SUPPLEMENTARY NOTE

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1 Studies contributing to systolic (SBP) and diastolic blood pressure (DBP) analyses

The cohorts contributing to the discovery meta-analysis for individuals of European ancestry comprise of studies that were directly genotyped using Cardio-MetaboChip, studies in the published ICBP-GWAS dataset[1], and new GWAS studies. The total sample size is N=201,529. The validation dataset comprised individuals of European ancestry from UK Biobank, N=140,886. A targeted lookup of 66 SNPs was performed in studies of non-European ancestry (East Asian N= 9,637, South Asian N= 20,875, and African and African-American ancestry N= 33,909). Details on each of the studies including study design and BP measurement are provided in **Supplementary Table 1**, genotyping information in **Supplementary Table 2**, and participant characteristics in **Supplementary Table 3.**

All participants provided written informed consent and the studies were approved by their local Research Ethics Committees and/or Institutional Review Boards.

2 Consortia and studies providing association results for cardiovascular outcomes

We obtained phenotype-genotype association summary statistics (effect size, standard error, and *P* value) for up to 66 SNPs of interest, by requesting "look-ups" in the results of analyses that had already been conducted by consortia and research groups for cardiovascular and other end-organ outcomes. In this section, we briefly summarize relevant information about each consortium.

2.1 CHARGE - Heart Failure Working Group

We obtained association summary statistics for SNPs of interest from the meta-analysis of 4 cohorts of European ancestry with a total of 20,926 participants free of clinical heart failure at baseline, in whom 2,526 incident heart failure events occurred during follow-up[2]. All cohorts included in the heart failure analysis are included in the published ICBP-GWAS discovery dataset[1].

2.2 EchoGen (LM mass and LV weight)

Association summary statistics for left ventricular (LV) mass and LV wall thickness were obtained from the discovery meta-analysis described previously[3]. The discovery analysis for this study combined data from 5 cohorts of European ancestry with a total sample size of N = 12,612. Four of the cohorts (CHS, RS, KORA F3, FHS) with total N = 9,312, overlap the studies which are included in the published ICBP-GWAS discovery dataset[1].

2.3 NEURO-CHARGE (stroke)

Association summary statistics for risk of incident stroke were obtained from the discovery meta-analysis of the CHARGE consortium, described previously[4]. The discovery analysis for these phenotypes

combined data from 4 cohorts of European ancestry with a total sample size of N = 19,602, all of which were included in the ICBP-GWAS dataset[1].

2.4 MetaStroke (stroke)

Association summary statistics for ischemic risk stroke were obtained from the discovery meta-analysis of the MetaStroke consortium, described previously[5]. The discovery analysis for these phenotypes included N = 11,012 ischemic stroke cases and N = 40,824 controls after excluding four cohorts (ARIC, CHS, FHS and RS) which are included in the NEURO-CHARGE dataset. There is some overlap of individuals from deCODE and 58BC contributing to the Cardio-MetaboChip BP analyses.

2.5 CARDIoGRAMplusC4D (CAD)

Association summary statistics were obtained from the Coronary ARtery DIsease Genome-wide Replication And Meta-analysis (CARDIoGRAM) plus C4D consortium which combines data from GWAS and Cardio-MetaboChip studies including 63,746 cases with coronary artery disease (CAD) and/or Myocardial Infarction (MI) and 130,681 controls of European and South Asian ancestry[6]. More than 80% of the individuals in these analyses are included in the Cardio-MetaboChip and GWAS BP analyses.

2.6 CHARGE CKDgen (CKD, eGFR, microalbuminuria, UACR)

Association summary statistics for estimated glomerular filtration rate estimated from creatinine (eGFRcr) were obtained from the discovery meta-analysis of the CKDGen consortium (all samples of European ancestry), described previously[7]. The discovery analysis for these phenotypes combined data from 26 cohorts with a total sample size of N = 74,354. Seventeen of these cohorts (AGES, Amish, ARIC, BLSA, CHS, 1300 samples from ERF, FHS, KORA F3, KORA F4, MICROS, NSPHS, ORCADES, RS, RSII, SHIP, WGHS and Vis) with total N = 65,818, overlap the ICBP-GWAS discovery dataset previously published[1]. Association summary statistics for dichotomous chronic kidney disease (CKD) were obtained by querying the same datasets[7]. There are 17 cohorts (AGES, Amish, ARIC, BLSA, CHS, 1300 samples from ERF, FHS, KORA F3, KORA F4, MICROS, NSPHS, ORCADES, RS, RSII, SHIP, WGHS and Vis), with total N = 60,498, overlapping the ICBP-GWAS discovery datasets. Association summary statistics for eGFR estimated from cystatin C (eGFRcys) were obtained from 10 datasets; 7 of these cohorts (Amish, ARIC, CHS, FHS, KORA F3&F4, MICROS, and SHIP) with N = 21,274 overlap the discovery cohorts in the published ICBP-GWAS dataset[1]. Association summary statistics for urinary albumin:creatinine ratio (UACR) phenotypes combined data from 12 cohorts with a total sample size of N = 31,580. Individuals in all 12 of the cohorts overlap the ICBP-GWAS dataset[1]. Microalbuminuria was defined as UACR > 25 mg/g in women or > 17 mg/g in men[8].

2.7 KidneyGen (creatinine)

Association summary statistics for serum creatinine were obtained from the discovery meta-analysis of the KidneyGen consortium, described previously[9]. The discovery analysis for this study combined data from 9 cohorts, all of European ancestry, with a total sample size of N = 23,812. Six of the cohorts (CoLaus, SardiNIA, 873 samples from TwinsUK, Fenland, InCHIANTI, NFBC1966) with a total sample size of N = 17,699, overlap the ICBP-GWAS discovery dataset[1].

2.8 CHARGE (cIMT)

Association summary statistics for carotid intimal thickness (cIMT) were obtained from the discovery meta-analysis of the CHARGE consortium[10]. Each study evaluated the carotid arteries with high-resolution B-mode ultrasonography, and cIMT was defined as the average of multiple measurements from both the left and right arteries. The discovery analysis combined data from 9 cohorts, all of European ancestry, with a total sample size N = 31,211. All cohorts (AGES, Amish, ARIC, CHS, ERF, FHS, RS, Sardinia and SHIP) overlap the ICBP-GWAS discovery dataset[1].

2.9 CHARGE (mild retinopathy, central retinal artery caliber)

Association summary statistics for mild retinopathy were obtained from the discovery meta-analysis of the CHARGE consortium. Retinopathy is defined as the presence of micro-aneurysms or dot-blot hemorrhages[11]. The discovery analysis combined data from 6 cohorts, all of European ancestry, with a total sample size of N = 18,411. Five of the cohorts, AGES, ARIC, CHS, RS, and MESA, overlap the ICBP-GWAS samples. Association summary statistics for central retinal artery caliber were obtained from the discovery meta-analysis of the CHARGE consortium. Participants underwent film or digital retinal photography, and the images were analyzed with a semi-automated retinal vessel measurement system[12]. The discovery analysis for this study combined data from 5 cohorts, with a total sample size of N = 18,722. Four of the cohorts (AGES, ARIC, CHS and RS) overlap the ICBP-GWAS discovery dataset[1].

2.10 SEED (mild retinopathy, central retinal artery caliber)

Association summary statistics for mild retinopathy were obtained from the discovery meta-analysis of the Singapore Epidemiology of Eye Diseases (SEED) Study (unpublished). Retinopathy and central retinal artery caliber were measured as previously described[11,12]. The discovery analysis for this study has a total sample size of N = 6,976. None of the studies overlap the BP cohorts analyzed in the current report.

3 European ancestry meta-analysis

A meta-analysis of 201,529 individuals of European descent was undertaken in four stages. The study design is summarized in **Supplementary Figure 1.** The stage 1 meta-analyses consisted of 109,096 individuals of European descent across 46 studies (**Supplementary Tables 2-3**). All samples were genotyped using the Cardio-MetaboChip genotype array[13]. Sample and SNP quality control (QC) were undertaken by each study separately. All SNPs with minor allele frequency (MAF) > 1%, Hardy-Weinberg Equilibrium (HWE) $P > 1x10^{-7}$ and per SNP call-rate > 0.98 were separately tested for association with SBP and DBP in a linear regression framework assuming an additive model. The BP values were treatment corrected by adding 15 mm Hg to the measured SBP and 10 mmHg to DBP in individuals on one or more anti-hypertensive medications[14]. Association analyses included sex (some studies stratified their analyses by gender instead), age, age-squared, and BMI as covariates, except where these covariates were identical for all individuals, such as birth cohorts of individuals born in the same year. Where available and appropriate, additional covariates were used to correct for potential within-cohort stratification. The results of each GWAS were corrected for residual stratification using the genomic control inflation factor[1,15]. As the Cardio-MetaboChip was designed in part on the basis of association results from the ICBP-GWAS analysis of SBP and DBP, we observed, as expected, test statistic inflation in association signals across the content of this array. The results of each study were therefore corrected for residual population structure using the genomic control inflation factor obtained from a subset of SNPs that were not found to be associated with BP in the earlier ICBP-GWAS. This set of "putative null BP SNPs" was chosen to be the overlap of the Cardio-MetaboChip SNPs with the GWAS SNPs imputed from HapMap if the association test significance for both SBP and DBP were both $P > 0.10$. All SNPs lying in fine mapping regions (defined as average inter-SNP distance < 5kb using a 10 inter-SNP sliding window) were also excluded from the "putative null BP SNPs" dataset, resulting in a final set of 44,951 "putative null BP SNPs". The results of all Cardio-MetaboChip studies were combined by inverse-variance weighted fixed-effects meta-analysis, with the results subsequently corrected by a second round of genomic-control using "putative null BP SNPs", with $\lambda_{GC} = 1.15$ for both SBP and DBP.

3.1 Stage 2 meta-analyses

The stage 2 meta-analyses consisted of 35,952 individuals of European descent across four GWA studies which were not part of the 2011 ICBP-GWAS (WGHS, JUPITER, NESDA, MESA, see **Supplementary Tables 1-3** for abbreviations and details) and SNPs overlapping with Cardio-MetaboChip SNPs were used. Samples were genotyped with a range of GWAS genotyping arrays and unmeasured SNPs were imputed using samples from the International HapMap Project for three of the studies and from the

1000 Genomes Project Consortium[16] for one study (see **Supplementary Table 2** for details of data cleaning and imputation reference panels). The same QC and analytical protocols implemented for studies in stage 1 were also applied to stage 2 studies with the exception that genome-wide SNPs were used per study for a first round of genomic-control (**Supplementary Figure 1**). For each SNP with imputation quality $r^2 > 0.3$, association summary statistics were combined across studies by means of inverse-variance weighted fixed-effects meta-analysis, with results subsequently corrected by a second round of genomic control based on all genome-wide SNPs (λ_{GC} = 1.02/1.01 for SBP/DBP respectively).

3.2 Stage 3 meta-analyses

The stage 3 meta-analyses consisted of 56,481 individuals of European ancestry from 24 published ICBP-GWAS studies[1] (**Supplementary Tables 1-3**). Samples were genotyped using a range of commercially available arrays with > 300,000 SNPs. Genotypes for unmeasured SNPs were imputed using CEU samples from Phase 2 of the International HapMap Project Consortium [17] and a common set of ~2.5M SNPs available across the samples were available for analysis. Within each study, sample and SNP quality control procedures were implemented[1]. SNPs with MAF > 1% and passing QC were tested for association with SBP and DBP under additive genetic models in a linear regression framework with adjustment for the same covariates as in stages 1 and 2. Genome-wide SNPs were used per study for a first round of genomic-control (**Supplementary Figure 1**). For each SNP with imputation quality $r^2 > 0.3$, association summary statistics were combined across studies by means of inverse-variance weighted fixed-effects meta-analysis, with results subsequently corrected by a second round of genomic control using all SNPs (λ_{GC} = 1.12/1.11 for SBP/DBP respectively).

3.3 Stage 4: combined meta-analyses and validation in UK Biobank

The results of the stage 1, stage 2, and stage 3 meta-analyses for SBP and DBP were combined for all Cardio-MetaboChip SNPs by means of inverse-variance weighted fixed-effects meta-analysis. The combined meta-analyses consisted of 201,529 individuals. A third round of genomic control was not applied to the combined meta-analyses results because of the ascertainment of the Cardio-MetaboChip SNPs and of the "putative null SNPs" using results from a subset of the stage 1+2+3 samples (λ_{GC} = 1.00/0.99 using the "putative null BP SNPs" for SBP/DBP respectively). Small sample size reduces the statistical power and increases the false positive rate (FDR), and variability in genotyping call rate makes SNP-by-SNP comparison of *P* values difficult. Therefore, SNPs were required to have passed quality control (whether directly genotyped and imputed) in at least 25% of the total sample size, or were otherwise excluded from downstream analyses. All meta-analyses were conducted in parallel by two analysts using a combination of custom scripts and a) the METAL software[18] and b) scripting using the R

statistical language[19] respectively. We sought independent validation of newly discovered BP loci using summary association results from an analysis of UK Biobank participants (**Supplementary Tables 1-3**). The analysis was restricted to Caucasians according to PCA based on a clustering algorithm, and unrelated individuals. The mean of two BP recordings was used, and medication-adjusted SBP and DBP variables were obtained by +10/15 mmHg for those on BP lowering treatment. All SNPs were tested for association with SBP and DBP in a linear regression framework assuming an additive model. The association analyses included sex, age, age^2, BMI, genotyping array, and the top 10 PCs.

3.4 Systematic PubMed search +/- 100kb of each newly discovered index SNP

To systematically assess whether genes near the index SNPs have been previously described to be involved in BP regulation or hypertension, we performed a systematic PubMed search. All genes with any overlap with a 200kb region centered around each of the 17 newly discovered index SNPs were identified using the UCSC Genome Browser [20]. Two loci did not contain any genes within their genomic spans (*TBC1D1-FLJ13197*, *CSNK1G3*), the remaining 15 loci overlapped with a total of 64 genes (1-11 genes per locus). A search term was constructed for each gene including the short and long gene name and the terms "blood pressure" and "hypertension" (e.g. for *NPPA* on chr 1: "NPPA OR natriuretic peptide A AND (blood pressure OR hypertension)") and the search results of each search term from PubMed were individually reviewed. Of the 17 newly discovered loci, 6 contained genes within the 200kb interval that were previously described to be related to blood pressure or hypertension (*ELAVL3*, *CHST12-LFNG*, *RAPSN-PSMC3-SLC39A13*, *DBH*, *CRYAA-SIK1*, *INSR*). Among the 49 known loci there are 3 genes in gene-poor regions without any UCSC Gene in the 200kb interval (*FIGN-GRB14*, *EBF1*, *TBX5-TBX3*). The same search on previous knowledge based on molecular biology could not be performed in a meaningful way for the known loci as here molecular biology experiments could have been carried out with the knowledge of a BP GWAS signal.

3.5 Trait variance explained

The trait variance explained by all 66 SNPs at novel and known loci was evaluated in one study that had also been used for the discovery effort (the Atherosclerosis Risk in Communities (ARIC) study. We constructed a linear regression model with all 66 or the subset of 49 known SNPs in the model, regressing in the residual from the covariate-adjusted treatment-corrected BP phenotype (SBP or DBP). R^2 from the regression model was used as trait variance explained. Some over-fitting of these estimates may exist due to the sample overlap between the individual cohorts and the overall meta-analysis samples and because each regression model will estimate the best estimate of the per-SNP effect for

that sample. The variance explained (r^2 implemented in the lm() function of R Statistical language) were calculated for SBP and DBP respectively (one SNP per locus). The phenotypes used in the regression were adjusted for BP lowering medication in the same way as in the meta-analysis and we used age, age^2, sex, and BMI as covariates. One SNP (rs9268977) was missing in ARIC and was replaced by a perfect proxy.

4 European ancestry GCTA-COJO analysis

To identify multiple distinct association signals within BP loci we undertook a model selection procedure implemented in the GCTA-COJO software package[21,22]. SNPs are selected by GCTA-COJO as conditionally-independently associated with a trait, at a pre-determined level of significance. GCTA-COJO employs approximate conditional analyses using association summary statistics from the meta-analysis and the linkage disequilibrium (LD) between variants (and estimates the correlation between allelic effects in a joint association model) estimated from a reference dataset of individual-level genotype data, preferentially a study contributing to the meta-analysis. Although the set of SNPs selected and their effect estimates are expected to depend somewhat on the reference dataset, the results should be fairly robust when the LD pattern between variants in the cohorts under consideration is well represented by the reference dataset (when it is large and includes individuals with similar ancestral histories and therefore genotype frequencies and correlations) and thus offers good coverage of the SNPs in the meta-analysis[21].

To evaluate the robustness of the GCTA-COJO results to the choice of reference data set, model selection was performed using the LD between variants in separate analyses from two datasets of European descent, both with individuals from the UK with Cardio-MetaboChip genotype data: GoDARTS with 7,006 individuals and WTCCC1-T2D/58BC with 2,947 individuals. Assuming that the LD between SNPs more than 10 Mb away or on different chromosomes is zero, we undertook the GCTA-COJO step-wise model selection to select SNPs independently associated with SBP and DBP, in turn, at a genome-wide significance, given by $P < 5\times10^{-8}$ (**Supplementary Tables 6-8**) using the stage 4 combined European GWAS+ Cardio-MetaboChip meta-analysis.

Although the sets of SNPs selected by GCTA-COJO as associated with SBP or DBP when using either reference dataset were very similar, with the estimated effect sizes in the joint association model highly correlated, a small number of differences were observed. These were always the result of minor differences between the estimated association *P* value for the joint model, with some SNPs falling on either side of the $P < 5 \times 10^{-8}$ threshold when using one dataset as reference but not the other. Given these observations, we chose to report, as primary, the results when using GoDARTS as reference data

set given its larger sample size. **Supplementary Figure 7** present locus zoom plots[23] for the 13 BP loci with more than one association signal.

5 Conditional analyses in the Women's Genome Health Study (WGHS)

To further test for the presence of independent signals of association at the same locus, we performed multivariable regression modeling in a large single cohort study with simultaneous adjustment for each possible combination of putative independent SNPs from a) the Cardio-MetaboChip analysis and b) a comprehensive manual review of the literature (**Supplementary Table 9**). A total of 46 SNPs were considered (**Supplementary Table 10**). We used genome-wide genotyping data imputed to 1000 Genomes in the WGHS, N = 23,047. The regression modeling was performed in the R statistical language with adjustment for age, age2, sex, and BMI[19]. If a locus included 3 different SNPs (a, b and c), we tested association of each SNP in an individual model (model #1: a; model #2: b; model #3: c), as well as the three models with 2 SNPs (model #4: a, b; model #5: b, c; model #6: a, c) and finally a model with all 3 SNPs (model #7: a, b, c).

6 Fine mapping and determination of credible sets of causal SNPs

We used association summary statistics from the European ancestry meta-analyses to define credible sets of variants that are most likely to drive the association signal (or tag an unobserved variant driving the association signal) across Cardio-MetaboChip fine mapping regions. Given the summary statistics from the European ancestry meta-analysis, an approximate Bayes' factor[24] in favor of association of SNP *j* with the trait can be defined by

$$ABF_j = \sqrt{1-r}\,\exp\left(\frac{z_j^2}{2}r\right)$$

where $z_j = \frac{\beta_j}{\sigma_j}$ is the Z-statistic for SNP j, with β_j the allelic effect and σ_j the corresponding standard error. The shrinkage factor

$$r = \frac{\varepsilon^2}{\sigma_j^2 + \varepsilon^2}$$

is the ratio of the prior variance, ε^2, to the total variance. Here, we assume ε = 0.2 in the prior distribution for β_j[25]. Under the assumption that there is exactly one variant driving the association signal in a given region, and taking a uniform prior on any of the *k* SNPs in the region being the causal variant, the total Bayes' factor for the region, measuring the evidence that there is one causal variant in the region, is then the mean of the single-SNP Bayes' factors[26],

$$BF_{region} = \frac{1}{k}\sum_{j=1}^{k} ABF_j \, .$$

The posterior probability that a given SNP is driving the signal given our data is proportional to its Bayes' factor

$$\Pr(\text{SNP } j \text{ is driving association} \mid \text{data}) = \frac{ABF_j}{k \times BF_{region}} \propto BF_j \, .$$

A 99% credible set of variants can then be constructed by ranking all SNPs in the region based on their posterior probability and combining them until the cumulative posterior probability exceeds 0.99. Given the data under analysis and if the causal variant is among the genotyped variants or perfectly correlated to one of the variants, there is therefore at least 99% probability that the constructed set of variants contains the variant driving the association signal or tags an unobserved variant driving the association signal.

The loci represented on the Cardio-MetaboChip are not all densely covered by design[13]. We therefore only consider for this analysis the Cardio-MetaboChip fine mapping loci where SNP coverage is dense. Of these fine mapping regions, some of which selected for a non-BP trait originally, only 24 loci included at least one SNP that reached genome-wide significance for the BP association in the Stage 4 combined meta-analysis of GWAS+Cardio-MetaboChip among those of European ancestry. The Cardio-MetaboChip-only analyses often include more eligible SNPs (broader coverage of variants) than GWAS+Cardio-Metabochip meta-analyses, because some SNPs are only present on the Cardio-MetaboChip array, but at the cost of reduced power to detect association due to the smaller sample size. We therefore determined, for comparison, the credible sets for both the GWAS+Cardio-MetaboChip and the Cardio-MetaboChip-only meta-analyses. Given that there must be a) adequate power to detect association[24], and b) a relatively even sample size across all SNPs that are being compared, the credible sets were determined using only SNPs with sample size greater than 80% of our total sample size (Cardio-MetaboChip and GWAS combined). In constructing credible sets, we assume that there is a single variant driving the association signal in each locus. However, the GCTA-COJO analyses identified multiple signals of association at 13 of the 66 loci identified in our study as associated with SBP and/or DBP, while review of the literature identified additional association signals at two loci that appear to be independent of those identified in our study (**Supplementary Table 9**). Of the 24 loci considered in our fine mapping analyses, 16 had no evidence for the existence of multiple association signals, so it is reasonable to assume that there is a single causal SNP and therefore the credible sets of variants could be constructed as described above using the association summary statistics from the unconditional meta-analyses. However, in the remaining 8 loci, where evidence of secondary signals

was observed from GCTA-COJO, we performed approximate conditional analyses across the region by conditioning on each index SNP (**Supplementary Table 11**). By adjusting for the other index SNPs at the locus, we can therefore assume a single variant is driving each "conditionally-independent" association signal, and we can construct the 99% credible set of variants on the basis of the approximate conditional analysis from GCTA-COJO (**Supplementary Tables 12-13**). Note that at five of the eight loci with multiple signals of association, one index SNP mapped outside of the fine mapping region so that a credible set could not be constructed.

7 Expression quantitative trait loci (eQTLs) analyses

7.1 Whole Blood (NESDA/NTR dataset)

The dataset used for eQTL analyses came from samples from the Netherlands Study of Depression and Anxiety (NESDA)[27] and the Netherlands Twin Registry (NTR)[28] studies. The sample consisted of 5,071 subjects: 3,109 NTR (from 1,571 families: 614 dizygotic twin pairs; 1 monozygotic [MZ] triplet; 668 MZ twin pairs; 394 non-twin siblings; and 148 unrelated subjects) and 1,962 NESDA participants (all unrelated). The blood sampling, RNA and DNA extraction; gene expression measurements; and gene expression quality control (QC) for the eQTL analyses have been described previously[29,30]. RNA samples were hybridized to Affymetrix U219 arrays (Affymetrix, Santa Clara, CA). After filtering, data for analysis remained for 423,201 probes that were summarized into 44,241 probe sets targeting 18,238 genes. Further RNA analysis was performed in the statistical software R[19]. The residuals resulting from the linear regression analysis of the probe set intensity values onto the covariates sex, age, body mass index (kg/m^2), smoking status coded as a categorical covariate, several technical covariates (plate, well, hour of blood sampling, lab, *etc.*) and the scores on three principal components (PCs) as estimated from the imputed SNP genotype data using the EIGENSOFT package, were subjected to a principal component analysis, with the aim to further filter out environmental variation from the data. For each principal component a genome-wide association study was performed, and the first 50 expression PCs that did not display genome-wide significant SNP associations were, together with the above mentioned covariates, regressed out of the probe set intensity values before eQTL analysis.

SNP genotype pre-imputation quality control, haplotype phasing, and imputation were performed as described previously[31] using 1000 Genomes data. The mean imputation quality r^2 metric equaled 0.38 for all 30,051,533 imputed autosomal SNPs. Following filtering of SNPs based on Mendelian error rate in families, HWE *P* value, imputation quality r^2, MAF, and comparison of allele

frequencies to the 1,000 Genomes reference haplotypes, a total of 7,209,091 SNPs with a mean r^2 of 0.86 were available for eQTL analysis.

The eQTL effects were detected using a linear mixed model approach, including for each probe set the expression level (normalized, residualized and without the first 50 expression PCs) as dependent variable; the SNP genotype values as fixed effects; and family identifier and zygosity (in the case of twins) as random effects to account for family and twin relations[32].

The eQTL effects were defined as *cis* when probe set–SNP pairs were at distance < 1M base pairs (Mb), and as *trans* when the SNP and the probe set were separated by more than 1 Mb on the genome according to hg19. At a FDR of 0.01 used genome-wide, therefore not only considering the candidate SNPs, for cis-eQTL analysis the *P* value threshold was $1x10^{-4}$, and for trans-eQTL analysis $1x10^{-8}$. For each probe set that displayed a statistically significant association with at least one SNP located within its *cis* region, we identified the most significantly associated SNP and denoted this as the top *cis*-eQTL SNP.

7.2 Whole blood (FHS dataset)

We considered whether any blood pressure SNP association was likely to be explained by association of the SNP with expression of a nearby gene in whole blood in humans. We tested whether the BP SNP or a close proxy ($r^2 > 0.8$, usually almost 1.0) was associated with a transcript of a gene within 1 Mb of the lead BP SNP, at an FDR < 0.05. As association of a blood pressure SNP with expression of a *cis* transcript could arise due to LD with a stronger and independent eSNP in the region in a scenario in which two independent signals exist (one BP signal and one eSNP association), we considered conditional models. For every BP SNP significantly associated with a cis transcript, we identified the best *cis* eSNP for that transcript. We considered strong evidence of one signal and therefore a possible mediating effect of SNP association with blood pressure through association with expression of that transcript when the correlation of the BP SNP and best eSNP was strong ($r^2 > 0.8$) and the significance of the BP-transcript association was substantially attenuated (significance reduced) in a model adjusting for the best eSNP. In that circumstance, we considered that the BP and expression association signals coincide and thus nominate the expression effect of the signal as a potential mediator of the BP association. For SNPs with $0.3 < r^2 < 0.8$ and significant attenuation of the signal in conditional models, we considered possible coincidence of a single signal of BP and expression association. For SNPs with $r^2 < 0.3$ or SNPs that showed minimal attenuation of the BP-transcript association in conditional models two independent signals seemed more likely with probably no coincidence of those signals. Lastly, because BP signals in fine mapping regions are more precisely localized, we stratified on signal fine mapping (fine mapping of a prior BP SNP association), locus fine

mapping (fine mapping of the region) and no fine mapping in the region. The results are summarized in **Supplementary Table 15**.

7.3 Lymphoblastoid cell lines, skin and fat biopsies (MuTHER datasets)

In the MuTHER study, RNA levels were measured in LCLs (N = 826), skin (N = 705) and fat biopsies (N = 825) from 850 female twins (one-third monozygotic and two-thirds dizygotic) from the TwinsUK resource using the Illumina HumanHT-12v3 array[33]. Genotyping was performed using three different arrays - Illumina HumanHap300, HumanHap610Q, and 1M-Duo, 1.2M Duo 1 M chips. Imputation was done using the IMPUTE software package using two reference panels (HapMap2, a combined ancestry panel) and a 610K+ panel. We assessed genotype with gene expression associations, using an additive linear model across a 2Mb window centered on the index BP SNP or proxy SNP. At loci with significant *cis*-eQTL signal(s) ($P < 1 \times 10^{-4}$), the most strongly associated *cis*-eQTL SNP (eSNP) for the corresponding transcript was identified. If the BP SNP and the eSNP were the same or in high LD ($r^2 > 0.8$) the BP SNP was defined as an eSNP. All index BP SNPs (N = 91 at 66 loci see **Supplementary Table 9**) or proxies ($r^2 > 0.8$, if index SNP was not available) were considered. The results are summarized in **Supplementary Table 14**.

7.4 Monocytes and macrophages (Cardiogenics)

Monocytes and macrophages were collected from healthy subjects and individuals with coronary artery disease (CAD), and RNA was profiled with the Illumina Human Ref-8 array[34]. Genotyping was performed using either Human Custom1.2M or Human Quad custom 670 arrays from Illumina. The eQTL analysis was undertaken in 459 healthy individuals from Cambridge, UK using an additive linear model across a 2Mb window centered on the index BP SNP or proxy SNP. At loci with significant *cis*-eQTL signal(s) ($P < 1 \times 10^{-4}$), the most strongly associated *cis*-eQTL SNP (eSNP) for the corresponding transcript was identified. If the BP SNP and the eSNP were the same or in high LD ($r^2 > 0.8$), the BP SNP is defined as an eSNP. All index BP SNPs (N = 91 at 66 loci, see **Supplementary Table 9**) were considered or their proxies ($r^2 > 0.8$) if the index SNP was not available. The results are summarized in **Supplementary Table 14**.

7.5 Advanced Study of Aortic Pathology (ASAP) dataset

The ASAP study included five tissues: aorta adventitia ("AAdv"), aorta intima-media ("AMed"), mammary artery intima-media ("MMed"), heart ("H") and liver ("L"). The expression data were generated using the Affymetrix ST1.0 Exon array and genotyping was performed using the Illumina Human 610W- Quad Bead array[35]. The sample sizes ranged between 100 and 200 per data set, 86 of the

requested SNPs or proxies ($r^2 > 0.8$) were available in the datasets. There were no probes on the arrays for 9 genes (*c10orf22*, *DBH*, *EVX*, *FLJ32810*, *HOTTIP*, *LRRC10B*, *PLEKHG1*, and *TMEM133*), and data was not provided for 4 of the loci (*NCAPH*, *ADAMTS9*, *RAPSN* and *ELVL3*). Imputation was performed using Mach 1.0 and 1,000 Genomes as a reference. At loci with significant *cis*-eQTL signal(s) ($P < 1 \times 10^{-4}$), the most strongly associated *cis*-eQTL SNP (eSNP) for the corresponding transcript was identified. If the BP SNP and the eSNP were the same or in high LD ($r^2 > 0.8$) the BP SNP is defined as being an eSNP. For this analysis, the *P* value of all directly genotyped SNPs within 200 Kb of the index SNP in question were considered, which included around 100 proximal SNPs per locus. The results are summarized in **Supplementary Table 14**.

7.6 Kidney

The dataset comprises 81 biopsies of normal kidney cortex tissue from transplantation donors or nephrectomy patients[36,37]. The biopsies are drawn from two cohorts: Cohort 1 - gene expression data from Rodwell et al. 2004[36], and Cohort 2 - gene expression data from Wheeler et al.[37,38].

All samples for each cohort were analyzed on Affymetrix U133 A&B set. Expression was normalized within each cohort using dChip (perfect match probe sets only). Genotyping was performed using Affymetrix 6.0 Genome-wide chips. SNP probe sets were called with Affymetrix GTC Software.

Perl and R scripts were used to link every SNP probe set to the nearest upstream and downstream genes using the mapped RefSeq annotation from the Affymetrix annotation files (build 30). In total, 29,782 unique RefSeq annotations map to 18,930 unique genes. To determine eQTLs, R scripts were used to perform a linear multivariate regression within each cohort,

$$Y_{ij} = \beta_{0j} + \beta_{1j} g_{ij} + \beta_{2j} age_i + \beta_{3j} anc_i + \beta_{4j} s_i + \varepsilon_{ij}$$

where Y_{ij} is the $\log_2$ normalized expression for the U133 probe set of SNP j in the kidney sample i, g_{ij} denotes the respective genotype; age_i, anc_i and s_i are the age, ancestry (European ancestry or other) and sex (male or female) of the individual i, respectively; and ε_{ij} is a random error term. Only cortex samples were used, so tissue was not a variable. Coefficients β (1 to 4) are estimated by least squares.

R and Bioconductor scripts were used to calculate a meta-analysis *P* value over both cohorts using a Fisher's combined probability test. Only those eQTL combinations with a nominal $P < 0.05$ (for genotype) and an effect in the same direction in both cohorts were selected, yielding 9,989 eQTL combinations (meta-analysis *P* value range: 1.7×10^{-2} to 2.75×10^{-35}). The *P* values were then combined into one test statistic

$$X^2 = -2 \sum_{i=1}^{k} log_e(p_i)$$

which has an approximate chi-square distribution with 2k degrees of freedom.

The FDR was determined using R scripts by permutations, with labels swapped for the samples to preserve LD between SNPs. One thousand permutations on each cohort were seeded randomly using the Stanford BioX2 supercluster with a LSF batch system. A combined *P* value for each seed was calculated using Fisher's combined test (see previous paragraph). The FDR cutoff of Q<0.025 was iterated for the true dataset: At a cutoff *P* value of 2.90×10^{-05}, FDR is 0.025 (i.e. the average number of permuted eQTLs is 31 (peak at 28) which is 2.5% of the 1,220 true eQTLs for considered cutoff). The results are presented in **Supplementary Table 14**.

7.7 Selected published eQTL datasets

Index BP SNP and proxies ($r^2 > 0.8$) were also searched against a collected database of expression SNP (eSNP) results. The reported eSNP results met criteria for statistical thresholds for association with gene transcript levels as described in the original papers. The non-blood cell tissue eQTLs searched included aortic endothelial cells[39], left ventricle of the heart[40], CD41+ monocytes[41] and the brain[42]. The results are presented in **Supplementary Table 14**.

8 Enrichment of BP variants in experimentally annotated regulatory marks

8.1 Analysis of cell-specific DNase hypersensitivity sites (DHSs) using an OR method

The overlap of Cardio-MetaboChip SNPs with DHSs was examined using publicly available data from the Epigenomics Roadmap Project and ENCODE, choosing different cutoffs of Cardio-MetaboChip *P* values. The DHS mappings were available for 123 mostly adult cells and tissues[43] (downloaded from http://hgdownload.cse.ucsc.edu/goldenPath/hg19/encodeDCC/wgEncodeUwDnase/). The DHS mappings were specified as both "narrow" and "broad" peaks, referring to reduction of the experimental data to peak calls at 0.1% and 1.0% FDR thresholds, respectively. Thus, the "narrow" peaks are largely nested within the "broad" peaks. Experimental replicates of the DHS mappings (typically duplicates) were also available for the majority of cells and tissues.

SNPs from the Cardio-MetaboChip genome-wide scan were first clumped in PLINK[44] in windows of 100kb and maximum $r^2 = 0.1$ among LD relationships from the 1000 Genomes European data . Then, the resulting index SNPs at each *P* value threshold were tagged with $r^2 = 0.8$ in windows of 100kb, again using LD relationships in the 1000 Genomes, restricted to SNPs with MAF > 1% and also present in the HapMap2 CEU population. A reference set of SNPs was constructed using the same clumping and tagging procedures applied to GWAS catalog SNPs (available at http://www.genome.gov/gwastudies/, accessed 3/13/2013)[45] with discovery $P < 5 \times 10^{-8}$ in European populations. A small number of reference SNPs or their proxies overlapping with the BP SNPs or their proxies were excluded. After LD pruning and

exclusions, there were a total of 1,196 reference SNPs. For each cell type and *P* value threshold, the enrichment of SBP or DBP SNPs (or their LD proxies) mapping to DHSs was expressed as an odds ratio (OR) relative to the GWAS catalog reference SNPs (or their LD proxies), using logistic mixed effect models treating the experimental replicate peak determinations as random effects (glmer package in R). The significance of the enrichment ORs was derived from the significance of beta coefficients for the main effects in the mixed models (**Figure 3, Supplementary Table 16**).

8.2 Analysis of tissue-specific enrichment of BP variants and H3K4me3 sites

An analysis to test for significant cell-specific enrichment in the overlap of BP SNPs (or their proxies) with H3K4me3 sites was performed as described in Trynka et al, 2013[46]. The measure of overlap is a "score" that is constructed by dividing the height of an H3K4me3 ChIP signal in a particular cell by the distance between the nearest test SNP. The significance of the scores (i.e. *P* value) for all SNPs was determined by a permutation approach that compares the observed scores to scores of SNPs with similar properties to the test SNPs in terms of LD, proximity to genes, etc. The number of significant digits in the *P* value was determined by the number of permutations following the 10,000 iterations. .Results are shown in **Supplementary Table 19**.

8.3 Analysis of tissue-specific DHSs and chromatin states using Genomic Regulatory Elements and GWAS Overlap Algorithm (GREGOR)

Data acquisition and pre-processing

The DNase-seq ENCODE data for all available cell types were downloaded in the processed "narrowPeak" format. The local maxima of the tag density in broad, variable-sized "hotspot" regions of chromatin accessibility were thresholded at FDR 1% with peaks set to a fixed width of 150bp. Individual cell types were further grouped into 41 broad tissue categories (http://genome.ucsc.edu/ENCODE/cellTypes.html) by taking the union of DHSs for all related cell types and replicates. A set of BED files in hg19 assembly from the Integrative Analysis and original ENCODE analysis was also obtained. These data include uniformly processed datasets in 125 cell types generated by the "Open Chromatin" (Duke University) and University of Washington (UW) ENCODE groups. Data processed during the ENCODE Integrative Analysis were downloaded for available tissues. Otherwise, data from the original ENCODE analysis were obtained. The overlap of DHSs across different cell types was examined; we found that as expected, cell types derived from related tissues generally clustered together. The chromatin state segmentation by HMM generated from ENCODE/Broad in nine human cell types was also examined[47].

Selecting matched control SNPs for GWAS index SNPs

For each GWAS locus, a set of matched control SNPs was selected based on three criteria: 1) number of variants in LD ($r^2 > 0.7$; ± 8 variants), 2) MAF (± 1%), and 3) distance to nearest gene (± 11,655 bp). To calculate the distance to the nearest gene, the distance to the 5' flanking gene (start and end position) and to the 3' flanking gene was calculated and the minimum of these 4 values was used. If the SNP fell within the transcribed region of a gene, the distance was 0.

Estimating the probability of observed and expected overlap between a regulatory feature and GWAS locus

The probability that a set of GWAS loci overlap with a regulatory feature more often than we expect by chance was performed using the following method. A GWAS locus was represented by the GWAS index SNP or a SNP in LD with the index SNP ($r^2 > 0.7$). For each regulatory feature, the number of GWAS loci in which the physical overlap was observed with at least one experimentally defined genomic region of the feature was counted. The number of GWAS index SNPs in the ith matched control set that demonstrated a positional overlap with a given epigenomic feature, written as s_i, follows a binomial distribution with parameters n_i and p_i. The parameter n_i is equal to the number of index SNPs present in the ith control set. The second parameter p_i is calculated as the number of variants in the ith control set or their LD proxies that overlaps with the feature, divided by the total number of variants in the ith control set. If we assume there are r control sets in total, the number of index SNPs from all control sets that falls in a single feature is the sum of independent non-identical binomial random variables:

$$S = \sum_{i=1}^{r} s_i$$

In most cases, only one index variant was assigned to a matched control set, but there were some exceptions where more than one index SNP could match on the same 3 properties. An enrichment *P* value for any given s as $P(S \geq s)$ was estimated. P is the cumulative right tail probability based on the distribution of S and is calculated using a saddlepoint approximation method[48]. The results are shown in **Supplementary Tables 17-19** and **Supplementary Figure 8**. A collection of BP SNPs enriched in DHS sites in blood vessels is indicated in **Supplementary Table 20.**

8.4 Formaldehyde-assisted isolation of regulatory elements (FAIRE) analysis of BP variants in fine mapping regions in lymphoblastoid cell lines

FAIRE analysis was performed on a sample of 20 lymphoblastoid cell lines of European origin. All samples were genotyped using the Cardio-MetaboChip genotyping array, and BP SNPs and LD proxies ($r^2 > 0.8$) at the fine mapping loci (N = 24, see **Supplementary Table 23**) were assessed to identify heterozygous imbalance between non-treated and FAIRE-treated chromatin. A paired t-test was used to

compare the B allele frequency (BAF) arising from formaldehyde-fixed chromatin sheared by sonication and DNA purified to the BAF when the same chromatin sample underwent FAIRE to enrich for open chromatin. Three hundred and fifty-seven Cardio-MetaboChip BP SNPs were directly genotyped across the fine mapping regions. The Bonferroni-corrected threshold of significance is $P < 0.0001$ (0.05/357). The results for SNPs with $P < 0.05$ are reported in **Supplementary Table 23**. FAIRE results were not available for 54 SNPs: the missing data was due to genotype failure or not having >3 heterozygous individuals for statistical analysis. Therefore there are no results for three lower frequency BP loci (*SLC39A8*, *CYP17A1-NT5C2* and *GNAS-EDN3*) and for the second signal at the following loci: *MTHFR-NPPB* (rs2272803), *MECOM* (rs2242338) and *HFE* rs1800562).

9 Pathway analyses

9.1 MAGENTA

MAGENTA tests for enrichment of significant gene-wide *P* values in gene sets from a precompiled library derived from GO, KEGG, PATHTER, REACTOME, INGENUITY, and BIOCARTA and was performed as described by Segré et al, 2010[49]. Enrichment of significant gene-wide *P* values in gene sets is assessed by 1) using LD and distance criteria to define the span of each gene, 2) selecting the smallest *P* value among SNPs mapping to the gene span, and 3) adjusting this *P* value using a regression method that accounts for the number of SNPs, the LD, etc. In the second step, MAGENTA examines the distribution of these adjusted *P* values and defines thresholds for the 75%-ile and the 95%-ile. In the third step, MAGENTA calculates an enrichment for each gene set by comparing the number of genes in the gene set with *P* value less than either the 75th or 95th %ile to the number of genes in the gene set with *P* value greater than either the 75th or 95th %ile, and then comparing this quotient to the same quotient among genes not in the gene set. This gene-set quotient is assigned a *P* value based on reference to a hypergeometric distribution. The results based on our analyses are indicated in **Supplementary Table 21**.

9.2 Data-driven Expression Prioritized Integration for Complex Traits (DEPICT)

We applied the DEPICT[50] separately on genome-wide significant loci from the overall blood pressure (BP) Cardio-MetaboChip analysis including published blood pressure loci (see **Supplementary Table 22**). SNPs at the *HFE* and *BAT2-BAT5* loci (rs1799945, rs1800562, rs2187668, rs805303, rs9268977) could not be mapped. We also included associated loci ($P < 1x10^{-5}$) from the Cardio-MetaboChip stage 4 combined meta-analyses of SBP and the DBP. DEPICT assigned genes to associated regions if they overlapped or resided within associated LD blocks defined $r^2 > 0.5$ to a given associated SNP. After merging overlapping regions and discarding regions that mapped within the extended major

histocompatibility complex locus (we excluded chromosome 6, 20-40Mb), we were left with 76, 120, and 131 non-overlapping regions that covered 226, 292, and 329 genes for BP, SBP and DBP respectively. The gene counts differed from the loci used for manual lookups because DEPICT only included genes which passed quality control on Affymetrix gene expression microarrays (platforms U133 Plus 2.0, Human Genome U133 A, Mouse 430 2.0, and Rat 230 2.0). We used DEPICT to test enrichment at these regions for a total of 14,461 reconstituted gene sets, and for 209 tissue and cell type annotations. DEPICT relies on random loci to adjust for biases such as gene length and expression properties. In this work, we restricted the random loci construction to autosomal SNPs that were present on the Cardio-MetaboChip as well as in the 1000 Genomes data, which resulted in a total of 120,972 SNPs that covered >11,800 genes. To ensure that DEPICT worked well for the Cardio-MetaboChip-based analysis we performed 100 meta-analyses that were limited to the 120,972 Cardio-MetaboChip SNPs that passed quality control. Each simulated study comprised ~65 independent regions, which were subjected to DEPICT. Plotting of the gene set enrichment and tissue/cell type enrichment *P* values did not indicate any elevated type 1 error. We did, however, observe a slightly elevated type 1 error (data not shown) for the gene prioritization analyses and decided not to include this part of the DEPICT analysis in the results presented here. DEPICT was run using default settings, that is using 500 permutations for bias adjustment, 50 replications for false discovery rate estimation, normalized expression data from 77,840 Affymetrix microarrays for gene set reconstitution [51], assessing 14,461 reconstituted gene sets for enrichment (5,984 protein complexes that were derived from 169,810 high-confidence experimentally-derived protein-protein interactions[52]; 2,473 phenotypic gene sets derived from 211,882 gene-phenotype pairs from the Mouse Genetics Initiative[53]; 737 Reactome database pathways[54]; 184 KEGG database pathways[55]; and 5,083 Gene Ontology database terms[56]), and testing 209 tissue/cell types assembled from 37,427 Affymetrix U133 Plus 2.0 Array samples for enrichment in tissue/cell type expression.

10 Non-European meta-analysis

To assess the association of the 66 significant loci from the European ancestry meta-analysis in non-European ancestries, we obtained lookup results for the 66 index SNPs for participants of South-Asian ancestry (8 datasets, total N = 20,875), East-Asian ancestry (5 datasets, total N = 9,637), and African- and African-American ancestry (6 datasets, total N = 33,909). The association analyses were all conducted with the same covariates (age, age^2, sex, BMI) and treatment correction (+15/10 mm Hg in the presence of any hypertensive medication) as the association analyses for the discovery effort in Europeans. Quality control was conducted for each dataset, including a verification of the alignment of the coded

allele frequencies (**Supplementary Figure 9**). The full per-SNP meta-analysis results are given in **Supplementary Table 24**, including a trans-ethnic non-European meta-analysis. All meta-analyses were conducted using custom scripts in R statistical computing language[19]. The heterogeneity statistics were calculated using the software package GWAMA[57].

11 Genetic risk score and cardiovascular outcomes

In order to estimate the joint effect of the 66 BP SNPs on cardiovascular outcomes and other risk factors, we used a 66 SNP risk score, weighted by the effect size of SBP and DBP in the stage 4 combined meta-analysis for two separate risk scores (SBP-risk score and DBP-risk score). Individual-level data on cardiovascular outcomes were not available in large sample sizes. However, summary statistics from SNP-phenotype association studies can be used reliably to estimate the effect of predictor SNPs on the outcome phenotype as we have previously established[1,58]. The gtx package[59] for the R statistical programming language was used to estimate the effect of the SNP-risk score on the response variable in a regression model. The effect sizes are expressed as incremental change in the phenotype for quantitative traits and natural logarithm of the OR for binary traits, per 1 mmHg predicted increase in SBP or DBP (**Table 3**)**.** Some SNPs may be related to more than one risk factor for cardiovascular disease and such pleiotropic effects could potentially lead to increased or reduced association on the cardiovascular outcome than the BP effect would be expected to cause. Such confounding by pleiotropy would be expected to lead to a decrease in the goodness of fit of the regression model described above. We tested each model for such homogeneity of outcome/BP effects as implemented in the gtx package for R statistical computing language[59] and performed sensitivity analyses to determine whether removal of outlier predictor SNPs would alter the association of BP SNPs in aggregate to each cardiovascular outcome**.** We proceeded by iterative removal of the most extreme outlier SNP (proportional distance of the outcome/BP effect from the mean across all SNPs) and calculation of a heterogeneity *P* value until the deviation from homogeneity test is associated at a significance level of no less than 0.0028 (~0.05/number of phenotypes), see results in **Table 3.** The per-SNP results for each outcome are summarized in **Supplementary Table 25**. A graphical presentation of the relationship between predictor and response variable, before and after outlier removal is given in **Supplementary Figures 10.**

12 Literature review for genes at the newly discovered loci

Recognizing that the most significantly associated SNP at a locus may not be located in the causal gene and that the functional consequences of a SNP often extends beyond 100kb, we conducted a literature review of genes in extended regions around newly discovered BP index SNPs: The genes for this

extensive review were identified by DEPICT (see **Section 9.2, and Supplementary Table 27**). The DEPICT method assigns genes to associated regions if they overlap or reside within associated LD blocks defined by linkage disequilibrium $r^2 > 0.5$ to an index SNP. A literature review of candidate genes identified by this method was manually performed, and summary paragraphs are provided. Using the DEPICT method, two loci can be categorized as intergenic and not containing any genes in the genomic interval considered; for 10 of the loci there was only one gene at the locus (*HIVEP3, FGD5, ARHGAP24, TRIM36, CSNK1G3, ZC3HC1, LLRC10B, PDE3A, SETBP1* and *INSR*); for 7 loci there were multiple genes in the interval, a select few of these were considered for review (*DBH, SIK1, MYCBP3*).

12.1 FDG5

The *FGD5* gene encodes the FYVE Rho guanine exchange factor and pleckstrin homology domain containing 5 protein; a member of a larger family of FGD proteins characterised by a combination of highly conserved homology domains (eg Dbl, FYVE and PH). As guanine exchange factor (GEF) proteins, they act as a molecular switch facilitating GDP to GTP exchange in small GTPases such as Cdc42, RhoA, and Rac1. FGD5 is a unique member of the family with its specialized tissue distribution at mRNA and protein levels showing enrichment in human endothelial cells, mouse aorta, and carotid arteries[60]. FGD5 is shown to be of importance during various stages of mouse and zebrafish vasculature development. *In vitro* experiments in mouse and human cell lines implicate FGD5 in angiogenesis and vasculature remodelling, modulated by VEGF signalling and involving downstream Cdc42 activation[61].

12.2 ZC3HC1

The *ZC3HC1* gene encodes Zinc-finger C3HC-type protein 1, also known as Nuclear-Interacting Partner of ALK (NIPA). It is broadly expressed in human tissues, with highest expression in heart, skeletal muscle and testis[62]. The gene product is an F-box protein that is an interchangeable part of the SCF ubiquitin E3 ligase complex and, as such, is function defining. Phosphorylated NIPA targets cyclin B for SCF-dependent degradation. This control of cyclin B accumulation and degradation is one of key events in mitotic cell cycle progression and apoptotic events[63]. Recently, the same non-synonymous variant (rs11556924) in *ZC3HC1* has been reported to be associated with coronary disease[34]

12.3 DBH

Dopamine β-hydroxylase (DBH) catalyzes the conversion of dopamine to norepinephrine, a key neurotransmitter in maintaining heart rate and blood pressure. DBH is co-released with norepinephrine from noradrenergic nerve endings[64]. The resulting DBH activity is highly correlated with this enzyme's levels in the plasma and cerebrospinal fluid in humans and mice, as confirmed by QTL[65] and GWAS[66]

analyses. Genetic variation in *DBH* has been associated with hypertension and cardiovascular disease. To date, three SNPs in the *DBH* promoter region (rs161115[67], rs1989787[68], rs1076150) have been functionally characterized; all of these influence the binding motifs of transcription factors, regulating *DBH* gene expression. Furthermore, these variants have been shown to have additive effects, giving rise to a spectrum of dopamine beta hydroxylase traits[66].

12.4 INSR

The *INSR* (insulin receptor, IR) gene encodes a tyrosine kinase receptor; it mediates transduction of signals induced by pleiotropic endocrines, insulin and insulin-like growth factor 1 (IGF1), into the cellular *milieu*. This occurs via receptor homodimerization (IR-IR) and/or heterodimerization (IR-IGFR) and subsequent receptor autophosphorylation. Impaired insulin signaling is most commonly associated with diabetes mellitus, with most disease incidence attributed to IR malfunction. Impaired insulin signaling is identified as one of the key contributors to metabolic syndrome, a collective term given to a pathophysiological state including obesity, insulin resistance, hypertension and dyslipidemia, and an ultimate risk factor for cardiovascular disease[69]. Large-scale meta-analysis using the IBC (IMAT-Broad-CARe) array has identified a polymorphism in *INSR* (rs8112883) associated with altered plasma triglyceride levels, defining a novel gene locus for cardiovascular risk[70]. Insulin's tissue-specific effects on vascular endothelium[71] and smooth muscle[72] as well as cardiomyocytes[73] are well documented in modulating cardiovascular phenotypes, but the context-specific complexity of phenotypes in *in vitro* and *in vivo* IR model systems suggests involvement of many post-receptor modulators[74].

12.5 HIVEP3

HIVEP3, also known as *SHN3*, encodes for human immunodeficiency virus type 1 enhancer-binding protein 3, or Schnurri 3. In general, proteins of this family (HIVEP/SHN) bind to κB enhancer elements modulating gene expression in a rel/NFκB-independent manner[75]. They are relatively large proteins containing zinc-fingers. *HIVEP3* was initially described to undergo alternate splicing, leading to functional diversity of its isoforms[76]. Today, Schnurri 3 is best recognised for its role in adult osteoblast function and bone mass regulation[77] via involvement of Wnt and ERK pathways[78]. Importantly, through use of high-throughput transcript profiling in VSMCs, *HIVEP3* was identified as one of the novel transcripts to respond to Ang-II stimulus, implicating it in the maintenance of BP homeostasis[79].

12.6 TRIM36

The product of *TRIM36*, as well as the other members of this 71 gene family, contains a tripartite motif (TRIM) of the following domains: RING finger, B-box zinc finger, and C-terminal coil-coil.

It is expressed selectively in testis, prostate and brain as well as, to a lesser extent, in lung, kidney and heart[80,81] . TRIM36 is reported to be involved in post-translational protein modification known as sumoylation, aiding in transfer of small ubiquitin-related modifier 1 (SUMO1) from E2 ligase to a substrate, ultimately regulating processes such as cell cycle progression, cytoplasm-nucleus trafficking, and apoptosis[81,82]. TRIM36 expression is induced by actions of androgen receptor binding to intronic motifs within this gene, making it a candidate oncogene in progression of prostate cancer[83].

12.7 CSNK1G3

CSNK1G3 encodes for casein kinase 1 (CK 1/CK I) isoform ϒ 3. Kinases from this family are thought to be responsible for phosphorylation of 10% of the whole known eukaryotic phosphoproteome. CK1 serine/threonine kinases are ubiquitously expressed, monomeric proteins which are described as "constitutively active" for priming activity of other phosphoproteins[84].

12.8 SETBP1

SETBP1 encodes the translocation breakpoint-encoded protein (SET) binding protein 1, which is ubiquitously expressed in human tissues. SET is a nuclear phosphoprotein characterized by its inhibitory effect on a nuclear protein phosphatase 2A (PP2A), a regulator of cell proliferation, differentiation and transformation, and its close interaction with leukemia causing oncogenes. SET and SETBP were shown to form a complex and are postulated to be a part of multimeric protein aggregates[85]. Exome sequencing approaches have identified *de novo* mutations in this gene's SKI homology domain as an underlying cause for Schinzel-Giedion syndrome[86], as well as secondary mutations responsible for progression of myeloid leukemias. Although molecular mechanisms of SETBP1 function are still poorly understood, and are likely tumor-specific, observed mutations are believed to influence SETBP1 ubiquitination and its subsequent degradation and/or the proto-oncogene's interaction with homeobox genes (*HOXA9, HOXA10*)[87].

12.9 SIK1

The *SIK1* gene encodes a serine-threonine protein kinase family member known as the salt-inducible kinase isoform 1, further classified into the AMP-activated protein kinase (AMPK) subfamily. The SIK1 protein is ubiquitously expressed in many human tissues. Several kinase domains have been identified within the protein including: a cAMP-dependent domain[88], a calmodulin domain, a master regulator LKB1 domain (Thr-182)[89], and an autophosphorylation domain (Ser-186)[90]. The protein is best characterised as part of a signalling network involved in control of intracellular sodium homeostasis via direct interaction with the sodium-potassium ATPase, the key cellular housekeeper of salt and water

balance[91]. Angiotensin II is postulated to modulate SIK1 and, in turn, the sodium-potassium ATPase, most likely through regulation of its shuttling between the endosomal and plasma membrane pools[92]. In this tissue, blocking SIK1 activity prevents the hypertensive cell phenotype induced by hypertension-linked non-synonymous polymorphisms in α-adducin gene[93]. Furthermore, in the adrenal glands, similar mechanisms are thought to be involved in the angiotensin II regulation of CYP11B2, another BP gene candidate, and ultimately aldosterone secretion. However, the molecular identity of SIK1 in the adrenals has not been empirically confirmed[92]. In cardiac tissue, absence of SIK1 has been shown to be impair mouse cardiomyogenesis, suggesting this gene's involvement in cell cycle regulation and cellular differentiation[94].

12.10 MYBPC3

The *MYBPC3* gene encodes the cardiac myosin-binding protein C (MyBP-C), and mutations in *MYBPC3* are associated with familial hypertrophic cardiomyopathy (FHC or HCM), an autosomal dominant disease which is the most common cause of sudden death in young[95]. The MyBP-C protein binds myosin and titin within the thick filaments of the myocardial sarcomere, ultimately modulating cardiac muscle contractility. Its expression is strictly confined to heart tissue[96]. Two early independent genetic studies of unrelated families have identified mutations which produce aberrant MyBP-C protein, as a result of alternative splicing and gene duplication events[95,97]. To date, over 200 mutations in this gene alone have been associated with cardiomyopathy and heart failure, explaining 30-35% of its genetic component[96]. Animal model studies have also shown that expression of MyBP-C is important for determining diastolic function of the heart, independent of hypertrophy[98].

13 Supplementary table list and legends

The following supplementary tables are in a supplementary Excel file named "**03_NG-A41405R_SuppTables_final.xlsx**". The legends of the supplementary tables are below.

Supplementary Table 1: Individual cohort study information and blood pressure measurement methods.
Supplementary Table 2: Genotyping methods.
Supplementary Table 3: Data-type contribution and participant characteristics.
Supplementary Table 4: Meta-analysis stage 4 results
Supplementary Table 5: UK Biobank validation
Supplementary Table 6: Loci identified by GCTA with multiple signals of association.
Supplementary Table 7: All SNPs selected by GCTA as independently associated with SBP.
Supplementary Table 8: All SNPs selected by GCTA as independently associated with DBP.
Supplementary Table 9: SNPs at 66 genome-wide significant CM loci or in the literature for conditional analysis in WGHS, annotation in eSNP analyses or inclusion in pathway analyses.
Supplementary Table 10: Conditional analysis using the WGHS dataset.
Supplementary Table 11: Summary of Cardio-MetaboChip BP fine mapping regions.
Supplementary Table 12: Ninety-nine percent credible intervals at Cardio-MetaboChip BP fine mapping regions.
Supplementary Table 13: Ninety-nine percent credible causal SNPs at Cardio-MetaboChip BP fine mapping regions.
Supplementary Table 14: eSNP analysis for cell types other than whole blood.
Supplementary Table 15: eSNP analysis for whole blood.
Supplementary Table 16: Analysis of enrichment of DNase-hypersensitive sites among the BP loci, by cell type.
Supplementary Table 17: Tissue categorization for DNase-hypersensitive site analyses.
Supplementary Table 18: Analysis of enrichment of DNase-hypersensitive sites among the BP loci, grouping cell types by tissue.
Supplementary Table 19: Analysis of enrichment of methylation sites among the BP loci.
Supplementary Table 20: BP SNPs enriched in DHS sites in blood vessels.
Supplementary Table 21: MAGENTA analysis.
Supplementary Table 22: DEPICT analysis.
Supplementary Table 23: FAIRE analysis.
Supplementary Table 24: Non-European meta-analysis.
Supplementary Table 25: Detailed results of risk score analyses for each SNP.
Supplementary Table 26: Genetic BP risk-score analysis applied to related cardiovascular phenotypes.
Supplementary Table 27: Genes at new BP loci using DEPICT.

Supplementary Table 1: Individual cohort study information and blood pressure measurement methods.

All participating studies are listed in alphabetical order. Information is provided on the full name of the study, the parent study name (if the study is part of a consortium of studies), ethnicity and study design. Key characteristics of the BP values used in our analyses, including the device used for BP measurement, the number of BP values averaged when more than one value was available, and the position of the patient when taking the BP measurement is indicated. A published reference and/or a

website is indicated when available. CAD = coronary artery disease, EUR = European ancestry, SAS = South Asian ancestry, EAS = East Asian ancestry, AFR = African ancestry, MI = myocardial infarction, NA = not available.

Supplementary Table 2: Genotyping methods.

Information on genotyping and imputation methods for both Cardio-MetaboChip and imputed datasets are indicated. The platform, calling algorithm, the number of SNPs used for either discovery analysis or for a lookup is indicated. Filtering parameters before imputation for the studies supplying imputed genotypes are provided including the cutoffs for sample call rate, SNP call rate, Hardy-Weinberg equilibrium (HWE), minor allele frequency (MAF) and others used. For studies using imputed (imput.) genotypes, the number of SNPs used for imputation, the software and reference panel used for imputation, and the filtering parameters of imputed genotypes are provided.

Supplementary Table 3: Data-type contribution and participant characteristics.

Demographic data including BP are indicated for all studies (European-, South-Asian, East-Asian, and African-Ancestry). The general demographic information includes the number of participants analyzed (N) and genotyping platform used (CM indicates Cardio-Metabochip, and ICBP 2011 indicates if this dataset was included in the published ICBP-GWAS dataset). The basic description includes the percentage of categorical values and the mean and SD of continuous measurements. The BP values presented are after applying the treatment correction of +15/10mmHg to individuals on any anti-hypertensive medication (see Supplemental Text). The standard deviation (SD) of the residual from a linear regression on age, age^2, sex, and BMI are indicated for SBP and DBP. The percentage of participants on any anti-hypertensive medication and the percentage of participants with hypertension defined as SBP≥140mmHg or DBP≥90mmHg or presence of ≥1 anti-hypertensive medication (% HTN) are also indicated.

Supplementary Table 4: Meta-analysis stage 4 results.

The meta-analysis results of stage 4 is shown is this table, analogous to Table 1 of the main text.

Supplementary Table 5: UK Biobank validation.

The results of the 18 SNP lookup in the UK Biobank are shown here, analogous to Table 1 of the main text.

Supplementary Table 6: Loci identified by GCTA with multiple signals of association.

Loci for which the GCTA-COJO software identified multiple association signals for SBP and/or DBP using the GoDARTS study as a reference dataset at a threshold $P < 5x10^{-8}$. The SNPs selected and their summary statistics from the single-SNP and approximate conditional analyses are reported. For loci where both traits are observed with multiple association signals, if the same SNPs are selected, these are listed in the table. When GCTA-COJO selects different SNPs for each of the traits, but they are proxies ($r^2>0.8$), results for the signals with the lowest *P* value are reported. Otherwise, all SNPs selected for SBP and DBP can be found in the table with their summary statistics only for the trait for which they were selected. The lowest *P* values in the joint analysis are shown in bold. a: proxy SNP was selected for DBP in the joint analysis. b: proxy SNP was selected for SBP in the joint analysis.

Supplementary Table 7 and Supplementary Table 8: ALL SNPs selected by GCTA as independently associated with BP.

The results based on SBP results are in Supplementary Table 7 and the results based on DBP are in Supplementary Table 8. A threshold of $P < 5x10^{-8}$ was used and we utilized GoDARTS (primary analysis) and WTCCC1-T2D/58BC (secondary analysis) as reference datasets.

All SNPs for which the GCTA-COJO software identifies independent association at $P < 5x10^{-8}$. The coded allele (CA) and non-coded allele (NCA), the total sample size (N) are indicated for the analyses using GoDARTS and WTCCC1-T2D/58BC as a reference along with their association statistics. "LD r" denotes the correlation coefficient, r, in the reference dataset between a SNP and the one following in the table. Given that GCTA-COJO assumes the LD between SNPs more than 10 Mb away or on different chromosomes is zero, the correlation coefficient is omitted in the table for those SNPs. The final columns indicate whether the two analyses using the different reference datasets are in agreement and the r^2 between the two SNPs if different SNPs were selected. The yellow highlight indicates that a SNP was identified in one analysis, but not in the other.

Supplementary Table 9: List of SNPs at genome-wide significant Cardio-MetaboChip loci for secondary analyses.

Information is provided on SNPs selected for conditional analysis in WGHS, for annotation and inclusion in eSNP and DNase Hypersensitivity analyses, and for pathway analyses. CM1 = indicates associated SNP in the GCTA analyses; CM2 = indicates a second associated SNP at a locus in the GCTA analysis; NOT IN LIT = unpublished, not reported in the literature. The "notes" column indicates the provenance of the selected SNPs and references. Ho et al (2010)[99]; Padmanabhan et al (2010)[100], Takeuchi et al (2010)[101]; Ehret et al (2011)[1]; Johnson et al (2011a)[102]; Johnson et al (2011b)[103]; Kato et al (2011) [104]; Salvi et al (2011)[105]; Wain et al (2011)[106]; Ganesh et al (2013)[107]; Kato et al (2015)[108]; WGHS= Women's Genome

Health Study; GCTA_CM (using GWAS+CM) status refers to the results from GCTA analysis which are presented in full in **Supplementary Tables 6-8**.

Supplementary Table 10: Conditional analysis using the WGHS dataset.

Conditional association analyses were conducted in the WGHS by linear regression analyses using more than one predictor SNP at the same time. Each sub-table shows the association statistics for single association analyses and the conditional analyses for each locus where there was more than one signal identified in the GCTA analyses or based on comparison to the literature and reference to linkage disequilibrium patterns in reference samples. The BP trait is indicated for the genome-wide significant SNP. The highlighted bottom line of each sub-table shows our interpretation of the conditional analysis results, taking into account the conditional analysis results using GCTA-COJO software. All BP loci indicated in **Supplementary Table 6** were examined in the analysis, although only results for loci that were informative in the WGHS are presented for space reasons. Uninformative results are those in which no more than one SNP was nominally significant ($P < 0.05$) in a single or joint model.

Supplementary Table 11: Summary of Cardio-MetaboChip BP fine mapping regions.

The genomic positions (hg 19) of the Cardio-MetaboChip fine-mapping regions overlapping with SBP or DBP loci are shown. Consortia indicates which consortium has submitted the fine-mapping region at Cardio-MetaboChip design, trait/type/rank indicates the trait used for the analyses, the type of fine-mapping region (locus fine-mapping = LFM, signal fine-mapping - SFM) and its rank as indicated by Voight et al[13]. Start and End regions indicates the genomic region. Locus with multiple signals indicates whether there are multiple signals at the locus, based on GCTA or WGHS conditional analyses in this study. The traits (SBP or DBP) that reached genome-wide significance in our analyses are indicated, the main trait provides the trait with the most significant association, and the index SNPs of the independent signals observed in our results at the locus (main trait index SNP). SNPs that are not present in the FM interval are marked with a "*".

Supplementary Table 12: Ninety-nine percent credible intervals at Cardio-MetaboChip BP fine-mapping regions.

The 99% credible intervals were estimated in the Cardio-MetaboChip (MC) fine-mapping regions reaching genome-wide significance in our association analyses. Three sets of results are provided: A) the GWAS+MC meta-analyses (entire dataset), B) in the MC-only meta-analyses, and C) overlapping SNPs from both analyses (last columns). We have indicated whether the locus contains multiple signals, the identity of the index SNP, the conditioning SNP and their position. High resolution fine mapping is an

arbitrary metric of fine mapping success, defined as a number of 99% credible SNPs for SBP and DBP ≤5 and a reduction of the total number of SNPs in the credible interval by a factor 5 or more for SBP and DBP in the GWAS+MC analysis. The number of SNPs in the FM region that account for 99% of the posterior probability are indicated (#SNPs) in relation to the total number of SNPs in the fine-mapping region (#SNPs in fine-map.). The distance (kb) covered by the set of SNPs in the FM region that account for 99% of the posterior probability is indicated (distance). The start and end position denote the starting and end base position of the interval covered by the set of SNPs in the FM region that account for 99% of the posterior probability. For FM regions where a larger refinement was achieved (number of credible causal SNPs threshold arbitrarily set to <20; FM regions identified with NA otherwise), the list of missense/synonymous credible causal SNPs in given. The number of SNPs overlapping between the credible sets for GWAS+CM and CM-only are indicated in the last two columns (#overl. SNPs). The number of SNPs in the FM regions may vary between traits due to slight differences in the datasets included for each analysis as the results of the QC. ND = conditional analysis not performed for locus as second signal not present in the fine-mapping region. All coordinates are on b37.

Supplementary Table 13: Ninety-nine percent credible causal SNPs at Cardio-MetaboChip BP fine mapping regions.

The rs numbers of all SNPs that account for 99% of the posterior probability within the 99% credible intervals (within the fine-mapping regions- cf. **Supplementary Table 11**) are listed for both BP traits (SBP and DBP) and for the two analyses (GWAS + CM = all data or CM only). The last two columns (GWAS+CM vs CM- only) indicate the overlapping SNPs between both sets of analyses per trait.

Supplementary Table 14: eSNP analysis for cell types other than whole blood.

For the experiments including: macrophages, monocytes, skin, lymphoblastoid cell lines (LCLs), fat, blood vessels, heart and liver the results presented are the BP SNPs or a proxy SNP (r^2>0.8) if the index BP SNP was not directly genotyped which were significantly associated with expression of a *cis* transcript ($P < 1 \times 10^{-4}$), and the most significantly associated eSNP for that transcript was identical or in high LD with the BP SNP (r^2>0.8). Abbreviations: aorta adventitia =AAdv, aorta intima-media = AMed, mammary artery intima-media = MMed, heart = H and liver = L. For the experiment on kidney tissue, the results of a Fisher's combined test are presented at an FDR of <0.025. For the experiment with aortic endothelial cells the results with $-\log P < 1 \times 10^{-6}$ (Bonferroni corrected $\alpha < 0.05$) are presented. For the experiments on CD41+ monocytes, and brain tissue, the results met criteria for statistical thresholds for association with gene transcript levels as described in the original papers. The experiment is the tissues tested, and the coded allele (CA), non-coded allele (NCA), coded allele frequency (CAF) is provided.

Imputation quality (imput. qual.) is provided if available. Full details of the analysis per tissue and cell type are provided in **Section 7.**

Supplementary Table 15: eSNP analysis for whole blood.

Association results are shown for the index BP SNP to any transcript within 1 Mb achieving FDR < 0.05. The best eSNP for that transcript in whole blood is identified and then the association results for the index BP SNP are shown after adjustment for the best eSNP for that transcript (BP SNP conditional P-value). "BP SNP" denotes Cardio-MetaboChip index or proxy-SNP. "Input." denotes imputation quality r^2, the effect (beta) for both the BP SNP and eSNP effects are also provided.

Supplementary Table 16: Analysis of enrichment of DNase-hypersensitive sites among the BP loci, by cell type.

The odds ratios for each *P* value cutoff among the CM BP association data are listed for each cell type. The endothelial cell types are listed first, followed by all other cell types sorted alphabetically. The SNPs from the SBP or DBP discovery genome-wide scans meeting a series of *P* value thresholds in the range 10^{-4}-10^{-16} were clumped and tagged as described above and then compared to GWAS catalog SNPs for enrichment in narrow or broad DHS peaks for each of 123 cell types.

Supplementary Table 17: Tissue categorization for DNase-hypersensitive site analyses.

Grouping categorization for related tissues in the DNase-hypersensitive site analysis. Two different tissue categorizations were available (Broad tissue category and ENCODE tissue category). The published region definitions listed were used (see **Section 8**; the name is the concatenation of the experiment name and the experiment definition).

Supplementary Table 18: Analysis of enrichment of DNase-hypersensitive sites among the BP loci, grouping cell types by tissue.

The enrichment of DNase-hypersensitive sites among the BP loci is expressed by comparing the observed and expected number of SNPs overlapping DNA hypersensitive sites for each cell type. The enrichment is expressed numerically as "fold change".

Supplementary Table 19: Analysis of enrichment of methylation sites among the BP loci.

For each tissue, enrichment of overlap of BP SNPs (or proxies)[16] with H3K4me3 sites was calculated and the significance tested according to the approach in Trynka et al, 2013[46]. The *P* value is indicated for each of the two BP phenotypes (SBP and DBP) and their combination (SBP and DBP / SBP or DBP). The table is sorted by "SBP or DBP" *P* value.

Supplementary Table 20: BP SNPs enriched in DHS sites in blood vessels.

The index BP SNP is indicated and its chromosomal position, and the SNP that is enriched in DHSs in blood vessels. Further information on tissue categorisation and the DHS results is provided in **Supplementary Table 17.** DHS= DNase hypersensitivity site.

Supplementary Table 21: MAGENTA analysis.

In total 3,216 gene-sets were interrogated; only the gene sets (GS) yielding a FDR of < 0.5 (75% *P*-value threshold) are shown in this table. The original and effective gene-set sizes are indicated (orig. GS size and eff. GS size). The analyses were run using two conditions: using a *P* value cutoff at either 95% or 75% in the CM-BP analyses.

Supplementary Table 22: DEPICT analysis.

Data-driven Expression Prioritized Integration for Complex Traits (DEPICT)[50] was used to assess whether genes in genome-wide significant blood pressure regions were enriched for any of 14,461 reconstituted gene sets (see **Section 9**). Identifiers of reconstituted gene sets are prefixed by the Gene Ontology database, the Mouse Genome Project database, REACTOME, InWeb protein-protein interaction database, KEGG. The gene set name is based upon the source gene set. The column labeled Top 5 genes in reconstituted gene set provides the top 5 genes annotated to a given reconstituted gene set within an associated region along with the genes' strength of association (as Z score in brackets) for that reconstituted gene set. Among all tests conducted, only the tests yielding an FDR of ≤ 5% are retained in this table.

Supplementary Table 23: FAIRE analysis.

The *P* values for allele-specific FAIRE are provided for each SNP at each of the fine mapping loci (*P* < 0.05). The index and proxy SNPs, their positions (hg19), correlation (r2), and number (n) of heterozygotes are shown.

Supplementary Table 24: Non-European meta-analysis.

Association results for 66 SNPs from the European meta-analysis for each BP phenotype (SBP and DBP) in three samples of non-European ancestry (South Asian, East Asian and African). The coded allele (CA) and non-coding allele (NCA) are indicated alongside the coded allele frequencies (CAF) for European-ancestry participants (CAF_EUR), for South Asian ancestry participants (CAF_SAS), for East Asian ancestry participants (CAF_EAS), and for African ancestry participants (CAF_AFR). The association results for each ancestry include beta, standard error (SE), *P* value, and the total sample size (Total N). The association results for a meta-analysis across all non-European participants is provided, and include

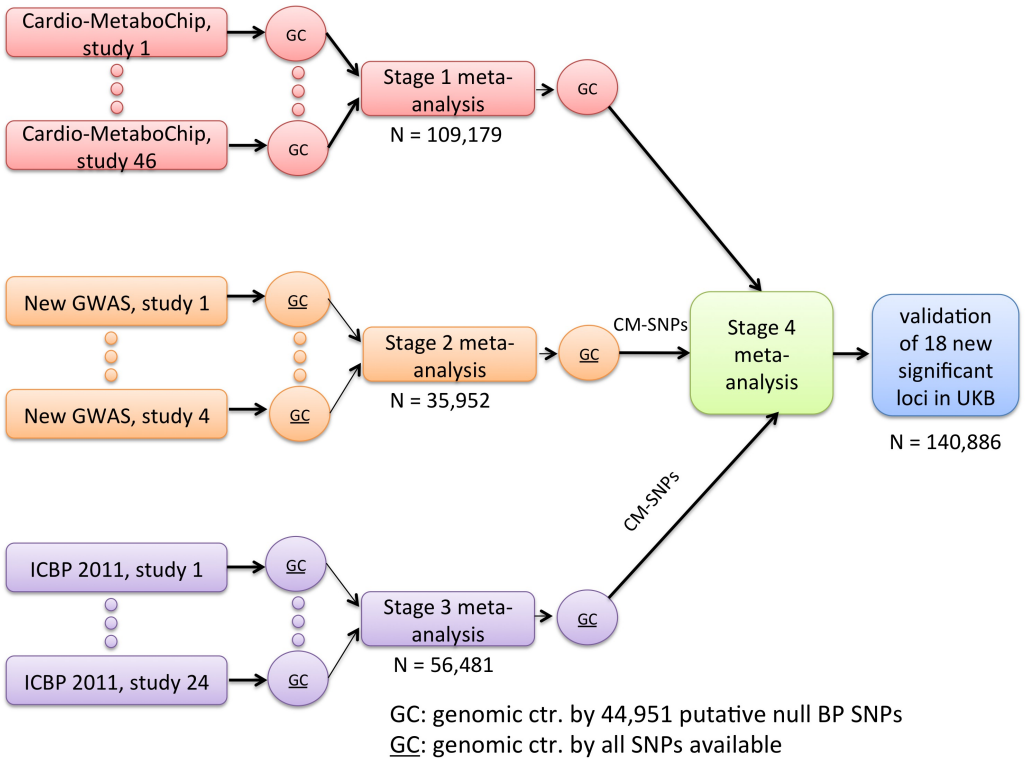
beta, SE, *P*-value and Total N. The previously significant (signif.) column indicates if the variant was previously reported to be associated with blood pressure in a non-European ancestry analyses. The heterogeneity metrics Cochrane Q (Coch_Q) and I^2 are indicated, calculated using summary results from all ancestries. Power indicates statistical power using an additive model, the effect size estimated in the European ancestry analyses, and an alpha of 0.05/66SNPs.

Supplementary Table 25: Detailed results of risk score analyses for each SNP per outcome.
The per SNP results underlying the risk score results shown in **Table 3** are presented. The chromosome (Chr) and position (hg19) of the index SNP is provided; the coded allele (CA) and non-coded allele (NCA) are indicated; and beta, SE and *P* value for each outcome. CAD: coronary artery disease, LV: left ventricle, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, cr: creatinine,

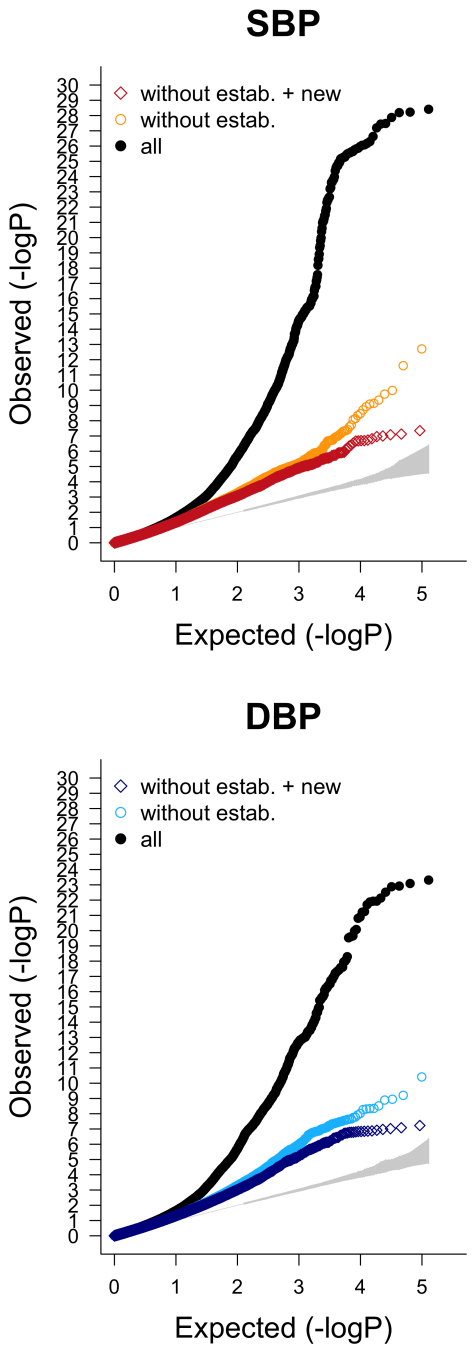
Supplementary Table 26: Genetic BP risk-score analysis applied to related cardiovascular phenotypes.
The BP genetic risk score was applied to related cardiovascular phenotypes using public databases (T2D: http://diagram-consortium.org/about.html; BMI and height: https://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files; lipids: http://csg.sph.umich.edu//abecasis/public/lipids2013/). Pt = phenotype investigated, noSNPs = number of SNPs used in the analysis, SBPeffect/DBPeffect = effect size of the genetic BP risk score, SBPpval/DBPpval = p-value of the genetic risk score analysis. Information is provided on candidate genes per new locus using the definition described in **Section 12** of this document.

Supplementary Table 27: Genes at new BP loci using DEPICT.
Information is provided on candidate genes per new locus using the definition described in **Section 12** of this document.

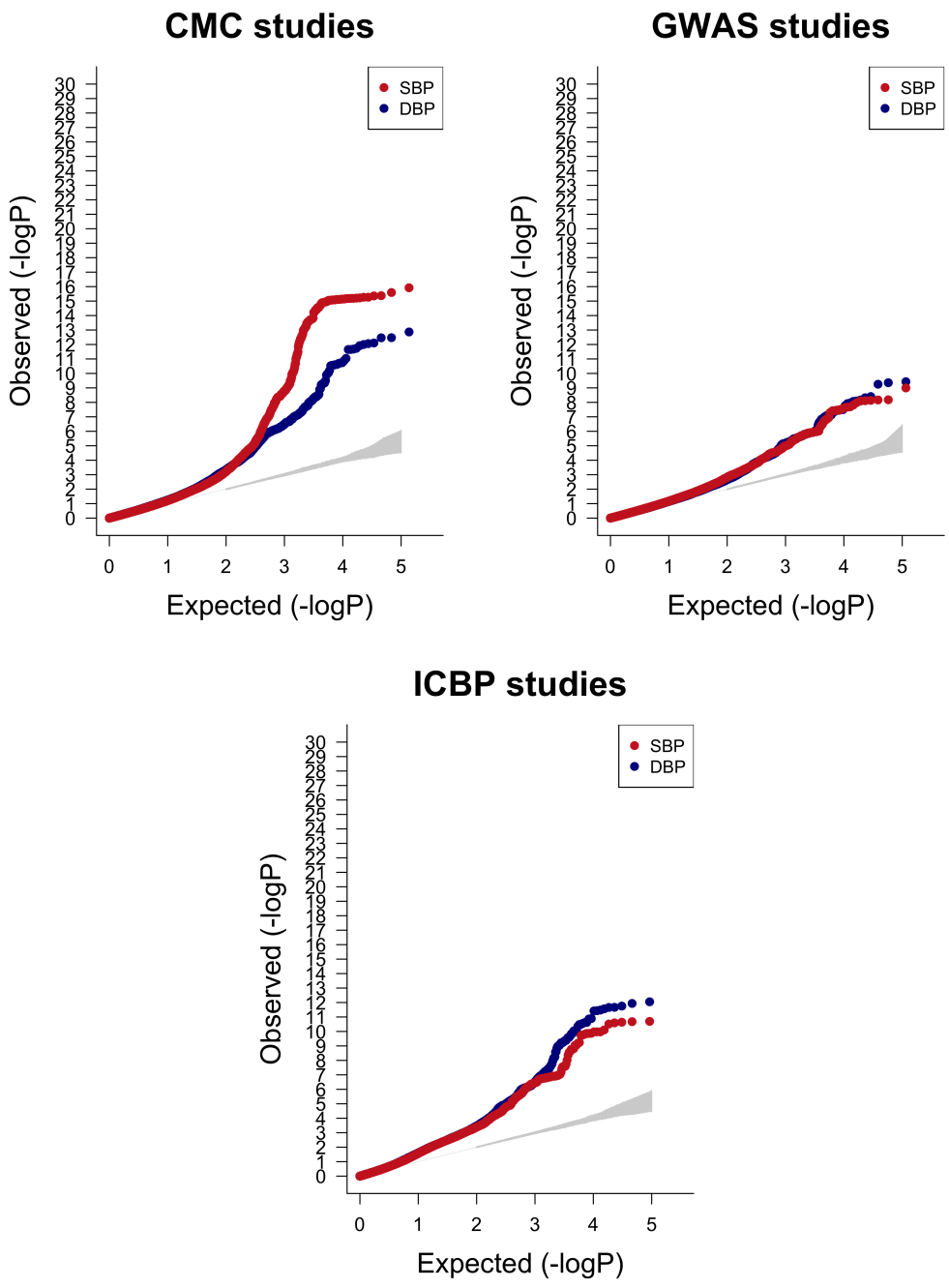
14 Supplementary figures



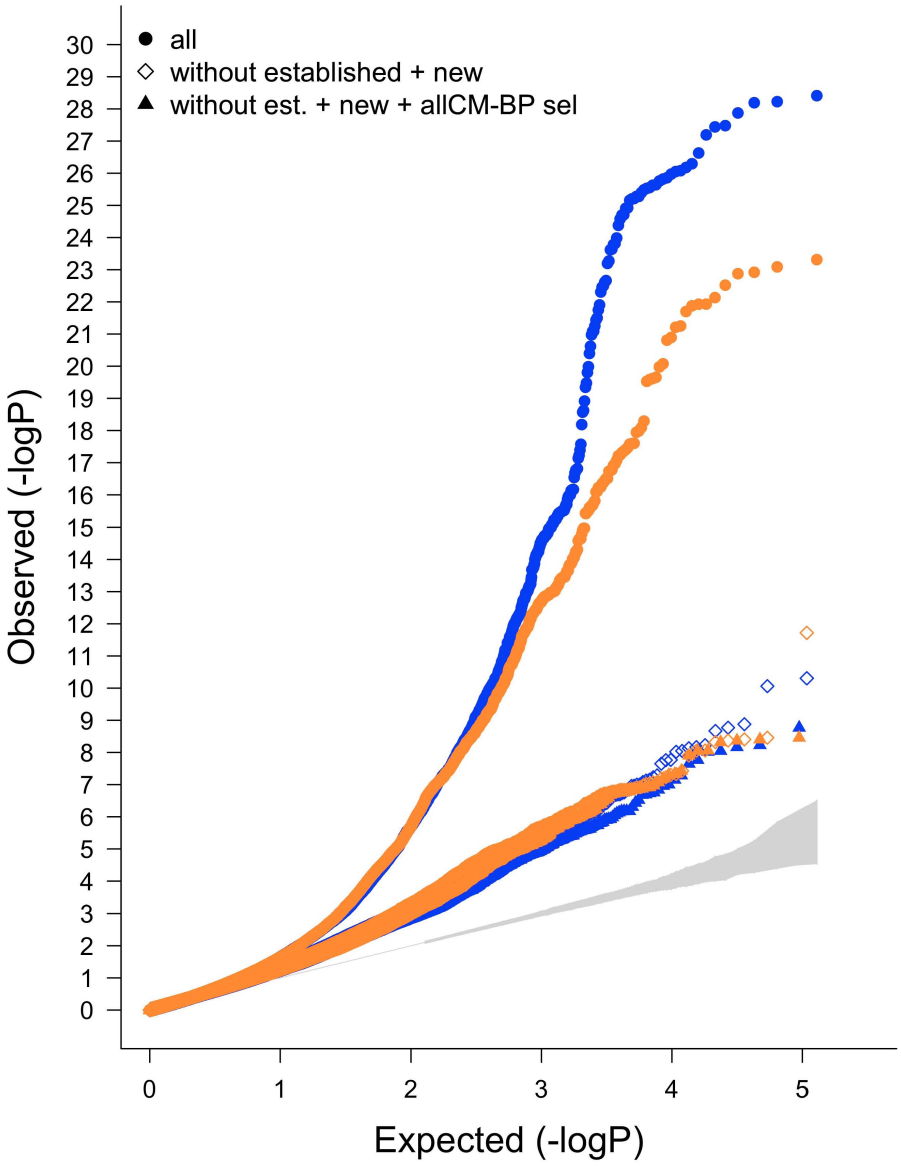
Supplementary Figure 1. Schematic of the experimental design of the meta-analyses. Meta-analyses were carried out in 4 stages (see **Supplementary Information**). Stage 1: results from 46 studies genotyped using Cardio-MetaboChip; Stage 2: unpublished results based on imputed genotypes from genome-wide genotyping arrays of 4 studies; Stage 3: results from published imputed genotypes from genome-wide genotyping arrays of 24 studies; Stage 4: meta-analysis of the 3 separate meta-analyses, including a total of 201,529 individuals. "GC" indicates at what stages genomic-control was applied and the SNPs that were used. The final meta-analysis was not corrected by genomic-control. Subsequently, a validation step was performed for 18 sentinel SNPs from genome-wide significant loci without prior support in the literature. UKB = UK Biobank.



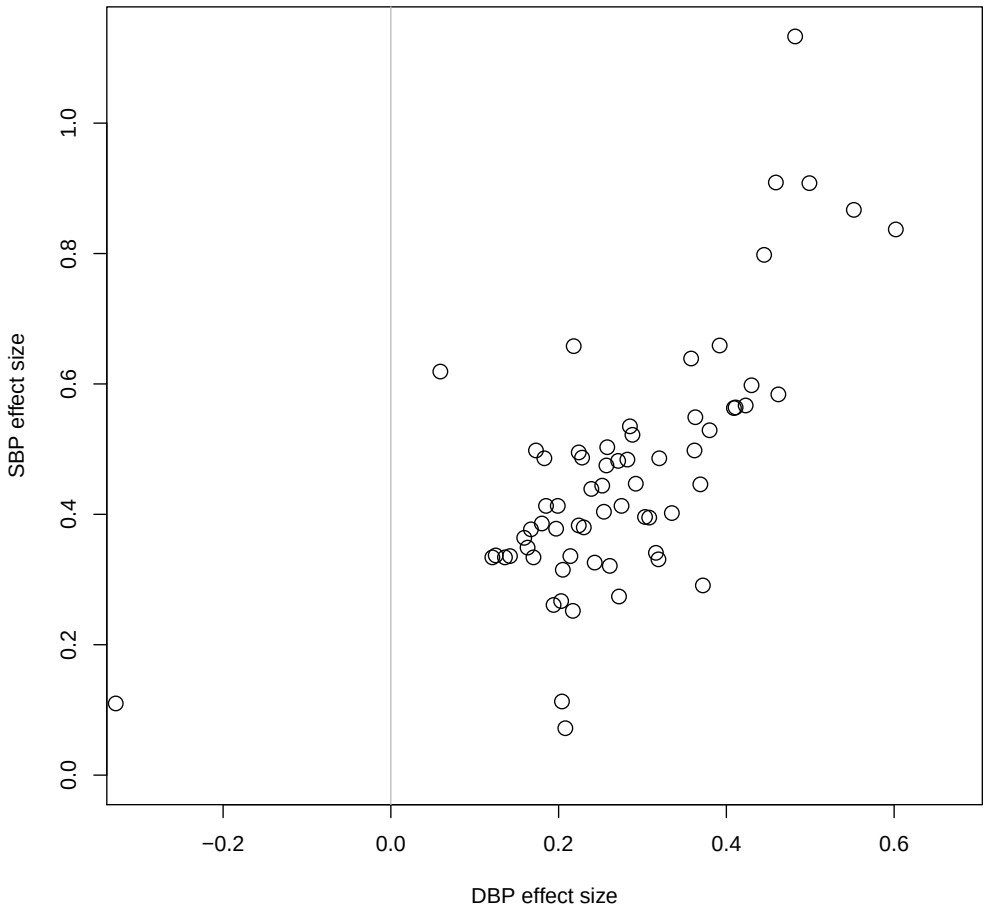
Supplementary Figure 2. Quantile-quantile-plots of the p-values from the Stage 4 Cardio-MetaboChip-wide meta-analysis for SBP and DBP. Observed $-log_{10}P$ are plotted against expected $-log_{10}P$ for three datasets: in black the entire dataset; in orange (SBP) and light blue (DBP) results after removal of all SNPs within a 3.5Mb window around index SNPs at previously reported loci; in red (SBP) and dark blue (DBP) results after removal of all 66 loci significant in our study.



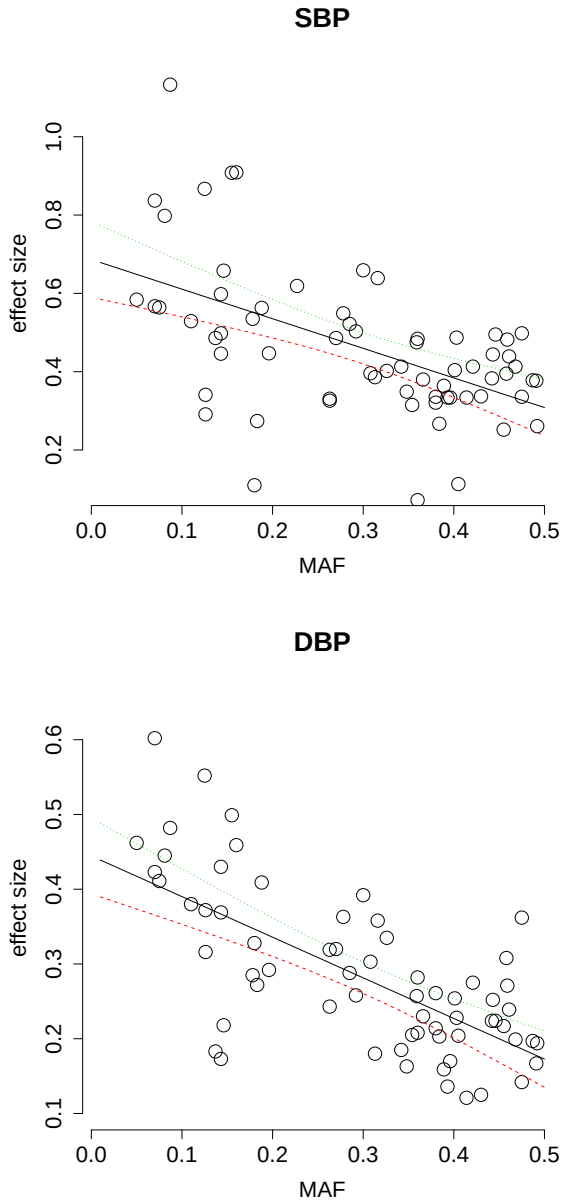
Supplementary Figure 3. Quantile-quantile-plots of the P values at each stage of the meta-analysis. The numbers include GC correction for the given stage.



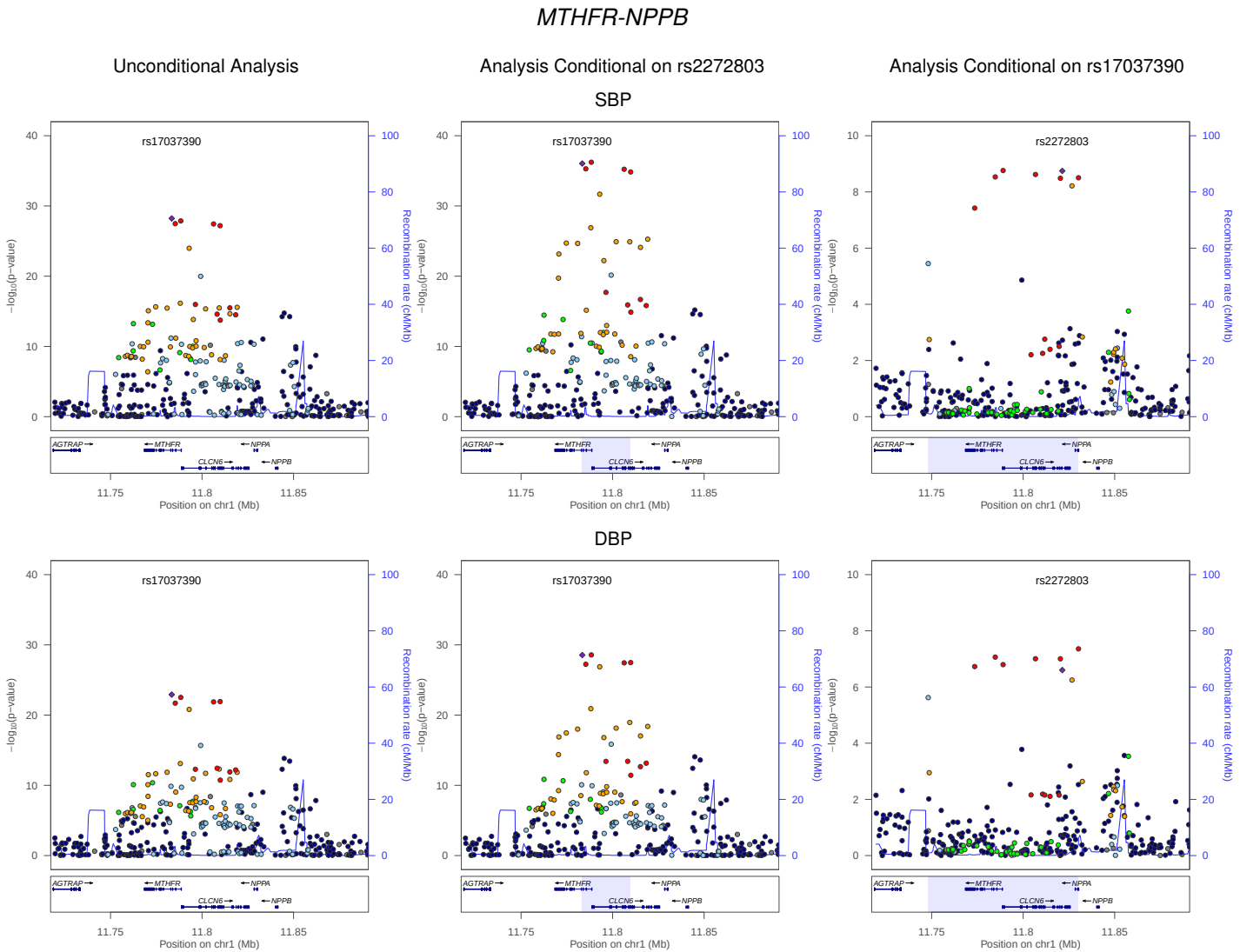
Supplementary Figure 4. Quantile-quantile-plots of the P values of final meta-analysis results after subtracting new, known, and all BP related SNPs contained on the Cardio-MetaboChip. In addition to the 5,000 SNPs selected from previous studies, the Cardio-MetaboChip contains additional SNPs selected for fine-mapping of BP regions, in total amounting to 36,855 SNPs. The figures explores the impact of removing these SNPs from the dataset.



Supplementary Figure 5. Effect-size plot for each of the 66 index SNPs. The effect sizes in mm Hg per allele at each of 66 index SNPs are plotted for both phenotypes: the SBP effect size (y-axis) is plotted as a function of the DBP effect size (x-axis).



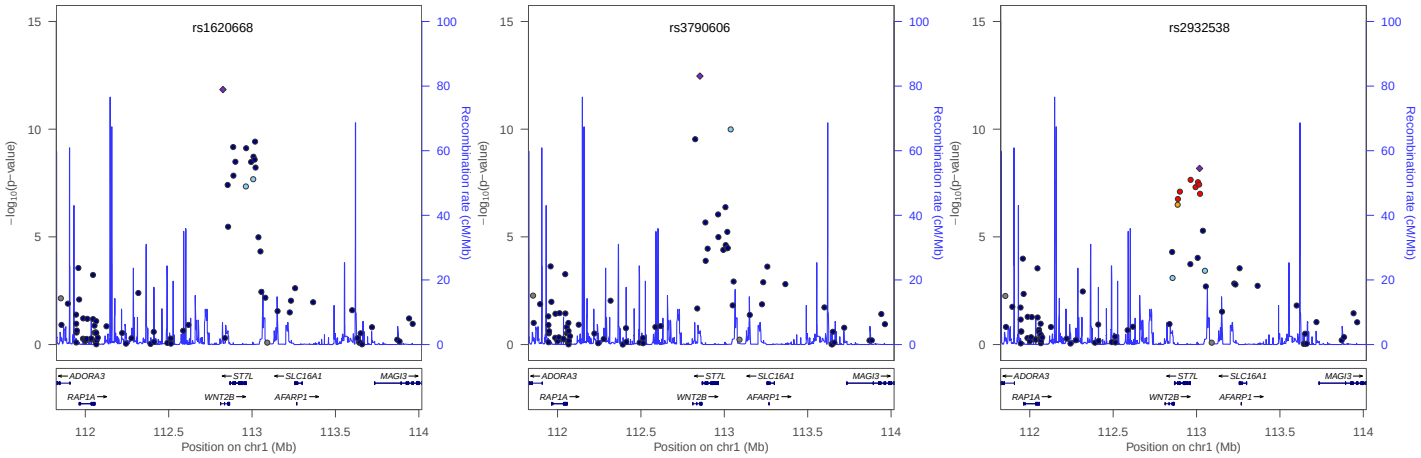
Supplementary Figure 6. Effect-size by allele frequency plot for SBP and DBP. The absolute effect size per allele at each of the 66 index SNPs is plotted as a function of minor allele frequency (MAF). The regression line includes 95%-confidence bounds (lower-bound in red, higher-bound in green).

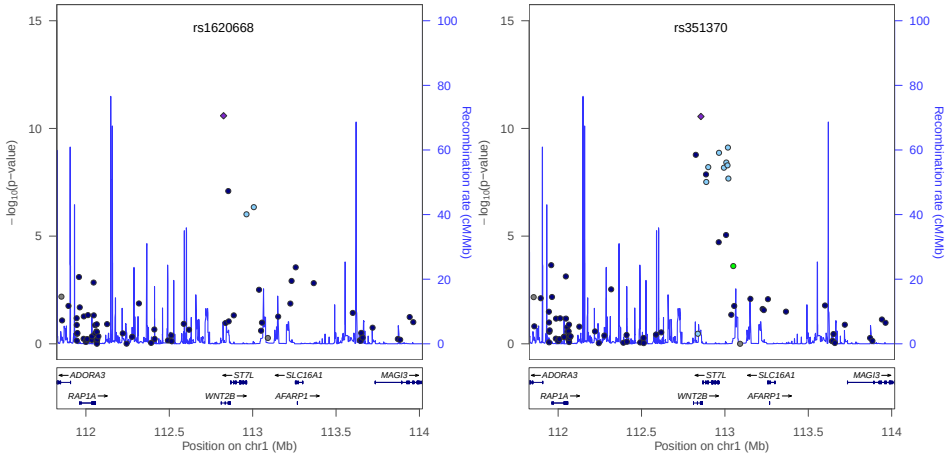


Supplementary Figures 7: Locus Zoom plots of BP loci. The unconditional analyses are shown to the left conditionals in the figures to the right.

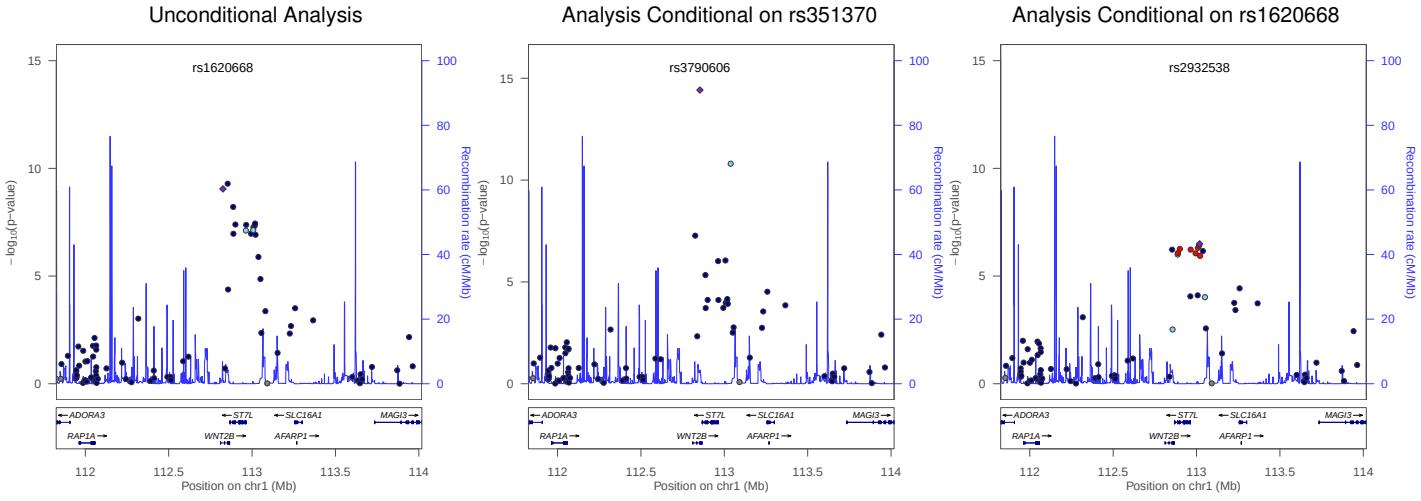
ST7L-CAPZA1-MOV10

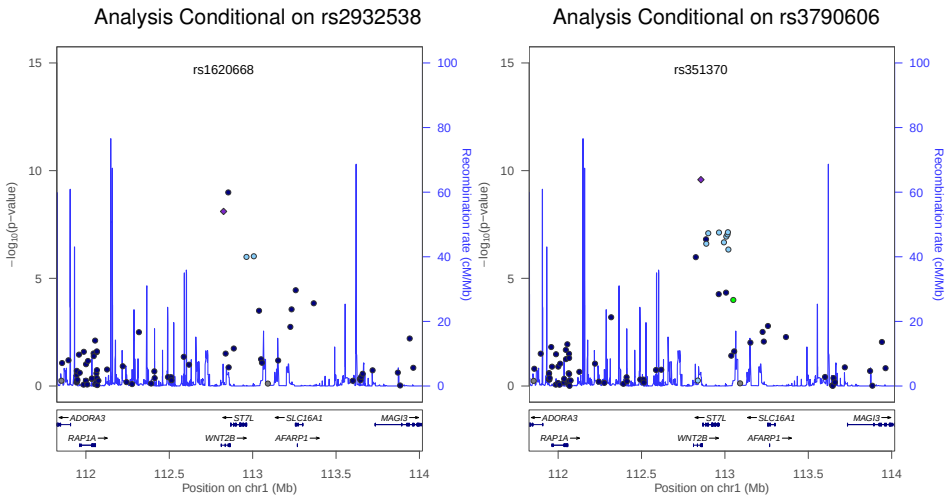
SBP



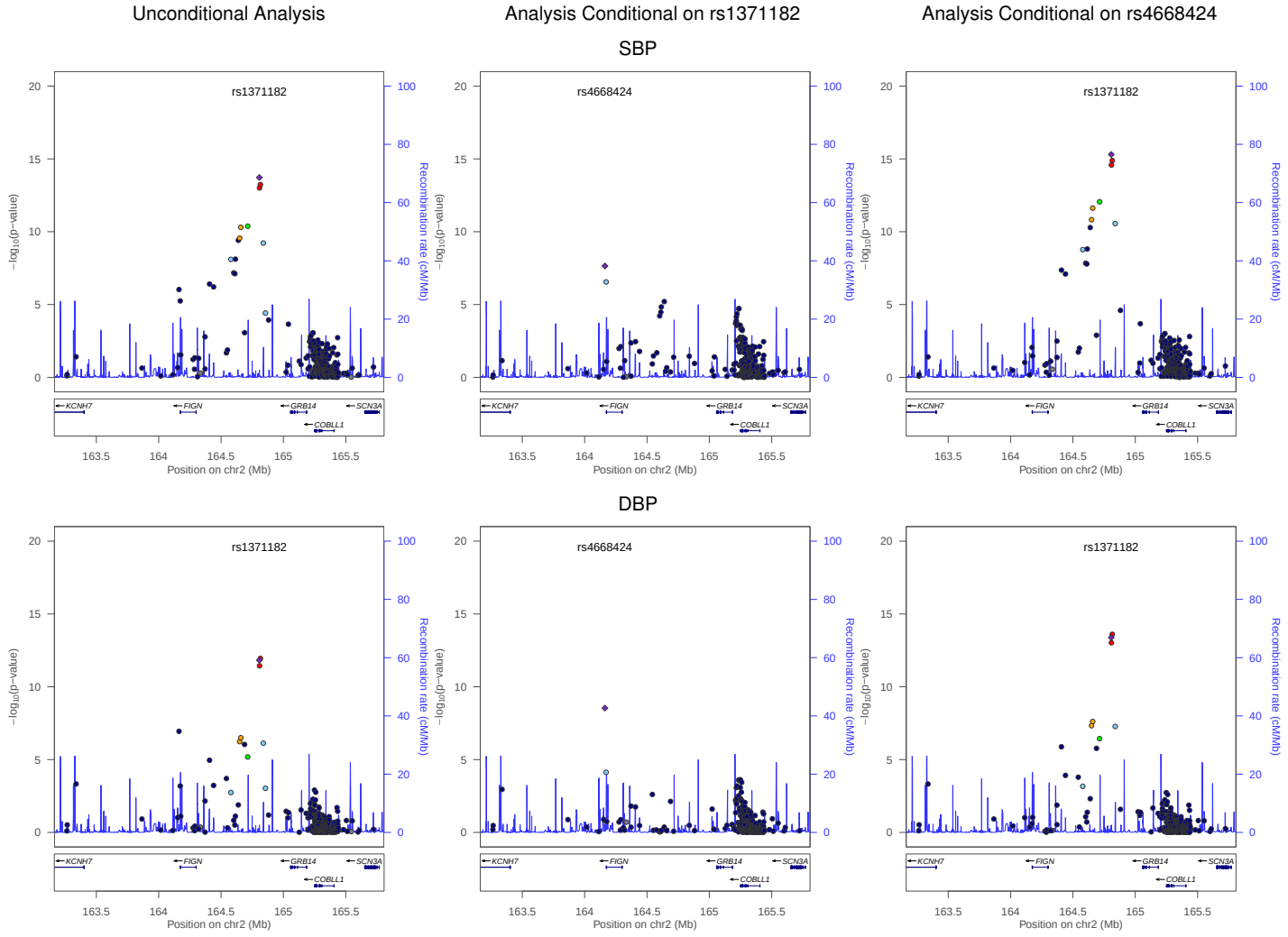


DBP

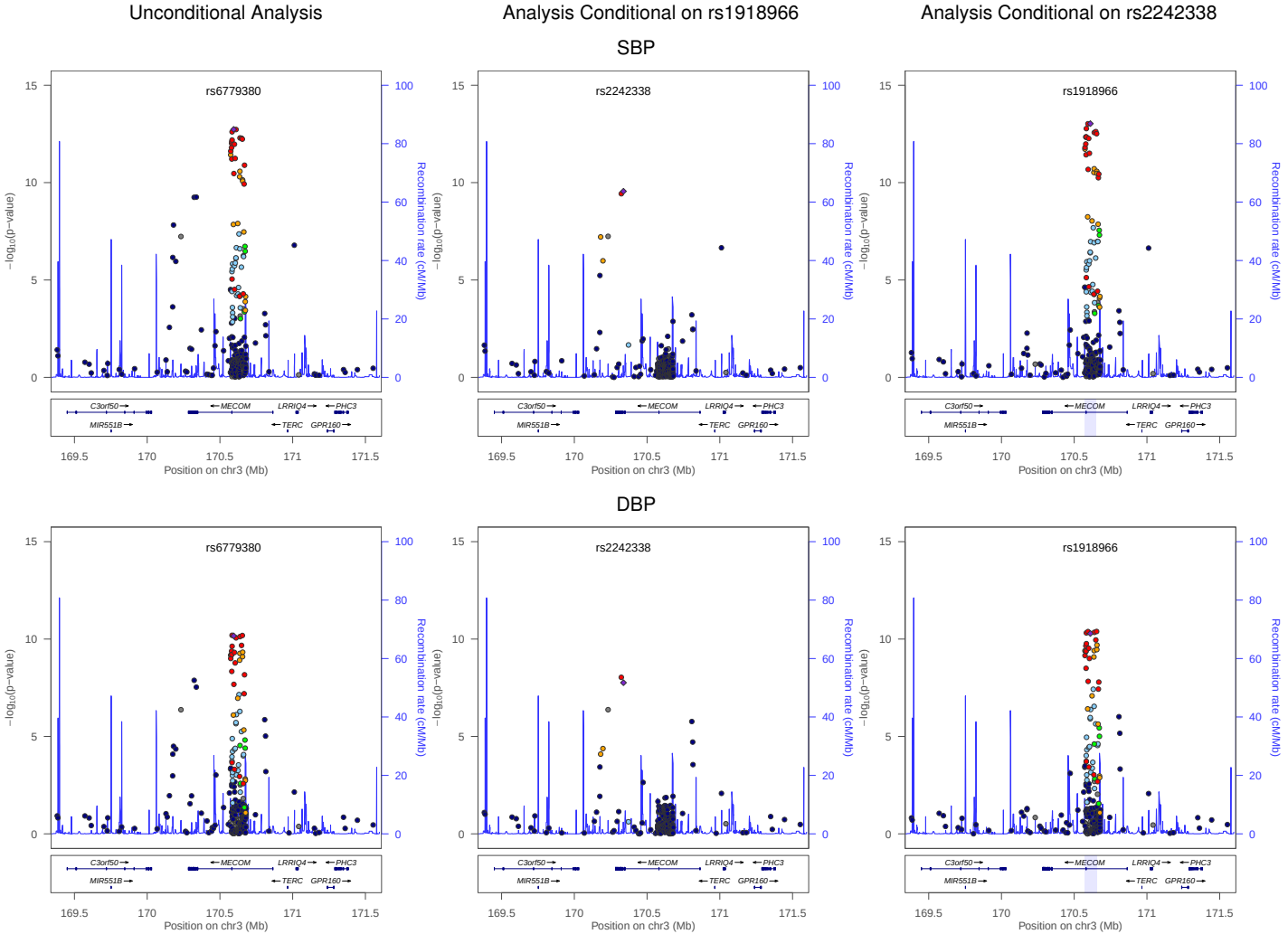




FIGN-GRB14


Unconditional Analysis
Analysis Conditional on rs1371182
Analysis Conditional on rs4668424
SBP
DBP
rs1371182
rs4668424
rs1371182
rs1371182
rs4668424
rs1371182
−log10(p−value)
Recombination rate (cM/Mb)
KCNH7
FIGN
GRB14
SCN3A
COBLL1
163.5
164
164.5
165
165.5
Position on chr2 (Mb)

MECOM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Analysis Conditional on rs1918966
Analysis Conditional on rs2242338
SBP
DBP
rs6779380
rs2242338
rs1918966
−log10(p-value)
Recombination rate (cM/Mb)
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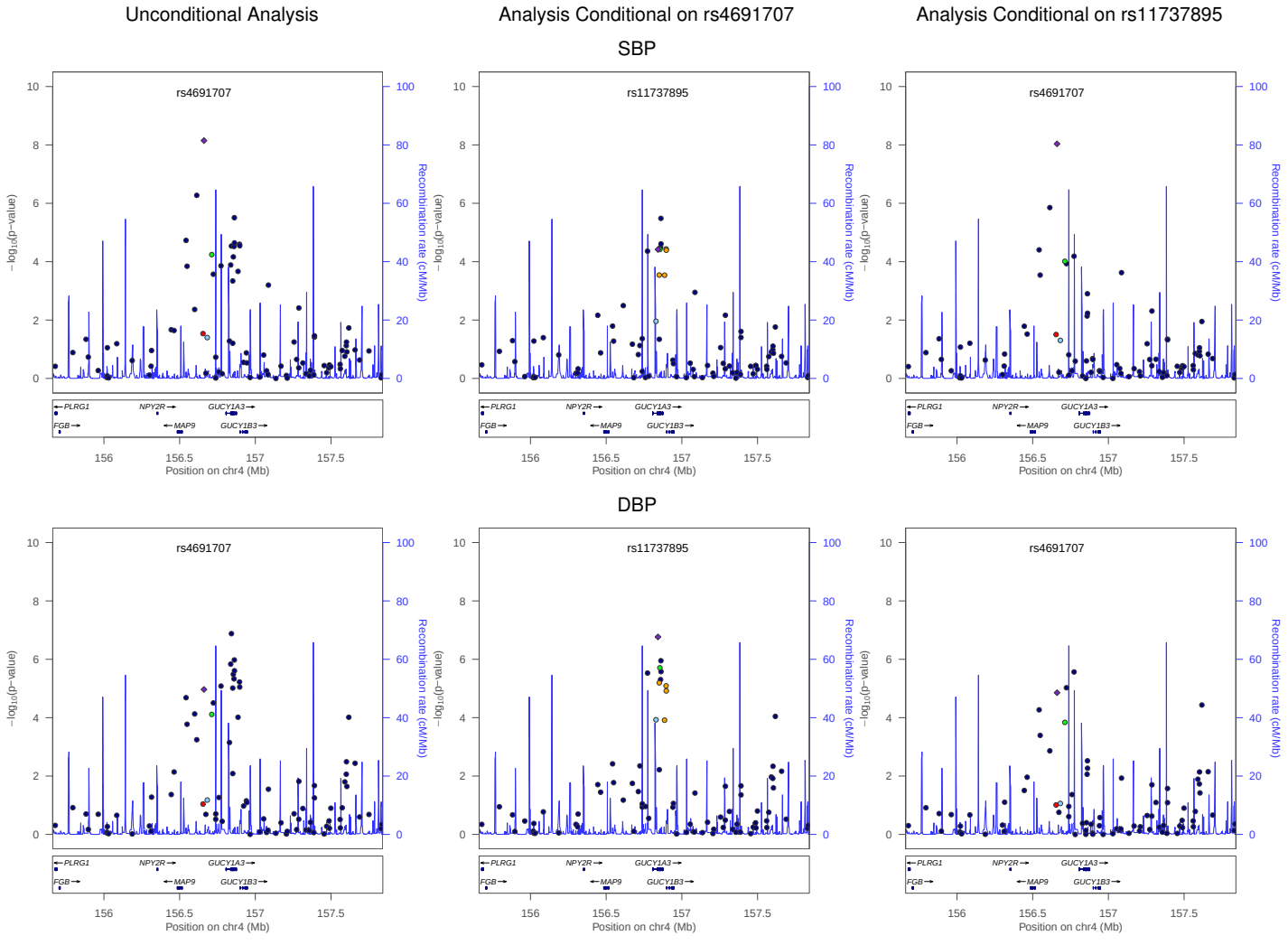
LRRIQ4
PHC3
MIR551B
TERC
GPR160
Position on chr3 (Mb)

GUCY1A3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Analysis Conditional on rs4691707
Analysis Conditional on rs11737895
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DBP
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rs4691707
−log10(p-value)
Recombination rate (cM/Mb)
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NPY2R
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FGB
MAP9
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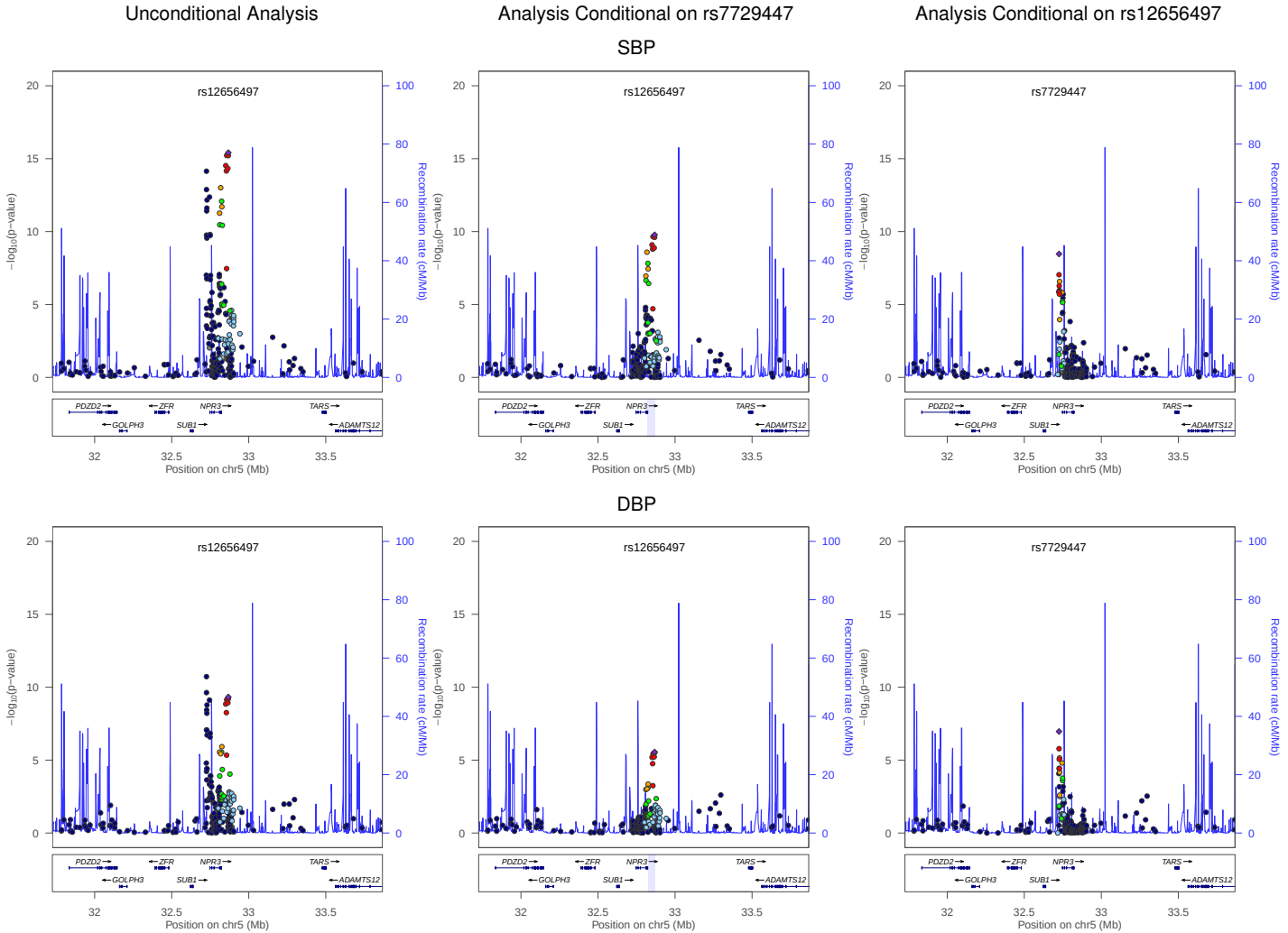
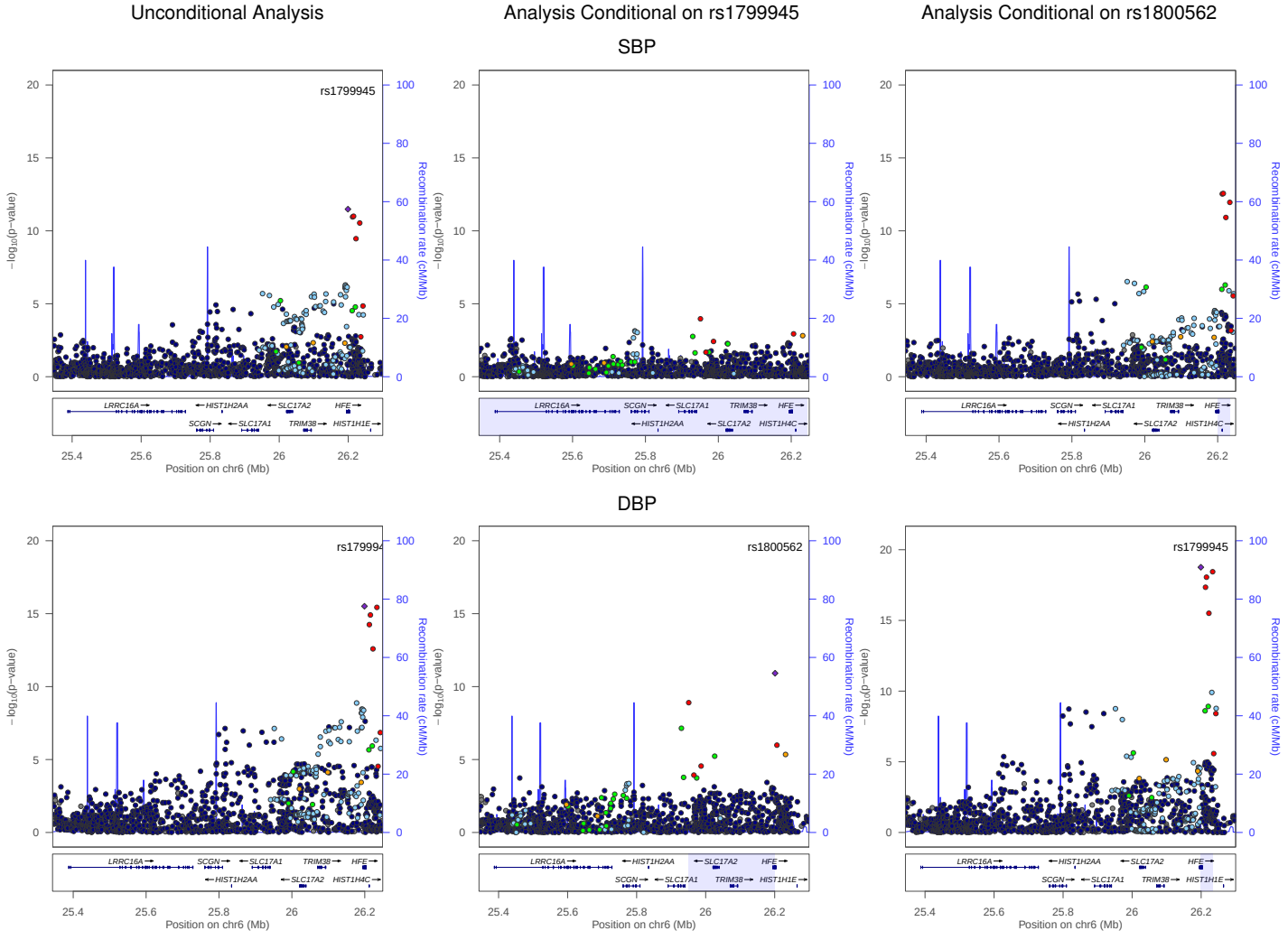
Position on chr4 (Mb)

NPR3-C5orf23



HFE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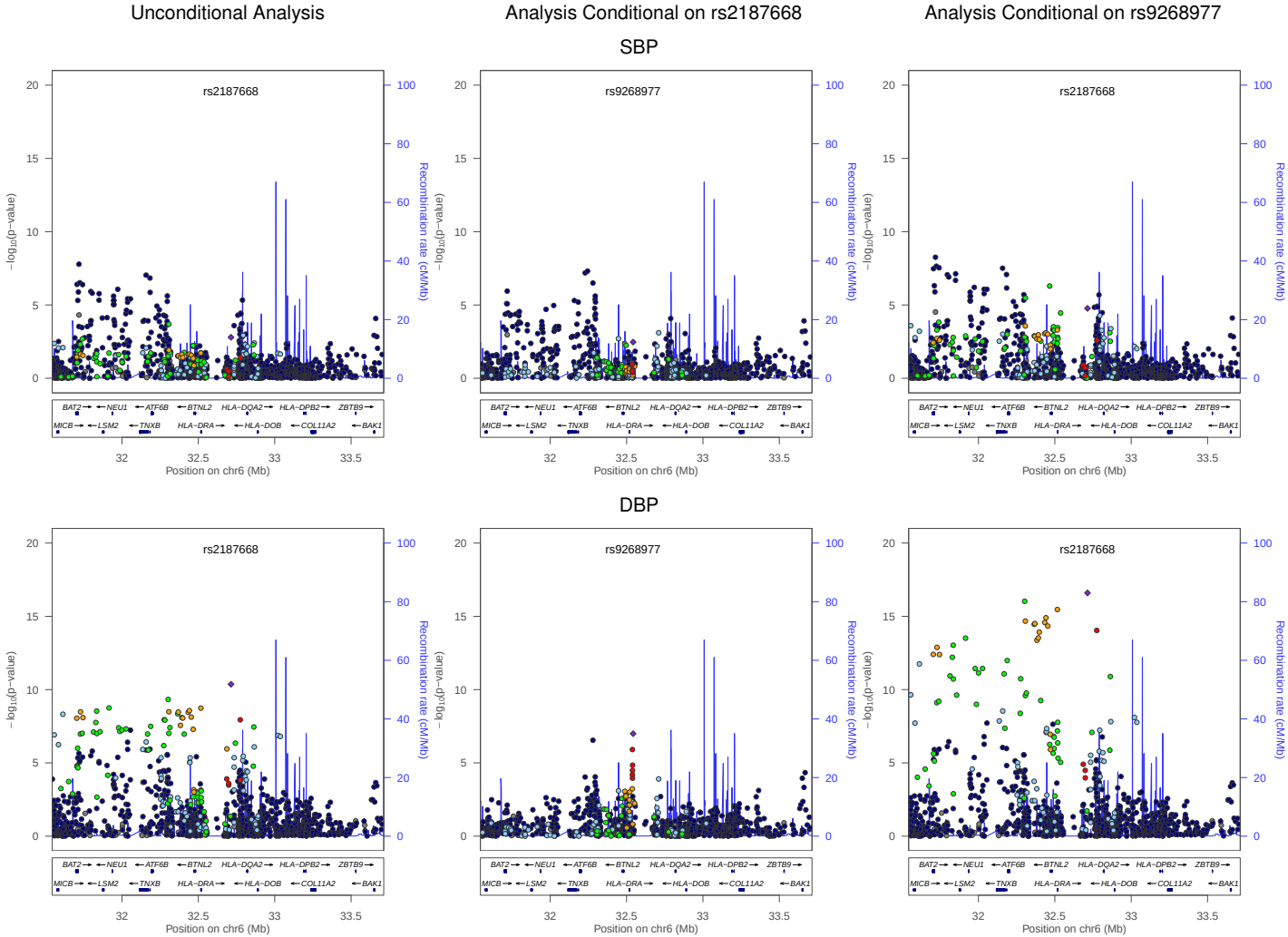
Analysis Conditional on rs1799945
Analysis Conditional on rs1800562
SBP
DBP
rs1799945
rs1800562
rs17999
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr6 (Mb)
LRRC16A
HIST1H2AA
SLC17A2
HFE
SCGN
SLC17A1
TRIM38
HIST1H1E
HIST1H4C

BAT2-BAT5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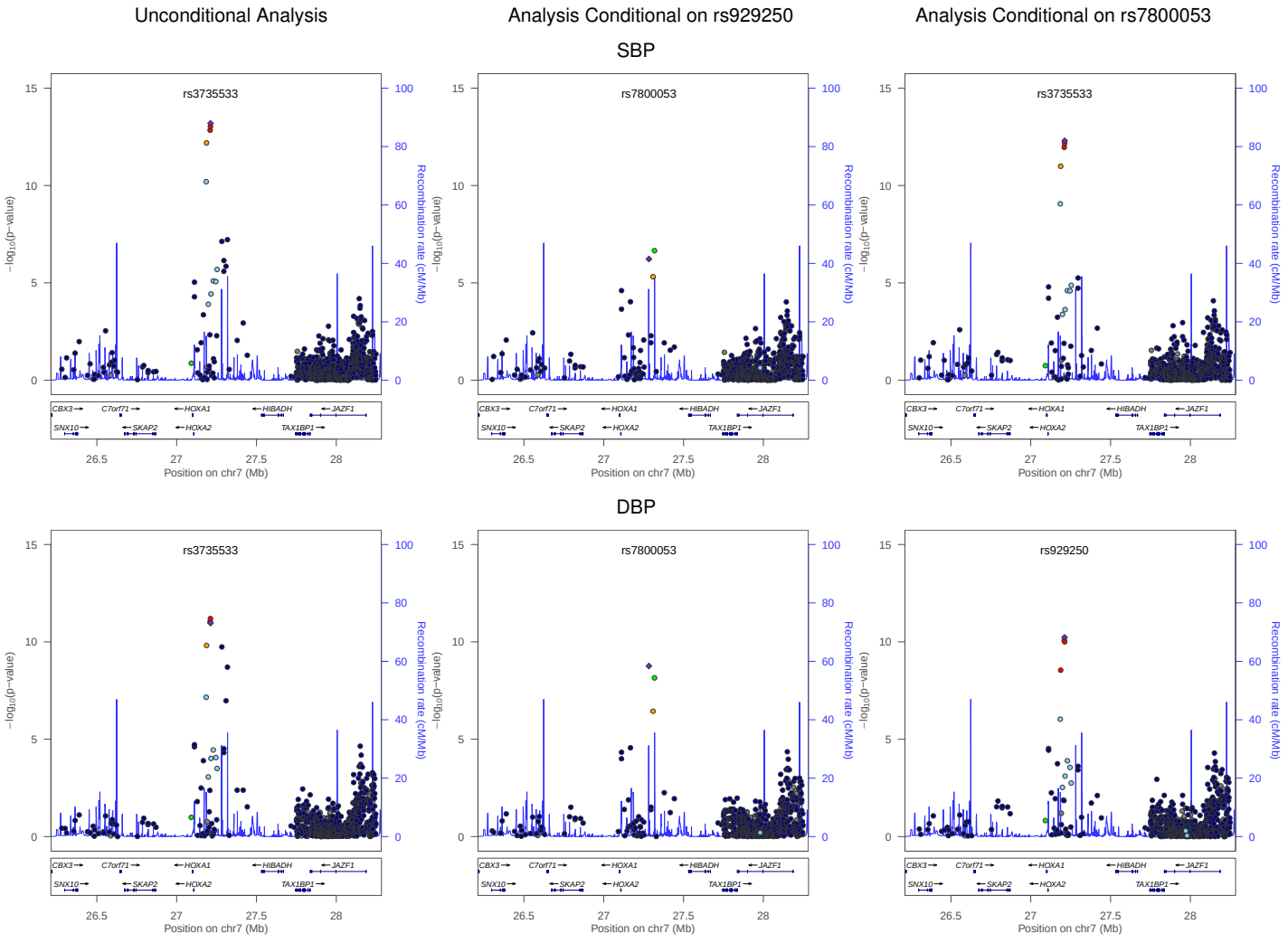
Analysis Conditional on rs2187668
Analysis Conditional on rs9268977
SBP
DBP
rs2187668
rs9268977
−log10(p-value)
Recombination rate (cM/Mb)
BAT2 NEU1 ATF6B BTNL2 HLA-DQA2 HLA-DPB2 ZBTB9
MICB LSM2 TNXB HLA-DRA HLA-DOB COL11A2 BAK1
Position on chr6 (Mb)

HOTTIP-EVX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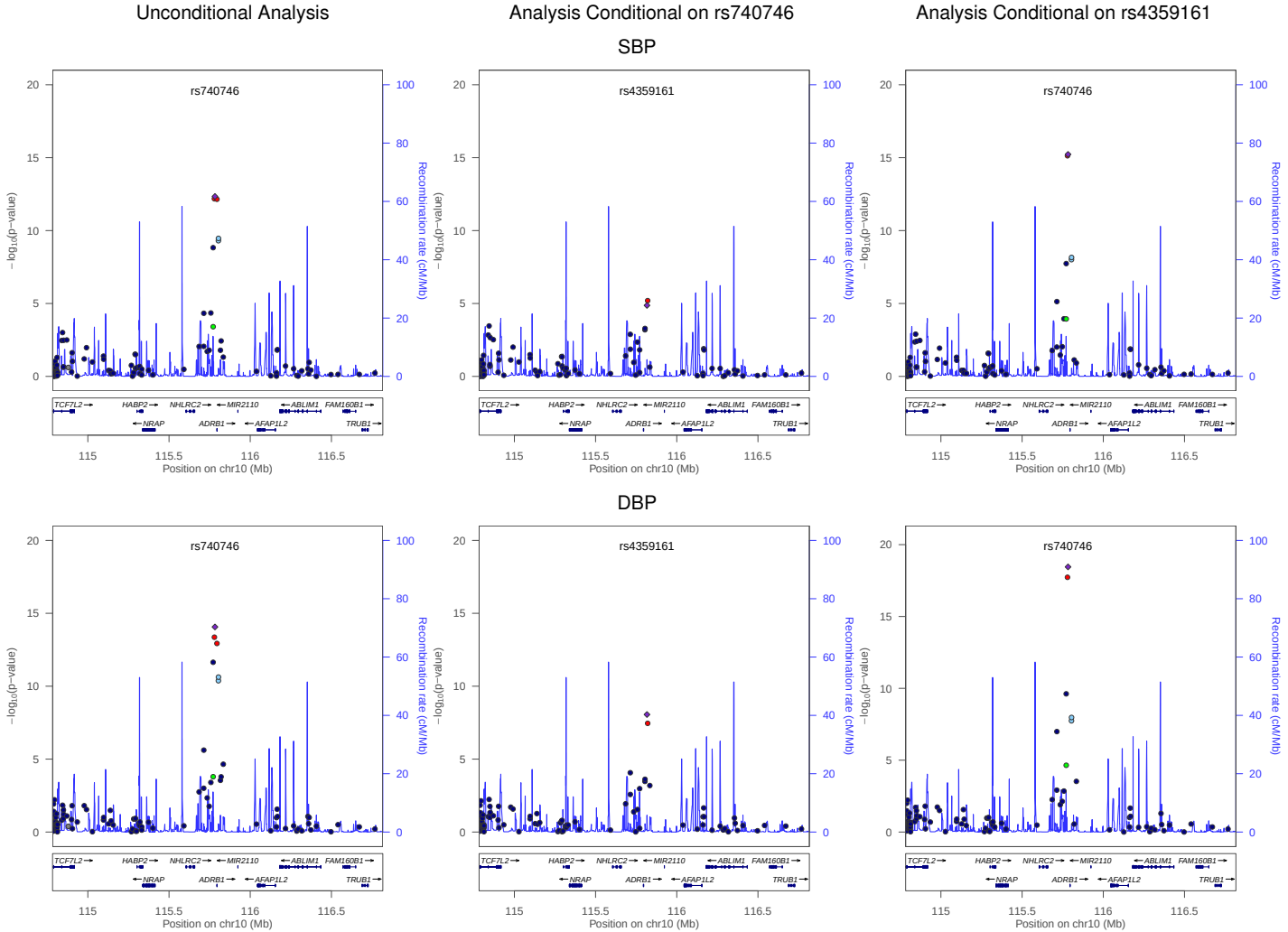
Analysis Conditional on rs929250
Analysis Conditional on rs7800053
SBP
DBP
rs3735533
rs7800053
rs929250
−log10(p−value)
Recombination rate (cM/Mb)
CBX3
C7orf71
HOXA1
HIBADH
JAZF1
SNX10
SKAP2
HOXA2
TAX1BP1
Position on chr7 (Mb)

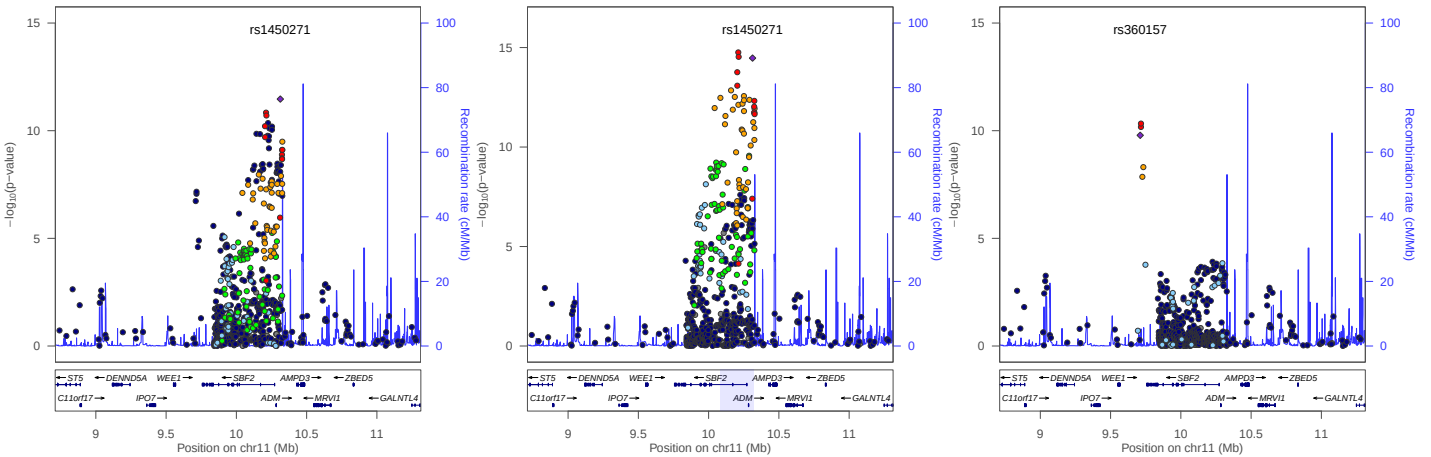
ADRB1


Unconditional Analysis
Analysis Conditional on rs740746
Analysis Conditional on rs4359161
SBP
DBP
rs740746
rs4359161
rs740746
rs740746
rs4359161
rs740746
−log10(p−value)
Recombination rate (cM/Mb)
TCF7L2
HABP2
NHLRC2
MIR2110
ABLIM1
FAM160B1
NRAP
ADRB1
AFAP1L2
TRUB1
Position on chr10 (Mb)

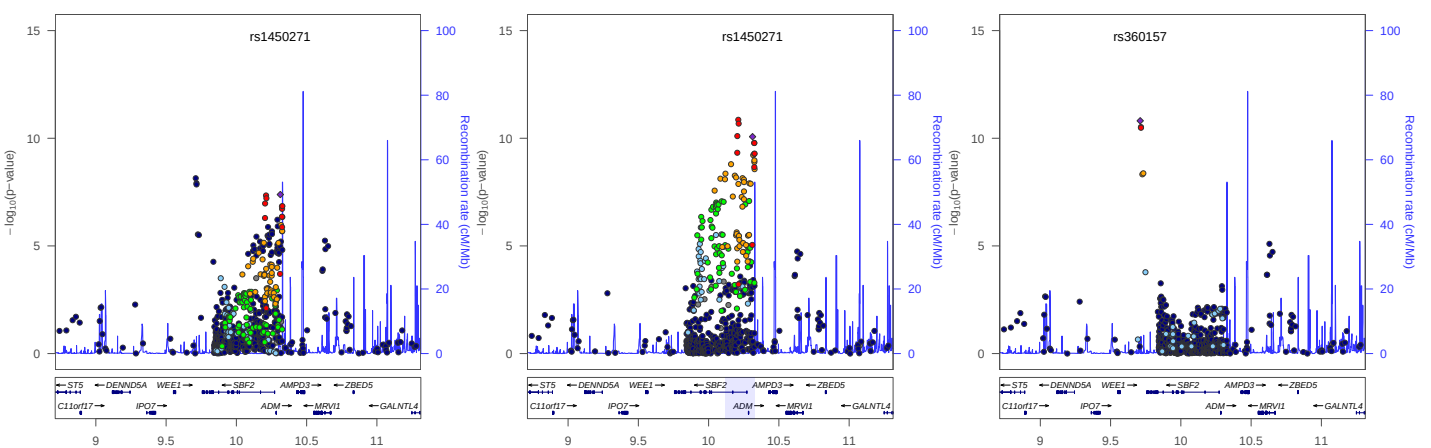
ADM

Unconditional Analysis | Analysis Conditional on rs360157 | Analysis Conditional on rs1450271

SBP

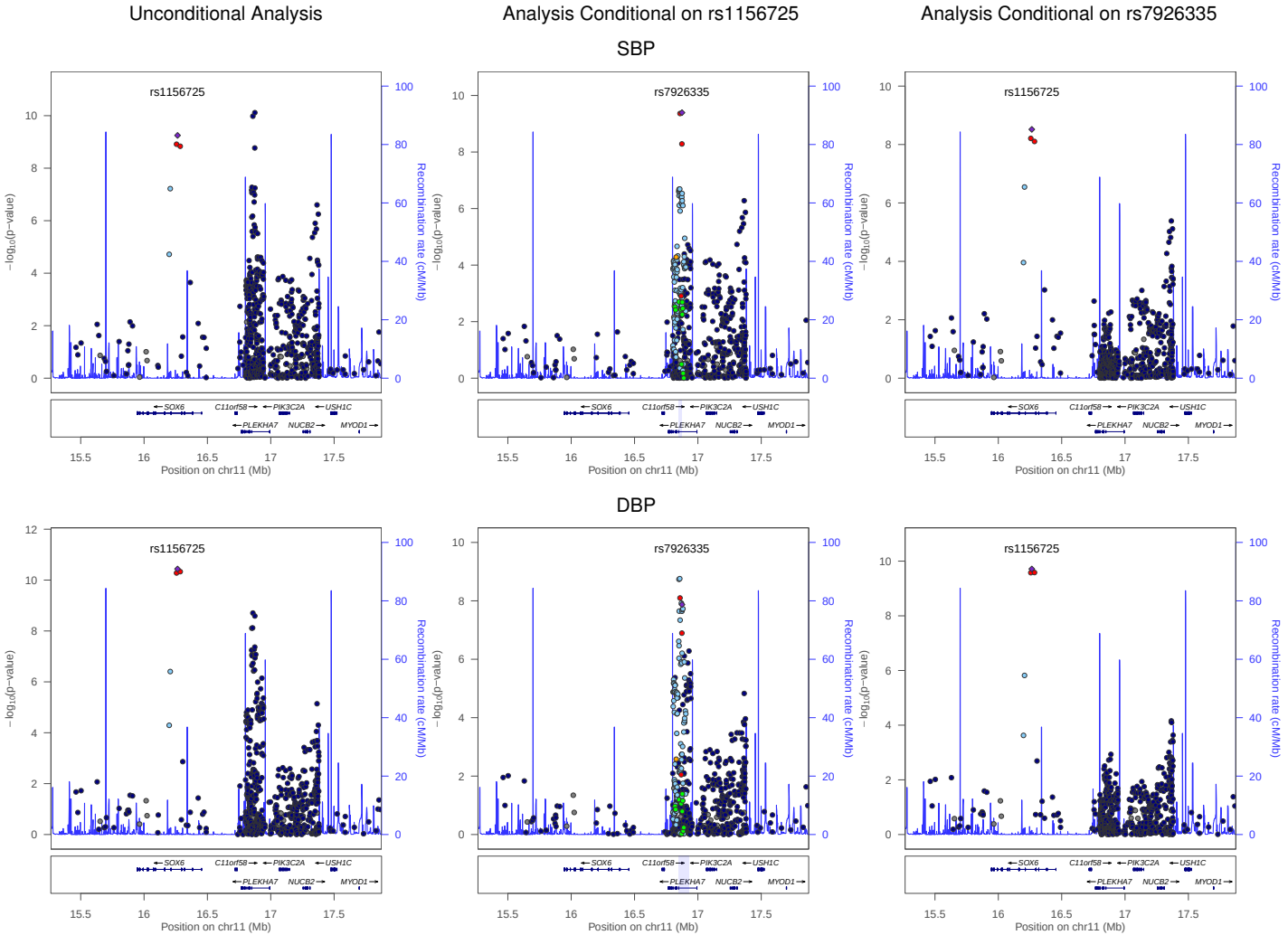


DBP

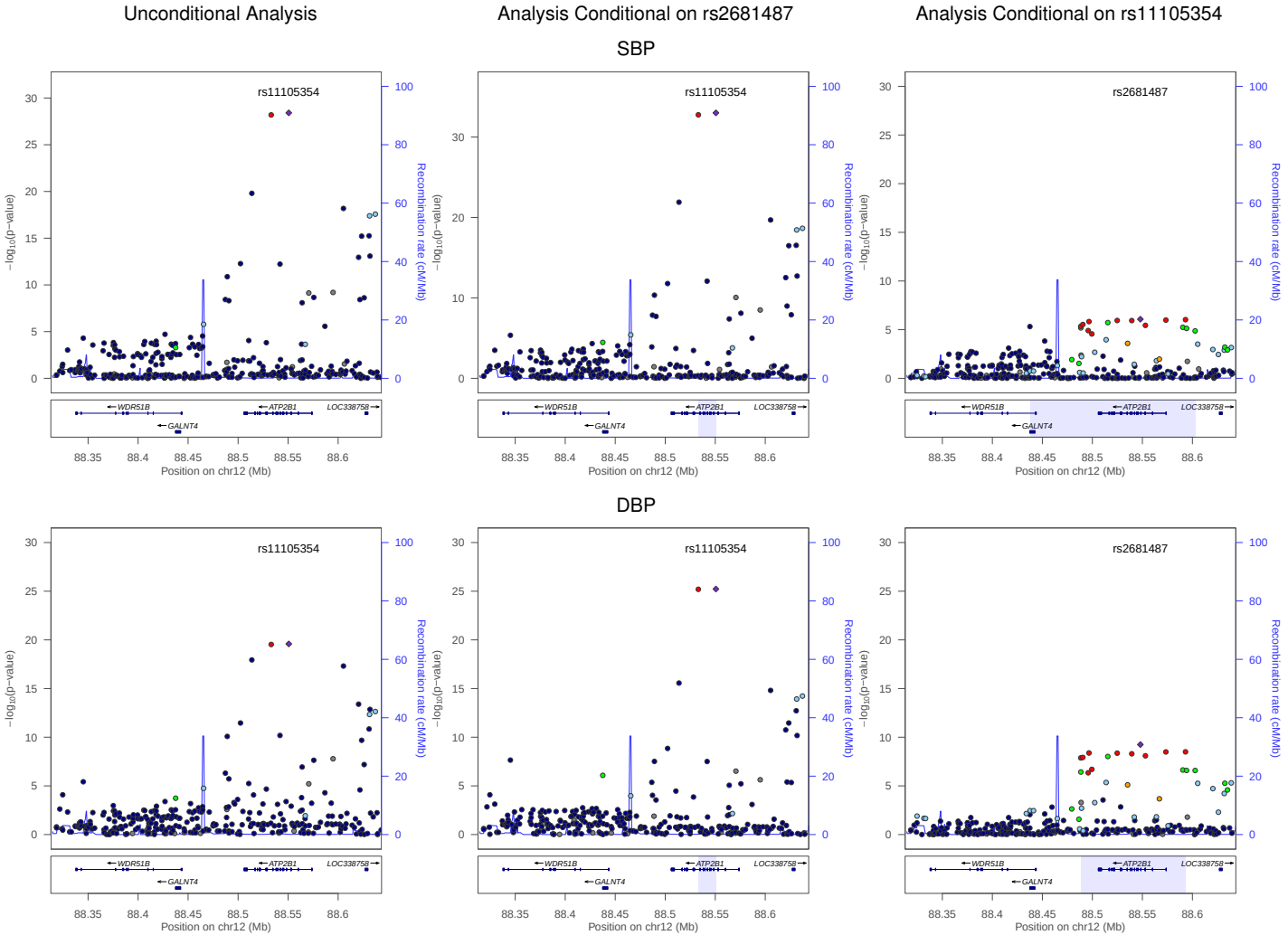


PLEKHA7

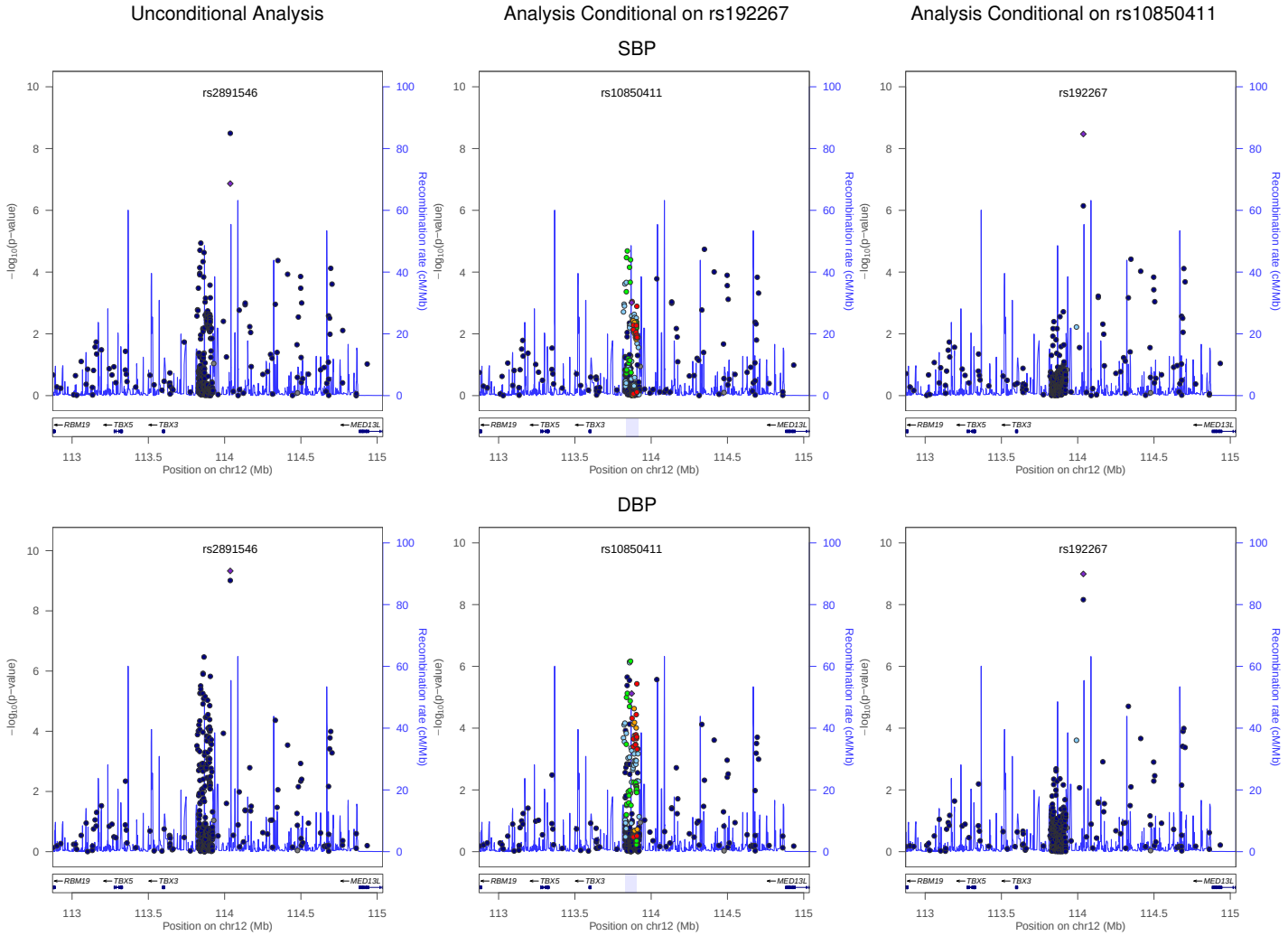
PLEKHA7

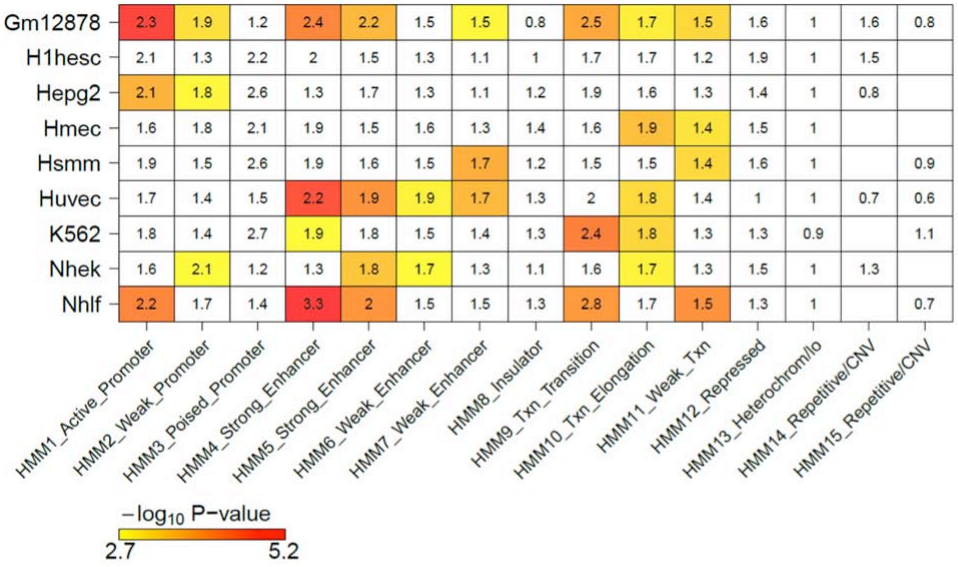

Unconditional Analysis
Analysis Conditional on rs1156725
Analysis Conditional on rs7926335
SBP
DBP
rs1156725
rs7926335
−log10(p−value)
Recombination rate (cM/Mb)
SOX6
C11orf58
PIK3C2A
USH1C
PLEKHA7
NUCB2
MYOD1
Position on chr11 (Mb)

ATP2B1

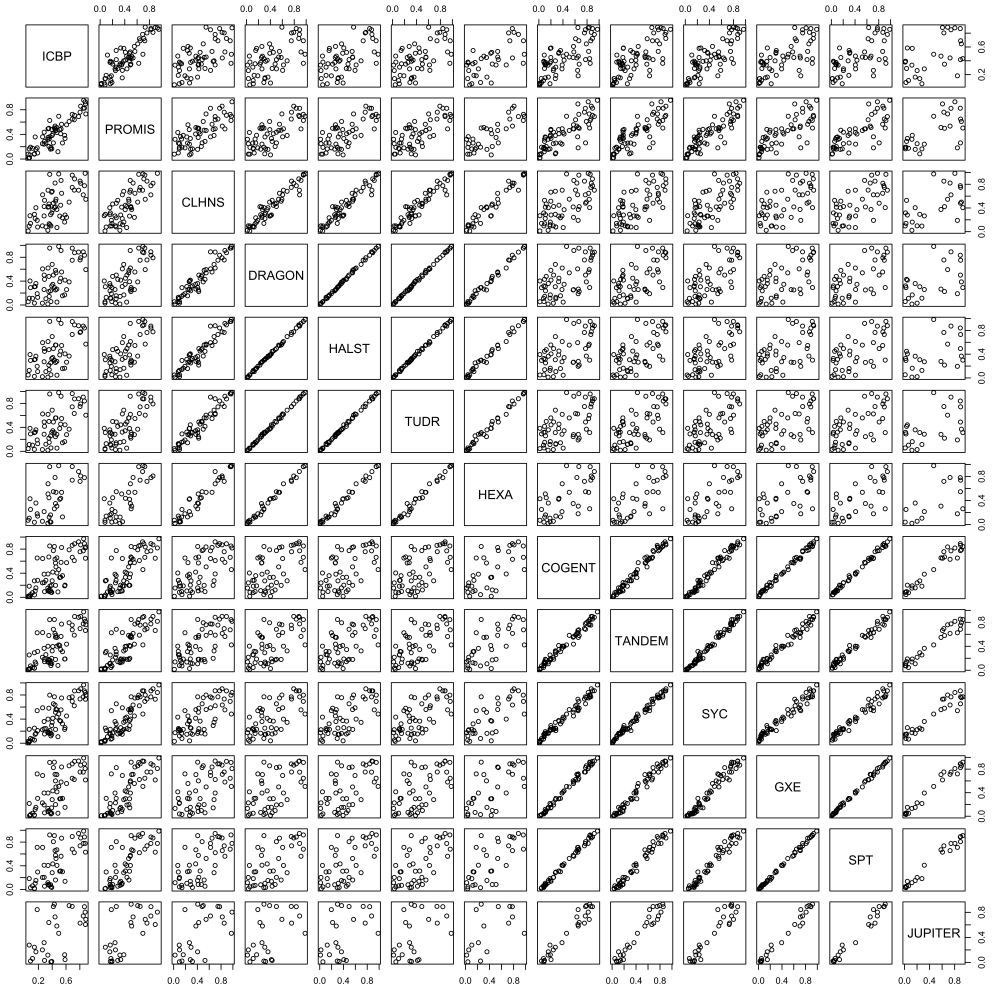

Unconditional Analysis
Analysis Conditional on rs2681487
Analysis Conditional on rs11105354
SBP
DBP
rs11105354
rs2681487
−log10(p−value)
Recombination rate (cM/Mb)
WDR51B
ATP2B1
LOC338758
GALNT4
88.35
88.4
88.45
88.5
88.55
88.6
Position on chr12 (Mb)

TBX5-TBX3

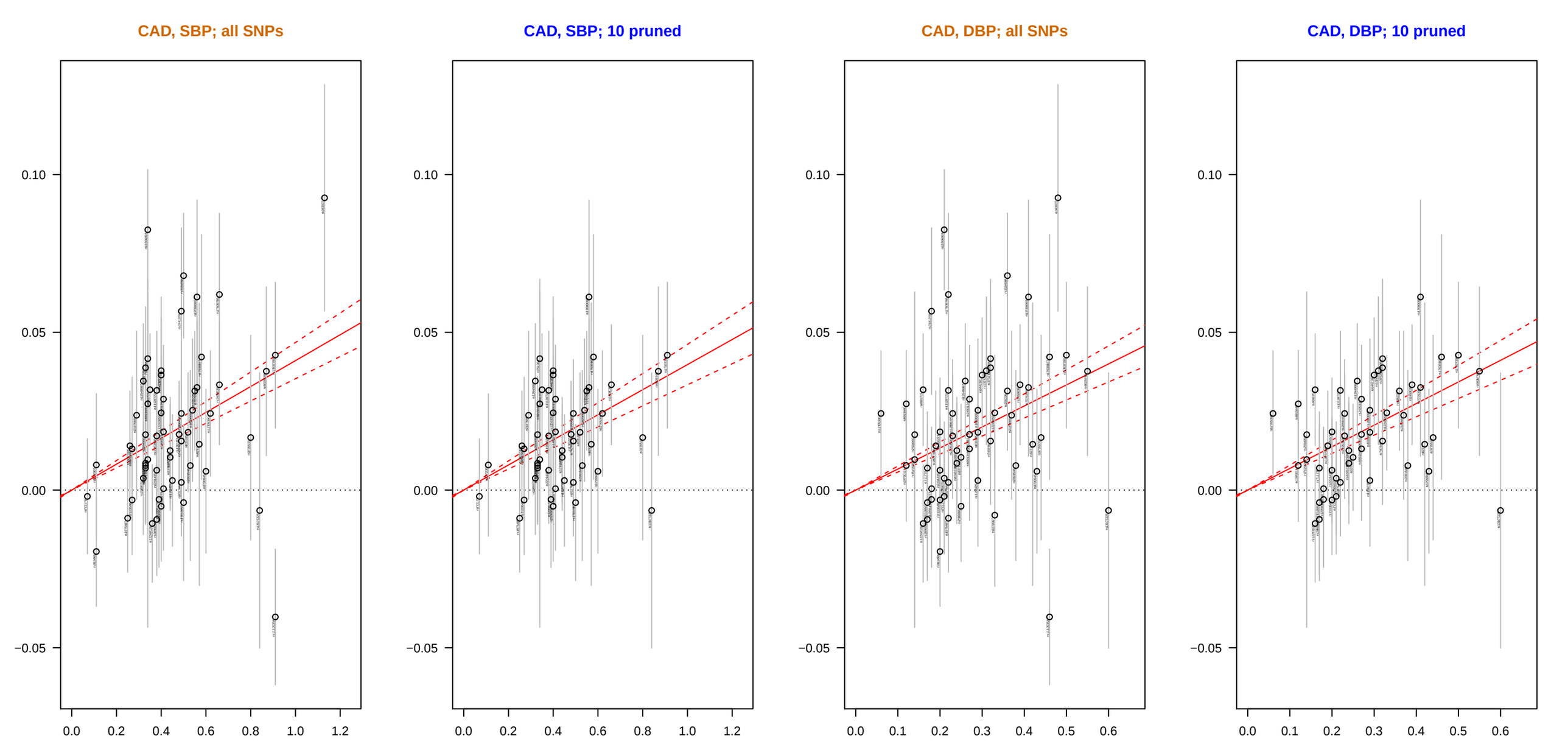

Unconditional Analysis
Analysis Conditional on rs192267
Analysis Conditional on rs10850411
SBP
DBP
rs2891546
rs10850411
rs192267
−log10(p-value)
Recombination rate (cM/Mb)
RBM19
TBX5
TBX3
MED13L
Position on chr12 (Mb)



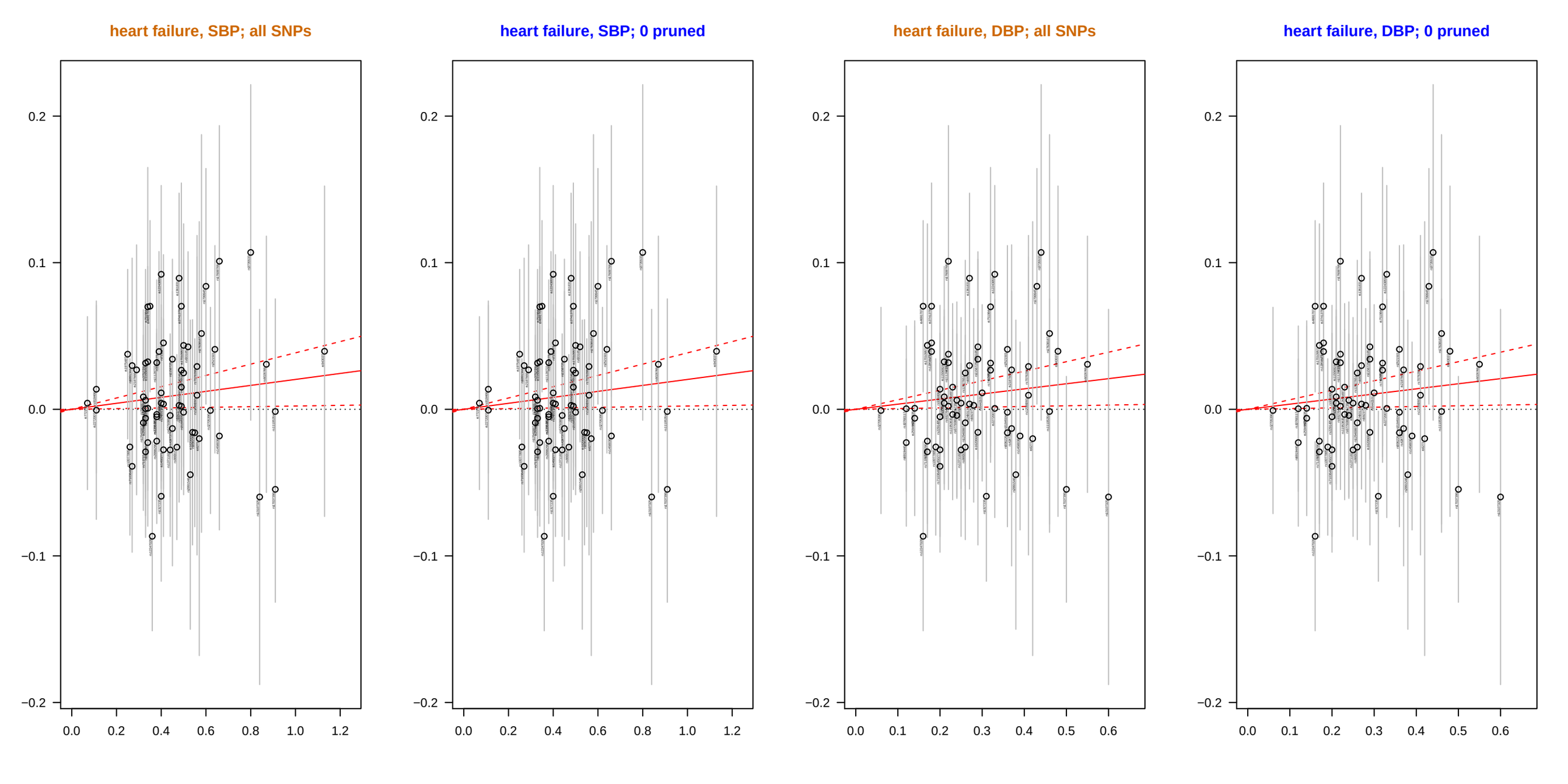
Supplementary Figure 8. Matrix of fold enrichment for BP SNPs in predicted chromatin states in nine human cell types. The boxes are colored by $-log_{10}P$ for enrichment. The white color indicates lack of significance after Bonferroni correction for 15 chromatin states and 9 tissues (see **Supplementary Information**). HMM = hidden Markov model; txn = transcription; lo=low signal; CNV = copy number variation. The ENCODE cell type codes are: embryonic stem cells (H1 ES), erythrocytic leukaemia cells (K562), B-lymphoblastoid cells (GM12878), hepatocellular carcinoma cells (HepG2), umbilical vein endothelial cells (HUVEC), skeletal muscle myoblasts (HSMM), normal lung fibroblasts (NHLF), normal epidermal keratinocytes (NHEK) and mammary epithelial cells (HMEC).



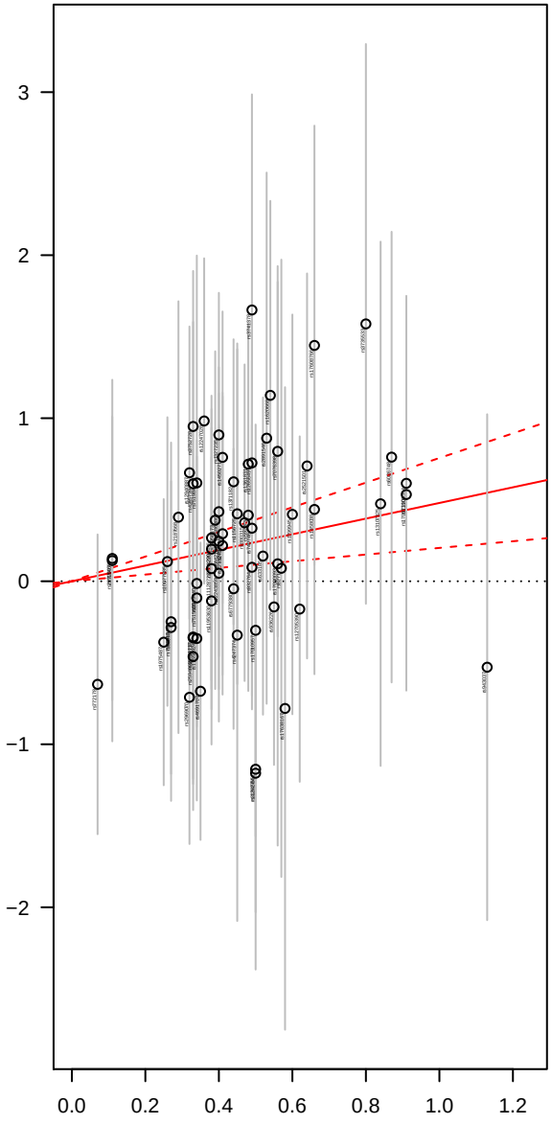
Supplementary Figure 9. Effect allele frequency plots for all samples of non-European ancestry. The effect allele frequency of each study is plotted against the effect allele frequency of every other study for all 66 index SNPs. The study names are indicated in the middle diagonal.



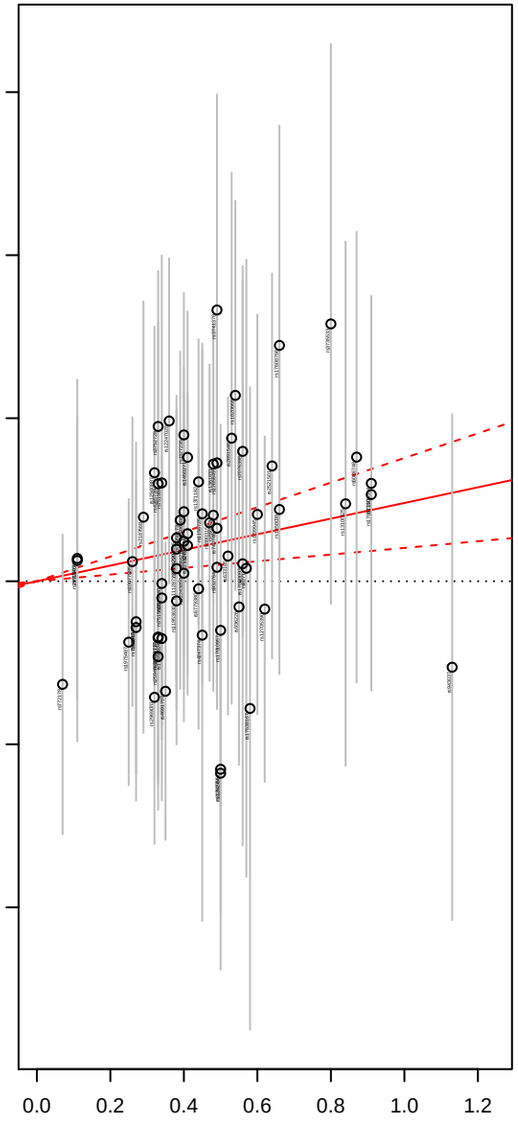
Supplementary Figures 10. Risk score analyses results for each SNP. The BP effect is on the x-axis, the outcome effect on the y-axis.


heart failure, SBP; all SNPs
heart failure, SBP; 0 pruned
heart failure, DBP; all SNPs
heart failure, DBP; 0 pruned
0.2
0.1
0.0
−0.1
−0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

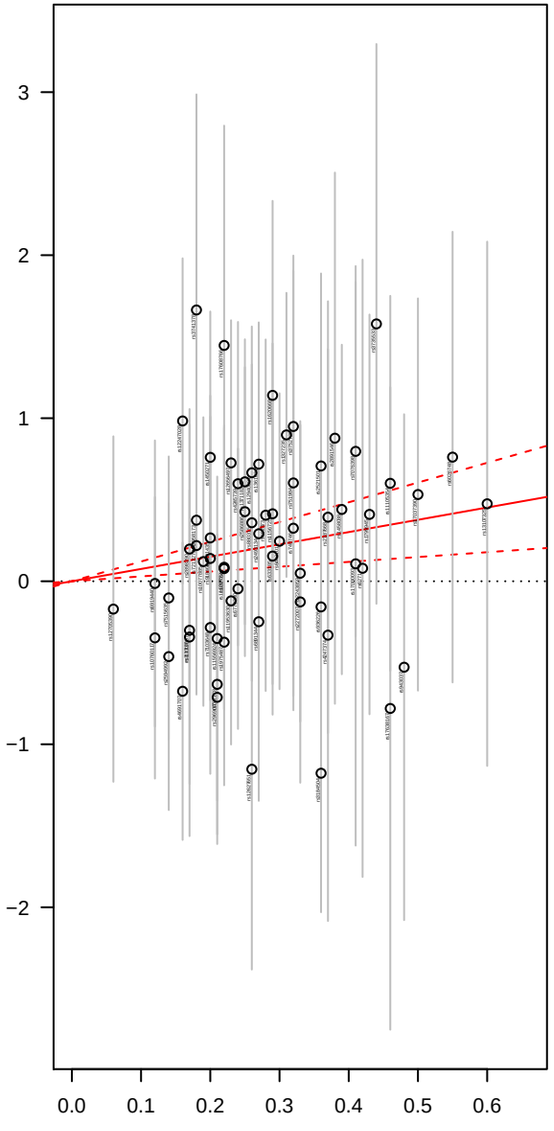
LV mass, SBP; all SNPs



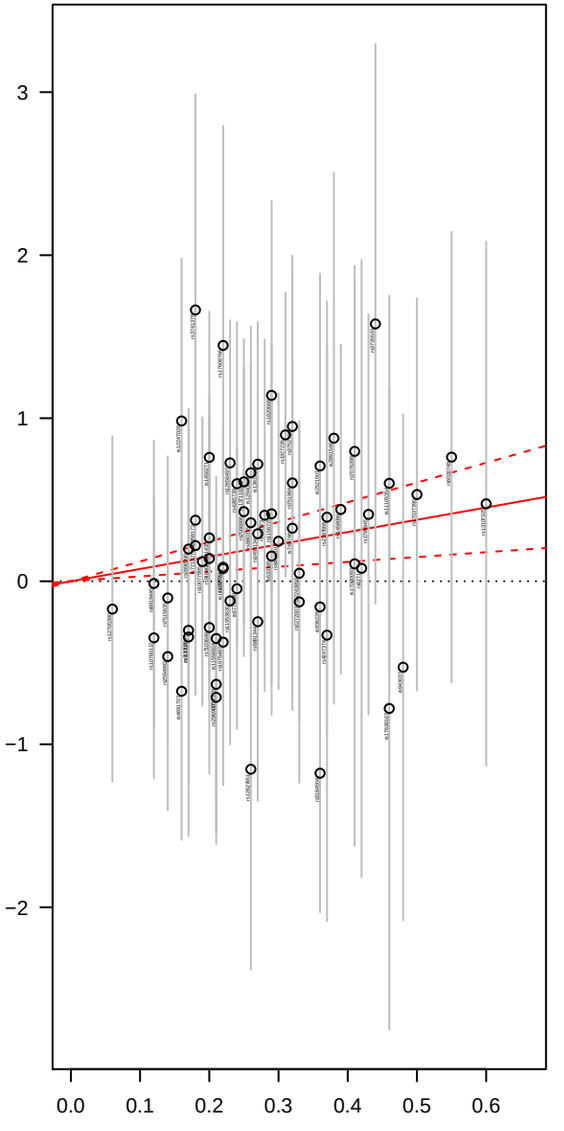
LV mass, SBP; 0 pruned

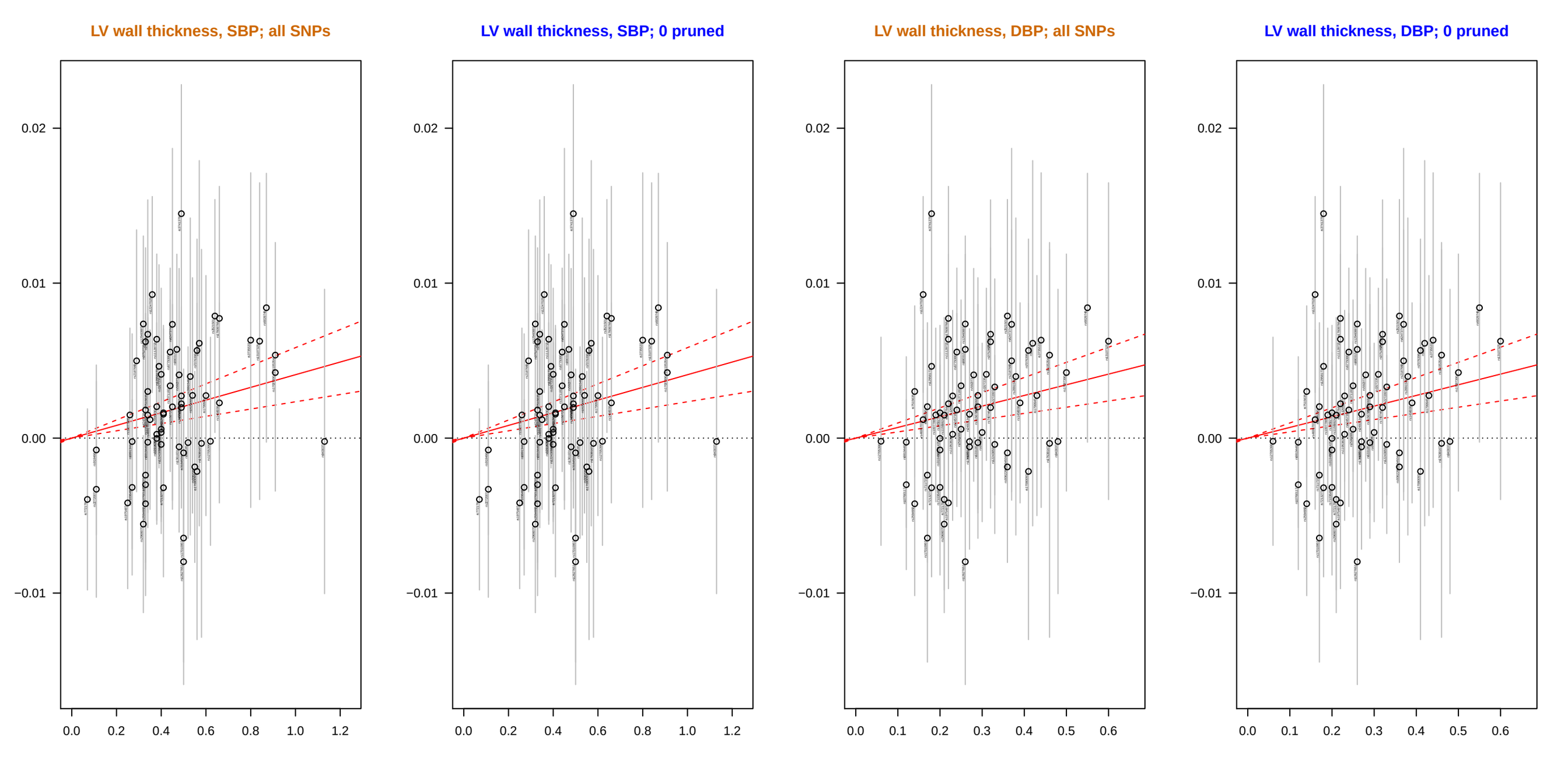


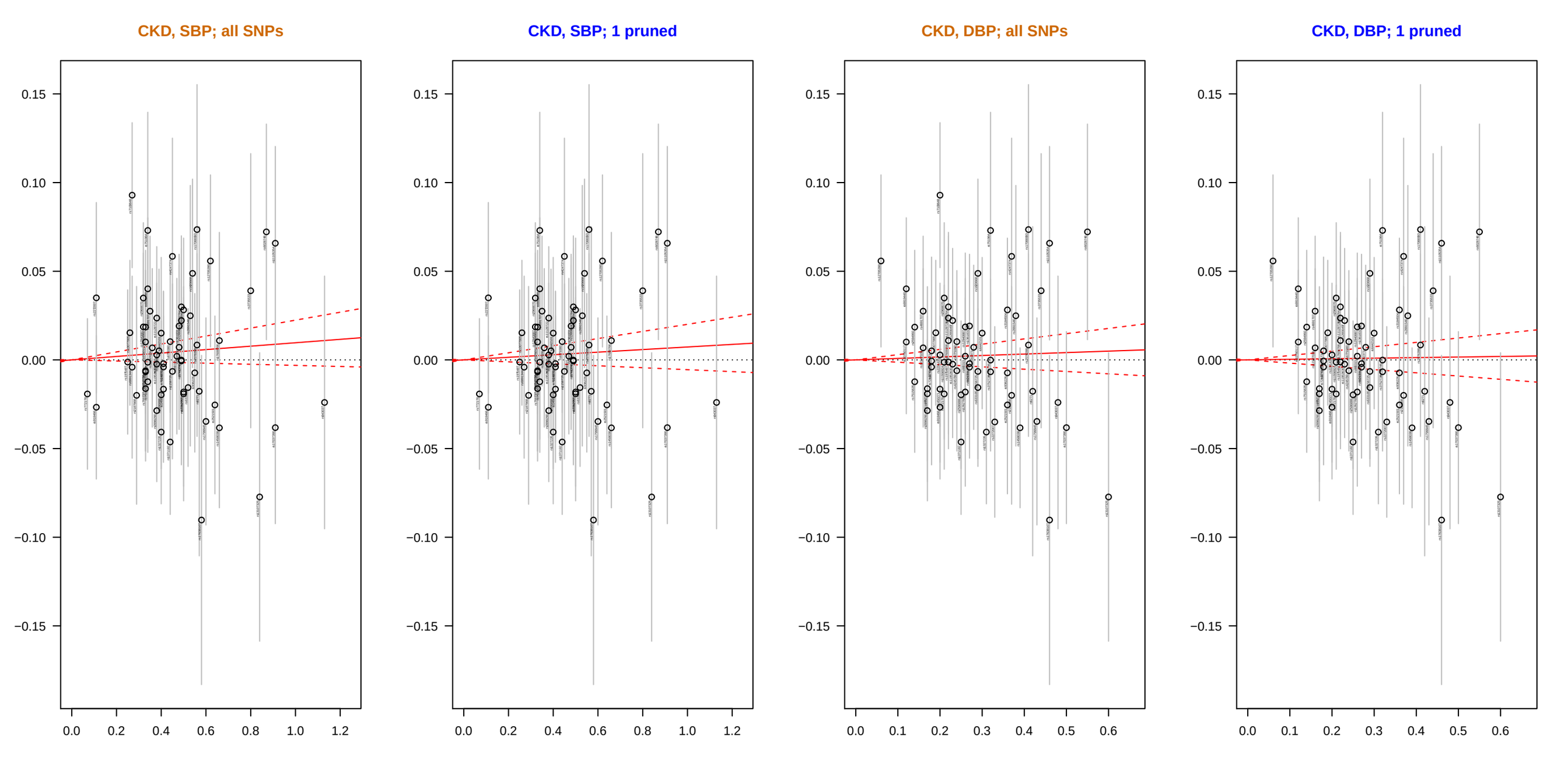
LV mass, DBP; all SNPs

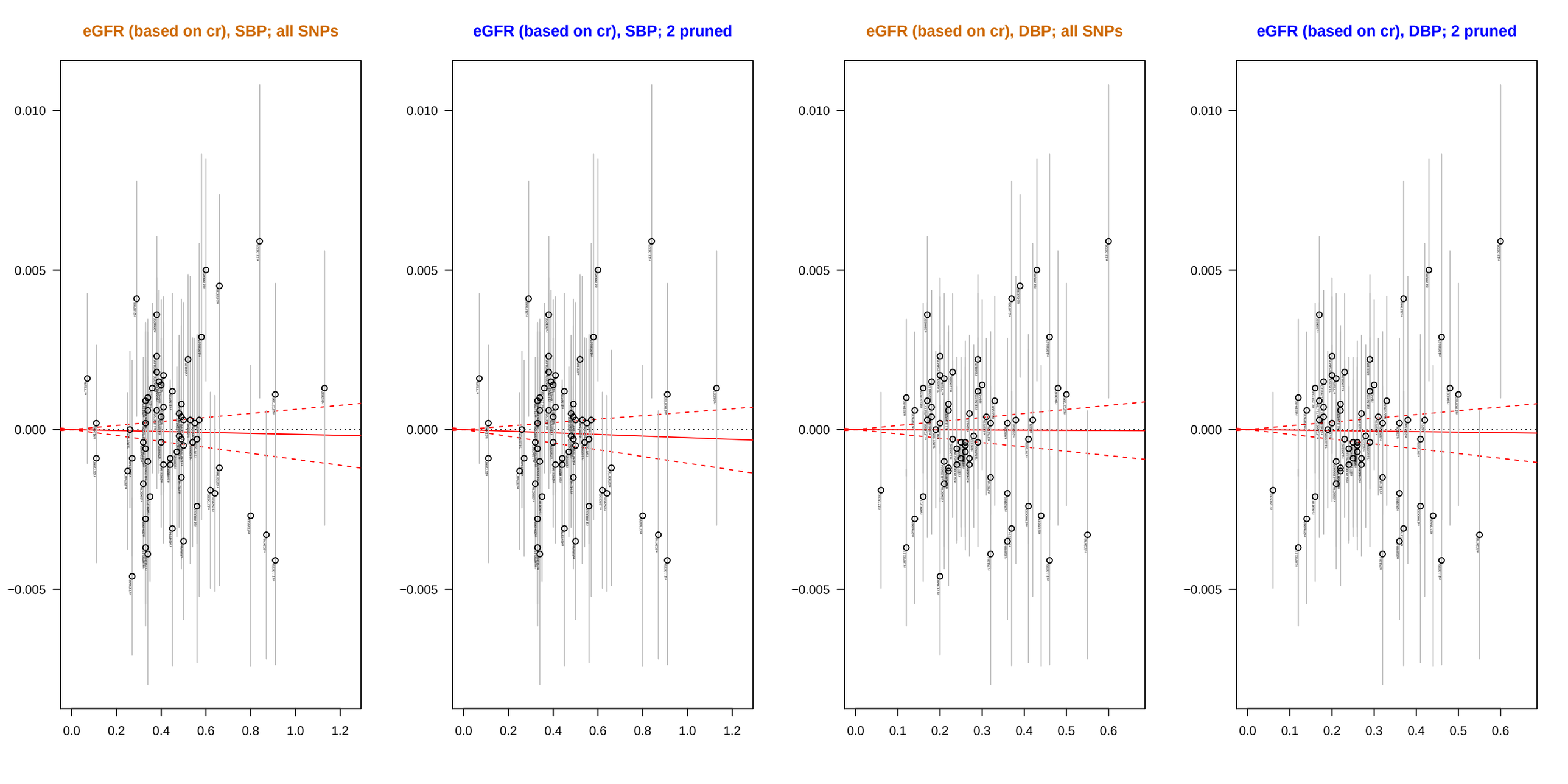


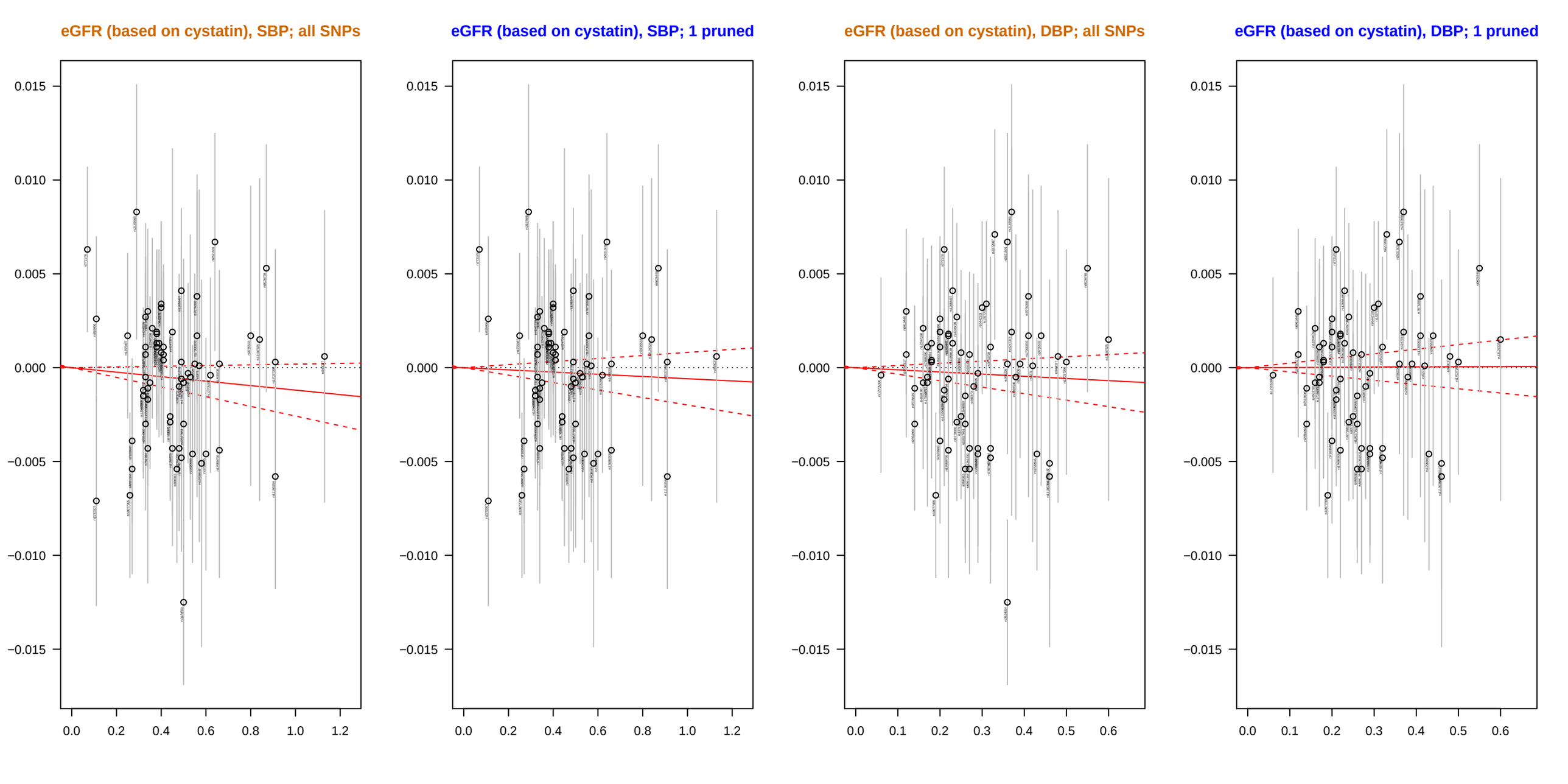
LV mass, DBP; 0 pruned

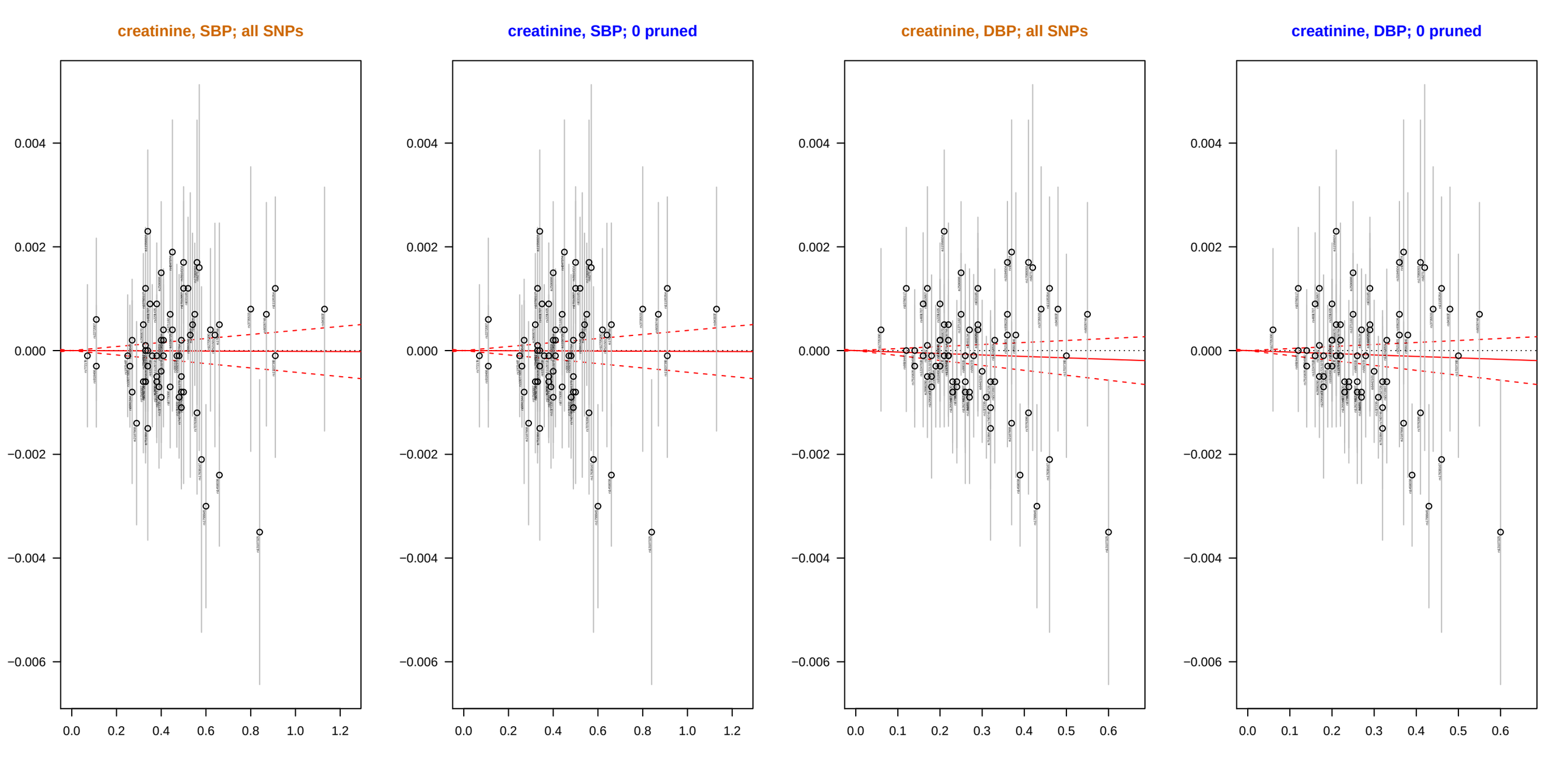


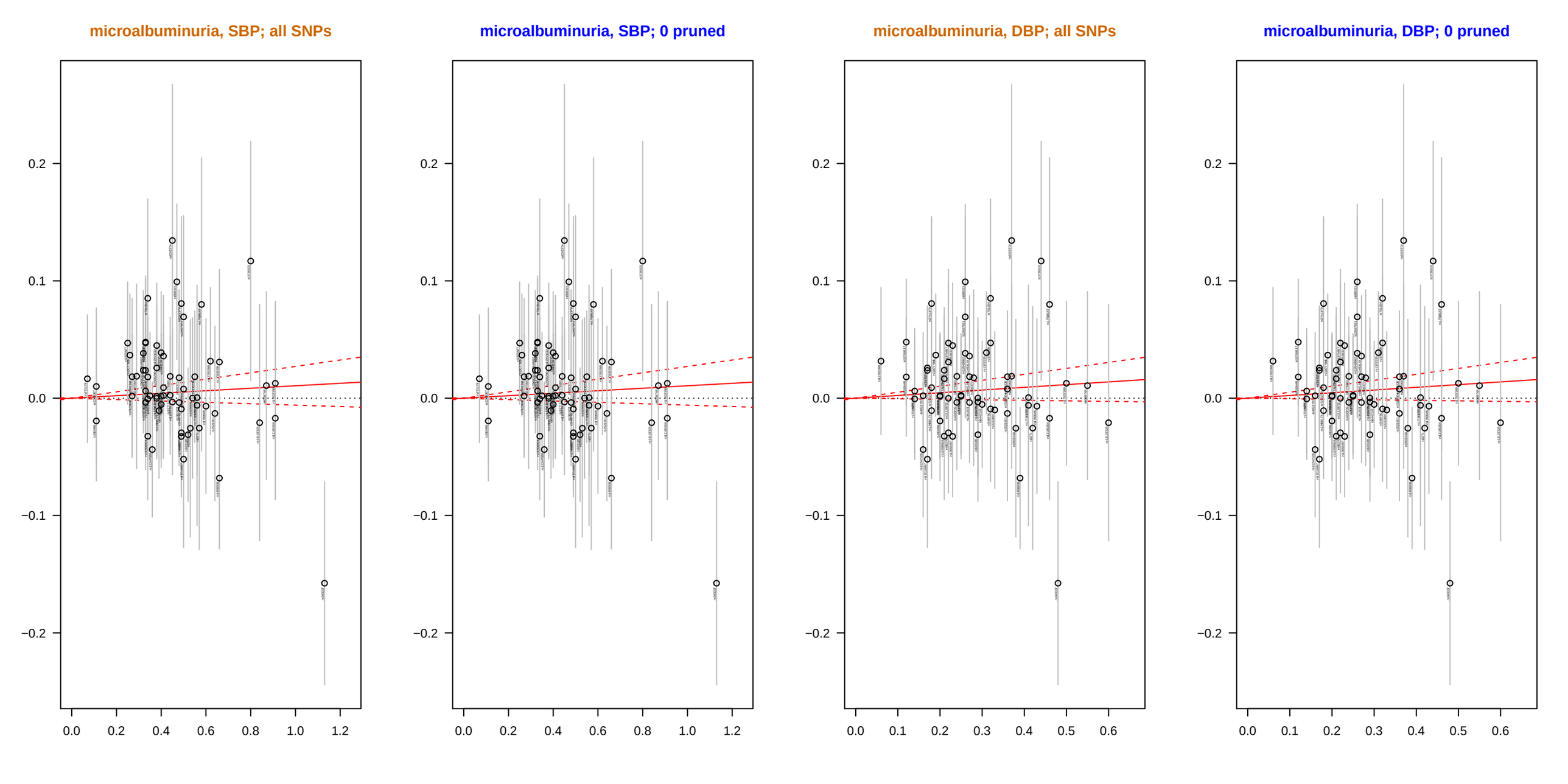

LV wall thickness, SBP; all SNPs
LV wall thickness, SBP; 0 pruned
LV wall thickness, DBP; all SNPs
LV wall thickness, DBP; 0 pruned
0.02
0.01
0.00
−0.01
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

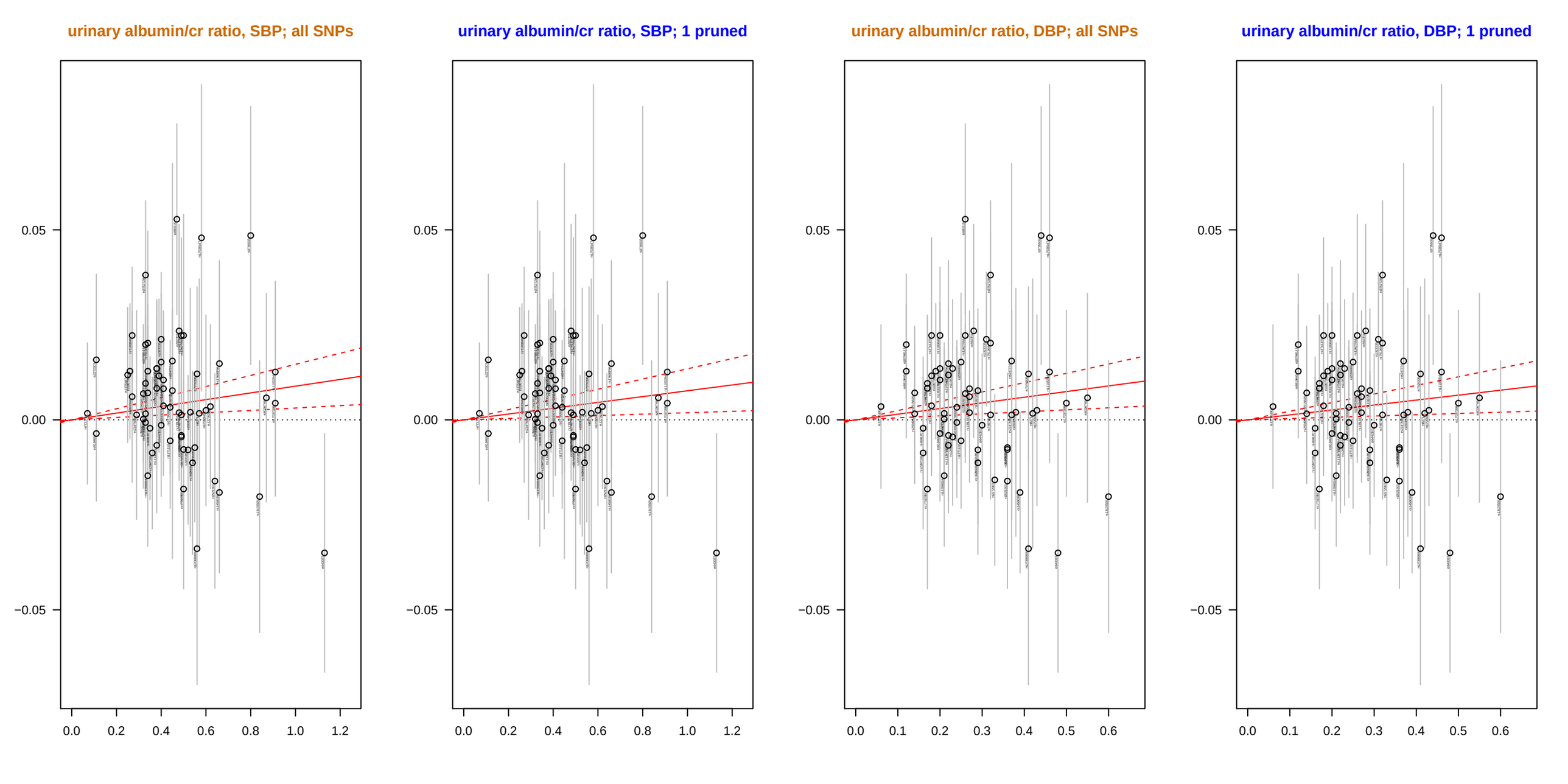

CKD, SBP; all SNPs
CKD, SBP; 1 pruned
CKD, DBP; all SNPs
CKD, DBP; 1 pruned
0.15
0.10
0.05
0.00
−0.05
−0.10
−0.15
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

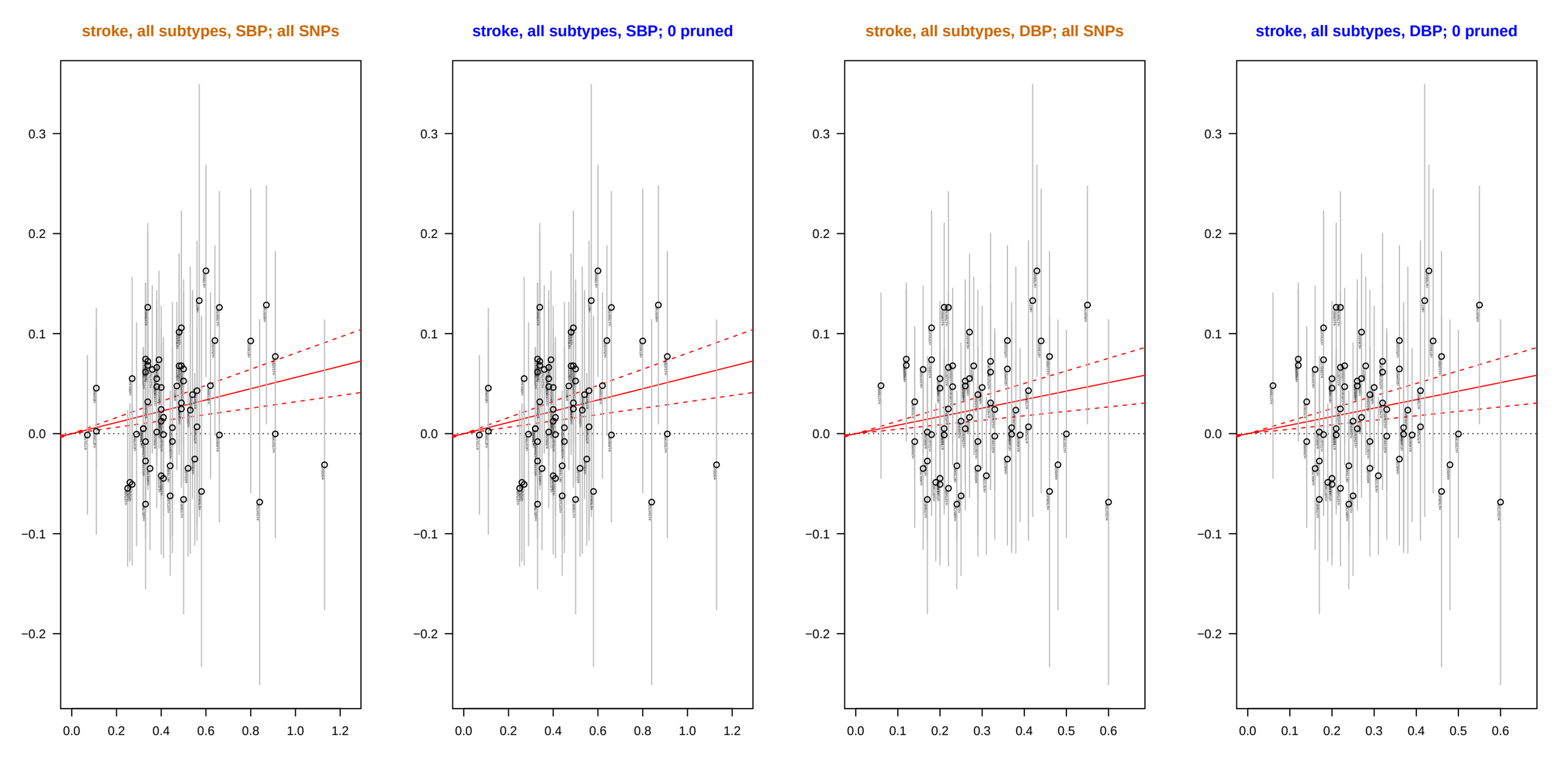

eGFR (based on cr), SBP; all SNPs
eGFR (based on cr), SBP; 2 pruned
eGFR (based on cr), DBP; all SNPs
eGFR (based on cr), DBP; 2 pruned
0.010
0.005
0.000
−0.005
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

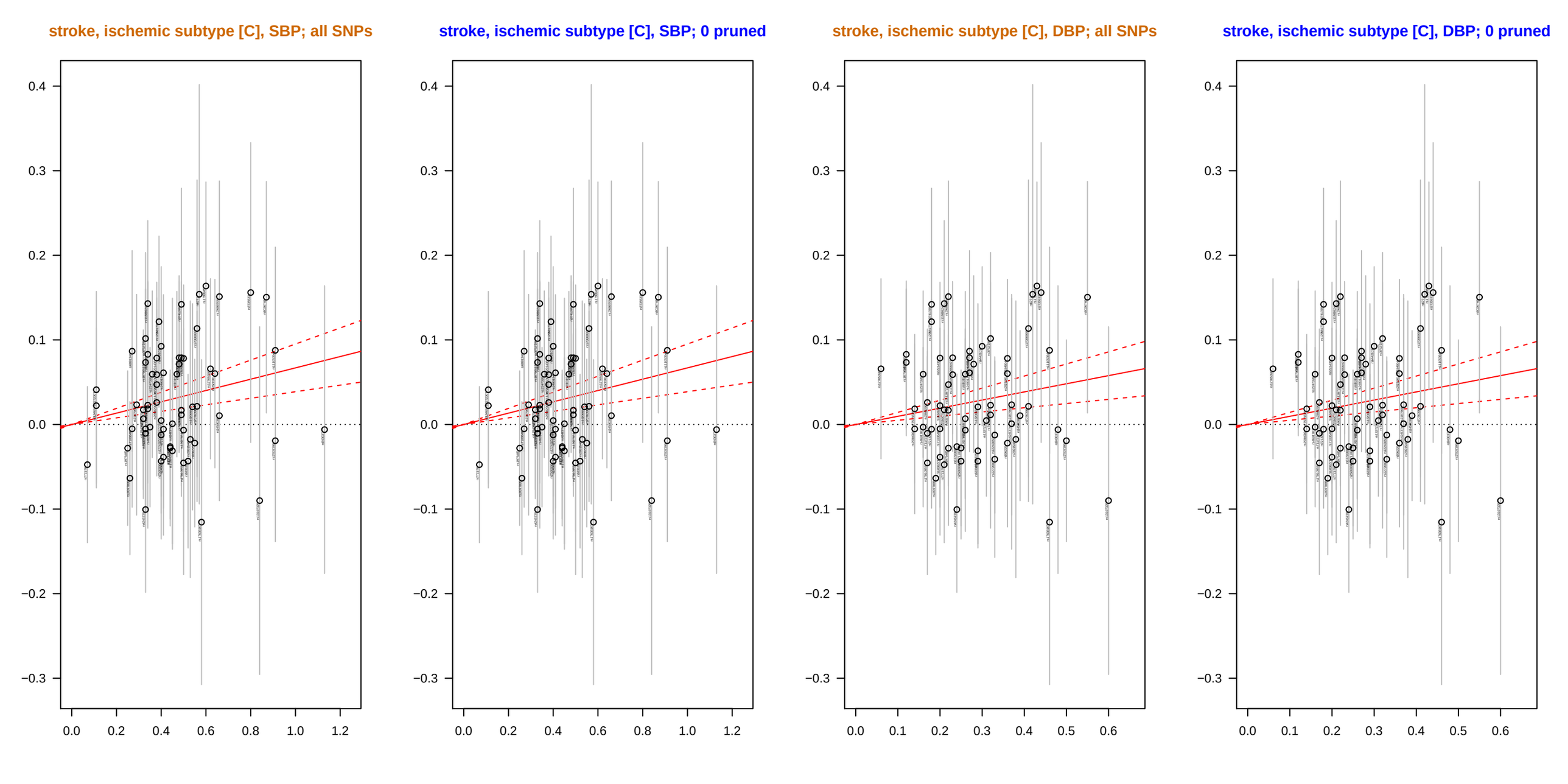

eGFR (based on cystatin), SBP; all SNPs
eGFR (based on cystatin), SBP; 1 pruned
eGFR (based on cystatin), DBP; all SNPs
eGFR (based on cystatin), DBP; 1 pruned
0.015
0.010
0.005
0.000
−0.005
−0.010
−0.015
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

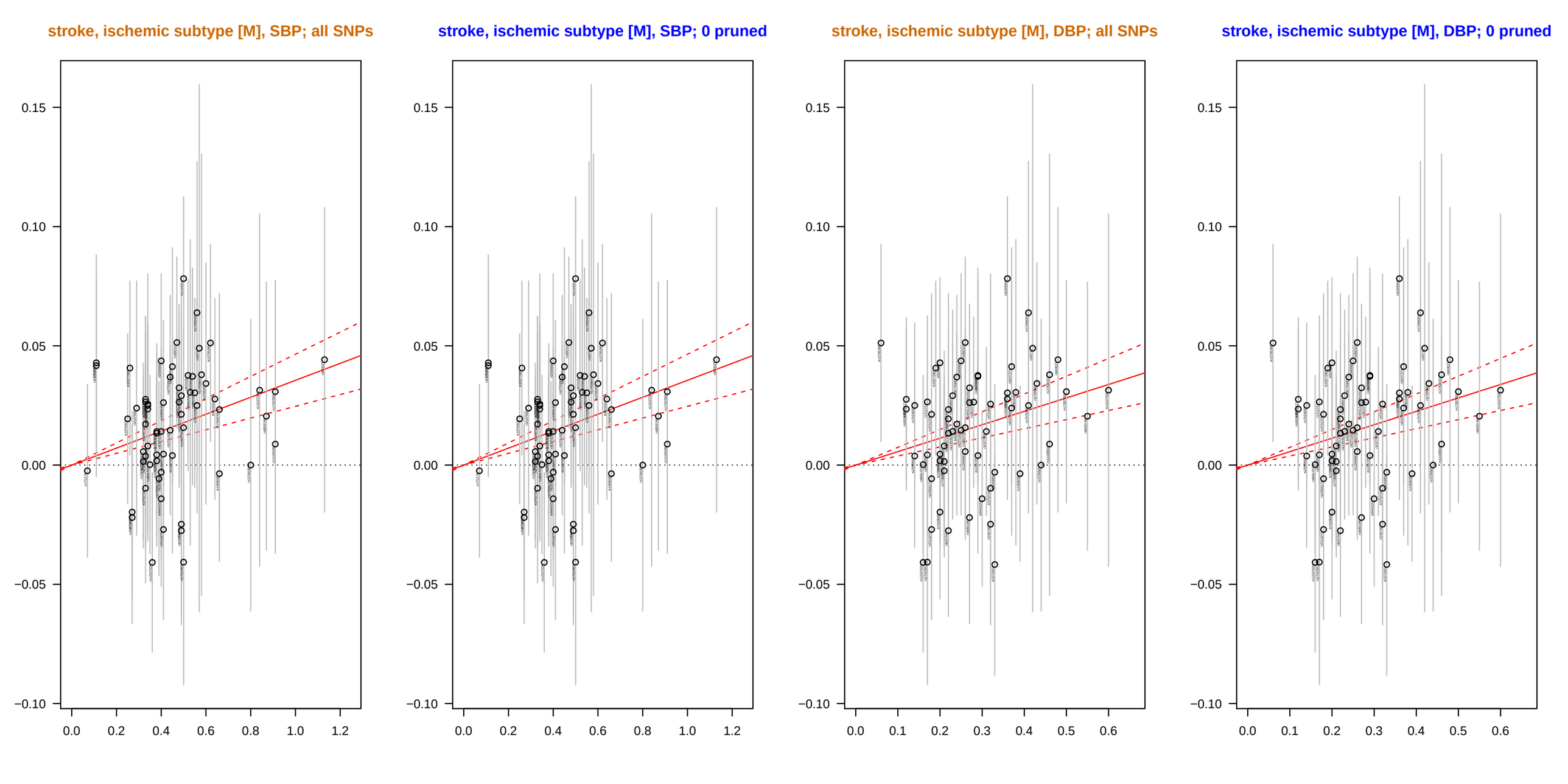

creatinine, SBP; all SNPs
creatinine, SBP; 0 pruned
creatinine, DBP; all SNPs
creatinine, DBP; 0 pruned
0.004
0.002
0.000
−0.002
−0.004
−0.006
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

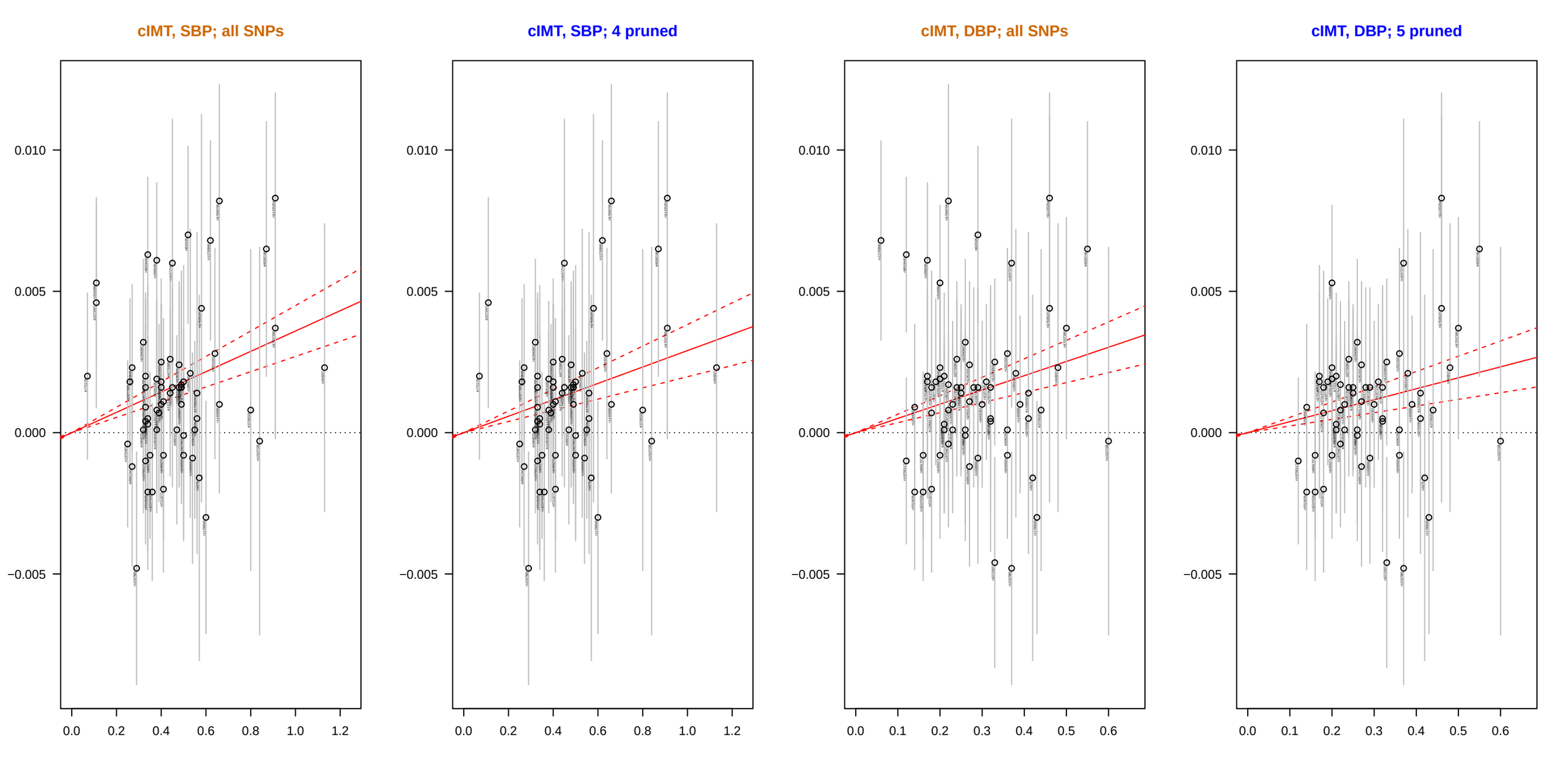

microalbuminuria, SBP; all SNPs
microalbuminuria, SBP; 0 pruned
microalbuminuria, DBP; all SNPs
microalbuminuria, DBP; 0 pruned
0.2
0.1
0.0
−0.1
−0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

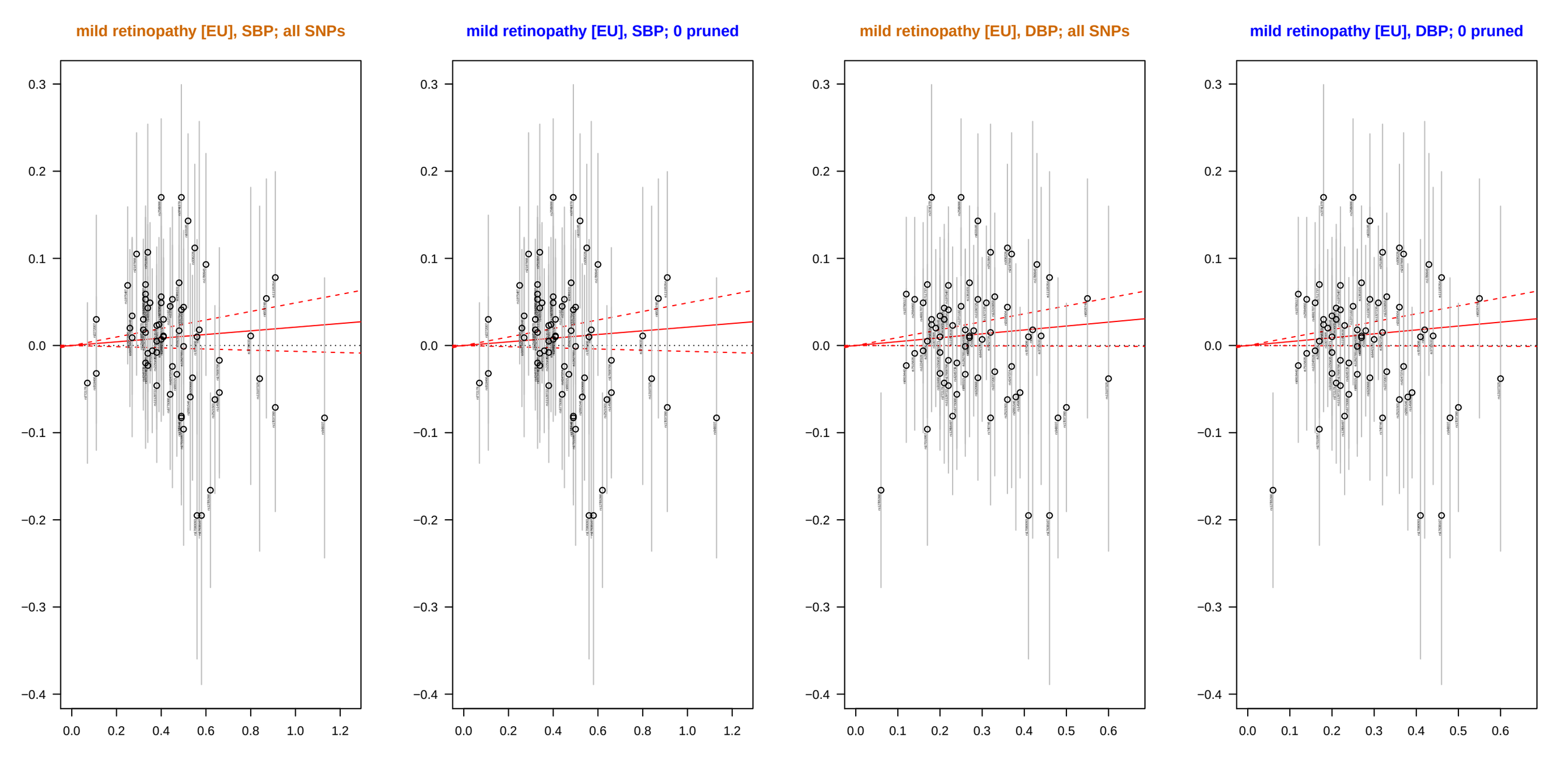

urinary albumin/cr ratio, SBP; all SNPs
urinary albumin/cr ratio, SBP; 1 pruned
urinary albumin/cr ratio, DBP; all SNPs
urinary albumin/cr ratio, DBP; 1 pruned
0.05
0.00
−0.05
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5


stroke, all subtypes, SBP; all SNPs
stroke, all subtypes, SBP; 0 pruned
stroke, all subtypes, DBP; all SNPs
stroke, all subtypes, DBP; 0 pruned
0.3
0.2
0.1
0.0
−0.1
−0.2
0.0 0.2 0.4 0.6 0.8 1.0 1.2
0.0 0.1 0.2 0.3 0.4 0.5 0.6

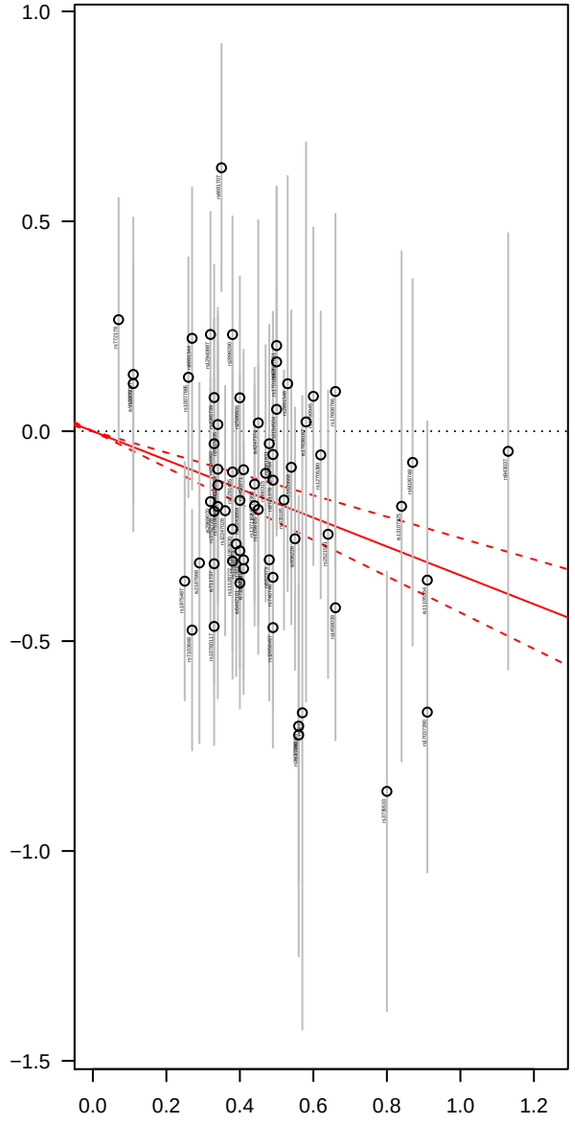

stroke, ischemic subtype [C], SBP; all SNPs
stroke, ischemic subtype [C], SBP; 0 pruned
stroke, ischemic subtype [C], DBP; all SNPs
stroke, ischemic subtype [C], DBP; 0 pruned


stroke, ischemic subtype [M], SBP; all SNPs
stroke, ischemic subtype [M], SBP; 0 pruned
stroke, ischemic subtype [M], DBP; all SNPs
stroke, ischemic subtype [M], DBP; 0 pruned
0.15
0.10
0.05
0.00
−0.05
−0.10
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

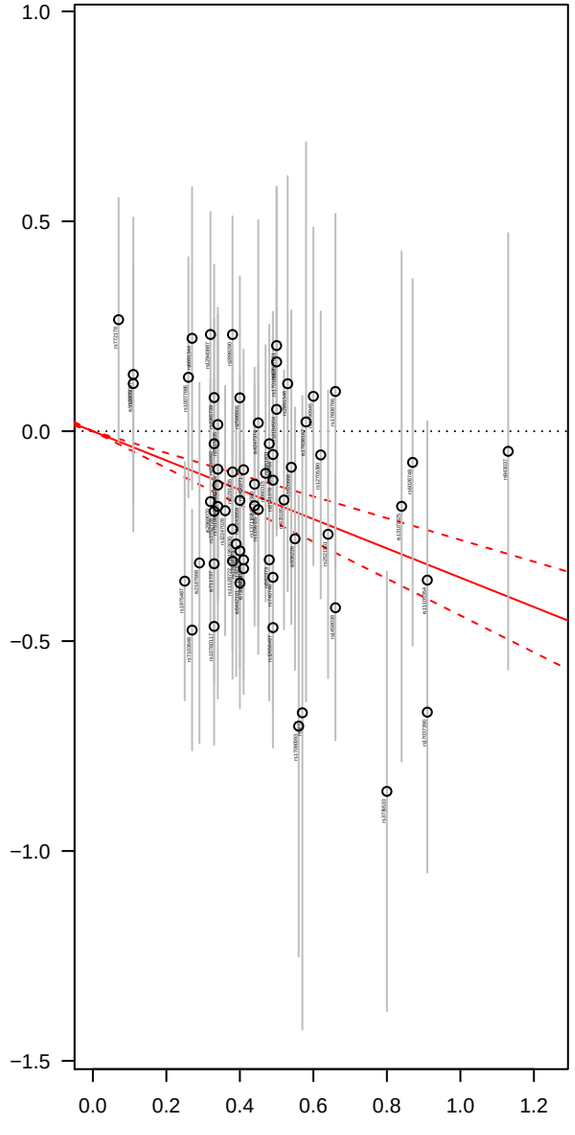

cIMT, SBP; all SNPs
cIMT, SBP; 4 pruned
cIMT, DBP; all SNPs
cIMT, DBP; 5 pruned
0.010
0.005
0.000
−0.005
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.8
1.0
1.2


mild retinopathy [EU], SBP; all SNPs
mild retinopathy [EU], SBP; 0 pruned
mild retinopathy [EU], DBP; all SNPs
mild retinopathy [EU], DBP; 0 pruned

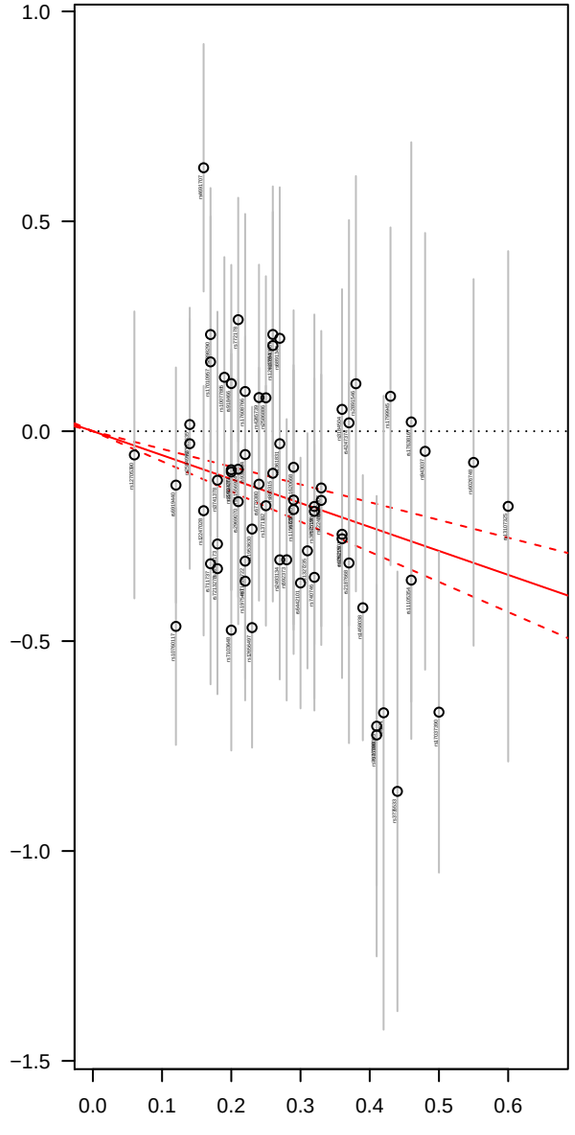
central retinal artery caliber [EU], SBP; all SNPs



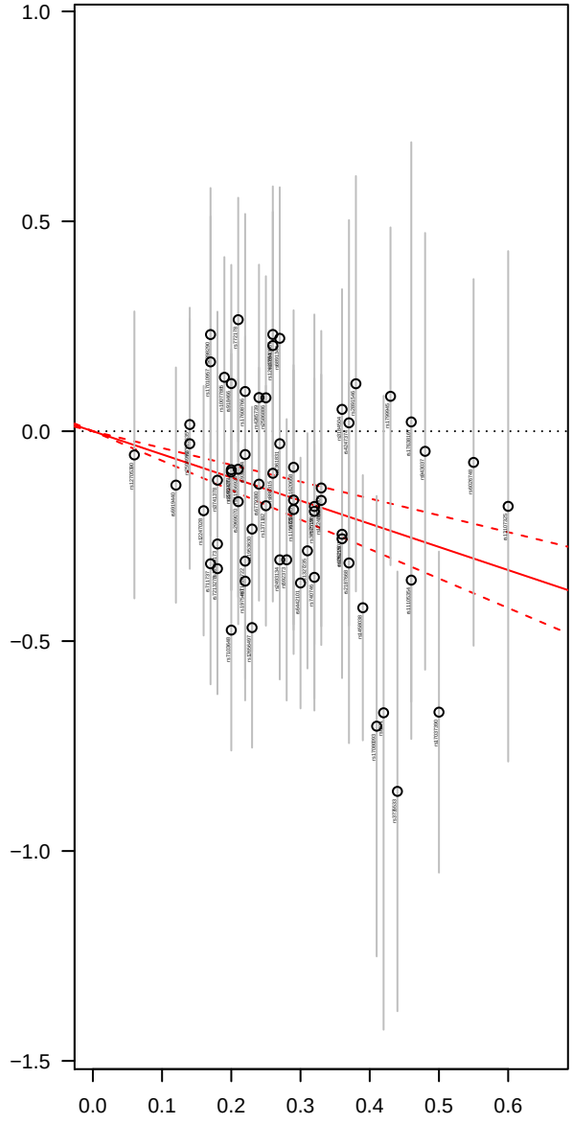
central retinal artery caliber [EU], SBP; 2 pruned

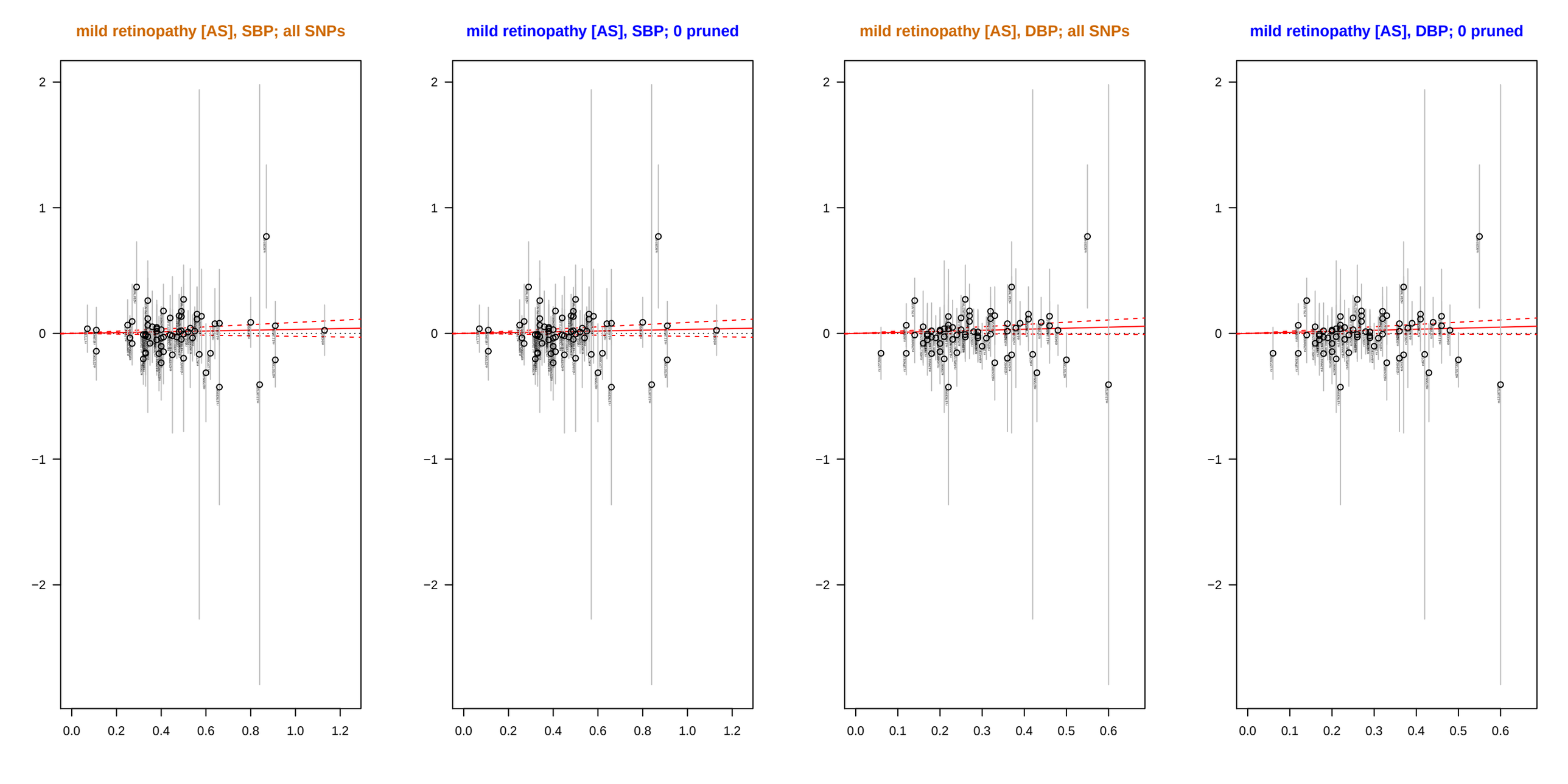


central retinal artery caliber [EU], DBP; all SNPs

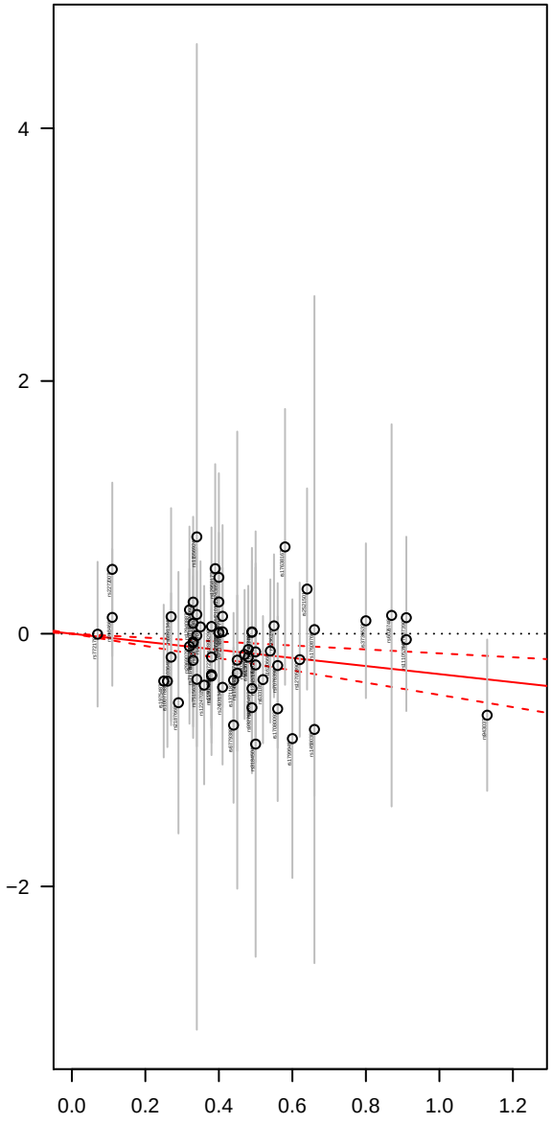


central retinal artery caliber [EU], DBP; 3 pruned

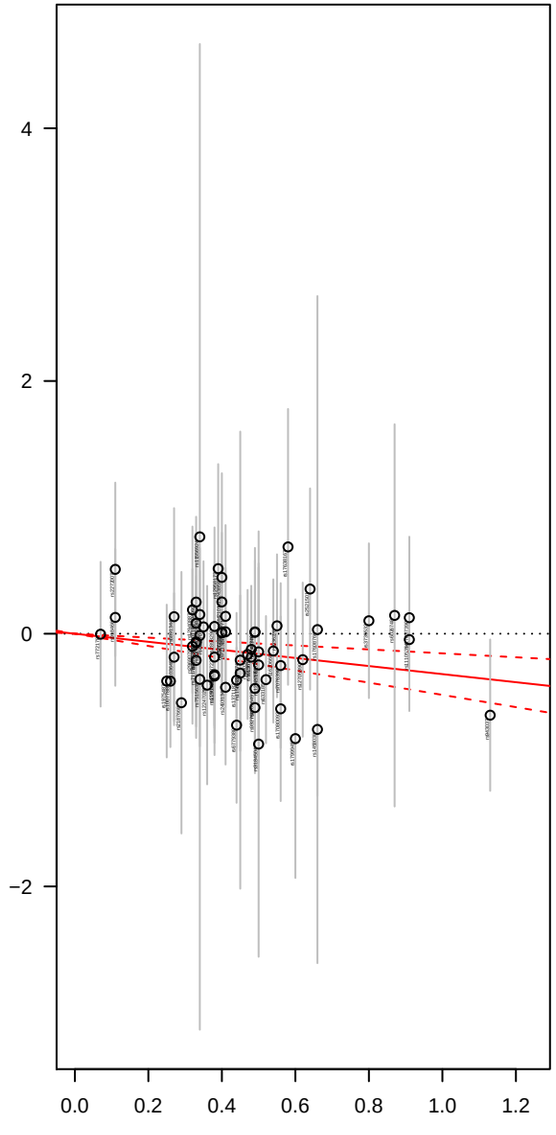



mild retinopathy [AS], SBP; all SNPs
mild retinopathy [AS], SBP; 0 pruned
mild retinopathy [AS], DBP; all SNPs
mild retinopathy [AS], DBP; 0 pruned
2
1
0
−1
−2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

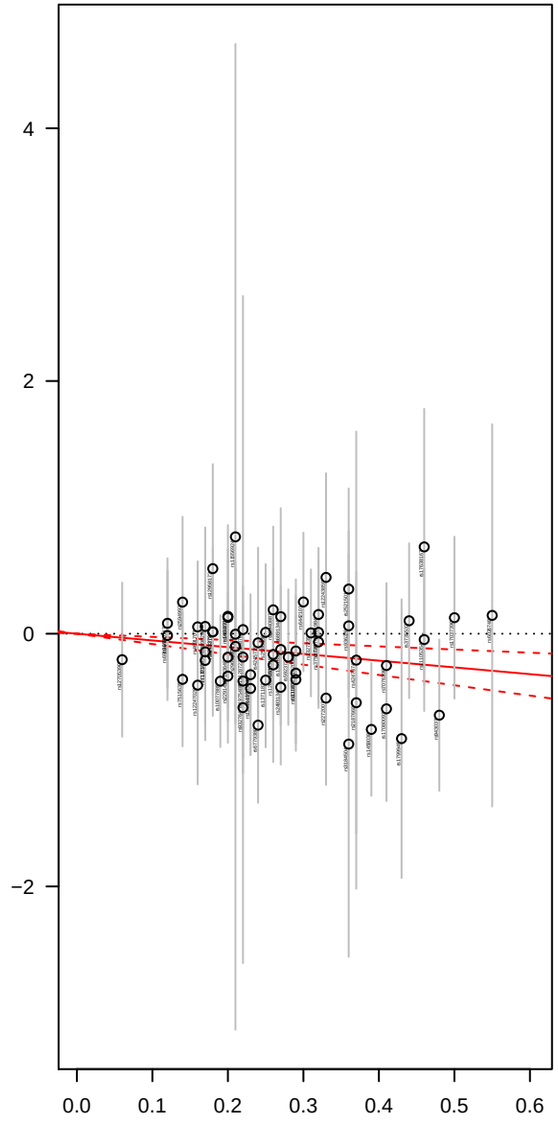
central retinal artery caliber [AS], SBP; all SNPs



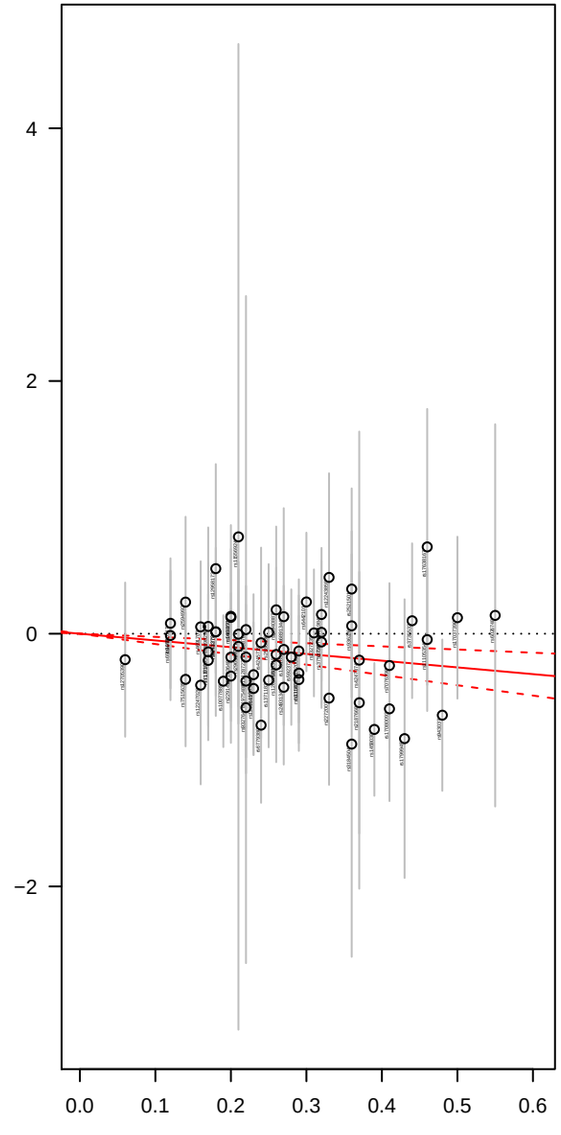
central retinal artery caliber [AS], SBP; 0 pruned

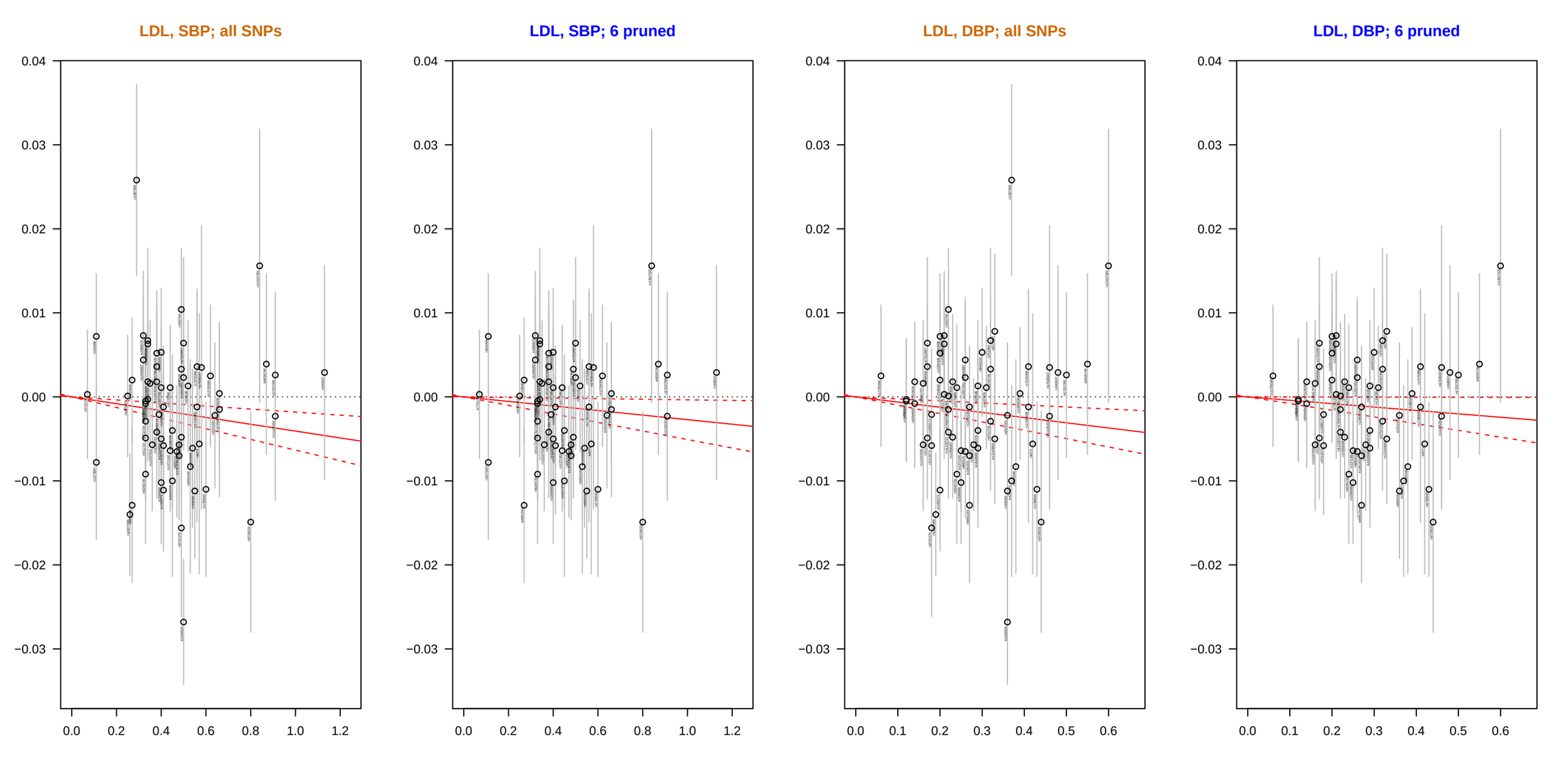


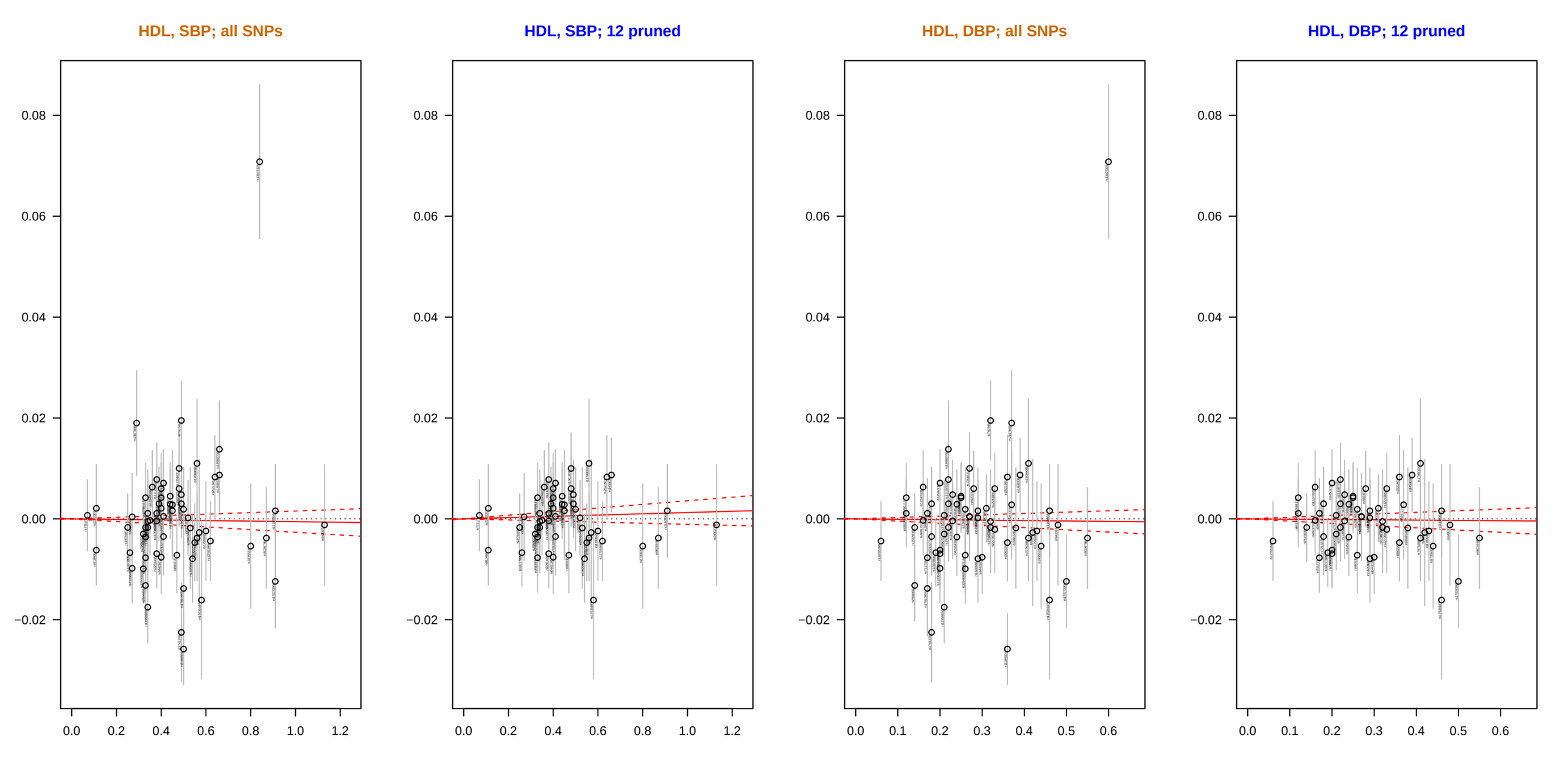
central retinal artery caliber [AS], DBP; all SNPs

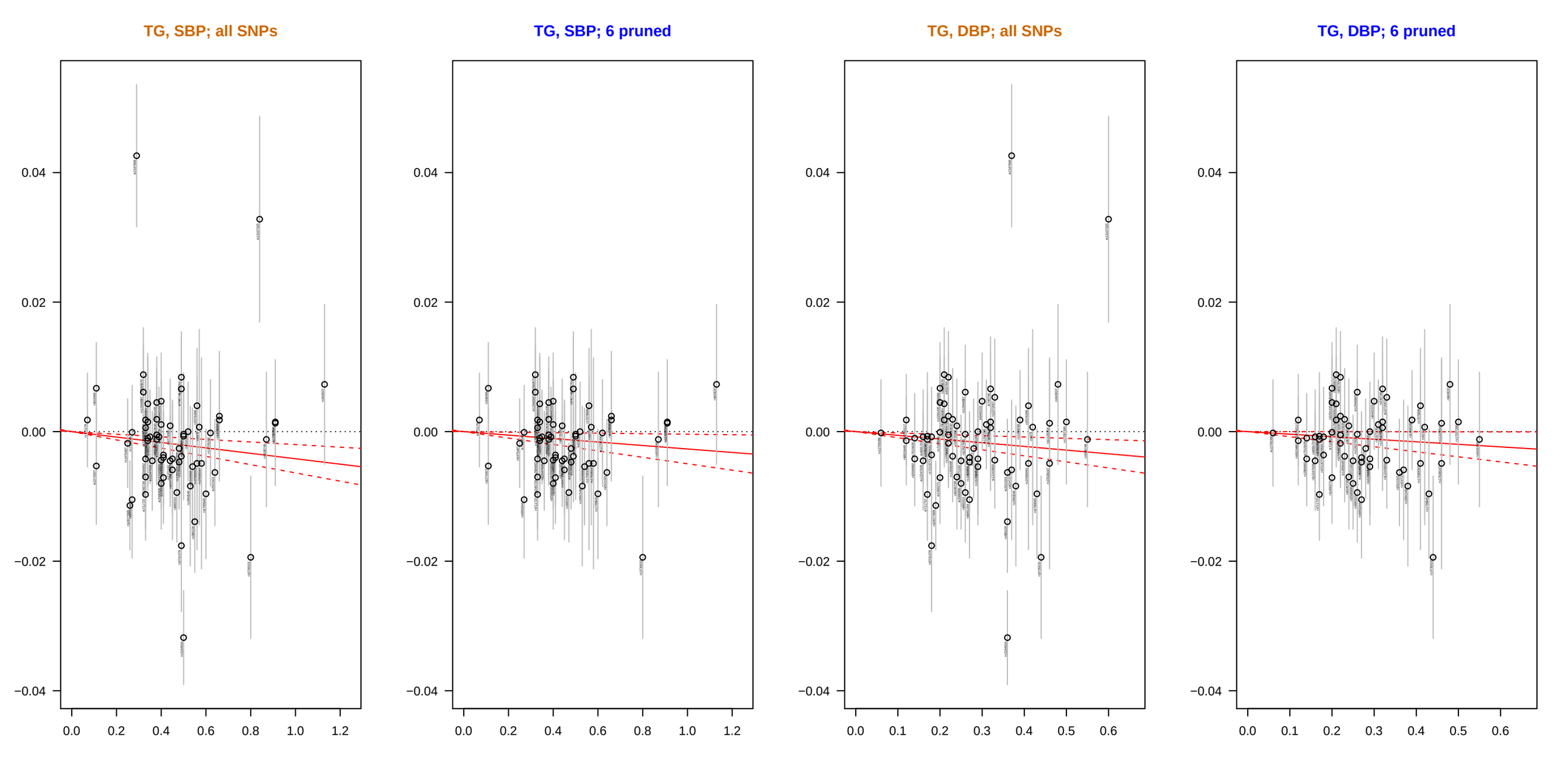


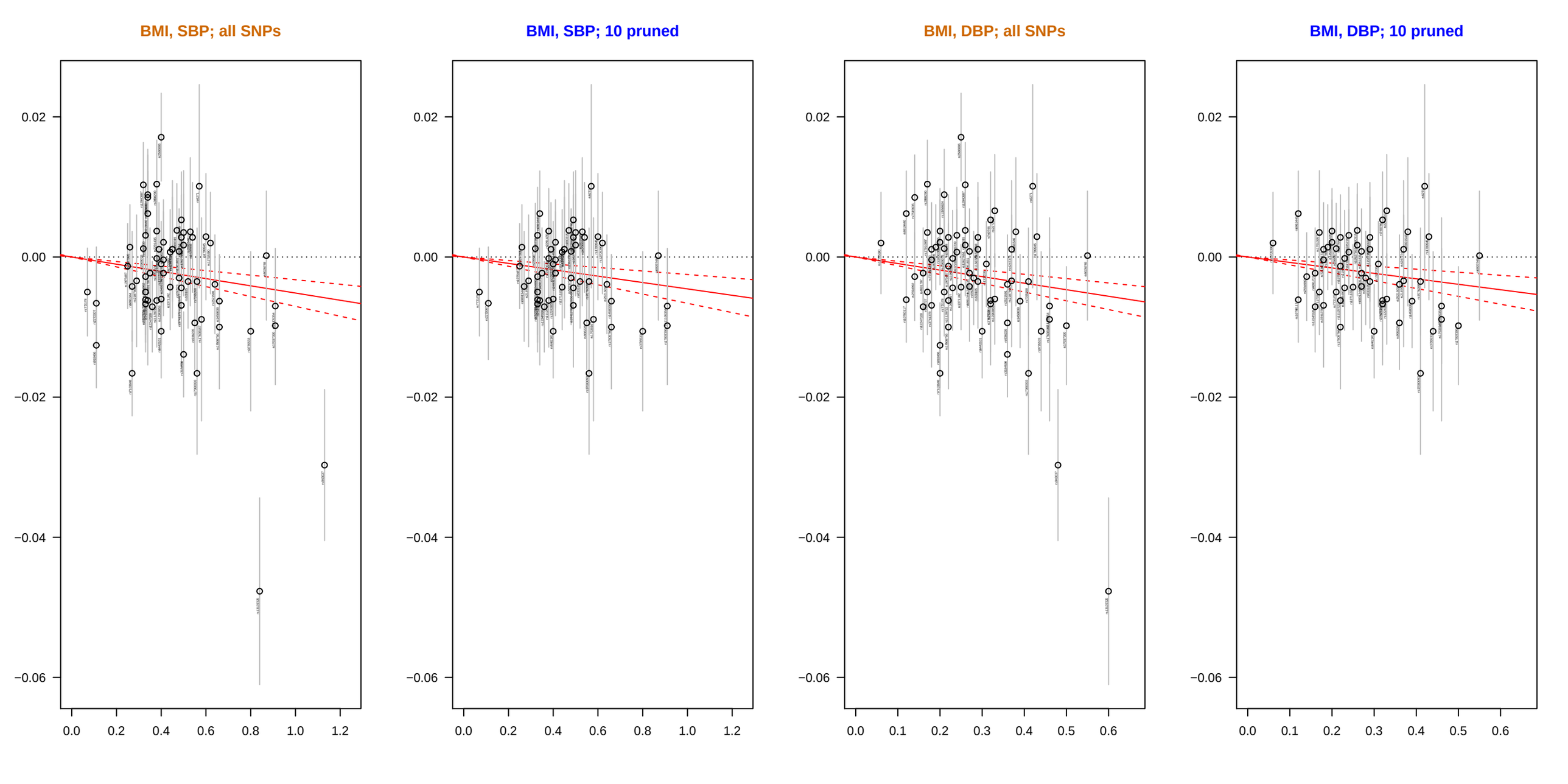
central retinal artery caliber [AS], DBP; 0 pruned

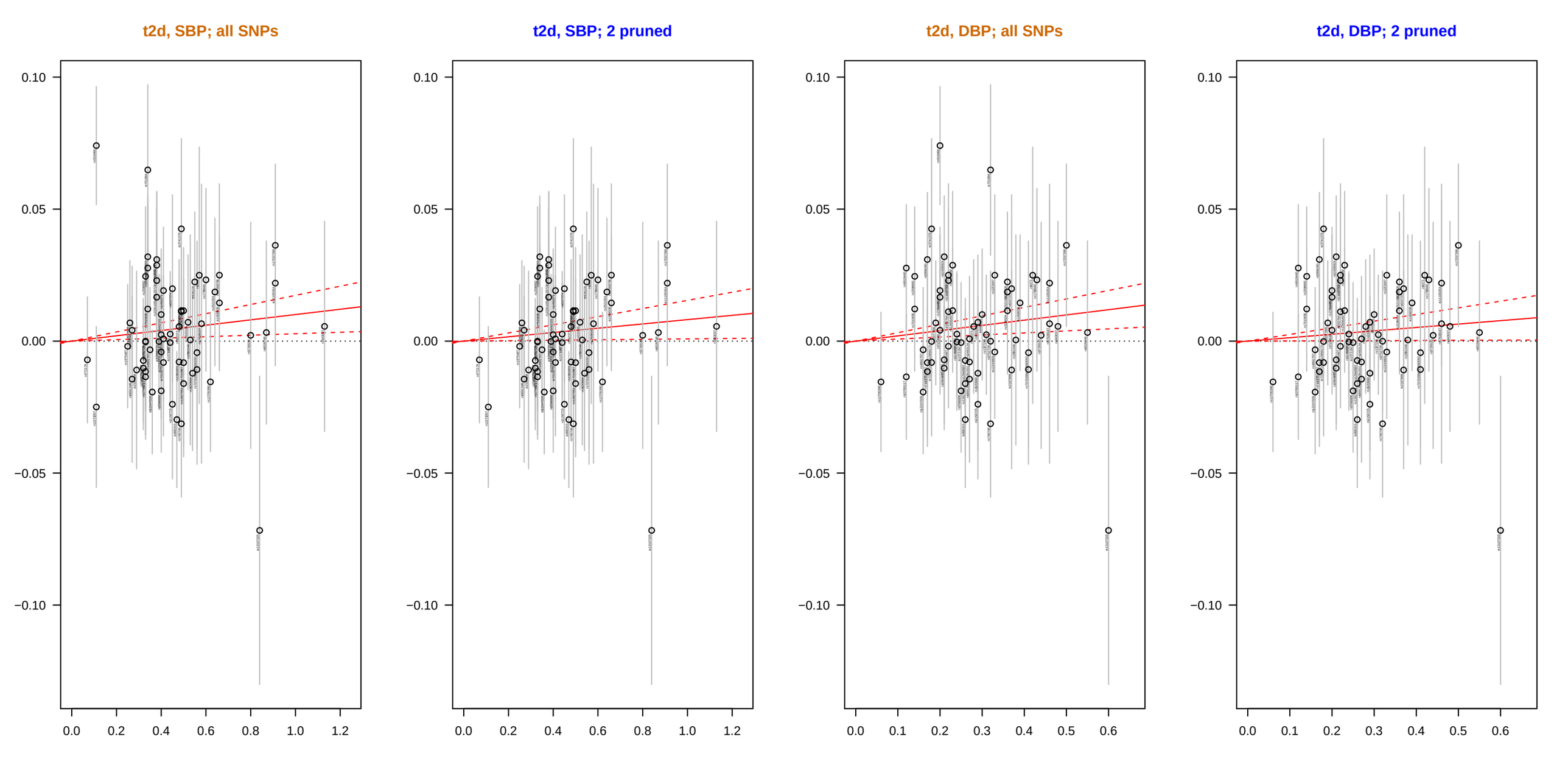



LDL, SBP; all SNPs
LDL, SBP; 6 pruned
LDL, DBP; all SNPs
LDL, DBP; 6 pruned
0.04
0.03
0.02
0.01
0.00
−0.01
−0.02
−0.03
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5


HDL, SBP; all SNPs
HDL, SBP; 12 pruned
HDL, DBP; all SNPs
HDL, DBP; 12 pruned
0.08
0.06
0.04
0.02
0.00
−0.02
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5


TG, SBP; all SNPs
TG, SBP; 6 pruned
TG, DBP; all SNPs
TG, DBP; 6 pruned
0.04
0.02
0.00
−0.02
−0.04
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5


BMI, SBP; all SNPs
BMI, SBP; 10 pruned
BMI, DBP; all SNPs
BMI, DBP; 10 pruned
0.02
0.00
−0.02
−0.04
−0.06
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5


t2d, SBP; all SNPs
t2d, SBP; 2 pruned
t2d, DBP; all SNPs
t2d, DBP; 2 pruned
0.10
0.05
0.00
−0.05
−0.10
0.0
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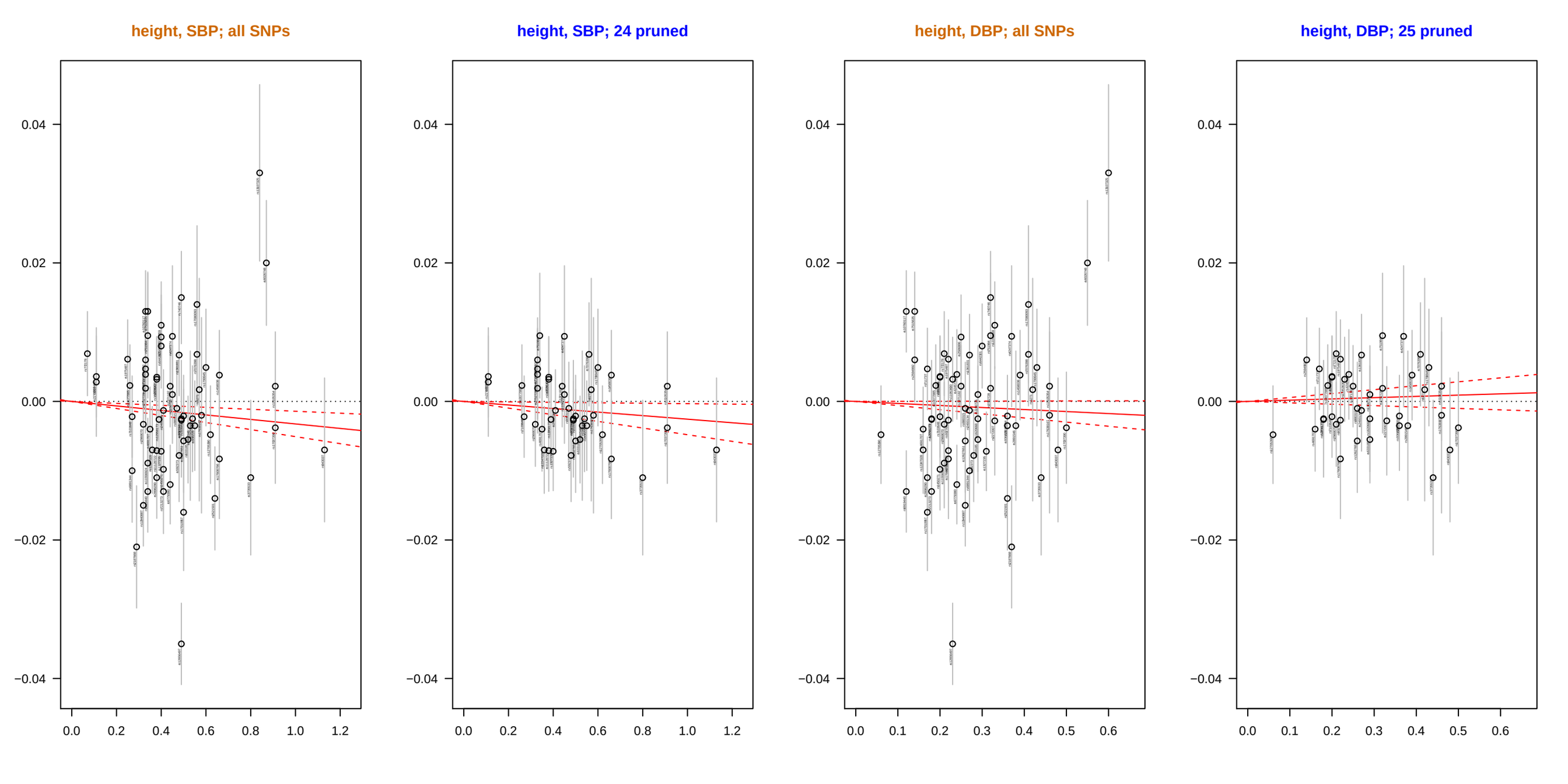
0.8
1.0
1.2
0.1
0.3
0.5


height, SBP; all SNPs
height, SBP; 24 pruned
height, DBP; all SNPs
height, DBP; 25 pruned
0.04
0.02
0.00
−0.02
−0.04
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.8
1.0
1.2

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16 Acknowledgments

58BC: We are grateful for using the British 1958 Birth Cohort DNA collection. Sample collection funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02. Genotyping was funded by the Wellcome Trust.

ADVANCE: The ADVANCE study was supported by a grant from the Reynold's Foundation and NHLBI grant HL087647.

AGES Reykjavik: The AGES Reykjavik study was supported by National Institutes of Health (contracts N01-AG-12100 and HHSN271201200022C); the National Institute on Aging Intramural Research Program; Hjartavernd (the Icelandic Heart Association);the Althingi (the Icelandic Parliament)

allele-specific FAIRE: AJPS was supported by a British Heart Foundation (BHF) grant (FS/13/6/29977), FD was supported by a BHF grant (RG08/008)

AMC-PAS: We thank Aicha Ait Soussan for technical assistance and the WTSI Genotyping Facility for conducting the genotyping

Amish: The Amish studies are supported by grants and contracts from the NIH, including R01 AG18728, R01 HL088119, U01 GM074518, U01 HL072515-06, U01 HL84756, R01 DK54261,the University of Maryland General Clinical Research Center, grant M01 RR 16500, the Mid-Atlantic Nutrition Obesity Research Center grant P30 DK72488, the Baltimore Diabetes Research and Training Center grant P60DK79637, and by the T32 training grant AG000219 . In addition, this project was supported by National Research Initiative Competitive Grant no. 2007-35205-17883 from the USDA National Institute of Food and Agriculture. We gratefully thank our Amish community and research volunteers for their long-standing partnership in research, and acknowledge the dedication of our Amish liaisons, field workers and the Amish Research Clinic staff, without which these studies would not have been possible.

analysis group: This work forms part of the research themes contributing to the translational research portfolio for the NIHR Barts Cardiovascular Biomedical Research Unit (Patricia Munroe). G.B.E. is supported by the University of Geneva, NHLBI (R01HL086694), the Swiss National Foundation (FN 33CM30-124087), and by the "Fondation pour Recherches Médicales" and the GeCor foundation. A.P.M. is a Wellcome Trist Senior Research Fellow in Basic Biomedical Science (grant number WT098017).

ARIC: The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. Funding support for the Genetic Epidemiology of Causal Variants Across the Life Course (CALiCo) program was provided through the NHGRI PAGE program (U01 HG007416). The authors thank the staff and participants of the ARIC study for their important contributions. G.B.E is supported by the Swiss National Foundation SPUM project FN 33CM30-124087, Geneva University, and the Fondation pour Recherches Médicales, Genève. The authors thank the staff and participants of the ARIC study for their important contributions.

ASCOT: This work was supported by Pfizer, New York, NY, USA, for the ASCOT study and the collection of the ASCOT DNA repository; by Servier Research Group, Paris, France; and by Leo Laboratories, Copenhagen, Denmark. We thank all ASCOT trial participants, physicians, nurses, and practices in the

participating countries for their important contribution to the study. In particular we thank Clare Muckian and David Toomey for their help in DNA extraction, storage, and handling. This work forms part of the research themes contributing to the translational research portfolio for the NIHR Barts Cardiovascular Biomedical Research Unit (Mark Caulfield and Patricia Munroe). Genotyping was funded by the Wellcome Trust.

BLSA: The BLSA was supported by the Intramural Research Program of the NIH, National Institute on Aging.

BRIGHT: This work was supported by the Medical Research Council of Great Britain (grant number G9521010D); and by the British Heart Foundation (grant number PG/02/128). A.F.D. was supportedby the British Heart Foundation (grant numbers RG/07/005/23633, SP/08/005/25115); and by the European Union Ingenious HyperCare Consortium: Integrated Genomics, Clinical Research, and Care in Hypertension (grant number LSHM-C7-2006-037093). The BRIGHT study is extremely grateful to all the patients who participated in the study and the BRIGHT nursing team. This work forms part of the research themes contributing to the translational research portfolio for the NIHR Barts Cardiovascular Biomedical Research Unit (Mark Caulfield and Patricia Munroe). Genotyping was funded by the Wellcome Trust.

Cardiogenics: Cardiogenics Project was funded by the European Union (LSHM-CT 2006-037593). We thank the WTSI Genotyping Facility for conducting the genotyping. Data analysis was in part funded by BHF programme grant CRM:0022772 to Deloukas.

CHARGE EYE: This work was supported by multiple funding agencies and details for each cohort were given below. The Age, Gene/Environment Susceptibility – Reykjavik Study was funded by the Intramural Research Program of the National Institute on Aging (ZIAAG007380, National Institutes of Health (NIH) contract N01-AG-12100); and the National Eye Institute (ZIAEY000401) at the NIH in the United States; Hjartavernd (the Icelandic Heart Association); and the Althingi (the Icelandic Parliament). The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C,HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. The Cardiovascular Health Study research reported in this article was supported by the National Heart, Lung, and Blood Institute (NHLBI) contracts N01-HC-85239, N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, and grants HL075366,HL080295, HL087652, with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). This research was also supported by the National Institute on Aging (NIA) contracts AG-023269, AG-15928, AG-20098, and AG-027058. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. DNA handling and genotyping was supported in part by National Center for Research Resources grant M01-RR00425 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center. Additional funding came from the Cedars-Sinai Board of Governors' Chair in Medical Genetics (JIR) and the National Heart, Lung, and Blood Institute Training Grant T32HL007902 (RAJ). The GWA database of the Rotterdam Study was funded through the Netherlands Organization of Scientific Research NWO (no. 175.010.2005.011). This study was further supported by the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) project nr. 050-060-810. The Rotterdam

Study is supported by the Erasmus Medical Center and Erasmus University, Rotterdam; the Netherlands Organization for scientific research (NWO); the Netherlands Organization for the Health Research and Development (ZonMw); The Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture, and Science; the Ministry for Health, Welfare, and Sports; The European commission (DG XII); and the Municipality of Rotterdam. The ophthalmic part of the Rotterdam Study was supported by Lijf en Leven, Krimpen a/d Lek; MD Fonds, Utrecht. Oogfonds Nederland, Utrecht; Stichting Nederlands Oogheelkundig Onderzoek, Nijmegen/Rotterdam; Swart van Essen, Rotterdam; Netherlands Organisation for Scientific Research (NWO); Bevordering van Volkskracht, Rotterdam; Blindenhulp, The Hague; Rotterdamse Vereniging Blindenbelangen, Rotterdam; OOG, The Hague; Algemene Nederlandse Vereniging ter Voorkoming van Blindheid, Doorn; Blinden-Penning, Amsterdam; Blindenhulp, Gravenzande; Henkes Stichting, Rotterdam; Topcon Europe BV, Capelle aan de IJssel; Medical Workshop BV, Groningen; all in the Netherlands; Heidelberg Engineering, Dossenheim, Germany. The Blue Mountains Eye Study has been supported by the Australian National Health & Medical Research Council, Canberra Australia (Grant Numbers 974159, 211069, 457349, 512423, 475604, 529912, and the funding for Centre for Clinical Research Excellence in Translational Clinical Research in Eye Diseases, CCRE in TCR-Eye); In addition, funding by the Wellcome Trust, UK as part of Wellcome Trust Case Control Consortium 2 (A Viswanathan, P McGuffin, P Mitchell, F Topouzis, P Foster) has supported the genotyping costs of the entire BMES population (Grant numbers 085475/B/08/Z and 085475/08/Z). We also acknowledge the funding body National Institutes of Health Research (NIHR) Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, UK. The Australian Twin Registry is supported by an Australian National Health and Medical Research Council (NHMRC) Enabling Grant (2004–2009). We also thank the following organisations for their financial support: Clifford Craig Medical Research Trust, Ophthalmic Research Institute of Australia (ORIA), Glaucoma Australia, American Health Assistance Foundation (AHAF), Peggy and Leslie Cranbourne Foundation, Foundation for Children, NHMRC project grant (2005–2007), Jack Brockhoff Foundation, NEI Project Grant (2007–2010). Genotyping for part of the Australian sample was funded by an NHMRC Medical Genomics Grant. Genotyping for the remainder was performed by the NIH Center for Inherited Research (CIDR) as part of an NIH/National Eye Institute (NEI) grant 1RO1EY018246, Principal Investigator Terri L Young and we are grateful to Dr Camilla Day and staff. Australian sample imputation analyses were carried out on the Genetic Cluster Computer, which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003). The Multi-Ethnic Study of Atherosclerosis (MESA) and MESA SNP Health Association Resource (SHARe) are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support is provided by grants and contracts N01 HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169 and RR-024156. Funding for SHARe genotyping was provided by NHLBI Contract N02-HL-6-4278. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CHARGE-HF consortium: ARIC Study: The ARIC Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute (NHLBI) contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. CHS: This CHS research was supported by NHLBI contracts HHSN268201200036C, HSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, and R01HL120393 with additional contribution from the National Institute

of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. FHS: The FHS was supported by NHLBI (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). This work was also supported in part by grants from the NHLBI 2K24HL04334, R01HL077477, and R01HL093328 (all to RSV). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. The analyses reflect intellectual input and resource development from the FHS investigators participating in the SNP Health Association Resource (SHARe) project. The generation and management of GWAS genotype data for the Rotterdam Study is supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters for their help in creating the GWAS database, and Karol Estrada and Maksim V. Struchalin for their support in creation and analysis of imputed data. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are grateful to the study participants, the staff of the Rotterdam Study and the participating general practitioners and pharmacists. For a full list of CHARGE-HF working group members contributing to this work, please see PMID 20445134.

CHS: Cardiovascular Health Study: This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, and R01HL120393 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CKDGen: Mathias Gorski - Else-Kröner-Fresenius-Stiftung (2012_A147)

CLHNS: We thank the Office of Population Studies Foundation research and data collection teams for the Cebu Longitudinal Health and Nutrition Survey. This work was supported by National Institutes of Health grants DK078150, TW05596, HL085144, TW008288 and pilot funds from RR20649, ES10126, and DK56350.

COGENT: The following studies contributed discovery data for the COGENT-BP consortium: BioVU: The dataset(s) used for the analyses described were obtained from Vanderbilt University Medical Center's BioVU which is supported by institutional funding and by the Vanderbilt CTSA grant 1UL1RR024975-01

from NCRR/NIH. Support was also provided by Vanderbilt Clinical and Translational Research Scholar award (5KL2RR024975 to TLE), and Additional support was provided by the Building Interdisciplinary Research Careers in Women's Health career development program (K12HD4383 to DRVE). Bogalusa Heart Study (BHS): NJS is supported in part by NIH/NCRR Grant Number UL1 RR025774. The BHS was supported by grants HD-061437 and HD-062783 from the National Institute of Child Health and Human Development, and AG-16592 from the National Institute on Aging. CARe Acknowledgement: The authors wish to acknowledge the support of the National Heart, Lung, and Blood Institute and the contributions of the research institutions, study investigators, field staff and study participants in creating this resource for biomedical research. The following nine parent studies have contributed parent study data, ancillary study data, and DNA samples through the Broad Institute (N01-HC-65226) to create this genotype/phenotype data base for wide dissemination to the biomedical research community. This work was also funded by the Center of Excellence in Personalized Medicine (CEPMED), the Canada Research Chair program, the "Fonds de recherche du Québec en Santé (FRQS)", and the "Fondation de l'Institut de Cardiologie de Montréal" (to GL). Atherosclerotic Risk in Communities (ARIC): University of North Carolina at Chapel Hill (N01-HC-55015), Baylor Medical College (N01-HC-55016), University of Mississippi Medical Center (N01-HC-55021), University of Minnesota (N01-HC-55019), Johns Hopkins University (N01-HC-55020), University of Texas, Houston (N01-HC-55017), University of North Carolina, Forsyth County (N01-HC-55018). Cardiovascular Health Study (CHS): University of Washington (N01-HC-85079), Wake Forest University (N01-HC-85080), Johns Hopkins University (N01-HC-85081), University of Pittsburgh (N01-HC-85082), University of California, Davis (N01-HC-85083), University of California, Irvine (N01-HC-85084), New England Medical Center (N01-HC-85085), University of Vermont (N01-HC-85086), Georgetown University (N01-HC-35129), Johns Hopkins University (N01 HC-15103), University of Wisconsin (N01-HC-75150), Geisinger Clinic (N01-HC-45133), University of Washington (N01 HC-55222, U01 HL080295); Cleveland Family Study (CFS): Case Western Reserve University (RO1 HL46380-01-16); Coronary Artery Risk in Young Adults (CARDIA): University of Alabama at Birmingham (N01-HC-48047), University of Minnesota (N01-HC-48048), Northwestern University (N01-HC-48049), Kaiser Foundation Research Institute (N01-HC-48050), University of Alabama at Birmingham (N01-HC-95095), Tufts-New England Medical Center (N01-HC-45204), Wake Forest University (N01-HC-45205), Harbor-UCLA Research and Education Institute (N01-HC-05187), University of California, Irvine (N01-HC-45134, N01-HC-95100); Multi-Ethnic Study of Atherosclerosis (MESA): MESA is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts N01-HC-95159 through N01-HC-95169 and UL1-RR-024156. Funding for genotyping was provided by NHLBI Contract N02-HL-6-4278 and N01-HC-65226. CHS: This CHS research was supported by NHLBI contracts N01-HC-85239, N01-HC-85079 through N01-HC-85086; N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, HHSN268201200036C and NHLBI grants HL080295, HL-085251, HL087652, HL105756 with additional contribution from NINDS. Additional support was provided through AG-023629, AG-15928, AG-20098, and AG-027058 from the NIA. See also http://www.chs-nhlbi.org/pi.htm. DNA handling and genotyping was supported in part by National Center of Advancing Translational Technologies CTSI grant UL1TR000124 and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center and the Cedars-Sinai Board of Governors' Chair in Medical Genetics (JIR). GeneSTAR: GeneSTAR was supported by NIH grants through the National Institute of Nursing Research (NR0224103) and the National Heart, Lung, and Blood Institute (HL58625-01A1, HL59684, HL071025-01A1, U01HL72518, and HL087698); and by M01-RR000052 to the Johns Hopkins General Clinical Research Center. GENOA: Genetic Epidemiology Network of Arteriopathy (GENOA) study is supported by the National Institutes of Health, grant numbers HL087660 and HL100245 from the National Heart, Lung, Blood Institute. HANDLS: The Healthy Aging in Neighborhoods of Diversity across the Life Span Study (HANDLS) research was supported by the Intramural Research Program of the NIH, National Institute on Aging and the National

Center on Minority Health and Health Disparities (project # Z01-AG000513 and human subjects protocol # 2009-149). Data analyses for the HANDLS study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, Md. (http://biowulf.nih.gov). HealthABC: Health ABC was funded by the National Institutes of Aging. This research was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106. The GWAS was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. HUFS: The Howard University Family Study was supported by National Institutes of Health grants S06GM008016-320107 to Charles Rotimi and S06GM008016-380111 to Adebowale Adeyemo. We thank the participants of the study, for which enrollment was carried out at the Howard University General Clinical Research Center, supported by National Institutes of Health grant 2M01RR010284. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the National Institutes of Health. This research was supported in part by the Intramural Research Program of the Center for Research on Genomics and Global Health (CRGGH). The CRGGH is supported by the National Human Genome Research Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the Center for Information Technology, and the Office of the Director at the National Institutes of Health (Z01HG200362). Genotyping support was provided by the Coriell Institute for Medical Research. HyperGEN: The hypertension network is funded by cooperative agreements (U10) with NHLBI: HL54471, HL54472, HL54473, HL54495, HL54496, HL54497, HL54509, HL54515, and 2 R01 HL55673-12. The study involves: University of Utah (Network Coordinating Center, Field Center, and Molecular Genetics Lab); Univ. of Alabama at Birmingham (Field Center and Echo Coordinating and Analysis Center); Medical College of Wisconsin (Echo Genotyping Lab); Boston University (Field Center); University of Minnesota (Field Center and Biochemistry Lab); University of North Carolina (Field Center); Washington University (Data Coordinating Center); Weil Cornell Medical College (Echo Reading Center); National Heart, Lung, & Blood Institute. For a complete list of HyperGEN Investigators please see: www.biostat.wustl.edu/hypergen/Acknowledge.html Loyola-Nigeria: The Loyola-Nigeria study was supported by NIH grant numbers R01-HL053353. The authors acknowledge the assistance of the research staff and participants in Ibadan and Igbo-Ora, Oyo State, Nigeria. Loyola-Maywood: Maywood African-American study is supported by the National Institutes of Health grant number HL074166 from National Heart, Lung, Blood Institute. SIGNET: We would like to thank all of the participants of the REGARDS Study for their valuable contributions, as well as REGARDS investigators and staff. The REGARDS Study research was supported by a cooperative agreement U01 NS041588 (Howard) and R01 DK084350 (Sale) from the National Institutes of Health. WHI: The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. COGENT-BP is funded through R21HL123677-02 to N.F.

CoLaus: The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 3200B0–105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468 and 33CS30-148401).

DEPICT: T.H.P is supported by The Danish Council for Independent Research Medical Sciences (FSS) The Alfred Benzon Foundation and The Lundbeck Foundation.

DESIR: We thank all the participants of the D.E.S.I.R study, Elodie Eury for technical support for the genotyping, Olivier Lantieri and Michel Marre from the D.E.S.I.R study. The genotyping was supported by

the "Conseil Régional Nord-Pas-de-Calais Fonds européen de développement économique et regional" CPER axe Cartdiodiabète 2010-2011 grant to NB-N.

DGI: We thank the participants of Sweden and Finland who contributed to the DGI study. C.N.-C. was supported by the National Institutes of Health (HL080025, HL098283, HL113933), a Doris Duke Charitable Foundation Clinical Scientist Development Award, a Burroughs Wellcome Fund Career Award for Medical Scientists and institutional support from the Massachusetts General Hospital Cardiovascular Research Center and the Department of Medicine. G.K. was supported by the National Institutes of Health (T32HL007208). This work was supported by the Novartis Institute for Biomedical Research.

DHS and methylation analysis by tissue: CJW received support from the National Institutes of Health (HL094535 and HL109946), and EMS from the National Science Foundation Open Data Integrative Graduate Education and Research Traineeship (IGERT) Grant 0903629.

DIAGEN: The DIAGEN study was supported by the Commission of the European Communities, Directorate C - Public Health and Risk Assessment, Health & Consumer Protection, Grant Agreement number - 2004310 and by the Dresden University of Technology Funding Grant, Med Drive. We are grateful to all of the patients who cooperated in this study and to their referring physicians and diabetologists in Saxony.

DILGOM: The DILGOM-study was supported by the Academy of Finland, grant # 118065. SM was supported by grants #136895 and #141005, VS by grants #139635 and 129494 and MP by grant #129322 from the Academy of Finland. KK was supported by Orion-Farmos Research Foundation and Academy of Finland (grant number 250207). V.S. was supported by the Finnish Foundation for Cardiovascular Research.

DPS: The DPS has been financially supported by grants from the Academy of Finland (117844 and 40758, 211497, and 118590; The EVO funding of the Kuopio University Hospital from Ministry of Health and Social Affairs (5254), Finnish Funding Agency for Technology and Innovation (40058/07), Nordic Centre of Excellence on Systems biology in controlled dietary interventions and cohort studies, SYSDIET (070014), The Finnish Diabetes Research Foundation, Yrjö Jahnsson Foundation (56358), Sigrid Juselius Foundation, Juho Vainio Foundation and TEKES grants 70103/06 and 40058/07.

DR's EXTRA: The DR.s EXTRA Study was supported by grants to R. Rauramaa by the Ministry of Education and Culture of Finland (627;2004-2011), Academy of Finland (102318; 123885), Kuopio University Hospital , Finnish Diabetes Association, Finnish Heart Association, Päivikki and Sakari Sohlberg Foundation and by grants from European Commission FP6 Integrated Project (EXGENESIS); LSHM-CT-2004-005272, City of Kuopio and Social Insurance Institution of Finland (4/26/2010).

DRAGON: This study was supported by the Taichung Veterans General Hospital, Taiwan (TCVGH-1013001C, TCVGH-1013002D).

EchoGen consortium: For a full list of EchoGen members contributing to this work and for acknowledgements, please see PMID 19584346.

Ely: The Ely Study was funded by the Medical Research Council. We are most grateful to all study participants and to the staff of the St. Mary's Street Surgery, Ely. We thank all the staff who worked on the study.

EPIC: The EPIC Norfolk Study is funded by program grants from the Medical Research Council UK and Cancer Research UK.

eQTL, EGCUT: TE and AM work was supported through the Estonian Genome Center of University of Tartu by the Targeted Financing from the Estonian Ministry of Science and Education [SF0180142s08]; the Development Fund of the University of Tartu (grant SP1GVARENG); the European Regional Development Fund to the Centre of Excellence in Genomics (EXCEGEN; grant 3.2.0304.11-0312); and through FP7 grant 313010.

eQTL, Groningen: L.F.,H-J.W.: This study was supported by grants from the Celiac Disease Consortium (an innovative cluster approved by the Netherlands Genomics Initiative and partly funded by the Dutch Government (grant BSIK03009), the Netherlands Organization for Scientific Research (NWO-VICI grant 918.66.620, NWO-VENI grant 916.10.135 to L.F.), the Dutch Digestive Disease Foundation (MLDS WO11-30), and a Horizon Breakthrough grant from the Netherlands Genomics Initiative (grant 92519031 to L.F.). This project was supported by the Prinses Beatrix Fonds, VSB fonds, H. Kersten and M. Kersten (Kersten Foundation), The Netherlands ALS Foundation, and J.R. van Dijk and the Adessium Foundation. The research leading to these results has received funding from the European Community's Health Seventh Framework Programme (FP7/2007-2013) under grant agreement 259867.

FENLAND: The Fenland Study is funded by the Wellcome Trust and the Medical Research Council, as well as by the Support for Science Funding programme and CamStrad. We are grateful to all the volunteers for their time and help, and to the General Practitioners and practice staff for help with recruitment. We thank the Fenland Study co-ordination team and the Field Epidemiology team of the MRC Epidemiology Unit for recruitment and clinical testing.

FHS: The National Heart, Lung, and Blood Institute's Framingham Heart Study is a joint project of the National Institutes of Health and Boston University School of Medicine and was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (contract No. N01-HC-25195) and its contract with Affymetrix, Inc. for genotyping services (contract No. N02-HL-6-4278). Analyses reflect the efforts and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. A portion of this research was conducted using the Linux Cluster for Genetic Analysis (LinGAII) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center.

FIN-D2D 2007: The FIN-D2D study has been financially supported by the hospital districts of Pirkanmaa, South Ostrobothnia, and Central Finland, the Finnish National Public Health Institute (current National Institute for Health and Welfare), the Finnish Diabetes Association, the Ministry of Social Affairs and Health in Finland, the Academy of Finland (grant number 129293),Commission of the European Communities, Directorate C-Public Health (grant agreement no. 2004310) and Finland's Slottery Machine Association.

FINCAVAS: This work was supported by the Competitive Research Funding of the Tampere University Hospital (Grant 9M048 and 9N035), the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research, the Emil Aaltonen Foundation, Finland, and the Tampere Tuberculosis Foundation. The authors thank the staff of the Department of Clinical Physiology for collecting the exercise test data.

FUSION: Support for FUSION was provided by NIH grants R01-DK062370 (to M.B.), R01-DK072193 (to K.L.M.), and intramural project number 1Z01-HG000024 (to F.S.C.). Genome-wide genotyping was conducted by the Johns Hopkins University Genetic Resources Core Facility SNP Center at the Center for Inherited Disease Research (CIDR), with support from CIDR NIH contract no. N01-HG-65403.

GenNet: We thank the study participants and NHLBI for funding (FBPP program).

GLACIER: The GLACIER Study is nested within the Northern Sweden Health and Disease Study and phenotyping was conducted as part of the Västerbotten Intervention Project. We thank the participants and the investigators from these studies for their valuable contributions, with specific thanks to Lars Weinehall, Åsa Agren, Kerstin Enquist, and Thore Johansson. The GLACIER Study and part of PWF's salary were funded by grants from the Swedish Research Council, Swedish Heart-Lung Foundation, Novo Nordisk, Umeå Medical Research Foundation, and the Swedish Diabetes Association (to PWF). Genotyping for this specific project was funded by the Wellcome Trust Sanger Institute. Inês Barroso acknowledges funding from the Wellcome Trust grant 098051, United Kingdom NIHR Cambridge Biomedical Research Centre and the MRC Centre for Obesity and Related Metabolic Diseases. We would like to thank Emma Gray, Douglas Simpkin, Sarah Hunt and staff of the WTSI Sample Logistics, Genotyping and Variation Informatics Facilities. Frida Restrom was supported in part by a post-doctoral fellowship from the Swedish Heart-Lung Foundation.

GoDARTS: The Wellcome Trust provides support for Wellcome Trust United Kingdom Type 2 Diabetes Case Control Collection (Go-DARTS) and the Scottish Health Informatics Programme. Further informatics support is provided by the Chief Scientist Office of Scotland. This work was also supported by the UK Medical Research Council (G0601261). We acknowledge the support of the Health Informatics Centre, University of Dundee for managing and supplying the anonymised data and NHS Tayside, the original data owner. We are grateful to all the participants who took part in the Go-DARTS study, to the general practitioners, to the Scottish School of Primary Care for their help in recruiting the participants, and to the whole team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

GOSH: This work was supported by grants from the US National Institutes of Health (AG028555, AG08724, AG04563, AG10175, AG08861), the Swedish Research Council, the Swedish Heart-Lung Foundation, the Swedish Foundation for Strategic Research, the Royal Swedish Academy of Science, and ENGAGE (within the European Union Seventh Framework Programme, HEALTH-F4-2007-201413). Genotyping was performed by the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University, Uppsala University Hospital and the Swedish Research Council for Infrastructures.

GxE/Spanish Town: Principally, our thanks go to the participants in the Spanish Town and GxE studies. We also thank Nurse Orgen Brown, Mr Windsor Cuffe, and other past and present members of the labs at TMRU for their assistance in carrying out these studies. This work was supported by NIH Grant R01HL53353.

HALST: HALST project are conducted and supported by the National Health Research Institutes (NHRI) in collaboration with HALST investigators. Support is provided by grant BS-097-SP-04, PH-098-PS-02, PH-099-SP-01, PH-100-SP-01, PH-101-SP-01, PH-102-SP-01, PH-103-SP-01. The authors thank the participants of the HALST study, the Coordinating Center, HALST investigators, and study staff for their valuable contributions.

HEXA: This work was supported by a grant from the Korea Center for Disease Control and Prevention, and intramural grant from the Korea National Institute of Health.

HUNT2: The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health.

HyperGEN: The hypertension network is funded by cooperative agreements (U10) with NHLBI: HL54471, HL54472, HL54473, HL54495, HL54496, HL54497, HL54509, HL54515, and 2 R01 HL55673-12. The study involves: University of Utah: (Network Coordinating Center, Field Center, and Molecular Genetics Lab); Univ. of Alabama at Birmingham: (Field Center and Echo Coordinating and Analysis Center); Medical College of Wisconsin: (Echo Genotyping Lab); Boston University: (Field Center); University of Minnesota: (Field Center and Biochemistry Lab); University of North Carolina: (Field Center); Washington University: (Data Coordinating Center); Weill Cornell Medical College: (Echo Reading Center); National Heart, Lung, & Blood Institute. For a complete list of HyperGEN Investigators: http://www.biostat.wustl.edu/hypergen/Acknowledge.html.

IMPROVE: The IMPROVE study was funded by the European Commission (Contract number: QLG1-CT-2002-00896), the Academy of Finland (Grant #110413) the British Heart Foundation (RG2008/014) and the Italian Ministry of Health (Ricerca Corrente), and the IMPROVE and SCARFSHEEP studies were funded by the Swedish Heart-Lung Foundation, the Swedish Research Council (8691), the Knut and Alice Wallenberg Foundation, the Foundation for Strategic Research, the Torsten and Ragnar Söderberg Foundation, the Strategic Cardiovascular and Diabetes Programmes of Karolinska Institutet and the Stockholm County Council, the Strategic support for epidemiological research at Karolinska Institutet and the Stockholm County Council, and the Stockholm County Council (560183).

InCHIANTI: The InCHIANTI study baseline (1998-2000) was supported as a "targeted project" (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts: 263 MD 9164 and 263 MD 821336).

JUPITER: Genetic Analysis in the JUPITER trial was funded by AstraZeneca

KidneyGen Consortium: The KidneyGen Consortium included 23,812 participants from the following cohort studies: BRIGHT, BWHHS, CoLaus, Fenland, InChianti, LOLIPOP, MDC-CC, NESDA, NFBC 1966, PREVEND, SardiNIA, and Twins UK. The acknowledgements and funding sources for each cohort can be found in Chambers JC, et al. Nat Genet 2010, 42:373-375 (PMID: 20383145). JCC, JSK and WZ acknowledge support from the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre (BRC) Imperial College Healthcare NHS Trust, the British Heart Foundation (SP/04/002), the Medical Research Council (G0601966,G0700931), the Wellcome Trust (084723/Z/08/Z) the NIHR (RP-PG-0407-10371), European Union FP7 (EpiMigrant, 279143) and Action on Hearing Loss (G51). We thank all the participants and researchers in the consortium who made the study possible. P .Elliott is supported by the National Institute for Health Research (NIHR) Imperial College Health Care NHS Trust and Imperial College Biomedical Research Centre, the MRC-PHE Centre for Environment and Health, the NIHR Health Protection Research Unit on Health Impact of Environmental Hazards and is an NIHR Senior Investigator.

KORA F3/F4: The KORA Augsburg studies were financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany and supported by grants from the German Federal Ministry of Education and Research (BMBF). Part of this work was financed by the German National Genome Research Network (NGFN). Our research was supported within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ.

LURIC: We extend our appreciation to the participants of the LURIC study. We thank the LURIC study team who were either temporarily or permanently involved in patient recruitment as well as sample and data handling, in addition to the laboratory staff at the Ludwigshafen General Hospital and the Universities of Freiburg and Ulm, Germany. This work was supported by the 7th Framework Program (integrated project AtheroRemo, grant agreement number 201668 and RiskyCAD, grant agreement

number 305739) of the European Union, by the INTERREG IV Oberrhein Program (Project A28, Genetic mechanisms of cardiovascular diseases) with support from the European Regional Development Fund (ERDF) and the Wissenschaftsoffensive TMO.

MDC-CVA: The authors acknowledge the Knut and Alice Wallenberg Foundation for its economic support of the SWEGENE DNA extraction facility. Source of funding: This study was supported by grants from the European Research Council (StG-282255) Swedish Medical Research Council, the Swedish Heart and Lung Foundation, the Medical Faculty of Lund University, Malmö University Hospital, the Albert Påhlsson Research Foundation, the Crafoord Foundation, the Ernhold Lundström Research Foundation, the Region Skane, Hulda and Conrad Mossfelt Foundation, King Gustaf V and Queen Victoria Foundation and the Lennart Hansson Memorial Fund.

MESA: MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support is provided by grants and contracts N01 HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, RR-024156 and H7 071025 and RR 025005. Funding for MESA SHARe genotyping was provided by NHLBI contract H2-6-4278. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The authors thank the participants of the MESA study, the Coordinating Center, MESA investigators, and study staff for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Metastroke: H.S.M. is supported by a National Institute for Health Research Senior Investigator award. H.S.M. and S.B. are supported by the Cambridge University Hospital National Institute for Health Research Biomedical Research Centre. Hugh Markus is supported by an NIHR Senior Investigator award and received support from the Cambridge Universities Trust NIHR Comprehensive BRC.

METSIM: The METSIM study was funded by the Academy of Finland (grants no. 77299 and 124243).

MICROS: In South Tyrol, the study was supported by the Ministry of Health and Department of Educational Assistance, University and Research of the Autonomous Province of Bolzano, the South Tyrolean Sparkasse Foundation, and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). For the MICROS study, we thank the primary care practitioners Raffaela Stocker, Stefan Waldner, Toni Pizzecco, Josef Plangger, Ugo Marcadent, and the personnel of the Hospital of Silandro (Department of Laboratory Medicine) for their participation and collaboration in the research project.

MIGen: The MIGen study was funded by the US National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute's STAMPEED genomics research program. Genotyping was partially funded by The Broad Institute Center for Genotyping and Analysis, which is supported by grant U54 RR020278 from the National Center for Research Resources. Specifc cohorts were supported by the grants (R01HL056931, P30ES007033) and a contract (N01HD013107) from US National Institutes of Health (HARPS); and by the Spanish Ministry of Economy and Innovation through the Carlos III Health Institute [Red HERACLES RD12/0042, CIBER Epidemiología y Salud Pública, PI09/90506], European Funds for Development (ERDF-FEDER), and by the Catalan Research and Technology Innovation Interdepartmental Commission [SGR 1195] (REGICOR).

MORGAM: Sites and key personnel of contributing MORGAM Centres: Finland FINRISK, National Institute for Health and Welfare, Helsinki: V. Salomaa (principal investigator), A. Juolevi, E. Vartiainen, P. Jousilahti; ATBC, National Institute for Health and Welfare, Helsinki: J. Virtamo (principal investigator), H. Kilpeläinen; MORGAM Data Centre, National Institute for Health and Welfare, Helsinki: K. Kuulasmaa (responsible person), Z. Cepaitis, A. Haukijärvi, B. Joseph, J. Karvanen, S. Kulathinal, M. Niemelä, O. Saarela; MORGAM Central Laboratory, National Institute for Health and Welfare, Helsinki: L. Peltonen (responsíble person), M. Perola, K. Silander, M. Alanne, P. Laiho, K. Kristiansson, K. Ahonen; France National Coordinating Centre, National Institute of Health and Medical Research (U258), Paris: P. Ducimetière (national coordinator), A. Bingham; PRIME/Strasbourg, Department of Epidemiology and Public Health, EA 3430, Faculty of Medicine, University of Strasbourg, Strasbourg: D. Arveiler (principal investigator), B. Haas, A. Wagner; PRIME/Toulouse, Department of Epidemiology, Toulouse University School of Medicine, Toulouse: J. Ferrières (Principal Investigator), J-B. Ruidavets, V. Bongard, D. Deckers, C. Saulet, S. Barrere; PRIME/Lille, Department of Epidemiology and Public Health, INSERM U744-Université Lille Nord de France – Institut Pasteur de Lille: P. Amouyel (principal investigator), M. Montaye, B. Lemaire, S. Beauchant, D. Cottel, C. Graux, N. Marecaux, C. Steclebout, S. Szeremeta; MORGAM Laboratory, INSERM U937, Paris: F. Cambien (responsible person), L. Tiret, V. Nicaud; Italy Brianza, Research Centre for Epidemiology and Preventive Medicine (EPIMED), Department of Clinical and Experimental Medicine, University of Insubria at Varese: M.M. Ferrario (principal investigator), G. Veronesi, F. Gianfagna, G. Cesana; Italy Brianza Laboratory, Department of Laboratory Medicine, Desio Hospital, University Milano-Bicocca, Milano: P. Brambilla (responsible person), S. Signorini; United Kingdom PRIME/Belfast, Queen's University Belfast, Belfast, Northern Ireland: F. Kee (principal investigator) A. Evans (former principal investigator), J. Yarnell, E. Gardner; MORGAM Coordinating Centre, Queen's University Belfast, Belfast, Northern Ireland: A. Evans (MORGAM coordinator), S. Cashman, F Kee; MORGAM Management Group: A. Evans (chair, Belfast, UK), S. Blankenberg (Hamburg, Germany), F. Cambien (Paris, France), M. Ferrario (Varese, Italy), K. Kuulasmaa (Helsinki, Finland), A. Palotie (Cambridge, UK), M. Perola (Helsinki, Finland), A. Peters (Neuherberg, Germany), V. Salomaa (Helsinki, Finland), H. Tunstall-Pedoe (Dundee, Scotland), P.G. Wiklund (Umeå, Sweden); Previous members: K. Asplund (Stockholm, Sweden), L. Peltonen (Helsinki, Finland), D. Shields (Dublin, Ireland), B. Stegmayr (Umeå, Sweden).

MRC NSHD: This work was funded by the Medical Research Council [MC_UU_12019/1]. We are very grateful to the members of this birth cohort for their continuing interest and participation in the study.

MuTHER eQTL: The MuTHER Study was funded by a program grant from the Wellcome Trust (081917/Z/07/Z).

NESDA: The infrastructure for the NESDA study is funded through the Geestkracht programme of the Dutch Scientific Organization (ZON-MW, grant number 10-000-1002) and matching funds from participating universities and mental health care organizations. Genotyping in NESDA was funded by the Genetic Association Information Network (GAIN) of the Foundation for the US National Institutes of Health. Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003) along with a supplement from the Dutch Brain Foundation.

NESDA eQTL: The Netherlands Study of Depression and Anxiety (NESDA) and the Netherlands Twin Register (NTR) were funded by the Netherlands Organization for Scientific Research (MagW/ZonMW; grants 904-61-090, 985-10-002, 904-61-193, 480-04-004, 400-05-717 and 912-100-20; Spinozapremie 56-464-14192; and Geestkracht program grant 10-000-1002), the Center for Medical Systems Biology (CMSB2; NWO Genomics), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL), the VU University EMGO+ Institute for Health and Care Research and the Neuroscience Campus

Amsterdam, NBIC/BioAssist/RK (2008.024), the European Science Foundation (EU/QLRT-2001-01254), the European Community's Seventh Framework Programme (FP7/2007-2013), ENGAGE (HEALTH-F4-2007-201413) and the European Research Council (ERC; 230374). Gene-expression data was funded by the US National Institute of Mental Health (RC2 MH089951) as part of the American Recovery and Reinvestment Act of 2009.

NeuroCHARGE: The Atherosclerosis Risk in Communities Study (ARIC) is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; National Institutes of Health contract HHSN268200625226C and NHLBI contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, and grants R01-HL087641, U01 HL096917 (Mosley). Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. ARIC analyses performed as part of this project were supported by NIH grant HL093029 to M. Fornage. Dr. Ikram was funded through the Netherlands Heart Foundation (2009B102)

NFBC1966: NFBC1966 and NFBC1986 received financial support from the Academy of Finland (project grants 104781, 120315, 129269, 1114194, 24300796, Center of Excellence in Complex Disease Genetics and SALVE), University Hospital Oulu, Biocenter, University of Oulu, Finland (75617), NHLBI grant 5R01HL087679-02 through the STAMPEED program (1RL1MH083268-01), NIH/NIMH (5R01MH63706:02), ENGAGE project and grant agreement HEALTH-F4-2007-201413, EU FP7 EurHEALTHAgeing -277849, the Medical Research Council, UK (G0500539, G0600705, G1002319, PrevMetSyn/SALVE) and the MRC, Centenary Early Career Award. The DNA extractions, sample quality controls, biobank up-keeping and aliquotting was performed in the National Public Health Institute, Biomedicum Helsinki, Finland and supported financially by the Academy of Finland and Biocentrum Helsinki. We thank the late Professor Paula Rantakallio (launch of NFBCs), and Ms Outi Tornwall and Ms Minttu Jussila (DNA biobanking). The authors would like to acknowledge the contribution of the late Academian of Science Leena Peltonen.

NFBC1986: NFBC1966 and NFBC1986 received financial support from the Academy of Finland (project grants 104781, 120315, 129269, 1114194, 24300796, Center of Excellence in Complex Disease Genetics and SALVE), University Hospital Oulu, Biocenter, University of Oulu, Finland (75617), NHLBI grant 5R01HL087679-02 through the STAMPEED program (1RL1MH083268-01), NIH/NIMH (5R01MH63706:02), ENGAGE project and grant agreement HEALTH-F4-2007-201413, EU FP7 EurHEALTHAgeing -277849, the Medical Research Council, UK (G0500539, G0600705, G1002319, PrevMetSyn/SALVE) and the MRC, Centenary Early Career Award. The DNA extractions, sample quality controls, biobank up-keeping and aliquotting was performed in the National Public Health Institute, Biomedicum Helsinki, Finland and supported financially by the Academy of Finland and Biocentrum Helsinki. We thank the late Professor Paula Rantakallio (launch of NFBCs), and Ms Outi Tornwall and Ms Minttu Jussila (DNA biobanking). The authors would like to acknowledge the contribution of the late Academian of Science Leena Peltonen. SS and MRJ received support for their research form the European Union under under grant agreement EU H2020-PHC-2014; 633595 for the DynaHEALTH action.

NSPHS: The Northern Swedish Population Health Study (NSPHS) was funded by the Swedish Medical Research Council (Project Number K2007-66X-20270-01-3, and 2011-2354), the Foundation for Strategic Research (SSF). NSPHS as part of EUROSPAN (European Special Populations Research Network) was also

supported by European Commission FP6 STRP grant number 01947 (LSHG-CT-2006-01947). This work has also been supported by the Swedish Society for Medical Research (SSMF).

ORCADES: ORCADES was supported by the Chief Scientist Office of the Scottish Government, the Royal Society, the MRC Human Genetics Unit, Arthritis Research UK and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). DNA extractions were performed at the Wellcome Trust Clinical Research Facility in Edinburgh. We would like to acknowledge the invaluable contributions of Lorraine Anderson and the research nurses in Orkney, the administrative team in Edinburgh and the people of Orkney.

PARC: This work was funded by National Institutes of Health grant U01 HL69757. DNA handling and genotyping was supported in part by CTSI grant UL1TR000124 from the National Center for Advancing Translational Sciences; in addition to the National Institute of Diabetes and Digestive and Kidney Disease grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

PIVUS: PIVUS has been supported by AstraZeneca, FORMAS, the Swedish Research Council, the Swedish Heart-Lung Foundation, and Uppsala University Hospital.

PROCARDIS: PROCARDIS was supported by the European Community Sixth Framework Program (LSHM-CT- 2007-037273), AstraZeneca, the British Heart Foundation, the Swedish Research Council, the Knut and Alice Wallenberg Foundation, the Swedish Heart-Lung Foundation, the Torsten and Ragnar Söderberg Foundation, the Strategic Cardiovascular Program of Karolinska Institutet and Stockholm County Council, the Foundation for Strategic Research and the Stockholm County Council (560283). M.F acknowledges the support of the Wellcome Trust core award (090532/Z/09/Z) and the BHF Centre of Research Excellence.

PROMIS: Genotyping in PROMIS was funded by the Wellcome Trust, UK and Pfizer. Biomarker assays in PROMIS have been funded through grants awarded by the NIH (RC2HL101834 and RC1TW008485) and the Fogarty International (RC1TW008485). Field-work, genotyping, and standard clinical chemistry assays in PROMIS were principally supported by grants awarded to the University of Cambridge from the British Heart Foundation, UK Medical Research Council, Wellcome Trust, EU Framework 6–funded Bloodomics Integrated Project, Pfizer, Novartis, and Merck. The founders of the Unit are: UK Medical Research Council, British Heart Foundation, the British Heart Foundation Cambridge Cardiovascular Centre of Excellence, UK National Institute for Health Research Cambridge Biomedical Research Centre, European Research Council, and European Commission Framework Programme 7. The Emerging Risk Factor Collaboration's website http://www.phpc.cam.ac.uk/ceu/research/erfc/studies/ has a compiled list of some of the funders of the component studies in this analysis. We also acknowledge the contributions made by the following: Philippe Frossard, Ayeesha Kamal, Mohammad Zeeshan Ozair, Usman Ahmed, Abdul Hakeem, Hamza Khalid, Kamran Shahid, Fahad Shuja, Ali Kazmi, Mustafa Qadir Hameed, Naeem Khan, Sadiq Khan, Ayaz Ali, Madad Ali, Saeed Ahmed, Muhammad Waqar Khan, Muhammad Razaq Khan, Abdul Ghafoor, Mir Alam, Riazuddin, Muhammad Irshad Javed, Abdul Ghaffar, Tanveer Baig Mirza, Muhammad Shahid, Jabir Furqan, Muhammad Iqbal Abbasi, Tanveer Abbas, Rana Zulfiqar, Muhammad Wajid, Irfan Ali, Muhammad Ikhlaq, Danish Sheikh and Muhammad Imran. J Danesh is a British Heart Foundation Professor, European Research Council Senior Investigator, and NIHR Senior Investigator.

public eSNP and methylation: ADJ and JDE were supported by National Heart, Lung and Blood Institute Division of Intramural Research funds.

RACe: The RACE study has been funded by the National Institute of Neurological Disorders (R21NS064908), the Fogarty International (R21NS064908) and the Center for Non-Communicable Diseases, Karachi, Pakistan. We also acknowledge the contributions made by the following: Philippe Frossard, Ayeesha Kamal, Mohammad Zeeshan Ozair, Usman Ahmed, Abdul Hakeem, Hamza Khalid, Kamran Shahid, Fahad Shuja, Ali Kazmi, Mustafa Qadir Hameed, Naeem Khan, Sadiq Khan, Ayaz Ali, Madad Ali, Saeed Ahmed, Muhammad Waqar Khan, Muhammad Razaq Khan, Abdul Ghafoor, Mir Alam, Riazuddin, Muhammad Irshad Javed, Abdul Ghaffar, Tanveer Baig Mirza, Muhammad Shahid, Jabir Furqan, Muhammad Iqbal Abbasi, Tanveer Abbas, Rana Zulfiqar, Muhammad Wajid, Irfan Ali, Muhammad Ikhlaq, Danish Sheikh and Muhammad Imran.

Rotterdam study: The Rotterdam Study is supported by the Erasmus Medical Center and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research; the Netherlands Organization for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly; The Netherlands Heart Foundation; the Ministry of Education, Culture and Science; the Ministry of Health Welfare and Sports; the European Commission; and the Municipality of Rotterdam. Support for genotyping was provided by the Netherlands Organization for Scientific Research (NWO Groot, 175.010.2005.011, 911.03.012) and Research Institute for Diseases in the Elderly (014.93.015; RIDE2). This study was supported by the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Michael Moorhouse, Marijn Verkerk and Sander Bervoets for their help in creating the database and Maxim Struchalin for his contributions to the imputations of the data. Further financial support was obtained from the Netherlands Heart Foundation nr. 2009B102.

SardiNIA: The SardiNIA (‘‘ProgeNIA”) team was supported by Contract NO1-AG-1-2109 from the National Institute on Aging. This work was supported, in part, by the Intramural Research Program of the National Institute on Aging, National Institutes of Health. We thank Monsignore Piseddu, Bishop of Ogliastra; the Mayors of Lanusei, Ilbono, Arzana, and Elini; the head of the local Public Health Unit ASL4; and the residents of the towns for volunteering and cooperation. In addition, we are grateful to the Mayor and the administration in Lanusei for providing and furnishing the clinic site. We thank the team of physicians and nurses, who carried out the physical examinations and the recruitment personnel who enrolled the volunteers.

SCARFSHEEP: The IMPROVE study was funded by the European Commission (Contract number: QLG1-CT-2002-00896), the Academy of Finland (Grant #110413) the British Heart Foundation (RG2008/014) and the Italian Ministry of Health (Ricerca Corrente), and the IMPROVE and SCARFSHEEP studies were funded by the Swedish Heart-Lung Foundation, the Swedish Research Council (8691), the Knut and Alice Wallenberg Foundation, the Foundation for Strategic Research, the Torsten and Ragnar Söderberg Foundation, the Strategic Cardiovascular and Diabetes Programmes of Karolinska Institutet and the Stockholm County Council, the Strategic support for epidemiological research at Karolinska Institutet and the Stockholm County Council, and the Stockholm County Council (560183).

SEED: The Singapore Epidemiology of Eye Diseases (SEED) Study includes the Singapore Chinese Eye Study (SCES), Singapore Malay Eye Study (SiMES) and Singapore Indian Eye Study (SINDI). They supported by the National Medical Research Council (NMRC), Singapore (grants 0796/2003, IRG07nov013, IRG09nov014, NMRC 1176/2008, STaR/0003/2008, CG/SERI/2010), and Biomedical Research Council (BMRC), Singapore (08/1/35/19/550 and 09/1/35/19/616). Ching-Yu Cheng is supported by an award from NMRC (CSA/033/2012). The Singapore Tissue Network and the Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore provided services for tissue archival and genotyping, respectively.

SEED: The Singapore Epidemiology of Eye Diseases (SEED) Study includes the Singapore Chinese Eye Study (SCES), Singapore Malay Eye Study (SiMES) and Singapore Indian Eye Study (SINDI). They supported by the National Medical Research Council (NMRC), Singapore (grants 0796/2003, IRG07nov013, IRG09nov014, NMRC 1176/2008, STaR/0003/2008, CG/SERI/2010), and Biomedical Research Council (BMRC), Singapore (08/1/35/19/550 and 09/1/35/19/616). Ching-Yu Cheng is supported by an award from NMRC (CSA/033/2012). The Singapore Tissue Network and the Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore provided services for tissue archival and genotyping, respectively.

SEY: The TANDEM and SEY studies were supported by the SNF grant 31–51115.97 and by the Fondation pour Recherches Médicales, Geneve. We thank the Ministry of Health of the Seychelles and the participants of the studies for their valuable contributions.

SHIP: SHIP was funded by grants from the German Federal Ministry of Education and Research (BMBF, Grants 01ZZ0403, 01ZZ0103, 01GI0883), the Ministry for Education, Research and Cultural Affairs as well as the Ministry of Social Affairs of the Federal State of Mecklenburg-West Pomerania. Genome-wide data have been supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg- West Pomerania. The University of Greifswald is a member of the 'Center of Knowledge Interchange' program of the Siemens AG.

SU.VI.MAX: This study was funded by the Association Robert Debré pour la Recherche Médicale, the Institut National pour la Santé et la Recherche Médicale, the Conservatoire National des Arts et Métiers, the Institut National de la Recherche Agronomique and the Université Paris 13.

TANDEM: The TANDEM and SEY studies were supported by the SNF grant 31–51115.97 and by the Fondation pour Recherches Médicales, Geneve. We thank the Ministry of Health of the Seychelles and the participants of the studies for their valuable contributions.

THISEAS: The Hellenic study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility (THISEAS) study thanks the Genotyping Facility at the Wellcome Trust Sanger Institute for typing the THISEAS samples. Prof Deloukas' work forms part of the research themes contributing to the translational research portfolio of Barts Cardiovascular Biomedical Research Unit which is supported and funded by the National Institute for Health Research.

Tromsø: University of Tromsø, Norwegian Research Council (project number 185764)

TUDR: This study was supported by the National Eye Institute of the National Institutes of Health (EY014684 to J.I.R., DK079888 to M.O.G.) and ARRA Supplement (EY014684-03S1, -04S1), the National Institute of Diabetes and Digestive and Kidney Disease grant DK063491 to the Southern California Diabetes Endocrinology Research Center, the Eye Birth Defects Foundation Inc., the National Science Council, Taiwan (NSC 98-2314-B-075A-002-MY3 to W.H.S.) and the Taichung Veterans General Hospital, Taichung, Taiwan (TCVGH-1003001C to W.H.S .). DNA handling and genotyping at Cedars-Sinai Medical Center were supported in part by the National Center for Research Resources, grant UL1RR033176, and is now at the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124.

TWINSUK: The study was funded by the Wellcome Trust; European Community's Seventh Framework Programme (FP7/2007-2013). The study also receives support from the National Institute for Health Research (NIHR)- funded BioResource, Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London. SNP

Genotyping was performed by The Wellcome Trust Sanger Institute and National Eye Institute via NIH/CIDR.
UK CardioMetabolic Consortium: This research has been conducted using the UK Biobank Resource. Mike Barnes, Claudia Cabrera & Helen R Warren are supported by the NIHR Cardiovascular Biomedical Research Unit at Barts. He Gao is supported by the NIHR Imperial College Health Care NHS Trust and Imperial College London Biomedical Research Centre.

ULSAM: ULSAM has been supported by the Swedish Research Council, the Swedish Heart-Lung Foundation, Uppsala University Hospital, the Foundation for Geriatric Research, and the Geriatric Fund.

VIS (EUROSPAN): The CROATIA-Vis study in the Croatian island of Vis was supported through the grants from the Medical Research Council UK and Ministry of Science, Education and Sport of the Republic of Croatia. (number 108-1080315-0302) and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). We would like to acknowledge the invaluable contributions of the recruitment team (including those from theInstitute of Anthropological Research in Zagreb) in Vis, the administrative teams in Croatia and Edinburgh and the people of Vis.

WGHS: The WGHS is supported by HL043851 and HL080467 from the National Heart, Lung, and Blood Institute and CA047988 from the National Cancer Institute with collaborative scientific support and funding for genotyping provided by Amgen.

Whitehall II: The Whitehall II study has been supported by grants from the Medical Research Council; Economic and Social Research Council; BHF; Health and Safety Executive; Department of Health; National Heart Lung and Blood Institute (HL36310), US, NIH: National Institute on Aging (AG13196), US, NIH; Agency for Health Care Policy Research (HS06516); and the John D and Catherine T MacArthur Foundation Research Networks on Successful Midlife Development and Socio-economic Status and Health. Whitehall II genotyping was in part supported by a MRC-GSK pilot programme grant (ID 85374).

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