 1 Diabetes Genetics Consortium (B58C-T1DGC), British 1958 Birth Cohort - Wellcome Trust Case Control Consortium (B58C-WTCCC), Baltimore Longitudinal Study of Ageing (BLSA), Busselton Health Study (BHS), Carlantino cohort (CARL), Cardiovascular Health Study (CHS), Cohorte Lausannoise (CoLaus), CROATIA-Vis, Diabetes Genetics Initiative controls only (DGI controls), Estonian Genome Project, University of Tartu (EGCUT), European Prospective Investigation of Cancer – Norfolk (EPIC Norfolk), ERF study, Fenland Study (Fenland), Framingham Heart Study (FHS), Finland-United States Investigation of NIDDM Genetics (FUSION controls), INGI Friuli Venezia Giulia (INGI FVG) study, Invecchiare in Chianti (INCHIANTI), Kooperative Gesundheitsforschung in der Region Augsburg S3 (KORA S3), Micro-Isolates in South Tyrol (EUROSPAN) (MICROS), Myocardial Infarction Genetics Consortium (MIGen controls), Netherlands Study of Depression and Anxiety (NESDA), Northern Finland Birth Cohort of 1966 (NFBC1966), Northern Swedish Population Health Study (EUROSPAN) (NSPHS), Netherlands Twin Registry (NTR), Orkney Complex Disease Study (ORCADES), Precocious Coronary Artery Disease (PROCARDIS entrols), Rotterdam Study I (RSI), Rotterdam Study II (RSII), Study of Health in Pomerania (SHIP), Supplemenation en Vitamines et Mineraux Antioxydants (SUVIMAX), TwinsUK, INGI Val Borbera, Stage 2: CROATIA-Korcula, CROATIA-Split, Estonian Genome Project, University of Tartu (EGCUT+), Kooperative Gesundheitsforschung in der Region Augsburg S4 (KORA F4), LifeLines, LONATIA, Porspective Study of Pravastatin in the Elderly at Risk (PROSPER/PHASE), Rotterdam Study III (RSIII), SardiNIA, Cardiovascular risk in Young Finns Study (YFS) and Women's Genome Health Study (WGHS).

									lambda			
		Age, years	Gender	PP mean	MAP mean	SBP mean	DBP mean	lambda	MAP		%Нур	
cohorts	n	(s.d.)	(% f)	(s.d.)	(s.d.)	(s.d.)	(s.d.)	PP (M/F)	(M/F)	%HTN	Ther	BMI
Stage 1												
AGES	3195	51	58	49.1 (11.1)	100.1 (12.0)	132.2 (16.9)	83.4 (9.6)	1.03	1.05	34.9	6.4	25.2 (3.5)
ARIC	9294	54.3 (5.7)	52	47.9 (12.9)	88.8 (12.0)	120.7 (18.0)	72.8 (10.4)	1.04	1.07	26.5	25.2	27.0 (4.8)
ASPS	767	65 (8.1)	58	57.2(17.76)	107.7 (14.3)	143.3 (22.8)	87.4 (9.9)	1.01	1.01	66.4	25.2	26.7 (4.0)
B58C-T1DGC	2580	44.3(0.3)	51	48.0 (8.5)	95.4 (11.7)	121.7 (15.3)	79.4 (10.5)	0.94/1.08	1.01/0.99	20.5	4.7	27.4 (4.9)
B58C-WTCCC	1473	44.9(0.4)	50	47.8 (8.5)	95.5 (12.0)	126.7 (15.2)	79.1 (10.2)	0.99/0.99	1.01/1.00	17.4	4.2	27.4 (4.7)
BLSA	701	42.4(13.2)	44	42.5 (10.9)	92.1 (11.6)	119.5 (15.0)	77.3 (10.2)	1.02/1.00	0.99/1.00	23.2	5.2	24.5 (3.6)
BHS	1038	47.2(13.3)	58	46.9 (12.4)	92.0(12.2)	121.2 (15.2)	75.0 (9.9)	1.01/0.99	1.00/1.00	23.8	13.8	26.0 (4.2)
CHS	3277	72.3 (5.39)	62	64.8 (18.5)	95.51 (14.2)	135 (21)	70 (11)	1.00	1.03	53	35	26.3 (4.4)
CoLaus	4969	51.7(9.5)	53	48.7 (12.1)	97.3 (13.9)	127.3 (17.4)	79.4 (10.8)	1.01/1.00	0.99/1.00	33.9	16	25.8 (4.6)
CROATIA-Vis	677	56.8 (15.6)	52	60.2 (27.5)	103.5 (13.8)	137.6 (24.5)	80.5 (11.5)	1.00	1.00	60.3	24.4	27.3 (4.3)
DGI controls	1277	56.1 (8.7)	51	52.5 (14.2)	98.9 (11.2)	133.3 (18.4)	80.1 (10.0)	0.99/1.01	1.02/1.01	41.4	18	26.7 (3.8)
												26.0
EGCUT	1835	41.5 (16.4)	53	48.6 (14.2)	95 (13.4)	127.1 (19.3)	78.7 (12.2)	0.95	0.98	34.4	20.7	(5.4)

		Age, years	Gender	PP mean	MAP mean	SBP mean	DBP mean	lambda	lambda MAP		%Hvp	
cohorts	n	(s.d.)	(% f)	(s.d.)	(s.d.)	(s.d.)	(s.d.)	PP (M/F)	(M/F)	%HTN	Ther	BMI
EPIC Norfolk	2100	57.2 (7.8)	54	52.9 (10.6)	101.5 (13.8)	136.7 (19.1)	83.9 (11.9)	0.93/0.98	1.01/1.01	45.6	16	26.3 (3.9)
ERF	2194	48.6 (14.5)	54	60.6 (16.7)	101.4 (13.4)	139.7 (20.8)	80.0 (10.00)	1.01	1.03	51.7	21.2	26.7 (4.7)
Fenland	1401	45.0 (7.3)	56	47.2 (9.6)	91.3 (12.1)	122.8 (16.3)	75.5 (10.7)	0.99/1.00	1.01/1.00	18.8	5.5	27.1 (4.9)
FHS	8096	38 (9)	54	43 (10)	91 (11)	119 (15)	77 (10)	1.05	1.06	17	5	25.9 (4.9)
FUSION controls	1046	62.3 (6.8)	51	60.8 (16.3)	105.0(13.4)	139.4 (19.3)	81.5 (10.3)	0.99/1.01	0.98/1.01	51.8	21	27.1 (4.0)
INCHIANTI	562	56.9(14.5)	55	58.1 (15.4)	103.0 (14.7)	138.4 (20.1)	81.4 (10.1)	1.00/1.00	1.00/1.00	59.6	23.7	27.1 (4.2)
INGI CARL	476	50.2	64	51.9 (15.6)	97.7 (13.8)	128.6 (25.6)	78.8 (13.1)	0.96	1.02	39.2	21.5	26.3 (5.7)
INGI FVG	617	51.5	59	52.1 (16.2)	102.7 (12.7)	137.3 (22.7)	85.6 (12.2)	0.99	0.99	58.4	21.9	25.0 (4.5)
INGI Val Borbera	1580	53.7 (18.1)	57	53.1 (14.8)	95 (12.5)	131.8 (22.1)	78.6 (10.9)	1.02	0.97	40.5	26.6	25.8 (4.5)
KORA S3	1644	52.5(10.1)	51	49.4 (13.0)	98.4 (11.8)	133.4 (18.5)	81.8 (10.9)	0.99/1.00	1.00/1.00	20.9	17	27.3 (4.1)
MICROS	1078	45.3 (16.1)	57	53.4 (14.4)	98.1 (13.8)	132.9 (20.2)	79.9 (11.1)	0.99	0.98	36.8	7.6	25.6 (4.8)
MIGen controls	1121	48.9(8.3)	38	47.4 (14)	97.1 (13.6)	127.1 (17.8)	80.2 (11.6)	1.00/1.00	0.99/1.01	36.4	13.4	27.1 (5.2)
NESDA	1591	41.6 (12.4)	69	53.3 (12.2)	99.2 (13.5)	134.9 (19.4)	81.6 (11.5)	0.91/0.91	0.91/0.91	36.0	36.0	25.5 (4.9)
NFBC1966	4761	31	52	47.5 (11.6)	93.0 (12.9)	125.2 (13.8)	77.5 (11.7)	0.97/0.90	1.01/1.03	21.7	2	24.6 (4.2)
NSPHS	636	47.0 (20.7)	53	49.6 (15.6)	91.6 (11.7)	122.8 (18.7)	74.1 (7.9)	1.00	1.01	37.6	19.1	26.3 (4.8)
NTR	241	36 (12)	66	46 (7)	89 (10)	122 (12)	74(10)	0.97	0.99	9.54	NA	25(4)
ORCADES	693	53.6 (15.7)	54	55.0 (14.9)	95.7 (12.9)	130.2 (19.3)	76.3 (10.1)	0.98	0.98	41	21.9	27.8 (4.9)
PROCARDIS												
controls	795	58.9 (6.9)	37	52.0 (13.5)	100.1 (11.9)	134.7 (18.6)	82.8 (10.0)	0.95/0.95	1.02/1.02	15	2	25.9 (3.7)
RSI	4737	68 (8)	60	66 (18)	97 (14)	139 (22)	74 (11)	1.03	1.04	53	18	26.2 (3.6)
RSII	1760	64 (7)	56	65 (17)	102 (13)	143 (21)	79 (11)	1.03	1.01	60	22	27.2 (4.2)
SHIP	3306	45.0 (13.9)	53	50.47 (13.7)	101.9 (15.3)	133.1 (20.2)	83.5 (11.3)	0.98/0.99	1.01/1.00	40.9	16.3	26.9 (4.7)
SUVIMAX	1673	50.5 (6.2)	60	43.0 (7.7)	92.4 (9.0)	120.9 (12.3)	78.0 (8.1)	1.00/1.00	1.00/1.00	19	0	23.5 (3.3)
TwinsUK	873	45.8 (11.9)	100	44.8 (10.0)	93.2 (12.5)	122.9 (15.4)	78.2 (10.3)	0.99	1.00	27.3	22	24.8 (4.6)
Total Stage 1	74064											

			Condor	DD moon			DPD moon	lambda	lambda		9/ Uvm	
cohorts	n	(s.d.)	(% f)	(s.d.)	(s.d.)	(s.d.)	(s.d.)	PP (M/F)	(M/F)	%HTN	70Hyp Ther	вмі
Stage 2		(0.0.1)	(((,.)			
CROATIA-		56.3										
Korcula	876	(13.9)	64	58.5 (23.2)	104.1 (18.4)	143.1 (24.9)	84.6 (19.4)	1.03	1.08	51.4	28.6	27.3 (4.2)
CROATIA-Split	498	49.0 (14.7)	57	52.2 (11.2)	96.2 (14.8)	130.9 (20.7)	78.7 (12.5)	0.99	0.99	35.4	21.5	26.9 (4.2)
												25.1
EGCUT+	600	38.1 (15.8)	46.1	46.6 (12.6)	92.7 (11.3)	123.8 (17.1)	77.2 (10.0)	1.01	1.01	29.0	NA	(4.35)
KORA F4	1709	60.6 (8.9)	52.2	53.53 (13.2)	104.1 (11.9)	124.8 (18.7)	76.3 (9.8)	1.01	1.00	35.2	34.5	28.0 (4.7)
LifeLines	3202	54.9 (9.7)	60.5	55.7 (13.4)	96.7 (12.2)	133.8 (18.8)	78.1 (10.3)	0.99	1.00	39.5	18.7	26.7 (4.2)
LOLIPOP_EW_A	878	53.3 (10.4)	23	53.1 (14.3)	101.1 (14.6)	136.5 (22.1)	83.4 (12.0)	0.99	0.99	47	25.6	27.9 (4.8)
LOLIPOP_EW_P	725	55.9 (8.9)	0	56.6 (13.6)	104.2 (14.8)	141.9 (21.8)	85.3 (12.4)	1.00	0.99	56.6	31.8	28.6 (5.3)
LOLIPOP_EW610	927	56.0 (9.8)	27	53.2 (13.4)	100.8 (13.8)	136.2 (20.9)	83.1 (11.3)	1.00	0.99	45.1	20	27.5 (4.7)
LBC1921	376	69.0 (0.6)	64	88.4 (21.1)	116.7 (16.8)	175.6 (27.3)	87.2 (14.1)	0.99	0.99	91.8	34.6	26.2 (4.2)
LBC1936	800	79.0 (0.8)	52	69.2 (15.2)	107.6 (13.0)	153.8 (20.3)	84.6 (11.1)	1.01	1.01	76.4	31.9	27.5 (4.3)
MESA	2501	62.7 (10.3)	52	55.0 (17.5)	91.7 (14.5)	128.3 (23.7)	73.4 (11.6)	1.00	1.00	38.6	33.3	27.4 (5.1)
PROSPER/PHASE	4535	75.3 (3.4)	55	75.0 (18.5)	116.5 (14.5)	166.4 (23.4)	91.5 (12.5)	NA	NA	65.3	73.2	26.8 (4.2)
RSIII	2063	56.0 (5.8)	56	50.9 (12.9)	101.6 (14.4)	132.4 (18.7)	82.6 (10.8)	1.01	1.01	47.2	20.8	27.7 (4.7)
SardiNIA	4305	43.6 (17.7)	56	48.6 (13.0)	93.3 (12.7)	125.7 (18.7)	77.1 (11.0)	1.10	1.11	14.1	11.6	25.3 (4.7)
YFS	1987	37.7 (5.0)	54	45.3 (9.1)	91.6 (12.5)	121.8 (15.3)	76.5 (12.0)	1.01	1.01	6	7	26.0 (4.8)
WGHS	22625	54.2 (7.1)	100.0%	47.6 (10.4)	93.8 (11.9)	125.5 (16.4)	78.0 (10.7)	1.09	1.07	24.7%	12.9%	25.9 (5.0)
Total Stage 2	48607											

B) Genotyping platforms, filters applied to SNPs and individuals (if any) before imputation, imputation software and genotype-phenotype association software are given. All individual study association results underwent genomic control before meta-analysis. Studies which used the short cut of PP and MAP effect sizes and standard errors are indicated in the last column.

	Genotyping platform	Calling algorithm	Filtering	g of genotyp	oes before ir	nputatio	n	No. SNPs	Imputati on	Imputati on panel	Filtering of	Genotype- phenotype	Genomic o lambda va	ontrol lues	Short cut for
Cohort			Sampl e Callrat e	SNP Callrate	SNP HWE	SNP MAF	Other filter	used for imputati on	software	(NCBI version)	impute d genotyp es	analysis software	SBP (males/ Females)	DBP (males/ Female s)	PP and MAP associati on
Stage 1															
AGES	Illumina 370CNV	Illumina BeadStudio	>= 95%	>=0.97	>=10 ⁻⁶	>=0. 01	none	325,094	MACH ¹ v1.0.16	36; v22	none	PLINK and R	1.06	1.05	n
ARIC	Affymetrix 6.0	Birdseed	>=95 %	>=0.95	>=10 ⁻⁵	>=0. 01	none	704,588	MACH ¹ v1.0.16	35; v21	none	PLINK, MACH2QTL	1.04	1.04	n
ASPS	Illumina Human610	Beadstudio	>=97. 5%	>=0.98	>=10 ⁻⁶	>=0. 01	none	550635	MACH ¹ v1.0.15	36; v22	none	ProbABEL	1.02	1.02	n
B58C-WTCCC	Affymetrix 500K	СНІАМО	>0.97	>0.95 MAF>0. 05, >0.99 MAF<0. 05	5.70x10 ⁻	none	none	490,032	IMPUTE ²	35; v21	none	SNPTEST	1.02/1.0 1	1.02/1. 00	У
B58C-T1DGC	Illumina 550K	ILLUMINUS	>0.98	none	none	none	SNPs mapping to >1 locus in the genome	539,548	MACH ¹ V1.0.13	35; v21	none	ProbABEL v0.0- 5b	1.00/1.0 0	1.01/1. 00	У
BLSA	Illumina 550K	Beadstudio	>0.97	>0.99	>10 ⁻⁴	>0.0 1	none	501,764	MACH ¹ v1.0.15	35; v21	r2hat <0.3, MAF < 1%	Merlin offline	1.04/1.0 1	1.05/1. 03	У
BHS	Illumina 610-Quad chip	Illumina BeadStudio	>0.94	99% for SNPS with MAF<1 %, 95% for all other SNPs	p<5.7x1 O ⁻⁷ for all SNPs at imputati on	Non e	Monomorphic SNPs removed	549,294	MACH ¹	36	none	mach2qtl	NA	NA	n

	Genotyping platform	Calling algorithm	Filtering	र of genotyp	Jes before ir	nputatio	n	No. SNPs used for imputati on	Imputati on software	Imputati Impu on on pa software (NCB versi	Imputati on panel (NCBI version)	Filtering of impute d genotyp es	Genotype- phenotype analysis software	Genomic c lambda va	ontrol lues	Short cut for PP and MAP associati on
Cohort			Sampl e Callrat e	SNP Callrate	SNP HWE	SNP MAF	Other filter						SBP	DBP		
СНЅ	Illumina 370CNV	BeadStudio	>=97 %	>0.95	>=10 ⁻⁵	none	>2 replicate or Mendelian errors, heterozyg. freq. =0	306,655	BIMBAM 10 ³ v0.99	36; v22	varianc e of allele dosage < 0.005	R	1.01	1.03	n	
CoLaus	Affymetrix 500K	BRLMM	>0.95	>0.70	>10 ⁻⁷	>0	none	390,631	IMPUTE ² v0.2	35; v21	none	custom C++	0.99/0.9 9	1.00/1. 01	У	
CROATIA-Vis	illumina 318K	Beadstudio	>98%	>98%	10 ⁻⁶	>0.0	ethnic outliers, gender mismatches, duplicates, excess IBS, incompatible with the pedigree, excess heterozygosity	275,093	MACH ¹	36 v22	none	ProbABEL	1.07	0.99	n	
DGI cntrols	Affymetrix 500K	BRLMM	none	>0.95	>10 ⁻⁶ in controls	≥0 0 1	SNPs mapping to >1 locus in the genome	378,860	MACH ¹ v1.0.9	35; v21	none	SNPTEST	1.01/1.0	1.00/0. 99	У	
EGCUT	Illumina 370CNV	Illumina BeadStudio	≥95%	≥98%	10-6	≥0. 1	Cryptic relatedness; Incomplete phenot pe information	326,339	IMPUTE ² v0.5.0	36; v22	none	SNPTEST	0.99	0.99	n	
EPIC Norfolk	Affymetrix 500K	BRLMM	≥0.94	≥0.90	>10 ⁻⁶	≥0.0 1	none	397,438	IMPUTE ²	35; v21	none	SNPTEST	1.00/1.0 1	0.99/1. 01	У	

	Genotyping platform	Calling algorithm	Filtering	g of genotyp	es before i	mputatio	n	No. SNPs used for imputati on	Imputati on • software i	Imputati In on oi software (N	Imputati Imputati on on panel software (NCBI version)	Filtering of impute d genotyp es	Genotype- phenotype analysis software	Genomic c lambda va	ontrol lues	Short cut for PP and MAP associati on
Cohort			Sampl e Callrat e	SNP Callrate	SNP HWE	SNP MAF	Other filter						SBP	DBP		
ERF	illumina 318K, 370K, Affymetrix 250K	BRLMM	>98%	>96%	10 ⁻⁶	>0.0	ethnic outliers, gender mismatches, duplicates, excess IBS, incompatible with the pedigree, excess heterozygosity	487,573	MACH ¹	36 v22	none	ProbABEL	1.01	1.01	n	
Fenland	AffymetrixS NP 5.0	BRLMM	≥0.95	≥0.90	>10 ⁻⁶	≥0.0 1	none	362, 59	IMPUTE ² v0.4.2	36; v22	none	SNPTEST	0.99	0.99	У	
FHS	Affymetrix 500K and MIPS 50K combined	BRLMM	>=97 %	>=0.97	>=10 ⁻⁶	>0.0 1	Mishap p < 10-9, Mendelian err. > 100	378,163	MACH ¹ v1.0.15	36; v22	none	LMEKIN package in R	1.07	1.04	n	
FUSION controls	Illumina HumanHap 300	Beadstudio , clustering with FUSION	97%	≥0.90	>10 ⁻⁶	>0.0 1	>3 Mendel or duplicate errors	304,581	MACH ¹	35; v21	r2hat <0.3	Merlin	0.99/1.0 0	1.00/1. 01	n	
INCHIANTI	Illumina 550K	Beadstudio	>0.97	>0.99	>10 ⁻⁴	>0.0 1	none	484,115	MACH ¹ v1.0.15	35; v21	r2hat <0.3, MAF < 1%	Merlin offline	0.99/1.0 1	0.99/1. 01	У	
INGI CARL	Illumina 370CNV	BeadStudio	>95%	>90%	>10 ⁻⁴	>=0. 01	None	266389	MACH ¹ v1.0.16	36; v22	r2hat <0.3	GenABEL/Prob ABEL	1.00	0.99	n	
INGI FVG	Illumina 370CNV	BeadStudio	>95%	>90%	>10 ⁻⁴	>=0. 01	None	276271	MACH ¹ v1.0.16	36; v22	r2hat <0.3	GenABEL/Prob ABEL	0.99	1.00	n	

	Genotyping platform	Calling algorithm	Filtering	g of genotyp	oes before ir	nputatio	n	No. SNPs used for imputati on	Imputati on software	Imputati on panel (NCBI version)	Filtering of impute d genotyp es	Genotype- phenotype analysis software	Genomic c lambda va	ontrol lues	Short cut for PP and MAP associati on
Cohort			Sampl e Callrat e	SNP Callrate	SNP HWE	SNP MAF	Other filter						SBP	DBP	
INGI Val Borbera	Illumina HumanCNV 370-Quadv3	Beadstudio	>95%	>90%	>10 ⁻⁴	>=0. 01	none	324,319	MACH ¹	36 v22	r2hat < 0.3, average posterio r probabil ity < 0.9, MAF >= 0.01	GenABEL/Prob ABEL	1/0.99	1.00/0. 99	n
KORA S3	Affymetrix 500K	BRLMM	>0.93 each chip	>0.90	None	≥0.0 1	none	490,032	MACH ¹ v1.0.9	35; v21	none	PLINK	1.01/0.9 9	1.01/1. 00	У
MICROS	Illumina 318K	Beadstudio	>98%	>98%	10 ⁻⁶	>0.0	ethnic outliers, gender mismatches, duplicates, excess IBS, incompatible with the pedigree, excess heterozygosity	309,008	MACH ¹	36 v22	none	ProbABEL	0.973	0.98	n
MIGen controls	Affymetrix 6.0 (1M)	BirdSuite1	≥0.95	≥0.95	≥10 ⁻⁶	≥0.0 1	close relatives	750,407	MACH ¹ v1.013	36; v22	none	SNPTEST	0.999/1. 036	0.99/1. 02	У

	Genotyping platform	Calling algorithm	Filtering	g of genotyp	oes before ii	nputatio	n	No. SNPs used for imputati on	Imputati on software	Imputati on panel (NCBI version)	Filtering of impute d genotyp es	Genotype- phenotype analysis software	Genomic c lambda va	ontrol lues	Short cut for PP and MAP associati on
Cohort			Sampl e Callrat e	SNP Callrate	SNP HWE	SNP MAF	Other filter						SBP	DBP	
NESDA	Perlegen 600K	Perlegen	≥ .95	≥0.95	None	>0.0	SNPSZZZ5% genotype mismatches, Z5% Mendelian errors, unknown SNP location; SAMPLES: ethnic outliers, XO and XXY samples, high genome- wide homo- or heterozygosity, excess IBS	435,291	IMPUTE ² v0.3.2	36; v22	none	SNPTEST v1.1.4		1.02	У
NFBC1966	Illumina 370	Beadstudio	NA	>0.95	>10 ⁻⁴	≥0.0 1	none	328,007	IMPUTE ²	35; v21	none	SNPTEST	1.02/1.0 3	1.01/1. 03	У
NSPHS	Illumina 318K	Beadstudio	>98%	>98%	10 ⁻⁶	>0.0	ethnic outliers, gender mismatches, duplicates, excess IBS, excess heterozygosity		MACH ¹	36 v22	none	ProbABEL	1.00	1.00	n

	Genotyping platform	Calling algorithm	Filtering	g of genotyg	oes before ir	nputatio	n	No. SNPs used for imputati on	Imputati on software	Imputati on panel (NCBI version)	Filtering of impute d genotyp es	Genotype- phenotype analysis software	Genomic c lambda va	ontrol lues	Short cut for PP and MAP associati on
Cohort			Sampl e Callrat e	SNP Callrate	SNP HWE	SNP MAF	Other filter						SBP	DBP	
NTR	Affymetrix 600K/Perleg en	Perlegen Proprietary Calling Algorithm	>0.90	>0.95	None	≥0.0 1	Mendel errors > 2; Duplicate errors > 2	425,05	IMPUTE ² 0.5	36; v24	proper info > 0.30; r2hat > 0.30; MAF > 0.005	SNPTEST	0.97	0.97	n
ORCADES	Illumina 318K	Beadstudio	>98%	>98%	10 ⁻⁶	>0.0	ethnic outliers, gender mismatches, duplicates, excess IBS, incompatible with the pedigree, excess heterozygosity	298,785	MACH ¹	36 v22	none	ProbABEL	0.99	0.98	n
PROCARDIS cntrols	Illumina 1M	Bead studio	>0.95	>0.95	>10 ⁻³	Non e	none	882,598	IMPUTE ² v0.3.2	36; v22	none	SNPTEST	0.99/1.0	0.99/1. 02	У
RSI	Illumina 550K	Beadstudio	>=97. 5%	>=0.98	>=10 ⁻⁶	>=0. 01	none	530,683	MACH ¹ v1.0.15	36; v22	none	ProbABEL	1.05	1.04	n

	Genotyping platform	Calling algorithm	Filtering	g of genotyp	oes before ir	nputatio	n	No. SNPs used for imputati on	Imputati on software	Imputati on panel (NCBI version)	Filtering of impute d genotyp es	Genotype- phenotype analysis software	Genomic c lambda va	ontrol lues	Short cut for PP and MAP associati on
Cohort			Sampl e Callrat e	SNP Callrate	SNP HWE	SNP MAF	Other filter						SBP	DBP	
RSII	Illumina 550K	Beadstudio	>=97. 5%	>=0.98	>10 ⁻⁶	>0.0 1	none	495,478	MACH ¹ v1.0.15	36; v22	none	ProbABEL	1.01	1.01	n
SHIP	Affymetrix SNP6.0	BirdsuiteV2	>0.92	none	None	NA	QC CR ≥0.86	869,224	IMPUTE ² v0.5.0	36; v22	none	SNPTEST	1.01/1.0	1.01/0. 99	У
SUVIMAX	Illumina 317K	Beadstudio	>0.94	none	None	NA	none	302,607	IMPUTE ² v0.3.2	35; v21	none	Custom C++	1.01/0.9 9	1.02/0. 99	У
TwinsUK	Illumina 317K	Beadstudio	NA	>0.95	>10 ⁻⁶ in controls	≥0.0 1	SNPs mapping >1 loci	303940	IMPUTE ² V 0.4.2	36; v22	none	SNPTEST	1.00	1.01	У
Stage2															
CROATIA- Korcula	Illumina CNV370_Du o	Beadstudio	>97	>98	>10 ⁻⁶	>0.0 1	none	316730	MACH ¹ v1.0.15	36; v22	none	probABEL with mmscore function	0.98*	0.99*	n
CROATIA- Split	Illumina CNV370_Qu ad	Beadstudio	>97	>98	>10 ⁻⁶	>0.0 1	none	331012	MACH ¹ v1.0.15	36; v22	none	probABEL with mmscore function	0.99*	0.99*	n
EGCUT+	Illumina 370CNV	Illumina BeadStudio	≥95%	≥98%	10 ⁻⁶	≥0.0 1	Gryptic relatedness; Incomplete phenotype information	326,339	IMPUTE ² v0.5.0	36; v22	none	SNPTEST	0.99	0.99	n
KORA F4	Affymetrix 6.0	Birdseed2	≥ 0.93	none	None	none	none	651596	IMPUTE ² v0.4.2	36; v22	none	SNPTEST	1	1.00	n

	Genotyping platform	Calling algorithm	Filterin	g of genotyp	oes before i	mputatio	n	No. SNPs used for imputati on	Imputati on software	Imputati on panel (NCBI version)	Filtering of impute d genotyp es	Genotype- phenotype analysis software	Genomic o lambda va	control ilues	Short cut for PP and MAP associati on
Cohort			Sampl e Callrat e	SNP Callrate	SNP HWE	SNP MAF	Other filter						SBP	DBP	
LifeLines	Illumina CytoSNP v 2.0- 300K	GenomeSt udio	>95	>99	>10 ⁻⁴	≥0.0 1	none	234833	IMPUTE ² v0.3.2	36; v22	None	SNPTEST	0.99	1.00	n
LOLIPOP_EW _A	Affymetrix 500K	BRLMM	NA	>0.90	>10 ⁻⁶	≥0.0 1	none	374773	MACH ¹	35; v21	MACH Rsq ≥ 0.3, maf ≥0.01	mach2qtl	0.99	0.99	n
LOLIPOP_EW _P	Perlegen custom	NA	NA	>0.90	>10 ⁻⁶	≥0.0 1	none	184469	MACH ¹	35; v21	MACH Rsq ≥ 0.3, maf ≥0.01	mach2qtl	0.99	0.99	n
LOLIPOP_EW 610	Illumina Human610	Beadstudio	NA	>0.90	>10 ⁻⁶	≥0.0 1	none	544620	MACH ¹	36; v22	MACH Rsq ≥ 0.3, maf ≥0.01	mach2qtl	0.99	0.99	n
LBC1921	Illumina Human 610_Quadv 1	Beadstudio	> 0.9 5	>=0.98	>0.001	≥0.0 1	none	535709	MACH ¹	36; v22	None	mach2qtl	0.99	0.99	n
LBC1936	Illumina Human 610_Quadv 1	Beadstudio	>=0.9 5	>=0.98	>0.001	≥0.0 1	none	535709	MACH ¹	36; v22	None	mach2qtl	1.01	1.01	n
MESA	Affymetrix SNP6.0	Beadstudio	>=95 %	>=0.95	N/A	>=0. 01	heterozygosity< =0.53	872,242	IMPUTE ² 2.1.0	36	none	SNPTEST	1	1.00	n
PROSPECT/P HASE		Beadstudio	>=97. 5%	>=0.98	>10E-6	>0.0 1	none	NA	NA	NA	NA	SPSS	NA	NA	n
RSIII	Illumina Human610	Beadstudio	>=97. 5%	>=0.95	>=10 ⁻⁶	>=0. 01	none	587,388	MACH ¹ v1.0.15	36; v22	none	ProbABEL	1.00	1.01	n
SardiNIA	Affymetrix 500	BRLMM	>0.95	>0.95	>10 ⁻⁶	>0.0 1	none	356,359	MACH ¹ v1.0.15	35; v21	none	Merlin offline	1.14	1.14	n

	Genotyping platform	Calling algorithm	Filtering	g of genotyp	oes before ir	nputatio	n	No. SNPs used for imputati on	Imputati on software	Imputati on panel (NCBI version)	Filtering of impute d genotyp es	Genotype- phenotype analysis software	Genomic c lambda va	ontrol lues	Short cut for PP and MAP associati on
Cohort			Sampl e Callrat e	SNP Callrate	SNP HWE	SNP MAF	Other filter						SBP	DBP	
YFS	Illumina custom made BeadChip Human 670-	Illuminus	> 97	≥ 95%	>=10 ⁻⁶	≥ 0.01	none	546674	MACH ¹	36;v22	none	probABEL	0.99	1.01	n
WGHS	Illumina HumanHap 300 DuoPlus	Beadstudio 3.3	>=98 %	>90%	>=10 ⁻⁶	<0.0 1	none	317,186	MACH ¹ v1.0.15	36; v22	none	ProbABEL, R, bash scripting	1.06	1.06	n

Supplementary Table 2 Association results for pulse pressure, mean arterial pressure, systolic blood pressure and diastolic blood pressure at all loci previously reported as showing association with SBP or DBP (or both), at all novel loci showing association with pulse pressure or mean arterial pressure (or both) and at loci selected for follow-up in stage 2.

A) Pulse pressure association results from stage 1 (discovery), stage 2 (follow-up) and stages 1 and 2 combined for all previously reported SNPs at the 29 loci showing association with diastolic and/or systolic blood pressure and SNPs which reached nominal significance after stage 1 ($P < 1 \times 10^{-5}$) for association with pulse pressure in those regions in this study. For each region, the results for the top SNP in the pulse pressure analysis is shown along with the pulse pressure association results for the corresponding independently reported SNP in that region. * Study which first reported the SNP: Ehret *et al*⁴, Levy *et al*.⁵, Newton-Cheh *et al*.⁶ . # r² of the top SNP in the region for pulse pressure and the independently reported SNP. rs1173756 is a synonymous coding SNP in *C5orf23*.

		Study of	Coded												
	SNP	origin*	allele												
Region	chr: NCBI 36 posn	(r ^{2#})	& freq		Stag	e 1			Stag	ge 2		Cor	nbined Sta	ige 1 + Stag	ge 2
				Ν				Ν				Ν			
				effective	Beta	SE	Р	effective	Beta	SE	Р	effective	Beta	SE	Р
	rs17367504		G												
MTHFR	chr1: 11785365	Ehret <i>et al</i>	0.167	73689	-0.253	0.082	1.99E-03	46754	-0.198	0.104	5.66E-02	120442	-0.232	0.064	3.09E-04
	rs2932538		G												
MOV10	chr1: 113018066	Ehret <i>et al</i>	0.742	67059	0.246	0.070	4.55E-04	38265	0.074	0.090	4.15E-01	105324	0.181	0.055	1.08E-03
	rs13082711		Т												
SLC4A7	chr3: 27512913	Ehret <i>et al</i>	0.798	69548	0.031	0.071	6.61E-01	39400	-0.181	0.092	4.90E-02	108948	-0.048	0.056	3.89E-01
	rs3774372		Т												
ULK4	chr3: 41852418	Ehret <i>et al</i>	0.775	73758	0.295	0.077	1.16E-04	44028	0.303	0.099	2.13E-03	117786	0.298	0.060	8.32E-07
	rs9815354		G												
ULK4	chr3: 41887655	Levy <i>et al</i>	0.772	68807	0.277	0.079	4.27E-04	38418	0.291	0.104	4.92E-03	107224	0.282	0.063	6.63E-06
	rs419076		Т												
MECOM	chr3: 170583580	Ehret <i>et al</i>	0.436	73481	0.176	0.059	2.75E-03	41247	0.198	0.076	9.33E-03	114727	0.184	0.047	7.55E-05
	rs1458038		Т												
FGF5	chr4: 81383747	Ehret <i>et al</i>	0.3	68314	0.211	0.067	1.64E-03	39239	0.185	0.087	3.28E-02	107553	0.201	0.053	1.47E-04
	rs13107325		Т												
SLC39A8	chr4: 103407732	Ehret <i>et al</i>	0.117	63443	-0.338	0.124	6.52E-03	46534	-0.214	0.151	1.57E-01	109977	-0.288	0.096	2.69E-03
GUCY1A3-	rs13139571		C												
GUCY1B3	chr4: 156864963	Ehret <i>et al</i>	0.742	71136	0.088	0.070	2.09E-01	40739	0.139	0.089	1.20E-01	111875	0.107	0.055	5.14E-02
NPR3-	rs1173756		Т												
C5orf23	chr5: 32825609	This study	0.525	73207	-0.324	0.059	4.10E-08	48371	-0.178	0.073	1.54E-02	121577	-0.267	0.046	6.85E-09

		Study of	Coded												
_ ·	SNP	origin*	allele		<i>.</i>				. .					4 . 6	
Region	chr: NCBI 36 posh	(r)	& freq	N	Stag	e 1		N	Stag	ge 2		Cor	nbined Sta	ige 1 + Staj	ge 2
				N effective	Beta	SE	Р	N effective	Beta	SE	Р	N effective	Beta	SE	Р
NPR3-	rs1173771	Ehret <i>et al</i>	G								-				-
C5orf23	chr5: 32850785	(0.759)	0.525	73371	0.304	0.060	3.47E-07	43737	0.230	0.077	2.72E-03	117108	0.276	0.047	4.56E-09
	rs11953630		Т												
EBF1	chr5: 157777980	Ehret <i>et al</i>	0.342	73190	-0.214	0.061	4.32E-04	40852	-0.077	0.079	3.31E-01	114042	-0.163	0.048	7.16E-04
	rs1799945		G												
HFE	chr6: 26199158	Ehret <i>et al</i>	0.182	70871	0.159	0.084	5.75E-02	40739	0.219	0.107	4.15E-02	111611	0.182	0.066	5.92E-03
	rs805303		G												
BAT2-BAT5	chr6: 31724345	Ehret <i>et al</i>	0.653	73090	0.188	0.061	2.00E-03	45953	0.066	0.077	3.92E-01	119043	0.141	0.048	3.14E-03
	rs4373814		G												
CACNB2(5')	chr10: 18459978	Ehret <i>et al</i>	0.633	71465	-0.143	0.060	1.68E-02	39833	0.034	0.078	6.62E-01	111298	-0.077	0.047	1.04E-01
	rs1813353		Т												
CACNB2(3')	chr10: 18747454	Ehret <i>et al</i>	0.649	72095	0.116	0.064	6.82E-02	40515	0.100	0.083	2.27E-01	112610	0.110	0.050	2.91E-02
	rs4590817		G												
C10orf107	chr10: 63137559	Ehret <i>et al</i>	0.825	72693	0.236	0.081	3.42E-03	41049	0.352	0.104	7.35E-04	113742	0.280	0.064	1.18E-05
BL 85 4	rs9663362		G					10000					0.074		
PLCE-1	chr10: 95885167	This study	0.533	/359/	-0.297	0.059	4.48E-07	43806	-0.228	0.075	2.48E-03	11/404	-0.271	0.046	5.18E-09
	rs932764	Ehret et al	G	72440	0.201	0.050	2.005.00	40000	0.244	0.070	C 745 00	111007	0.255	0.047	C 005 00
PLCE-I	cnr10: 95885930	(0.845)	0.425	/3110	0.281	0.059	2.09E-06	40896	0.211	0.078	6.71E-03	114007	0.255	0.047	6.08E-08
CYP17A1-	rs1004467	Levy $et a$	0.067	00770	0 5 0 7	0.000	1 075 00	11226	0.200	0 1 2 7	2 715 02	112054	0.470	0.079	6 47E 10
NT3C2	cill 10. 104564497	(1.0)	0.007	12120	-0.597	0.098	1.072-09	41220	-0.260	0.127	2.71E-02	115954	-0.479	0.078	0.472-10
NT5C2	chr10.101585830	This study	0 0 2 3	72054	0 507	0 008	0 96E-10	11266	0.274	0 1 2 7	2 07F-02	11///20	0 477	0.077	7 225-10
CVP1741-	rs11191548	Fhret <i>et al</i>	0.933 T	73034	0.557	0.098	9.90L-10	41300	0.274	0.127	3.071-02	114420	0.477	0.077	7.551-10
NT5C2	chr10: 104836168	(0.485)	0 942	71891	0 573	0 104	3.59F-08	43947	0 459	0 1 3 0	4 18F-04	115837	0 529	0.081	7.68F-11
111302	rs17296765	(0.103)	<u>т</u>	71001	0.575	0.101	0.001 00	100 17	0.135	0.150		110007	0.525	0.001	71002 22
ADM	chr11: 10288865	This study	0.142	72230	0.472	0.090	1.50E-07	40152	0.157	0.120	1.92E-01	112382	0.359	0.072	6.05E-07
	rs7129220	Ehret <i>et al</i>	G		-										
ADM	chr11: 10307114	(0.932)	0.867	69401	-0.470	0.094	6.12E-07	41420	-0.223	0.124	7.31E-02	110821	-0.380	0.075	4.25E-07
		This													
	rs381815	study/	Т												
PLEKHA7	chr11: 16858844	Ehret <i>et al</i>	0.297	72901	0.308	0.066	3.47E-06	41243	0.113	0.087	1.91E-01	114144	0.236	0.053	7.48E-06

		Study of	Coded												
	SNP	origin*	allele												
Region	chr: NCBI 36 posn	(r²*)	& freq		Stag	e 1			Sta	ge 2		Cor	nbined Sta	ge 1 + Sta	ge 2
				N				N				N			
				effective	Beta	SE	Ρ	effective	Beta	SE	Ρ	effective	Beta	SE	Ρ
FLJ32810-	rs633185		G												
TMEM133	chr11: 100098748	Ehret <i>et al</i>	0.317	72563	-0.258	0.065	7.94E-05	40956	-0.126	0.085	1.37E-01	113519	-0.209	0.052	5.49E-05
	rs2681472	Levy <i>et al</i>	G												
ATP2B1	chr12: 88533090	(1.0)	0.11	73533	-0.383	0.080	1.75E-06	45786	-0.342	0.101	7.30E-04	119320	-0.367	0.063	5.07E-09
	rs2681492	Levy <i>et al</i>	Т												
ATP2B1	chr12: 88537220	(0.92)	0.883	70236	0.381	0.078	1.18E-06	44422	0.307	0.099	1.96E-03	114658	0.353	0.062	9.91E-09
		This													
	rs17249754	study/	G												
ATP2B1	chr12: 88584717	Ehret <i>et al</i>	0.892	72022	0.393	0.081	1.09E-06	43658	0.391	0.102	1.25E-04	115680	0.392	0.063	5.54E-10
	rs3184504		Т												
ATXN2	chr12: 110368991	Ehret <i>et al</i>	0.408	69741	0.097	0.060	1.09E-01	45074	0.199	0.075	7.94E-03	114815	0.137	0.047	3.57E-03
	rs2384550		G												
ATXN2	chr12: 113837114	Levy et al	0.658	73810	0.130	0.062	3.46E-02	48126	0.075	0.078	3.37E-01	121936	0.109	0.048	2.43E-02
	rs10850411		Т												
TBX5-TBX3	chr12: 113872179	Ehret <i>et al</i>	0.717	69558	0.088	0.065	1.77E-01	38948	0.170	0.086	4.79E-02	108506	0.118	0.052	2.30E-02
	rs1378942		C												
CSK	chr15: 72864420	Ehret <i>et al</i>	0.333	73412	0.108	0.061	7.89E-02	48324	0.210	0.077	6.63E-03	121736	0.147	0.048	2.18E-03
	rs2521501		Т												
FES	chr15: 89238392	Ehret <i>et al</i>	0.373	43863	0.295	0.083	3.72E-04	28743	0.109	0.096	2.55E-01	72606	0.216	0.063	5.90E-04
		This													
	rs17608766	study/	Т												
GOSR2	chr17: 42368270	Ehret <i>et al</i>	0.908	62353	-0.578	0.088	5.18E-11	41303	-0.467	0.109	1.90E-05	103656	-0.534	0.069	6.39E-15
	rs12940887		Т												
ZNF652	chr17: 44757806	Ehret <i>et al</i>	0.417	72190	0.055	0.061	3.69E-01	43164	-0.024	0.078	7.58E-01	115355	0.025	0.048	6.06E-01
	rs1327235		G												
JAG1	chr20:10917030	Ehret <i>et al</i>	0.575	72861	0.105	0.059	7.56E-02	43734	0.116	0.075	1.23E-01	116595	0.109	0.047	1.88E-02
GNAS-	rs6015450		G												
EDN3	chr20: 57184512	Ehret <i>et al</i>	0.067	71156	0.358	0.092	9.47E-05	35995	0.343	0.122	5.12E-03	107151	0.352	0.073	1.56E-06

B) Mean arterial pressure association results from stage 1 (discovery), stage 2 (follow-up) and stages 1 and 2 combined for all previously reported SNPs at the 29 loci showing association with diastolic and/or systolic blood pressure and SNPs which reached nominal significance after stage 1 (P<1x10⁻⁵) for association with mean arterial pressure in those regions in this study. For each region, the results for the top SNP in the mean arterial pressure analysis is shown along with the mean arterial pressure association results for the corresponding independently reported SNP in that region. * Study which first reported the SNP: Ehret *et al*⁴, Levy *et al*⁵, Newton-Cheh *et al*⁶. # r² of the top SNP in the region for mean arterial pressure and the independently reported SNP.

		Study of	Coded												
Region	SNP ID	origin* (r ^{2#})	freq		Sta	ge 1			Stag	e 2		Com	bined Stag	e 1 + Sta	ge 2
				N effective	Beta	SE	Р	N effective	Beta	SE	Р	N effective	Beta	SE	P
		This study/ Ehret <i>et al</i> /													
MTHFR-	rs17367504	Newton- Cheh	G		-										
NPPB	chr1:11785365	et al	0.167	73689	0.464	0.082	1.86E-08	48460	-0.652	0.106	8.03E-10	122149	-0.534	0.065	2.18E-16
	rs2932538		G												
MOV10	chr1:113018066	Ehret <i>et al</i>	0.742	67059	0.286	0.070	4.55E-05	38236	0.189	0.096	4.79E-02	105295	0.252	0.057	8.25E-06
	rs13082711	This study/	Т		-										
SLC4A7	chr3: 27512913	Ehret <i>et al</i>	0.798	69548	0.350	0.071	8.08E-07	39379	-0.309	0.097	1.47E-03	108927	-0.336	0.057	4.62E-09
	rs3774372		Т		-										
ULK4	chr3: 41852418	Ehret <i>et al</i>	0.775	73758	0.211	0.076	5.46E-03	44030	0.008	0.104	9.40E-01	117788	-0.135	0.061	2.77E-02
	rs9815354		G		-										
ULK4	chr3: 41887655	Levy et al	0.772	68807	0.224	0.078	4.09E-03	38405	-0.004	0.110	9.70E-01	107212	-0.150	0.064	1.81E-02
	rs419076	Ehret <i>et al</i>	Т												
MECOM	chr3:170583580	(0.872)	0.436	73481	0.348	0.059	3.00E-09	41240	0.326	0.081	5.94E-05	114721	0.340	0.048	8.11E-13
	rs1343040		G		-										
MECOM	chr3:170668987	This study	0.6	67087	0.370	0.062	2.22E-09	35208	-0.287	0.087	1.04E-03	102295	-0.342	0.050	1.22E-11
	rs13149993		G		-										
FGF5	chr4: 81377569	This study	0.633	71616	0.415	0.063	3.29E-11	42618	-0.191	0.086	2.60E-02	114234	-0.337	0.051	2.55E-11
	rs1458038	Ehret <i>et al</i>	Т												
FGF5	chr4: 81383747	(0.503)	0.3	68314	0.430	0.066	5.34E-11	40797	0.352	0.090	9.36E-05	109111	0.403	0.053	2.88E-14
FGF5	rs16998073 chr4: 81403365	Newton-Cheh <i>et al</i> (0.503)	T 0.192	55070	0.486	0.077	3.33E-10	32592	0.389	0.106	2.42E-04	87662	0.453	0.063	4.53E-13

			Coded												
Pogion		Study of origin* (r ^{2#})	allele &		Sta	70 1			Stag	~ 7		Com	hinad Staa	o 1 + 6ta	~ 7
Region	SINF ID		печ	N	Sta	gei		N	Jiag	e 2		N	Diffed Stag	e I + Sla	ge z
				effective	Beta	SE	Р	effective	Beta	SE	Р	effective	Beta	SE	P
	rs13107325	This study/	Т		-										
SLC39A8	chr4:103407732	Ehret <i>et al</i>	0.117	63443	0.670	0.127	1.34E-07	46594	-0.577	0.156	2.13E-04	110037	-0.633	0.098	1.30E-10
GUCY1A3-	rs13139571		C												
GUCY1B3	chr4:156864963	Ehret <i>et al</i>	0.742	71136	0.298	0.070	1.93E-05	40732	0.272	0.095	4.05E-03	111869	0.289	0.056	2.69E-07
NPR3-	rs1173771	This study/	G												
C5orf23	chr5:32850785	Ehret <i>et al</i>	0.525	73371	0.289	0.059	1.07E-06	43737	0.271	0.081	8.58E-04	117109	0.283	0.048	3.51E-09
	rs9313772		Т		-										
EBF1	chr5:157737035	This study	0.317	70895	0.279	0.062	6.24E-06	43103	-0.436	0.083	1.63E-07	113998	-0.335	0.050	1.48E-11
	rs11953630	Ehret <i>et al</i>	Т		-										
EBF1	chr5:157777980	(0.012)	0.342	73190	0.268	0.061	1.06E-05	40829	-0.457	0.084	5.72E-08	114019	-0.332	0.049	1.51E-11
	rs1799945	Ehret <i>et al</i>	G												
HFE	chr6: 26199158	(1.0)	0.182	70871	0.440	0.085	2.06E-07	40730	0.515	0.114	6.07E-06	111601	0.467	0.068	6.55E-12
	rs198846		G		-										
HFE	chr6: 26215442	This study	0.858	71385	0.445	0.085	1.53E-07	40292	-0.539	0.115	2.55E-06	111677	-0.478	0.068	2.26E-12
	rs805303		G												
BAT2-BAT5	chr6:31724345	Ehret <i>et al</i>	0.653	73090	0.186	0.061	2.14E-03	45959	0.098	0.080	2.24E-01	119049	0.154	0.048	1.45E-03
	rs4373814		G		-										
CACNB2(5')	chr10:18459978	Ehret <i>et al</i>	0.633	71465	0.244	0.060	4.55E-05	39854	-0.044	0.083	5.99E-01	111318	-0.175	0.048	3.01E-04
	rs1813353	Ehret <i>et al</i>	Т												
CACNB2(3')	chr10:18747454	(0.826)	0.649	72095	0.407	0.064	1.71E-10	40513	0.391	0.088	8.40E-06	112608	0.402	0.052	7.01E-15
	rs11014166	Levy <i>et al</i>	Т		-										
CACNB2(3')	chr10:18748804	(0.826)	0.367	73317	0.385	0.062	4.84E-10	41146	-0.363	0.085	1.99E-05	114464	-0.377	0.050	4.59E-14
	rs12258967		G		-										
CACNB2(3')	chr10:18767965	This study	0.364	67411	0.418	0.065	1.37E-10	38762	-0.456	0.089	2.67E-07	106173	-0.431	0.052	2.05E-16
	rs4590817	This study/	G												
C10orf107	chr10:63137559	Ehret <i>et al</i>	0.825	72693	0.544	0.082	2.98E-11	41049	0.634	0.111	1.03E-08	113742	0.576	0.066	2.14E-18
	rs1530440	Newton-Cheh	Т		-										
C10orf107	chr10:63194597	et al (0.592)	0.175	70613	0.442	0.075	4.77E-09	42677	-0.638	0.103	5.15E-10	113290	-0.511	0.061	4.50E-17
	rs932764	Ehret <i>et al</i>	G												
PLCE-1	chr10:95885930	(0.845)	0.425	73110	0.184	0.059	1.86E-03	40896	0.243	0.083	3.27E-03	114006	0.204	0.048	2.22E-05

		Chudu of	Coded												
Region	SNP ID	origin* (r ^{2#})	freq		Sta	ge 1			Stag	e 2		Com	bined Stag	e 1 + Sta	ge 2
				N		<u> </u>		N	0.008	_		N			<u> </u>
				effective	Beta	SE	Ρ	effective	Beta	SE	Ρ	effective	Beta	SE	Р
CYP17A1-	rs1004467	Levy <i>et al</i>	G		-										
NT5C2	chr10:104584497	(0.867)	0.067	72728	0.563	0.096	5.01E-09	41208	-0.658	0.135	1.01E-06	113937	-0.595	0.078	2.94E-14
		Newton-Cheh													
CYP17A1-	rs11191548	et al / Ehret <i>et</i>	Т												
NT5C2	chr10:104836168	al (0.485)	0.942	71891	0.589	0.102	8.68E-09	43943	0.759	0.137	2.91E-08	115834	0.650	0.082	2.19E-15
CYP17A1-	rs11191593		Т												
NT5C2	chr10:104929205	This study	0.942	71214	0.612	0.102	1.86E-09	41171	0.749	0.140	9.01E-08	112385	0.660	0.082	1.20E-15
4544	rs/129220	Ehret <i>et al</i>	G	60.404	-	0.000	4 055 04		0.01.4	0.400	4 775 00	110011	0.005	0.076	2 075 05
ADM	chr11:1030/114	(0.932)	0.867	69401	0.330	0.093	4.05E-04	41440	-0.314	0.132	1.//E-02	110841	-0.325	0.076	2.07E-05
	rs381815	Church at al	0 207	72001	0.270	0.000	2 745 05	41221	0.240	0.000	2 255 04	114122	0.200	0.054	2 755 00
PLEKHA7	cnr11:16858844	Ehret et al	0.297	72901	0.276	0.066	2.74E-05	41221	0.340	0.092	2.25E-04	114122	0.298	0.054	2.75E-08
FLJ32810-	r\$033185	Enret et al	0.217	72562	-	0.065		40062	0.206	0.000	1 015 02	112526	0.225	0.052	6 595 10
TIVIEIVI33	ciii 11: 100098748	(1.0)	0.317	/2503	0.340	0.065	1.57E-07	40963	-0.296	0.090	1.01E-03	113520	-0.325	0.053	0.395-10
FLJ52810- TN/FN/22	rsou4725 chr11.100115756	This study	0 217	72268	03/3	0.065	1 10F-07	15581	-0.252	0.087	3 83E-U3	1180/0	_0 210	0.052	2 20E-00
TWILIWISS	rs2681/72		0.317	73308	0.545	0.005	1.192-07	45561	-0.232	0.087	3.83L-03	110949	-0.310	0.052	2.301-03
ΔΤΡ2Β1	chr12.88533090	levvet al (1.0)	0 11	73533	0 5 5 3	0.081	1 00F-11	45787	-0 516	0 106	1 02E-06	119321	-0 539	0.064	5 51F-17
A11201	rs2681492	Levy et al	0.11 T	75555	0.555	0.001	1.001 11	43707	0.510	0.100	1.021 00	115521	0.555	0.004	J.JIL 17
ATP2B1	chr12:88537220	(0.92)	0.883	70236	0.530	0.080	3.36E-11	44426	0.524	0.106	8.37E-07	114662	0.528	0.064	1.46E-16
	rs17249754	This study/	G												
ATP2B1	chr12:88584717	Ehret <i>et al</i>	0.892	72022	0.563	0.082	6.01E-12	43664	0.545	0.107	3.74E-07	115686	0.557	0.065	1.21E-17
-		Levy et al/													
	rs3184504	Ehret <i>et al</i>	Т												
ATXN2	chr12:110368991	(1.0)	0.408	69741	0.394	0.060	4.25E-11	45072	0.446	0.078	1.33E-08	114813	0.413	0.048	3.64E-18
		This study /													
	rs653178	Newton-Cheh	Т		-										
ATXN2	chr12:110492139	et al	0.592	70336	0.401	0.060	1.74E-11	48308	-0.475	0.076	4.97E-10	118644	-0.429	0.047	6.91E-20
		This													
	rs2384550	study/Levy <i>et</i>	G												
TBX5-TBX3	chr12:113837114	al	0.658	73810	0.277	0.062	7.72E-06	48126	0.142	0.081	7.99E-02	121936	0.227	0.049	3.89E-06

		Study of	Coded												
Region	SNP ID	origin* (r ^{2#})	freq		Sta	ge 1			Stag	e 2		Com	bined Stag	e 1 + Sta	ge 2
				N		ĺ		N				N			Ĩ
				effective	Beta	SE	Ρ	effective	Beta	SE	Ρ	effective	Beta	SE	Ρ
	rs10850411		Т												
TBX5-TBX3	chr12:113872179	Ehret <i>et al</i>	0.717	69558	0.247	0.066	1.66E-04	38921	0.240	0.091	8.71E-03	108479	0.245	0.053	4.44E-06
		This study/													
		Ehret <i>et al</i>													
		/Newton-													
	rs1378942	Cheh et al	C												
CSK	chr15:72864420	(2009)	0.333	73412	0.365	0.061	1.90E-09	48323	0.424	0.080	1.39E-07	121735	0.386	0.048	1.63E-15
	rs6495122	Levy et al	С		-										
CSK	chr15:72912698	(0.585)	0.583	72332	0.310	0.059	1.69E-07	45465	-0.337	0.079	1.83E-05	117797	-0.320	0.047	1.42E-11
	rs2521501		Т												
FES	chr15:89238392	Ehret <i>et al</i>	0.373	43863	0.337	0.078	1.71E-05	30021	0.356	0.101	4.47E-04	73884	0.344	0.062	2.88E-08
	rs17608766		Т		-										
GOSR2	chr17:42368270	Ehret <i>et al</i>	0.908	62353	0.359	0.088	4.91E-05	41327	-0.372	0.114	1.12E-03	103681	-0.364	0.070	1.94E-07
	rs12940887		Т												
ZNF652	chr17:44757806	Ehret <i>et al</i>	0.417	72190	0.290	0.061	1.77E-06	43157	0.182	0.082	2.68E-02	115347	0.252	0.049	2.47E-07
		This													
	rs16948048	study/Newton	G												
ZNF652	chr17:44795465	-Cheh et al	0.425	73219	0.304	0.060	4.49E-07	43510	0.147	0.082	7.12E-02	116730	0.249	0.049	2.88E-07
	rs1327235		G												
JAG1	chr20:10917030	Ehret <i>et al</i>	0.575	72861	0.234	0.059	6.85E-05	43732	0.305	0.080	1.30E-04	116594	0.259	0.047	4.35E-08
	rs6026748		G		-										
GNAS-EDN3	chr20:57179210	This study	0.933	71668	0.416	0.089	2.81E-06	40270	-0.674	0.127	1.00E-07	111938	-0.501	0.073	5.45E-12
	rs6015450		G												
GNAS-EDN3	chr20:57184512	Ehret <i>et al</i>	0.067	71156	0.413	0.089	3.62E-06	35998	0.756	0.131	8.54E-09	107154	0.521	0.074	1.58E-12
C) Pulse pressure and mean arterial pressure association results from stage 1 (discovery), stage 2 (follow-up) and stages 1 and 2 combined for all 46 SNPs that showed nominally significant association ($P<1x10^{-5}$) after stage 1. Both rs1595373 and rs1156725 in SOX6 were included because rs1595373 ($P=4.23x10^{-6}$) had an N effective of 75% which was above the threshold (70%) at which we would choose a proxy but the second strongest signal in the region (rs1156725) had a very similar P value ($P=4.24x10^{-6}$) and an N effective of 99.6%. These SNPs were correlated (r= 0.64) and it was deemed appropriate to take both SNPs for forward to stage 2.

		Coded												
		allele &							-					
SNP ID	gene	freq	 	Stage	e 1	[Stage	e 2	[Com	bined Sta	ige 1 + St	age 2
Pulse Pressure			N effective	Beta	SE	Р	N effective	Beta	SE	Р	N effective	Beta	SE	Р
rs11222084		Т												
chr11:129778440	near ADAMTS-8	0.375	67704	0.415	0.064	8.45E-11	40391	0.211	0.081	9.17E-03	108095	0.337	0.050	1.90E-11
rs17477177		Т												
chr7:106199094	near PIK3CG	0.717	72997	-0.460	0.071	1.19E-10	39999	-0.344	0.094	2.72E-04	112996	-0.418	0.057	2.27E-13
rs8069437		Т												
chr17:42261948	near WNT3	0.167	62041	0.479	0.076	3.85E-10	38084	0.276	0.097	4.46E-03	100125	0.401	0.060	2.45E-11
rs1427547		Т												
chr2:19603457	near OSR1	0.467	73703	0.288	0.059	1.13E-06	45889	0.007	0.075	9.25E-01	119591	0.180	0.046	1.04E-04
rs7788972		Т												
chr7:19000805	HDAC9 (intron)	0.76	69597	-0.360	0.075	1.57E-06	39481	-0.040	0.099	6.84E-01	109078	-0.243	0.060	4.70E-05
rs917275		G												
chr7:28625047	CREB5 (intron)	0.405	73606	0.287	0.060	1.84E-06	47283	0.030	0.075	6.86E-01	120889	0.187	0.047	6.92E-05
rs12052878		G												
chr2:237892333	near COL6A3	0.707	62708	0.323	0.069	2.51E-06	35420	0.083	0.086	3.33E-01	98128	0.229	0.054	1.84E-05
rs429150		Т												
chr6:32183541	TNXB (intron)	0.65	66730	-0.289	0.062	2.65E-06	34553	-0.196	0.081	1.52E-02	101283	-0.255	0.049	1.93E-07
rs480211		Т												
chr11:63496015	near COX8A	0.517	69801	-0.280	0.060	3.52E-06	47928	-0.120	0.075	1.07E-01	117729	-0.217	0.047	3.87E-06
rs10762174		G												
chr10:69006097	CTNNA3 (intron)	0.892	72322	-0.329	0.071	3.98E-06	41064	-0.141	0.093	1.30E-01	113386	-0.259	0.057	4.55E-06
rs8009633		G												
chr14:52456586	FERMT2 (intron)	0.742	63871	-0.333	0.072	4.27E-06	38595	-0.117	0.090	1.96E-01	102466	-0.249	0.057	1.10E-05

		Coded												
SNP ID	gene	freq		Stage	e 1			Stage	e 2		Com	bined Sta	ge 1 + St	age 2
							Ν				Ν			
			N effective	Beta	SE	Р	effective	Beta	SE	Р	effective	Beta	SE	Р
rs2165094		G												
chr2:164881280	near GRB14	0.092	56187	-0.452	0.098	4.34E-06	30047	-0.206	0.139	1.39E-01	86235	-0.370	0.080	4.12E-06
rs13002573		G												
chr2:164623454	near <i>FIGN</i>	0.203	73043	-0.320	0.070	5.43E-06	43955	-0.296	0.089	8.58E-04	116998	-0.310	0.055	1.76E-08
rs999958		С												
chr4:169935448	PALLD (intron)	0.475	73539	0.267	0.059	5.49E-06	45892	0.056	0.074	4.51E-01	119431	0.186	0.046	5.47E-05
rs2071518		Т												
chr8:120504993	<i>NOV</i> (3' UTR)	0.167	73252	0.304	0.067	5.72E-06	45804	0.323	0.086	1.60E-04	119056	0.312	0.053	3.66E-09
rs4870322		G												
chr6:155315056	near <i>TIAM2</i>	0.467	53999	0.318	0.070	5.87E-06	46157	0.046	0.076	5.45E-01	100157	0.193	0.052	1.83E-04
rs10410907		Т												
chr19:45724949	SPTBN4 (intron)	0.093	56263	-0.502	0.111	6.50E-06	36522	0.089	0.139	5.24E-01	92785	-0.271	0.087	1.81E-03
rs9296832	COL21A1	G												
chr6:56208868	(intron)	0.558	63322	-0.281	0.062	6.85E-06	33362	-0.195	0.083	1.87E-02	96685	-0.250	0.050	5.46E-07
rs137602		G												
chr22:38023354	near RPL3	0.425	70724	0.276	0.061	6.92E-06	44829	-0.004	0.077	9.55E-01	115553	0.167	0.048	5.01E-04
rs4778850	FAM108C1	G												
chr15:78821473	(intron)	0.231	72975	-0.328	0.073	7.03E-06	41097	-0.014	0.095	8.83E-01	114073	-0.211	0.058	2.67E-04
rs2865531		Т												
chr16:73947817	CFDP1 (intron)	0.467	73439	-0.265	0.059	7.94E-06	41244	0.076	0.078	3.30E-01	114683	-0.139	0.047	3.15E-03
rs4147046		Т												
chr4:18309880	near LCORL	0.596	69266	-0.277	0.062	9.20E-06	39886	-0.023	0.080	7.73E-01	109152	-0.182	0.049	2.33E-04
rs871606		Т												
chr4:54494002	near CHIC2	0.85	71444	0.428	0.096	9.28E-06	44082	0.431	0.121	3.75E-04	115525	0.429	0.075	1.32E-08
rs13250217		G												
chr8:124367626	near ZHX1	0.317	56943	-0.323	0.073	9.50E-06	31134	0.042	0.094	6.54E-01	88077	-0.187	0.058	1.23E-03
Mean Arterial Pres	sure													
rs754868		G												
chr2:43039036	near HAAO	0.533	72880	-0.313	0.059	1.16E-07	45717	-0.113	0.079	1.49E-01	118597	-0.241	0.047	3.35E-07

		Coded												
SNP ID	gene	freq		Stag	e 1			Stag	e 2		Com	bined Sta	ge 1 + St	age 2
	Ŭ						N				N		<u> </u>	<u> </u>
			N effective	Beta	SE	Р	effective	Beta	SE	Р	effective	Beta	SE	Р
rs9290370		Т												
chr3:170807707	near MECOM	0.267	70889	-0.337	0.067	4.72E-07	43539	-0.155	0.089	8.35E-02	114428	-0.272	0.054	3.97E-07
rs7213273		G												
chr17:40511440	PLCD3	0.4	71459	0.311	0.063	7.06E-07	43397	0.137	0.084	1.02E-01	114856	0.249	0.050	7.33E-07
rs1687295		Т												
chr3:14864760	FGD5 (intron)	0.392	68990	0.329	0.067	9.93E-07	39081	0.226	0.091	1.32E-02	108071	0.293	0.054	6.37E-08
rs2782980		Т												
chr10:115771517	near ADRB1	0.198	61284	-0.345	0.071	1.14E-06	37788	-0.326	0.094	5.55E-04	99072	-0.338	0.057	2.46E-09
rs17432448		G												
chr7:18514944	HDAC9 (intron)	0.342	63902	0.308	0.064	1.26E-06	35734	-0.026	0.089	7.71E-01	99636	0.195	0.052	1.60E-04
rs16893776		Т												
chr8:96042780	C8orf38 (intron)	0.533	73714	-0.282	0.058	1.41E-06	43891	0.037	0.079	6.38E-01	117605	-0.170	0.047	3.13E-04
rs1446468		Т												
chr2:164671732	near <i>FIGN</i>	0.534	69264	-0.291	0.061	1.68E-06	39650	-0.418	0.082	3.80E-07	108914	-0.336	0.049	6.46E-12
rs10841376		G												
chr12:19871148	near AEBP2	0.2	70805	-0.340	0.072	2.18E-06	42157	-0.161	0.095	9.12E-02	112961	-0.275	0.057	1.58E-06
rs2969070		G												
chr7:2479071	near CHST12	0.367	70046	0.299	0.063	2.23E-06	46598	0.168	0.081	3.88E-02	116644	0.250	0.050	5.61E-07
rs4403412		Т												
chr8:10190691	MSRA (intron)	0.263	72942	0.297	0.063	2.31E-06	40811	0.227	0.087	8.92E-03	113753	0.273	0.051	8.33E-08
rs9276348		G												
chr6:32814187	near HLA-DQA2	0.206	68860	-0.340	0.073	2.92E-06	39026	-0.081	0.098	4.08E-01	107886	-0.248	0.058	2.16E-05
rs2180768		G												
chr1:52490409	ZFYVE9 (intron)	0.9	62194	-0.472	0.101	2.94E-06	41084	0.162	0.125	1.93E-01	103278	-0.221	0.078	4.94E-03
rs7246865		G												
chr19:17080105	MYO9B (intron)	0.767	66984	-0.326	0.070	2.97E-06	41002	-0.224	0.093	1.66E-02	107986	-0.289	0.056	2.25E-07
rs1957563		Т												
chr5157407168	near CLINT1	0.208	73786	0.314	0.067	3.28E-06	44019	0.202	0.090	2.45E-02	117805	0.273	0.054	3.96E-07

		Coded												
SNP ID	gene	freq		Stage	e 1			Stag	e 2		Com	bined Sta	ge 1 + St	age 2
							N				N			
			N effective	Beta	SE	Р	effective	Beta	SE	Р	effective	Beta	SE	Р
rs2838351		G												
chr21:43935212	RRP1B (intron)	0.508	64473	0.294	0.063	3.47E-06	35756	0.161	0.088	6.60E-02	100229	0.248	0.051	1.30E-06
rs319690		Т												
chr3:47902488	MAP4 (intron)	0.51	59137	0.306	0.066	3.88E-06	34359	0.280	0.090	1.89E-03	93496	0.297	0.053	2.69E-08
rs1595373		G												
chr11:16223316	SOX6 (intron)	0.098	55351	0.450	0.098	4.23E-06	36981	0.283	0.122	2.00E-02	92332	0.385	0.076	4.59E-07
rs1156725		Т												
chr11:16264276	SOX6 (intron)	0.817	73779	-0.342	0.074	4.24E-06	45957	-0.263	0.099	7.64E-03	119736	-0.314	0.059	1.30E-07
rs919734		G												
chr5:148329466	near SH3TC2	0.775	70685	0.326	0.071	4.26E-06	38952	0.189	0.100	5.86E-02	109637	0.280	0.058	1.26E-06
rs7110667		Т												
chr11:33984657	near CAPRIN1	0.258	62249	0.336	0.074	4.77E-06	32108	0.220	0.106	3.83E-02	94357	0.299	0.060	7.82E-07
rs10175915		Т												
chr2:72341668	EXOC6B (intron)	0.817	73114	0.366	0.082	7.13E-06	43748	0.091	0.108	4.01E-01	116861	0.267	0.065	4.28E-05
rs1161267		G												
chr2:72975689	near SPR	0.883	68021	0.477	0.107	7.78E-06	38735	0.021	0.140	8.82E-01	106756	0.309	0.085	2.69E-04

D) Systolic blood pressure association results for the 8 SNPs at the seven loci found to have novel association with pulse pressure and/or mean arterial pressure in Europeans in the present study and all 29 loci previously associated with diastolic and/or systolic blood pressure. Stage 1 and stage 2 samples are those described in Supplementary Table 1 and which were used for the primary pulse pressure and mean arterial pressure analyses. Loci which reach genome-wide significance (P<5x10⁻⁸) after the combined stage 1 and stage 2 analysis are highlighted in bold.

	SNP	Coded												
Region	Chr: NCBI 36	allele &		SBP S	tage 1			SBP S	tage 2		SBP C	ombined S	tage 1 +	Stage 2
Region		neq	N eff	Beta	SE	Р	N eff	Beta	SE	Р	N eff	Beta	SE	P
Novel loci as	sociated with Pulse I	Pressure in	this study		-	I			-				-	
	rs13002573	G												
near FIGN	chr2:164623454	0.203	73076	-0.411	0.104	7.59E-05	43956	-0.424	0.131	1.25E-03	117033	-0.416	0.081	3.25E-07
	rs871606	Т												
near CHIC2	chr4:54494002	0.85	68870	0.423	0.143	3.11E-03	44042	0.372	0.178	3.69E-02	112912	0.403	0.112	3.04E-04
near	rs17477177	Т												
PIK3CG	chr7:106199094	0.717	72959	-0.513	0.106	1.17E-06	39984	-0.621	0.140	9.09E-06	112943	-0.552	0.084	5.67E-11
<i>NOV</i> (3'	rs2071518	Т												
UTR)	chr8:120504993	0.167	73118	0.156	0.100	1.18E-01	45807	0.220	0.126	8.03E-02	118925	0.181	0.078	2.08E-02
near	rs11222084	Т												
ADAMTS-8	chr11:129778440	0.375	67856	0.325	0.095	5.95E-04	40395	0.164	0.120	1.73E-01	108251	0.263	0.074	4.00E-04
Novel loci as	sociated with Mean	Arterial Pr	essure in t	his study										
	rs1446468	Т												
near FIGN	chr2:164671732	0.534	69382	-0.458	0.090	3.47E-07	39650	-0.565	0.115	8.58E-07	109032	-0.499	0.071	1.82E-12
MAP4	rs319690	Т												
(intron)	chr3:47902488	0.51	59312	0.457	0.098	3.45E-06	34366	0.368	0.126	3.36E-03	93678	0.423	0.077	4.74E-08
near	rs2782980	Т												
ADRB1	chr10:115771517	0.198	61020	-0.389	0.105	2.14E-04	37792	-0.433	0.132	1.00E-03	98811	-0.406	0.082	7.66E-07
Loci previous	sly associated with S	BP and/or	DBP (Ehre	t et al 201:	1)									
MTHFR-	rs17367504	G												
NPPB	chr1:11785365	0.167	71215	-0.837	0.121	5.26E-12	48460	-0.817	0.150	4.65E-08	119675	-0.829	0.094	1.38E-18
	rs2932538	G												
MOV10	chr1:113018066	0.825	67279	0.533	0.104	3.22E-07	38127	0.241	0.134	7.08E-02	105406	0.422	0.082	2.72E-07
	rs13082711	Т												
SLC4A7	chr3:27512913	0.798	69820	-0.338	0.106	1.40E-03	39384	-0.449	0.136	9.36E-04	109204	-0.380	0.083	5.28E-06

	SNP	Coded												
	Chr: NCBI 36	allele &												
Region	posn	freq		SBP S	tage 1			SBP S	tage 2		SBP C	ombined S	tage 1 +	Stage 2
			N eff	Beta	SE	Р	N eff	Beta	SE	Р	N eff	Beta	SE	Р
	rs3774372	Т												
ULK4	chr3:41852418	0.717	73830	-0.018	0.113	8.76E-01	44031	0.219	0.146	1.33E-01	117861	0.071	0.089	4.26E-01
	rs419076	Т												
MECOM	chr3:170583580	0.436	73554	0.523	0.087	1.89E-09	41244	0.461	0.113	4.43E-05	114799	0.500	0.069	4.09E-13
	rs1458038	Т												
FGF5	chr4:81383747	0.3	65888	0.643	0.099	8.03E-11	40780	0.475	0.126	1.54E-04	106667	0.579	0.078	9.42E-14
	rs13107325	Т												
SLC39A8	chr4:103407732	0.117	61128	-1.033	0.185	2.17E-08	46585	-0.709	0.222	1.38E-03	107713	-0.900	0.142	2.16E-10
GUCY1A3-	rs13139571	C												
GUCY1B3	chr4:156864963	0.772	71406	0.486	0.103	2.52E-06	40813	0.369	0.132	5.12E-03	112220	0.442	0.081	5.60E-08
NPR3-	rs1173771	G												
C5orf23	chr5:32850785	0.525	73338	0.578	0.089	6.62E-11	43736	0.416	0.114	2.53E-04	117074	0.517	0.070	1.39E-13
	rs11953630	Т												
EBF1	chr5:157777980	0.342	73093	-0.461	0.090	3.34E-07	40844	-0.514	0.117	1.19E-05	113936	-0.480	0.072	1.86E-11
	rs1799945	G	= 4 0 = 0			4 4 9 5 9 5		0.000	0.450			0.500		
HFE	chr6:26199158	0.182	/1053	0.549	0.125	1.18E-05	40734	0.656	0.159	3.75E-05	111/8/	0.590	0.098	2.04E-09
	rs805303	G	70000	0.415	0.000	2.045.00	45024	0.151	0.112	1 005 01	110000	0.212	0.070	0 535 00
BAIZ-BAIS	CNF6:31724345	0.575	70902	0.415	0.090	3.84E-06	45924	0.151	0.113	1.80E-01	116826	0.313	0.070	8.52E-06
CACNIDO(E')	rs4373814	G 409	71202	0 421	0.000	2 1 4 5 0 6	40020	0.022	0.115	7 745 01	111112	0.276	0.070	
CACINB2(5)	CIII 10:18459978	0.408	/1383	-0.421	0.089	2.14E-00	40029	-0.033	0.115	7.74E-01	111412	-0.276	0.070	8.00E-05
CACNP2(21)	151813333 chr10:197474E4	0.640	71774	0 500	0.004	1 155 07	40514	0.402	0 1 2 2		117700	0.407	0.075	2 775 11
CACIVEZ(S)	rc/500817	0.049	/1//4	0.500	0.094	1.15E-07	40514	0.495	0.122	5.00E-05	112200	0.497	0.075	2.//E-11
C10orf107	chr10.63137559	0.825	72405	0 729	0 1 2 0	1 22F-09	41050	0.886	0 155	9 98F-09	113455	0 788	0.095	9 24F-17
<i>cionjio</i> /	rs932761	0.025	72403	0.725	0.120	1.221-05	41050	0.000	0.155	J.JOL-0J	113433	0.788	0.055	J.24L-17
PLCE-1	chr10:95885930	0.425	72821	0.442	0.088	4.99F-07	40896	0.393	0.115	6.30F-04	113717	0.424	0.070	1.28E-09
CYP17A1-	rs11191548	т	, 2021	0.172	0.000			0.000	0.110	51502 04	110,11	0.124	0.070	1.101 00
NT5C3	chr10:104836168	0.942	71609	1.069	0.155	5.44E-12	43945	1.049	0.192	4.76E-08	115553	1.061	0.121	1.44E-18
	rs7129220	G												
ADM	chr11:10307114	0.867	69577	-0.806	0.140	7.86E-09	41429	-0.452	0.184	1.43E-02	111006	-0.676	0.111	1.21E-09
		1	1	1		1		1		1	1	1		1

	SNP	Coded												
Region	posn	freg		SBP S	tage 1			SBP S	tage 2		SBP C	ombined S	tage 1 +	Stage 2
Region	posn	ncq	Neff	Beta	SF	P	Neff	Beta	SF	P	N eff	Beta	SF	
	rs381815	т		Detta	52			Detta	52	-		Detta		-
PLEKHA7	chr11:16858844	0.297	72949	0.657	0.099	2.64E-11	41227	0.433	0.128	7.52E-04	114176	0.574	0.078	2.16E-13
FLJ32810-	rs633185	G												
TMEM34	chr11:100098748	0.317	72605	-0.571	0.097	3.90E-09	40955	-0.383	0.126	2.31E-03	113561	-0.501	0.077	6.89E-11
	rs17249754	G												
ATP2B1	chr12:88584717	0.892	72147	0.960	0.120	1.51E-15	43660	0.821	0.151	5.17E-08	115807	0.906	0.094	6.02E-22
	rs3184504	Т												
ATXN2	chr12:110368991	0.408	67880	0.548	0.089	7.28E-10	45075	0.568	0.110	2.60E-07	112954	0.556	0.069	9.92E-16
	rs10850411	Т												
TBX5-TBX3	chr12:113872179	0.167	69830	0.390	0.097	5.58E-05	38735	0.360	0.127	4.60E-03	108565	0.379	0.077	8.47E-07
	rs1378942	C												
СЅК	chr15:72864420	0.333	70901	0.611	0.091	1.49E-11	48323	0.556	0.113	9.36E-07	119224	0.590	0.071	7.96E-17
	rs2521501	G												
FES	chr15:89238392	0.633	44549	0.678	0.117	7.53E-09	30012	0.439	0.140	1.70E-03	74561	0.580	0.090	1.16E-10
	rs17608766	Т												
GOSR2	chr17:42368270	0.908	62617	-0.742	0.129	9.65E-09	41296	-0.708	0.161	1.03E-05	103912	-0.729	0.101	4.68E-13
	rs12940887	Т												
ZNF652	chr17:44757806	0.417	72137	0.342	0.091	1.63E-04	43158	0.177	0.115	1.24E-01	115295	0.279	0.071	9.03E-05
	rs1327235	G												
JAG1	chr20:10917030	0.117	72799	0.320	0.088	2.58E-04	43735	0.388	0.111	5.02E-04	116534	0.346	0.069	5.11E-07
GNAS-	rs6015450	G												
EDN3	chr20:57184512	0.067	71029	0.761	0.136	2.20E-08	36000	1.006	0.181	2.93E-08	107029	0.849	0.109	5.94E-15

E) Diastolic blood pressure association results for the 8 SNPs at the seven loci found to have novel association with pulse pressure and/or mean arterial pressure in Europeans in the present study and all 29 loci previously associated with diastolic and/or systolic blood pressure. Stage 1 and stage 2 samples are those described in Supplementary Table 1 and which were used for the primary pulse pressure and mean arterial pressure analyses. Loci which reach genome-wide significance (P<5x10⁻⁸) after the combined stage 1 and stage 2 analysis are highlighted in bold.

	SNP	Coded												
Region	Chr: NCBI 36 posn	& freq		DBP S	Stage 1			DBP S	tage 2		DBP C	ombined S	tage 1 +	Stage 2
			N eff	Beta	SE	Р	N eff	Beta	SE	Р	N eff	Beta	SE	Р
Novel loci asso	ociated with Pulse Pro	essure in	this stud	У										
	rs13002573	G												
near FIGN	chr2:164623454	0.203	73054	-0.091	0.066	1.68E-01	43957	-0.136	0.086	1.15E-01	117011	-0.107	0.052	4.02E-02
	rs871606	Т												
near CHIC2	chr4:54494002	0.85	71475	0.028	0.091	7.54E-01	44067	-0.075	0.117	5.22E-01	115542	-0.010	0.072	8.85E-01
	rs17477177	Т												
near PIK3CG	chr7:106199094	0.717	72958	0.003	0.068	9.64E-01	39972	-0.243	0.094	9.66E-03	112930	-0.081	0.055	1.40E-01
	rs2071518	Т												
<i>NOV</i> (3' UTR)	chr8:120504993	0.167	73112	-0.161	0.063	1.09E-02	45812	-0.117	0.082	1.54E-01	118924	-0.145	0.050	3.89E-03
near	rs11222084	Т												
ADAMTS-8	chr11:129778440	0.375	67932	-0.110	0.060	6.66E-02	40414	-0.085	0.079	2.78E-01	108347	-0.101	0.048	3.44E-02
Novel loci asso	ciated with Mean A	rterial Pr	essure in	this study										
	rs1446468	Т												
near FIGN	chr2:164671732	0.534	69351	-0.219	0.057	1.28E-04	39653	-0.346	0.076	5.41E-06	109003	-0.265	0.046	6.88E-09
MAP4	rs319690	Т												
(intron)	chr3:47902488	0.51	59301	0.309	0.063	8.09E-07	34360	0.234	0.083	5.07E-03	93662	0.282	0.050	1.84E-08
	rs2782980	Т												
near ADRB1	chr10:115771517	0.198	60990	-0.294	0.067	1.05E-05	37787	-0.263	0.087	2.52E-03	98777	-0.283	0.053	9.60E-08
Loci previousl	y associated with SB	P and/or	DBP (Ehi	et et al 20	11)									
MTHFR-	rs17367504	G												
NPPB	chr1:11785365	0.167	73894	-0.489	0.077	2.41E-10	48460	-0.573	0.097	3.41E-09	122354	-0.522	0.060	5.81E-18
	rs2932538	G												
MOV10	chr1:113018066	0.825	67265	0.318	0.066	1.55E-06	38124	0.157	0.071	2.75E-02	105389	0.243	0.048	5.24E-07

	SNP	Coded allele												
Region	Chr: NCBI 36 posn	& freq		DBP	Stage 1			DBP S	tage 2		DBP C	ombined S	tage 1 +	Stage 2
			N eff	Beta	SE	Ρ	N eff	Beta	SE	Ρ	N eff	Beta	SE	Ρ
	rs13082711	Т												
SLC4A7	chr3:27512913	0.798	69757	-0.365	0.067	5.00E-08	39384	-0.226	0.090	1.20E-02	109141	-0.315	0.054	4.37E-09
	rs3774372	Т												
ULK4	chr3:41852418	0.717	73830	-0.384	0.072	9.96E-08	44031	-0.109	0.078	1.65E-01	117861	-0.257	0.053	1.17E-06
	rs419076	Т												
MECOM	chr3:170583580	0.436	73555	0.324	0.055	4.56E-09	41238	0.262	0.075	4.82E-04	114793	0.302	0.044	1.11E-11
	rs1458038	Т												
FGF5	chr4:81383747	0.3	68540	0.455	0.063	4.11E-13	40811	0.301	0.083	3.02E-04	109351	0.399	0.050	1.71E-15
	rs13107325	Т												
SLC39A8	chr4:103407732	0.117	63737	-0.653	0.116	1.68E-08	46581	-0.523	0.142	2.33E-04	110318	-0.601	0.090	2.11E-11
GUCY1A3-	rs13139571	C												
GUCY1B3	chr4:156864963	0.772	71353	0.376	0.066	9.93E-09	40820	0.218	0.070	2.01E-03	112172	0.302	0.048	2.97E-10
NPR3-	rs1173771	G												
C5orf23	chr5:32850785	0.525	73354	0.246	0.056	1.16E-05	43740	0.198	0.075	8.25E-03	117094	0.229	0.045	3.57E-07
	rs11953630	Т												
EBF1	chr5:157777980	0.342	73116	-0.249	0.057	1.37E-05	40819	-0.411	0.078	1.33E-07	113935	-0.306	0.046	3.44E-11
	rs1799945	G												
HFE	chr6:26199158	0.182	71071	0.438	0.079	3.23E-08	40730	0.424	0.105	5.77E-05	111801	0.433	0.063	8.05E-12
	rs805303	G												
BAT2-BAT5	chr6:31724345	0.575	73560	0.203	0.057	3.81E-04	45927	0.037	0.060	5.39E-01	119487	0.124	0.041	2.66E-03
	rs4373814	G												
CACNB2(5')	chr10:18459978	0.408	71381	-0.243	0.056	1.63E-05	40016	-0.052	0.061	4.01E-01	111397	-0.155	0.041	1.83E-04
	rs1813353	Т												
CACNB2(3')	chr10:18747454	0.649	71792	0.354	0.060	3.47E-09	40515	0.337	0.081	3.40E-05	112307	0.348	0.048	5.38E-13
	rs4590817	G												
C10orf107	chr10:63137559	0.825	72386	0.502	0.076	3.69E-11	41048	0.527	0.102	2.56E-07	113434	0.511	0.061	5.01E-17
	rs932764	G												
PLCE-1	chr10:95885930	0.425	72804	0.134	0.056	1.59E-02	40896	0.175	0.077	2.25E-02	113700	0.148	0.045	1.00E-03
CYP17A1-	rs11191548	Т												
NT5C3	chr10:104836168	0.942	71588	0.521	0.098	1.03E-07	43944	0.612	0.126	1.11E-06	115532	0.555	0.077	6.35E-13
	rs7129220	G												• • • • •
ADM	chr11:10307114	0.867	69576	-0.280	0.090	1.79E-03	41443	-0.224	0.122	6.62E-02	111020	-0.260	0.072	3.13E-04

	SNP	Coded												
Region	Chr: NCBI 36 posn	& freq		DBP	Stage 1			DBP S	tage 2		DBP C	ombined S	tage 1 +	Stage 2
			N eff	Beta	SE	Р	N eff	Beta	SE	Р	N eff	Beta	SE	Р
	rs381815	Т												
PLEKHA7	chr11:16858844	0.297	72936	0.374	0.063	2.31E-09	41223	0.287	0.085	7.67E-04	114159	0.344	0.050	9.98E-12
FLJ32810-	rs633185	G												
TMEM34	chr11:100098748	0.317	72600	-0.314	0.061	3.21E-07	40970	-0.248	0.083	2.90E-03	113570	-0.291	0.049	4.09E-09
	rs17249754	G												
ATP2B1	chr12:88584717	0.892	72151	0.495	0.076	6.31E-11	43666	0.390	0.098	7.37E-05	115818	0.456	0.060	3.08E-14
	rs3184504	Т												
ATXN2	chr12:110368991	0.408	70613	0.466	0.056	1.31E-16	45068	0.390	0.072	6.86E-08	115681	0.437	0.044	7.22E-23
	rs10850411	Т												
TBX5-TBX3	chr12:113872179	0.167	69859	0.298	0.061	1.27E-06	38733	0.200	0.068	3.27E-03	108591	0.254	0.046	2.56E-08
	rs1378942	C												
CSK	chr15:72864420	0.333	73570	0.457	0.058	2.23E-15	48324	0.351	0.074	1.91E-06	121894	0.417	0.045	4.38E-20
	rs2521501	G												
FES	chr15:89238392	0.633	44344	0.426	0.074	8.57E-09	30039	0.320	0.074	1.50E-05	74382	0.373	0.052	1.01E-12
	rs17608766	Т												
GOSR2	chr17:42368270	0.908	62637	-0.205	0.083	1.37E-02	41363	-0.189	0.105	7.15E-02	104000	-0.199	0.065	2.28E-03
	rs12940887	Т												
ZNF652	chr17:44757806	0.417	72150	0.300	0.058	1.86E-07	43159	0.191	0.076	1.15E-02	115309	0.260	0.046	1.36E-08
	rs1327235	G												
JAG1	chr20:10917030	0.117	72795	0.262	0.056	2.44E-06	43735	0.258	0.059	1.41E-05	116530	0.260	0.041	1.44E-10
	rs6015450	G												
GNAS-EDN3	chr20:57184512	0.067	71013	0.458	0.087	1.16E-07	35992	0.615	0.122	4.41E-07	107005	0.511	0.071	4.39E-13

F) All loci which were genome-wide significant (P<5x10⁻⁸) after meta-analysis of Stage 1 and Stage 2 for pulse pressure and mean arterial pressure, including loci previously shown to be associated with SBP and/or DBP.

		Coded allele &												
SNP ID	gene	freq		Stag	e 1			Stage	2		Co	mbined St	tage 1 + Sta	age 2
			N effective	Beta	SE	Р	N effective	Beta	SE	Р	N effective	Beta	SE	Р
Pulse Pressure														
rs13002573		G												
chr2:164623454	near FIGN	0.203	73043	-0.320	0.070	5.43E-06	44060	-0.296	0.089	8.58E-04	117102	-0.310	0.055	1.76E-08
rs871606		Т												
chr4:54494002	near CHIC2	0.85	71444	0.428	0.096	9.28E-06	44911	0.431	0.121	3.75E-04	116355	0.429	0.075	1.32E-08
rs17477177		Т												
chr7:106199094	near PIK3CG	0.717	72997	-0.460	0.071	1.19E-10	40406	-0.344	0.094	2.72E-04	113404	-0.418	0.057	2.27E-13
rs2071518		Т												
chr8:120504993	<i>NOV</i> (3' UTR)	0.167	73252	0.304	0.067	5.72E-06	46744	0.323	0.086	1.60E-04	119996	0.312	0.053	3.66E-09
rs11222084		Т												
chr11:129778440	near ADAMTS-8	0.375	67704	0.415	0.064	8.45E-11	40728	0.211	0.081	9.17E-03	108432	0.337	0.050	1.90E-11
rs1173756*		T					10000	0.470	0.070					
chr5:32825609	NPR3-C5orf23	0.525	/320/	-0.324	0.059	4.10E-08	48938	-0.178	0.073	1.54E-02	122144	-0.267	0.046	6.85E-09
rs9663362*		G	72507	0.007	0.050	4 405 07	44450	0.000	0.075	2 405 02	447750	0.074	0.046	- 405 00
chr10:95885167	PLCE-1	0.533	/359/	-0.297	0.059	4.48E-07	44152	-0.228	0.075	2.48E-03	117750	-0.271	0.046	5.18E-09
rs3824755*		G	72054	0 507	0.000	0.005.10	41704	0 274	0 1 2 7	2 075 02	114750	0 477	0.077	7 225 40
cnr10:104585839	CIP1/A1-N15C3	0.933	73054	0.597	0.098	9.96E-10	41704	0.274	0.127	3.07E-02	114758	0.477	0.077	7.33E-10
151/249/54 chr12:8858/717	ΛΤΟ2Ρ1	0 802	72022	0 303	0.081	1.005-06	13967	0 201	0 102	1 25E-04	115088	0 202	0.063	5 5/E-10
rc17609766	AIFZDI	0.092 T	72022	0.393	0.081	1.092-00	43907	0.391	0.102	1.232-04	113900	0.392	0.005	5.546-10
chr17·42368270	GOSR2		62353	-0 578	0 088	5 18F-11	42927	-0.467	0 109	1 90F-05	105280	-0 534	0 069	6 39F-15
CIII 17.42300270	005/12	0.508	02333	-0.578	0.000	J.10L-11	42527	-0.407	0.109	1.306-03	105200	-0.554	0.009	0.352-13

		Coded												
SNP ID	gene	freq		Stag	e 1			Stage	2		Co	mbined St	age 1 + Sta	age 2
	Ŭ		N								N		0	0
			effective	Beta	SE	Р	N effective	Beta	SE	Р	effective	Beta	SE	Р
Mean Arterial														
Pressure														
rs1446468		Т												
chr2:164671732	near FIGN	0.534	69264	-0.291	0.061	1.68E-06	39996	-0.418	0.082	3.80E-07	109259	-0.336	0.049	6.46E-12
rs319690		Т												
chr3:47902488	MAP4 (intron)	0.51	59137	0.306	0.066	3.88E-06	34637	0.280	0.090	1.89E-03	93774	0.297	0.053	2.69E-08
rs2782980		Т												
chr10:115771517	near ADRB1	0.198	61284	-0.345	0.071	1.14E-06	41537	-0.326	0.094	5.55E-04	102821	-0.338	0.057	2.46E-09
rs17367504		G												
chr1:11785365	MTHFR-NPPB	0.167	73689	-0.464	0.082	1.86E-08	49370	-0.652	0.106	8.03E-10	123059	-0.534	0.065	2.18E-16
rs13082711		Т												
chr3:27512913	SLC4A7	0.798	69548	-0.350	0.071	8.08E-07	39910	-0.309	0.097	1.47E-03	109458	-0.336	0.057	4.62E-09
rs1343040*		G	67087	-0.370	0.062	2.22E-09	35208	-0.287	0.087	1.04E-03	102295	-0.342	0.050	1.22E-11
chr3: 170668987	МЕСОМ	0.6												
rs13149993*		G	71616	-0.415	0.063	3.29E-11	42618	-0.191	0.086	2.60E-02	114234	-0.337	0.051	2.55E-11
chr4: 81377569	FGF5	0.633												
rs13107325		Т												
chr4:103407732	SLC39A8	0.117	63443	-0.670	0.127	1.34E-07	45769	-0.577	0.156	2.13E-04	109212	-0.633	0.098	1.30E-10
rs1173771		G												
chr5:32850785	NPR3-C5orf23	0.525	73371	0.289	0.059	1.07E-06	43869	0.271	0.081	8.58E-04	117241	0.283	0.048	3.51E-09
rs9313772*		Т	70895	-0.279	0.062	6.24E-06	43103	-0.436	0.083	1.63E-07	113998	-0.335	0.050	1.48E-11
chr5: 15//3/035	EBF1	0.317												
rs198846*		G	71385	-0.445	0.085	1.53E-07	40292	-0.539	0.115	2.55E-06	111677	-0.478	0.068	2.26E-12
chr6: 26215442	HFE	0.858												
rs12258967*	CA CN (D.2/21)	G	67411	-0.418	0.065	1.37E-10	38762	-0.456	0.089	2.67E-07	106173	-0.431	0.052	2.05E-16
cnr10: 18/6/965	CACNB2(3')	0.364												
rs4590817	C10 (107	G	72000	0 5 4 5	0.000	0.005.44	44545	0.00	0.114	4 005 00	444200	0 576	0.000	
chr10:63137559	C100rf107	0.825	/2693	0.544	0.082	2.98E-11	41515	0.634	0.111	1.03E-08	114208	0.576	0.066	2.14E-18
rs11191593*			71214	0.612	0.102	1.86E-09	41171	0.749	0.140	9.01E-08	112385	0.660	0.082	1.20E-15
cnr10: 104929205	CYP1/A1-N15C2	0.942												

		Coded												
SNP ID	gene	freq	Stage 1			Stage 2			Combined Stage 1 + Stage 2					
			N			_				_	N	-		_
			effective	Beta	SE	Р	N effective	Beta	SE	Р	effective	Beta	SE	Р
rs381815		Т												
chr11:16858844	PLEKHA7	0.297	72901	0.276	0.066	2.74E-05	41623	0.340	0.092	2.25E-04	114523	0.298	0.054	2.75E-08
rs604723*	FLJ32810-	Т	73368	-0.343	0.065	1.19E-07	45581	-0.252	0.087	3.83E-03	118949	-0.310	0.052	2.30E-09
chr11: 100115756	TMEM33	0.317												
rs17249754		G												
chr12:88584717	ATP2B1	0.892	72022	0.563	0.082	6.01E-12	43975	0.545	0.107	3.74E-07	115997	0.557	0.065	1.21E-17
rs653178*		Т	70336	-0.401	0.060	1.74E-11	48308	-0.475	0.076	4.97E-10	118644	-0.429	0.047	6.91E-20
chr12: 110492139	ATXN2	0.592												
rs1378942		С												
chr15:72864420	CSK	0.333	73412	0.365	0.061	1.90E-09	49210	0.424	0.080	1.39E-07	122622	0.386	0.048	1.63E-15
rs2521501		Т	43863	0.337	0.078	1.71E-05	30021	0.356	0.101	4.47E-04	73884	0.344	0.062	2.88E-08
chr15:89238392	FES	0.373												
rs1327235		G	72861	0.234	0.059	6.85E-05	43732	0.305	0.080	1.30E-04	116594	0.259	0.047	4.35E-08
chr20:10917030	JAG1	0.575												
rs6026748*		G	71668	-0.416	0.089	2.81E-06	40270	-0.674	0.127	1.00E-07	111938	-0.501	0.073	5.45E-12
chr20: 57179210	GNAS-EDN3	0.933												

* The top SNP for this region from the previous analysis of SBP and DBP⁴ was used in place of the top SNP from this study for calculation of the risk score (see Supplementary tables 2A and 2B for the alternative SNP used (Ehret *et al*⁴) and r² with the top SNP in the region from this study).

Supplementary Table 3 Risk score analysis: association of combined risk score from sentinel SNPs associated with PP and MAP with cardiovascular and renal outcomes, and comparison of 10-SNP PP risk score with matched 10-SNP SBP risk scores

A) Association of combined risk score using the sentinel SNPs from 10 loci associated with pulse pressure and 22 loci associated with mean arterial pressure with dichotomous outcomes of hypertension, stroke, coronary artery disease (CAD), chronic kidney disease and continuous measures of hypertensive target organ damage.

The SNPs included are listed in Supplementary Table 2F. (a) units are the unit of phenotypic measurement per SD of genetic risk score, (b) units are ln(odds ratio) per SD of genetic risk score, (c) units are ln(hazard ratio) per SD of genetic risk score, (d) units are ln(phenotype) per SD of genetic risk score. Estimated glomerular filtration rate (eGFR) was calculated from calibrated creatinine using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. # Pulse wave velocity was inverted (1/PWV), therefore a negative value is indicative of higher pulse wave velocity.

			Pressure	(10 SNPs)	Mean Arterial Pressure (22 SNPs)			
Disease endpoints	Source	Effect	SE	P value	Effect	SE	P value	N case/control
		(per SD o	f genetic r	isk score)	(per SD of ge	netic risk sco	re)	
	CHARGE Consortium							
Incident heart failure	Heart Failure							
	Working Group	-0.001	0.020	0.96	0.022	0.021	0.29	2,526/18,400
Incident ischemic stroke ^(c)	NEURO-CHARGE	0.074	0.033	0.03	0.079	0.036	0.03	1,164/18,058
Incident all stroke ^(c)	NEURO-CHARGE	0.083	0.024	4.87E-04	0.071	0.023	1.93E-03	1,544/18,058
Prevalent CAD ^(b)	CARDIoGRAM	0.030	0.010	1.66E-03	0.070	0.010	4.67E-12	22,233/64,726
Prevalent CAD ^(b)	C4D PROCARDIS	0.033	0.021	0.13	0.145	0.022	2.66E-11	5720/4381
Prevalent CAD ^(b)	C4D HPS	0.017	0.026	0.51	0.048	0.027	0.07	2704/2887
	CARDioGRAM &							
Prevalent CAD – combined ^(b)	C4D	0.029	0.008	4.26E-04	0.081	0.009	4.02E-20	30,657/71,911
Prevalent chronic kidney disease ^(b)	CKDGen	0.034	0.015	0.02	-0.007	0.015	0.66	5,807/61,286
Prevalent microalbuminuria ^(b)	CKDGen	0.020	0.018	0.25	-0.007	0.019	0.71	3,698/27,882
Hypertension ^(b)	DECODE	0.106	0.024	7.93E-06	0.118	0.015	5.12E-16	6788/24960
Continuous measures of target organ damage								
Left ventricular mass [g] ^(a)	EchoGen	0.309	0.304	0.31	0.720	0.313	0.02	NA
Left ventricular wall thickness [mm] ^(a)	EchoGen	0.002	0.002	0.20	0.007	0.002	2.07E-04	NA
Serum creatinine ^(d)	KidneyGen	0.000	0.001	0.52	-0.0011	0.0020	0.58	NA
eGFR (4 parameter MDRD equation) ^(d)	CKDGen	-0.002	0.001	0.07	-0.0003	0.0009	0.73	NA
Urinary albumin/creatinine ratio (d)	CKDGen	0.004	0.006	0.56	-0.0008	0.0064	0.90	NA
Pulse wave velocity ^{(a)#}	AortaGen	-0.018	0.007	0.01				

B) Comparison of 10-SNP PP risk score with matched 10-SNP SBP risk scores.

The 1000 permutations of 10-SNP SBP risk scores (matched with the 10-SNP PP risk score on SBP effects) generate an empirical distribution of *P* values for the SBP risk score for each outcome, used as a null distribution to test the hypothesis of no difference between the PP and SBP risk scores. Two-tailed empirical *P* values (shown in table) for this test are derived by comparing the PP risk score *P* values with the SBP risk score empirical *P* value distribution. *median *P* value from the 1000 permutations of 10-SNP SBP risk scores for each outcome, indicating association of the (average) SBP risk score with each outcome. Outcomes with Empirical *P* < 0.05 are shown in bold. ^(a)Of the 1000 permutations there were no SBP risk score *P* values as large as the corresponding PP score *P* value of 0.13. Estimated glomerular filtration rate (eGFR) was calculated from calibrated creatinine using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. CAD: coronary artery disease.

		Pulse Pressure	Systolic Blood Pressure	Difference between risk scores:
Disease endpoints	Source	P value	Median [®] <i>P</i> value	Empirical P value (2-tailed)
Incident heart failure	CHARGE Consortium Heart Failure Working	0.96	0.47	0.07
	Group			
		0.03	0.45	0.03
Incident ischemic stroke	NEURO-CHARGE	4.075.04	0.07	0.00
Incident all stroke	NEURO-CHARGE	4.87E-04	0.07	0.06
		1.66E-03	0.12	0.28
Prevalent CAD	CARDIoGRAM			
		0.13	6.70E-06	0 ^(a)
Prevalent CAD	C4D PROCARDIS	0.54	0.40	0.00
Prevalent CAD	C4D HPS	0.51	0.16	0.32
		4.26E-04	0.18	0.13
Prevalent CAD – combined	CARDioGRAM & C4D			
		0.02	0.42	0.06
Prevalent chronic kidney disease	CKDGen		0.54	
Prevalent microalbuminuria	CKDGen	0.26	0.54	0.38
Continuous measures of target organ	ono och			
damage				
		0.31	0.09	0.52
Left ventricular mass [g]	EchoGen			
Left contribution will this loss on from 1	Fab a Care	0.20	0.01	0.06
Left ventricular wall thickness [mm]	EchoGen	0.52	0.20	0.64
Serum creatinine	KidnevGen	0.53	0.29	0.64
		0.07	0.24	0.36
eGFR (4 parameter MDRD equation)	CKDGen			
		0.56	0.55	0.96
Urinary albumin/creatinine ratio	CKDGen			

Supplementary Note

Phenotype modelling

In the Stage 1 studies, in individuals taking antihypertensive therapies, SBP and DBP were imputed by either adding 15 mm Hg to measured SBP and 10 mm Hg to measured DBP, or by adding 10 mm Hg to measured SBP and 5 mm Hg to measured DBP. In Stage 2, all studies added 15 mm Hg to measured SBP and 10 mm Hg to measured DBP in individuals taking anti-hypertensive therapies. The different constants used for this imputation step did not impact on PP and had little impact on MAP in Stage 1 only.

PP and MAP were derived from these imputed SBP and DBP values as follows:

PP_{imputed} = SBP_{imputed} - DBP_{imputed} MAP_{imputed} = (2 DBP_{imputed} + SBP_{imputed})/3

PP and MAP were adjusted for sex, age, age² and body mass index (BMI) along with additional covariates necessary to control for population stratification as necessary.

Genotype-phenotype association analysis

Genotype-phenotype association of PP and MAP were carried out under an additive model using software as described in **Supplementary Table 1B**. For a subset of studies which already had GWAS data for SBP and DBP, the effect estimates and standard errors for SBP and DBP were used to derive the effect estimates and standard errors for PP and MAP as follows:

$$\beta_{\rm PP} = \beta_{\rm SBP} - \beta_{\rm DBP}$$

$$s_{\rm PP} = \sqrt{s_{\rm SBP}^2 + s_{\rm DBP}^2 - 2s_{\rm SBP} s_{\rm DBP} r_{SD}}$$

$$\beta_{\rm MAP} = \frac{1}{3}\beta_{\rm SBP} + \frac{2}{3}\beta_{\rm DBP}$$

$$s_{\rm MAP} = \sqrt{\frac{1}{9}s_{\rm SBP}^2 + \frac{4}{9}s_{\rm DBP}^2 + \frac{4}{9}s_{\rm SBP} s_{\rm DBP} r_{SD}}$$

Where β is the GWAS effect size estimate for the subscripted trait, *s* is the corresponding standard error and r_{SD} is the phenotypic correlation of SBP and DBP. Studies comprising 25% of the total sample size used this method (**Supplementary Table 1B**). All other studies estimated PP and MAP directly from SBP and DBP as described above and undertook association testing on these values.

Selection of SNPs for follow-up in Stage 2

All SNPs with P<1x10-5 for association with either PP or MAP (or both) were divided into independent regions based on LD and the most significant SNP was selected from each region. A total of 67 loci were identified. Of these, 45 loci had not previously shown association with SBP and/or DBP and 47 SNPs were selected for follow-up: for one SNP with a low N effective, a proxy was also included and for one locus which showed association with both PP and MAP, the sentinel SNPs were close together but statistically independent and so both were taken forward to Stage 2.

For all regions that showed association with PP and/or MAP and which had previously shown association with SBP or DBP (22 loci), the sentinel SNP for PP and MAP and the previously reported SNP for SBP and DBP were followed up (44 SNPs).

In addition, 8 SNPs from 7 regions which do not show association with MAP or PP in our study, but which previously showed association with SBP and/or DBP were also included.



Risk score analyses using multi-SNP predictors

Risk scores can be calculated in the following way: Using a set of *m* SNPs, for the *i*-th SNP in the *j*-th individual denote x_{ij} as the 0/1/2 coded genotype (for directly genotyped markers) or expected allele count (which takes real values between 0.0 and 2.0 for imputed markers). Using results from Stages 1+2, define the set of regression coefficients to be $w_1, w_2, ..., w_m$. Then the risk score for subject j is defined to be

(1) $s_+ = s_0 + w_1 x_{1j} + w_2 x_{2j} + \dots + w_m x_{mj}$

where s_0 is the intercept. We specify the coefficients w_1 , w_2 , ..., w_m to be the effect sizes, in mmHg per coded allele, estimated in single SNP analyses of either PP or MAP in Stages 1+2.

When considering multiple SNPs that are in linkage equilibrium with each other, and small effect sizes per SNP, effect sizes estimated jointly for all SNPs using a multiple regression model are effectively identical to those estimated in a series of single SNP regression models. Thus regression on the risk score can be reconstructed from regressions on each of the *m* SNPs in turn, without further access to individual-level data.

The calculations involved are of the same type as for meta-analysis; the coefficient of the risk score is the mean of the per-SNP regression coefficients, where each is weighted by its corresponding w_i (in our analysis, the observed effect of the SNP on PP or MAP defined from Stage1+2 results). The estimated variance of the risk score is given by similarly weighting the estimated variances (squared standard errors) of each per-SNP regression coefficient. The assumption of zero LD between SNPs ensures that these contributions are independent. Importantly, as with inverse-variance weighted meta-analysis, in large samples this procedure gives valid *P*-values under the null, i.e. when there is no relationship between the "lookup" phenotype and any variants at the SNPs contributing to the risk score.

Using SNP-specific results in this way, we estimated and tested the coefficient of the risk score in independent "lookup" results using linear regression for continuous phenotypes, logistic regression for binary phenotypes, and proportional hazards regression for time-to-event phenotypes. These estimates and tests inherit the covariate adjustment performed in the original SNP-specific analysis. Results are presented in **Supplementary Table 3A**.

Comparison of PP and SBP risk scores

To investigate whether the association between the PP variants and cardiovascular and renal outcomes is different to that expected from their association with SBP, we compared the 10-SNP PP risk score (weighted by PP effect sizes) to a series of 10-SNP SBP risk scores (weighted by SBP effect sizes). Each SBP risk score comprised 10 SNPs selected from the 26 blood pressure SNPs from Ehret et al. (2011) and the present study that are associated with SBP but not PP. SNPs selected for the SBP risk scores are constrained to have similar sized effects for SBP as those of the 10 PP SNPs; this was in order to provide a like-for-like comparison of PP and SBP scores in terms of SBP effect. The 10 PP SNPs have an average (absolute) effect on SBP (Stages 1 and 2 of the present study) of 0.5452 mmHg per coded allele, thus a total effect across the 10 risk alleles of 5.452 mmHg. So for comparison, the SBP risk scores were calculated for sets of 10 SBP variants with a total additive (absolute) effect on SBP in the range 5.447-5.557 mmHg. Thus the sum of the weights, w_i for $i=\{1, ..., m\}$,10}, for each SBP risk score was between 5.447 and 5.557. This range was chosen to closely match the total SBP effect of the 10 PP SNPs, while ensuring that each permutation of 10 SBP SNPs was not restrictive in terms of SNP selection. One thousand permutations (each with a unique set of SNPs) of the SBP risk scores were calculated in order to generate a distribution of SBP risk score results. The P-value associated with each outcome from the PP risk score is then converted to an empirical Pvalue using this distribution of SBP risk score P-values. The empirical P-values (presented in Supplementary Table 3B) correspond to two-tailed tests of the null hypothesis of no difference between the association of the PP risk score with each outcome and the SBP risk score. Outcomes for which data were available for all SNPs shown to be associated with blood pressure in Ehret et al¹ and the present study were tested.

Functional SNPs in linkage disequilibrium with novel PP and MAP SNPs

Using SNAP⁷, functional SNPs (i.e. which are synonymous or non-synonymous or which lie within a 3'UTR, 5'UTR or regulatory region) correlated (r^2 >0.3) with the sentinel SNP in each of the novel loci were identified. SNP rs11222084 has r^2 =0.4 with a non-synonymous SNP in *ADAMTS8*. SNP rs2071518 has r^2 >0.55 with 6 other SNPs in the 3'UTR of *NOV* and r^2 =0.35 with a synonymous SNP in *ENPP2*. SNP rs319690 has r^2 =0.74 with two non-synonymous SNPs in *MAP4* and r^2 =0.64 with two SNPs in *CSPG5*, one of which lies within the 5'UTR and the other being a non-synonymous SNP previously associated with schizophrenia⁸.

RNA sequence expression analysis

Remnant aortic tissue was obtained from donor kidneys after transplantation.

Total RNA was isolated from ten aorta samples according to a phenol-chloroform extraction. The selection of four samples for direct mRNA sequencing was based on Lab-on-a chip quality control (QC) and real-time PCR of the household gene *GPDH*. Sample characteristics and QC are presented below:

Sample ID	Sex	Age	RIN ^a	Ct⁵
1	female	68	6.2	25.5
2	male	53	5.8	24.2
3	male	35	3.5	24.1
4	female	19	7.5	36.3

^a RNA Integrity Number measured using lab-on-a-chip

^b relative copy number of *GPDH*, measured using real time PCR.

Total mRNA was sequenced directly using a Helicos Helisphere according the manufacturer's protocols (helicosbio.com) at the Leiden Genome Technology Center (www.LGTC.nl). Helicos reads (length 25 to 57) were aligned to the h19 reference sequence with the Helicos alignment software. Automated annotation of tags relevant to transcript positions was based on BioMart (www.ensembl.org). Absolute read count per transcript were calculated by dividing the total coverage of all the covered nucleotides in the exonic regions of a transcript by the number of nucleotides covered and expressed as "reads per kilo base per million" (RpKM). Wiggle tracks (truncated at coverage of three) from each individual sample as well as cumulative wiggle files were generated for viewing in the UCSC genome browser (www.genomes.ucsc.edu) (Supplementary Figures 3A and 3B). Transcripts which were covered by reads located in only very confined exonic -or intronic regions were regarded as not expressed.

Selection of negative and positive expressed control transcripts was based on literature -and database search (genecards.org) of genes with tissue specific expression. The adipokines, leptin (*LEP*) and adiponectin (*ADIPOQ*) were expected to be expressed solely in adipose tissues. Furthermore, apolipoprotein 5 (*APOAV*) was expected to be expressed primarily in the liver. Epidermal growth factor receptor (*EGFR*), actin alpha 2 (*ACTA2*), collagen type IV alpha 1 (*COL4A1*) and elastin (*ELN*) were expected to be highly expressed in aortic tissue.

The relative read counts for negative controls were below the filtering threshold value of 3 RpKM and were therefore set to 0 (data not shown). Relative counts of positive controls ranged however from 10 for *EGFR* to 1232 for *ACTA2* (**Supplementary Figure 3C**). The relative read count for the pulse-pressure top hits *ADAMTS15*, *ADAMTS8*, *NOV* and *PDGFRA* (near 3' *CHIC2*) were 8, 9, 287, and 22, respectively, while *PIK3CG* and *FIGN* were not expressed in aorta (**Supplementary Figure 3C** and c). From the *MAP* top hits, only *MAP4* was detectably expressed in aorta at 99 RpKM, while expression of *FIGN*, *GRB14*, and *ADRB1* was not detectable (**Supplementary Figure 3D**).

eQTL analyses

For each of the 8 sentinel genome-wide significant blood pressure SNPs (**Table 1**), all proxy SNPs with r²>0.6 were determined in HapMap CEU. All sentinel SNPs and their proxies were searched against a collected database of expression quantitative trait locus (eQTL) results, including the following tissues: fresh lymphocytes⁹, fresh leukocytes¹⁰, leukocyte samples in individuals with Celiac disease¹¹, lymphoblastoid cell lines (LCL) derived from asthmatic children¹², HapMap LCL from 3 populations¹³, a separate study on HapMap CEU LCL¹⁴, fibroblasts, T cells and LCL derived from cord blood¹⁵, 2 studies on peripheral blood monocytes ^{16,17}, CD4+ lymphocytes¹⁸, adipose and blood samples¹⁹, 2 studies on brain cortex^{16,20}, 3 large studies of brain regions including prefrontal cortex, visual cortex and cerebellum (Emilsson, personal communication), a study of cerebellum, frontal cortex, temporal cortex and caudal pons²¹, a separate study on prefrontal cortex²², liver²³, and osteoblasts²⁴. The collected eQTL results met criteria for statistical significance for association with gene transcript levels as described in the original papers.

The genome-wide significant SNP associated with MAP, rs2782980, was also significantly associated with transcript levels of *ADRB1* in visual cortex tissue from Alzheimer cases and controls ($P=3.2\times10^{-9}$), and in visual cortex tissue and prefrontal cortex tissue from Alzheimer cases only ($P=3.4\times10^{-5}$ and $P=5.4\times10^{-7}$, respectively) (**Supplementary Figure 4A**).

A proxy for SNP rs319690, rs319689 (r^2 =0.737 with rs319690, association with MAP:*P*=2.7x10⁻⁸) showed significant association with transcript levels of *ZNF589* in monocytes (P=2.9x10⁻¹²). An independent database of eQTL results from monocytes was also interrogated (see Cardiogenics consortium study description). This analysis replicated the finding in monocytes and gave a significant association with another proxy SNP for rs319690 (rs319684 r^2 =0.74) with *ZNF589* expression (**Supplementary Figure 4B**).

Two additional proxy SNPs for rs319690, rs1301913 and rs11130148 (each with r^2 =0.644 with rs319690 and showing genome-wide significant association, P=2.7x10⁻⁸, with MAP) showed significant association with transcript levels of *DHX30* in lymphoblastoid cell lines (P=1.3x10⁻⁸ and P=1.6x10⁻⁸, respectively), with rs11130148 also showing significant association with transcript levels of *CDC25A* in adipose tissue (P=9.2x10⁻⁵) and *ZNF589* in blood (P=4.2x10⁻⁴). A proxy SNP for rs2071518, rs7816205 (r^2 =0.714 with rs2071518, association with PP: P=3.7x10⁻⁹) showed significant association with transcript levels of *ENPP2* in cerebellum tissue (P=9.4x10⁻⁵).

Study Descriptions

AGES Reykjavik

The Age Gene/Environment Susceptibility-Reykjavik Study originally comprised a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967. A total of 19,381 people attended, resulting in a 71% recruitment rate. The study sample was divided into six groups by birth year and birth date within month. One group was designated for longitudinal follow up and was examined in all stages; another was designated as a control group and was not included in examinations until 1991. Other groups were invited to participate in specific stages of the study. Between 2002 and 2006, the AGES-Reykjavik study re-examined 5,764 survivors of the original cohort who had participated before in the Reykjavik Study²⁵. The midlife data blood pressure measurement was taken from stage 3 of the Reykjavik Study (1974-1979), if available. Half of the cohort attended during this period. Otherwise an observation was selected closest in time to the stage 3 visit. The supine blood pressure was measured twice by a nurse using a mercury sphygmomanometer after 5 minutes rest following World Health Organization recommendations ²⁶. Individuals with previous MI were excluded from the analyses (N=12).

ARIC

The Atherosclerosis Risk In Communities Study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792 individuals aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities²⁷. Cohort members completed four clinic examinations each spread over about three years, conducted approximately three years apart between 1987 and 1998. The data used in this study are from the first visit in 1987-1989. A detailed study protocol is available on the ARIC study website (http://www.cscc.unc.edu/aric). Blood pressure was measured using a standardized Hawskley random-zero mercury column sphygmomanometer with participants in a sitting position after a resting period of 5 minutes. The size of the cuff was chosen according to the arm circumference. Three sequential recordings for systolic and diastolic blood pressure were obtained; the mean of the last two measurements was used in this analysis, discarding the first reading. Blood pressure lowering medication use was recorded from the medication history. Outliers (>4SD from the mean) with respect to the systolic or diastolic blood pressure distribution were excluded from the analysis. For this study the sample was restricted to individuals of European descent by self report and principal component analysis using genome-wide genotypes.

ASPS

The Austrian Stroke Prevention study is a single center prospective follow-up study on the effects of vascular risk factors on brain structure and function in the normal elderly population of the city of Graz, Austria. The procedure of recruitment and diagnostic work-up of study participants has been described previously²⁸. A total of 2007 participants were randomly selected from the official community register stratified by gender and 5 year age groups. Individuals were excluded from the study if they had a history of neuropsychiatric disease, including previous stroke, transient ischemic attacks, and dementia, or an abnormal neurologic examination determined on the basis of a structured clinical interview and a physical and neurologic examination. During two study panels between September 1991 and March 1994 and between January 1999 and December 2003 an extended diagnostic work-up including MRI and neuropsychologic testing was done in 1076 individuals aged 45 to 85 years randomly selected from the entire cohort. Since 1992 blood was

drawn from all study participants for DNA extraction. They were all European Caucasians. There were 767 participants included in the present study after exclusion those with recognized myocardial infarction and congestive heart failure at the time of blood pressure measurement. Blood pressure is measured in sitting position on two occasions. The first time after about 10 minutes the participant arrived on the left and on the right side, and at a second time at the end of the physical examination only on the left side. The mean of these 3 measurements are used for imputation.

B58C-T1DGC

The British 1958 Birth Cohort – Type 1 Diabetes Genetics Consortium is a sample from the national population-based sample followed periodically from birth to age 44-45 years (http://www.b58cgene.sgul.ac.uk/collection.php) and 2,580 individuals were included in this analysis. Blood pressure was recorded using the Omron 705CP machine three times, seated. The average of three readings was used for the analysis.

B58C-WTCCC

The British 1958 Birth Cohort – Wellcome Trust Case Control Consortium is a second sample from the national population-based sample followed periodically from birth to age 44-45 years (http://www.b58cgene.sgul.ac.uk/collection.php); 1,473 individuals were included in the analysis and are distinct from individuals included in the B58C-T1DGC cohort. Blood pressure was recorded using the Omron 705CP machine three times, seated. The average of three readings was used for the analysis.

BHS

The Busselton Health Study includes a series of seven cross sectional population health surveys of adult residents of the Shire of Busselton in the South-West of Western Australia, undertaken between 1966 and 1990. A cross-sectional community follow-up study in 1994-1995 included the collection of blood for DNA extraction for all survivors of previous surveys. A total of 4,554 individuals participated in this follow-up. Data from a subset of 1038 unrelated individuals with complete data were analysed for the present study. BP was measured in the 1994-1995 follow-up study using a standard mercury sphygmomanometer (Baumanometer, New York) as described in ²⁹. The participants were asked to refrain from caffeine for 12 hours and to not smoke prior to attending the survey. Three BP readings were recorded on the participant's survey chart to the nearest 2 mmHg and the average of the readings was used for the analyses.

BLSA

The Baltimore Longitudinal Study of Ageing is an ongoing prospective study of human ageing which started in 1958³⁰. The study recruited volunteers predominantly from Washington DC and Baltimore, MD, USA. Healthy volunteers aged >17 years were recruited; only European-origin individuals were included in the analysis, there were no other exclusion criteria. Blood pressure was measured using a mercury sphygmomanometer in the seated position, the average of the 2nd and 3rd readings were recorded for both the right and left arm and used for the analyses.

CHS

The Cardiovascular Health Study is a population-based cohort study of risk factors for cardiovascular disease in adults 65 years of age or older conducted across four field centres. The original predominantly white cohort of 5,201 persons was recruited in 1989-1990 from random samples of

the Medicare eligibility lists and an additional 687 African-Americans were enrolled in 1992-93 for a total sample of 5,888. Details of the study design are summarized elsewhere ³¹. A total of 1,908 persons were excluded from the study sample due to prevalent coronary heart disease (N=1195), congestive heart failure (N=86), peripheral vascular disease (N=93), valvular heart disease (N=20), stroke (N=166), or transient ischemic attack (N=56). Participants with missing BMI (N=10) or BP measurements (N=8) were also excluded. Research staff with central training in blood pressure measurement assessed repeated right-arm seated systolic and diastolic blood pressure levels at baseline with a Hawksley random-zero sphygmomanometer. Means of the repeated blood pressure measurements from the baseline examination from 3,277 CHS subjects of European ancestry were used for the analyses.

CoLaus

The Cohorte Lausannoise is a population-based study aimed at assessing the prevalence and molecular determinants of cardiovascular risk factors in the population of Lausanne, Switzerland³². Participants in the study (4,969) were randomly selected from the population register of Lausanne in 2003 (N=56,694, aged 35-75 years). All individuals were of European origin, defined as having both parents and grandparents born in a defined list of European countries. Blood pressure was measured using the Omron HEM-907 machine, in the seated position. Three measures were taken on the left arm; the mean of the last two measures was used in the analyses.

CROATIA-Korcula

The KORCULA study sampled Croatians from the Adriatic island of Korcula (N=969), between the ages of 18 and 88. The fieldwork was performed in 2007 in the eastern part of the island, targeting healthy volunteers from the town of Korcula and the villages of Lumbarda, Žrnovo and Racišce³³. Over 150 quantitative traits were measured to each participant. Blood pressure was measured using standard procedures, briefly, the subject was seated in a quiet room, and they were advised to not have done any exercise, or have been exposed to the cold, eaten, or smoked for half an hour prior to the recording. Following 5 minutes of rest, blood pressure was recorded twice during the examination and the mean of the two reading were used for the analyses.

CROATIA-Split

The SPLIT study is a cross-sectional study that samples Croatians from the town of Split (N=1012), between the ages 18 and 85. The sampling was performed between 2008 and 2010³⁴. A wide range of phenotypic measurements is available. Blood pressure was measured using standard procedures. Briefly, the subject was seated in a quiet room and they were advised to not have done any exercise, or have been exposed to the cold, eaten, or smoked for half an hour prior to the recording. Following 5 minutes of rest, blood pressure was recorded twice during the examination and the mean of the two reading were used for the analyses.

CROATIA-Vis

The CROATIA-Vis (EUROSPAN) study includes Croatians, aged 18 to 93 years, who were recruited during 2003 and 2004 in a population-based study in the villages of Vis and Komiza on the Dalmatian island of Vis, Croatia^{34,35}. Biochemical and physiological measurements were performed, detailed genealogies reconstructed, questionnaire of lifestyle and environmental exposures collected, and blood samples and lymphocytes extracted and stored for further analyses. Blood pressure was measured using standard procedures, briefly, the subject was seated in a quiet room, and they were

advised to not have done any exercise, have been exposed to cold, eaten, or smoked for half an hour prior to the recording. Following 5 minutes of rest, blood pressure was recorded twice during the examination and the mean of the two reading were used for the analyses.

DGI

The Diabetes Genetics Initiative (DGI) is a type 2 diabetes (T2D) case-control study of Swedish and Finnish individuals matched on age, gender and BMI³⁶. GWAS data from 1,467 normoglycemic male and female controls were included in these analyses. Blood pressure traits were the average of two seated measurements using a mercury sphygmomanometer.

EGCUT

Estonian Genome Center, University of Tartu (EGCUT); The Estonian cohort is from the populationbased biobank of the Estonian Genome Project of University of Tartu. The whole project is conducted according to the Estonian Gene Research Act and all participants have signed the broad informed consent³⁷ (www.geenivaramu.ee). The current cohort size is over 48,000, from 18 years of age and up, which reflects closely the age distribution in the adult Estonian population. Subjects are recruited by the general practitioners (GP) and physicians in the hospitals were randomly selected from individuals visiting GP offices or hospitals. Each participant filled out a Computer Assisted Personal interview during 1-2 hours at a doctor's office, including personal data (place of birth, place(s) of living, nationality etc.), genealogical data (family history, four generations), educational and occupational history and lifestyle data (physical activity, dietary habits, smoking, alcohol consumption, women's health, quality of life). Anthropometric and physiological measurements were also taken. GWAS was performed on randomly selected individuals³⁸ with the Illumina HumanHapCNV370 or OmniExpress array, according to the Illumina protocol (www.illumina.com) in the Estonian Biocenter Genotyping Core Facility.

EPIC-Norfolk

The European Prospective Investigation of Cancer is a population-based cohort study of 25,663 Europid men and women aged 39-79 years recruited in Norfolk, UK between 1993 and 1997³⁹. 2,100 randomly selected control subjects were chosen from a BMI study in which genome-wide genotyping data had been obtained. Blood pressure was measured using the Accutorr oscillometric BP machine; the mean of two readings was taken and used in the analysis.

ERF

The ERF (EUROSPAN) study is a family based study which includes over 3,000 participants descending from 22 couples living in the Rucphen region, the Netherlands, in the 19th century. All descendants were invited to visit the regional clinical research centre where they were examined and a fasting blood sample was drawn. All participants filled out a questionnaire on risk factors. The participants included in these analyses consisted of the first series of participants.

Fenland

The Fenland Study is an ongoing population-based cohort study (started in 2005) designed to investigate the association between genetic and lifestyle environmental factors and the risk of obesity, insulin sensitivity, hyperglycaemia, and related metabolic traits in men and women aged 30 to 55 years. Potential volunteers were recruited from general practice sampling frames in the Fenland, Ely, and Cambridge areas of the Cambridgeshire Primary Care Trust in the U.K. Exclusion criteria for the study were: prevalent diabetes, pregnant, and lactating women, inability to

participate including terminal illness, psychotic illness, or inability to walk unaided. Currently, the study comprises more than 3,000 participants of whom the first 1,500 volunteers with complete anthropometric data were genotyped and included in the current analyses. All participants were measured at the MRC Epidemiology Unit Clinical Research Facilities in Ely, Wisbech and Cambridge. Blood pressure measurements were taken with an Accutorr automated sphygmomanometer using the average of three measurements made at one-minute intervals with the participant seated for 5 minutes prior to measurement. Of the 1,500individuals that were genotyped 98 individuals were excluded as their genotyping data did not meet the quality control criteria applied such that 1,402 individuals were included in the genome-wide association analyses.

FHS

The Framingham Heart Study began in 1948 with the recruitment of an original cohort of 5,209 men and women (mean age 44 years; 55 percent women). In 1971 a second generation of study participants was enrolled; this cohort consisted of 5,124 children and spouses of children of the original cohort. The mean age of the offspring cohort was 37 years; 52 percent were women. A third generation cohort of 4,095 children of offspring cohort participants(mean age 40 years; 53 percent women) was enrolled beginning in 2002. Details of study designs for the three cohorts are summarized elsewhere⁴⁰⁻⁴². At each clinic visit, a medical history was obtained with a focus on cardiovascular content, and participants underwent a physical examination including measurement of height and weight from which BMI was calculated. Systolic and diastolic blood pressures were measured twice by a physician on the left arm of the resting and seated participant using a mercury column sphygmomanometer. Pressures were recorded to the nearest even number. The means of two separate systolic and diastolic blood pressure readings at the first clinic examination of each cohort were used for this GWAS analyses. For a subset of offspring cohort participants only one measurement was obtained. Individuals under 20 years of age, those who had a myocardial infarction, or congestive heart failure were excluded from the analyses because those conditions may affect blood pressure levels.

FUSION

The Finland-United States Investigation Of NIDDM Genetics study aims to discover variants predisposing to type 2 diabetes (T2D) and T2D-related quantitative traits (<u>http://fusion.sph.umich.edu/</u>)^{43,44}. The FUSION GWAS sample includes 1,161 Finnish T2D cases and 1,174 normal glucose tolerant (NGT) controls and 122 offspring of case/control pairs (1T2D, 119 NGT, 2 with impaired glucose tolerance). GWAS data from the controls and NGT offspring were used for these analyses. The blood pressure trait was the average of two seated measurements using a mercury sphygmomanometer after 5 minutes of rest⁴⁵. FUSION analyses were adjusted for birth province.

InChianti

The Invecchiare in Chianti study is a representative population-based study of older people living in the Chianti area of Tuscany, Italy⁴⁶. All participants were >21 years of age and of white European origin. Blood pressure was measured using a mercury sphygmomanometer in the supine position; the average of the 2nd and 3rd readings was used for the analysis.

INGI CARL

The Carlantino cohort comprehends about 900 samples from an isolated village of southern Italy (Carlantino). Genotyping data for 679 people is available, of these 521 had also phenotypic data. Mean age of the participants was 45.9 years (SD 19.920). Ethics approval was obtained from the Ethics Committee of the Burlo Garofolo children hospital in Trieste. Written informed consent was obtained from every participant of the study. Blood pressure for each participant was measured 3 times for each arm. Systolic and diastolic blood pressure was calculated taking the higher value between the mean of the three readings at each arm. All samples were typed with illumina 370k CNV chip (Illumina, San Diego, USA). Imputation of genotypes was carried out using the software MACH. The following QC filters were applied prior to imputation: call rate > 95%, MAF $\ge 1\%$, HWE P-value $\ge 10^{-4}$ and per SNP call rate $\ge 90\%$. 266,389 SNPs where then used as backbone for the imputation. The total number of SNPs used for the analysis was 2,599,375.

INGI FVG

The Friuli Venezia Giulia cohort comprehends about 1300 samples from 5 isolated villages of Friuli Venezia Giulia, a region of northern Italy. The villages are: Resia, Illegio, San Martino del Carso, Erto/Casso, Clauzetto. Genotyping data for 1266 people is available, of these 1046 had also phenotypic data. Mean age of the participants was 51.7 years (SD 16.4). Because of the particular structure of this cohort we used both molecular kinship and the village as covariate for the statistical analysis. Ethics approval was obtained from the Ethics Committee of the Burlo Garofolo children hospital in Trieste. Written informed consent was obtained from every participant to the study. Blood pressure for each participant was measured 3 times for each arm. Systolic and diastolic blood pressure was calculated taking the higher value of the mean of the three readings at each arm. All samples were typed with illumina 370k CNV chip (Illumina, San Diego, USA). Imputation of genotypes was carried out using the software MACH. The following QC filters were applied prior to imputation: call rate > 95%, MAF ≥ 1%, HWE P-value ≥ 10^{-4} and per SNP call rate ≥ 90%. 276,271 SNPs where then used as backbone for the imputation. The total number of SNPs used for the analysis was 2,599,375.

INGI Val Borbera

Val Borbera project was initiated in 2005 and represents the collection of phenotypic and genotypic data from a geographically isolated population of North West Italy living in the Val Borbera Valley in Piedmont. Inhabitants of the valley were invited to participate in the study by public advertisements through local authorities, televisions and newspapers as well as local physicians and mailings. Meetings were organized in all villages to present the project and its aims. The importance of the participation of entire families was underscored in all instances, nevertheless all people that volunteered to participate were included in the study, providing they had at least one grand parent from the valley. The study, including the overall plan and the informed consent form was reviewed and approved by the institutional review boards of San Raffaele Hospital in Milan and by the Regione Piemonte ethical committee. Information and biological samples were obtained from 1803 inhabitants between 18 and 102 years of age⁴⁷. 1664 DNAs were genotyped with the genome-wide 370k Illumina chip. Only individuals aged 18 years or older were eligible. Blood pressure was measured with a mercury sphygmomanometer. SBP and DBP were the average of four measurements done with subjects in a seated position in a quiet environment.

KORA S3

The KOoperative Gesundheitsforschung in der Region Augsburg (third survey: S3/F3) is an epidemiological cohort recruited from the general population of Augsburg, Germany in 1994-1995^{48,49}. A subset of this survey (1,644 subjects) were genotyped using the Affymetrix 500K array (http://epi.helmholtz-muenchen.de/kora-gen/). In this study subjects with BMI<35 kg/m² were included; diabetics were excluded. Final number of subjects entering the association analysis with blood pressure was 1,503. Blood pressure was measured using a random zero sphygmomanometer in the seated position at the first examination cycle. Three measurements were taken at least three minutes apart and the numbers entering the database were the mean of the last two measurements.

KORA F4

The KORA S4 survey, a population-based sample from the general population living in the region of Augsburg, Southern Germany, was conducted in 1999/2001. The standardized examinations applied in the survey (4,261 participants, response 67%) have been described in detail elsewhere⁴⁹. A total of 3,080 subjects participated in a follow-up examination of S4 in 2006/08 (KORA F4). For the genome-wide KORA F4 study we selected 1,814 subjects of these participants. Informed consent has been given. The local ethical committee has approved the study. The KORA S3 and S4 samples do not overlap. In this study 1709 of these participants with blood pressure measurements were analysed.

Blood pressure was measured using a OMRON HEM-705CP machine in the seated position at the first examination cycle.

Three measurements were taken at least three minutes apart and the numbers entering the database were the mean of the last two measurements.

LBC1921/1936

The LBC1921 cohort consists of 550 relatively healthy individuals, 316 females and 234 males, assessed on cognitive and medical traits at 79 years of age. They were born in 1921, most took part in the Scottish Mental Survey of 1932, and almost all lived independently in the Lothian region (Edinburgh City and surrounding area) in Scotland. When tested, the sample had a mean age of 79.1 years (SD = 0.6). A full description of participant recruitment and testing can be found elsewhere⁵⁰. The LBC1936 consists of 1,091 relatively healthy individuals assessed on cognitive and medical traits at 70 years of age. They were born in 1936, most took part in the Scottish Mental Survey of 1947, and almost all lived independently in the Lothian region of Scotland. The sample of 548 men and 543 women had a mean age 69.6 years (SD = 0.8). A full description of participant recruitment and testing can be found elsewhere⁵¹. Ethics permission for the study was obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56) and from Lothian Research Ethics Committee (LBC1936: LREC/2003/2/29 and LBC1921: LREC/1998/4/183). The research was carried out in compliance with the Helsinki Declaration. All subjects gave written, informed consent.

In LBC1921, blood pressure was measured once in a sitting position. In LBC1936, blood pressure was measured three times in a sitting position using the B026 Omron 705IT monitor. Individuals were excluded with the following criteria: recognized myocardial infarction, heart failure or coronary artery diseases.

LifeLines

The LifeLines Cohort Study is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 165,000 persons living in the North East region of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity. In addition, the LifeLines project comprises a number of cross-sectional sub-studies which investigate specific age-related conditions. These include investigations into metabolic and hormonal diseases, including obesity, cardiovascular and renal diseases, pulmonary diseases and allergy, cognitive function and depression, and musculoskeletal conditions. All survey participants are between 18 and 90 years old at the time of enrollment. Recruitment has been going on since the end of 2006, and until August 2010 over 30000 participants have been included.

At the baseline examination, the participants in the study have been asked to fill in a questionnaire (on paper or online) before the first visit. During the first and second visit, the first or second part of the questionnaire, respectively, are checked for completeness, a number of investigations are conducted and blood and urine samples are taken. In the first visit to the LifeLines' study center, trained technicians measure subjects' systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse rate, in every minute for a period of 10 minutes using a DINAMAP Monitor i.e. 10 measures for each of the indices. The reported level for each of the blood pressure indices is an average estimate of all the 10 corresponding measures.

LOLIPOP

The LOndon LIfe Sciences POPulation study is an ongoing population-based cohort study of ~30,000 individuals (18,000 Indian Asians and 12,000 European white men and women), aged 35-75 years and recruited from the lists of 58 general practitioners in West London, United Kingdom^{52,53}. Blood pressure was measured using an Omron 705CP sphygmomanometer (mean of 3 measurements) with the subject seated. For the European ancestry validation stage of the present study, lookups were performed in 3 subgroups of European White (EW) ancestry that had been genotyped using 3 GWAS platforms - LOLIPOP (EW_A), LOLIPOP (EW_P) and LOLIPOP (EW_610) - comprising in total 1,603 individuals. For the South Asian ancestry replication stage of the present study, we used genotype data from 7 SNPs that had been genotyped in 12,900 individuals during previous work ⁶, and complemented these with lookups for 22 SNPs in 2 subgroups of Indian Asian ancestry that had been genotyped using 2 GWAS platforms - LOLIPOP (IA317) and LOLIPOP (IA610) - comprising in total 8,688 individuals. Analyses in GWAS datasets were adjusted for ancestry principal components, and analyses in the larger IA sample were adjusted for self-reported religion.

MESA

The Multi-Ethnic Study of Atherosclerosis investigation is a population-based study of 6,814 men and women age 45 to 85 years, without clinical cardiovascular disease, recruited from six United States communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN). The main objective of MESA is to determine the characteristics of subclinical cardiovascular disease and its progression. Sampling and recruitment procedures have been previously described in detail⁵⁴. Adults with symptoms or history of medical or surgical treatment for cardiovascular disease were excluded. During the recruitment process, potential participants were asked about their race/ethnicity. Self-reported ethnicity was used to classify

participants into groups⁵⁵. After a 5-min rest BP was measured three times at 1 minute intervals using a Dinamap PRO 100 automated oscillometric device (Critikon, Tampa, FL) with the subject in a seated and the average of the second and third BP measurements was used in the analysis.

MICROS

The Micro-Isolates in South Tyrol (MICROS, EUROSPAN) study

(http://www.biomedcentral.com/1471-2350/8/29) is part of the genomic health care program 'GenNova' and was carried out in three villages of the Val Venosta on the populations of Stelvio, Vallelunga and Martello. This study was an extensive survey carried out in South Tyrol (Italy) in the period 2001-2003. Study participants were volunteers from three isolated villages located in the Italian Alps, in a German-speaking region bordering with Austria and Switzerland. Due to geographical, historical and political reasons, the entire region experienced a prolonged period of isolation from surrounding populations. The 1,096 participants included in this study are those which had both phenotypic and GWAS data available. Blood pressure was taken after 3 minutes rest and 3 consecutive measurements were recorded on the right upper arm using an HEM-705CP (OMRON). The median for each person was used in the analysis.

MIGen

The Myocardial Infarction Genetics Consortium cohort is composed of a subset of the controls of a case-control study aimed at identifying genetic variants associated with early-onset myocardial infarction. Most of the controls are selected from population based cross-sectional or cohort studies and come from five different studies: Heart Attack Risk in Puget Sound (Seattle, USA), REGICOR (Girona, Spain), MGH Premature Coronary Artery Disease Study (Boston, USA), FINRISK (Finland); Malmö Diet and Cancer Study (Malmö, Sweden). There is a minimal overlap of samples between the resources (N=30). For the majority of studies, blood pressure was measured twice using calibrated sphygmomanometers, in the seated position after at least 5 minutes of rest; the mean of the two measurements was used in the analysis. The first two principle components from an IBS analysis were used to adjust for potential population stratification.

NESDA

The Netherlands Study of Depression and Anxiety (NESDA)⁵⁶, is a multi-centre study designed to examine the long-term course and consequences of depressive and anxiety disorders (http://www.nesda.nl). NESDA included both individuals with depressive and/or anxiety disorders and controls without psychiatric conditions. Inclusion criteria were age 18-65 years and self-reported western European ancestry, exclusion criteria were not being fluent in Dutch and having a primary diagnosis of another psychiatric condition (psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe substance use disorder).

For all participants DNA was isolated from the baseline blood sample. Through funding from the fNIH GAIN program (www.fnih.gov/gain), whole genome scan analysis was conducted for 1859 NESDA (1702 depressed cases and 157 controls) participants. A hundred subjects were excluded because of various quality control issues⁵⁷. Additional exclusions were made based on disease history, medication use (e.g., 50 subjects using tricyclic antidepressants were excluded⁵⁸) and phenotype leaving 1591 subjects in the final analysis dataset. Systolic blood pressure and diastolic blood pressure were measured twice using an OMRON IntelliSense Professional Digital Blood

Pressure Monitor, HEM-907XL (Omron Healthcare, Inc., Bannockburn, Illinois) during supine rest on the right arm, and were averaged over the two measurements⁵⁸.

NFBC1966

The North Finland Birth Cohort of 1966 was designed to study factors affecting preterm birth, low birth weight, and subsequent morbidity and mortality (http://kelo.oulu.fi/NFBC/). The longitudinal data collection includes clinical examination and blood sampling at age 31 years, from which data in the current study are drawn. The attendees in the follow-up (71% response rate) were adequately representative of the original cohort⁵⁹ as is the final study sample in the present analyses. Blood pressure was measured using a mercury sphygmomanometer, seated, from the right arm after 15 minutes rest. The average of two readings taken 5 minutes apart was used for the analyses. Both questionnaire and national medication reimbursement data were used for anti-hypertensive medication information.

NSPHS

The Northern Swedish Population Health Study (EUROSPAN) represents a family-based prospective population study located in the parish of Karesuando, in the subartic region of the County of Norrbotten, Sweden. This parish has about 1,500 inhabitants, of whom 740 participated in the study. Historic population accounts show that there has been little immigration or other dramatic population changes in this area during the last 200 years. The study includes a comprehensive health investigation and collection of data on family structure, lifestyle, diet, medical history, and samples for clinical chemistry, RNA and DNA analyses. Blood pressure was taken once by the auscultatory method using a sphygmomanometer and a stethoscope.

NTR

Blood pressure data of Dutch twins and siblings participating in four different studies of the Netherlands Twin Register (NTR) were collected over the last decade⁶⁰⁻⁶³. These studies were approved by the medical ethical committee of the Free University of Amsterdam. Four triplets were included as pairs by discarding the data from the middle child. Study 1 was part of a project in which cardiovascular risk factors were studied in 160 twin families⁶⁰. Addresses of twins living in and around Amsterdam were obtained from City Council population registries. Twins and both their biological parents were invited to participate. The age of the twins was between 14 and 21 years at the time of blood pressure measurement. Study 2 was also part of a cardiovascular risk factor project. Here, middle aged Dutch twins were recruited by a variety of means including advertisement in twin newsletters and through city councils⁶¹. A total of 213 families participated and twins were between 34 and 63 years old at time of measurement. In Study 3 blood pressure was measured in 261 extended Dutch twin families (twins and their siblings) who took part in a study of cognition and brain function⁶². The age of the subjects ranged between 14 and 71 years at time of measurement, with a somewhat bimodal distribution. Study 4 was a project studying the genetics of anxious-depression and cardiovascular risk factors⁶³. Twins and siblings from the NTR were invited and 792 subjects from 339 families agreed to participate. The age of twins and siblings ranged between 17 and 81 years at the time of blood pressure measurement.

Blood pressure measurements were done using brachial cuff measurements on the non-dominant arm by an automated Dynamap 845 recorder in the laboratory or by an ambulatory monitoring

device (Spacelabs 90207)⁶⁴. The laboratory measurements were obtained with subjects sitting quietly for periods varying from 3 to 8 minutes. A mean of 3 to 6 BP measurements was taken as the BP resting value. In the ambulatory BP study the mean of all evening measurements when subjects were seated calmly was taken as the resting value (the mean number of measurements was 3.8, ranging from 1 to 10 per subject). The observed BP values in all four studies were corrected for the use of antihypertensive medication^{64,65}. If subjects were taking antihypertensive medication at the time of measurement a correction of +14 mmHg for SBP and +10 mmHg for DBP was made for the laboratory studies. For the ambulatory study, the correction was drug class specific, but average values were close to +14 mmHg for SBP and +10 mmHg for DBP. From these corrected values, the PP value was calculated by subtracting DBP from SBP.

ORCADES

The Orkney Complex Disease Study (ORCADES) is an ongoing family-based cross-sectional study in the isolated Scottish archipelago of Orkney. Genetic diversity in this population is decreased compared to Mainland Scotland, consistent with the high levels of endogamy historically. Data for participants from a subgroup of ten islands were used for this analysis. Fasting blood samples were collected and over 200 health-related phenotypes and environmental exposures were measured in each individual. BP was recorded twice five minutes apart using a calibrated OMRON digital Sphygmomanometer, after at least 10 minutes of supine rest; the mean of the readings was used for the analyses.

PROCARDIS

The Precocious Coronary Artery Disease study (PROCARDIS) (www.procardis.org) is a European consortium investigating the genetics of precocious coronary artery disease (CAD) in German, Italian, Swedish, and British CAD patients and controls⁶⁶. Country of origin was a covariate in all analyses. The controls were included in this study; these had no personal history of CAD, hypertension, or diabetes. Blood pressure was measured twice using various sphygmomanometers, in the seated position after at least 5 minutes of rest; the mean of the two measurements was used.

PROSPER/PHASE

All data come from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). A detailed description of the study has been published elsewhere^{67,68}. PROSPER was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly. Between December 1997 and May 1999, we screened and enrolled subjects in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5804 subjects were randomly assigned to pravastatin or placebo. A large number of prospective tests were performed including Biobank tests and cognitive function measurements. Blood pressure was measured in all subjects during the trial every 3 months by a standardized technique using Omron M4 sphygmomanometers (Omron Healthcare Inc, Bannockburn, Illinois). A whole genome wide screening has been performed in the sequential PHASE project with the use of the Illumina 660K beadchip.

RS-I, RS-II and RS-III

The Rotterdam Study I (RS-I), Rotterdam Study II (RS-II) and Rotterdam Study III (RS-III) are prospective population-based cohort studies; the RS-I comprises 7,983 subjects aged 55 years or older. Participants completed an interview at home and at the research centre, where participants were subsequently examined. Baseline data were collected between 1990 and 1993. In 1999, inhabitants who turned 55 years of age or moved into the study district since the start of the study were invited to participate in an extension of the RS (RS-II), 3,011 participated (67% response rate). In 2006 a further extension of the cohort was initiated in which 3,932 subjects were included (RSIII), aged 45 years and older, out of 6,057 subjects invited, living in the Ommoord district The rationale and design of the RS have been described in detail elsewhere⁶⁹. At the research centre, we obtained two seated blood pressure measurements of the right brachial artery with a random zero sphygmomanometer. The mean of two consecutive measurements was used in association analyses. We excluded participants who were older than 85 years of age and those who had a history myocardial infarction or congestive heart failure, because of the impact of these conditions on blood pressure levels.

SardiNIA

The SardiNIA study is a longitudinal study examining age-related quantitative traits in individuals from the Ogliastra region of Sardinia, Italy⁷⁰. The SardiNIA GWAS examined 4,305 related individuals (age >14 years), of whom 3,998 individuals were included in this study. Blood pressure was measured using a mercury sphygmomanometer; the average of the second and third reading was used for the analyses.

SHIP

The Study of Health In Pomerania is a population-based survey in West Pomerania, the North-East area of Germany^{71,72}. A sample from the adult population aged 20 to 79 years was drawn based on population registries of cities and towns in the region. SHIP finally comprised 4,308 participants (corresponding to a final response rate of 68.8%). 3,310 individuals with GWAS data were included in this study. Blood pressure was measured three times, seated, after 5 minutes of rest, using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan), after a rest period of 3 minutes for each measurement. The mean of the second and third measurements was used in the analyses.

SUVIMAX

The SUpplementation en Vltamines et Mineraux AntioXydants study is a longitudinal study performed on a national sample of healthy volunteers from France between 1996 and 2001. 1,823 individuals, aged 35-65 years at baseline were included in this study⁷³. Blood pressure was measured using a mercury sphygmomanometer in the seated position; the average of three readings taken from the first examination (1996) was used in the analysis.

TwinsUK

The TwinsUK Study comprises a sample of healthy female whites recruited through the TwinsUK registry in London (http://www.twin-research.ac.uk/indexscience.html). All participants were recruited from the general population without presence or interest in any particular disease or trait through national media campaigns. One of each twin pair was selected, with ages ranging from 18 to 76 years. Blood pressure was measured using an Omron HEM-907 machine, seated. Three readings

were taken, the first was discarded and the average of the other two was used in the analyses. In the GWAS discovery (stage 0) data from 873 Twins UK participants was used (TwinsUK). During the study data from a further 2,163 independent individuals from study became available for analyses (TwinsUK2), which were used for lookups in stage 3 validation.

YFS

Cardiovascular risk in Young Finns Study was set up to determine the contribution of childhood lifestyle, biological, and psychological measures to the risk of cardiovascular diseases in adulthood. In 1980, over 3,500 children and adolescents from all over Finland participated in the baseline study. Thereafter these subjects were followed up with several examinations including comprehensive risk factor assessments. The 27-year follow-up was performed in 2007 and the blood pressure measurements at this time point were used for this study. Blood pressure was measured by nursing staff three times using a random-zero sphygmomanometer, the average of the three measurements were taken. Individuals were excluded if BMI, systolic or diastolic blood pressure measurements were missing or genotype data.

WGHS

The Women's Genome Health Study (WGHS) is a prospective cohort of female North American health care professionals representing participants in the Women's Health Study (WHS) trial who provided a blood sample at baseline and consent for blood-based analyses. Participants in the WHS were 45 years or older at enrolment and free of cardiovascular disease, cancer or other major chronic illness. For the primary WHS endpoints of cardiovascular disease, full medical records were obtained for reported endpoints and reviewed by an endpoints committee of physicians unaware of randomized treatment assignment. The current data are derived from 23,294 WGHS participants for whom whole genome genotype information was available at the time of analysis and for whom selfreported European ancestry could be confirmed by multidimensional scaling analysis of 1,443 ancestry informative markers in PLINK v. 1.06. Baseline BP in the WGHS was ascertained by a selfreported questionnaire, an approach which has been validated in the WGHS demographic, namely female health care professionals⁷⁴⁻⁷⁶. Questionnaires recorded systolic blood pressure in 9 categories (<110, 110-119, 120-129, 130-139, 140-149, 150-159, 160-169, 170-179, =180 mmHg), and diastolic blood pressure in 7 categories (<65, 65-74, 75-84, 85-89, 90-94, 95-104, =105 mmHg). The midpoint of each category was used for analysis. Hypertension was defined as a history of physician-diagnosed HTN and ongoing HTN treatment, or SBP = 140 or DBP = 90 mmHg. To account for treatment effects, 10 and 5 mmHg were added to the measured systolic and diastolic blood pressures respectively, if a participant was taking antihypertensive medication⁶⁵.

Outcome and eQTL studies

AortaGen consortium

Association statistics for pulse wave velocity (PWV) were obtained from the discovery meta-analysis of the AortaGen Consortium (n=20,634), including 9 cohort studies that completed genome-wide genotyping and had measured CFPWV plus 2 cohort studies that had measured CFPWV and collected DNA for replication genotyping. Six cohorts, AGES, FHS, ERF, RSI, RSII and Sardinia overlap the discovery resources studies here. Sex-specific standardized regression residual for 1000/CFPWV, adjusted for age, age², height and weight were used for the within-cohort association analyses, using

an additive gene-dose model. Results were combined across cohorts using a standard inverse variance weighted meta-analysis. During meta-analysis, results were filtered for weighted mean minor allele frequency <0.01 and the genomic control parameters were calculated to adjust each study. After meta-analysis, the genomic control parameter was recalculated to adjust for among-study heterogeneity.

C4D Consortium (CAD)

The C4D consortium comprises CHD cases and controls of European origin from PROCARDIS and the Heart Protection Study (HPS) and of South Asian origin from the LOLIPOP and PROMIS studies. Data analysed with respect to risk of CHD all relate to the European origin participants from PROCARDIS and HPS. The PROCARDIS study included 5,720 cases of CHD (74.9% male, 80.4% myocardial infarction) and 1,684 controls recruited from Germany, Italy, Sweden and the UK. The controls were supplemented with N=2697 unselected individuals provided from the National Blood Service and used as common controls by the WTCCC. Many of the PROCARDIS cases are related to each other, and familial clustering was accounted for by using robust sandwich estimation of the variance, using Stata version 10. The HPS included 2704 CHD cases included in the HPS trial⁷⁷ and 2887 controls from the 1958 Birth Cohort. The HPS was a large clinical trial of patients with either (i) CAD (ie, MI, unstable or stable angina, coronary artery bypass grafting, or angioplasty); or (ii) occlusive disease of non-coronary arteries (ie, stroke, leg artery stenosis; or (iii) diabetes mellitus; or (iv) treated hypertension (if also male and aged 65 or older). A total of 20,536 individuals (15,454 men and 5,082 women) were recruited. Previous MI was reported by 8,510, some other history of CAD by 4,876, and no history of CAD by 7,150. Among the 13,386 with known CAD, 1,460 had cerebrovascular disease, 4,047 had peripheral arterial disease, and 1,981 had diabetes mellitus. GWAS genotyping was performed for a random sample of 4,000 participants with sufficient DNA and complete phenotypic information, and of these there were 2,704 CAD cases after quality control exclusions.

Cardiogenics

The Cardiogenics study included 758 individuals, including 363 patients with coronary artery disease (CAD) or myocardial infarction (MI) and 395 healthy individuals of European descent recruited in five centres within the Cardiogenics consortium (http://www.cardiogenics.eu). Healthy individuals were recruited in Cambridge (UK). CAD/MI patients (n=459) were recruited in Leicester (n=161), Lübeck (n=102), Regensburg (n=122) and Paris (n=74). The study was approved by the Institutional Ethical Committee of each participating centre. Blood samples (30ml) from fasting subjects were collected into EDTA and monocytes were isolated with CD14 micro beads using AutoMAcs/AutoMacs Pro (Miltenyi) according to the manufacturer's instructions. Monocyte purity was measured as the percentage of CD14+ve cells analyzed by flow cytometry. Isolated monocytes were lysed in Trizol and RNA was extracted in chloroform and ethanol, washed in RNeasy columns (Qiagen) and incubated with DNase 1 before extracting in RNase-free water. RNA was quantified by the NanodropÒ method. Genomic DNA was extracted from peripheral blood monocytes by standard procedures (Qiagen) and sent to the Sanger Institute for genotyping. Gene expression profiling was performed using the Illumina's Human Ref-8 Sentrix Bead Chip arrays (Illumina Inc., San Diego, CA) containing 24,516 probes corresponding to 18,311 distinct genes and 21,793 Ref Seq annotated

transcripts. mRNA was amplified and labelled using the Illumina Total Prep RNA Amplification Kit (Ambion, Inc., Austin, TX). After hybridization, Array images were scanned using the Illumina BeadArray Reader and probe intensities were extracted using the Gene expression module (version 3.3.8) of the Illumina's Bead Studio software (version 3.1.30). Raw intensities were processed in R statistical environment using the Lumi and beadarray packages. All array outliers were excluded and only arrays with high concordance in terms of gene expression measures (pairwise Spearman correlation coefficients within each cell type >0.85) were included in the analyses. After data quality control, 849 monocyte RNA samples were available for statistical analyses. Whole-genome genotyping was carried out using two arrays, the Sentrix Human Custom 1.2M array (1,115,839 SNPs and 80,128 CNVs) and the Human 610 Quad Custom array (594,398 SNP s and 66,049 CNVs) (Illumina). After filtering, which was based on sample call rate, ancestry, duplications and genetic relatedness; 758 were used for further analyses. Subsequent filtering removed SNPs if they had (i) a per-SNP call rate lower than 95% in cases or controls on the two arrays, and/or (ii) a minor allele frequency (MAF) of 1% in cases or in controls and/or (iii) a MAF in controls generated using the Illumina 1.2 M or in those generated on the 670k array and/or (iv) a significant deviation from Hardy-Weinberg equilibrium in the controls (P < 10-5). Furthermore, all SNPs on the Y and mitochondrial chromosomes as well as CNV markers were excluded from statistical analysis. After per-SNP data quality control, 522,603 SNPs represented on the two arrays and that passed the quality control, were used for further analyses.

CARDIoGRAM (CAD)

The Coronary ARtery DIsease Genome-wide Replication And Meta-analysis (CARDIoGRAM) consortium combines data from 14 GWAS, all published and several unpublished, in individuals with European ancestry including >22,000 cases with CAD and/or MI and >60,000 controls, and unifies samples from Atherosclerotic Disease VAscular functioN and genetiC Epidemiology study, CADomics, Cohorts for Heart and Aging Research in Genomic Epidemiology, deCODE, the German Myocardial Infarction Family Studies I, II, and III, Ludwigshafen Risk and Cardiovascular Heath Study/AtheroRemo, MedStar, Myocardial Infarction Genetics Consortium, Ottawa Heart Genomics Study, PennCath, and the Wellcome Trust Case Control Consortium. These studies have a casecontrol design or are prospective cohort studies both having detailed phenotyping for CAD and/or MI as previously described⁷⁸. Control subjects have been derived from population-based studies in most investigations. For all of the participating studies, genome-wide scans were performed in the years 2006-2009 using either Affymetrix or Illumina platforms followed by imputation of genotypes in most studies. Statistical methods have been standardized across the studies, and an analysis platform has been created to allow summarized analyses on CAD, MI, and related phenotypes. Data were combined across all studies (prevalent CAD case/control comparisons). Overall prevalence of MI within the CAD cases was 66%.

CHARGE Consortium Heart Failure Working Group

We obtained association data for SNPs of interest from the meta-analysis of 4 cohorts (ARIC, CHS, FHS and RS) with a total of 20,926 participants free of clinical heart failure at baseline, in whom 2,526 incident heart failure events occurred during follow-up⁷⁹. All cohorts included in the heart failure analysis are also included in PP and MAP-GWAS. Methods of ascertainment of incident heart failure events are discussed in detail by⁷⁹. Briefly, potential events were identified during follow-up

using self-report, administrative data or in-person examinations, mostly validated by review of the medical data by a physician using published criteria⁷⁹. Cox proportional hazards regression models were used for within-cohort analyses of the association between each SNP and time to incident heart failure, adjusting for sex and age. Results of individual cohorts were meta-analyzed using inverse variance weighted fixed-effect meta-analysis.

CKDGen

Association statistics for estimated glomerular filtration rate (eGFR) were obtained from the discovery meta-analysis of the CKDGen consortium, described previously⁸⁰. eGFR was calculated from calibrated creatinine using the 4-variable MDRD Study equation. The discovery analysis for these phenotypes combined data from 20 cohorts with total sample size N=67,093. 14 of the cohorts: AGES, Amish, ARIC, BLSA, CHS, 1300 samples from ERF, FHS, KORA F3, MICROS, ORCADES, RS, RSII, SHIP and Vis, with total N=39,361, overlap the discovery cohorts studied here. Association statistics for dichotomous chronic kidney disease (CKD), urinary albumin/creatinine ratio (UACR), and dichotomous microalbuminuria, were obtained in collaboration with the CKDGen consortium by querying their datasets. CKD was defined as eGFR <60 ml/min/1.73m2, in the same set of samples in which eGFR was studied. The discovery analysis for urinary albumin/creatinine phenotypes combined data from 12 cohorts with total sample size N=31,580. 12 of the cohorts, Amish, ARIC, BLSA, CHS, CoLaus, EPIC, Fenland, FHS, KORA F3, MICROS, NSPHS, and SHIP, with total N=30,342, overlap those studied here. Microalbuminuria was defined as UACR >25mg/g [women] or >17 mg/g [men]. For CKD there were 5,807 cases and 61,286 controls available. For microalbuminuria 3,698 cases and 27,882 controls were used. eGFR and urinary albumin/creatinine ratio were (natural) log transformed prior to analysis. Within-cohort association analyses regressed phenotype onto genotype using an additive genetic model with age and sex as covariates, using linear regression for continuous phenotypes and logistic regression for dichotomous phenotypes. Family-based methods were used where relevant. Results were combined across cohorts using an inverse variance weighted meta-analysis.

DECODE

Hypertension cases are composed of (1) self-reported hypertension (2) received the diagnosis of hypertension at discharge from the Landspitali University Hospital, Reykjavik or (3) attended the hypertemsion medical clinic at Landspitali University Hospital. The controls in the study consist of individuals from other ongoing genetic studies at deCODE. All individuals diagnosed with other cardiovascular diseases and hypertension were excluded from the control group. All hypertension case and control samples were directly genotyped with the Illumina HumanHap300/CNV370 chips. Only SNPs present on both chips were included in the analysis and SNPs were excluded if they had (i) yield lower than 95% in cases or controls, (ii) minor allele frequency less than 1% in the population, or (iii) showed significant deviation from Hardy-Weinberg equilibrium in the controls (P < 0.001). All samples with a call rate below 98% were excluded from the analysis. Of the 40,000 that have currently been directly typed with Illumina HumanHap300/CNV370 chip at deCODE, 1000 individuals were genotyped with the Illumina Human1M-Duo chip and the Metabochip and the longe-range phased haplotypes that have been determined for the 40,000 individuals were used for the imputation of the Illumina Human1M-Duo chip and the Metabochip data to the hypertension cases and controls⁸¹. For the imputation of the HapMap v22 dataset to the hypertension case control set the IMPUTE model was used².
EchoGen

Association statistics for left ventricular (LV) wall thickness and LV mass were obtained from the discovery meta-analysis described previously⁸². The discovery analysis for this study combined data from 5 cohorts with total sample size N=12,612. Four of the cohorts CHS, RS, KORA F3, FHS, with total N=9,312, overlap those studied here.

Subjects underwent routine transthoracic echocardiography, and methodology for measurements of LV dimensions, and calculations of mass and wall thickness, are given in detail by⁸². Within-cohort association analyses regressed LV mass and LV wall thickness onto additively coded (expected) genotype dose, with age, sex, height and weight as covariates, using linear regression (with random effects to account for relatedness where necessary). Results were combined across cohorts using an inverse variance weighted meta-analysis.

KidneyGen consortium

Association statistics for serum creatinine were obtained from the discovery meta-analysis of the KidneyGen consortium, described previously⁸³. The discovery analysis for this study combined data from 9 cohorts, with total sample size N=23,812. Six cohorts, CoLaus, SardiNIA, 873 samples from TwinsUK, Fenland, InCHIANTI, NFBC1966, with total sample size N=17,699, overlap the discovery resource studied here. Serum creatinine concentrations were log10 transformed prior to analysis. Within-cohort association analyses were linear regressions of transformed serum creatinine on genotype, using an additive genetic model with age, sex and ancestry principal components as covariates. Results were combined across cohorts using a standard inverse variance weighted metaanalysis. Effect sizes were converted to a natural log transformed scale for presentation in Table 2 and Suppl. Table 11, for comparability with other phenotypes.

NEURO-CHARGE (stroke)

Association statistics for risk of incident stroke were obtained from the discovery metaanalysis of the CHARGE consortium, described previously⁸⁴. The discovery analysis for these phenotypes combined data from 4 cohorts with total sample size N=19,602, of which there is a 100% overlap the ICBP-GWAS⁴ discovery samples. For the stroke analysis, individuals who were stroke-free at recruitment were followed up for an average of 11 years, and there were 1544 incident strokes (of which 1164 were ischemic strokes). The association analysis was a survival (time-to-event) analysis using a proportional hazards model, adjusted for age and sex as covariates.

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