



Gene-educational attainment interactions in a multi-ancestry genome-wide meta-analysis identify novel blood pressure loci

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Abstract

Educational attainment is widely used as a surrogate for socioeconomic status (SES). Low SES is a risk factor for hypertension and high blood pressure (BP). To identify novel BP loci, we performed multi-ancestry meta-analyses accounting for gene-educational attainment interactions using two variables, “Some College” (yes/no) and “Graduated College” (yes/no). Interactions were evaluated using both a 1 degree of freedom (DF) interaction term and a 2DF joint test of genetic and interaction effects. Analyses were performed for systolic BP, diastolic BP, mean arterial pressure, and pulse pressure. We pursued genome-wide interrogation in Stage 1 studies ($N = 117\,438$) and follow-up on promising variants in Stage 2 studies ($N = 293\,787$) in five ancestry groups. Through combined meta-analyses of Stages 1 and 2, we identified 84 known and 18 novel BP loci at genome-wide significance level ($P < 5 \times 10^{-8}$). Two novel loci were identified based on the 1DF test of interaction with educational attainment, while the remaining 16 loci were identified through the 2DF joint test of genetic and interaction effects. Ten novel loci were identified in individuals of African ancestry. Several novel loci show strong biological plausibility since they involve physiologic systems implicated in BP regulation. They include genes involved in the central nervous system-adrenal signaling axis (*ZDHH17*, *CADPS*, *PIK3C2G*), vascular structure and function (*GNB3*, *CDON*), and renal function (*HAS2* and *HAS2-AS1*, *SLIT3*). Collectively, these findings suggest a role of educational attainment or SES in further dissection of the genetic architecture of BP.

Introduction

Educational attainment is among the most widely used indices of socioeconomic status (SES) in epidemiologic studies [1,2]. Multiple studies have demonstrated a step-wise decline in all-cause mortality with increasing levels of education [1]. Compared with other measures of SES, such as income and occupation, the use of educational attainment has several advantages: it is stable after young adulthood, simple to capture, has a low nonresponse rate, and is not affected by poor health in adulthood [1,3]. Furthermore, the relationship between educational attainment and cardiovascular disease traits tend to be more consistent and

stronger [4]. Higher educational attainment is related to improved health efficacy (such as preventive health behaviors and problem-solving capacity), improved access to health care, and more favorable socio-psychological conditions (such as personal control and social support) [2,3].

Several variables of educational attainment investigated in epidemiologic studies in relation to cardiovascular risk traits include continuous variables (such as years of education) and various partitions (such as completing high school or completing college degree) [5–11]. Low educational attainment is related to high blood pressure (BP) and increased hypertension (HTN) risk as evidenced in a meta-analysis of 51 studies across 20 countries [3]. Educational attainment is also related to coronary artery disease [12], coronary calcification [13], and other cardiovascular risk traits including metabolic syndrome [10], lipid levels [9,10,14], smoking behavior [12,15], salt intake [16,17], and leisure-time physical activity [18]. Furthermore, the genetic effects on HTN may vary as a function of educational attainment. For example, a heritability study of EUR-ancestry male twins showed higher heritability of HTN at higher education levels ($h^2 = 0.63$ with >14 years of education compared with $h^2 = 0.46$ with ≤ 14

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years of education) [19], suggesting interactions between genes and educational attainment.

While genome-wide association studies have investigated the genetic contributions to educational attainment [6], there has been no comprehensive effort to examine the role played by gene-environment interactions in BP using educational attainment as the environmental exposure. Within the CHARGE Gene-Lifestyle Interactions Working Group [20], we performed genome-wide meta-analysis of systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and pulse pressure (PP), accounting for gene-educational attainment interactions. Based on the availability of data across participating studies, we considered two educational attainment variables, “Some College” (yes/no, for any education beyond high school) and “Graduated College” (yes/no, for completing a 4-year college degree). Herein, we report our findings based on up to 411,225 individuals from five ancestry groups.

Subjects and methods

Participating studies

We performed our analysis in two stages (Fig. 1). A total of 42 cohorts including 117 438 men and women (aged 18–80 years) from European (EUR), African (AFR), Asian (ASN), Hispanic (HIS), and Brazilian (BRZ) ancestries contributed to Stage 1 genome-wide interaction analyses (Table S1). An additional 49 cohorts including 293 787 individuals contributed to Stage 2 analyses of top single nucleotide variants (SNVs, also including a small number of insertion and deletion [indels] variants) selected from Stage 1 (Table S2). Participating studies are described in Supplementary

Material. Since discoveries to date are largely from EUR populations, considerable effort was made to recruit most of the available non-EUR cohorts into Stage 1. Each study obtained informed consent from participants and approval from the appropriate institutional review boards.

Phenotype and lifestyle variables

We performed our analysis for SBP, DBP, MAP, and PP. After computing SBP and DBP when multiple measurements were available, we adjusted for antihypertensive medication use by adding 15 mmHg and 10 mmHg to SBP and DBP, respectively [21]. After medication adjustment, MAP was computed as $(SBP + 2DBP)/3$, and PP was computed as $SBP - DBP$ (SBP–DBP). To reduce the influence of possible outliers, Winsorizing was performed for each BP value that was more than six standard deviations away from the mean. Descriptive statistics for these four BP traits are presented in Tables S3 and S4. For educational attainment, two dichotomous variables were created. The first variable, “Some College” (SomeCol), was coded as 1 if the subject received any education beyond high school, including vocational school (and as 0 if no education beyond high school). The second variable, “Graduated College” (GradCol), was coded as 1 if the subject completed at least a 4-year college degree (and as 0 for any education less than a 4-year degree). Subjects with missing data for BP, education attainment, or any covariates were excluded from analysis.

Genotype data

Genotyping was performed by each participating study using Illumina (San Diego, CA, USA) or Affymetrix (Santa Clara, CA, USA) genotyping arrays. Imputation was performed using the 1000 Genomes Project [22] Phase I Integrated Release Version 3 Haplotypes (2010-11 data freeze, 2012-03-14 haplotypes) as a reference panel, in most cohorts. Information on genotype and imputation for each study is presented in Tables S5 and S6.

Analysis methods

Each study performed association analyses using the following model:

$$E(Y) = \beta_0 + \beta_G G + \beta_E \text{Educ} + \beta_{GE} G \times \text{Educ} + \beta_C C,$$

where Y is the BP variable (SBP, DBP, MAP, or PP value), Educ is the educational variable (SomeCol or GradCol), and G is the dosage of the imputed genetic variant coded additively from 0 to 2. C is the vector of covariates, including age, sex, field center (for multi-center studies), and principal components. In addition, studies in Stage 1 performed

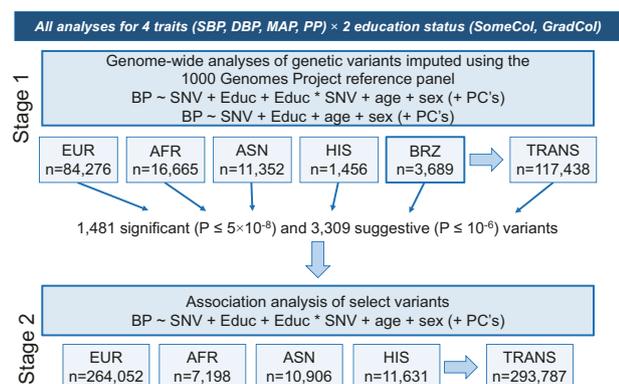


Fig. 1 Study design with summary of data included in this study. Educ: education status (considering either SomeCol or GradCol status separately); PC principal component, EUR European, AFR African, ASN Asian, HIS Hispanic, BRZ Brazilian, SNV single nucleotide variant, TRANS trans-ancestry (i.e., combining all ancestry groups through meta-analysis).

association analysis using the following genetic main-effect model with education attainment:

$$E(Y) = \beta_0 + \beta_G G + \beta_E \text{Educ} + \beta_C C.$$

Each study provided the estimated SNV effect (β_G), estimated SNV-educational attainment interaction effect (β_{GE}), their robust standard errors (SEs), and a robust estimate of the covariance between β_G and β_{GE} . We performed meta-analysis using the 1 degree of freedom (DF) test of the interaction effect (β_{GE}) and 2DF test of both SNV (β_G) and interaction effects (β_{GE}). Inverse-variance weighted meta-analysis was performed for the 1DF test and the joint meta-analysis of Manning et al. [23] for the 2DF test, both using METAL [24]. In Stage 1 EUR, AFR, ASN meta-analyses, variants were included if they were available in more than 5,000 samples or at least three cohorts (these filters were not applied to BRZ or HIS because of the fewness of cohorts included in these meta-analyses). We applied genomic control correction [25] twice in Stage 1, first for study-specific GWAS results and again for meta-analysis results. Genome-wide significant ($P < 5 \times 10^{-8}$) and suggestive ($P < 1 \times 10^{-6}$) variants in Stage 1 were taken forward into Stage 2 analysis. Genomic control correction was not applied to the Stage 2 results as association test was performed for select variants. Results presented reflect meta-analyses combining Stages 1 and 2. Loci were defined by physical distance (± 1 Mb around the index SNV of the respective locus).

Quality control (QC)

Each participating cohort in Stage 1 excluded variants with minor allele frequency (MAF) $< 1\%$. We performed extensive QC using the R package EasyQC [26] for all cohort-specific and meta-analysis results. For Stages 1 and 2, we excluded all variants with imputation quality measure < 0.5 . In addition, to remove unstable study-specific results that reflected small sample size, low minor allele count (MAC), or low imputation quality, we excluded variants for which the minimum of (MAC0, MAC1) \times imputation quality < 20 , where MAC0 and MAC1 are the MAC in the two education strata (Educ = 0 and Educ = 1). The allele frequencies provided by each cohort were compared against those from the relevant ancestry-specific 1000 Genomes reference panel. Marker names were harmonized to ensure consistency across cohorts. In addition, we visually compared summary statistics (e.g., mean, median, standard deviation, inter-quartile range) of all effect estimates, SEs, and P values. We examined SE-N plots [26] and quantile-quantile (QQ) plots to reveal issues with trait transformation or other analytical problems. Any problems encountered during QC steps were resolved through communication with the analysts from the participating studies. More detailed information about the QC steps, including major

QC problems encountered and how they were resolved, are described elsewhere [20,27].

Characterization of functional roles

A suite of tools implemented in FUMA GWAS [28] was used to identify functional roles for the index variants and nearby variants in linkage disequilibrium (LD; $r^2 \geq 0.2$) in each of the novel BP loci. LD information was obtained from the 1000 Genomes Project reference genome for the ancestry with the most significant ancestry-specific association. If the most significant association was in trans-ancestry analyses, the reference genome for the ancestry with the next most significant association was used instead [29]. One index insertion/deletion locus was not identified in any of the reference genomes by FUMA and therefore not detailed. Nearest gene annotations were limited to protein coding, long non-coding RNAs, and non-coding RNAs within 10 kb of index variants and variants in LD ($r^2 \geq 0.2$) with the index variant [30].

For the index and LD variants, we used the RegulomeDB score [31], which reflects a summary of annotations with known and predicted regulatory elements such as DNAase hypersensitivity, binding sites of transcription factors, and promoter regions, and Combined Annotation Dependent Depletion (CADD) [32] scores, which predict deleteriousness of variants. The 15-core chromatin state (ChromHMM) [33,34] was assessed for 129 epigenomes (labeled E001-E129) to identify histone modifications consistent with epigenetic regulation of gene expression. Expression quantitative trait loci (eQTLs) were determined using the GTEx_v7 database [35] for index and LD variants. Using nearest-gene annotations, FUMA GWAS was used to generate tissue-specific gene expression data (GTEx V7 dataset, 53 tissue types); significance was determined as a Benjamini–Hochberg false discovery rate (FDR) < 0.05 .

Results

Overview

We performed a meta-analysis of gene-education interactions on SBP, DBP, MAP, and PP in two stages (Fig. 1). In Stage 1, we pursued genome-wide interrogation in 117 438 individuals of EUR, AFR, ASN, HIS, and BRZ ancestries (summary information, Table 1). After extensive quality control (QC), we performed genome-wide meta-analyses at ~ 18.8 million SNVs and a small number of insertion and deletion (indels) variants imputed using the 1000 Genomes Project reference panel (QQ plots, Fig. S1). Through the 1DF test of the interaction effect and the 2DF joint test of the SNV and interaction effects, we identified 1481

Table 1 Basic characteristics of cohorts in Stages 1 and 2 in each ancestry.

Stage	Max. N	Some College? (Yes/No)		Grad. College? (Yes/No)	% Male	% HT	% HT Meds	Age	SBP		DBP		MAP		PP		
		N	% Yes						Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Stage 1																	
EUR	84,276	47,870	57.7	79,040	32.9	28.7	17.0	54.7	7.8	130.3	19.1	78.3	11.2	95.6	12.6	52.0	13.1
AFR	16,665	16,665	48.8	16,665	40.6	52.4	40.3	51.5	9.2	134.4	23.2	81.2	13.4	98.9	15.5	53.2	16.1
ASN	11,352	11,352	10.0	748	53.0	49.6	29.5	56.8	9.4	139.3	16.1	80.2	11.1	99.9	13.5	59.1	16.2
BRZ	3689	3689	36.8	3689	45.6	29.0	7.6	34.5	3.8	123.4	15.3	76.6	10.0	92.2	11.1	46.8	10.2
HIS	1456	1456	35.2	1456	48.4	41.4	33.3	60.8	9.73	131.2	24.8	74.9	11.7	93.6	14.9	56.4	18.5
Stage 1 Total	117,438	81,032	47.8	101,598	36.5	34.2	21.4	53.9	8.1	131.6	19.4	78.8	11.5	96.4	13.1	52.8	13.8
Stage 2																	
EUR	264,052	242,524	54.3	257,037	47.6	48.5	21.7	54.9	8.9	138.5	20.2	83.3	11.4	101.7	13.4	55.2	13.6
AFR	7198	7198	20.8	7198	40.4	56.8	44.1	54.7	9.5	137.6	21.8	83.8	12.9	101.7	14.8	53.8	14.9
ASN	10,906	10,906	21.4	5947	40.1	37.4	24.9	55.8	9.0	134.2	23.1	80.7	12.8	98.6	15.4	53.5	14.8
HIS	11,631	11,631	35.5	11,631	41.1	25.4	15.0	45.3	13.6	123.6	19.7	75.0	11.8	91.2	13.6	48.6	13.1
Stage 2 Total	293,787	272,259	51.3	281,813	46.6	47.4	22.1	54.6	9.1	137.7	20.3	82.9	11.5	101.2	13.6	54.8	13.7
TOTAL	411,225	353,291	50.5	383,411	43.7	43.6	21.9	54.4	8.8	136.0	20.1	81.7	11.5	99.8	13.4	54.2	13.7

The cell entries for the covariates and BP traits corresponds to sample-size weighted averages across all cohorts in each category.

genome-wide significant ($P < 5 \times 10^{-8}$) and 3309 suggestive ($P < 1 \times 10^{-6}$) variants associated with any BP trait in any ancestry and/or in trans-ancestry analysis. All significant and suggestive variants were tested for association in 293 787 additional individuals of EUR, AFR, ASN, and HISP ancestries in Stage 2.

We performed meta-analyses combining Stages 1 and 2 (Manhattan Plots, Fig. S2). We identified 84 known BP loci. This includes 82 loci identified through main-effect only analyses [36–41], including 18 recently reported by Hoffmann et al. [42], Evangelou et al. [43], and Giri et al. [44]; and two loci (*TFAP2A* and *PCDH9*) recently reported by our consortium through gene-smoking and gene-alcohol interaction analyses [27,45], which suggest the inter-correlated nature of the various lifestyle traits.

We identified 18 novel genome-wide significant loci ($P < 5 \times 10^{-8}$) located at least 1 Mb away from any known BP loci (Table 2). Nine loci were identified through the combined analyses of Stage 1 and 2; the remaining nine loci were identified in Stage 1 but not available in Stage 2 for combined analyses (Tables S7). The LocusZoom plots of these novel loci are presented in Fig. S3. Two loci (*SLIT3* and *HRH4*) were identified through the 1DF test of interaction effects. At both loci, the genetic effect on DBP was stronger and beneficial in higher education and weaker and detrimental in lower education. For example, at *SLIT3*, the minor allele A was associated with a 4.82 mmHg lower DBP in higher education (GradCol = 1), whereas it was associated with a 2.25 mmHg higher DBP in GradCol = 0. The remaining 16 loci were identified through the 2DF joint test of the SNV and interaction effects; twelve loci were identified considering ‘Some College’ (SomeCol) and four loci were identified considering ‘Graduated College’ (GradCol).

Ancestry-specific and trans-ancestry analyses

Novel loci were identified through separate analyses of AFR (12 loci), EUR (1 locus), trans-ancestry (4 loci), and in both AFR and trans-ancestry (1 locus). This highlights the importance of including non-EUR populations to identify novel BP loci. By nature, AFR populations carry more rare and low-frequency variants that may be very rare or monomorphic in other ancestral groups [22]; the MAF for the novel index SNVs range from 0.02 to 0.04 in AFR. The enhanced discovery of novel loci in AFR ancestry may be attributable to the relatively higher MAF in this population versus in EUR. For example, rs141962517 (*CAPDS*) with a MAF = 0.02 in AFR was significantly associated with SBP (2DF $P = 3.07 \times 10^{-10}$; 1DF Interaction $P = 1.99 \times 10^{-7}$); this variant was not present in other ancestries after filtering.

Among the 18 novel loci, three loci were identified only through trans-ancestry analyses, as none of the

Table 2 Eighteen new loci associated with BP traits that are at least 1 Mb away from any known BP locus.

Locus	Nearest Gene	rsID	Chr:Pos	EA	EAF (AFR/ASN/EUR/HIS)	Genetic Effect		GxE Interaction		P value		Trait	Educ.	Anc.
						Effect	SE	Effect	SE	Interaction	2DF Joint			
1	<i>CDC14A</i>	rs114558965	1:100829685	a	0.97/. / .1.00	-0.23	1.02	5.02	1.27	2.54E-03	2.86E-09	SBP	SC	AFR
2	<i>LIN01249</i>	rs9308788	2:4711095	a	0.02/0.22/0.06/0.06	2.97	2.13	-11.93	2.64	5.04E-05	4.47E-08	SBP	GC	AFR
3	<i>ARL4C</i>	rs145586115	2:235604646	t	0.97/. / .0.99	4.80	0.87	-2.57	1.29	1.16E-01	1.92E-08	SBP	SC	AFR
4	<i>CADPS</i>	rs141962517	3:62514061	t	0.98/. / . /	-2.46	1.54	12.85	2.23	1.99E-07	3.07E-10	SBP	GC	AFR
5	<i>PCDH7</i>	rs74458816	4:31363388	a	0.03/. / .0.00	-0.18	0.70	-3.46	0.91	2.26E-03	4.90E-09	MAP	SC	AFR
6	<i>E1F4E</i>	rs2141284	4:99704167	a	. / . / .0.01/0.01	-1.35	0.22	1.01	0.38	2.16E-02	6.73E-09	MAP	GC	TRANS
7	<i>SPEF2</i>	rs115523707	5:35756623	t	0.03/. / .0.00/0.00	-0.83	0.64	-2.73	0.88	5.91E-02	7.22E-09	PP	SC	AFR
8	<i>ANKRD34B</i>	rs66907226	5:79863455	d	0.46/0.81/0.58/0.69	0.48	0.14	0.04	0.18	9.86E-01	4.43E-08	SBP	SC	EUR
9	<i>SLC04C1</i>	rs114175587	5:100994204	t	0.02/. / .0.00	-4.84	0.83	3.84	1.29	3.55E-03	2.40E-08	PP	SC	TRANS
10	<i>SLIT3</i>	rs142385399	5:168166731	a	0.04/. / .0.00/0.01	2.25	0.74	-7.07	1.22	2.79E-08	4.76E-08	DBP	GC	AFR
11	<i>THSD7A</i>	rs200612978	7:11493906	d	0.03/0.03/. / .0.01	-0.40	1.27	-4.94	1.57	5.71E-02	4.81E-08	SBP	SC	AFR
12	<i>HAS2-AS1</i>	rs112332671	8:122673983	a	0.02/. / .0.00	-1.37	1.18	-4.55	1.52	6.03E-02	1.89E-09	PP	SC	AFR
13	<i>CDON</i>	rs12295584	11:125841078	a	0.95/. / .0.99/0.99	2.87	0.57	-1.07	0.84	2.20E-01	4.71E-08	SBP	SC	TRANS
14	<i>DSTNP2</i>	rs75535814	12:6996683	t	0.02/. / .0.00	-8.78	1.45	7.24	1.95	3.17E-04	5.79E-09	SBP	SC	AFR
15	<i>PIK3C2G</i>	rs189555401	12:18443065	t	0.03/. / .0.01	-3.23	0.57	1.82	1.15	8.92E-02	4.10E-08	DBP	GC	TRANS
16	<i>E2F7; ZDHC17</i>	rs17043233	12:77648216	t	0.02/. / .0.00	-4.07	0.58	4.26	0.90	1.72E-05	1.39E-11	MAP	SC	TRANS
17	<i>HRH4</i>	rs8099516	18:22108763	t	0.04/. / .0.01	1.71	0.61	-5.39	0.95	7.83E-09	5.04E-08	DBP	GC	AFR
18	<i>LOC100289473</i>	rs113809930	20:1711768	a	0.98/0.88/0.97/0.94	-0.69	0.79	3.67	0.94	1.70E-03	3.48E-08	DBP	SC	AFR

Positions are based on build 37. Effect is in mmHg unit.

BP blood pressure, DBP diastolic BP, EA effect allele, EAF effect allele frequency observed in our cohorts, MAP mean arterial pressure, P P value of the joint test with 2 degrees of freedom of genetic main and interaction effects, PP pulse pressure, SBP systolic BP, SE standard error, 2DF joint IDF interaction, P P value of the interaction test with 1 degree of freedom. The smallest P values between IDF interaction test and the joint 2DF test are in boldface, SC SomeCol, EUR European, AFR African, TRANS, trans-ancestry (i.e., combining all ancestry groups through meta-analysis).

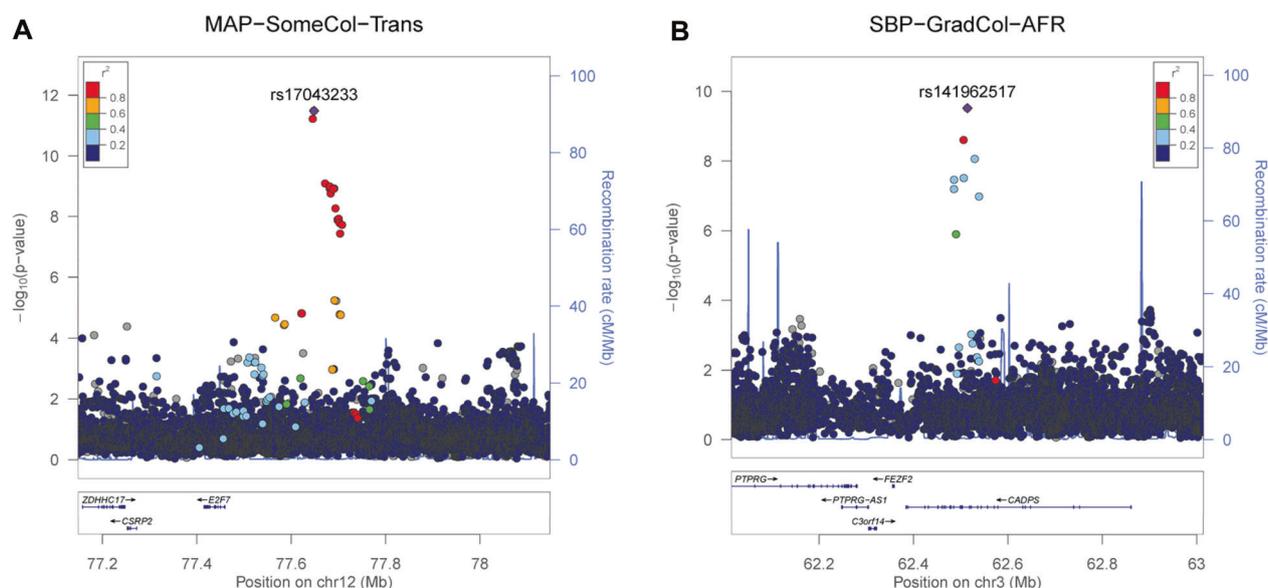


Fig. 2 LocusZoom plots for 2 BP loci related to CNS-adrenal signaling. **a** MAP-associated locus adjacent to *ZDHHC17*, identified in AFR and in trans-ancestry, shows roles in CNS-adrenal signaling. In neurons, *ZDHHC17* encodes a membrane protein that mediates fusion of synaptic vesicles to the plasma membrane, enabling the release of neurotransmitters. Murine *zdhhc17* knockout models show impaired hippocampal memory and reduced synaptic plasticity, providing potential biological links to working memory and subsequent educational attainment. **b** A locus intragenic to *CADPS*, identified in AFR, is

of potential biologic relevance given this gene's expression in CNS tissue and role in regulating the fusion of neuroendocrine vesicles and release of vasoactive catecholamines from both adrenal and neural tissue. Three LD SNVs have CADD scores >10, and four LD SNVs have ChromHMM state signals consistent with strong evidence of transcription regulation. SBP systolic blood pressure, DBP diastolic blood pressure, MAP mean arterial pressure, PP pulse pressure. The plots were created using LocusZoom (<http://locuszoom.sph.umich.edu/>).

ancestry-specific analyses reached genome-wide significance. For example, the index SNV (rs189555401) representing the four-variant locus within *PIK3C2G* was suggestively associated with DBP ($P = 1.31 \times 10^{-7}$) in AFR and not even nominally associated in HIS ($P = 9.67 \times 10^{-2}$). However, in trans-ancestry analysis combining these two ancestral groups, the association reached genome-wide significance ($P = 4.10 \times 10^{-8}$).

Functional annotation and eQTL evidence

To obtain functional annotations for the index variants and nearby variants in LD ($r^2 \geq 0.2$), we used FUMA GWAS [28]. Among the 18 index variants representing our novel loci, two variants were intronic to a non-coding RNA (ncRNA), six variants were intronic, nine variants were intergenic, and the remaining variant (rs66907226) was an indel without available annotation. Among the 499 variants that include both the index variants and nearby variants in LD, there were four exonic, four exonic-ncRNA, 119 intronic, 67 intronic-ncRNA, two 3' untranslated region (UTR), seven up/downstream flanking, and 296 intergenic variants (Table S8). Of the 499 variants, 13 had RegulomeDB [31] scores better than or equal to 3a, suggesting at least moderate evidence for involvement in transcription regulation (Table S9). In total, 32 SNVs have CADD [32] scores ≥ 10 ,

representing the top 10% of predicted deleteriousness for SNVs genome-wide. A single SNV (rs112332671) ~20 kb upstream of *HAS2* and 16 kb downstream of the ncRNA *HAS2-AS1* had a CADD score of 20.1, placing it in the top 1% of predicted deleteriousness.

The 15-core chromatin state (ChromHMM) [33] was assessed for 127 epigenomes in the 17 index variants (Table S9). Two had histone chromatin markers in regions flanking the transcription start site and one in a region associated with strong transcription in relevant tissues including brain. Among all 499 LD variants, 45 had histone chromatin markers characteristic of a transcription start site, 64 had markers consistent with strong transcription, and 25 were in enhancer regions. One LD variant (rs555713705) was identified as *cis*-acting eQTLs [46,47] for heart tissue in the GTEx_v7 database (FDR P value ranging from 3.90×10^{-3}).

Biologic plausibility of the new BP loci

Three novel BP loci are related to the central nervous system (CNS)-adrenal signaling axis that is critical for BP regulation. A locus (Fig. 2a) adjacent to *ZDHHC17*, identified in AFR and in trans-ancestry analyses, encodes a membrane protein that mediates fusion of synaptic vesicles to the plasma membrane. *CADPS* (Fig. 2b), identified in

AFR, is expressed in CNS tissue. Three variants in LD have CADD scores >10, and four SNVs have ChromHMM state signals consistent with strong evidence of transcription regulation. *PIK3C2G*, identified in trans-ancestry analyses, also shows roles in CNS-adrenal signaling. Three variants in LD in this locus have CADD scores >10, including one with a CADD score of 18 that is predicted to reside in an enhancer region in fetal adrenal cells.

Two novel BP loci are related to renal fibrosis and cation exchange. A locus, which includes a variant intragenic to *SLIT3*, showed interaction evidence with educational attainment in AFR (rs142385399, $P = 2.79 \times 10^{-8}$). A locus also identified in AFR includes *HAS2* and *HAS2-ASI*, which play roles in renal fibrosis. In addition, we identified two novel BP loci related to pathways involved in vascular smooth muscle cell structure and function. A locus identified by trans-ancestry analyses included a variant intragenic to *CDON*, which is expressed in vascular smooth muscle cells. A locus identified in AFR includes *GNB3*, which encodes a subunit critical for signal transduction of several vasoactive peptide G protein-coupled receptors involved in BP regulation. A SNV in this locus shows ChromHMM chromatin states consistent with strong transcription regulation in multiple tissues, and three SNVs have strong *cis*-eQTL association with *GNB3* expression in nerve, artery, and skeletal muscle tissue (minimum FDR P value 1.20×10^{-43}).

Discussion

A relationship between educational attainment and BP has been well demonstrated [48–51]. Furthermore, AFR ancestry individuals have been shown to have a higher burden of HTN than EUR-ancestry [52]. However, higher-educated AFR ancestry individuals bear approximately twice the burden of HTN as compared with their EUR-ancestry counterparts [48,51], demonstrating that educational differences did not fully account for this observed racial disparity. Herein, we reported genome-wide meta-analyses for SBP, DBP, MAP, and PP accounting for gene-educational attainment interactions across five ancestry groups. We pursued a genome-wide interrogation in 117 438 individuals (in Stage 1) and follow-up analysis at selected variants in 293,787 additional individuals (in Stage 2). Through the combined meta-analysis of stages 1 and 2, we identified 84 known and 18 novel loci at genome-wide significance. As known loci have been discussed elsewhere, this report highlights several novel loci show biologic plausibility by involving physiologic systems implicated in BP regulation.

The CNS-adrenal signaling axis is critical for BP regulation. Three novel BP loci (*ZDHHC17*, *CADPS*, and *PIK3C2G*) are related to these pathways. In neurons, *ZDHHC17* encodes a membrane protein that mediates fusion

of synaptic vesicles to the plasma membrane, enabling the release of neurotransmitters [53]. Murine *zdhhc17* knockout models show impaired hippocampal memory and reduced synaptic plasticity, providing potential biological links to working memory and subsequent educational attainment [54]. Although a biological connection between *ZDHHC17* and BP traits is not well established, *zdhhc17* expression induces neurite outgrowth in a rodent adrenal-derived cell line [55]. *Cadps* plays a role in regulating the fusion of neuroendocrine vesicles and release of vasoactive catecholamines in calf adrenal and neural tissue [56]. *Pik3c2g* encodes a phosphoinositide kinases that are expressed in a sexually dimorphic pattern specifically in a zone of the mouse adrenal cortex believed to play a role in steroid sex hormone production [57]. Furthermore, *PIK3C2G* is under-expressed in human hypertensive kidneys, providing a potential biological link between the expression of adrenal mineralocorticoid hormones and their target organ [58]. Among alcohol-preferring rats, *pik3c2g* expression is also increased in the cerebral periaqueductal gray, a region involved in pain, fear, and anxiety responses [59], possibly providing a link to drivers of SES in humans [60]. Notably, the loci including *ZDHHC17* and *CADPS* demonstrated some evidence of interaction with educational attainment ($P = 1.72 \times 10^{-5}$ and 1.99×10^{-7} , respectively).

Two new BP loci (*HAS2* and *HAS2-ASI*, *SLIT3*) show potential roles in renal function. A locus that includes a variant intragenic to *SLIT3* had a significant interaction term with educational attainment. *SLIT3* encodes a cell-cell adhesion molecule that binds its receptor, ROBO4, in human-derived endothelial stem cells directing the formation of vascular networks [61]. *SLIT3* also plays a role in directing neuronal growth in the brain [62,63], and in renal and cardiac development [64]. A locus including *HAS2* and *HAS2-ASI* is also of interest for roles played in renal fibrosis. *HAS2-ASI* is an antisense ncRNA simultaneously expressed and thought to stabilize the *HAS2* transcript [65].

Two new BP loci (*GNB3*, *CDON*) have been shown to regulate pathways involved in vascular smooth muscle cell structure and function. We identified a locus in *GNB3*, which encodes a G protein-coupled receptor subunit involved in BP regulation. Several candidate gene association studies have identified the synonymous *GNB3* variant C825T (rs5443), resulting in a splice variant of the $\beta 3$ subunit, as significantly associated with essential HTN [66,67], with BP response to diuretic [68] and β -adrenergic receptor blockade [69], and other cardiovascular traits [70]. Another locus identified by trans-ancestry analyses included a variant intragenic to *CDON*; this gene is expressed in vascular smooth muscle cells [71], and encodes a cell-surface receptor complex that regulates myocyte differentiation in rodents [72].

This large-scale multi-ancestry study has several limitations. First, the practice of adjusting SBP and DBP by

adding 15 and 10 mmHg for antihypertensive use is based on a method derived from a EUR-ancestry cohort [21]. While this approach is common among GWAS of BP traits [36], we acknowledge that this practice may not be equally appropriate and/or justified in all ancestry groups. Second, while the sample sizes in diverse ancestries are a strength, resulting in the identification of several novel BP loci particularly in AFR ancestry, several identified loci included low-frequency variants that require further validation. Third, main effect only analysis without educational attainment was not performed, and this limits our ability to resolve if novel loci identified through the 2DF joint test could be found without considering educational attainment. Fourth, the use of educational attainment as a proxy for SES can present some challenges. The socioeconomic impact of education has changed over time and may differ according to birth cohort, as well as in other subgroups defined by gender, ancestry, region, and/or country [1,49]. Even with similar levels of educational attainment, social and environmental experiences were different between AFR and EUR individuals in the United States, especially those educated in the 1960s and 1970s, resulting in residual confounding inequities between the ancestral groups [9,73]. This additional source of heterogeneity may have reduced power for trans-ancestry analyses.

In summary, this multi-ancestry study that used gene-education interactions on BP traits identified 18 novel loci and validated 84 known BP loci. Ten novel loci were identified in individuals of AFR ancestry, demonstrating the need for pursuing genetic studies in diverse populations. Several novel loci involve physiologic systems implicated in BP regulation including genes involved in CNS-adrenal signaling, vascular structure and function, and renal function. Two loci showed interaction evidence with educational attainment. These findings may identify a role for educational attainment and SES in further dissection of the genetic architecture of BP.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Stage 1 Study Descriptions

Brief descriptions are provided below for each of stage 1 studies, some of which are based outside the United States:

AGES (Age Gene/Environment Susceptibility Reykjavik Study): The AGES 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 Study. 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.

ARIC (Atherosclerosis Risk in Communities): The ARIC 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, predominantly European American and African American, aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed three additional triennial follow-up examinations, a fifth exam in 2011-2013, and a sixth exam in 2016-2017. The ARIC study has been described in detail previously (The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: Design and objectives. *Am J Epidemiol.* 1989;129:687-702). Blood pressure was measured using a standardized Hawksley 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. Blood pressure measures and medication use at the baseline exam were used in this study.

Baependi Heart Study (Brazil): The Baependi Heart Study, is an ongoing family-based cohort conducted in a rural town of the state of Minas Gerais. The study has enrolled approximate 2,200 individuals (over 10% of the town's adult population) and 10-year follow up period of longitudinal data. Briefly, probands were selected at random across 11 out of the 12 census districts in Baependi. After enrolment, the proband's first-degree (parents, siblings, and offspring), second-degree (half-siblings, grandparents/grandchildren, uncles/aunts, nephews/nieces, and double cousins), and third-degree (first cousins, great uncles/aunts, and great nephews/nieces) relatives, and his/her respective spouse's relatives resident both within Baependi (municipal and rural area) and surrounding towns were invited to participate. Only individuals age 18 and older were eligible to participate in the study. The study is conducted from a clinic/office in an easily accessible sector of the town, where the questionnaires were completed. A broad range of phenotypes ranging from cardiovascular, neurocognitive, psychiatric, imaging, physiologic and several layers of endophenotypes like metabolomics and lipidomics have been collected throughout the years. Details about follow-up visits and available data can be found in the cohort profile paper (PMID: 18430212). DNA samples were genotyped using the Affymetrix 6.0 genechip. After quality control, the data were prephased using SHAPEIT and imputed using IMPUTE2 based on 1000 Genomes haplotypes.

CARDIA (Coronary Artery Risk Development in Young Adults): CARDIA is a prospective multicenter study with 5,115 Caucasian and African American participants 18-30 years of age at baseline, recruited from four centers in 1985-1986. The recruitment was done from the total community in Birmingham, AL; from selected census tracts in Chicago, IL and Minneapolis, MN; and from the Kaiser Permanente health

plan membership in Oakland, CA. The details of the study design for the CARDIA study have been previously published.¹ Nine examinations have been completed since initiation of the study, respectively in the years 0, 2, 5, 7, 10, 15, 20, 25, and 30. Written informed consent was obtained from participants at each examination and all study protocols were approved by the institutional review boards of the participating institutions.

Age and race were self-reported using standardized questionnaires, as were use of cholesterol-lowering medication, and smoking status (current, former, or never). All participants were asked to fast for 12 hours before each clinic visit. Lipid measures were performed on plasma blood samples drawn from the antecubital vein and stored at -70°C until analyzed. Plasma total cholesterol, HDL-cholesterol, and triglyceride concentrations were measured using enzymatic methods;² HDL-cholesterol concentrations were measured after dextran-sulfate-magnesium precipitation of other lipoproteins.³ LDL-cholesterol concentrations were estimated with the Friedewald equation for individuals with fasting triglyceride values less than 400 mg/dL.⁴ The test-retest correlations for total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were 0.98 to 0.99.⁵

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CHS (Cardiovascular Health Study): CHS (Cardiovascular Health Study): CHS is a population-based cohort study of risk factors for cardiovascular disease in adults 65 years of age or older conducted across four field centers (1). The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists and an additional predominately African-American cohort of 687 persons was enrolled in 1992-93 for a total sample of 5,888. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. European ancestry participants were excluded from the GWAS study sample due to prevalent coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke, or transient ischemic attack at baseline. After QC, genotyping was successful for 3271 European ancestry and 823 African-American participants. CHS was approved by institutional review committees at each site and individuals in the present analysis gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

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CROATIA-Korcula: The CROATIA-Korcula study is a family-based, cross-sectional study in the isolated island of Korcula that included 965 examinees aged 18-95. Blood samples were collected in 2007 along with many clinical and biochemical measures and lifestyle and health questionnaires.

CROATIA-Vis: The CROATIA-Vis study is a family-based, cross-sectional study in the isolated island of Vis that included 1,056 examinees aged 8-93. Blood samples were collected in 2003 and 2004 along with many clinical and biochemical measures and lifestyle and health questionnaires.

ERF (Erasmus Rucphen Family study): Erasmus Rucphen Family is a family based study that includes inhabitants of a genetically isolated community in the South-West of the Netherlands, studied as part of the Genetic Research in Isolated Population (GRIP) program.^{1,2} The goal of the study is to identify the risk factors in the development of complex disorders. Study population includes approximately 3,000 individuals who are living descendants of 22 couples who lived in the isolate between 1850 and 1900 and had at least six children baptized in the community church. All data were collected between 2002 and 2005. All participants gave informed consent, and the Medical Ethics Committee of the Erasmus University Medical Centre approved the study.

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FamHS (Family Heart Study): The NHLBI FamHS study design, collection of phenotypes and covariates as well as clinical examination have been previously described (<https://dsgweb.wustl.edu/fhscc/>; PMID: 8651220). In brief, the FamHS recruited 1,200 families (approximately 6,000 individuals), half randomly sampled, and half selected because of an excess of coronary heart disease (CHD) or risk factor abnormalities as compared with age- and sex-specific population rates. The participants were sampled from four population-based parent studies: the Framingham Heart Study, the Utah Family Tree Study, and two centers for the Atherosclerosis Risk in Communities study (ARIC: Minneapolis, and Forsyth County, NC). These individuals attended a clinic exam (1994-1996) and a broad range of phenotypes were assessed in the general domains of CHD, atherosclerosis, cardiac and vascular function, inflammation and hemostasis, lipids and lipoproteins, blood pressure, diabetes and insulin resistance, pulmonary function, diet, education, socioeconomic status, habitual behavior, physical activity, anthropometry, medical history and medication use. Approximately 8 years later, study participants belonging to the largest pedigrees were invited for a second clinical exam (2002-04). The most important CHD risk factors were measured again, including lipids, parameters of glucose metabolism, blood pressure, anthropometry, and several biochemical and hematologic markers. In addition, a computed tomography examination provided measures of coronary and aortic calcification, and abdominal and liver fat burden. Medical history and medication use was updated. A total of 2,756 European ancestry subjects in 510 extended random and high CHD risk families were studied. Also, 633 African ancestry subjects were recruited at ARIC field center at the University of Alabama in Birmingham. Informed consent was obtained from all participants.

FHS (Framingham Heart Study): FHS 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 (mean age 37 years; 52% women) consisted of 5,124 children and spouses of children of the original cohort. A third generation cohort of 4,095 children of offspring cohort participants (mean age 40 years; 53 percent women) was enrolled in 2002-2005 and are seen every 4 to 8 years. Details of study designs for the three cohorts are summarized elsewhere. 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. Blood pressures were recorded to the nearest even number. The means of two separate systolic and diastolic blood pressure readings at each clinic examination were used for statistical analyses.

GENOA (Genetic Epidemiology Network of Arteriopathy): GENOA is one of four networks in the NHLBI Family-Blood Pressure Program (FBPP). [The FBPP Investigators, 2002; Daniels et al., 2004] GENOA's long-term objective is to elucidate the genetics of target organ complications of hypertension, including both atherosclerotic and arteriolosclerotic complications involving the heart, brain, kidneys, and peripheral arteries. The longitudinal GENOA Study recruited European-American and African-American sibships with at least 2 individuals with clinically diagnosed essential hypertension before age 60 years. All other members of the sibship were invited to participate regardless of their hypertension status. Participants were diagnosed with hypertension if they had either 1) a previous clinical diagnosis of hypertension by a physician with current anti-hypertensive treatment, or 2) an average systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg based on the second and third readings at the time of their clinic visit. Exclusion criteria were secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes mellitus, or active malignancy. During the first exam (1995-2000), 1,583 European Americans from Rochester, MN and 1,854 African Americans from Jackson, MS were examined. Between 2000 and 2005, 1,241 of the European Americans and 1,482 of the African Americans returned for a second examination. Because African-American probands for GENOA were recruited through the Atherosclerosis Risk in Communities (ARIC) Jackson field center participants, we excluded ARIC participants from analyses.

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2. Daniels PR, Kardia SL, Hanis CL, Brown CA, Hutchinson R, Boerwinkle E, Turner ST; Genetic Epidemiology Network of Arteriopathy study. Familial aggregation of hypertension treatment and control in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. *Am J Med.* 2004;116:676-81. PubMed PMID: 15121494.

GenSalt (Genetic Epidemiology Network of Salt Sensitivity): GenSalt is a multi-center, family based study designed to identify, through dietary sodium and potassium intervention, salt-sensitivity susceptibility genes which may underlie essential hypertension in rural Han Chinese families. Approximately 629 families with at least one 'proband' with high blood pressure were recruited and tested for a wide variety of physiological, metabolic and biochemical measures at baseline and at multiple times during the 3-week intervention. The intervention consisted of one week on a low sodium diet, followed by one week on a high sodium diet, and finally one week on a high sodium diet with a potassium supplement.

GS:SFHS (Generation Scotland: Scottish Family Health Study): The GS:SFHS (www.generationscotland.org) is a family-based genetic epidemiology cohort with DNA, other biological samples (serum, urine and cryopreserved whole blood) and socio-demographic and clinical data from approximately 24,000 volunteers, aged 18-98 years, in ~7,000 family groups. An important feature of GS:SFHS is the breadth of phenotype information, including detailed data on cognitive function, personality traits and mental health. Although data collection was cross-sectional, GS:SFHS becomes a longitudinal cohort as a result of the ability to link to routine NHS data, using the community health index (CHI) number.

HANDLS (Healthy Aging in Neighborhoods of Diversity across the Life Span): HANDLS is a community-based, longitudinal epidemiologic study examining the influences of race and socioeconomic status (SES) on the development of age-related health disparities among a sample of socioeconomically diverse African Americans and whites. This unique study will assess over a 20-year period physical parameters and also evaluate genetic, biologic, demographic, and psychosocial, parameters of African American and white participants in higher and lower SES to understand the driving factors behind persistent black-white health disparities in overall longevity, cardiovascular disease, and cognitive decline. The study recruited 3,722 participants from Baltimore, MD with a mean age of 47.7 years, 2,200 African Americans and 1,522 whites, with 41% reporting household incomes below the 125% poverty delimiter.

Genotyping was done on a subset of self-reporting African American participants by the Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health (NIH). A larger genotyping effort included a small subset of self-reporting European ancestry samples. This research was supported by the Intramural Research Program of the NIH, NIA and the National Center on Minority Health and Health Disparities.

Health ABC (Health, Aging, and Body Composition): Cohort description: The Health ABC study is a prospective cohort study investigating the associations between body composition, weight-related health conditions, and incident functional limitation in older adults. Health ABC enrolled well-functioning, community-dwelling black (n=1281) and white (n=1794) men and women aged 70-79 years between April 1997 and June 1998. Participants were recruited from a random sample of white and all black Medicare eligible residents in the Pittsburgh, PA, and Memphis, TN, metropolitan areas. Participants have undergone annual exams and semi-annual phone interviews. The current study sample consists of 1559 white participants who attended the second exam in 1998-1999 with available genotyping data.

Genotyping: Genotyping was performed by the Center for Inherited Disease Research (CIDR) using the Illumina Human1M-Duo BeadChip system. Samples were excluded from the dataset for the reasons of sample failure, genotypic sex mismatch, and first-degree relative of an included individual based on genotype data. Genotyping was successful in 1663 Caucasians. Analysis was restricted to SNPs with minor allele frequency $\geq 1\%$, call rate $\geq 97\%$ and HWE $p \geq 10^{-6}$. Genotypes were available on 914,263 high quality SNPs for imputation based on the HapMap CEU (release 22, build 36) using the MACH software (version 1.0.16). A total of 2,543,888 imputed SNPs were analyzed for association with vitamin D levels.

Association analysis: Linear regression models were used to generate cohort-specific residuals of naturally log transformed vitamin D levels adjusted for age, sex, BMI and season defined as summer (June-August), fall (September-November), winter (December to February) and spring (March to May) standardized to have mean 0 and variance of 1. Association between the additively coded SNP genotypes and the vitamin D residuals standardized was assessed using linear regression models. For imputed SNPs, expected number of minor alleles (i.e. dosage) was used in assessing association with the vitamin D residuals.

HERITAGE (Health, Risk Factors, Exercise Training and Genetics): The HERITAGE is the only known family-based study of exercise intervention to evaluate the role of genes and sequence variants involved in the response to a physically active lifestyle. The current study is based on the data collected at baseline of the study from 99 White families (244 males, 255 females). All subjects were required to be sedentary and free of chronic diseases at baseline. There are over 18 trait domains (e.g. dietary, lipids and lipoproteins, glucose and insulin metabolism [fasting and IVGTT], steroids, body composition and body fat distribution, cardiorespiratory fitness), for a grand total of over one thousand variables. Moreover, most of the outcome traits were measured twice on two separate days both at baseline and after exercise training was completed. Marker data include a genome-wide linkage scan and GWAS, in addition to a large number of candidate genes.

HUFS (Howard University Family Study): HUFS followed a population-based selection strategy designed to be representative of African American families living in the Washington, DC metropolitan area. The major objectives of the HUFS were to study the genetic and environmental basis of common complex diseases including hypertension, obesity and associated phenotypes. Participants were sought through door-to-door canvassing, advertisements in local print media and at health fairs and other community gatherings. In order to maximize the utility of this cohort for the study of multiple common traits, families were not ascertained based on any phenotype. During a clinical examination, demographic information was collected by interview.

HyperGEN (Hypertension Genetic Epidemiology Network): HyperGEN is a family-based study that looks at the genetic causes of hypertension and related conditions in EA and AA subjects. HyperGEN

recruited hypertensive sibships, along with their normotensive adult offspring, and an age-matched random sample. HyperGEN has collected data on 2,471 Caucasian-American subjects and 2,300 African-American subjects, from five field centers in Alabama, Massachusetts, Minnesota, North Carolina, and Utah.

JHS (Jackson Heart Study): The Jackson Heart Study is a longitudinal, community-based observational cohort study investigating the role of environmental and genetic factors in the development of cardiovascular disease in African Americans. Between 2000 and 2004, a total of 5,306 participants were recruited from a tri-county area (Hinds, Madison, and Rankin Counties) that encompasses Jackson, MS. Details of the design and recruitment for the Jackson Heart Study cohort has been previously published.¹⁻³ Briefly, approximately 30% of participants were former members of the Atherosclerosis Risk in Communities (ARIC) study. The remainder were recruited by either 1) random selection from the Accudata list, 2) commercial listing, 3) a constrained volunteer sample, in which recruitment was distributed among defined demographic cells in proportions designed to mirror those in the overall population, or through the Jackson Heart Study Family Study.

1. Wyatt SB, Diekelmann N, Henderson F, Andrew ME, Billingsley G, Felder SH et al. A community-driven model of research participation: the Jackson Heart Study Participant Recruitment and Retention Study. *Ethn Dis* 2003; 13(4):438-455.
2. Taylor HA, Jr., Wilson JG, Jones DW, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn Dis* 2005; 15:S6-17.
3. Fuqua SR, Wyatt SB, Andrew ME, et al. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. *Ethn Dis* 2005; 15:S6-29.

Maywood-Loyola Study: Participants were self-identified African Americans from a working class suburb of Chicago, Illinois, USA who were enrolled in studies of BP at the Loyola University Medical Center in Maywood, Illinois, USA as part of the International Collaborative Study on Hypertension in Blacks (ICSHIB) which is described in detail elsewhere (**PMID: 9103091**). Briefly, nuclear families were identified through middle-aged probands who were not ascertained based on any phenotype. Thereafter all available first-degree relatives 18 years old and above were enrolled into the study cohort of families. A screening exam was completed by trained and certified research staff using a standardized protocol (**PMID: 9103091 & 10234089**). Information was obtained on medical history, age, body weight and height. Protocols were reviewed and approved by the IRB at the Loyola University Chicago Stritch School of Medicine prior to recruitment activities. This present study included unrelated adults sampled and for whom information on anthropometrics, BP and use of antihypertensive medication was available. BP measurements were obtained using an oscillometric device, previously evaluated in our field settings (**PMID: 10234089**). Three measurements were taken three minutes apart and the average of the final two was used in the analysis. Individuals with SBP \geq 140 mmHg, DBP \geq 90 mmHg or on anti-hypertensive medication at time of exam were defined as hypertensive. Participants with hypertension were offered treatment after detection at the screening exam.

Maywood-Nigeria Study: The sampling frame for the Nigeria cohort was also provided by the International Collaborative Study on Hypertension in Blacks (ICSHIB) as described in detail elsewhere (**PMID: 9103091**). Study participants were recruited from Igbo-Ora and Ibadan in southwest Nigeria as part of a long-term study on the environmental and genetic factors underlying hypertension. The base cohort consists of over 15,000 participants with information available on anthropometrics, BP and use of antihypertensive medication. BP measurements followed the same protocol described in the Loyola-Maywood study. This present study included unrelated adults samples from the cohort and some hypertensive participants who were recruited as controls in the Africa-America Diabetes Mellitus (AADM) Study recruited from Ibadan in similar neighborhoods (**PMID: 11164120**). Both projects were reviewed and approved by the sponsoring US institutions (Loyola University Chicago and Howard University) and

the University of Ibadan. All participants signed informed consent administered in either English or Yoruba. BP measurements were obtained using an oscillometric device, previously evaluated in our field settings (PMID: 10234089). Three measurements were taken three minutes apart and the average of the final two was used in the analysis. Individuals with SBP \geq 140 mmHg, DBP \geq 90 mmHg or on anti-hypertensive medication at time of exam were defined as hypertensive. Participants with hypertension were offered treatment after detection at the screening exam.

MESA (Multi-Ethnic Study of Atherosclerosis): The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. MESA consisted of a diverse, population-based sample of an initial 6,814 asymptomatic men and women aged 45-84. 38 percent of the recruited participants were white, 28 percent African American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. Participants were recruited from six field centers across the United States: Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and University of California - Los Angeles. Participants are being followed for identification and characterization of cardiovascular disease events, including acute myocardial infarction and other forms of coronary heart disease (CHD), stroke, and congestive heart failure; for cardiovascular disease interventions; and for mortality. The first examination took place over two years, from July 2000 - July 2002. It was followed by four examination periods that were 17-20 months in length. Participants have been contacted every 9 to 12 months throughout the study to assess clinical morbidity and mortality.

1. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol.* 2002 Nov 1;156(9):871-81. PubMed PMID: 12397006.

NEO (The Netherlands Epidemiology of Obesity study): The NEO was designed for extensive phenotyping to investigate pathways that lead to obesity-related diseases. The NEO study is a population-based, prospective cohort study that includes 6,671 individuals aged 45–65 years, with an oversampling of individuals with overweight or obesity. At baseline, information on demography, lifestyle, and medical history have been collected by questionnaires. In addition, samples of 24-h urine, fasting and postprandial blood plasma and serum, and DNA were collected. Genotyping was performed using the Illumina HumanCoreExome chip, which was subsequently imputed to the 1000 genome reference panel. Participants underwent an extensive physical examination, including anthropometry, electrocardiography, spirometry, and measurement of the carotid artery intima-media thickness by ultrasonography. In random subsamples of participants, magnetic resonance imaging of abdominal fat, pulse wave velocity of the aorta, heart, and brain, magnetic resonance spectroscopy of the liver, indirect calorimetry, dual energy X-ray absorptiometry, or accelerometry measurements were performed. The collection of data started in September 2008 and completed at the end of September 2012. Participants are currently being followed for the incidence of obesity-related diseases and mortality.

Pelotas Birth Cohort Study (The 1982 Pelotas Birth Cohort Study, Brazil): The maternity hospitals in Pelotas, a southern Brazilian city (current population ~330,000), were visited daily in the year of 1982. The 5,914 liveborns whose families lived in the urban area were examined and their mothers interviewed. Information was obtained for more than 99% of the livebirths. These subjects have been followed-up at the following mean ages: 11.3 months (all children born from January to April 1982; n=1457), 19.4 months (entire cohort; n=4934), 43.1 months (entire cohort; n=4742), 13.1 years (random subsample; n=715), 14.7 years (systematic subsample; n=1076); 18.2 (male cohorts attending to compulsory Army recruitment examination; n=2250), 18.9 (systematic subsample; n=1031), 22.8 years (entire cohort; n=4297) and 30.2 years (entire cohort; n=3701). Details about follow-up visits and available data can be found in the two Cohort Profile papers (PMID: 16373375 and 25733577). DNA samples (collected at the mean age of 22.8 years) were genotyped for ~2.5 million of SNPs using the Illumina HumanOmni2.5-8v1 array (which includes autosomal, X and Y chromosomes, and mitochondrial variants). After quality

control, the data were prephased using SHAPEIT and imputed using IMPUTE2 based on 1000 Genomes haplotypes.

RS (Rotterdam Study): The Rotterdam Study is a prospective, population-based cohort study among individuals living in the well-defined Ommoord district in the city of Rotterdam in The Netherlands.¹ The aim of the study is to determine the occurrence of cardiovascular, neurological, ophthalmic, endocrine, hepatic, respiratory, and psychiatric diseases in elderly people. The cohort was initially defined in 1990 among 7,983 persons, aged 55 years and older, who underwent a home interview and extensive physical examination at the baseline and during follow-up rounds every 3-4 years (RS-I). Cohort was extended in 2000/2001 (RS-II, 3,011 individuals aged 55 years and older) and 2006/2008 (RS-III, 3,932 subjects, aged 45 and older).¹ Written informed consent was obtained from all participants and the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the study. By the end of 2008, the Rotterdam Study comprised 14,926 individuals. Written informed consent was obtained from all participants and the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports, approved the study.

1. Ikram, M. Arfan, et al. "The Rotterdam Study: 2018 update on objectives, design and main results." *European journal of epidemiology* 32.9 (2017): 807-850.

SCES (Singapore Chinese Eye Study): SCES is a population-based, cross-sectional study of Chinese adults aged 40–80+ years residing in the South-Western part of Singapore, which is part of the Singapore Epidemiology of Eye Diseases (SEED). Age stratified random sampling was used to select 6,350 eligible participants, of which 3,500 participated in the study (72.8% response rate). Detailed methodology has been published [PMID: 19995197; 25953847]. Two readings of blood pressure were taken from participants after 5 minutes of rest, seated, using an automated blood pressure monitor (Dinamap Pro100V2; Criticon, Norderstedt, Germany) by trained observers. One of two cuff sizes (regular, large) was chosen on the basis of the circumference of the participant's arm. A third reading was performed if the difference between two readings of either the systolic blood pressure was greater than 10mmHg or the diastolic blood pressure was greater than 5mmHg. The mean values of the closest two readings were calculated.

SCHS-CHD (Singapore Chinese Health Study - Coronary Heart Disease): SCHS-CHD is a case-control study of coronary heart disease that was nested within the Singapore Chinese Health Study (SCHS), a prospective cohort study of 63,257 Singaporean Chinese men and women aged 45-74 years living in Singapore. We selected cases and controls from participants that provided blood samples and were free of coronary heart disease and stroke at the time of blood collection (N=24,454). Cases (N=760) had acute myocardial infarction (AMI) or died of coronary heart disease. AMI was identified through the Singapore Myocardial Infarction Registry or through the nationwide hospital discharge database followed by confirmation of AMI by cardiologists' review of medical records using the Multi-Ethnic Study of Atherosclerosis criteria (available at: <http://www.mesa-nhlbi.org/manuals.aspx>). Coronary heart disease deaths were identified through the Singapore Registry of Births and Deaths (ICD9 410-414 as first stated cause of death). Matched controls (N=1,491) were selected using a risk-set sampling strategy. Controls were participants who were alive and free of coronary heart disease at the time of the diagnosis or death of the index cases and were matched for age, sex, dialect group, year of recruitment and date of blood collection. In-person interviews and phlebotomy were conducted before the onset of disease and non-fasting venous blood was stored at -80°C for extraction of DNA and blood biochemistry.

SiMES (Singapore Malay Eye Study): SiMES is a population-based cross-sectional epidemiological study of 3,280 individuals from one of the three major ethnic groups residing in Singapore. SiMES is part of the Singapore Epidemiology of Eye Diseases (SEED) study. In summary, 5,600 individuals have been selected by an age-stratified sampling strategy. Among these 4,168 individuals are eligible for this study. 3,280 individuals finally participated in the study (78.7% response rate). All subjects were Malay and aged 40-80 years [PMID: 17365815; 25953847]. Two readings of blood pressure were taken from participants after 5 minutes of rest, seated, using an automated blood pressure monitor (Dinamap

Pro100V2; Criticon, Norderstedt, Germany) by trained observers. One of two cuff sizes (regular, large) was chosen on the basis of the circumference of the participant's arm. A third reading was performed if the difference between two readings of either the systolic blood pressure was greater than 10mmHg or the diastolic blood pressure was greater than 5mmHg. The mean values of the closest two readings were calculated.

SINDI (Singapore Indian Eye Study): SINDI is a population-based, cross-sectional study of Asian Indian adults aged 40–80+ years residing in the South-Western part of Singapore, which is part of the Singapore Epidemiology of Eye Diseases (SEED). Age stratified random sampling was used to select 6,350 eligible participants, of which 3,400 participated in the study (75.6% response rate). Detailed methodology has been published [PMID: 19995197; 25953847]. Two readings of blood pressure were taken from participants after 5 minutes of rest, seated, using an automated blood pressure monitor (Dinamap Pro100V2; Criticon, Norderstedt, Germany) by trained observers. One of two cuff sizes (regular, large) was chosen on the basis of the circumference of the participant's arm. A third reading was performed if the difference between two readings of either the systolic blood pressure was greater than 10mmHg or the diastolic blood pressure was greater than 5mmHg. The mean values of the closest two readings were calculated.

WGHS (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 [PMID: 18070814]. Participants in the WHS were 45 years or older at enrollment and free of cardiovascular disease, cancer or other major chronic illness. 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 self-reported European ancestry could be confirmed by multidimensional scaling analysis of 1,443 ancestry informative markers in PLINK v. 1.06. At baseline, BP and lifestyle habits related to smoking, consumption of alcohol, and physical activity as well as other general clinical information were ascertained by a self-reported questionnaire, an approach which has been validated in the WGHS demographic, namely female health care professionals. Questionnaires recorded systolic BP in 9 categories (<110, 110-119, 120-129, 130-139, 140-149, 150-159, 160-169, 170-179, ≥180 mmHg), and diastolic BP in 7 categories (<65, 65-74, 75-84, 85-89, 90-94, 95-104, ≥105 mmHg). All analyses treated these BP responses as quantitative variables representing each category with its midpoint value. Hypertension was defined as one or more of reported physician diagnosis, systolic BP ≥140 mmHg, or diastolic BP ≥90 mmHg.

Stage 2 Study Descriptions

Brief descriptions are provided below for each of stage 2 studies/cohorts:

AA-DHS (African American Diabetes Heart Study): AA-DHS objectives are to improve understanding of ethnic differences in CAC and CP in populations of African and European ancestry. The AA-DHS consists of self-reported African Americans with T2D recruited from two Wake Forest School of Medicine (WFSM) studies: the family-based Diabetes Heart Study (DHS) and unrelated individuals in the AA-DHS. DHS is a cross-sectional study of European American and African American families with siblings concordant for T2D. AA-DHS started after DHS and enrolled unrelated African Americans. The AA-DHS GWAS utilized the Illumina 5M chip with imputation to 1,000 Genomes.

Airwave (The Airwave Health Monitoring Study): The Airwave Health Monitoring Study (22) was established to evaluate possible health risks associated with use of TETRA, a digital communication system used by police forces and other emergency services in Great Britain since 2001. The study has been broadened to investigate more generally the health of the work force. From 2004, participants from each force who agreed to participate were enrolled either with an enrolment questionnaire or a comprehensive health screening performed locally. This includes questionnaire, 7-day food diaries, anthropometry, measurements of cardiovascular and cognitive function, blood chemistry, coagulation and hematology. Systolic and diastolic blood pressures were measured as three consecutive readings

using a digital blood pressure monitor (Omron HEM 705-CP digital BP monitor). By March 2015, the study had recruited 53,606 participants, of whom 45,433 had attended the health screening, and 14,002 have genotype data (1000G imputed).

1. Elliott, P. et al. The Airwave Health Monitoring Study of police officers and staff in Great Britain: rationale, design and methods. *Environ Res* 134, 280-5 (2014).

BES (Beijing Eye Study): The Beijing Eye Study is a population-based study that assesses the associated and risk factors of ocular and general diseases in a Chinese population. The study was initialized in 2001 and collected data from 4439 subjects aged ≥ 40 years and living in seven communities in the Beijing area. Three of these communities were located in a rural district and four were located in an urban district. The BES was followed-up in 2006, with 3251 of the original subjects participating, and in 2011, with 2695 subjects returning for the follow-up examination. At the examinations in 2006 and 2011, trained research staffs asked the subjects questions from a standard questionnaire providing information on the family status, level of education, income, quality of life, psychic depression, physical activity, and known major systemic diseases. Fasting blood samples were taken for measurement of concentrations of substances such as blood lipids, glucose, and glycosylated hemoglobin. Individuals were classified as self-reported non-smokers or self-reported current smokers. Alcohol consumption habits based on number of drinks per day were collected. Physical activity was assessed in questions on the number of hours per day and number of days per week spent on intensively or moderately performed sport activities, spent on walking, on riding a bicycle, and spent on sitting. All variables used in analyses were taken from examinations in 2006 or in 2011. The BES subjects were genotyped on two arrays, Illumina Human610-Quad (N = 832) and Illumina OmniExpress (N = 814).

BRIGHT (British Genetics of Hypertension): Participants of the BRIGHT Study are recruited from the Medical Research Council General Practice Framework and other primary care practices in the UK. Each case had a history of hypertension diagnosed prior to 60 years of age with confirmed blood pressure recordings corresponding to seated levels $>150/100$ mmHg (1 reading) or mean of 3 readings $>145/95$ mmHg. BRIGHT is focused on recruitment of hypertensive individuals with BMI <30 . Sample selection for GWAS was based on DNA availability and quantity.

1. Caulfield M, Munroe P, Pembroke J, Samani N, Dominiczak A, Brown M, Benjamin N, Webster J, Ratcliffe P, O'Shea S, Papp J, Taylor E, Dobson R, Knight J, Newhouse S, Hooper J, Lee W, Brain N, Clayton D, Lathrop GM, Farrall M, Connell J, MRC British Genetics of Hypertension Study. Genome-wide mapping of human loci for essential hypertension. *Lancet*. 2003;361:2118-23.

Colaus (Cohorte Lausannoise): The cohort is a random population sample of the city of Lausanne aged 35-75 years. Recruitment began in June 2003 and ended in May 2006, and the first follow-up was conducted between April 2009 and September 2012. The CoLaus study was approved by the Institutional Ethics Committee of the University of Lausanne and informed consent was appropriately obtained by all participants. Both at baseline and follow-up, all participants attended the outpatient clinic of the University Hospital of Lausanne in the morning after an overnight fast. Data were collected by trained field interviewers in a single visit lasting about 60 min. More details of the selection procedure, genotyping and phenotype measurement as well as data access can be found in www.colaus-psycolaus.ch.

1. Firmann M, Mayor V, Vidal PM, Bochud M, Pécoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, Danoff TM, Stirnadel HA, Waterworth D, Mooser V, Waeber G, Vollenweider P. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord*. 2008;8:6. doi: 10.1186/1471-2261-8-6.

DESIR (Data from an Epidemiological Study on the Insulin Resistance): The DESIR cohort study aims to: describe and understand the relations between the abnormalities of the syndrome, their evolution, according to age and sex; search for risk factors of insulin resistance, in particular factors associated with the environment, lifestyle and genetic markers; quantify the links between the syndrome and both cardiovascular disease and diabetes; evaluate the frequency of the syndrome in terms of its consequences on public health.

DFTJ (Dongfeng-Tongji Cohort Study): The DFTJ-cohort study includes 27,009 retired employees from a state-owned automobile enterprise in China. This study was launched in 2008 and will be followed up every 5 years. In 2013 we conducted the first follow-up. By using semi-structural questionnaire and health examination, those having cancer or severe diseases were excluded. Fasting blood samples and detailed epidemiology data were collected. The main goal of the cohort was to identify the environmental and genetic risk factors and the gene-environment interactions on chronic diseases, and to find novel biomarkers for chronic disease and mortality prediction. Finally, 1,461 included in the present study with GWAS data. All of the participants wrote informed consent and the ethical committees in the Tongji Medical College approved this research project. Detailed information has been described in elsewhere(1).

QC criteria and imputation methods:

We did the GWAS scan on the DFTJ-cohort with Affymetrix Genome-Wide Human SNP Array 6.0 chips. In total, we genotyped 906,703 SNPs among 1,461 subjects. After stringent QC filtering, SNPs with MAF < 0.01, Hardy-Weinberg Equilibrium (HWE) < 0.0001, and SNP call rate < 95% were excluded. Individuals with call rates < 95% were also not included for further analysis. In total, we retained 1,452 subjects with 658,288 autosomal SNPs for statistical analyses, with an overall call rate of 99.68%. We used MACH 1.0 software to impute untyped SNPs using the LD information from the HapMap phase II database (CHB+JPT as a reference set (2007-08_rel22, released 2007-03-02). Imputed SNPs with high genotype information content ($R_{sq} > 0.3$ for MACH) were kept for the further association analysis.

1. Wang, F., Zhu, J., Yao, P., Li, X., He, M., Liu, Y., Yuan, J., Chen, W., Zhou, L., Min, X. et al. (2012) Cohort profile: The Dongfeng-Tongji cohort study of retired workers. International journal of epidemiology.

DHS (Diabetes Heart Study): The Diabetes Heart Study (DHS) is an ongoing family-based cohort study investigating the epidemiology and genetics of cardiovascular disease (CVD) in a population-based sample. The DHS recruited T2D-affected siblings without advanced renal insufficiency from 1998 through 2005 in western North Carolina. DHS has collected genetic data on 1,220 self-described European American (EA) individuals from 475 families. Genotyping was completed using an Affymetrix Genome-Wide Human SNP Array 5.0 with imputation of 1,000 Genomes project SNPs from this array using IMPUTE2 and the Phase I v2, cosmopolitan (integrated) reference panel, build 37.

DR's EXTRA (Dose-Responses to Exercise Training): The Dose-Responses to Exercise Training (DR's EXTRA) Study is a 4-year RCT on the effects of regular physical exercise and healthy diet on endothelial function, atherosclerosis and cognition in a randomly selected population sample (n=3000) of Eastern Finnish men and women, identified from the national population register, aged 55-74 years. Of the eligible sample, 1410 individuals were randomized into one of the 6 groups: aerobic exercise, resistance exercise, diet, combined aerobic exercise and diet, combined resistance exercise and diet, or reference group following baseline assessments. During the four year intervention the drop-out rate was 15%.

EGCUT (Estonian Genome Center - University of Tartu (Estonian Biobank)): The Estonian Biobank is the population-based biobank of the Estonian Genome Center at the University of Tartu (www.biobank.ee; EGCUT). The entire project is conducted according to the Estonian Gene Research Act and all of the participants have signed the broad informed consent. The cohort size is up to 51535

individuals from 18 years of age and up, which closely reflects the age, sex and geographical distribution of the Estonian population. All of the subjects are recruited randomly by general practitioners and physicians in hospitals. A Computer Assisted Personal interview is filled within 1-2 hours at a doctor's office, which includes personal, genealogical, educational, occupational history and lifestyle data. Anthropometric measurements, blood pressure and resting heart rate are measured and venous blood taken during the visit. Medical history and current health status is recorded according to ICD-10 codes.

EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk: The European Prospective Investigation of Cancer (EPIC)-Norfolk study is a population-based cohort study established to study the links diet, lifestyle factors and cancer and other health outcomes. Participants are men and women who were aged between 40 and 79 when they joined the study and who lived in Norwich, UK and the surrounding towns and rural areas. They have been contributing information about their diet, lifestyle and health through questionnaires and health checks over two decades. The Norwich Local Research Ethics Committee granted ethical approval for the study. All participants gave written informed consent.

The EPIC-InterAct Case-Cohort Study: EPIC- InterAct is a type 2 diabetes case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study. EPIC was initiated in the late 1980s and involves collaboration between 23 research institutions across Europe in 10 countries. The majority of EPIC cohorts were recruited from the general population, with some exceptions. French cohorts included women who were members of a health insurance scheme for school and university employees; Turin and Ragusa (Italy) and the Spanish centres included some blood donors. Participants from Utrecht (Netherlands) and Florence (Italy) were recruited via a breast cancer screening program. The majority of participants recruited by the EPIC Oxford (UK) centre consisted of vegetarian and "health conscious" volunteers from England, Wales, Scotland, and Northern Ireland. EPIC-InterAct sampled a random sub-cohort and all individuals who subsequently developed incident T2DM over follow up from the full cohort of participants in EPIC who provided blood samples at baseline in Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden and the UK. Smoking status was determined at baseline and lipid measurements at baseline were undertaken in a centralized laboratory on all participants in the case-cohort study.

GeneSTAR (Genetic Studies of Atherosclerosis Risk): GeneSTAR is a family-based prospective study of more than 4000 participants begun in 1983 to determine phenotypic and genetic causes of premature cardiovascular disease. Families were identified from 1983-2006 from probands with a premature coronary disease event prior to 60 years of age who were identified at the time of hospitalization in any of 10 hospitals in the Baltimore, Maryland area. Their apparently healthy 30-59 year old siblings without known coronary disease were recruited and screened between 1983 and 2006. From 2003-2006, adult offspring over 21 years of age of all participating siblings and probands, as well as the coparents of the offspring were recruited and screened. Genotyping was performed in 3,232 participants on the Illumina 1Mv1_c platform. Demographic information including education level was self-reported by participants. Medical history including medication use was assessed by the study nurse or physician. Blood pressure was measured three times over the course of the screening day, and the average of the three measures was used in analysis.

GLACIER (Gene x Lifestyle Interactions and Complex Traits Involved in Elevated Disease Risk): The Gene-Lifestyle interactions And Complex traits Involved in Elevated disease Risk (GLACIER) Study is nested within the Västerbotten Intervention Programme, which is part of the Northern Sweden Health and Disease Study, a population-based prospective cohort study from northern Sweden. Participants were genotyped with Illumina CardioMetaboChip array. This array contains ~200,000 variants, the majority being common variants. Systolic and diastolic blood pressures were measured once following a period of five minutes rest with the participant in the supine position using a mercury-gauge sphygmomanometer. Analysis of serum lipids (HDL-C, triglycerides and total cholesterol) were undertaken at the Department of Clinical Chemistry at Umeå University Hospital using routine methods.

LDL-C was determined using the Friedewald formula. All participants completed a detailed, optically readable, health and lifestyle questionnaire including questions about smoking status and alcohol intake (FFQ). Cohort description - PMID: 25396097

GRAPHIC (Genetic Regulation of Arterial Pressure of Humans in the Community): The GRAPHIC Study comprises 2024 individuals from 520 nuclear families recruited from the general population in Leicestershire, UK between 2003-2005 for the purpose of investigating the genetic determinants of blood pressure and related cardiovascular traits. A detailed medical history was obtained from study subjects by standardized questionnaires and clinical examination was performed by research nurses following standard procedures. Measurements obtained included height, weight, waist-hip ratio, clinic and ambulatory blood pressure and a 12-lead ECG.

HCHS/SOL (Hispanic Community Health Study/ Study of Latinos): The HCHS/SOL is a community-based cohort study of 16,415 self-identified Hispanic/Latino persons aged 18–74 years and selected from households in predefined census-block groups across four US field centers (in Chicago, Miami, the Bronx, and San Diego). The census-block groups were chosen to provide diversity among cohort participants with regard to socioeconomic status and national origin or background. The HCHS/SOL cohort includes participants who self-identified as having a Hispanic/Latino background; the largest groups are Central American (n = 1,730), Cuban (n = 2,348), Dominican (n = 1,460), Mexican (n = 6,471), Puerto Rican (n = 2,728), and South American (n = 1,068). The HCHS/SOL baseline clinical examination occurred between 2008 and 2011 and included comprehensive biological, behavioral, and sociodemographic assessments. Consenting HCHS/SOL subjects were genotyped at Illumina on the HCHS/SOL custom 15041502 B3 array. The custom array comprised the Illumina Omni 2.5M array (HumanOmni2.5-8v.1-1) ancestry-informative markers, known GWAS hits and drug absorption, distribution, metabolism, and excretion (ADME) markers, and additional custom content including ~150,000 SNPs selected from the CLM (Colombian in Medellin, Colombia), MXL (Mexican Ancestry in Los Angeles, California), and PUR (Puerto Rican in Puerto Rico) samples in the 1000Genomes phase 1 data to capture a greater amount of Amerindian genetic variation. QA/QC procedures yielded a total of 12,803 unique study participants for imputation and downstream association analyses.

HRS (Health & Retirement Study): The Health and Retirement Study (HRS) is a longitudinal survey of a representative sample of Americans over the age of 50. The current sample is over 26,000 persons in 17,000 households. Respondents are interviewed every two years about income and wealth, health and use of health services, work and retirement, and family connections. DNA was extracted from saliva collected during a face-to-face interview in the respondents' homes. These data represent respondents who provided DNA samples and signed consent forms in 2006, 2008, and 2010. Respondents were removed if they had missing genotype or phenotype data.

1. Juster, F. T., Suzman, R. (1995). An Overview of the Health and Retirement Study, *Journal of Human Resources* 30:Suppl: S7-S56.
2. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort Profile: the Health and Retirement Study (HRS). *Int. J. Epidemiol.* 2014; 43 (2): 576-585. PMID: 24671021.
3. Crimmins, E.M., Guyer H., Langa K.M., Ofstedal M.B., Wallace R.B., and Weir D.R. (2008). Documentation of Physical Measures, Anthropometrics and Blood Pressure in the Health and Retirement Study. HRS Documentation Report DR-011. <http://hrsonline.isr.umich.edu/sitedocs/userg/dr-011.pdf>

HyperGEN-AXIOM (Hypertension Genetic Epidemiology Network): HyperGEN is a family-based study that investigates the genetic causes of hypertension and related conditions in EA and AA subjects. HyperGEN recruited hypertensive sibships, along with their normotensive adult offspring, and an age-matched random sample. HyperGEN has collected data on 2,471 Caucasian-American subjects and 2,300 African-American subjects, from five field centers in Alabama, Massachusetts, Minnesota, North Carolina, and Utah. HyperGEN participates as a discovery study using GWAS available in a large

subset of the samples. The remaining AA subjects without GWAS data were genotyped on the Affymetrix Axiom chip as part of a HyperGEN admixture mapping ancillary study. After excluding subjects already included in the original HyperGEN (or with family members included), this subset of approximately 450 AA subjects are included in the HyperGEN-AXIOM study which participates in replications.

1. Shetty PB, Tang H, Tayo BO, Morrison AC, Hanis CL, Rao DC, Young JH, Fox ER, Boerwinkle E, Cooper RS, Risch NJ, Zhu X; Candidate Gene Association Resource (CARE) Consortium. Variants in CXADR and F2RL1 are associated with blood pressure and obesity in African-Americans in regions identified through admixture mapping. *J Hypertens.* 2012 Oct;30(10):1970-6. PMID:22914544

INGI-CARL and INGI-FVG (Italian Network Genetic Isolates): INGI-FVG and INGI-CARL studies include samples coming from isolated populations and belong to the ITALIAN NETWORK OF GENETIC ISOLATES (INGI). INGI-CARL examined about 1000 subjects between 1998 and 2005 coming from a small village of the South of Italy situated in the extreme northern part of Puglia Region, while INGI FVG involved about 1700 subjects between 2008 and 2011 coming from six different villages located in the North-East of Italy in Friuli Venezia Giulia region. A questionnaire was administered to each participant to obtain socio-demographic information, as well as data on professional activity, family history, eating habits and lifestyle, such as smoking, coffee and alcohol consumption, physical activity. Furthermore, a medical screening, including anamnesis, blood pressure, drugs and clinical chemistry evaluation (blood count and different biochemical parameters, such as lipids) were made. All participants gave their written informed consent.

IRAS (Insulin Resistance Atherosclerosis Study): The Insulin Resistance Atherosclerosis Study (IRAS) was an epidemiologic cohort study designed to examine the relationship between insulin resistance and carotid atherosclerosis across a range of glucose tolerance. Individuals of self-reported Mexican-American ethnicity were recruited in San Antonio, TX and San Luis Valley, CO. Recruitment was balanced across age and glucose tolerance status. Inclusion of IRAS data is limited to 194 normoglycemic individuals with genotype data from the Illumina OmniExpress and Omni 1S arrays and imputation to the 1000 Genome Integrated Reference Panel (phase I).

IRAS Family Study (Insulin Resistance Atherosclerosis Study): The IRASFS was a family study designed to examine the genetic and epidemiologic basis of glucose homeostasis traits and abdominal adiposity. Briefly, self-reported Mexican American pedigrees were recruited in San Antonio, TX and San Luis Valley, CO. Proband with large families were recruited from the initial non-family-based IRAS, which was modestly enriched for impaired glucose tolerance and T2D. Inclusion of IRASFS data is limited to 1040 normoglycemic individuals in 88 pedigrees with genotype data from the Illumina OmniExpress and Omni 1S arrays and imputation to the 1000 Genome Integrated Reference Panel (phase I).

JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin): Genetic analysis was performed in a sub-population from JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), an international, randomized, placebo-controlled trial of rosuvastatin (20mg/day) in the primary prevention of cardiovascular disease conducted among apparently healthy men and women with LDL-C < 130 mg/dL and hsCRP \geq 2 mg/L (1, 2). Individuals with diabetes or triglyceride concentration >500mg/dL were excluded. The present analysis includes only individuals who provided consent for genetic analysis, had successfully collected genotype information, and who had either verified European or verified South African black ancestry.

1. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ;

JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008 Nov 20; 359(21):2195-207

2. Chasman DI, Giulianini F, MacFadyen J, Barratt BJ, Nyberg F, Ridker PM. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. *Circ Cardiovasc Genet*. 2012 Apr 1;5(2):257-64. doi: 10.1161/CIRCGENETICS.111.961144. Epub 2012 Feb 13. Erratum in: *Circ Cardiovasc Genet*. 2012 Jun;5(3):e27. PubMed PMID: 22331829.

KORA (Cooperative Health Research in the Augsburg Region): The KORA study is a series of independent population-based epidemiological surveys of participants living in the region of Augsburg, Southern Germany. All survey participants are residents of German nationality identified through the registration office and were examined in 1994/95 (KORA S3) and 1999/2001 (KORA S4). In the KORA S3 and S4 studies 4,856 and 4,261 subjects have been examined implying response rates of 75% and 67%, respectively. 3,006 subjects participated in a 10-year follow-up examination of S3 in 2004/05 (KORA F3), and 3080 of S4 in 2006/2008 (KORA F4). The age range of the participants was 25 to 74 years at recruitment. Informed consent has been given by all participants. The study has been approved by the local ethics committee. Individuals for genotyping in KORA F3 and KORA F4 were randomly selected and these genotypes are taken for the analysis of the phenotypes in KORA S3 and KORA S4.

LBC1921 (Lothian Birth Cohort 1921): LBC1921 consists of 550 (234 male) relatively healthy individuals, assessed on cognitive and medical traits at a mean age of 79.1 years (SD = 0.6). 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) of Scotland.¹

1. Deary IJ, Gow AJ, Pattie A, Starr JM. Cohort profile: the Lothian Birth Cohorts of 1921 and 1936. *Int J Epidemiol* 2012;41:1576-1584.

LBC1936 (Lothian Birth Cohort 1936): LBC1936 consists of 1091 (548 male) relatively healthy individuals who underwent cognitive and medical testing at a mean age of 69.6 years (SD = 0.8). 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.¹

1. Deary IJ, Gow AJ, Pattie A, Starr JM. Cohort profile: the Lothian Birth Cohorts of 1921 and 1936. *Int J Epidemiol* 2012;41:1576-1584.

Lifelines (Netherlands Biobank): Lifelines (<https://lifelines.nl/>) is a multi-disciplinary prospective population-based cohort study using a unique three-generation design to examine the health and health-related behaviors 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, behavioral, 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 over 130,000 participants had been included by April 2013. At the baseline examination, the participants in the study were 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. Lifelines is a facility that is open for all researchers. Information on application and data access procedure is summarized on www.lifelines.nl.

1. Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol*. 2014 Dec 14.

LLFS (The Long Life Family Study): LLFS is a family-based cohort study, including four clinical centers: Boston University Medical Center in Boston, MA, USA, Columbia University College of Physicians and Surgeons in New York City, NY, USA, the University of Pittsburgh in Pittsburgh PA, USA, and University of Southern Denmark, Denmark. The study characteristics, recruitment, eligibility and enrollment have been previously described (Pedersen et al., 2006, PMID: 17150149; Sebastiani et al., 2009, PMID: 19910380; Newman et al., 2011, PMID: 21258136). In brief, the LLFS was designed to determine genetic, behavioral, and environmental factors related to families of exceptionally healthy, elderly individuals. Phase 1 was conducted between 2006 and 2009 recruiting 4,953 individuals from 539 families. The probands were at least 79 years old in the USA centers, and 90 years old or above in Denmark. The families were selected to participate in the study based on The Family Longevity Selection Score (FLoSS) (Sebastiani et al., 2009, PMID: 19910380), a score generated according to birth-year cohort survival probabilities of the proband and siblings; probands and their families with FLoSS score of 7 or higher, at least one living sibling, and at least one living offspring (minimum family size of 3), who were able to give informed consent and willing to participate were recruited. The individuals were genotyped using ~2.3 million SNPs from the Illumina Omni chip, and then imputed on phased 1000 Genomes with Cosmopolitan data as a reference using MACH and MINIMAC. After excluding participants with 80 years and older, ~3,200 individuals have been included in the analyses for replication.

Loyola GxE (Kingston Gene-by-environment; subset of International Collaborative Study of Hypertension in Blacks (ICSHIB)): The Kingston GxE cohort was obtained from a survey conducted in Kingston, Jamaica as part of a larger project to examine gene by environment interactions in the determination of blood pressure among adults 25-74 years [PMID: 9103091]. The principal criterion for eligibility was a body mass index in either the top or bottom third of BMI for the Jamaican population. Participants were identified principally from the records of the Heart Foundation of Jamaica, a non-governmental organization based in Kingston, which provides low-cost screening services (height and weight, blood pressure, glucose, cholesterol) to the general public. Other participants were identified from among participants in family studies of blood pressure at the Tropical Metabolism Research Unit (TMRU) and from among staff members at the University of the West Indies, Mona.

Loyola SPT (Spanish Town; subset of International Collaborative Study of Hypertension in Blacks (ICSHIB)): Participants were recruited from Spanish Town, a stable, residential urban area neighboring the capital city of Kingston, Jamaica as part of the ICSHIB [PMID: 9103091]. A stratified random sampling scheme was used to recruit adult males and females aged 25–74 years from the general population. Spanish Town was chosen because its demographic make-up was broadly representative of Jamaica as a whole.

NESDA (Netherlands Study of Depression and Anxiety): NESDA is a multi-center study designed to examine the long-term course and consequences of depressive and anxiety disorders (<http://www.nesda.nl>)¹. 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 while 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).

1. Penninx, B.W. et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res* 17, 121-40 (2008).

PREVEND (The Prevention of RENal and Vascular ENd stage Disease study): The PREVEND study is an ongoing prospective study investigating the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease. Inhabitants 28 to 75 years of age

(n=85,421) in the city of Groningen, The Netherlands, were asked to complete a short questionnaire, 47% responded, and individuals were then selected with a urinary albumin concentration of at least 10 mg/L (n = 7,768) and a randomly selected control group with a urinary albumin concentration less than 10 mg/L (n = 3,395). Details of the protocol have been described elsewhere (Hillege HL et al. *Circulation* 2002;106:1777-82).

RHS (Ragama Health Study): The Ragama Health Study (RHS) is a population-based study of South Asian men and women aged 35-64yrs living in the Ragama Medical Officer of Health (MOH) area, near Colombo, Sri Lanka.* Consenting adults attended a clinic after a 12-h fast with available health records, and were interviewed by trained personnel to obtain information on medical, sociodemographic, and lifestyle variables. A 10-mL sample of venous blood was obtained from each subject. The concurrent study was performed in two tea plantation estates in the Lindula MOH area, near Nuwara Eliya (180 km from Colombo), to investigate the gene-environment interaction in a community with differing lifestyles (e.g., physical activity and diet). BP was measured using the Omron 750CP (Omron Co., Japan) in the seated position. The average of two readings was used for the analysis. The RHS is a collaborative effort between the Faculty of Medicine, University of Kelaniya and the National Center for Global Health and Medicine, Japan.

1. Dassanayake, A.S. et al. Prevalence and risk factors for non-alcoholic fatty liver disease among adults in an urban Sri Lankan population. *J Gastroenterol Hepatol* 24, 1284-8 (2009).

SHEEP (Stockholm Heart Epidemiology Project): The SHEEP is a population based case-control study of risk factors for first episode of acute myocardial infarction. The study base comprised all Swedish citizens resident in the Stockholm county 1992-1994 who were 45-70 years of age and were free of previous clinically diagnosed myocardial infarction.

Cases were identified using three different sources: 1) coronary units and internal medicine wards for acute care in all Stockholm hospitals; 2) the National Patient Register; and 3) death certificates. For the present study, only cases who survived at least 28 days were considered (n=1213).

First time incident myocardial infarction cases (n=1213) were identified during a 2-year period (1992-1993) for men and during a 3-year period (1992-1994) for women. Controls (n=1561) were randomly recruited from the study population continuously over time within 2 days of the case occurrence and matched to cases on age (5-years interval), sex and hospital catchment area using computerized registers of the population of Stockholm. Five control candidates were sampled simultaneously to be able to replace potential non-respondent controls. Occasionally, because of late response of the initial control, both the first and alternative controls were considered resulting in the inclusion of more controls than cases. Postal questionnaires covering a wide range of exposure areas including occupational exposures, life style factors, social factors and health related factors were distributed to the participants. Clinical investigations were performed at least three months after myocardial infarction of cases and their matched controls. The investigations included blood samplings under fasting conditions with collection of whole blood for DNA extraction, serum and plasma. A biobank was established containing DNA, serum and plasma.

Exposure information based on both the questionnaire and biological data from the health examination was available for 78% of the male and 67% of the female non-fatal cases; the corresponding figures for their controls were 68% and 64%.

SHIP (Study of Health in Pomerania): The Study of Health In Pomerania (SHIP) is a prospective longitudinal population-based cohort study in Mecklenburg-West Pomerania assessing the prevalence and incidence of common diseases and their risk factors (PMID: 20167617). SHIP encompasses the two independent cohorts SHIP and SHIP-TREND. Participants aged 20 to 79 with German citizenship and principal residency in the study area were recruited from a random sample of residents living in the three local cities, 12 towns as well as 17 randomly selected smaller towns. Individuals were randomly selected stratified by age and sex in proportion to population size of the city, town or small towns,

respectively. A total of 4,308 participants were recruited between 1997 and 2001 in the SHIP cohort. Between 2008 and 2012 a total of 4,420 participants were recruited in the SHIP-TREND cohort. Individuals were invited to the SHIP study centre for a computer-assisted personal interviews and extensive physical examinations. The study protocol was approved by the medical ethics committee of the University of Greifswald. Oral and written informed consents was obtained from each of the study participants

Genome-wide SNP-typing was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 or the Illumina Human Omni 2.5 array (SHIP-TREND samples). Array processing was carried out in accordance with the manufacturer's standard recommendations. Genotypes were determined using GenomeStudio Genotyping Module v1.0 (GenCall) for SHIP-TREND and the Birdseed2 clustering algorithm for SHIP. Imputation of genotypes in SHIP and SHIP-TREND was performed with the software IMPUTE v2.2.2 based on 1000 Genomes release March 2012.

SP2 (Singapore Prospective Study Program): The SP2 is a population-based study of diabetes and cardiovascular disease in Singapore. It first surveyed subjects (Chinese, Malay and Indian) from four cross-sectional studies that were conducted in Singapore between 1982 and 1998. Subjects were between the ages of 24-95 years and represented a random sample of the Singapore population. Subjects were re-visited between 2003 and 2007. Among the 10,747 individuals who were eligible, 5,157 subjects completed a questionnaire and the subsequent clinical examinations. Data from this re-visit were utilized for this study [PMID: 19406920]. Two readings of blood pressure were taken from participants after 5 min of rest, seated, using an automated blood pressure monitor (Dinamap Pro100V2; Criticon, Norderstedt, Germany) by trained observers. One of two cuff sizes (regular, large) was chosen on the basis of the circumference of the participant's arm. A third reading was performed if the difference between two readings of either the systolic blood pressure was greater than 10mmHg or the diastolic blood pressure was greater than 5mmHg. The mean values of the closest two readings were calculated.

SWHS/SMHS (Shanghai Women's Health Study/ Shanghai Men's Health Study): The Shanghai Women's Health Study (SWHS) is an ongoing population-based cohort study of approximately 75,000 women who were aged 40-70 years at study enrollment and resided in in urban Shanghai, China; 56,832 (75.8%) provided a blood samples. Recruitment for the SWHS was initiated in 1997 and completed in 2000. The self-administered questionnaire includes information on demographic characteristics, disease and surgery histories, personal habits (such as cigarette smoking, alcohol consumption, tea drinking, and ginseng use), menstrual history, residential history, occupational history, and family history of cancer.

The blood pressure were measured by trained interviewers (retired nurses) with a conventional mercury sphygmomanometer according to a standard protocol, after the participants sat quietly for 5 min at the study recruitment. Included in the current project were 2970 women who had GWAS data and blood pressure measurements at the baseline interview.

The Shanghai Men's Health Study (SMHS) is an ongoing population-based cohort study of 61,480 Chinese men who were aged between 40 and 74 years, were free of cancer at enrollment, and lived in urban Shanghai, China; 45,766 (74.4%) provided a blood samples. Recruitment for the SMHS was initiated in 2002 and completed in 2006. The self-administered questionnaire includes information on demographic characteristics, disease and surgery histories, personal habits (such as cigarette smoking, alcohol consumption, tea drinking, and ginseng use), residential history, occupational history, and family history of cancer. The blood pressure were measured by trained interviewers (retired nurses) with a conventional mercury sphygmomanometer according to a standard protocol, after the participants sat quietly for 5 min at the study recruitment. Included in the current project were 892 men who had GWAS data and blood pressure measurements at the baseline interview or 298 men who had GWAS data and lipids data.

Genotyping and imputation: Genomic DNA was extracted from buffy coats by using a Qiagen DNA purification kit (Valencia, CA) or Puregene DNA purification kit (Minneapolis, MN) according to the manufacturers' instructions and then used for genotyping assays. The GWAS genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affy6.0) platform or Illumina 660, following manufacturers' protocols. After sample quality control, we exclude SNPs with 1) MAF <0.01; 2) call rate <95%; 2) bad genotyping cluster; and 3) concordance rate <95% among duplicated QC samples. Genotypes were imputed using the program MACH (<http://www.sph.umich.edu/csg/abecasis/MACH/download/>), which determines the probable distribution of missing genotypes conditional on a set of known haplotypes, while simultaneously estimating the fine-scale recombination map. Phased autosome SNP data from HapMap Phase II Asians (release 22) were used as the reference. To test for associations between the imputed SNP data with BMI, linear regression (additive model) was used, in which SNPs were represented by the expected allele count, an approach that takes into account the degree of uncertainty of genotype imputation (<http://www.sph.umich.edu/csg/abecasis/MACH/download/>).

The lipid profiles were measured at Vanderbilt Lipid Laboratory. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured using an ACE Clinical Chemistry System (Alfa Wassermann, Inc, West Caldwell, NJ). Low-density lipoprotein (LDL) cholesterol levels were calculated by using the Friedwald equation. The levels of LDL cholesterol were directly measured using an ACE Clinical Chemistry System for subjects with TG levels ≥ 400 mg/dL. Fasting status was defined as an interval between the last meal and blood draw of 8 hours or longer.

TWINGENE (TwinGene of the Swedish Twin Registry): The aim of the TwinGene project has been to systematically transform the oldest cohorts of the Swedish Twin Registry (STR) into a molecular-genetic resource. Beginning in 2004, about 200 twins were contacted each month until the data collection was completed in 2008. A total of 21 500 twins were contacted where of 12 600 participated. Invitations to the study contained information of the study and its purpose. Along with the invitations consent forms and health questionnaire were sent to the subjects. When the signed consent forms were returned, the subjects were sent blood sampling equipment and asked to contact a local health facility for blood sampling. The study population was recruited among twins participating in the Screening Across the Lifespan Twin Study (SALT) which was a telephone interview study conducted in 1998-2002. Other inclusion criteria were that both twins in the pair had to be alive and living in Sweden. Subjects were excluded from the study if they previously declined participation in future studies or if they had been enrolled in other STR DNA sampling projects. The subjects were asked to make an appointment for a health check-up at their local health-care facility on the morning Monday to Thursday and not the day before a national holiday, this to ensure that the sample would reach the KI biobank the following morning by overnight mail. The subjects were instructed to fast from 20.00 the previous night. By venipuncture a total of 50 ml of blood was drawn from each subject. Tubes with serum and blood for biobanking as well as for clinical chemistry tests were sent to KI by overnight mail. One 7ml EDTA tube of whole blood is stored in -80°C while a second 7ml EDTA tube of blood is used for DNA extraction using Puregene extraction kit (Gentra systems, Minneapolis, USA). After excluding subjects in which the DNA concentration in the stock-solution was below $20\text{ng}/\mu\text{l}$ as well as subset of 302 female monozygous twin pairs participating in a previous genome wide effort DNA from 9896 individual subjects was sent to SNP&SEQ Technology Platform Uppsala, Sweden for genome wide genotyping with Illumina OmniExpress bead chip (all available dizygous twins + one twin from each available MZ twin pair).

UKB (United Kingdom Biobank, www.ukbiobank.ac.uk): UK Biobank is a major national health resource with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses. UK Biobank includes data from 502,682 individuals (94% of self-reported European ancestry), with extensive health and lifestyle questionnaire data, physical measures and genetic data. A total of 152,249 participants had genetic and phenotypic (blood pressure) data. Central genotyping quality control (QC) had been performed by UK Biobank [The UK Biobank. UK Biobank Genotyping QC documentation. (2015)]. Further QC was also performed locally.

YFS (The Cardiovascular Risk in Young Finns Study): The YFS is a population-based follow up-study started in 1980. The main aim of the YFS is to determine the contribution made by childhood lifestyle, biological and psychological measures to the risk of cardiovascular diseases in adulthood. In 1980, over 3,500 children and adolescents all around Finland participated in the baseline study. The follow-up studies have been conducted mainly with 3-year intervals. The latest 30-year follow-up study was conducted in 2010-11 (ages 33-49 years) with 2,063 participants. The study was approved by the local ethics committees (University Hospitals of Helsinki, Turku, Tampere, Kuopio and Oulu) and was conducted following the guidelines of the Declaration of Helsinki. All participants gave their written informed consent.

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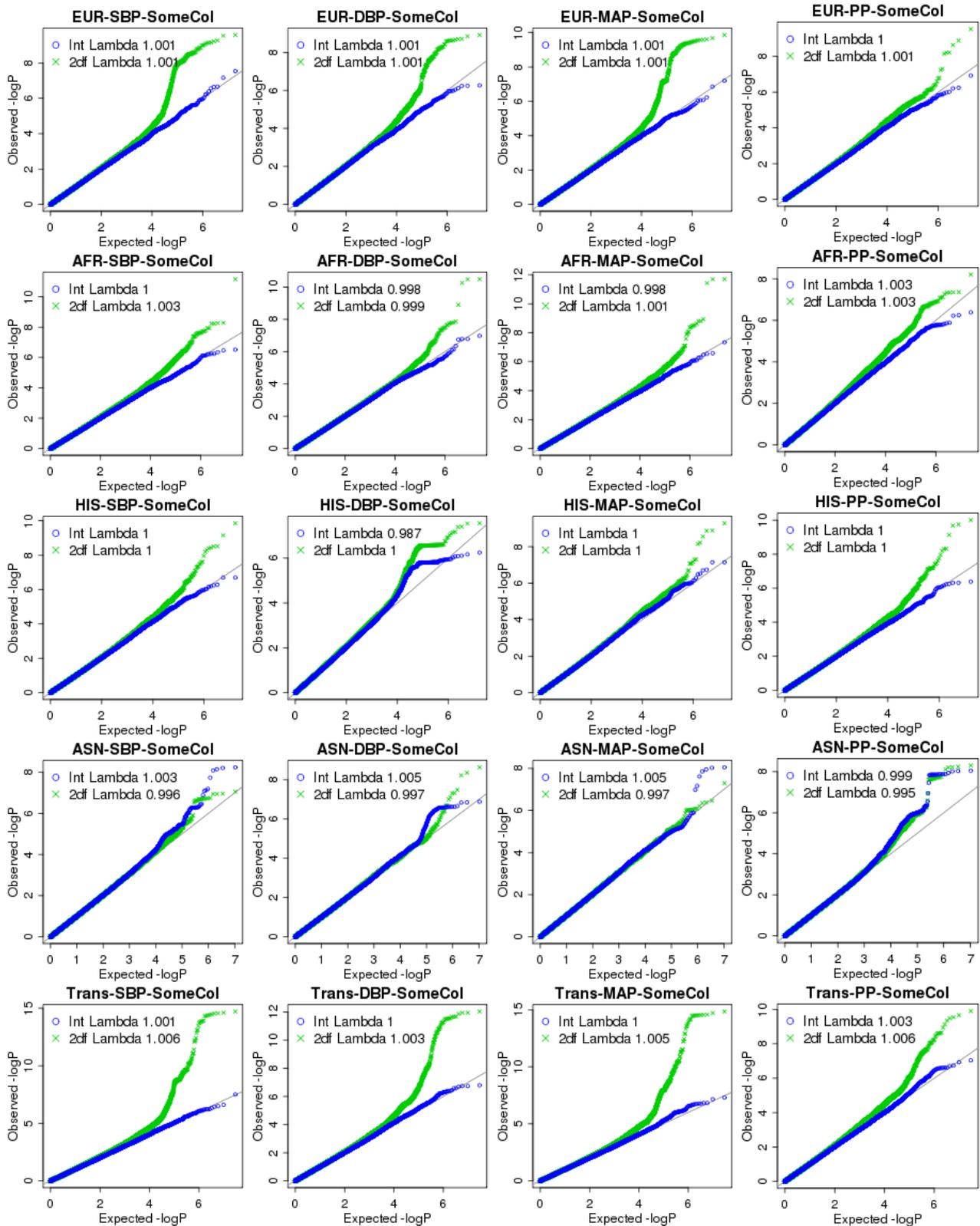
UKB (United Kingdom Biobank, www.ukbiobank.ac.uk): This research has been conducted using the UK Biobank Resource. The UK Biobank data was analysed from the data set corresponding to UK Biobank access application no. 236, application title “Genome-wide association study of blood pressure”, with Paul Elliott as the PI/applicant. Central analysts from Queen Mary University of London (QMUL) and Imperial College London are funded by the NIHR Cardiovascular Biomedical Research Unit at Barts and The London School of Medicine, QMUL, and the NIHR Imperial College Health Care NHS Trust and Imperial College London Biomedical Research Centre respectively. This work was supported by the UK Biobank CardioMetabolic Consortium (UKB-CMC) and the BP working group. The UKB-CMC was supported by the British Heart Foundation (grant SP/13/2/30111). The UK CardioMetabolic Consortium (UK-CMC) was supported by British Heart Foundation (SP/13/2/30111 - Large-scale comprehensive genotyping of UK Biobank for cardiometabolic traits and diseases: UK-CMC).

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Figure S1: QQ plots of Stage 1 meta-analyses.

Each plot displays P-values and their genomic inflation factor. The P-values are based on the genome-wide meta-analysis results in Stage 1 (18.8 million variants total with a larger number of variants in AFR ancestry).



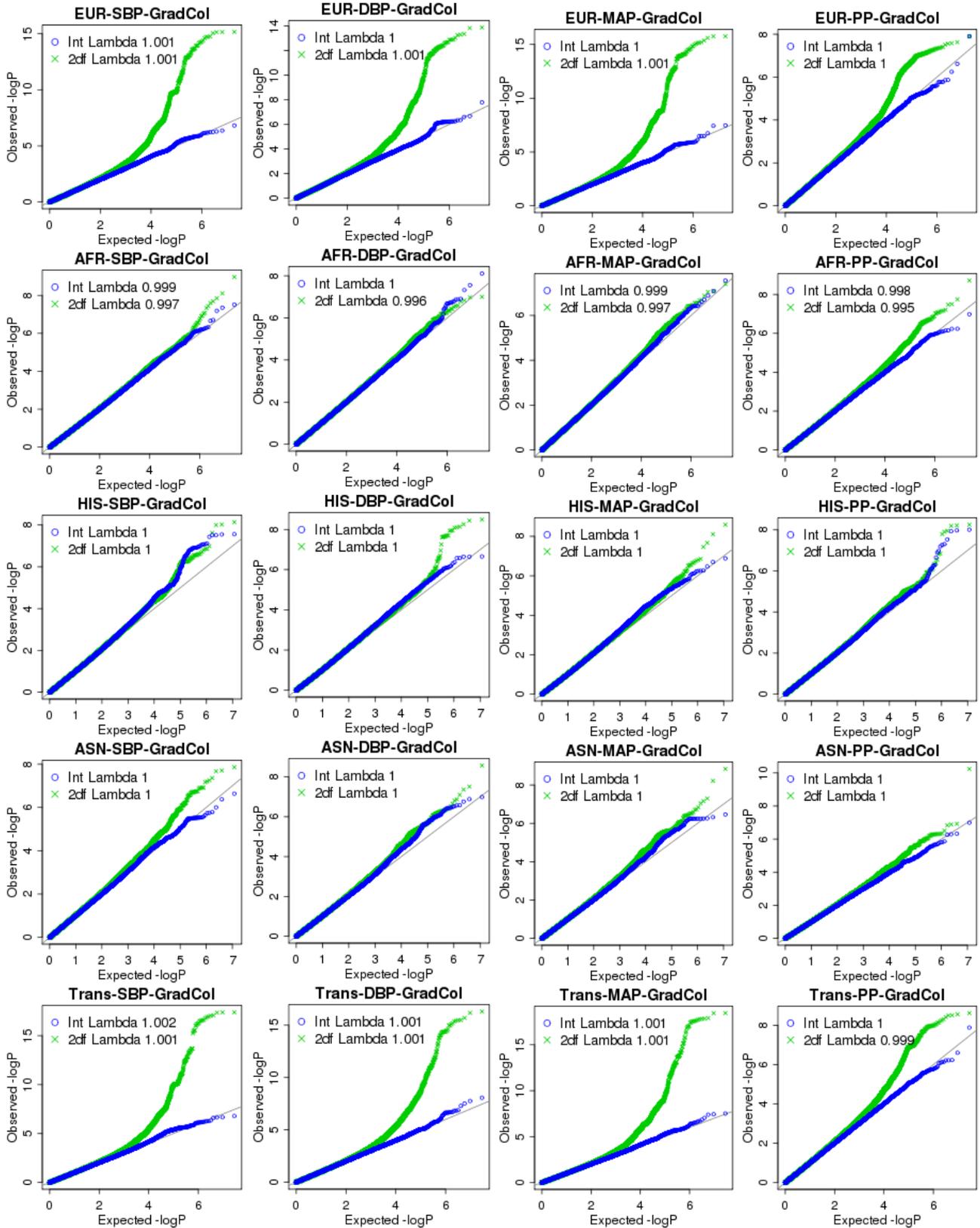


Figure S2: Manhattan plots of the combined analyses of Stages 1 and 2 using the 2DF joint test.

The $-\log_{10}(P)$ of each SNV was plotted at the chromosomal location of each variant. The P-values reflect the most significant across phenotypes and across two educational attainment variables. For the select 4,790 variants, P-values are based on the meta-analysis combining Stages 1 and 2 analysis and the Stage 1 analysis for the remaining 18.8 million variants.

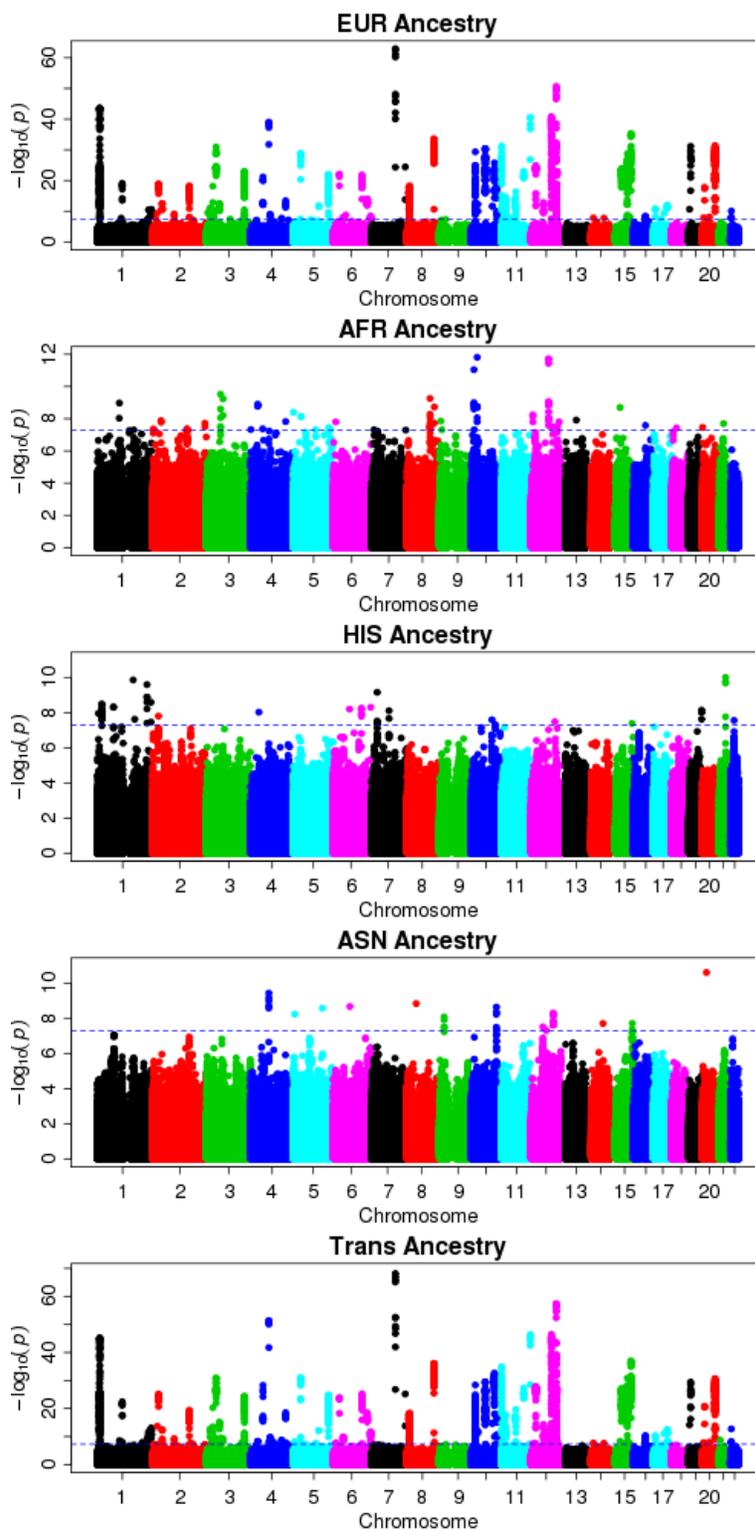
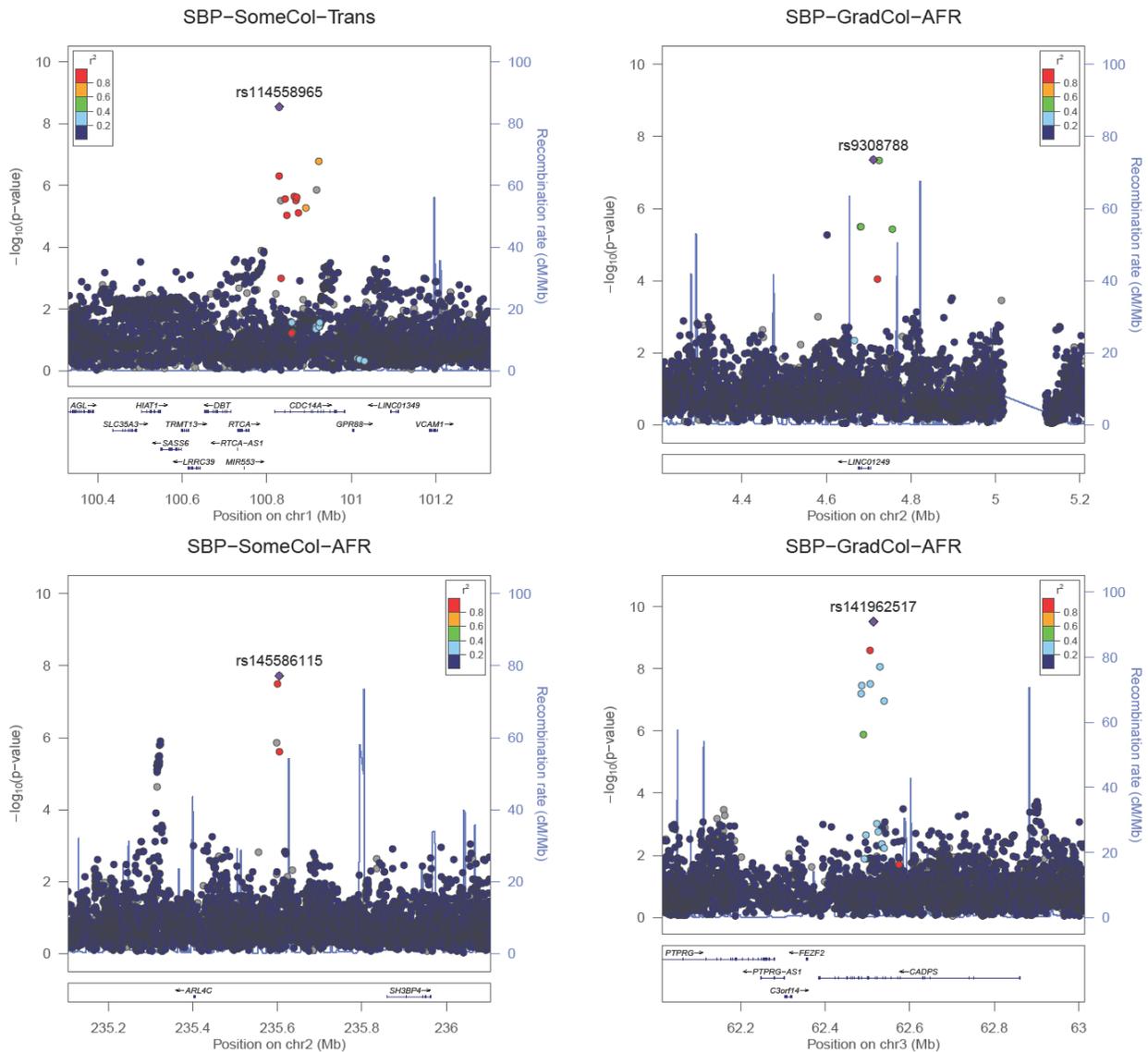
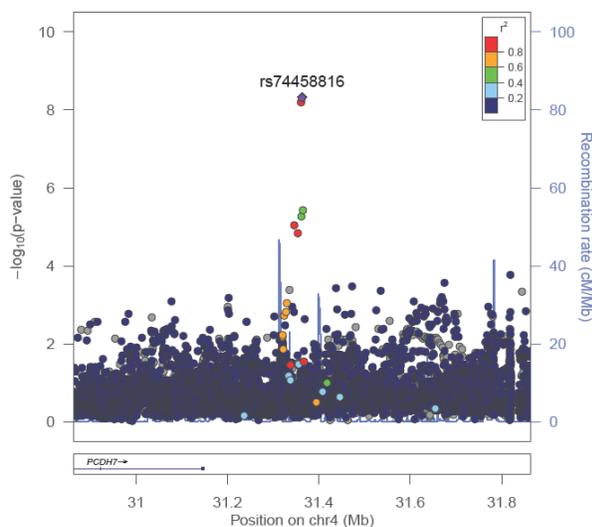


Figure S3: LocusZoom plots for 18 newly identified loci (Table 2).

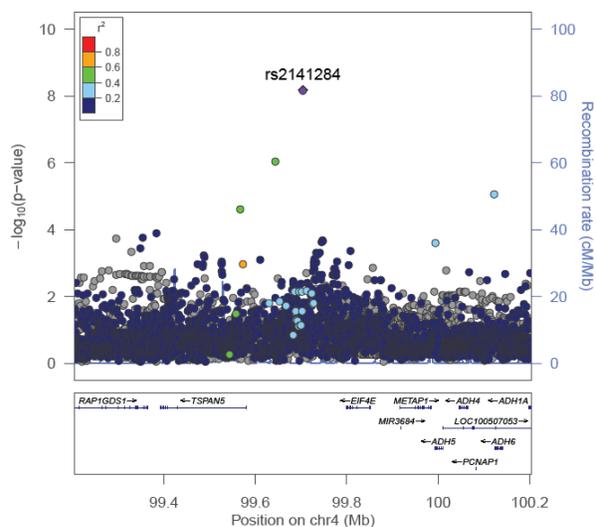
Each locus has at least one BP trait reaching genome-wide significance in any ancestry group. P-values reflect the most significant across phenotypes and across two educational attainment variables. LD substructure is not available for two insertion/deletion index variants.



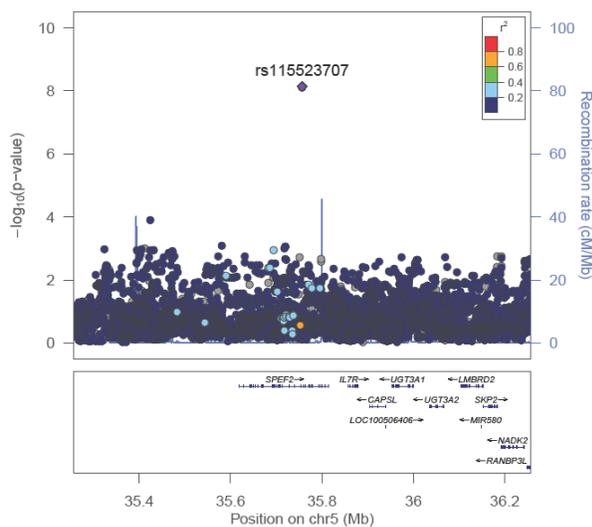
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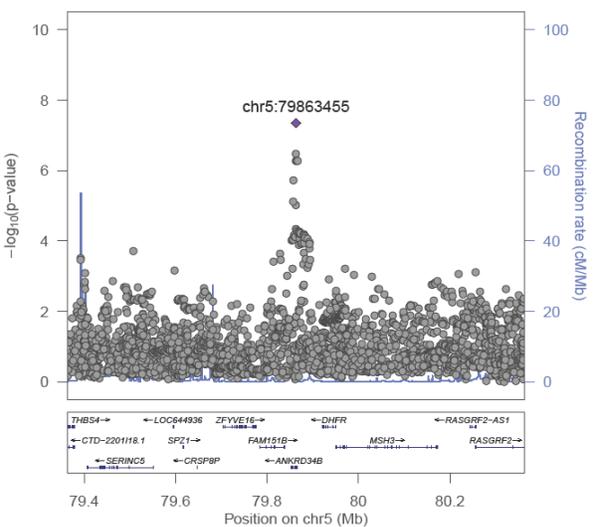
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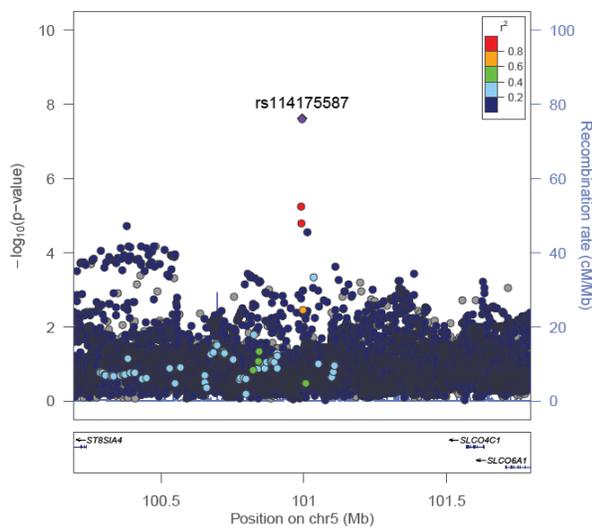
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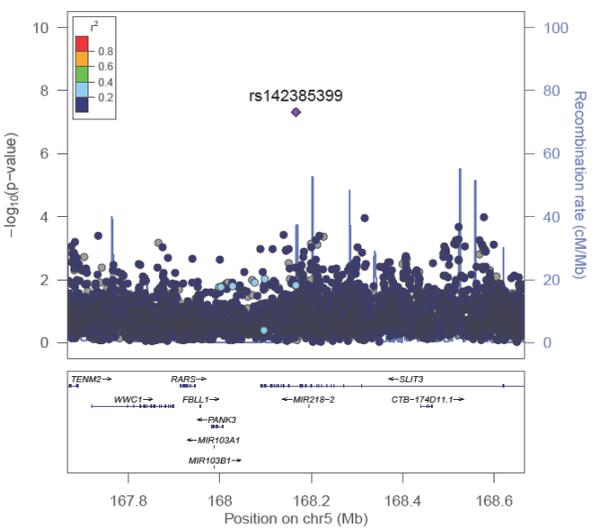
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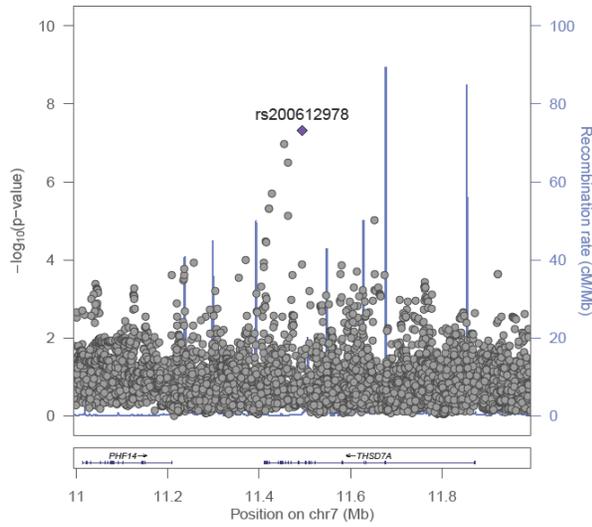
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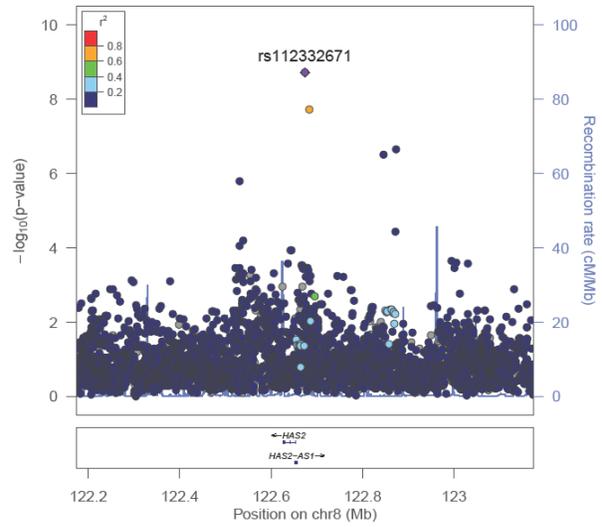
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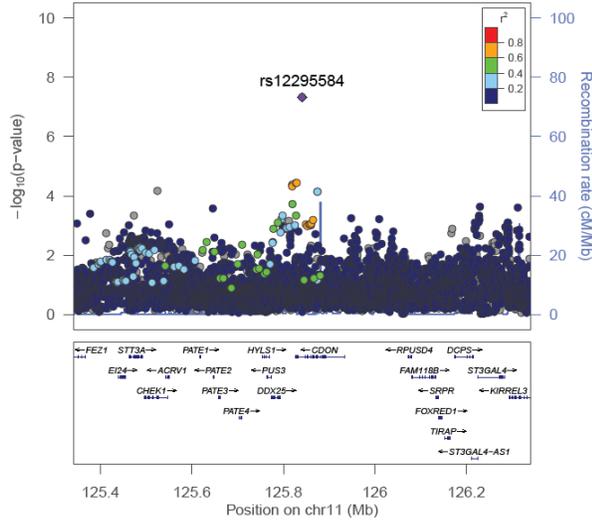
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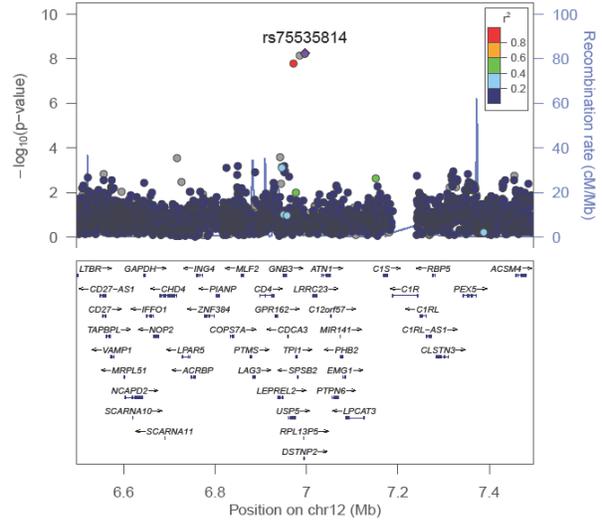
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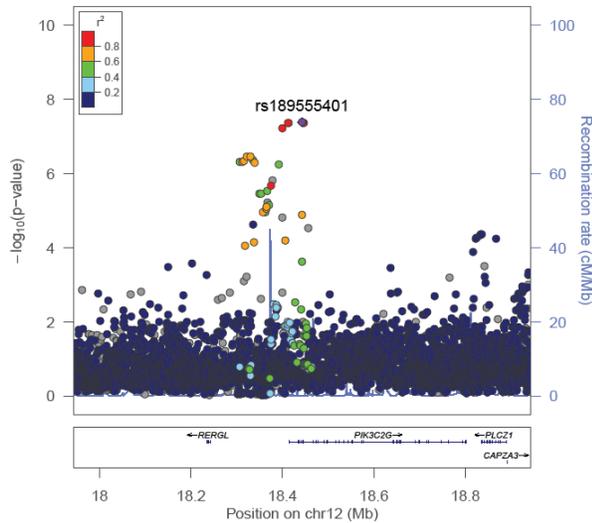
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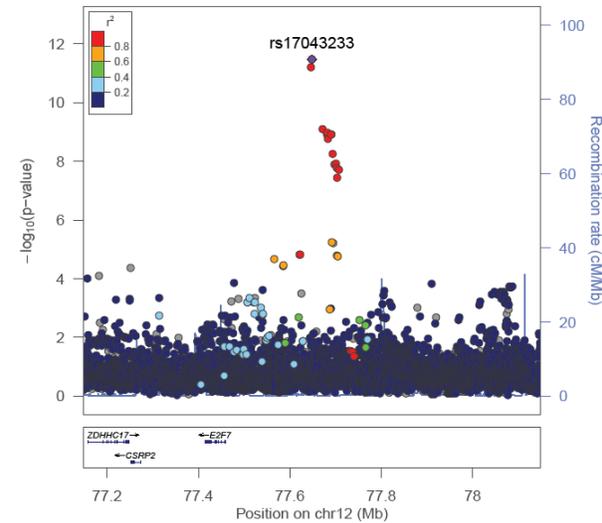
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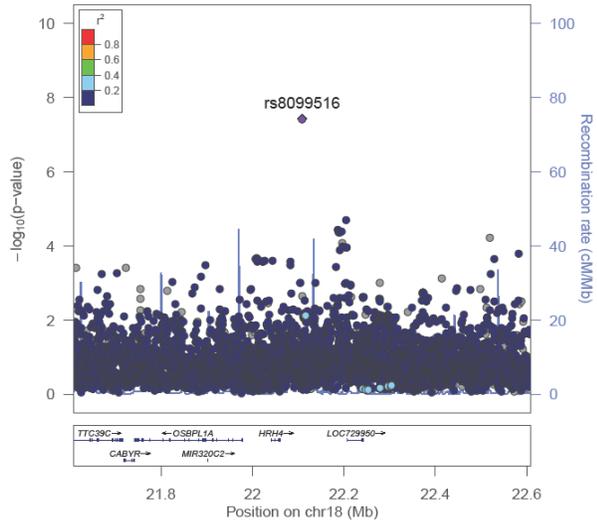
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