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Supplemental Data

Gene-Age Interactions in Blood Pressure Regulation: A Large-Scale Investigation with the CHARGE, Global BPgen, and ICBP Consortia

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Acknowledgments

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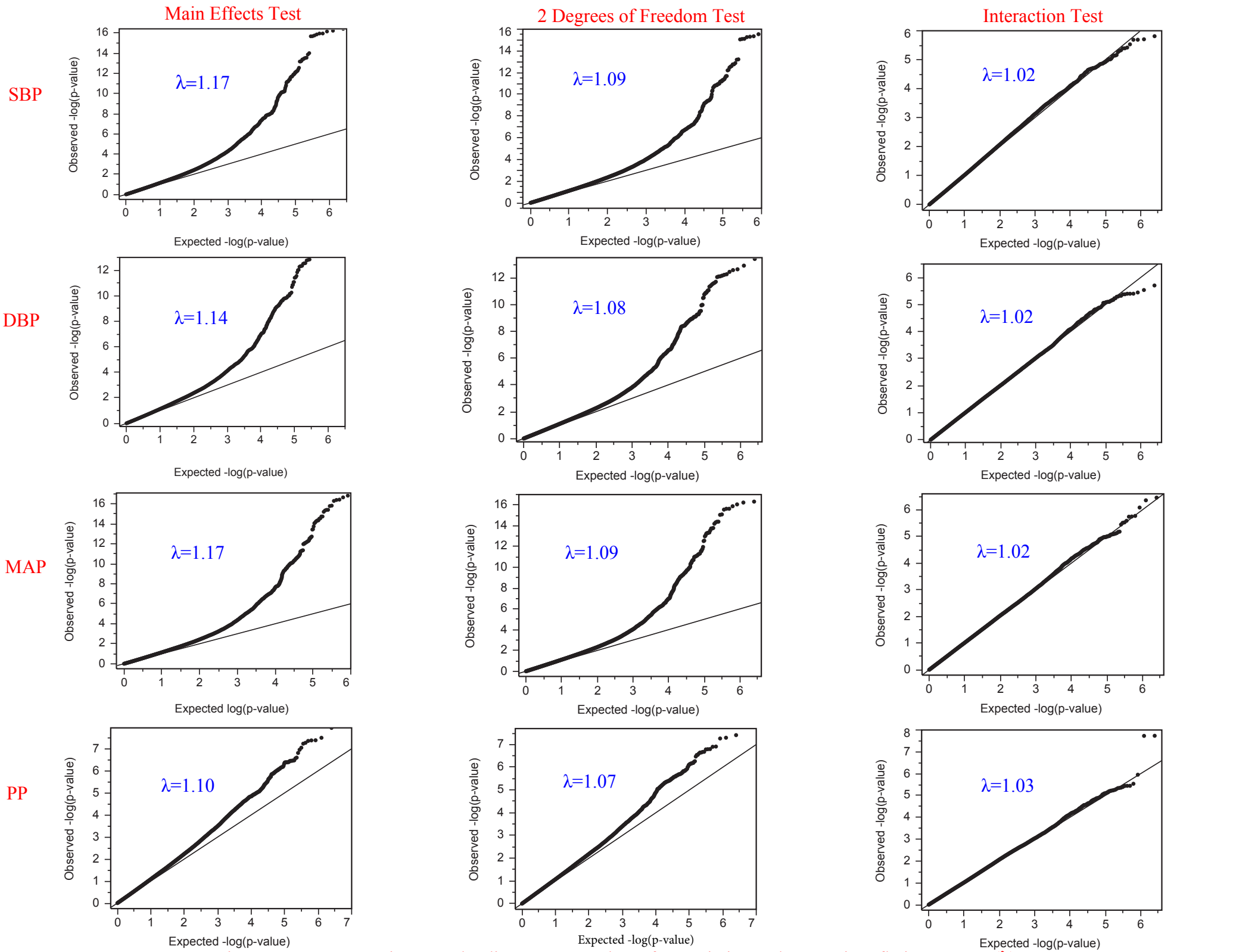
References



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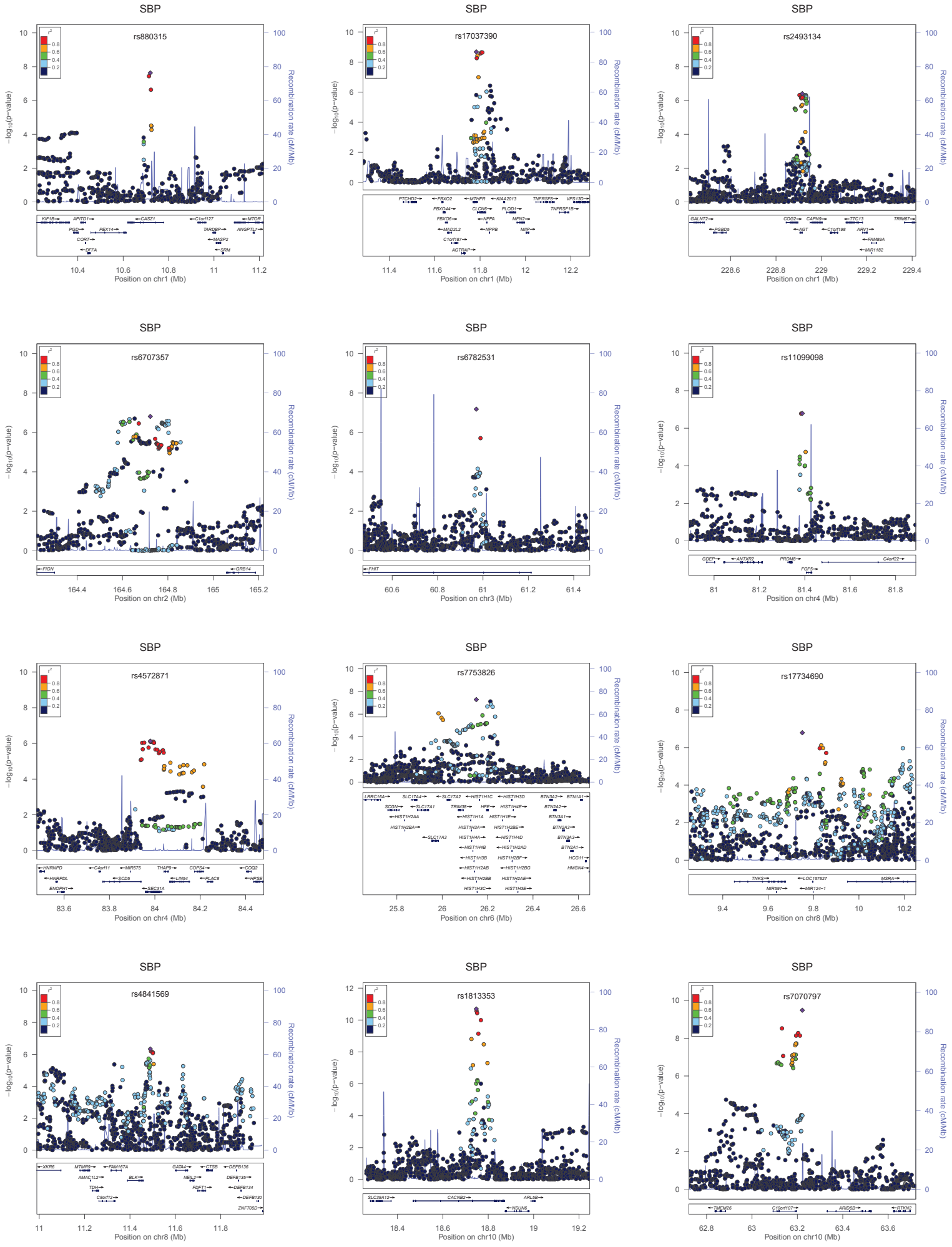

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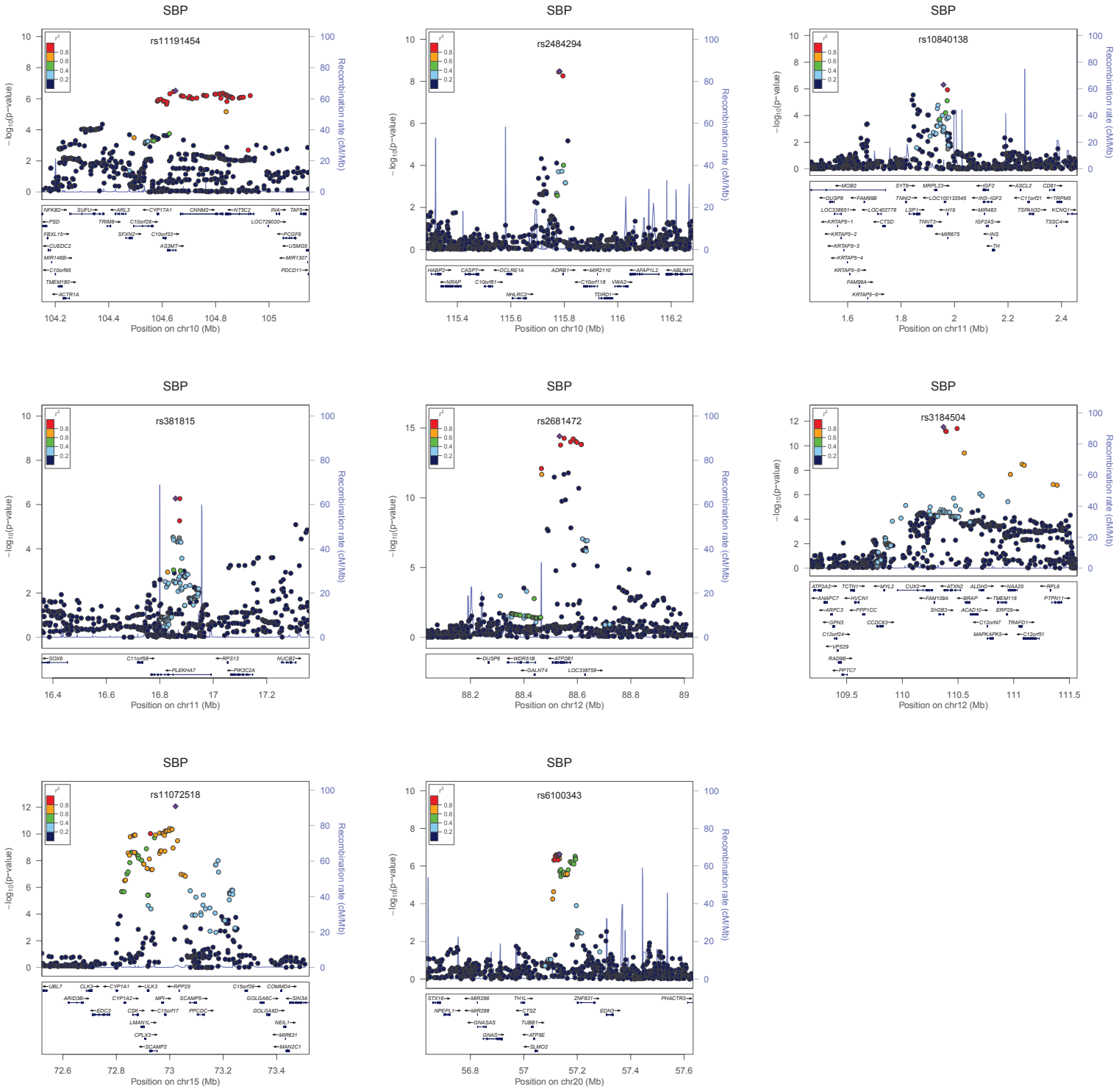

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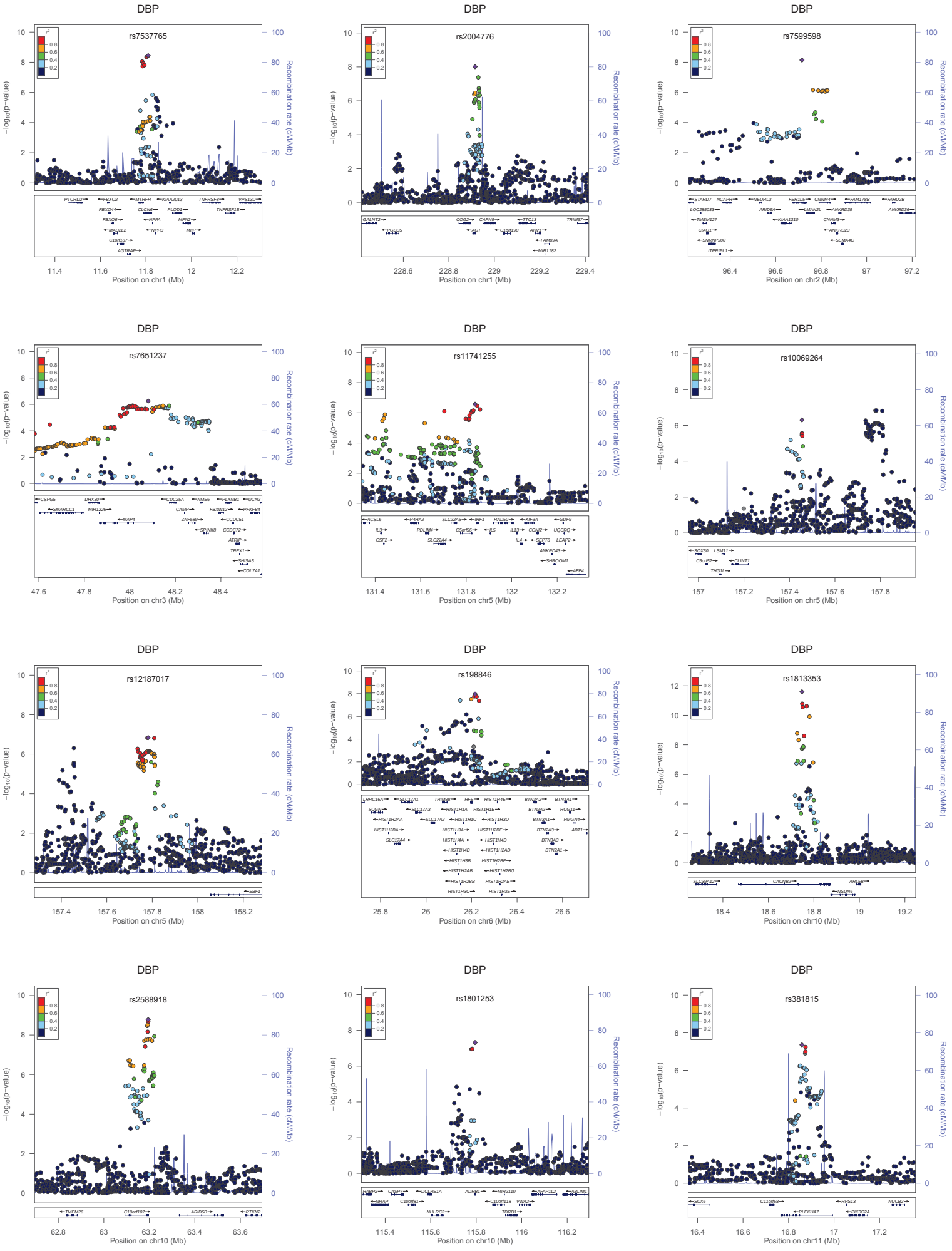

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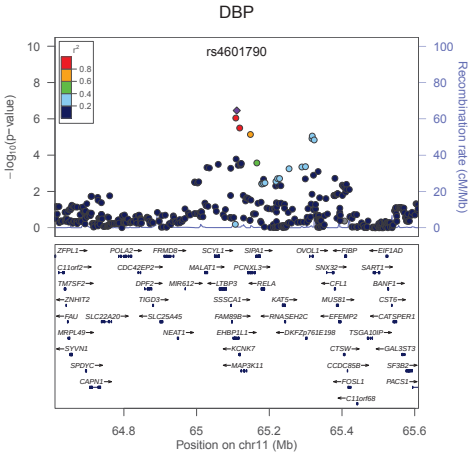

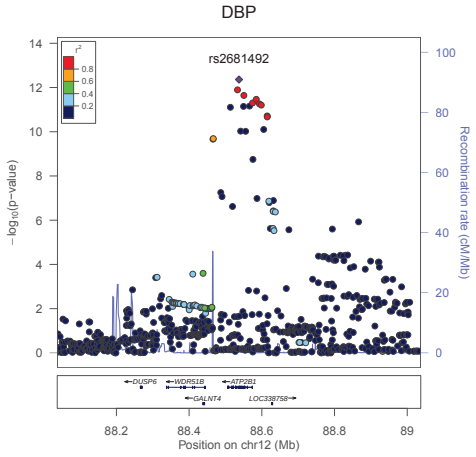

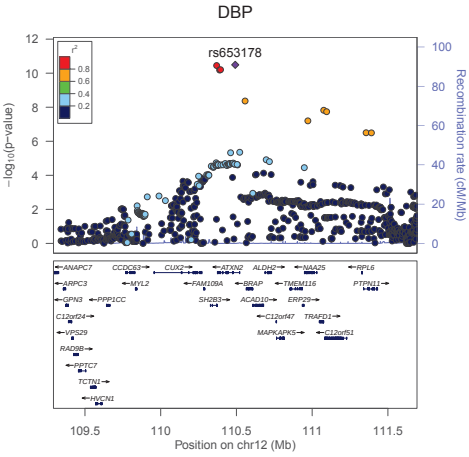

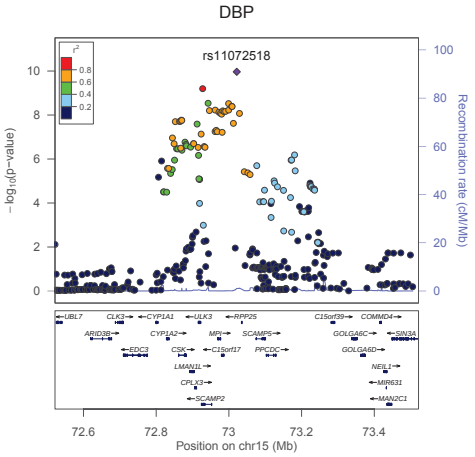

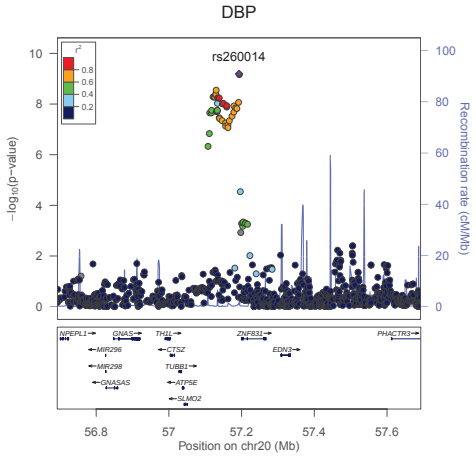

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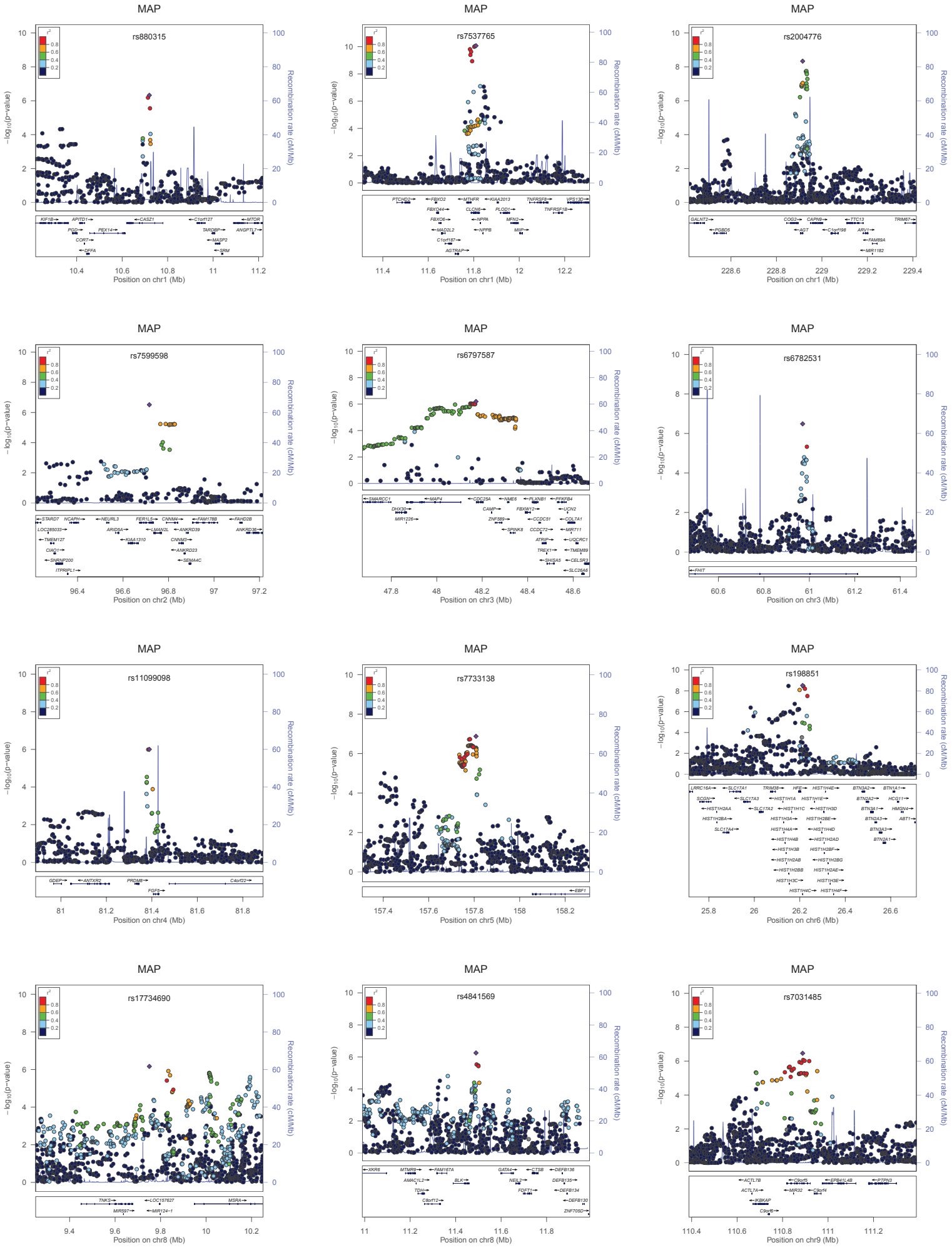

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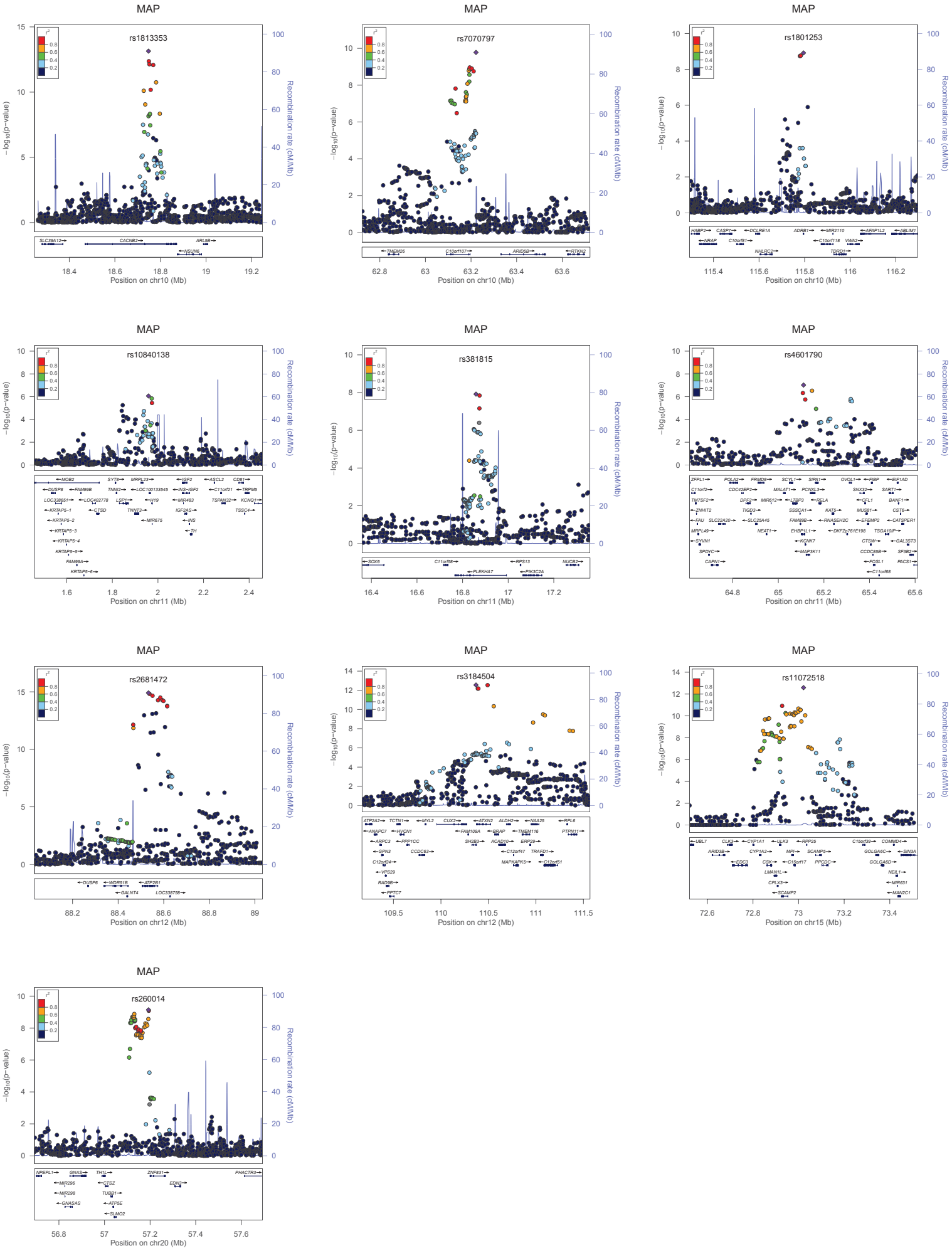

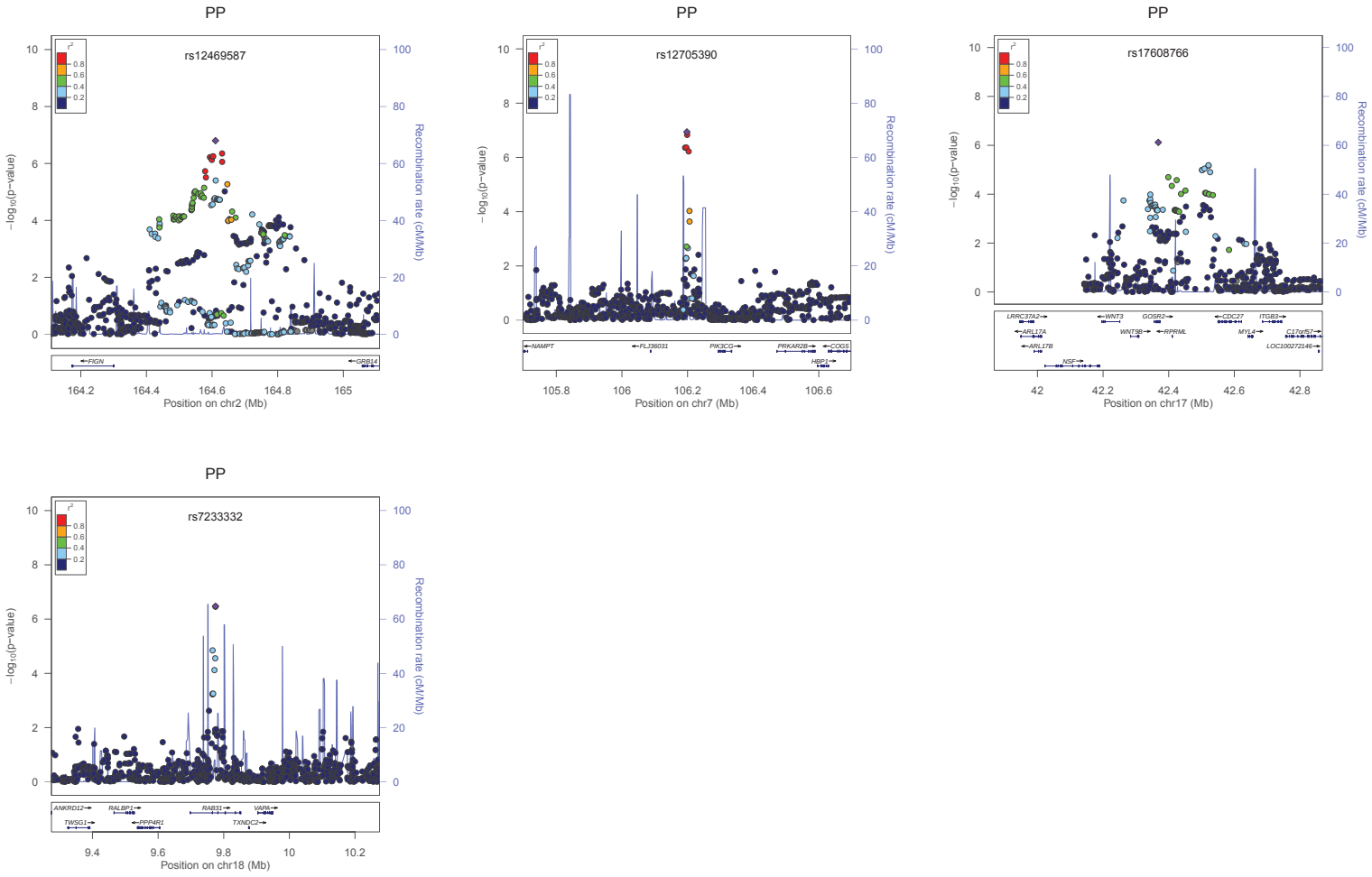

Figure S2: Regional Associations Plots for Suggestive and Significant Loci Identified by the Meta-Regression of Stage 1 Studies (Joint 2df tests of SNP Main Effects and SNP-age Interactions). Plots are presented by trait in ascending chromosome and basepair position.

STAGE 1 (CHARGE) STUDIES

Study Descriptions

The Age Gene/Environment Susceptibility-Reykjavik (AGES) 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 [1]. 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[2]. Individuals with previous MI were excluded from the analyses (N=12).

The Atherosclerosis Risk In Communities (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 aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities[3]. Cohort members completed four clinic examinations each spread over about three years, conducted approximately three years apart between 1987 and 1998. A detailed study protocol is available on the ARIC study website (http://www2.cscc.unc.edu/aric/). 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. For this study the sample was restricted to individuals of European descent by self-report and principal component analysis using genome-wide genotypes.

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a prospective multicenter study with 5,115 adults Caucasian and African American participants of the age group 18-30 years, recruited from four centers at the baseline examination 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[4]. Eight examinations have been completed since initiation of the study, respectively in the years 0, 2, 5, 7, 10, 15, 20 and 25. 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. Systolic and diastolic blood pressure was measured in triplicate on the right arm using a random-zero sphygmomanometer with the participant seated and following a 5-min. rest. The average of the second and third measurements was taken as the blood pressure value. Blood pressure medication use was obtained by questionnaire. Baseline data were used for this study. In addition, the sample was restricted to individuals of European descent by self-report and principal component analysis using genome-wide genotypes.

The 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. The original predominantly white cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists and an additional 687 African-Americans were enrolled in 1992-93 for a total sample of 5,888. Details of the study design are summarized elsewhere[5]. A total of 1,908 persons were excluded from the study sample due to prevalent coronary heart disease (N=1,195), congestive heart failure (N=86), peripheral vascular disease (N=93), valvular heart disease (N=20), stroke (N=166), or transient ischemic attack (N=56). Participants with missing BMI (N=10) or BP measurements (N=8) were also excluded. Research staff with central training in blood pressure measurement assessed repeated right-arm seated systolic and diastolic blood pressure levels at baseline with a Hawksley random-zero sphygmomanometer. Means of the repeated blood pressure measurements from the baseline examination of subjects of European ancestry were used for the analyses.

The 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 beginning in 2002. Details of study designs for the three cohorts are summarized elsewhere [6-8]. 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. To maximize the number of participants with age ranged from 20 to 80, we applied blood pressure measurements for the original cohort at the tenth examination, the second generation at the third examination, and the third generation at the first examination for GWAS. Individuals who had a myocardial infarction or congestive heart failure were excluded from the analyses because those conditions may affect blood pressure levels. We excluded participants with extreme values of systolic blood

pressures (greater or less than mean± 4 standard deviations) for the GWAS.

The Multi-Ethnic Study of Atherosclerosis (MESA) investigation is a population-based study of 6,814 men and women age 45 to 85 years, without clinical cardiovascular disease, recruited from six United States communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN). The main objective of MESA is to determine the characteristics of subclinical cardiovascular disease and its progression. Sampling and recruitment procedures have been previously described in detail [9]. Adults with symptoms or history of medical or surgical treatment for cardiovascular disease were excluded. During the recruitment process, potential participants were asked about their race/ethnicity. Self-reported ethnicity was used to classify participants into groups [10]. After a 5-minute rest BP was measured three times at 1 minute intervals using a Dinamap PRO 100 automated oscillometric device (Critikon, Tampa, FL) with the subject seated, and the average of the second and third BP measurements was used in the analysis. This analysis included only individuals of European descent.

The Rotterdam Study (RS-I) and Rotterdam Extension Study (RS-II) are prospective population-based cohort studies; the RS-I comprises 7,983 subjects aged 55 years or older. Participants completed an interview at home and at the research center, where participants were subsequently examined. Baseline data were collected between 1990 and 1993. In 1999, inhabitants who turned 55 years of age or moved into the study district since the start of the study were invited to participate in an extension of the RS (RS-II), 3,011 participated (67% response rate). The rationale and design of the RS have been described in detail elsewhere [11-13]. At the research center, two seated blood pressure measurements of the right brachial artery were obtained with a random zero sphygmomanometer. The mean of two consecutive measurements was used in association analyses. Participants who had a history myocardial infarction or congestive heart failure were excluded because of the impact of these conditions on blood pressure levels.

The Women's Genome Health Study (WGHS) is a prospective cohort of female North American health care professionals representing participants in the Women's Health Study (WHS) trial who provided a blood sample at baseline and consent for blood-based analyses [14]. 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. Baseline BP in the WGHS was ascertained by a self-reported questionnaire, an approach which has been validated in the WGHS demographic, namely female health care professionals[15-17]. Questionnaires recorded systolic blood pressure in 9 categories (<110, 110-119, 120-129, 130-

139, 140-149, 150-159, 160-169, 170-179, ≥180 mmHg), and diastolic blood pressure in 7 categories (<65, 65-74, 75-84, 85-89, 90-94, 95-104, ≥105 mmHg). We adjusted for antihypertensive medication use (SBP + 10 mmHg and DBP + 5 mmHg) when assigning WGHS participants to BP categories. The midpoint of each category was used for this analysis.

Table S1: Descriptive Statistics for the Stage 1 (CHARGE) Studies

Discovery Study	Age Bin	N	Median Age	Female (%)	HT (%)	BMI Mean (SD)	SBP Mean (SD)	DBP Mean (SD)	MAP Mean (SD)	PP Mean (SD)
AGES	[40,50)	1,260	45							
	[50,60)	1,603	54							
	[60,70)	265	62							
ARIC	[40,50)	2,392	47	56.9	17.2	26.8 (5.1)	112.8 (14.4)	71.3 (9.9)	85.1 (10.7)	41.5 (9.3)
	[50,60)	4,772	54	52.6	24.9	27.0 (4.8)	118.0 (16.1)	71.9 (9.8)	87.2 (10.9)	46.1 (11.7)
	[60,70)	2,142	62	48.8	35.3	27.0 (4.5)	125.0 (17.6)	71.1 (10.0)	89.1 (11.2)	53.9 (14.2)
CARDIA†	[17,32)	1,713	26	52.4	2.1	23.7 (3.8)	109.3 (10.9)	68.3 (9.0)	82.0 (8.6)	41.0 (9.0)
CHS	[60,70)	1,230	68	66.0	47.0	26.8 (4.8)	134.6 (20.6)	74.8 (12.4)	94.7 (13.7)	59.8 (15.7)
	[70,80)	1,672	73	59.5	55.0	26.1 (4.3)	139.8 (22.6)	73.8 (12.8)	95.8 (14.2)	66.1 (18.5)
FHS	[20,30)	533	26	52.2	0.9	25.3 (5.0)	112.9 (11.7)	71.6 (9.2)	85.4 (9.2)	41.4 (9.1)
	[30,40)	1,926	36	54.2	3.6	26.0 (5.1)	114.0 (12.5)	74.8 (9.6)	87.9 (10.0)	39.2 (7.8)
	[40,50)	2,608	44	53.6	9.2	26.8 (5.3)	119.6 (15.0)	77.9 (9.8)	91.8 (10.9)	41.8 (9.4)
	[50,60)	1,916	54	54.6	16.8	26.8 (4.8)	128.9 (18.0)	80.6 (10.1)	96.7 (12.0)	48.3(12.3)
	[60,70)	537	62	54.6	27.9	26.7 (4.3)	138.3 (20.1)	81.5 (10.1)	100.4(12.3)	56.9(14.9)
MESA	[40,50)	342	48	53.2	14.9	27.5 (5.6)	112.9 (15.8)	70.2 (10.3)	84.5 (11.6)	42.9 (9.7)
	[50,60)	708	55	52.8	28.3	28.2 (5.4)	119.9 (18.8)	71.9 (10.4)	87.9 (12.3)	47.8 (12.8)
	[60,70)	726	66	50.3	44.2	28.0 (5.0)	130.3 (21.0)	72.8 (10.3)	92.0 (12.5)	57.7 (16.5)
	[70,80)	563	75	50.8	53.6	27.0 (4.3)	136.5 (22.4)	71.3 (10.3)	93.0 (13.0)	65.3 (17.4)
RS I	[50,60)	910	58	58.5	35.6	25.9 (3.4)	129.3 (20.4)	75.0 (11.0)	93.0 (14.0)	56.0 (15.0)
	[60,70)	2,060	65	57.7	51.8	26.4 (3.6)	137.3 (20.8)	75.0 (12.0)	97.0 (14.0)	64.0 (17.0)
	[70,80)	1,419	74	62.8	65.8	26.3 (3.7)	144.9 (21.3)	75.0 (12.0)	99.0 (14.0)	73.0 (18.0)
RS II	[50,60)	740	58	54.9	50.7	27.4 (4.7)	137.8 (19.1)	90.0 (11.0)	100.0 (13.0)	59.0 (14.0)
	[60,70)	851	63	53.8	58.4	27.3 (4.0)	142.0 (20.1)	81.0 (11.0)	102.0 (13.0)	64.0 (17.0)
	[70,80)	321	75	58.9	78.5	26.9 (3.6)	152.1 (21.7)	79.0 (11.0)	104.0 (14.0)	76.0 (18.0)
WGHS	[40,50)	7,219	47	100.0	15.5	25.9 (5.3)	120.5 (12.9)	75.4 (9.5)	90.5 (10.0)	45.1 (8.5)
	[50,60)	10,386	53	100.0	24.2	26.0 (4.9)	124.6 (15.0)	77.5 (9.7)	93.2 (10.8)	46.9 (9.6)
	[60,70)	4,271	63	100.0	37.2	25.8 (4.6)	131.0 (16.5)	79.6 (9.6)	96.7 (11.0)	51.3 (11.6)
	[70,80)	711	72	100.0	45.7	24.9 (3.9)	135.0 (16.4)	79.6 (9.1)	98.1 (10.4)	55.4 (12.9)

† Except for N and the median age, the descriptive statistics for CARDIA were derived on those 20 to 30 years old.

Table S2: Genotyping, Imputation, and Analysis Software Information for the Stage 1 (CHARGE) Studies

Discovery Study	Genotyping Platform	NCBI human genome reference used	Imputation Procedure	Pre-Imputation QC filter information	Pre-Association Filters (sample or SNP)	Association Analysis Software
AGES	Illumina 370 CNV	NCBI36/HapMap22	MACH			R & ProbABEL
ARIC	Affymetrix 6.0		MACH			
CARDIA	Affymetrix 6.0	Build 36	BEAGLE with reference HapMap2, release 22	Sample: Call rate ≥ 98%; duplicate samples, gender mismatch; outlier in PCA. SNP: MAF ≥ 2%; SNP call rate ≥ 95%; HWE ≥ 10^{-4}	Imputation quality R^2>0.3; MAF≥ 1%	ProbABEL
CHS	Illumina 370 CNV	Build 36, release 22	BIMBAM, single imputation of posterior mean genotype (dosage); CEPH Build 36 reference haplotypes; Build 36 positions.	Samples were excluded from analysis for: sex mismatch, discordance with prior genotyping, or call rate < 95%. SNPS: the following exclusions were applied to identify a final set of 306,655 autosomal SNPs: call rate < 97%, HWE P < 10^{-5}, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap.	Variance of imputed SNP dosage < 0.01	R
FHS	Affymetrix 500k and MIPS 50K combined	36.2	MACH	Call-rate ≥97%, HWE p≤ 10^{-6}, Mishap p < 1e-9	Call-rate ≥97%, subject heterozygosity ≤ 5 SD from the mean	R statistics, LMEKIN. the linear mixed model for GWAS
MESA	Affymetrix 6.0	36.3	HapMap1+2 IMPUTE2	Not Applicable	HWE>=≥1E-6 MAF>=0.01	SNPTEST v 2.1.1
RS I & RS II	Illumina 550 K	36	MACH, Hapmap r22 (build 36)			ProbABEL
WGHS	Illumina Human-Hap300 Duo-plus BeadChip platform	36	Imputation used HapMap2 CEU r.22 reference panel with MaCH v. 1.0.16	HWE p-value < 10^{-6}	None	ProbABEL

Table S3: Genomic Inflation Factors of the GWAS Results from Each Stage 1 (CHARGE) Study and Age Bin

Study	Age Bin	SBP		DBP		MAP		PP	
		# SNPs after QC filtering	Genomic Inflation Factor	# SNPs after QC filtering	Genomic Inflation Factor	# SNPs after QC filtering	Genomic Inflation Factor	# SNPs after QC filtering	Genomic Inflation Factor
AGES	3	2,367,558	1.003	2,367,573	1.005	2,367,573	1.004	2,367,573	1.002
	4	2,391,184	1.055	2,391,199	1.044	2,391,199	1.052	2,391,199	1.049
	5	1,973,973	1.012	1,973,977	1.023	1,973,977	1.018	1,973,977	1.003
ARIC	3	2,458,877	1.020	2,458,877	1.011	2,458,877	1.010	2,458,877	1.023
	4	2,481,308	1.024	2,481,308	1.028	2,481,308	1.030	2,481,308	1.011
	5	2,453,141	1.022	2,453,141	1.010	2,453,141	1.026	2,453,141	1.018
CARDIA	1	2,272,313	1.017	2,272,244	1.001	2,272,244	1.001	2,272,244	1.014
CHS	5	2,186,656	1.024	2,186,085	1.021	2,186,085	1.021	2,186,085	1.023
	6	2,190,440	1.015	2,189,859	1.027	2,189,859	1.024	2,189,859	1.013
FHS	1	2,135,392	1.040	2,224,899	1.038	2,224,373	1.036	2,224,899	1.015
	2	2,333,148	1.035	2,405,991	1.017	2,406,012	1.025	2,406,012	1.019
	3	2,352,606	1.027	2,421,561	1.013	2,421,543	1.018	2,421,487	1.023
	4	2,377,100	1.020	2,405,583	1.007	2,405,662	1.014	2,405,428	1.022
	5	2,192,250	1.049	2,226,881	1.049	2,226,881	1.057	2,221,888	1.046
MESA	3	*2,210,077	1.008	2,190,470	1.010	2,190,470	1.011	2,190,470	1.012
	4	*2,428,339	0.997	2,401,091	1.010	2,401,091	1.007	2,401,091	0.977
	5	*2,431,813	1.012	2,403,807	0.993	2,403,807	1.001	2,403,807	1.008
	6	*2,376,153	1.013	2,351,180	0.997	2,351,180	1.004	2,351,180	1.011
RS I	4	2,361,278	1.010	2,361,278	1.005	2,361,278	1.009	2,361,278	1.004
	5	2,449,265	1.005	2,449,265	1.018	2,449,265	1.011	2,449,265	1.012
	6	2,418,155	1.008	2,418,155	1.000	2,418,155	1.001	2,418,155	0.997
RS II	4	2,322,498	1.000	2,322,498	1.004	2,322,498	1.000	2,322,498	1.000
	5	2,349,165	1.002	2,349,165	1.003	2,349,165	1.001	2,349,165	1.000
	6	2,077,844	1.004	2,077,844	1.014	2,077,844	1.012	2,077,844	0.998
WGHS	3	2,477,551	1.045	2,477,551	1.029	2,477,551	1.040	2,477,551	1.031
	4	2,481,199	1.047	2,481,199	1.038	2,481,199	1.051	2,481,159	1.019
	5	2,468,197	1.017	2,468,197	1.009	2,468,197	1.010	2,468,142	1.015

	6	2,308,858	1.006	2,308,858	1.013	2,308,858	1.010	2,308,858	1.001

* Some SNPs in the MESA datasets were exclusive to that cohort and did not match back to our HapMap legend file.
For SBP in MESA: We analyzed 2,117,061 SNPs in age bin 3; 2,327,960 in age bin 4; 2,331,257 in age bin 5; and 2,277,690 in age bin 6
For DBP, MAP, and PP in MESA: We analyzed 2,097,712 in age bin 3; 2,301,058 in age bin 4; 2,303,611 in age bin 5; 2,253,038 in age bin 6

STAGE 2 STUDIES

Study Descriptions

The Busselton Health Study (BHS) includes a series of seven cross sectional population health surveys of adult residents of the Shire of Busselton in the South-West of Western Australia, undertaken between 1966 and 1995. A cross-sectional community follow-up study in 1994-1995 included the collection of blood for DNA extraction for all survivors of previous surveys. A total of 4,554 individuals participated in this follow-up. BP was measured in the 1994-1995 follow-up study using a standard mercury sphygmomanometer (Baumanometer, New York) as described previously[18]. The participants were asked to refrain from caffeine for 12 hours and to not smoke prior to attending the survey. Three BP readings were recorded on the participant's survey chart to the nearest 2 mmHg and the average of the readings was used for the analyses.

The Cohorte Lausannoise (CoLaus) is a population-based study aimed at assessing the prevalence and molecular determinants of cardiovascular risk factors in the population of Lausanne, Switzerland[19]. Participants in the study (4,969) were randomly selected from the population register of Lausanne in 2003 (N=56,694, aged 35-75 years). All individuals were of European origin, defined as having both parents and grandparents born in a defined list of European countries. Blood pressure was measured using the Omron HEM-907 machine, in the seated position. Three measures were taken on the left arm; the mean of the last two measures was used in the analyses.

The European Prospective Investigation of Cancer (EPIC-Norfolk) is a population-based cohort study of Europid men and women aged 39-79 years recruited in Norfolk, UK between 1993 and 1997[20]. Blood pressure was measured using the Accutorr oscillometric BP machine; the mean of two readings was taken and used in the analysis. This analysis was performed based on the subcohort sample of the EPIC-Norfolk case-cohort design (N=2,417) of which 2,411 had information on blood pressure and 2,408 had passed quality control (QC).The study design and more detailed information is available from Loos et al.[21].

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

the study comprises more than 3,000 participants; volunteers with complete anthropometric data were genotyped and included in the current analyses. All participants were measured at the MRC Epidemiology Unit Clinical Research Facilities in Ely, Wisbech and Cambridge. Blood pressure measurements were taken with an Accutorr automated sphygmomanometer using the average of three measurements made at one-minute intervals with the participant seated for 5 minutes prior to measurement. Of the 1,500 individuals that were genotyped 98 individuals were excluded as their genotyping data did not meet the quality control criteria applied. In total, 1,399 individuals were included in the genome-wide association analyses.

The Kooperative Gesundheitsforschung in der Region Augsburg Third Survey (KORA S3) is an epidemiological cohort recruited from the general population of Augsburg, Germany in 1994-1995[22; 23]. A subset of this survey (1,644 subjects), were genotyped using the Affymetrix 500K array (http://epi.helmholtz-muenchen.de/kora-gen/). In this study subjects with BMI<35 kg/m2 were included; diabetics were excluded. Blood pressure was measured using a random zero sphygmomanometer in the seated position at the first examination cycle. Three measurements were taken at least three minutes apart and the numbers entering the database were the mean of the last two measurements.

The LifeLines Cohort Study [24] 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. In the first visit to the LifeLines' study center, trained technicians measure subjects' systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse rate, every minute for a period of 10 minutes using a DINAMAP Monitor i.e. 10 measures for each of the indices.

The Myocardial Infarction Genetics Consortium (MIGen) cohort is composed of a subset of the controls of a case-control study aimed at identifying genetic variants associated with early-onset myocardial infarction. Most of the controls are selected from population

based cross-sectional or cohort studies and come from five different studies: Heart Attack Risk in Puget Sound (Seattle, USA), REGICOR (Girona, Spain), MGH Premature Coronary Artery Disease Study (Boston, USA), FINRISK (Finland); Malmö Diet and Cancer Study (Malmö, Sweden). There is a minimal overlap of samples between the resources (N=30). For the majority of studies, blood pressure was measured twice using calibrated sphygmomanometers, in the seated position after at least 5 minutes of rest; the mean of the two measurements was used in the analysis. The first two principal components from an identical by state (IBS) analysis were used to adjust for potential population stratification.

The Netherlands Study of Depression and Anxiety (NESDA)[25], is a multi-center study designed to examine the long-term course and consequences of depressive and anxiety disorders (http://www.nesda.nl). NESDA included both individuals with depressive and/or anxiety disorders and controls without psychiatric conditions. Inclusion criteria were age 18-65 years and self-reported western European ancestry 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). For all participants DNA was isolated from the baseline blood sample. Through funding from the fNIH GAIN program (www.fnih.gov/gain), whole genome scan analysis was conducted for 1859 NESDA (1702 depressed cases and 157 controls) participants. A hundred subjects were excluded because of various quality control issues [26]. Additional exclusions were made based on disease history, phenotype availability and medication use (e.g., all subjects using antidepressants other than SSRIs were excluded) [27]. Systolic blood pressure and diastolic blood pressure were measured twice using an OMRON IntelliSense Professional Digital Blood Pressure Monitor, HEM-907XL (Omron Healthcare, Inc., Bannockburn, Illinois) during supine rest on the right arm, and were averaged over the two measurements [27].

The Prevention of Renal and Vascular End Stage Disease (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 [28; 29]. 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 (www.prevend.org). Blood pressure was measured in the supine position every minute for 10 and 8 minutes, respectively, with an automatic Dinamap XL Model 9300 series monitor (Critikon, Tampa, Florida). Systolic and diastolic blood pressures were calculated as the mean of the last two measurements at the two visits.

The Precocious Coronary Artery Disease study (PROCARDIS) (www.procardis.org) is a European consortium investigating the genetics of precocious coronary artery disease (CAD) in

German, Italian, Swedish, and British CAD patients and controls [30]. Country of origin was a covariate in all analyses. The CAD cases (N= 5,480) and controls (N= 1,570) were included in this study; the controls had no personal history of CAD, hypertension, or diabetes. Blood pressure was measured twice using various sphygmomanometers, in the seated position after at least 5 minutes of rest; the mean of the two measurements was used.

The SardiNIA study is a longitudinal study examining age-related quantitative traits in individuals from the Ogliastra region of Sardinia, Italy[31]. Genotype data was available for 4,305 related individuals (age >14 years). Blood pressure was measured using a mercury sphygmomanometer; the average of the second and third reading was used for the analyses. Due to the family-based nature of the SardiNIA study, this analysis allowed each family to appear in only one age bin; the selection of individuals maximized the sample size while trying to achieve 250 individuals in each age bin.

The Study of Health In Pomerania (SHIP) is a population-based survey in West Pomerania, the northeast area of Germany [32]. A sample from the adult population aged 20 to 79 years was drawn based on population registries of cities and towns in the region. SHIP finally comprised 4,308 participants (corresponding to a final response rate of 68.8%). Blood pressure was measured three times in a seated position using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan). The initial reading occurred after 5 minutes of rest, with 3 minutes between sequential measurements. The mean of the second and third measurements was used in the analyses.

The Supplementation en Vitamines et Mineraux Antioxydants study (SUVIMAX) is a longitudinal study performed on a national sample of healthy volunteers from France between 1996 and 2001. 1,673 individuals, aged 35-65 years at baseline were included in this analysis [33]. Blood pressure was measured using a mercury sphygmomanometer in the seated position; the average of three readings taken from the first examination (1996) was used in the analysis.

TRacking Adolescents' Individual Lives Survey (TRAILS) is a prospective cohort study of Dutch adolescents with bi- or triennial measurements from age 11 to at least age 25 and consists of a general population and a clinical cohort (for a cohort profile see [34]). In the population cohort, four assessment waves have been completed to date, which ran from March 2001 to July 2002 (T1), September 2003 to December 2004 (T2), September 2005 to August 2007 (T3), and October 2008 to September 2010 (T4). Data for the present study were collected during the third assessment wave. At T1, 2230 (pre)adolescents were enrolled in the study (response rate 76.0%, mean age 11.09, SD 0.55, 50.8% girls [35], of whom 81.4% (N = 1816, mean age 16.27, SD 0.73, 52.3% girls) participated at T3. The TRAILS Clinical Cohort runs in parallel with the TRAILS

general population cohort. The clinical cohort consists of 543 children of initially 10–12 years of age (mean age 10.89 years) who have been referred to one child psychiatric outpatient clinic in the Northern Netherlands at any point in their life. Systolic and diastolic blood pressure were measured in duplicate with a Dinamap Critikon 1846SX (Critikon Inc, Tampa, FL), from which we calculated means. Blood samples were obtained after at least 8 hours of fasting. Genome-wide genotyping was done with the Illumina Cyto SNP12 v2 array. This data was imputed using IMPUTE2 and association analysis was performed with SNPTEST v2.2.0.

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

Table S4: Descriptive Statistics for the Stage 2 Studies

Stage 2 Study	Age Bin	N	Median Age	Female (%)	HT (%)	BMI Mean (SD)	SBP Mean (SD)	DBP Mean (SD)	MAP Mean (SD)	PP Mean (SD)
BHS	[20,40)	276	34	60.1	2.9	25.0 (3.7)	115.6 (11.8)	71.6 (9.4)	86.3 (8.9)	44.0 (10.4)
	[40,50)	223	45	58.7	6.7	25.9 (4.1)	117.8 (14.4)	75.6 (10.4)	89.7 (11.2)	42.2 (8.8)
	[50,60)	225	55	51.1	14.7	26.7 (4.5)	125.9 (15.7)	79.1 (10.1)	94.7 (11.2)	46.7 (10.7)
	[60,70)	207	65	61.4	36.2	26.8 (4.0)	135.3 (17.8)	79.0 (9.4)	97.8 (10.8)	56.3 (14.8)
	[70,80)	204	74	55.4	50.0	26.2 (3.9)	145.3 (18.9)	77.8 (10.7)	100.3 (11.8)	67.5 (16.0)
CoLaus	[30,40)	534	37	50.4	2.4	24.9 (4.1)	118.5 (12.4)	75.6 (9.6)	95.7 (12.1)	49.0 (12.2)
	[40,50)	1,437	45	49.8	6.4	25.0 (4.3)	122.1 (15.0)	78.0 (10.4)	92.5 (11.1)	43.7 (8.1)
	[50,60)	1,334	55	55.5	16.4	26.0 (4.8)	130.0 (17.8)	81.1 (11.0)	96.0 (12.2)	49.2 (12.3)
	[60,70)	1,195	64	54.8	32.3	26.8 (4.6)	139.9 (19.6)	81.4 (10.6)	96.2 (12.3)	49.4 (12.3)
	[70, 80)	443	73	56.3	38.7	26.7 (4.4)	145.5 (19.6)	78.1 (10.9)	95.9 (12.2)	49.2 (12.3)
EPIC	[40,50)	442	47	56.3	5.7	25.4 (4.0)	127.4 (14.1)	80.1 (10.6)	95.9 (11.4)	47.4 (6.9)
	[50,60)	775	55	56.3	10.1	26.1 (3.8)	132.5 (17.0)	81.9 (10.8)	98.8 (12.4)	50.5 (9.6)
	[60,70)	819	65	49.8	19.1	26.9 (3.7)	143.1 (18.4)	85.6 (11.1)	104.7 (13.0)	57.5 (11.1)
	[70, 80)	371	72	50.1	24.3	26.8 (3.9)	147.8 (18.5)	86.4 (11.3)	106.9 (13.0)	61.4 (11.5)
Fenland	[30,40)	388	36	50.0	8.0	26.3 (4.7)	117.7 (13.0)	72.5 (9.4)	87.6 (9.9)	45.2 (8.7)
	[40,50)	607	45	58.2	16.6	27.4 (5.0)	121.9 (15.0)	75.5 (10.2)	91.0 (11.3)	46.4 (8.7)
	[50,60)	404	54	59.4	31.9	27.4 (4.8)	127.8 (17.7)	77.4 (10.9)	94.2 (12.6)	50.4 (10.5)
KORA S3	[40,50)	191	46	49.7	32.5	26.5 (4.5)	126.9 (18.7)	82.5 (10.8)	97.3 (12.8)	44.4 (11.5)
	[50,60)	984	55	51.3	45.0	27.7 (4.1)	134.9 (19.3)	84.3 (11.1)	101.2 (13.1)	50.5 (12.6)
	[60,70)	419	64	47.7	60.9	28.4 (3.9)	144.4 (20.6)	83.4 (11.4)	103.8 (13.1)	61.0 (15.8)
LifeLines	[20,30)	393	27	58.5	10.7	24.3 (3.8)	124.2 (12.2)	70.5 (6.5)	88.4 (7.4)	53.7 (10.2)
	[30,40)	1,576	36	57.1	14.2	25.7 (4.6)	123.7 (12.8)	72.9 (7.9)	89.8 (9.1)	50.8 (10.2)
	[40,50)	3,039	45	58.6	24.7	26.1 (4.4)	126.9 (16.2)	75.8 (10.0)	92.7 (11.6)	50.9 (11.1)
	[50,60)	1,893	51	56.0	37.3	26.7 (4.2)	131.2 (17.1)	77.8 (10.0)	95.5 (11.9)	53.5 (11.9)
	[60,70)	899	64	55.1	58.6	27.3 (3.9)	138.3 (20.8)	78.2 (10.1)	97.8 (13.9)	60.1 (14.8)
	[70,80)	288	72	54.5	75.3	27.8 (3.9)	145.2 (20.8)	78.5 (9.2)	100.0 (14.2)	65.4 (17.1)
MIGen	[30,40)	124	36	23.4	16.1	25.8 (4.5)	119.1 (14.4)	74.9 (9.7)	89.6 (10.4)	44.1 (10.6)
	[40,50)	527	45	26.9	20.1	26.7 (4.5)	123.9 (15.6)	79.7 (10.7)	94.4 (11.5)	44.3 (10.5)
	[50,60)	391	54	62.1	30.2	27.8 (5.4)	132.2 (19.8)	82.7 (11.9)	99.2 (13.6)	49.5 (13.6)
	[60,80)	154	64	29.9	46.1	28.0 (4.1)	141.0 (21.8)	82.7 (11.5)	102.1 (13.9)	58.3 (15.4)

NESDA	[20,30)	340	25	76.5	0.9	23.6 (4.4)	126.5 (13.0)	74.9 (7.9)	92.1 (8.5)	51.6 (10.6)
	[30,40)	361	35	72.9	3.3	25.1 (5.1)	126.6 (13.6)	77.6 (9.1)	94.0 (9.7)	49.1 (9.4)
	[40,50)	424	44	64.9	9.7	26.0 (5.0)	133.4 (17.1)	82.2 (10.5)	99.3 (12.0)	51.1 (11.2)
	[50, 60)	422	54	61.6	27.0	26.7 (4.7)	144.1 (21.3)	86.4 (11.3)	105.6 (13.8)	57.6 (13.8)
PREVEND	[30,40)	853	34	55.2	8.3	24.5 (4.0)	119.4 (14.0)	64.4 (8.0)	85.4 (9.2)	50.9 (9.9)
	[40,50)	980	45	50.4	16.8	25.8 (4.3)	124.4 (17.2)	73.7 (9.9)	90.6 (11.9)	50.8 (10.4)
	[50,60)	820	54	48.6	32.1	27.0 (4.2)	133.2 (20.8)	78.6 (10.8)	96.7 (13.3)	54.5 (13.6)
	[60,70)	650	64	42.0	52.0	27.5 (4.0)	146.5 (22.4)	82.1 (10.7)	103.6 (13.8)	64.1 (15.4)
PROCARDIS	[40,50)	649	47	20.6	*	27.8 (4.9)	131.5 (16.7)	84.7 (10.4)	100.3 (11.6)	46.8 (11.7)
	[50,60)	2,399	56	24.3	*	28.3 (4.6)	137.6 (18.4)	85.3 (10.6)	102.8 (12.2)	52.2 (13.4)
	[60,70)	3,362	65	29.3	*	27.9 (4.3)	144.3 (20.8)	83.5 (10.8)	103.8 (12.7)	60.9 (16.5)
	[70,80)	640	72	30.8	*	27.9 (4.3)	148.5 (22.1)	81.8 (11.8)	104.0 (13.7)	66.7 (17.4)
SardiNIA	[20,40)	287	30	59.2	0.7	23.2 (3.6)	117.0 (12.0)	72.0 (8.0)	87.0 (9.0)	45.0 (10.0)
	[40,50)	232	45	63.3	3.9	25.8 (4.3)	126.0 (16.0)	81.0 (10.0)	96.0 (11.0)	45.0 (12.0)
	[50,60)	268	54	49.6	21.6	28.0 (4.0)	138.0 (19.0)	86.0 (11.0)	103.0 (13.0)	53.0 (13.0)
	[60,70)	257	64	49.0	30.0	28.9 (4.3)	142.0 (17.0)	85.0 (10.0)	104.0 (11.0)	57.0 (13.0)
	[70,80)	204	74	51.0	46.1	28.5 (4.6)	151.0 (20.0)	85.0 (11.0)	107.0 (12.0)	66.0 (17.0)
SHIP	[20,30)	550	25	54.5	19.5	24.3 (4.3)	121.9 (14.4)	75.7 (8.4)	91.1 (9.6)	46.2 (10.4)
	[30,40)	729	35	53.4	24.8	25.7 (4.3)	125.9 (17.1)	81.3 (10.4)	96.2 (12.1)	44.5 (10.3)
	[40,50)	726	45	53.2	38.0	27.7 (4.8)	135.4 (20.8)	87.1 (11.9)	103.2 (14.4)	48.3 (11.7)
	[50,60)	760	55	52.5	44.7	28.4 (4.8)	142.5 (21.3)	88.8 (11.5)	106.7 (14.1)	53.8 (13.6)
	[60,70)	733	64	46.1	53.2	28.8 (4.5)	148.9 (21.3)	87.2 (10.7)	107.8 (13.2)	61.7 (15.6)
	[70,80)	560	74	44.5	58.0	28.5 (4.2)	154.6 (22.4)	85.0 (12.5)	108.2 (14.5)	69.6 (16.7)
SUVIMAX	[35, 50)	819	46	74.6	11.6	22.8 (3.1)	117.5 (11.1)	76.0 (7.8)	89.8 (8.4)	41.5 (6.8)
	[50,65)	854	55	47.1	26.1	24.3 (3.3)	124.4 (12.6)	80.0 (7.9)	94.8 (8.9)	44.3 (8.0)
TRAILS: clinical Cohort	<20	266	16	30.0	0.0	21.6 (3.6)	119.2 (12.6)	61.0 (6.6)	80.4 (7.3)	58.2 (11.4)
TRAILS: population cohort	<20	1,290	16	52.0	0.0	21.3 (3.2)	118.1 (12.4)	61.1 (6.9)	80.1 (7.4)	57.0 (11.1)
YFS	[30,40)	1,562	36	53.7	5.4	25.8 (4.8)	120.0 (13.9)	74.7 (11.3)	89.8 (11.5)	45.3 (8.9)
	[40,50)	686	42	54.2	13.3	26.4 (4.6)	124.3 (15.7)	78.6 (11.7)	93.8 (12.4)	45.7 (9.3)

* The PROCARDIS study was a case-control study of coronary artery disease; the % of cases in age bins 3 through 6 were 56.7%, 74.3%, 81.8%, and 90.6%, respectively.

Table S5: Genotyping, Imputation, and Association Analysis Information for the Stage 2 Studies

Stage 2 Study	Genotyping Platform	NCBI human genome reference used	Imputation Procedure	Pre-Imputation QC filter information	Pre-Association Filters (sample or SNP)	Association Analysis Software
BHS	Illumina 610K Chip	36	MACH v1.0.16.b with reference HapMap II CEU v22, Build 36	Hardy-weinberg eqilibrium(HWE) p-value: 1E-07, SNP callrate: 0.95, Sample callrate: 0.97, MAF:0.01, IBD>0.1875 removed, Ethnic outliers and gender mismatches removed		Mach2qtl V1.0.8
CoLaus	Affymetrix 500K	35v21	MACH	HWE p-values:1E-7, SNP Callrate: 0.9, MAF:0.01		In house Matlab script
EPIC	Affymetrix 500K	35	IMPUTE v0.3.1	HWE p-values:1E-6, SNP Callrate: 0.9, MAF:0.01		SNPTEST v1.1.5
Fenland	Affymetrix GeneChip Human Mapping 500K Array Set	36.2	IMPUTE v2.1.2	Sample callrate: 0.95; Heterozygosity between 27.3% and 28.8%; Duplicate Check, Relatedness Check, SNP callrate: 0.90, HWE p-value: 1E-06, MAF: 0.01		SNPTEST v1.1.5
KORA S3	Affymetrix 500k platform	36.1	MACH1 with HapMap release 22	MAF: 0.0008, HWE p-value: 1E-5, SNP callrate:0.9		ProbABEL 0.1-9e
LifeLines	Illumina Cyto SNP12 v2	HapMap II build 36, release 24	Beagle	SNP callrate: 0.95, MAF: 0.01, HWE p-value:1E-4, Sample callrate: 0.95, unrelatedness (pi-hat<0.4), gender match, caucasians	Analyze SNPs with MAF>0	PLINK
MIGen	Affymetrix 6.0 GeneChip	35	MACH 1.0	SNP call rate: 0.95, sample call rate 0.95; HWE p-value:1E-6; MAF: 0.01; SNPs with CHI-MISSING p < 1e-3		ProbABEL v0.0-6
NESDA	Perlegen 600k chip (N=1,747) and the Affymetrix 6.0 array (N=100)	36 release 23	IMPUTE v2	SNP call rate: 0.95, MAF: 0.01, not mapped, HWE p-value: 1E-6, strand ambiguities, high concordance between genotyping platforms or between positive controls, random genotypic failure, <5% Mendelian errors, samples callrate: 0.95, unrelatedness, gender match, caucasians	None	SNPTEST v2
PREVEND	Illumina CytoSNP12 v2	37	Beagle	Sample callrate 0.95, Relatedness >0.1, Ethnic outliers Z-score > 3 for first 5 PCA, MAF: 0.01, HWE p-value: 1E-03, SNP Callrate 0.9	plink filters on INFO <0.1, MAF <0.01	PLINK 1.07
PROCARDIS	Illumina Infinium BeadChips (1M and HumanHap	36	MACH with reference HapMap2 release 22	SNP callrate: 0.955, sample callrate: 0.955, HWE p-value: 1E-6, Non-European ancestry dropped, Duplicates dropped	Exclude SNPs with MAF<5% and MACH	Stata accounting for clustering in covariance due to sibships

Stage 2 Study	Genotyping Platform	NCBI human genome reference used	Imputation Procedure	Pre-Imputation QC filter information	Pre-Association Filters (sample or SNP)	Association Analysis Software
	610)				R^2 <0.3	
SardiNIA	Combination of Affymetrix 10K, 500K, 6.0 chip	36	MACH 1.0 with reference HapMap CEU v22	Sample callrate: 0.95, SNP callrate>0.90 for 10K and 500K chips, SNP callrate>0.95 for 6.0 chip, HWE p-value: 1E-06, MAF>0.05 for 10K and 500K chips, MAF>0.01 for Affymetrix 6.0 chip		MERLIN
SHIP	Affymetrix 6.0	36.1 36 (dbSNP 126)	IMPUTE v0.5.0 with reference HapMap II CEU v22, Build 36	Excluded arrays with call rates < 86%; Final, Duplicate samples (by IBD), gender mismatch		QUICKTEST v0.95
SUVIMAX	Illumina HumanHap 317	35 CEU release 21	IMPUTE v0.3.2	Samples call rate: 0.94, SNP call rate: 0.97, HWE p-value: 1E-7		QUICKTEST
TRAILS	Illumina Cyto SNP12 v2	Data were imputed using HapMap II build 36, release 22	IMPUTE v2	SNPs callrate: 0.95, MAF: 0.01, HWE p-value:1E-4, chr X >1%, heterozygous in men, samples callrate: 0.95, heterozygosity <4SD from mean, non-duplicates, gender match, caucasians	None	SNPTEST v2
YFS	Illumina 670k custom	36.3 dbSNP 126	MACH 1.0 with reference HapMap II CEU v22	HWE p-value: 1E-06, Sample callrate: 0.95, SNP callrate: 0.95, MAF: 0.01		ProbABEL v. 0.1-3

SINGAPORE STUDIES

Study Descriptions

The 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 Disease (SEED). Age stratified random sampling was used to select 6,350 eligible participants, of which 3,300 participated in the study (73% response rate). Detailed methodology has been published [36]**.** 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.

The 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[37; 38]. SiMES is part of the Singapore Epidemiology of Eye Disease (SEED) study. In summary, 5600 individuals have been selected by an age-stratified sampling strategy. Among these 4168 individuals are eligible for this study. 3280 individuals finally participated in the study. All subjects were Malay and aged 40-80 years. 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.

The 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 Disease (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 [36]. 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.

The Singapore Prospective Study Program (SP2) is a population-based study of diabetes and cardiovascular disease in Singapore that has been described previously [39]. Eligible subjects included 10,633 Chinese, Malay, and Indian subjects from four cross-sectional studies that were conducted in Singapore between 1984 and 1998.

Subjects were aged 18-69 at baseline and represented a random sample of the Singapore population. Subjects were re-visited between 2003 and 2007. Data from this re-visit were utilized for this study. 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.

Table S6: Descriptive Statistics for the Singapore Studies

Singapore Study	Age Bin	N	Median Age	Female (%)	HT (%)	BMI Mean (SD)	SBP Mean (SD)	DBP Mean (SD)	MAP Mean (SD)	PP Mean (SD)
SCES	[40,50)	470	47	49.8	14.7	23.8 (3.7)	130.1 (17.5)	79.4 (10.8)	96.3 (12.3)	50.7 (11.6)
	[50,60)	633	55	52.3	26.7	23.8 (3.4)	137.1 (18.6)	80.8 (10.1)	99.6 (12.0)	56.3 (13.4)
	[60,70)	497	63	46.9	46.7	23.7 (3.4)	146.9 (18.6)	81.7 (9.4)	103.4 (11.2)	65.2 (14.7)
	[70,80)	249	73	39.8	59.8	23.8 (3.5)	155.9 (19.3)	80.5 (8.1)	105.6 (10.3)	75.4 (16.6)
SiMES	[40,50)	590	45	52.2	41.4	26.4 (5.4)	134.9 (19.8)	79.7 (11.2)	98.1 (13.3)	55.2 (13.2)
	[50,60)	750	54	55.1	65.5	27.1 (4.9)	147.2 (22.8)	82.4 (11.6)	104.0 (14.2)	64.8 (16.6)
	[60,70)	599	65	50.1	84.0	26.7 (5.0)	156.9 (23.8)	81.7 (11.3)	106.7 (14.2)	75.3 (18.0)
	[70,80)	563	74	43.3	89.9	25.1 (5.0)	162.3 (23.8)	81.0 (11.5)	108.1 (14.5)	81.3 (17.4)
SINDI	[40,50)	632	46	51.7	23.3	26.2 (4.6)	127.9 (18.6)	78.6 (11.0)	95.1 (12.7)	49.3 (12.3)
	[50,60)	799	54	50.3	36.1	27.0 (4.8)	135.9 (19.3)	80.2 (10.7)	98.8 (12.6)	55.6 (13.7)
	[60,70)	723	63	46.2	48.6	25.8 (4.7)	146.1 (20.6)	79.9 (10.0)	102.0 (12.2)	66.2 (16.2)
	[70,80)	322	73	47.5	60.3	25.6 (5.0)	152.1 (19.9)	77.0 (8.6)	102.0 (11.0)	75.1 (16.6)
SP2 (Illumina 1M platform)	[30,40)	205	36	42.9	7.3	22.4 (3.5)	120.1 (14.1)	73.3 (9.4)	88.9 (10.4)	46.8 (8.7)
	[40,50)	405	45	39.8	11.9	22.9 (3.4)	126.1 (14.6)	78.0 (10.6)	94.0 (11.3)	48.0 (9.1)
	[50,60)	203	54	28.6	23.2	23.6 (3.6)	134.7 (18.2)	82.3 (11.3)	99.8 (12.8)	52.4 (12.0)
SP2 (Illumina 610 platform)	[30,40)	201	35	75.1	4.0	22.2 (4.7)	115.7 (13.1)	70.8 (8.2)	85.8 (9.2)	44.9 (8.7)
	[40,50)	366	45	80.6	11.2	22.5 (3.7)	122.4 (16.4)	73.8 (9.9)	90.0 (11.4)	48.6 (10.7)
	[50,60)	337	54	78.0	23.7	23.1 (3.7)	132.1 (18.3)	77.0 (10.9)	95.3 (12.3)	55.2 (13.2)
	[60,70)	138	65	73.2	37.7	23.4 (3.2)	150.0 (20.2)	78.4 (9.2)	102.3 (11.6)	71.6 (16.1)

Table S7: Genotyping, Imputation, and Association Analysis Information for the Singapore Studies

Singapore Study	Genotyping Platform	NCBI human genome reference used	Imputation Procedure	Pre-Imputation QC filter information	Pre-Association Filters (sample or SNP)	Association Analysis Software
SCES	Illumina610 Quad	Build 36/hg18	IMPUTE2.2, HapMap phase2 release22 JPT+CHB	Sample callrate: 0.95, SNP callrate>0.95, HWE p-value: 1E-06, MAF>0; Sample call rate >0.95, population outlier, cryptic relationship, excessive heterozygosity, gender mismatch.	None	SNPTEST v2.2
SiMES	Illumina610 Quad	Build 36/hg18	IMPUTE0.5, HapMap phase2 release22 JPT+CHB+CEU+YRI	Sample callrate: 0.95, SNP callrate>0.95, HWE p-value: 1E-06, MAF>0; Sample call rate >0.95, population outlier, cryptic relationship, excessive heterozygosity, gender mismatch.	None	SNPTEST v2.2 Covariates PC1 and PC2
SINDI	Illumina610 Quad	Build 36/hg18	IMPUTE0.5, HapMap phase2 release22 JPT+CHB+CEU+YRI	Sample callrate: 0.95, SNP callrate>0.95, HWE p-value: 1E-06, MAF>0; Sample call rate >0.95, population outlier, cryptic relationship, excessive heterozygosity, gender mismatch.	None	SNPTEST v2.2 Covariates PC1, PC2 and PC3
SP2	Illumina 1M and Illumina 610	Build 36/hg18	IMPUTE0.5, HapMap phase2 release22 JPT+CHB	Sample callrate: 0.95, SNP callrate>0.95, HWE p-value: 1E-06, MAF>0; Sample call rate >0.95, population outlier, cryptic relationship, excessive heterozygosity, gender mismatch.	None	SNPTEST v2.2

TITLES OF SUPPLEMENTAL TABLES 8-22

NOTE: Red text denotes a table with results from all stages of analysis.

Table S8: Joint Effects of the SNP and SNP-age Interaction on Systolic Blood Pressure from the Meta-regression Using Stage 1 Subgroups (CHARGE)

Table S9: Joint Effects of the SNP and SNP-age Interaction on Diastolic Blood Pressure from the Meta-regression Using Stage 1 Subgroups (CHARGE)

Table S10: Joint Effects of the SNP and SNP-age Interaction on Mean Arterial Pressure from the Meta-regression Using Stage 1 Subgroups (CHARGE)

Table S11: Joint Effects of the SNP and SNP-age Interaction on Pulse Pressure from the Meta-regression Using Stage 1 Subgroups (CHARGE)

Table S12: Combined Meta-regression of all Stage 1 (CHARGE) and Stage 2 (largely Global BPgen) Subgroups for Loci with Suggestive or Significant Evidence by the Joint 2 DF test; Replication in the Singapore Subgroups

Table S13: Five Loci Identified With the Joint 2DF Test That Would Have Been Missed By a Two-Stage Main Effects Only Analysis

Table S14: One Degree of Freedom Test of SNP-age Interactions on Mean Arterial Pressure in Stage 1 Subgroups (CHARGE)

Table S15: One Degree of Freedom Test of SNP-age Interactions on Pulse Pressure in Stage 1 Subgroups (CHARGE)

Table S16: Replication of Loci Chosen Through the 1DF Test of the SNP-age Interaction; Combined Meta-regression of All Stage 1 and Stage 2 Subgroups (Individuals of European Ancestry)

Table S17: Genomic Inflation Factors from the Inverse-variance Weighted Meta-Analysis Conducted Within Each Age Bin; the Secondary Analysis Using Stage 1 Subgroups (CHARGE)

Table S18: Within Age Bin Meta-analysis of the SNP Effect on Systolic Blood Pressure: Significant and Suggestive Associations in the Secondary Analysis of Stage 1 (CHARGE)

Table S19: Within Age Bin Meta-analysis of the SNP Effect on Diastolic Blood Pressure: Significant and Suggestive Associations in the Secondary Analysis of Stage 1 (CHARGE)

Table S20: Within Age Bin Meta-analysis of the SNP Effect on Mean Arterial Pressure: Significant and Suggestive Associations in the Secondary Analysis of Stage 1 (CHARGE)

Table S21: Within Age Bin Meta-analysis of the SNP Effect on Pulse Pressure: Significant and Suggestive Associations in the Secondary Analysis of Stage 1 (CHARGE)

Table S22: Combined Within-Age Bin Meta-analysis of Stage 1 and Stage 2 Subgroups; Replication of Secondary Within-Age Bin Analyses Using Singapore Subgroups.

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