The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals

A list of authors and their affiliations appears at the end of the manuscript

ABSTRACT

To dissect the genetic architecture of blood pressure (BP) and assess how its elevation promotes downstream cardiovascular diseases, we analyzed 128,272 SNPs from targeted and genome-wide arrays in 201,529 individuals of European ancestry. Genotypes from an additional 140,886 individuals of European ancestry were used as validation for loci reaching genome-wide significance but without prior support in the literature. We identified 66 BP loci, of which 17 were novel and 15 harbored multiple distinct association signals, and which together explain up to 3.5% of BP variation. The 66 index SNPs were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells, consistent with a primary role in BP control through modulating blood vessel tone and fluid filtration across multiple tissues, not solely the kidney. Importantly, the 66 index SNPs combined in a risk score showed comparable effects in 64,421 individuals of non-European descent (South-Asian, East-Asian and African), confirming that these are ancestral physiological effects that arose prior to human migration out of Africa. The 66-SNP BP risk score was significantly associated with target-organ damage in multiple tissues, with minor effects in the kidney. Our data expand current knowledge of BP pathways, and also, highlight that BP regulation and its effects may occur in multiple organs and tissues beyond the classic renal system.

There are considerable physiological, clinical and genetic data that implicate the kidney as the major regulator of BP through maintaining salt-water balance and that renal damage is consequent to long-term BP elevation. However, alternative hypotheses, such as increasing systemic vascular resistance, are also serious contenders to explain the rise of BP with increasing age. The genetic basis of elevated blood pressure or hypertension (HTN) involves many loci that have been identified using large-scale analyses of candidate genes[1,2], linkage studies, and genome-wide association studies (GWAS)[3-12]. The genes underlying BP regulation can help resolve many of the open questions regarding BP (patho-) physiology. While ~40-50% of BP variability is heritable[13,14], the identified genetic variation explains only ~2%[1-12]. This is considerably less than that observed for other cardiovascular disease (CVD) risk factors, such as plasma lipid fractions, despite the fact that they have comparable heritability[15]. The sources of this discrepancy could be many, but the major reasons are likely to be the constraints on physiological variation of BP and contributions from diverse organs and tissues, potentially resulting in hundreds or thousands of genetic variants of weak effects. Consequently, the fundamental causes of hypertension susceptibility also remain unknown.

The Cardio-MetaboChip is a custom genotyping microarray designed to facilitate cost-effective follow-up of nominal associations for metabolic and cardiovascular traits, including BP. This array comprises 196,725 variants, including ~5,000 SNPs with nominal (P <0.016) evidence of BP association in our previous GWAS meta-analysis[5]. Furthermore, the array includes several dense scaffolds for fine mapping of selected loci spanning, on average, genomic regions of 350 kilobases[5,16], of which 24 include genome-wide significant BP association in the current study[5,16]. Here we performed BP GWAS meta-analysis of both systolic (SBP) and diastolic (DBP) BP using data from 109,096 individuals directly genotyped using the Cardio-MetaboChip array, in combination with imputed data from an additional 92,433 individuals with genome-wide genotyping, all of European (EUR) ancestry. Validation of loci reaching genome-wide significance but without previous support in the literature was sought using association results from an additional 140,886 individuals of European ancestry from the UK Biobank. We assessed whether the genome-wide significant BP SNPs identified, which are largely in non-coding DNA, were associated with expression levels of nearby genes, and tested for enrichment of BP SNPs in *cis*-regulatory sequences. Signal refinement and analyses of associated variants were performed in 64,421 individuals of South-Asian (SAS), East-Asian (EAS), and African (AFR) ancestry to assess their global distribution. Finally, a genotype risk score was constructed to examine the impact of the BP SNPs on cardiovascular and other end-organ outcomes.

RESULTS

Novel genetic loci associated with SBP and DBP

We performed meta-analyses of association summary statistics from a total of 201,529 individuals of EUR ancestry from 74 studies: (i) 109,096 individuals from 46 studies genotyped on Cardio-MetaboChip; and (ii) 92,433 individuals from 28 studies with imputed genotype data from genome-wide genotyping at SNPs overlapping the variants on Cardio-MetaboChip. Twenty-four of the 28 studies with genome-wide genotyping data had contributed to previous analyses (**Supplementary Tables 1-3**)[5,7].

BP was measured using standardized protocols in all studies (**Supplementary Table 1**), regardless of whether the primary focus was BP or another trait. We initially analyzed affected and unaffected individuals from samples selected as cases (e.g. type 2 diabetes) or controls, separately. However, because sensitivity analyses did not reveal any significant difference in BP effect size estimates between case and control samples (data not shown), we analyzed all samples combined. When available, the average of two BP measurements was used for association analyses (**Supplementary Table 1**). If an individual was taking a BP-lowering treatment, the underlying SBP and DBP were estimated by adding 15 mmHg and 10 mmHg, respectively, to the measured values, as done in prior analyses[5,17]. Association statistics, in models adjusting for age, age^2, sex, and body mass index (BMI), were obtained for each study separately, with genomic control applied to correct for study-specific population structure. Fixed-effects meta-analysis proceeded in 4 stages, separately for the following associations: Stage 1, using results based on 46 studies using Cardio-MetaboChip genotypes of 109,096 participants; Stage 2, using additional results based on imputed genotypes from genome-wide genotyping arrays in 4 previously unpublished studies; Stage 3 using imputed genotypes from genome-wide genotyping arrays in 24 previously published studies[5]; and Stage 4, the joint meta-analysis of Stages 1-3 including a total of 201,529 independent individuals (**Supplementary Figure 1, Supplementary Tables 2-3, Supplementary Note**). To account for population structure between studies in Stages 1-3 of our meta-analysis, genomic control correction was applied in each of these stages. The "double" genomic control correction applied is the same approach as other published large-scale studies of quantitative cardio-metabolic traits that combine genotype data from GWAS and Cardio-MetaboChip [18,19].

At stage 4, 67 loci attained genome-wide significance ($P < 5 \times 10^{-8}$), 18 of which without prior support in the literature (**Supplementary Table 4**). Quantile-quantile plots (**Supplementary Figure 2**) of

the stage 4 meta-analysis showed an excess of small *P* values, with an elevated genomic control lambda estimate that were persistent, albeit attenuated, after excluding all 66 loci. This observation is compatible with either residual uncorrected population stratification or the presence of a large number of variants that are truly associated with BP but fail to achieve genome-wide significance in the current meta-analysis. The Cardio-MetaboChip array's inclusion of SNPs from a prior BP GWAS[5] does not appear to be the sole explanation, as we did not observe a significant decrease of the excess of small *P* values when we excluded all SNPs that were selected based on BP for the Cardio-MetaboChip. Given that the quantile-quantile plots continued to show deviation from the null expectation even after removing new, known, and additional variants related to BP (**Supplementary Figures 3 and 4**), we sought additional validation to support variants (N=18) attaining genome-wide significance, but without prior support in the literature, in up to 140,886 individuals of European ancestry from UK Biobank[20]. For these SNPs, stage 5 meta-analysis combined association summary statistics from stage 4 and UK Biobank, in a total of 342,415 individuals (**Supplementary Table 5**).

Upon stage 5 meta-analysis, 17 of 18 variants retained genome-wide significance for the primary trait (SBP or DBP result with lower *P* value). The one variant that was not genome-wide significant had a borderline *P* value of 4.49×10^{-8} at stage 4. These findings are consistent with appropriate calibration of the association test statistics at stage 4 such that observing one failure among 18 validation tests is consistent with the use of a threshold designed ($P < 5 \times 10^{-8}$) to have a 1 in 20 chance of a result as or more extreme solely due to chance.

In total, 66 loci attained genome-wide significance: 13 loci for SBP only, 12 loci for DBP only, and 41 for both traits. Of these, 17 BP loci were novel, while 49 were previously reported at genome-wide significance (**Table 1**). The new loci were defined based on mapping >1Mb from any previously established locus, with the exception of one region characterized by long-range LD spanning several mega-bases, which was considered a single locus. Plots of association results across the genome show the genomic features of each locus and SNP *P* values, with loci labeled arbitrarily according to the gene(s) nearest the lead SNP (**Figure 1**).

Compared with previous BP variants[5,7,21], the average absolute effect size of the newly discovered variants is smaller, although the minor allele frequency (MAF) is comparable, presumably owing to the increased power of a larger sample size (**Figure 2**). As expected from the high correlation between SBP and DBP values, the observed directions of effects for the two traits were generally concordant (**Supplementary Figure 5**), and the absolute effect sizes were inversely correlated with MAF (**Table 1** and **Supplementary Figure 6**). The 66 BP SNPs explained 3.46% and 3.36% of SBP and DBP

variance, respectively, an increase from 2.95% and 2.78% for SBP and DBP for the 49 previously reported SNPs alone (**Supplementary Note**). The low percent of variance explained is consistent with earlier estimates of large numbers of common variants of weak effects and a large number of genes influencing BP levels[5].

Signal refinement at the 66 BP loci

Quantitative trait associations are often reported in the literature based on a single index SNP, despite the fact that linkage disequilibrium (LD) to the causal variant can implicate many nearby variants. To identify distinct signals of association at the 66 BP loci and the variants most likely to be causal for each, we started with an approximate conditional analysis using a model selection procedure implemented in the GCTA-COJO package[22,23] as well as a detailed literature review of all published BP association studies. GCTA-COJO analysis was performed using the association summary statistics for SBP and DBP from the Stage 4 EUR ancestry meta-analyses, with the LD between variants estimated on the basis of Cardio-MetaboChip genotype data from 7,006 individuals of EUR ancestry from the GoDARTS cohort[24]. More than one distinct BP association signal was identified at 13 loci at $P < 5 \times 10^{-8}$ (**Supplementary Table 6**, **Supplementary Figures 7, and Supplementary Note**). At six loci, the distinct signals were identified in separate analyses of both SBP and DBP; these trait-specific associations were represented by the same or highly correlated ($r^2 > 0.8$) SNPs at 5 of the 6 loci (**Supplementary Tables 7-8**). We repeated GCTA-COJO analyses using the same summary association results, but with a different reference sample for LD estimates (WTCCC1-T2D/58BC, N = 2,947, **Supplementary Note**) and observed minimal differences arising from minor fluctuations in the association *P* value in the joint regression models (**Supplementary Table 7-8**). LD-based comparisons of published association signals at established BP loci, and the current study's findings suggested that at 10 loci, the signals identified by the single-SNP and the GCTA-COJO analyses were distinct from those in the literature (**Supplementary Table 9**).

We then performed multivariable regression modeling in a single large cohort (Women's Genome Health Study, WGHS, N = 23,047) with simultaneous adjustment for 1) all combinations of putative index SNPs for each distinct signal from the GCTA-COJO conditional analyses, and 2) all index SNPs for all potential distinct signals identified by our literature review (**Supplementary Table 9, Supplementary Note**). Although WGHS is very large as a single study, power is reduced in a single sample compared to that in the overall meta-analysis (23k vs. 201k individuals) and consequently the failure to reach significance does not represent non-replication for individual SNPs. The WGHS analysis

supported two distinct signals of association from the GCTA-COJO analysis at eight of 13 loci, but could not provide support for the remaining five loci (**Supplementary Table 10**). The joint SNP modeling in WGHS, however, indicated two distinct signals of association at three additional loci (*GUCY1A3-GUCY1B3*, *SYNPO2L* and *TBX5-TBX3*), at which the SNP identified in the current study is distinct from that previously reported in the literature[5,11].

Established loci often extend over hundreds of kilobases and contain many genes that could plausibly underlie the BP association. We sought to refine the localization of likely functional variants at loci with high-density coverage on the Cardio-MetaboChip. We followed a Bayesian approach and used the association summary statistics from the EUR ancestry meta-analyses to define, for each signal, credible sets of variants that have 99% probability of containing or tagging the causal variant (**Supplementary Note**). To improve the resolution of the method, the analyses were restricted to 24 regions selected to fine-map (FM) genetic associations, and that included at least one SNP reaching genome-wide significance in the current meta-analyses (**Supplementary Table 11**). Twenty-one of the Cardio-MetaboChip FM regions were BP loci in the original design, with three of the newly discovered BP loci in FM regions that were originally selected for other traits. We observed that the 99% credible sets at five BP loci spanned a small region, <10 kb (*PLCE1* and *SLC39A8* for SBP and DBP; *FGF5* for SBP, with <20kb for DBP; *JAG1* and *ZC3HC1* for DBP, with <20kb for SBP). The greatest refinement was observed at the *SLC39A8* locus for SBP and DBP, and at the *ZC3HC1* and *PLCE1* loci for DBP, where the 99% credible sets included only the index variants (**Supplementary Table 12**). Although credible sets mapped primarily to non-coding sequence, they included one synonymous and seven non-synonymous variants that attained high posterior probability of driving seven distinct association signals at six BP loci (**Supplementary Table 12**). Of these, three variants alone account for more than 95% of the posterior probability of driving the association signal observed at each of three loci: rs13107325 at the *SLC39A8* locus with posterior probability 99.4% for SBP and nearly 100% for DBP; rs1800562 at the *HFE* locus accounting for 98.1% of the posterior probability for DBP; and rs11556924 at the *ZC3HC1* locus with posterior probability 97.8% for SBP and 99.9% for DBP. Despite reduced statistical power, the analyses restricted to the samples with Cardio-MetaboChip genotypes only (N = 109,096) identified as credible causal SNPs the majority of those identified in the analyses of the GWAS+Cardio-MetaboChip data (**Supplementary Table 12**). Given that the Cardio-MetaboChip-only data included more eligible SNPs, a larger number of credible causal SNPs were identified. The full list of SNPs in the 99% credible sets are listed in **Supplementary Table 13**.

What do the BP SNPs do?

Index SNPs or their proxies ($r^2 > 0.8$) altered amino acid sequence at 11 of 66 BP loci (**Table 1**). Thus, the majority of BP-association signals are likely driven by non-coding variants hypothesized to regulate expression of some nearby gene in *cis*. To identify their effects we first sought SNPs associated with gene expression (eSNPs) from a range of available expression data which included hypertension target end organs and cells of the circulatory system (heart tissue, kidney tissue, brain tissue, aortic endothelial cells, blood vessels) and other tissue/cell types ($CD4^+$ macrophages, monocytes lymphoblastoid cell lines, skin tissue, fat tissue, and liver tissue). Fourteen BP SNPs at the *MTHFR-NPPB*, *MDM4*, *ULK4*, *CYP1A1-ULK3*, *ADM, FURIN-FES, FIGN,* and *PSMD5* loci were eSNPs across different tissues (**Supplementary Table 14)**. Of these 14 eSNPs, three were predicted to alter the amino acid sequence at the *MTHFR-NPPB*, *MAP4* and *ULK4* loci, providing two potential mechanisms to explore in functional studies. Second, we used gene expression levels measured in whole blood in two different samples each including >5,000 individuals of EUR descent. We tested whether the lead BP SNP was associated with expression of any transcript in *cis* (<1Mb from the lead SNP at each locus) at a false discovery rate (FDR) of < 0.05, accounting for all possible *cis*-transcript association tests genome-wide. It is likely that we did not genotype the causal genetic variant underlying a BP association signal. A nearby SNP-transcript association, due to LD, may therefore reflect an independent genetic effect on expression that is unrelated to the BP effect. Consequently, we assumed that the lead BP SNP and the most significant eSNP for a given transcript should be highly correlated ($r^2 > 0.7$). Furthermore, we assumed that the significance of the transcript association with the lead BP SNP should be substantially reduced in a conditional model adjusting for the best eSNP for a given transcript. Eighteen SNPs at 15 loci were associated with 22 different transcripts, with a total of 23 independent SNP-transcript associations (three SNPs were associated with two transcripts each, **Supplementary Table 15, Supplementary Note**). The genes expressed in a BP SNP allele-specific manner are clearly high-priority candidates to mediate the BP association. In whole blood, these genes included obvious biological candidates such as *GUCY1A3*, encoding the alpha subunit of the soluble guanylate cyclase protein, and *ADM*, encoding adrenomedullin, both of which are known to induce vasodilation[25,26]. There was some overlap of eSNPs between the whole blood and other tissue datasets at the *MTHFR-NPPB*, *MDM4*, *PSMD5*, *ULK4* and *CYP1A1-ULK3* loci, illustrating additional potentially causal genes for further study (*MTHFR* and *CLCN6*, *MDM4*, *PSMD5*, *ULK4*, *CYP1A1*, and *ULK3*).

An alternative method for understanding the effect on BP of non-coding variants is to determine whether they fall within DNaseI hypersensitivity sites (DHSs). DHSs represent open regions of chromatin

that are accessible to protein binding and can indicate transcriptional activity. We performed two analyses to investigate whether BP SNPs or their LD proxies ($r^2 > 0.8$) were enriched in DHSs in a cell-type-specific manner (**Supplementary Note**). First, we used Epigenomics Roadmap and ENCODE DHS data from 123 adult cell lines or tissues[27-29] to estimate the fold increase in the proportion of BP SNPs mapping to DHSs compared to SNPs associated at genome-wide significance with non-BP phenotypes from the NHGRI GWAS catalog[30]. We observed that 7 out of the 10 cell types with the greatest relative enrichment of BP SNPs mapping to DHSs were from blood vessels (vascular or micro-vascular endothelial cell-lines or cells) and 11 of the 12 endothelial cells were among the top quarter most enriched among the 123 cell types (**Figure 3** and **Supplementary Table 16**). In a second analysis of an expanded set of tissues and cell lines, in which cell types were grouped into tissues (**Supplementary Table 17**), BP-associated SNP enrichment in DHSs in blood vessels was again observed ($P = 1.2 \times 10^{-9}$), as well as in heart samples ($P = 5.3 \times 10^{-8}$; **Supplementary Table 18**).

We next tested whether there was enrichment of BP SNPs in H3K4me3[31] sites, a methylation mark associated with both promoter and enhancer DNA. We observed significant enrichment in a range of cell types including CD34 primary cells, adult kidney cells, and muscle satellite cultured cells (**Supplementary Table 19)**. Enrichment of BP SNPs in predicted strong and weak enhancer states and in active promoters[32] in a range of cell types was also observed (**Supplementary Table 20, Supplementary Figure 8**).

We used Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA)[33] to attempt to identify pathways over-represented in the BP association results. No gene sets meeting experiment-wide significance for enrichment for BP association were identified by MAGENTA after correction for multiple testing, although some attained nominal significance (**Supplementary Table 21**, **Supplementary Note**). We also adapted the DEPICT[34] pathway analysis tool (Data-driven Expression Prioritized Integration for Complex Traits) to identify assembled gene-sets that are enriched for genes near associated variants, and to assess whether genes from associated loci were highly expressed in particular tissues or cell types. Using the extended BP locus list based on genome-wide significant loci from this analysis and previously published SNPs that may not have reached genome-wide significance in the current analysis (**Supplementary Table 9**), we identified six significant (FDR ≤ 5%) gene sets: embryonic growth retardation, abnormal cardiovascular system physiology, abnormal cardiac muscle contractility, SNTB1 protein complex, G Alpha 1213 signaling events, and prolonged QRS complex duration. We also found that suggestive SBP and DBP associations ($P < 1 \times 10^{-5}$) were enriched for reconstituted gene-sets at DBP loci (mainly related to developmental pathways), but not at SBP loci

(**Supplementary Table 22**, **Supplementary Note**). In a final analysis, we assessed Cardio-MetaboChip SNPs at the fine-mapping loci using formaldehyde-assisted isolation of regulatory elements (FAIRE-gen) in lymphoblastoid cell lines[35]. Our results provided support for two SNPs, one of which SNP (rs7961796 at the *TBX5-TBX3* locus) was located in a regulatory site. Although the other SNP (rs3184504 at the *SH2B3* locus) is a non-synonymous variant, there was also a regulatory site indicated by DNaseI and H3K4me1 signatures at the locus, making the SNP a potential regulatory variant (**Supplementary Table 23**)[36]. Both SNPs were included in the list of 99% credible SNPs at each locus.

Asian- and African ancestry BP SNP association

We tested the 66 lead SNPs at the established and novel loci for association with BP in up to 20,875 individuals of South Asian (SAS) ancestry, 9,637 individuals of East Asian (EAS) ancestry, and 33,909 individuals of AFR ancestry. As expected, the effect allele frequencies are very similar across studies of the same ethnicity, but markedly different across different ancestry groups (**Supplementary Figure 9**). Many associations of individual SNPs failed to reach $P < 0.05$ for the BP trait with the lower P value (**Supplementary Table 24**), which could potentially be due to the much lower statistical power at the sample sizes available, different patterns of LD at each locus across ancestries, variability in allele frequency, or true lack of association in individuals of non-European ancestry. The low statistical power for the great majority of SNPs tested is visible considering SNP-by-SNP power calculations using European ancestry effect sizes (**Supplementary Table 24**). However, concordant directions of allelic effects for both SBP and DBP were observed for 45/66 SNPs in SAS, 36/60 SNPs in EAS, and 42/66 SNPs in AFR samples: the strongest concordance with SAS is not surprising because South Asians are more closely related to Europeans than are East Asians or Africans. Moreover, strong correlation of effect sizes was observed between EUR samples with SAS, EAS, or AFR samples (r = 0.55, 0.60, and 0.48, respectively). To test the overall effect of ancestry, where the BP effect may be detectable at only a subset of SNPs, a more powerful test is to construct a combined risk score weighted by allele-specific effects across 66 index SNPs, separately for SBP and DBP, as a predictor of BP in each population sample. A shortcoming of the use of a score test aggregating effects across multiple variants is that they obscure the subset of variants that does not show reliable association in multiple ethnicities. The score represents the predicted mm Hg change for an individual based on their genotype at all 66 SNPs. The SBP and DBP risk scores were significant predictors of SBP and DBP, respectively, in all samples. The change in risk score associated with a 1 mm Hg higher SBP/DBP in EUR samples was associated with a 0.58/0.50 mm Hg higher SBP/DBP in SAS samples (SBP $P = 1.5 \times 10^{-19}$, DBP $P = 3.2 \times 10^{-15}$), 0.49/0.50 mm

Hg SBP/DBP in EAS samples (SBP $P = 1.9 \times 10^{-10}$, DBP $P = 1.3 \times 10^{-7}$), and 0.51/0.47 mm Hg SBP/DBP in AFR samples (SBP $P = 2.2 \times 10^{-21}$, DBP $P = 6.5 \times 10^{-19}$). The attenuation of the genetic risk score estimates in non-European ancestries is presumably due to inclusion of a subset of variants that lack association in the non-European samples. In the admixed populations tested (mainly African ancestry studies), the degree of European admixture influences the extent of association. We subsequently performed a trans-ethnic meta-analysis of the 66 SNPs in all 64,421 samples across the three non-European ancestries. After correcting for 66 tests, 12/66 SNPs were significantly associated with either SBP or DBP ($P < 7.6 \times 10^{-4}$), with a correlation of EUR and non-EUR effect estimates of 0.77 for SBP and 0.67 for DBP; the European-ancestry SBP or DBP risk score was associated with 0.53/0.48 mm Hg higher BP per predicted mm Hg SBP/DBP respectively (SBP $P < 6.6 \times 10^{-48}$, DBP $P < 1.3 \times 10^{-38}$). For 7 of the 12 significant SNPs, no association has previously been reported in genome-wide studies of non-European ancestry. While some heterogeneity of effects was observed between European and non-European effect estimates (Cochran's Q p-value <0.05 for 30/132 tests), these were not distinguishable from chance effects when considering a multiple test correction (**Supplementary Table 24**). Taken together, these findings suggest that, in aggregate, BP loci identified using data from individuals of EUR ancestry are also predictive of BP in non-EUR samples, but larger non-European sample sizes will be needed to establish precisely which individual SNPs are associated in a given ethnic group.

Impact on hypertensive target organ damage

Long-term elevated BP causes target organ damage, especially in the heart, kidney, brain, large blood vessels, and the retinal vessels[37]. Consequently, the genetic effect of the 66 SBP and DBP SNPs on end-organ outcomes can be directly tested using the risk score, although some outcomes lacked results for a small number of SNPs. Interestingly, BP risk scores significantly predicted (**Supplementary Note**) coronary artery disease risk, left ventricular mass and wall thickness, stroke, urinary albumin/creatinine ratio, carotid intima-medial thickness and central retinal artery caliber, but not heart failure or other kidney phenotypes, after accounting for the number of outcomes examined (**Table 2**). Some SNPs could contribute to the risk score with effects that are stronger or weaker than their BP effects would suggest when considering all BP variants collectively. We sought to test the robustness of our risk scores to removal of SNPs with such outlier effects. We therefore repeated the risk score analysis removing iteratively SNPs that contributed to statistical heterogeneity (SNP trait effects relative to SNP BP effects). Heterogeneity was defined based on a multiple testing adjusted significance threshold for Cochran's Q test of homogeneity of effects (**Supplementary Note**). The risk score analyses restricted to the subset of

SNPs showing no heterogeneity of effect revealed essentially identical results, with the exception that urinary albumin/creatinine ratio was no longer significant. The per-SNP results are provided in **Supplementary Table 25** and **Supplementary Figures 10.** Because large-scale GWAS of non-BP cardiovascular risk factors are available, we examined the BP risk scores as predictors of other cardiovascular risk factors: LDL-cholesterol, HDL-cholesterol, triglycerides, type 2 diabetes, BMI, and height. We observed nominal (P <0.05) associations of the BP risk scores with risk factors, although mostly in the opposite direction to the risk factor-CVD association (**Supplementary Table 26**). The failure to demonstrate an effect of hypertension on heart failure may reflect power from a modest sample size, but the lack of significant effects on renal measures suggests that the epidemiologic relationship of higher BP and worse renal function may not reflect direct consequences of BP elevation.

DISCUSSION

The study reported here is the largest to date to investigate the genomics of BP in multiple continental ancestries. Our results highlight four major features of inter-individual variation in BP: (1) we identified 66 (17 novel) genome-wide significant loci for SBP and DBP by targeted genotyping of up to 342,415 individuals of European ancestry that cumulatively explain ~3.5% of the trait variance (novel loci validated using data from additional 140,886 individuals); (2) the variants were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells; (3) the variants had broadly comparable BP effects in South Asians, East Asian and Africans, albeit in smaller sample sizes; and, (4) a 66 SNP risk-score predicted target organ damage in the heart, cerebral vessels, carotid artery and the eye with little evidence for an effect in kidneys. Overall, there was no enrichment of a single genetic pathway in our data; rather, our results are consistent with the effects of BP arising from multiple tissues and organs.

Genetic and molecular analyses of Mendelian syndromes of hypertension and hypotension point to a renal origin, involving multiple rare deleterious mutations in proteins that regulate salt-water balance[38]. This is strong support for Guyton's hypothesis that the regulation of sodium excretion by the kidney and its effects on extracellular volume is the main pathway determining intra-arterial pressure[39]. However, our genetic data from unselected individuals in the general community argues against a single dominant renal effect.

First, the 66 SNPs we identified are not chance effects, but have a global distribution and impact on BP that are consistent as measured by their effects across the many studies meta-analyzed. That they are polymorphic across all continental ancestries argues for their origin and functional effects prior to human continental differentiation.

The adrenergic autonomic system has been considered an important mediator of BP regulation, and is targeted by beta-adrenergic antagonists for the treatment of hypertension. The SNP rs6271 lies within the coding sequence of the dopamine beta hydroxylase gene (*DBH*), encoding the enzyme that catalyzes the conversion of dopamine to norepinephrine, a critical neurotransmitter and effector of sympathetic control of BP. The variant results in an arginine to cysteine amino acid change at the highly conserved position 549 (R549C) and is predicted to be potentially damaging by Polyphen2. Rare loss-of-function mutations in this gene are associated with low plasma dopamine beta hydroxylase activity, low plasma norepinephrine and high plasma dopamine, and a clinical syndrome including orthostatic hypotension[40,41]. Several of the 17 novel loci contain other strong biological candidates; these are described in greater detail in **Supplementary Table 27 and** the **Supplementary Note**.

The single most common feature we identified was the enrichment of regulatory elements for gene expression in vascular endothelial cells. The broad distribution of these cells across both large and small vessels and across all tissues and organs suggest that functional variation in these cells affect endothelial permeability or vascular smooth muscle cell contractility via multiple pathways. These hypotheses will need to be rigorously tested, in appropriate models, to assess the contribution of these pathways to BP control, and these pathways could be targets for systemic anti-hypertensive therapy as they are for the pulmonary circulation[42]. In summary, the genetic observations will contribute to a new and improved understanding of BP biology and a re-evaluation of the pathways considered relevant for therapeutic BP control.

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SUPPLEMENTARY NOTE

Supplementary Note is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

See Supplementary Note for Author Contributions.

AUTHOR INFORMATION

The authors declare competing financial interests (see corresponding section in the **Supplementary Note).**

TABLE LEGENDS

Table 1. SBP and DBP association at 66 loci.

Meta-analysis results of up to 342,415 individuals of European ancestry for SBP and DBP: Established and new loci are grouped separately. Nearest genes are shown as locus labels but this should not be interpreted as support that the causal gene is the nearest gene. The lead SNP with the lowest *P* value for either BP trait is shown as the lead SNP and both SBP and DBP results are presented even if both are not genome-wide significant. The SNP effects are shown according to the effect in mm Hg per copy of the coded allele (that is the allele coded 0, 1, 2) under an additive genetic model. "*" in the lead SNP column indicates a non-synonymous coding SNP (either the SNP itself or another SNP in r^2 >0.8). # Established loci have smaller total sample sizes relative to novel loci (see **Supplementary Note**).

Table 2. Prediction of hypertensive target organ damage by a multi-BP SNP score.

Shown are the estimated effects of a BP risk score comprised of up to 66 SNPs (see column "Total #SNPs") on risk of dichotomous outcome (as odds ratios) or increment in continuous measures per predicted mmHg of the SBP or DBP score. The effect sizes are expressed as incremental change in the phenotype for quantitative traits and natural logarithm of the odds ratio for binary traits, per 1 mmHg predicted increase in SBP or DBP. *P* values are bolded if they meet an analysis-wide significance threshold (< 0.05/18 = 0.0028). Results for all SNPs ("all") and for pruned results ("p") are shown. The pruned results were obtained by iterative removal of SNPs from the risk score starting with the SNP with lowest heterogeneity *P* value. Iterations to remove SNPs were continued until the heterogeneity *P* value was < 0.0028 (see **Supplementary Note**). The number of SNPs removed when calculating the pruned results is indicated by "# SNPs rem.". The results per individual SNP can be found in **Supplementary Table 15**. CAD: coronary artery disease, LV: left ventricle, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, cr: creatinine, cIMT: carotid intima: media thickness. Var. type denotes the variable type and cont. for continuous, or dic. for dichotomous. Eth. = Ethnicity, Consort. = Consortium, EUR = European ancestry, EAS = East Asian ancestry.

1 Table 1. New and known BP loci.

Locus no.	Locus name	Lead SNP	Chr	Position (hg19)	CA /NC	Coded allele freq	Traits	SBP				DBP			
								Effect	SE	*P* value	Total N	Effect	SE	*P* value	Total N#
NEW 1	***HIVEP3***	rs7515635	1	42,408,070	T/C	0.468	**SBP**	**0.307**	**0.0444**	**4.81E-12**	**340,969**	0.1365	0.0263	2.05E-07	340,934
NEW 2	***PNPT1***	rs1975487	2	55,809,054	A/G	0.464	**DBP**	-0.2107	0.045	2.81E-06	337,522	**-0.1602**	**0.0266**	**1.75E-09**	**337,517**
NEW 3	***FGD5***	rs11128722	3	14,958,126	A/G	0.563	**SBP** & DBP	**-0.3103**	**0.0469**	**3.61E-11**	**310,430**	**-0.1732**	**0.0279**	**5.16E-10**	**310,429**
NEW 4	***ADAMTS9***	rs918466	3	64,710,253	A/G	0.406	**DBP**	-0.0865	0.0459	5.94E-02	336,671	**-0.1819**	**0.027**	**1.73E-11**	**336,653**
NEW 5	***TBC1D1-FLJ13197***	rs2291435	4	38,387,395	T/C	0.524	**SBP** & DBP	**-0.3441**	**0.0449**	**1.90E-14**	**331,382**	**-0.156**	**0.0266**	**4.26E-09**	**331,389**
NEW 6	***TRIM36***	rs10077885	5	114,390,121	A/C	0.501	SBP & **DBP**	**-0.284**	**0.0444**	**1.64E-10**	**338,328**	**-0.1735**	**0.0263**	**3.99E-11**	**338,323**
NEW 7	***CSNK1G3***	rs6891344	5	123,136,656	A/G	0.819	**DBP**	0.2811	0.058	1.24E-06	338,688	**0.2311**	**0.0343**	**1.58E-11**	**338,678**
NEW 8	***CHST12-LFNG***	rs2969070	7	2,512,545	A/G	0.639	SBP & **DBP**	**-0.2975**	**0.0464**	**1.44E-10**	**335,991**	**-0.1821**	**0.0274**	**2.92E-11**	**335,972**
NEW 9	***ZC3HC1***	rs11556924	7	129,663,496	T/C	0.384	SBP & **DBP**	**-0.2705**	**0.0468**	**7.64E-09**	**325,929**	**-0.2141**	**0.0276**	**8.15E-15**	**325,963**
NEW 10	***PSMD5***	rs10760117	9	123,586,737	T/G	0.415	**SBP**	**0.283**	**0.0457**	**6.10E-10**	**333,377**	0.0999	0.0269	2.08E-04	333,377
NEW 11	***DBH***	rs6271*	9	136,522,274	T/C	0.072	SBP & **DBP**	**-0.5911**	**0.0899**	**4.89E-11**	**306,394**	**-0.4646**	**0.0532**	**2.42E-18**	**306,463**
NEW 12	***RAPSN, PSMC3, SLC39A13***	rs7103648	11	47,461,783	A/G	0.614	SBP & **DBP**	**-0.3349**	**0.0462**	**4.43E-13**	**335,614**	**-0.2409**	**0.0272**	**9.03E-19**	**335,592**
NEW 13	***LRRC10B***	rs751984	11	61,278,246	T/C	0.879	SBP & **DBP**	**0.4074**	**0.0691**	**3.80E-09**	**334,583**	**0.3755**	**0.0409**	**4.20E-20**	**334,586**
NEW 14	***SETBP1***	rs12958173	18	42,141,977	A/C	0.306	**SBP** & DBP	**0.3614**	**0.0489**	**1.43E-13**	**331,007**	**0.1789**	**0.0289**	**5.87E-10**	**331,010**
NEW 15	***INSR***	rs4247374	19	7,252,756	T/C	0.143	SBP & **DBP**	**-0.5933**	**0.0673**	**1.23E-18**	**302,458**	**-0.3852**	**0.0396**	**2.08E-22**	**302,459**
NEW 16	***ELAVL3***	rs17638167	19	11,584,818	T/C	0.047	**DBP**	-0.4784	0.1066	7.13E-06	333,137	**-0.3479**	**0.0632**	**3.71E-08**	**333,107**
NEW 17	***CRYAA-SIK1***	rs12627651	21	44,760,603	A/G	0.288	**SBP** & DBP	**0.3905**	**0.0513**	**2.69E-14**	**310,738**	**0.2037**	**0.0301**	**1.36E-11**	**310,722**
EST 1	***CASZ1***	rs880315	1	10,796,866	T/C	0.641	**SBP** & DBP	**-0.475**	**0.062**	**2.09E-14**	**184,226**	**-0.257**	**0.038**	**1.34E-11**	**184,212**
EST 2	***MTHFR-NPPB***	rs17037390	1	11,860,843	A/G	0.155	**SBP** & DBP	**-0.908**	**0.081**	**5.95E-29**	**195,493**	**-0.499**	**0.05**	**1.20E-23**	**195,481**
EST 3	***ST7L-CAPZA1-MOV10***	rs1620668	1	113,023,980	A/G	0.822	**SBP** & DBP	**-0.535**	**0.076**	**1.45E-12**	**197,966**	**-0.285**	**0.047**	**9.00E-10**	**197,948**
EST 4	***MDM4***	rs4245739	1	204,518,842	A/C	0.737	**DBP**	0.326	0.068	1.37E-06	191,594	**0.243**	**0.041**	**4.63E-09**	**191,578**
EST 5	***AGT***	rs2493134*	1	230,849,359	T/C	0.579	SBP & **DBP**	**-0.413**	**0.058**	**9.65E-13**	**199,505**	**-0.275**	**0.036**	**9.53E-15**	**199,502**
EST 6	***KCNK3***	rs2586886	2	26,932,031	T/C	0.599	SBP & **DBP**	**-0.404**	**0.059**	**5.94E-12**	**197,269**	**-0.254**	**0.036**	**1.92E-12**	**197,272**
EST 7	***NCAPH***	rs772178	2	96,963,684	A/G	0.64	**DBP**	-0.072	0.061	2.39E-01	192,513	**-0.208**	**0.038**	**3.58E-08**	**192,501**
EST 8	***FIGN-GRB14***	rs1371182	2	165,099,215	T/C	0.443	**SBP** & DBP	**-0.444**	**0.058**	**1.89E-14**	**196,262**	**-0.252**	**0.036**	**1.50E-12**	**196,240**
EST 9	***HRH1-ATG7***	rs2594992	3	11,360,997	A/C	0.607	**SBP**	**-0.334**	**0.06**	**2.31E-08**	**189,895**	-0.136	0.037	2.20E-04	189,854
EST 10	***SLC4A7***	rs711737	3	27,543,655	A/C	0.604	**SBP**	**0.334**	**0.058**	**9.93E-09**	**200,282**	**0.17**	0.036	2.24E-06	200,260
EST 11	***ULK4***	rs2272007*	3	41,996,136	T/C	0.18	**DBP**	-0.11	0.077	1.52E-01	193,915	**0.328**	**0.047**	**3.94E-12**	**193,900**
EST 12	***MAP4***	rs6442101*	3	48,130,893	T/C	0.692	SBP & **DBP**	**0.396**	**0.062**	**1.62E-10**	**200,543**	**0.303**	**0.038**	**1.60E-15**	**200,534**
EST 13	***MECOM***	rs6779380	3	169,111,915	T/C	0.539	**SBP** & DBP	**-0.439**	**0.06**	**1.85E-13**	**186,535**	**-0.239**	**0.037**	**6.87E-11**	**186,521**
EST 14	***FGF5***	rs1458038	4	81,164,723	T/C	0.3	**SBP** & DBP	**0.659**	**0.065**	**5.36E-24**	**188,136**	**0.392**	**0.04**	**7.36E-23**	**188,088**
EST 15	***ARHGAP24***	rs17010957	4	86,719,165	T/C	0.857	**SBP**	**-0.498**	**0.082**	**1.51E-09**	**196,325**	-0.173	0.051	6.63E-04	196,292
EST 16	***SLC39A8***	rs13107325	4	103,188,709	T/C	0.07	SBP & **DBP**	**-0.837**	**0.127**	**4.69E-11**	**175,292**	**-0.602**	**0.078**	**1.63E-14**	**175,372**
EST 17	***GUCY1A3-GUCY1B3***	rs4691707	4	156,441,314	A/G	0.652	**SBP**	**-0.349**	**0.06**	**7.10E-09**	**198,246**	-0.163	0.037	1.08E-05	198,226
EST 18	***NPR3-C5orf23***	rs12656497	5	32,831,939	T/C	0.403	**SBP** & DBP	**-0.487**	**0.06**	**3.85E-16**	**194,831**	**-0.228**	**0.037**	**4.73E-10**	**194,829**
EST 19	***EBF1***	rs11953630	5	157,845,402	T/C	0.366	**SBP** & DBP	**-0.38**	**0.065**	**3.91E-09**	**167,698**	**-0.23**	**0.04**	**8.07E-09**	**167,708**
EST 20	***HFE***	rs1799945*	6	26,091,179	C/G	0.857	SBP & **DBP**	**-0.598**	**0.086**	**3.28E-12**	**185,306**	**-0.43**	**0.053**	**3.10E-16**	**185,273**
EST 21	***BAT2-BAT5***	rs2187668	6	32,605,884	T/C	0.126	**DBP**	-0.291	0.092	1.60E-03	189,806	**-0.372**	**0.057**	**4.31E-11**	**189,810**
EST 22	***ZNF318-ABCC10***	rs6919440	6	43,352,898	A/G	0.57	**SBP**	**-0.337**	**0.058**	**4.92E-09**	**200,733**	-0.125	0.035	4.25E-04	200,730
EST 23	***RSPO3***	rs1361831	6	127,181,089	T/C	0.541	**SBP** & DBP	**-0.482**	**0.058**	**7.38E-17**	**197,027**	**-0.271**	**0.036**	**2.34E-14**	**197,012**
EST 24	***PLEKHG1***	rs17080093	6	150,997,440	T/C	0.075	**DBP**	-0.564	0.111	3.83E-07	194,728	**-0.411**	**0.068**	**1.71E-09**	**194,734**
EST 25	***HOTTIP-EVX***	rs3735533	7	27,245,893	T/C	0.081	**SBP** & DBP	**-0.798**	**0.106**	**6.48E-14**	**197,881**	**-0.445**	**0.065**	**1.09E-11**	**197,880**
EST 26	***PIK3CG***	rs12705390	7	106,410,777	A/G	0.227	**SBP**	**0.619**	**0.069**	**2.69E-19**	**198,297**	0.059	0.042	1.63E-01	198,290
EST 27	***BLK-GATA4***	rs2898290	8	11,433,909	T/C	0.491	**SBP**	**0.377**	**0.058**	**8.85E-11**	**197,759**	0.167	0.036	3.17E-06	197,726
EST 28	***CACNB2***	rs12243859	10	18,740,632	T/C	0.326	SBP & **DBP**	**-0.402**	**0.061**	**6.13E-11**	**199,136**	**-0.335**	**0.038**	**8.11E-19**	**199,124**
EST 29	***C10orf107***	rs7076398	10	63,533,663	A/T	0.188	SBP & **DBP**	**-0.563**	**0.076**	**1.72E-13**	**187,013**	**-0.409**	**0.047**	**2.55E-18**	**187,024**
EST 30	***SYNPO2L***	rs12247028	10	75,410,052	A/G	0.611	**SBP**	**-0.364**	**0.063**	**8.16E-09**	**180,194**	-0.159	0.039	3.89E-05	180,094
EST 31	***PLCE1***	rs932764*	10	95,895,940	A/G	0.554	**SBP** & DBP	**-0.495**	**0.059**	**6.88E-17**	**195,577**	**-0.224**	**0.036**	**6.28E-10**	**195,547**
EST 32	***CYP17A1-NT5C2***	rs943037	10	104,835,919	T/C	0.087	**SBP** & DBP	**-1.133**	**0.105**	**2.35E-27**	**193,818**	**-0.482**	**0.064**	**4.48E-14**	**193,799**
EST 33	***ADRB1***	rs740746	10	115,792,787	A/G	0.73	SBP & **DBP**	**0.486**	**0.067**	**4.59E-13**	**184,835**	**0.32**	**0.041**	**8.63E-15**	**184,868**
EST 34	***LSP1-TNNT3***	rs592373	11	1,890,990	A/G	0.64	**SBP** & DBP	**0.484**	**0.063**	**2.02E-14**	**177,149**	**0.282**	**0.039**	**3.61E-13**	**177,134**
EST 35	***ADM***	rs1450271	11	10,356,115	T/C	0.468	**SBP** & DBP	**0.413**	**0.059**	**3.40E-12**	**191,246**	**0.199**	**0.036**	**4.11E-08**	**191,221**
EST 36	***PLEKHA7***	rs1156725	11	16,307,700	T/C	0.804	SBP & **DBP**	**-0.447**	**0.072**	**5.65E-10**	**200,889**	**-0.292**	**0.044**	**3.67E-11**	**200,899**
EST 37	***SIPA1***	rs3741378*	11	65,408,937	T/C	0.137	**SBP**	**-0.486**	**0.084**	**8.04E-09**	**194,563**	-0.183	0.052	4.17E-04	194,551
EST 38	***FLJ32810-TMEM133***	rs633185	11	100,593,538	C/G	0.715	**SBP** & DBP	**0.522**	**0.067**	**6.97E-15**	**183,845**	**0.288**	**0.041**	**2.38E-12**	**183,825**
EST 39	***PDE3A***	rs3752728	12	20,192,972	A/G	0.737	**DBP**	0.331	0.066	4.32E-07	200,440	**0.319**	**0.04**	**2.35E-15**	**200,408**
EST 40	***ATP2B1***	rs11105354	12	90,026,523	A/G	0.84	**SBP** & DBP	**0.909**	**0.081**	**3.88E-29**	**195,206**	**0.459**	**0.05**	**2.61E-20**	**195,195**
EST 41	***SH2B3***	rs3184504*	12	111,884,608	T/C	0.475	SBP & **DBP**	**0.498**	**0.062**	**9.97E-16**	**177,067**	**0.362**	**0.038**	**1.28E-21**	**177,122**
EST 42	***TBX5-TBX3***	rs2891546	12	115,552,499	A/G	0.11	**DBP**	-0.529	0.1	1.36E-07	172,012	**-0.38**	**0.061**	**4.71E-10**	**171,980**
EST 43	***CYP1A1-ULK3***	rs936226	15	75,069,282	T/C	0.722	SBP & **DBP**	**-0.549**	**0.067**	**3.06E-16**	**187,238**	**-0.363**	**0.041**	**1.03E-18**	**187,221**
EST 44	***FURIN-FES***	rs2521501	15	91,437,388	A/T	0.684	**SBP** & DBP	**-0.639**	**0.069**	**3.35E-20**	**164,272**	**-0.358**	**0.042**	**1.85E-17**	**164,255**
EST 45	***PLCD3***	rs7213273	17	43,155,914	A/G	0.658	**SBP**	**-0.413**	**0.066**	**4.71E-10**	**164,795**	**-0.185**	0.041	7.23E-06	164,788
EST 46	***GOSR2***	rs17608766	17	45,013,271	T/C	0.854	**SBP**	**-0.658**	**0.083**	**2.27E-15**	**188,895**	-0.218	0.051	1.95E-05	188,928
EST 47	***ZNF652***	rs12940887	17	47,402,807	T/C	0.38	**DBP**	0.321	0.06	7.06E-08	192,546	**0.261**	**0.037**	**1.07E-12**	**192,524**
EST 48	***JAG1***	rs1327235	20	10,969,030	A/G	0.542	SBP & **DBP**	**-0.395**	**0.059**	**2.23E-11**	**192,680**	**-0.308**	**0.036**	**1.78E-17**	**192,659**
EST 49	***GNAS-EDN3***	rs6026748	20	57,745,815	A/G	**0.125**	SBP & **DBP**	**0.867**	**0.089**	**3.15E-22**	**192,338**	**0.552**	**0.055**	**4.86E-24**	**192,327**

Table 2. BP risk score effects on disease outcomes.

Phenotype	Var. type (cont./ dic.)	Eth.	Consort.	Total N or no. ca/co	Total #SNPs	SBP_score					DBP_score				
						effect (all)	*P* value (all)	het. *P* value (all)	*P* value (p)	# SNPs rem.	effect (all)	*P* value (all)	het. *P* value (all)	*P* value (p)	# SNPs rem.
HEART															
CAD	dich.	EUR SAS	CARDIoGRAMplusC4D	63,746 /130,681	61	1.042	**1.72E-44**	1.75E-25	**4.08E-32**	10	1.069	**1.19E-42**	6.63E-27	**2.2E-38**	10
heart failure	dich.	EUR	CHARGE	2,526 /18,400	66	1.021	2.77E-02	1.63E-01	2.77E-02	0	1.035	2.31E-02	1.70E-01	2.31E-02	0
LV mass	cont.	EUR	CHARGE	11,273	66	0.480	**6.43E-04**	3.58E-01	**6.43E-04**	0	0.754	**1.23E-03**	3.21E-01	**1.23E-03**	0
LV wall thickness	cont.	EUR	CHARGE	11,311	66	0.004	**4.45E-06**	5.83E-02	**4.45E-06**	0	0.007	**3.19E-06**	6.40E-02	**3.19E-06**	0
KIDNEY															
CKD	dich.	EUR	CHARGE	6,271 /68,083	65	1.010	1.37E-01	1.77E-03	2.65E-01	1	1.008	4.49E-01	1.25E-03	7.69E-01	1
eGFR (based on cr)	cont.	EUR	CHARGE	74,354	65	0.000	7.07E-01	3.12E-05	3.22E-01	2	0.000	9.41E-01	3.02E-05	9.65E-01	2
eGFR (based on cystatin)	cont.	EUR	CHARGE	74,354	65	0.001	9.05E-02	9.28E-06	4.11E-01	1	0.001	3.30E-01	5.64E-06	6.9E-01	1
creatinine	cont.	EUR	KidneyGEN	23,812	66	0.000	9.42E-01	6.31E-03	9.42E-01	0	0.000	4.11E-01	7.16E-03	4.11E-01	0
microalbuminuria	dich.	EUR	CHARGE	2,499 /29,081	65	0.011	2.10E-01	4.79E-02	2.1E-01	0	0.023	1.02E-01	5.66E-02	1.02E-02	0
urinary albumin/cr ratio	cont.	EUR	CHARGE	31,580	65	0.009	**2.52E-03**	3.02E-04	0.53E-03	1	0.015	**2.40E-03**	3.08E-04	8.31E-03	1
STROKE															
stroke, all subtypes	dich.	EUR	CHARGE	1,544 /18,058	66	0.056	**6.11E-06**	8.26E-02	**6.11E-06**	0	0.085	**3.79E-05**	4.98E-02	**3.79E-05**	0
stroke, ischemic subtype	dich.	EUR	CHARGE	1,164 /18,438	66	0.067	**3.33E-06**	1.75E-01	**3.33E-06**	0	0.096	**5.63E-05**	8.82E-02	**5.63E-05**	0
stroke, ischemic subtype	dich.	EUR	MetaStroke	11,012 /40,824	66	0.036	**1.69E-10**	4.72E-02	**1.69E-10**	0	0.056	**1.29E-09**	2.51E-02	**1.29E-09**	0
VASCULATURE															
cIMT	cont.	EUR	CHARGE	27,610	66	0.004	**4.80E-15**	5.06E-08	**7.32E-10**	4	0.005	**4.15E-11**	3.84E-10	**6.2E-07**	5
EYE															
mild retinop.	dich.	EUR	CHARGE	1,122 /18,289	66	1.021	1.37E-01	6.01E-03	1.37E-01	0	1.046	5.78E-02	7.81E-03	5.78E-02	0
central retinal artery caliber	cont.	EUR	CHARGE	18,576	66	0.343	**3.29E-14**	2.56E-06	**2.06E-13**	2	0.570	**3.61E-14**	2.44E-06	**7.05E-13**	3
mild retinop.	dich.	EAS	SEED	289 /5,419	66	1.033	2.55E-01	2.42E-01	2.55E-01	0	1.087	8.55E-02	2.87E-01	8.55E-02	0
central retinal artery caliber	cont.	EAS	SEED	6,976	63	0.320	**1.39E-04**	9.07E-01	**1.39E-04**	0	0.533	**2.19E-04**	8.91E-01	**2.19E-04**	0

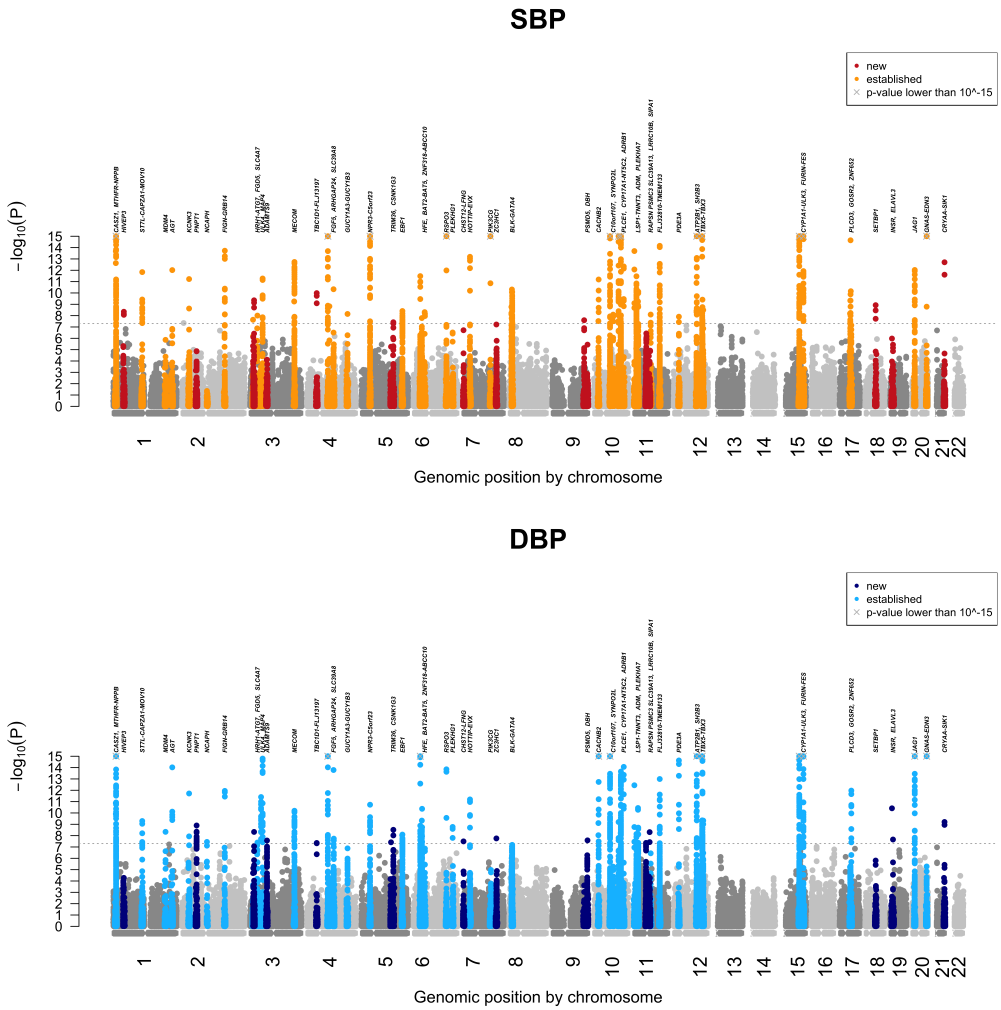

Figure 1. Manhattan plots for SBP and DBP from the stage 4 Cardio-MetaboChip-wide meta-analysis. P values (expressed as $-log_{10}P$) are plotted by physical genomic position labeled by chromosome. SNPs in new loci (3.5MB window around the index SNP), identified in this study, are labeled in dark red (SBP) or dark blue (DBP); SNPs in previously known loci are labeled in orange (SBP) or light blue (DBP). The locus names are indicated. The grey crosses indicate genomic positions at which the y-axis was truncated (SNPs with $P < 10^{-15}$).

	17 new loci	49 established loci	all 66 loci
Minor allele frequency, (mean, range)	32.1% [5%-50%]	28.9% [7%-49%]	29.8% [5%-50%]
Effect size SBP [mmHg], (range, mean)	0.09-0.59 0.34	0.07-1.13 0.5	0.07-1.13 0.46
Effect size DBP [mmHg] (range, mean)	0.1-0.46 0.23	0.06-0.6 0.3	0.06-0.6 0.28
Variance explained SBP	0.52%	2.95%	3.46%
Variance explained DBP	0.58%	2.78%	3.36%
Previously known for BP	5/20	-	-

Figure 2. Overview of novel and known BP variant properties. Key characteristics of the novel and established BP loci are shown. MAF and effect size estimates are derived from the Cardio-MetaboChip data. Variance explained estimates are estimated from one large study (**Supplementary Note**). Novel loci are classified as previously unknown to be linked to BP by a systematic PubMed review of all genes in a 200kb window (**Supplementary Note**).

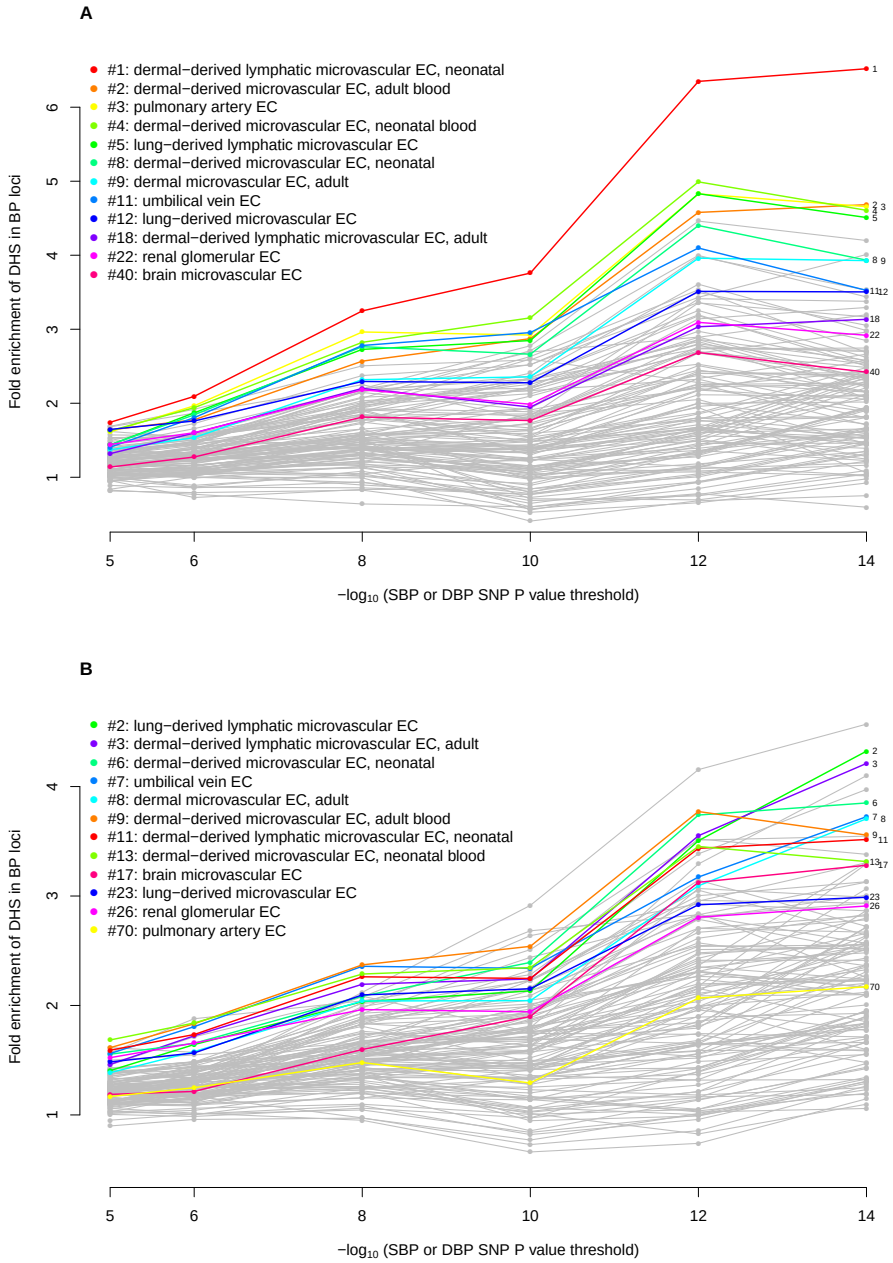

Figure 3. Enrichment of DNAse hypersensitive sites among BP loci in different cell-types. Enrichment analyses of SBP or DBP associated loci according to discovery *P* value using narrow peaks (panel A) or broad peaks (panel B). SNPs were selected according to different *P* value cutoffs (x-axis) and a fold enrichment of overlap with DNAse hypersensitive sites compared to unrelated GWAS SNPs was calculated (y-axis) (see **Supplementary Note**). The 12 endothelial cell-lines are indicated in color and for each endothelial cell-type the rank using the 10^{-14} *P* value cutoff is indicated. EC denotes endothelial cells.

AUTHORS

Georg B. Ehret[1,2,3*], Teresa Ferreira[4*], Daniel I. Chasman[5,6], Anne U. Jackson[7], Ellen M. Schmidt[8], Toby Johnson[9,10], Gudmar Thorleifsson[11], Jian'an Luan[12], Lousie A. Donnelly[13], Stavroula Kanoni[14], Ann-Kristin Petersen[15], Vasyl Pihur[1], Rona J. Strawbridge[16,17], Dmitry Shungin[18,19,20], Maria F. Hughes[21], Osorio Meirelles[22], Marika Kaakinen[23], Nabila Bouatia-Naji[24,25], Kati Kristiansson[26,27], Sonia Shah[28], Marcus E. Kleber[29], Xiuqing Guo[30], Leo-Pekka Lyytikäinen[31,32], Cristiano Fava[33,34], Niclas Eriksson[35], Ilja M. Nolte[36], Patrik K. Magnusson[37], Elias L. Salfati[38], Loukianos S. Rallidis[39], Elizabeth Theusch[40], Andrew J.P. Smith[41], Lasse Folkersen[16], Kate Witkowska[9,42], Tune H. Pers[43,44,268,269], Roby Joehanes[45], Stuart K. Kim[46], Lazaros Lataniotis[14], Rick Jansen[47], Andrew D. Johnson[45,48], Helen Warren[9,42], Young Jin Kim[49], Wei Zhao[50], Ying Wu[51], Bamidele O. Tayo[52], Murielle Bochud[3], Devin Absher[53], Linda S. Adair[54], Najaf Amin[55], Dan E. Arking[1], Tomas Axelsson[56], Damiano Baldassarre[57,58], Beverley Balkau[59], Stefania Bandinelli[60], Michael R. Barnes[14,42], Ines Barroso[61,62], Stephen Bevan[63], Joshua C. Bis[64], Gyda Bjornsdottir[11], Michael Boehnke[7], Eric Boerwinkle[65], Lori L. Bonnycastle[66], Dorret I. Boomsma[67], Stefan R. Bornstein[68], Morris J. Brown[69], Michel Burnier[70], Claudia P. Cabrera[9,42], John C. Chambers[71,72,73], I-Shou Chang[74], CHARGE-EchoGen consortium, CHARGE-HF consortium CHARGE-HF consortium, Ching-Yu Cheng[75,76,77], Peter S. Chines[66], Ren-Hua Chung[78], Francis S. Collins[66], John M. Connell[79], Angela Döring[80,81], Jean Dallongeville[82], John Danesh[83], Ulf de Faire[84], Graciela Delgado[29], Vaidya Dhananjay[85], Anna F. Dominiczak[86], Alex S.F. Doney[13], Fotios Drenos[41], Sarah Edkins[61], John D. Eicher[45,48], Roberto Elosua[87], Stefan Enroth[88], Jeanette Erdmann[89,90], Per Eriksson[16], Tonu Esko[91,92,93], Evangelos Evangelou[71,94], Alun Evans[21], Tove Fall[95], Martin Farrall[4,96], Janine F. Felix[97], Jean Ferrières[98], Luigi Ferrucci[99], Myriam Fornage[100], Terrence Forrester[101], Nora Franceschini[102], Oscar H. Franco Duran[97], Anders Franco-Cereceda[103], Ross M. Fraser[104,105], Santhi K. Ganesh[106], He Gao[71], Karl Gertow[16,17], Francesco Gianfagna[107,108], Bruna Gigante[84], Franco Giulianini[5], Anuj Goel[4,96], Alison H. Goodall[109,110], Mark O. Goodarzi[111], Mathias Gorski[112,113], Jürgen Gräßler[114], Christopher Groves[115], Vilmundur Gudnason[116,117], Ulf Gyllensten[88], Göran Hallmans[18], Anna-Liisa Hartikainen[118,119], Maija Hassinen[120], Aki S. Havulinna[26], Caroline Hayward[121], Serge Hercberg[122], Karl-Heinz Herzig[123,124,125], Andrew A. Hicks[126], Aroon Hingorani[28], Joel N. Hirschhorn[43,44,127], Albert Hofman[97], Jostein Holmen[128], Oddgeir Lingaas Holmen[128,129], Jouke-Jan Hottenga[67], Phil Howard[41], Chao A. Hsiung[78], Steven C. Hunt[130,131], M. Arfan Ikram[97,132,133], Thomas Illig[134,135,136], Carlos Iribarren[137], Richard A. Jensen[64,138], Mika Kähönen[139,140], Hyun Kang[7], Sekar Kathiresan[141,142,143,144], Brendan J. Keating[145,146], Kay-Tee Khaw[147], Yun Kyoung Kim[49], Eric Kim[148], Mika Kivimaki[28], Norman Klopp[134,135], Genovefa Kolovou[149], Pirjo Komulainen[120], Jaspal S. Kooner[150,72,73], Gulum Kosova[151,141,152], Ronald M. Krauss[153], Diana Kuh[154], Zoltan Kutalik[155,156], Johanna Kuusisto[157], Kirsti Kvaløy[128], Timo A Lakka[158,120,159], Nanette R. Lee[160], I-Te

Lee[161,162], Wen-Jane Lee[163], Daniel Levy[45,164], Xiaohui Li[30], Kae-Woei Liang[165,166], Honghuang Lin[167,45], Li Lin[2], Jaana Lindström[26], Stéphane Lobbens[168,169,170], Satu Männistö[26], Gabriele Müller[171], Martina Müller-Nurasyid[15,172,173], François Mach[2], Hugh Markus[63], Eirini Marouli[14,174], Mark I. McCarthy[115], Colin A. McKenzie[101], Pierre Meneton[175], Cristina Menni[176], Andres Metspalu[91], Vladan Mijatovic[177], Leena Moilanen[178,179], May E. Montasser[180], Andrew D. Morris[13], Alanna C. Morrison[181], Antonella Mulas[182], Ramaiah Nagaraja[22], Narisu Narisu[66], Kjell Nikus[183,184], Christopher J. O'Donnell[185,45,186], Paul O'Reilly[187], Ken K. Ong[12], Fred Paccaud[3], Cameron D. Palmer[188,189], Afshin Parsa[180], Nancy L. Pedersen[37], Brenda W. Penninx[190,191,192], Markus Perola[26,27,193], Annette Peters[81], Neil Poulter[194], Peter P. Pramstaller[126,195,196], Bruce M. Psaty[64,197,198,199], Thomas Quertermous[38], Dabeeru C. Rao[200], Asif Rasheed[201], N William N.W.R. Rayner[202,203,61], Frida Renström[19,204,18], Rainer Rettig[205], Kenneth M. Rice[206], Robert Roberts[207,208], Lynda M. Rose[5], Jacques Rossouw[209], Nilesh J. Samani[109,210], Serena Sanna[182], Jouko Saramies[211], Heribert Schunkert[212,213,214], Sylvain Sebert[215,124,159], Wayne H.-H. Sheu[216,162,217], Young-Ah Shin[49], Xueling Sim[7,218], Johannes H. Smit[190], Albert V. Smith[116,117], Maria X. Sosa[1], Tim D. Spector[176], Alena Stančáková[219], Alice Stanton[220], Kathleen E. Stirrups[14,221], Heather M. Stringham[7], Johan Sundstrom[56], Amy J. Swift[66], Ann-Christine Syvänen[56], E-Shyong Tai[222,76,218], Toshiko Tanaka[99], Kirill V. Tarasov[223], Alexander Teumer[224], Unnur Thorsteinsdottir[11,225], Martin D. Tobin[226], Elena Tremoli[57,58], Andre G. Uitterlinden[97,227], Matti Uusitupa[228,229], Ahmad Vaez[36], Cornelia M. van Duijn[97,230], Erik P.A. van Iperen[231,232], Ramachandran S. Vasan[45,233], Germaine C. Verwoert[97], Jarmo Virtamo[26], Veronique Vitart[121], Benjamin F. Voight[234,235], Peter Vollenweider[236], Aline Wagner[237], Louise V. Wain[226], Nicholas J. Wareham[12], Hugh Watkins[4,96], Alan B. Weder[238], Wellcome Trust Case Control Consortium, Harm-Jan Westra[239], Rainford Wilks[240], Tom Wilsgaard[241,242], James F. Wilson[104,121], Tien Y. Wong[75,76,77], Tsun-Po Yang[14,243], Jie Yao[244], Loic Yengo[168,169,170], Weihua Zhang[71,72], Jing Hua Zhao[12], Xiaofeng Zhu[245], Pascal Bovet[246,3], Richard S. Cooper[52], Karen L. Mohlke[51], Danish Saleheen[247,201], Jong-Young Lee[49], Paul Elliott[71,248], Hinco J. Gierman[46,249], Cristen J. Willer[8,250,251], Lude Franke[252], G Kees Hovingh[253], Kent D. Taylor[30], George Dedoussis[174], Peter Sever[194], Andrew Wong[154], Lars Lind[56], Themistocles L. Assimes[38], Inger Njølstad[241,242], Peter EH. Schwarz[68], Claudia Langenberg[12], Harold Snieder[36], Mark J. Caulfield[9,42], Olle Melander[33], Markku Laakso[157], Juha Saltevo[254], Rainer Rauramaa[120,159], Jaakko Tuomilehto[26,255,256,257], Erik Ingelsson[95,4], Terho Lehtimäki[31,32], Kristian Hveem[128], Walter Palmas[258], Winfried März[259,260], Meena Kumari[28], Veikko Salomaa[26], Yii-Der I. Chen[30], Jerome I. Rotter[30], Philippe Froguel[168,169,170,23], Marjo-Riitta Jarvelin[215,124,261,262], Edward G. Lakatta[223], Kari Kuulasmaa[26], Paul W. Franks[19,204,18], Anders Hamsten[16,17], H.-Erich Wichmann[80,263,264], Colin N.A. Palmer[13], Kari Stefansson[11,225], Paul M Ridker[5,6], Ruth J.F. Loos[12,265], Aravinda Chakravarti[1], Panos Deloukas[14,266], Andrew P. Morris[267,4*#], Christopher Newton-

Cheh[141,189,152*#$], Patricia B. Munroe[9,42*#$]

[*] These authors contributed equally to this work.
[#] These authors jointly supervised this work.
[$] Corresponding authors: Christopher Newton-Cheh (cnewtoncheh@mgh.harvard.edu) and Patricia B. Munroe (p.b.munroe@qmul.ac.uk).

AUTHOR AFFILIATIONS

1. Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
2. Cardiology, Department of Medicine, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland
3. Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois and University of Lausanne, Route de la Corniche 10, 1010 Lausanne, Switzerland
4. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK
5. Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave. East, Boston, MA 02215, USA
6. Harvard Medical School, Boston, MA 02115, USA
7. Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI 48109, USA
8. Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109, USA
9. Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London, EC1M 6BQ, UK
10. GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY, UK
11. deCODE Genetics/Amgen, Inc., Reykjavik, Iceland
12. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK
13. Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK
14. William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
15. Institute of Genetic Epidemiology, Helmholtz Zentrum München, Neuherberg 85764, Germany
16. Atherosclerosis Research Unit, Center for Molecular Medicine L8:03, Department of Medicine, Karolinska Institutet, 171 76 Stockholm, Sweden
17. Center for Molecular Medicine, Karolinska University Hospital Solna, Stockholm, Sweden
18. Department of Public Health and Clinical Medicine, Ume University, Sweden
19. Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Skåne University Hospital Malmö, SE-205 02 Malmö, Sweden
20. Department of Odontology, Ume University, Sweden
21. Centre of Excellence for Public Health, Queens University Belfast, Grosvenor Road, Belfast BT126JP, UK
22. Laboratory of Genetics, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA
23. Department of Genomics of Common Disease, School of Public Health, Imperial College London, Hammersmith Hospital, London, UK
24. INSERM UMR970, Paris Cardiovascular Research Center PARCC, 56 rue Leblanc, 75015 Paris, France
25. University Paris-Descartes, Sorbonne Paris Cité, 12 rue de l'Ecole de medicine F-75006 Paris, France
26. National Institute for Health and Welfare, FI-00271 Helsinki, Finland
27. Institute for Molecular Medicine Finland FIMM, University of Helsinki, 00290 Helsinki, Finland
28. Genetic Epidemiology Group, Dept. Epidemiology and Public Health, UCL, London, WC1E 6BT, UK
29. Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany
30. Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA 90502, USA

31. Department of Clinical Chemistry, Fimlab Laboratories, Tampere 33520, Finland
32. Department of Clinical Chemistry, University of Tampere School of Medicine, Tampere 33014, Finland
33. University of Lund, Dept Internal Medicine, Malmo, SE 20502, Sweden
34. University of Verona, Dept of Internal Medicine, Verona, Italy 37134
35. Uppsala University, Uppsala Clinical Research Center, SE-75185 Uppsala, Sweden
36. Department of Epidemiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
37. Dept of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77 Stockholm, Sweden
38. Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA
39. Second Department of Cardiology, Attikon Hospital, School of Medicine, University of Athens, Athens, Greece
40. Children's Hospital Oakland Research Institute, Oakland, CA 94609, USA
41. Department of Cardiovascular Genetics, Institute of Cardiovascular Sciences, University College London, London WC1E 6JF, UK
42. NIHR Barts Cardiovascular Biomedical Research Unit, Queen Mary University of London, London, EC1M 6BQ, UK
43. Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA 02115, USA
44. Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, 02142, USA
45. National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA 01702, USA
46. Dept. Dev. Bio. And Genetics, Stanford University Medical Center, Stanford, CA 94305, USA
47. Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands
48. National Heart, Lung and Blood Institute, Cardiovascular Epidemiology and Human Genomics Branch, Bethesda, MD 20814, USA
49. Center for Genome Science, National Institute of Health, Osong Health Technology Administration Complex, Chungcheongbuk-do, Republic of Korea
50. Division of Translational Medicine and Human Genetics, Department of Medicine, University of Pennyslvania, USA
51. Department of Genetics, University of North Carolina, Chapel Hill, NC 27599, USA
52. Department of Preventive Medicine and Epidemiology, Loyola University Chicago Stritch School of Medicine, Maywood, IL, 60153, USA
53. HudsonAlpha Institute for Biotechnology, Huntsville, AL 35086, USA
54. Department of Nutrition, University of North Carolina, Chapel Hill, NC 27599, USA
55. Genetic Epidemiology Unit, Department of Epidemiology, Erasmus MC, Rotterdam, 3015CN, The Netherlands
56. Uppsala University, Department of Medical Sciences, SE-75185 Uppsala, Sweden
57. Dipartimento di Scienze Farmacologiche e Biomolecolari, Università di Milano, Milan, Italy
58. Centro Cardiologico Monzino, IRCCS, Milan, Italy
59. INSERM Centre for Research in Epidemiology and Population Health, U1018, Villejuif, France University Paris-Sud, URMS 1018, Villejuif, France
60. Geriatric Unit, Azienda Sanitaria Firenze (ASF), Florence, Italy
61. Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, CB10 1SA, Hinxton, UK
62. University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Level 4, Institute of Metabolic Science Box 289 Addenbrookes Hospital Cambridge CB2 OQQ, UK

63. Neurology Unit, University of Cambridge, R3, Box 83, Cambridge Biomedical Campus, Cambridge, Cb2 0QQ, UK
64. Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA 98101, USA
65. Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, 1200 Pressler St., Suite 453E, Houston, TX 77030, USA
66. Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD 20892, USA
67. Department of Biological Psychology, VU University, Amsterdam, The Netherlands
68. Dept of Medicine III, University of Dresden, Medical Faculty Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany
69. Clinical Pharmacology Unit, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK
70. Nephrology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Bugnon 17, 1005 Lausanne, Switzerland
71. Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK
72. Department of Cardiology, Ealing Hospital NHS Trust, Uxbridge Road, Southall, Middlesex UB1 3EU, UK
73. Imperial College Healthcare NHS Trust, London, UK
74. National Institute of Cancer Research, National Health Research Institutes. 35 Keyan Rd., Zhunan Town, Miaoli County 350, Taiwan
75. Singapore Eye Research Institute, Singapore National Eye Centre, Singapore 168751, Singapore
76. Duke-NUS Graduate Medical School Singapore, Singapore 169857, Singapore
77. Department of Ophthalmology, National University of Singapore and National University Health System, Singapore 119228
78. Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes. 35 Keyan Rd., Zhunan Town, Miaoli County 350, Taiwan
79. University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK
80. Institute of Epidemiology I, Helmholtz Zentrum München, Neuherberg 85764, Germany
81. Institute of Epidemiology II, Helmholtz Zentrum München, Neuherberg 85764, Germany
82. UMR744 Inserm-Lille2-Institut Pasteur Lille, France
83. Department of Public Health and Primary Care, University of Cambridge, UK
84. Division of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
85. Johns Hopkins Medical Institutions, 1830 East Monument St., Baltimore, MD 21287, USA
86. BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow, G12 8QT, UK
87. Cardiovascular Epidemiology and Genetics. IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain
88. Dept of Immunology, Genetics, Pathology, Science for Life Laboratory, University of Uppsala, Box 815, Biomerical center, 751 08 Uppsala, Sweden
89. Institut für Integrative und Experimentelle Genomik, Universiät zu Lübeck, RatzeburgerAllee 160, 23538 Lübeck, Germany
90. Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), partner site Hamburg, Kiel, Lübeck, Universität zu Lübeck, Lübeck, Germany
91. Estonian Genome Center, University of Tartu, Tartu, 51010, Estonia
92. Divisions of Endocrinology/Children's Hospital, Boston, MA 02115, USA

93. Broad Institute of MIT and Harvard, Cambridge, MA, 02142, USA
94. Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, 45110, Greece
95. Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
96. Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, OX3 9DU, UK
97. Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, P.O.Box 2040, 3000 CA Rotterdam, The Netherlands
98. Toulouse University School of Medicine, Rangueil University Hospital, INSERM UMR1027, Toulouse, France
99. Translational Gerontology Branch, National Institute on Aging, Baltimore MD, USA
100. Institute of Molecular Medicine, University of Texas Health Science Center at Houston, TX, USA
101. Tropical Metabolism Research Unit, Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston 7, Jamaica
102. Department of Epidemiology, University of North Carolina, Chapel Hill, NC 27599, USA
103. Cardiothoracic Surgery Unit, Department of Molecular Medicine and Surgery, Karolinska Institutet, 171 76 Stockholm, Sweden
104. Institute for Population Health Sciences and Informatics, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland
105. Synpromics Ltd, 9 Bioquarter, Little France Road, Edinburgh, EH16 4UX, Scotland
106. University of Michigan Medical School, 7220 MSRB III, Ann Arbor MI 48109, USA
107. EPIMED Research Centre - Epidemiology and Preventive Medicine, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy
108. Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo NEUROMED, 86077 Pozzilli, Italy
109. Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester LE3 9QP, UK
110. National Institute for Health Research Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester LE3 9QP, UK
111. Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA
112. Department of Genetic Epidemiology, Institute of Epidemiology and Preventive Medicine, University of Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
113. Department of Nephrology, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
114. Department of Medicine III, Division Pathobiochemistry, Technische Universität Dresden, Dresden, Germany
115. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford,UK
116. Icelandic Heart Association, Kopavogur, Iceland
117. Faculty of medicine, University of Iceland, Reykjavik, Iceland
118. Institute of Clinical Medicine/Obstetrics and Gynaecology, University of Oulu, Oulu, Finland
119. Medical Research Center, Oulu University Hospital, Oulu, Finland
120. Kuopio Research Institute of Exercise Medicine, Kuopio, Finland
121. Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, EH4 2XU Scotland, UK
122. UREN, INSERM U557, INRA U1125, CNAM, SMBH, Sorbonne Paris Cité, Université Paris 13, Bobigny, France

123. Institute of Biomedicine, University of Oulu, Medical Research Center Oulu and Oulu University Hospital, Finland
124. Biocenter Oulu, P.O.Box 5000, Aapistie 5A, FI-90014 University of Oulu, Finland
125. Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan, Poland
126. Center for Biomedicine, European Academy Bozen/Bolzano (EURAC), Bolzano, 39100, Italy - affiliated institute of the University of Lübeck, Germany
127. Department of Genetics, Harvard Medical School, Boston, 02115, USA
128. HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, 7600 Levanger, Norway
129. St. Olav Hospital, Trondheim University Hospital, Trondheim, Norway
130. Cardiovascular Genetics Division, University of Utah School of Medicine, Salt Lake City, Utah, USA
131. Department of Genetic Medicine, Weill Cornell Medical College Qatar, Doha, Qatar
132. Department of Radiology, Erasmus MC, The Netherlands
133. Department of Neurology, Erasmus MC, University Medical Center Rotterdam, P.O.Box 2040, 3000 CA Rotterdam, The Netherlands
134. Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Neuherberg 85764, Germany
135. Hannover Unified Biobank, Hannover Medical School, Hannover 30625, Germany
136. Hannover Medical School, Institute for Human Genetics, Carl-Neuberg-Strasse 1, 30625 Hanover, Germany
137. Kaiser Permanente, Division of Research, Oakland, CA 94612, USA
138. Department of Medicine, University of Washington, Seattle, Washington 98101, USA
139. Department of Clinical Physiology, Tampere University Hospital, Tampere 33521, Finland
140. Department of Clinical Physiology, University of Tampere School of Medicine, Tampere 33014, Finland
141. Center for Human Genetic Research, Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA 02114, USA
142. Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA
143. Department of Medicine, Harvard Medical School, Boston, MA, USA
144. Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA and Cardiology Division, Massachusetts General Hospital, Boston, MA, USA
145. Division of Transplantation, Department of Surgery, University of Pennsylvania, PA 19104 USA
146. Department of Pediatrics, University of Pennsylvania, Philadelphia, PA, USA
147. Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge CB2 2SR, UK
148. Institute for Translational Genomics and Population Sciences, Department of Pediatrics, LABioMed at Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA 90502, USA
149. 1st Cardiology Department, Onassis Cardiac Surgery Center 356, Sygrou Ave, Athens, Greece
150. National Heart and Lung Institute, Imperial College London, Hammersmith Hospital Campus, Ducane Road, London W12 0NN, UK
151. Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA 02114, USA
152. Broad Institute of Harvard and MIT, Cambridge, MA 02139 USA
153. Department of Medicine, Children's Hospital Oakland Research Institute, Oakland, CA 94609, USA
154. MRC Unit for Lifelong Health and Ageing at UCL, London, WC1B 5JU, UK
155. Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland
156. Swiss Institute of Bioinformatics, Lausanne, Switzerland

157. Department of Medicine, University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland
158. Institute of Biomedicine/Physiology, University of Eastern Finland, Kuopio Campus, Finland
159. Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland
160. Office of Population Studies Foundation Inc. and Department of Anthropology, Sociology, and History, University of San Carlos, Talamban, Cebu City, 6000, Philippines
161. Division of Endocrine and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung 40705, Taiwan
162. School of Medicine, National Yang-Ming University, Taipei, Taiwan
163. Department of Medical Research, Taichung Veterans General Hospital, Taichung 407, Taiwan
164. Population Sciences Branch, National Heart Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA
165. Cardiovascular Center, Taichung Veterans General Hospital, Taichung, 40705, Taiwan
166. Institute of Clinical Medicine, National Yang Ming University School of Medicine, Taipei 112, Taiwan
167. Section of Computational Biomedicine, Department of Medicine, Boston University School of Medicine, Boston, 02446 MA, USA
168. European Genomic Institute for Diabetes (EGID), FR 3508 Lille, France
169. Centre National de la Recherche Scientifique (CNRS) UMR 8199, Lille Pasteur Institute, 1 rue du Prof Calmette, 59019 Lille Cedex, France
170. Lille 2 University, Lille, France
171. Center for Evidence-based Healthcare, University of Dresden, Medical Faculty Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany
172. Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians University, Munich, Germany
173. Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-University of Munich, Munich, Germany
174. Department of Dietetics-Nutrition, Harokopio University, 70 El. Venizelou Str, Athens, Greece
175. INSERM U1142 LIMICS, UMR_S 1142 Sorbonne Universités, UPMC Université Paris 06, Université Paris 13, Paris, France
176. Department of Twin Research and Genetic Epidemiology, King's College London, London, UK
177. Department of Life and Reproduction Sciences, University of Verona, Strada le Grazie 8, 37134 Verona, Italy
178. Department of Medicine, Kuopio University Hospital, Kuopio, Finland
179. Unit of General Practice, Oulu University Hospital, Oulu, Finland
180. Department of Medicine, Program for Personalized and Genomic Medicine, University of Maryland, School of Medicine, Baltimore, Maryland 21201, USA
181. Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, 1200 Pressler St., Suite 453E, Houston, TX 77030, USA
182. Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monseratto, Monserrato, Cagliari 09042, Italy
183. Department of Cardiology, School of Medicine, University of Tampere, Tampere 33014, Finland
184. School of Medicine, University of Tampere, Tampere 33014, Finland
185. National Heart, Lung and Blood Institute, Division of Intramural Research, Bethesda, MD, USA
186. Cardiology Division, Department of Medicine, Massachusetts General Hospital
187. Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK

188. Divisions of Endocrinology and Genetics and Program in Genomics, Children's Hospital Boston, Massachusetts 02115, USA
189. Program in Medical and Population Genetics, Broad Institute, 7 Cambridge Center, Cambridge, MA 02142, USA
190. Department of Psychiatry, EMGO Institute, Neuroscience Campus, VU University Medical Centre, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands
191. Department of Psychiatry, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
192. Department of Psychiatry, Leiden University Medical Centre, P.O. Box 9600, 2300 RC Leiden, The Netherlands
193. The Estonian Genome Center, University of Tartu, Estonia
194. International Centre for Circulatory Health, Imperial College London, W2 1PG, UK
195. Department of Neurology, General Central Hospital, Bolzano, 39100, Italy
196. Department of Neurology, University of Lübeck, Lübeck, Germany
197. Department of Epidemiology, University of Washington, Seattle, WA, USA
198. Department of Health Services, University of Washington, Seattle, WA
199. Group Health Research Institute, Group Health Cooperative, Seattle, WA
200. Division of Biostatistics, Washington University School of Medicine, Saint Louis, MO, 63110, USA
201. Center for Non-Communicable Diseases, Karachi, Pakistan
202. Oxford Centre for Diabetes Endocrinology and Metabolism, University of Oxford, Oxford, UK
203. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK
204. Department of Nutrition, Harvard School of Public Health, Boston, MA, USA
205. Institute of Physiology, University Medicine Greifswald, Greifswald, Germany
206. Department of Biostatistics, University of Washington, Seattle, WA, USA
207. University of Ottawa Heart Institute, Cardiovascular Research Methods Centre Ontario, Canada
208. Ruddy Canadian Cardiovascular Genetics Centre, Ontario, Canada
209. National Heart, Lung, and Blood Institute, 6701 Rockledge Ave., Bethesda, MD 20892, USA
210. Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester LE3 9QP, UK
211. South Karelia Central Hospital, Lappeenranta, Finland
212. Deutsches Herzzentrum München and Technische Universität München, Germany
213. Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), München, Germany
214. Munich Heart Alliance, Germany
215. Center For Life-course Health Research, P.O.Box 5000, FI-90014 University of Oulu, Finland
216. Division of Endocrine and Metabolism, Department of Internal Medicine, Chichung Veterans General Hospital, Taichung 40705, Taiwan
217. College of Medicine, National Defense Medical Center, Taipei, Taiwan
218. Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore 117597
219. University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland
220. Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin 4, Ireland
221. Department of Haematology, University of Cambridge, Cambridge, UK
222. Department of Medicine, National University of Singapore and National University Health System, Singapore 119228, Singapore
223. Laboratory of Cardiovascular Science, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, 21224, USA
224. Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany

225. Faculty of Medicine, University of Iceland, Reykjavik, Iceland
226. Department of Health Sciences, University of Leicester, University Rd, Leicester LE1 7RH, UK
227. Department of internal medicine, Erasmus MC, Rotterdam, 3000CA, The Netherlands
228. Department of Public Health and Clinical Nutrition, University of Eastern Finland, Finland
229. Research Unit, Kuopio University Hospital, Kuopio, Finland
230. Centre of Medical Systems Biology (CMSB 1-2), NGI Erasmus Medical Center, Rotterdam, The Netherlands
231. Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands
232. Durrer Center for Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht, The Netherlands
233. Sections of Preventive medicine and Cardiology, Department of Medicine, Boston University School of Medicine, Boston, 02446 MA, USA
234. Medical Population Genetics, The Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA
235. Department of Pharmacology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
236. Department of Internal medicine, University Hospital Lausanne, Lausanne, Switzerland
237. Department of Epidemiology and Public Health, EA3430, University of Strasbourg, Strasbourg, France
238. Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA
239. University Medical Center Groningen, University of Groningen, Groningen, 9700RB, The Netherlands
240. Epidemiology Research Unit, Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston 7, Jamaica
241. Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway
242. Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway
243. MRC Cancer Unit, University of Cambridge, Cambridge, UK
244. Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 West Carson Street, Torrance, CA 90502, USA
245. Department of Epidemiology and Biostatistics, School of Medicine, Case Western Reserve University, Cleveland, OH, 44106, USA
246. Ministry of Health, Victoria, Republic of Seychelles
247. Department of Biostatistics and Epidemiology, University of Pennsylvania, USA
248. MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK
249. Enterprise Informatics, Illumina Inc., Santa Clara CA, 95050, USA
250. Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI 48109, USA
251. Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA
252. Department of Genetics, University of Groningen, University Medical Centre Groningen, Groningen, 9711, The Netherlands
253. Dept Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
254. Department of Medicine, Central Finland Health Care District, Jyväskylä, Finland
255. South Ostrobothnia Central Hospital, 60220 Seinäjoki, Finland

256. Red RECAVA Grupo RD06/0014/0015, Hospital Universitario La Paz, 28046 Madrid, Spain
257. Centre for Vascular Prevention, Danube-University Krems, 3500 Krems, Austria
258. Department of Medicine, Columbia University, 622 West 168th St., New York, NY 10032, USA
259. Synlab Academy, Synlab Services GmbH, P5, 7, 68161 Mannheim, Germany
260. Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, 8036 Graz, Austria
261. Unit of Primary Care, Oulu University Hospital, Kajaanintie 50, P.O.Box 20, FI-90220 Oulu, 90029 OYS, Finland
262. MRC-PHE Centre for Environment and Health, Imperial College London, London, United Kingdom
263. Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-Universität, München 81377, Germany
264. Grosshadern, Klinikum, München 81377, Germany
265. The Charles Bronfman Institute for Personalized Medicine and the Mindich Child health Development Institute, The Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
266. Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah 21589, Saudi Arabia
267. Department of Biostatistics, University of Liverpool, Liverpool L69 3GA, UK
268. Novo Nordisk Foundation Centre for Basic Metabolic Research, Section of Metabolic, Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, 2100, Denmark
269. Department of Epidemiology Research, Statens Serum Institut, 2300, Copenhagen, Denmark

ONLINE METHODS

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

Studies contributing to BP association discovery including community- and population-based collections as well as studies of non-BP traits, analyzed as case and control samples separately. 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 local Research Ethics Committees and/or Institutional Review Boards.

European ancestry meta-analysis

A meta-analysis of 340,934 individuals of European descent was undertaken in four stages with subsequent validation in an independent cohort. Because stage 1 Cardio-MetaboChip samples included many SNPs selected on the basis of association with BP in earlier GWAS, we performed genomic control using a set of putative null SNPs based on $P > 0.10$ in earlier GWAS of SBP and DBP or both. Stage 2 samples with genome-wide genotyping used the entire genome-wide set of SNPs for genomic control given the lack of ascertainment. The study design is summarized in **Supplementary Figure 1**, and further details are provided in **Supplementary Tables 2-5** and the **Supplementary Note**.

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

All genes with any overlap with a 200kb region centered around each of the 20 newly discovered lead SNPs were identified using the UCSC Genome Browser. 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.

Trait variance explained

The trait variance explained by 66 lead SNPs at novel and known loci was evaluated in one study that contributed to 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 as a set of predictors of the BP residual after adjustment for covariates of the adjusted treatment-corrected BP phenotype (SBP or DBP). The r^2 from the regression model was used as the estimate of trait variance explained.

European ancestry GCTA-COJO analysis

To identify multiple distinct association signals at any given BP locus, we undertook approximate conditional analyses using a model selection procedure implemented in the GCTA-COJO software package[44,45]. 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 that were conditionally-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.

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

Multivariable regression modeling was performed for each possible combination of putative independent SNPs from a) model selection implemented in GCTA-COJO and b) a comprehensive manual

review of the literature (**Supplementary Table 9**). Any SNP with $P < 5x10^{-8}$ in a previous reported BP GWAS was considered. A total of 46 SNPs were examined (**Supplementary Table 10**). Genome-wide genotyping data imputed to 1000 Genomes in the WGHS (N = 23,047) were used. Regression modeling was performed in the R statistical language (**Supplementary Table 10**).

Fine mapping and determination of credible sets of causal SNPs

The GCTA-COJO and WGHS conditional analyses identified multiple distinct signals of association at multiple loci (**Supplementary Tables 6 and 10**). Of the 24 loci considered in fine-mapping analyses, 16 had no evidence for the existence of multiple distinct 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 using the association summary statistics from the unconditional meta-analyses. However, in the remaining eight 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**). At five of the eight loci with multiple distinct signals of association, one index SNP mapped outside of the fine-mapping region, so a credible set could not be constructed.

eQTL analysis: Whole Blood

NESDA/NTR: Whole blood eQTL analyses were performed in samples from the Netherlands Study of Depression and Anxiety (NESDA)[46] and the Netherlands Twin Registry (NTR)[47] studies. RNA expression analysis was performed in the statistical software R. 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, and three principal components were used. 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[48].

The eQTL effects were defined as *cis* when probe set–SNP pairs were at distance < 1M base pairs. 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 $1x10^{-4}$. 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. See **Supplementary Note** for details.

eQTL analysis: Selected published eQTL datasets

Lead BP SNP and proxies ($r^2 > 0.8$) were 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[49], left ventricle of the heart [50], cd14+ monocytes [51] and the brain [52]. The results are presented in **Supplementary Tables 14-15**.

Enrichment analyses: 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 [53] (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 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)[54] with discovery $P < 5x10^{-8}$ in European populations. A small number of reference SNPs or their proxies overlapping 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 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**).

Enrichment analyses: 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[55]. 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, essentially in terms of LD and proximity to genes (**Supplementary Note**). The number of significant digits in the *P* values is determined by the number of permutations and we conducted 10,000 iterations. Results are shown in **Supplementary Table 19**.

Enrichment analyses: Analysis of tissue-specific DHSs and chromatin states using GREGOR

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. 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. The probability that a set of GWAS loci overlap with a regulatory feature more often than we expect by chance was estimated.

Enrichment analyses: 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 some SNPs with missing data 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).

Pathway analyses: MAGENTA

MAGENTA tests for enrichment of gene sets from a precompiled library derived from GO, KEGG, PATHTER, REACTOME, INGENUITY, and BIOCARTA was performed as described by Segré et al, 2010[56]. 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**.

Pathway analyses: DEPICT

We applied the DEPICT [57] analysis 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. As a secondary analysis, we additionally 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 with $r^2 > 0.5$ to a given associated SNP.

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 (**Supplementary Table 22**).

Non-European meta-analysis

To assess the association of the 66 significant loci from the European ancestry meta-analysis in non-European ethnicities, 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. Tests for heterogeneity across effect estimates in European, South Asian, East Asian and African derived samples were performed using GWAMA[58].

Genetic risk score and cardiovascular outcomes

The gtx package 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[45].

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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 Figures 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, 20 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 2**)**.** 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 2.** 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 "**05_CM-BP_SuppInform_tables_NGrevision2_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

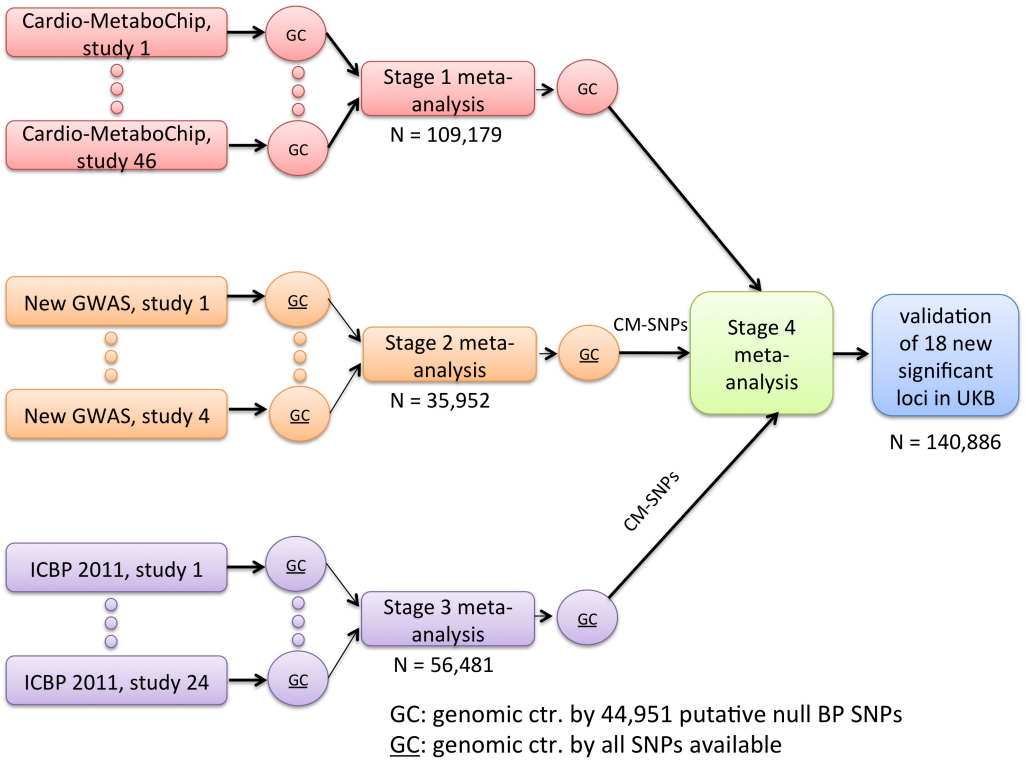
beta, SE, *P*-value and Total N. The previously significant (signif.) column indicates if the variant was previously reported to be associated with blood pressure in a non-European ancestry analyses. The heterogeneity metrics Cochrane Q (Coch_Q) and I^2 are indicated, calculated using summary results 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 2** 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,

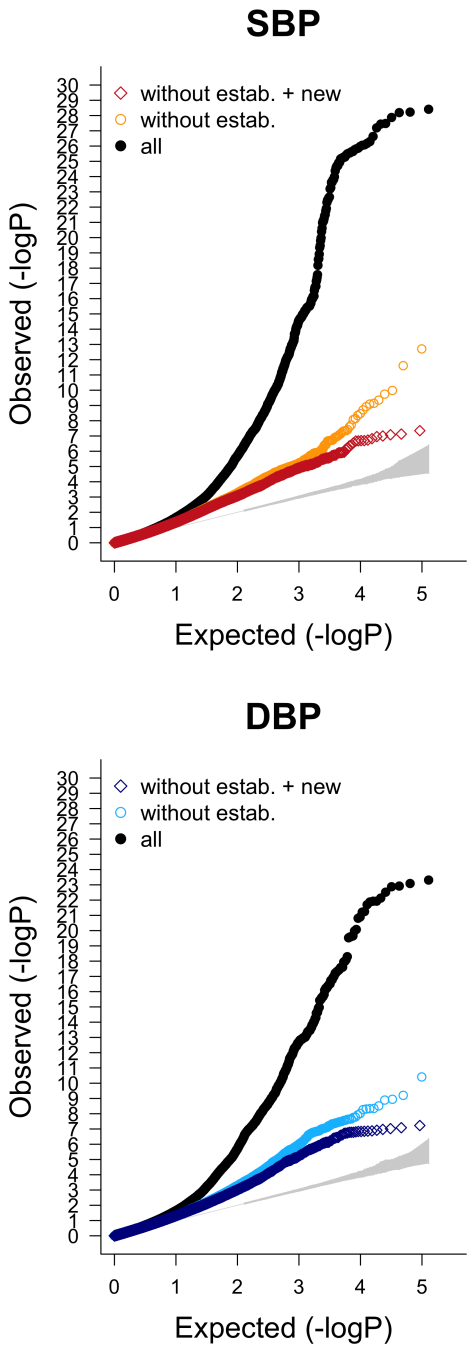
Supplementary Table 26: Genetic BP risk-score analysis applied to related cardiovascular phenotypes.
The BP genetic risk score was applied to related cardiovascular phenotypes using public databases (T2D: http://diagram-consortium.org/about.html; BMI and height: https://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files; 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.

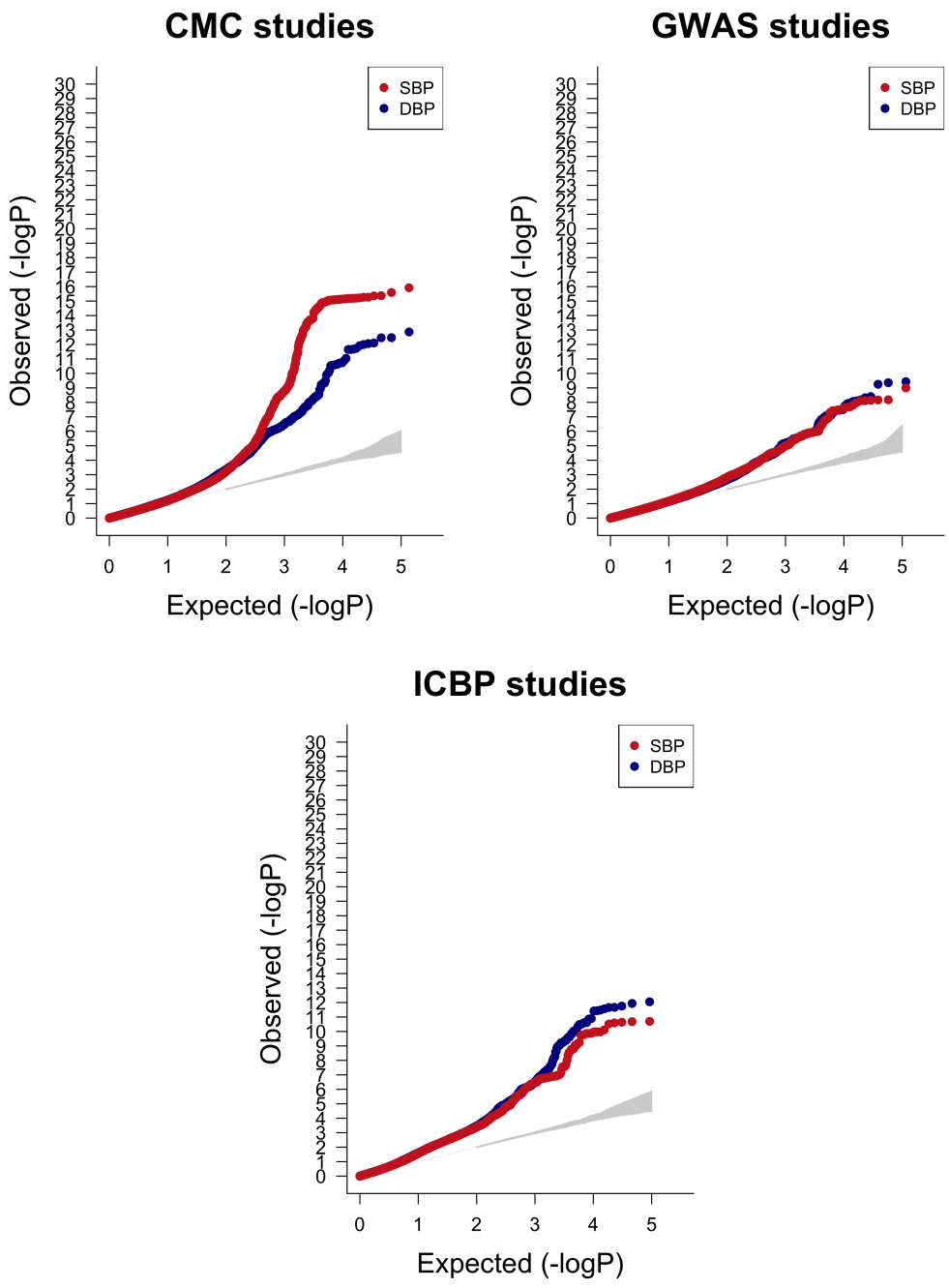
14 Supplementary figures



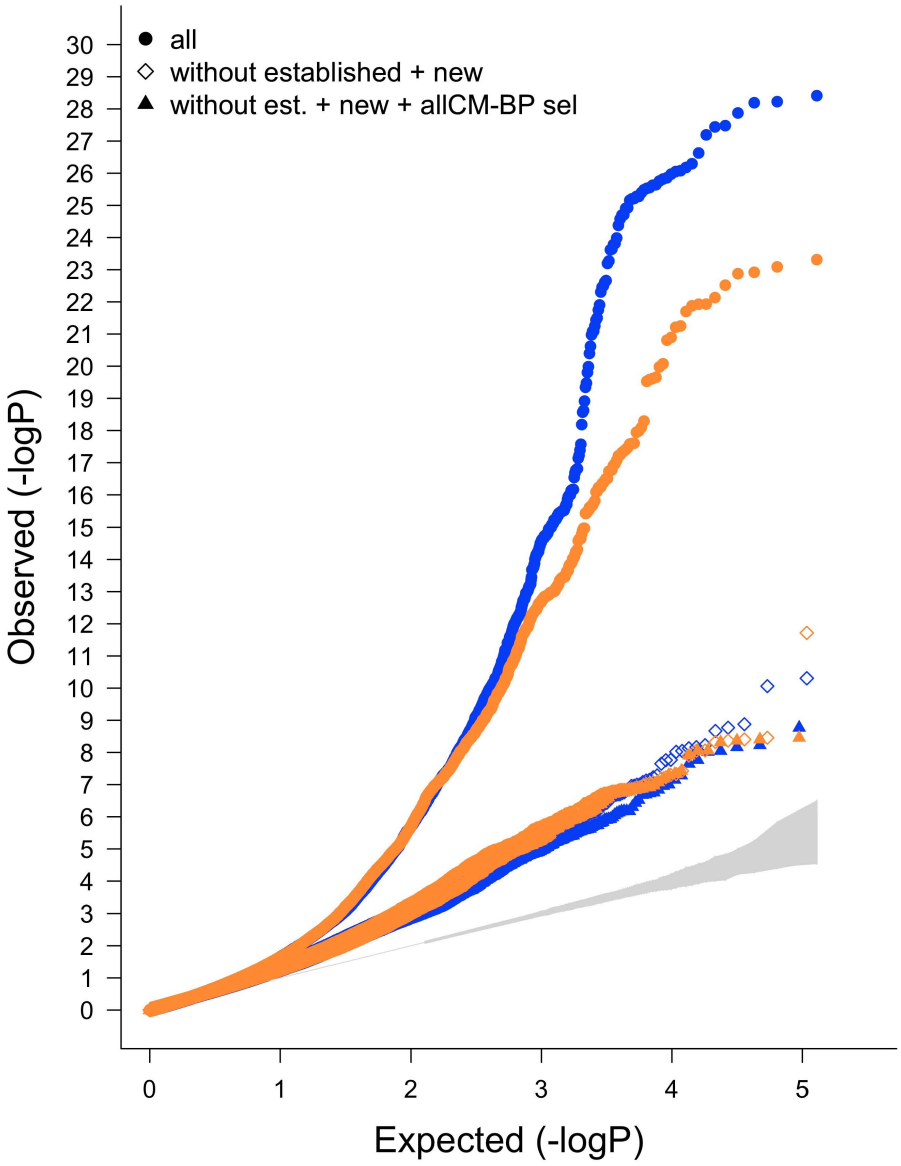
Supplementary Figure 1. Schematic of the experimental design of the meta-analyses. Meta-analyses were carried out in 4 stages (see **Supplementary Information**). Stage 1: results from 46 studies genotyped using Cardio-MetaboChip; Stage 2: unpublished results based on imputed genotypes from genome-wide 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.



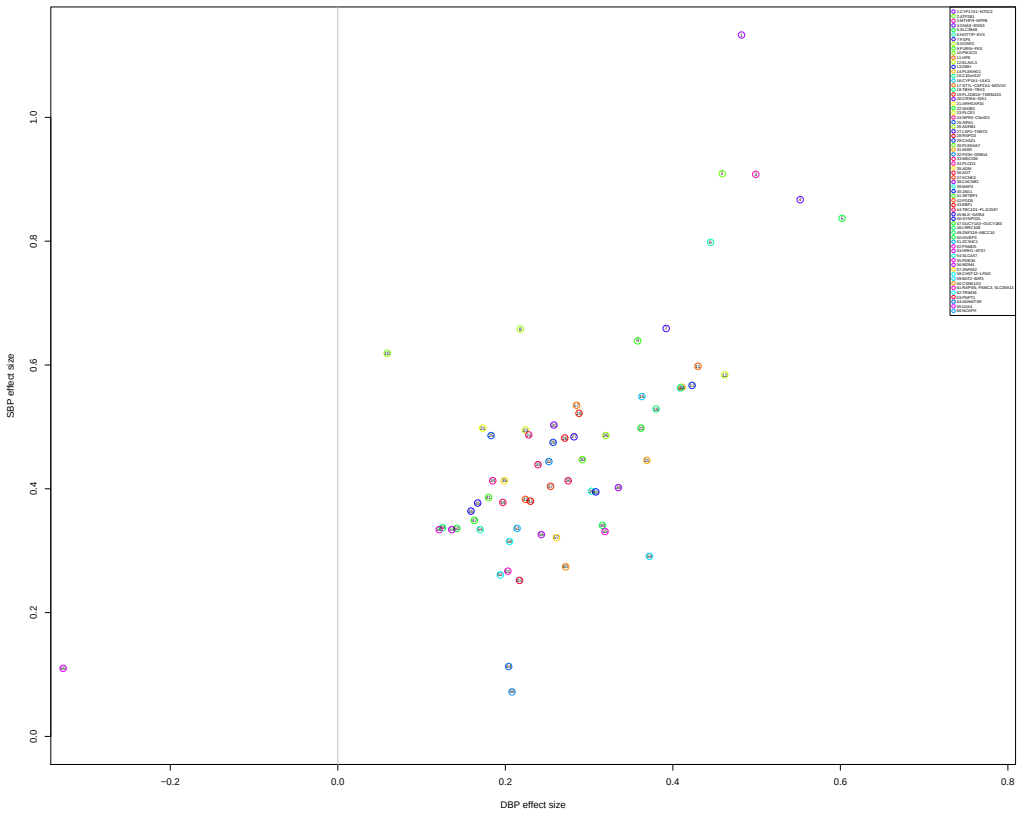
Supplementary Figure 2. Quantile-quantile-plots of the p-values from the Stage 4 Cardio-MetaboChip-wide meta-analysis for SBP and DBP. Observed $-log_{10}P$ are plotted against expected $-log_{10}P$ for three datasets: in black the entire dataset; in orange (SBP) and light blue (DBP) results after removal 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.



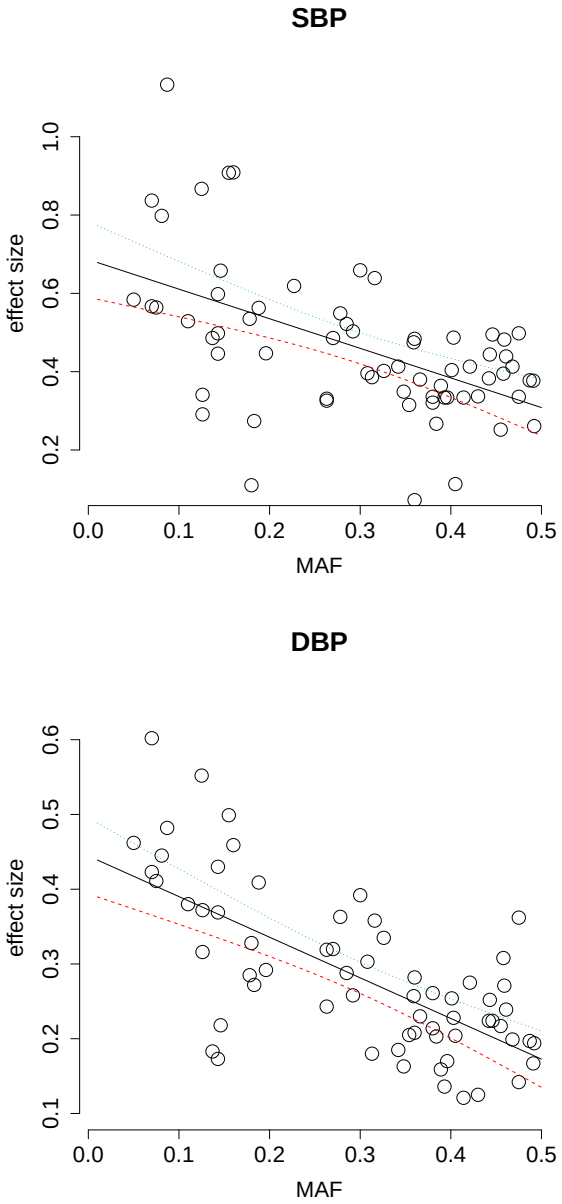
Supplementary Figure 3. Quantile-quantile-plots of the P values at each stage of the meta-analysis. The numbers include GC correction for the given stage.



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.

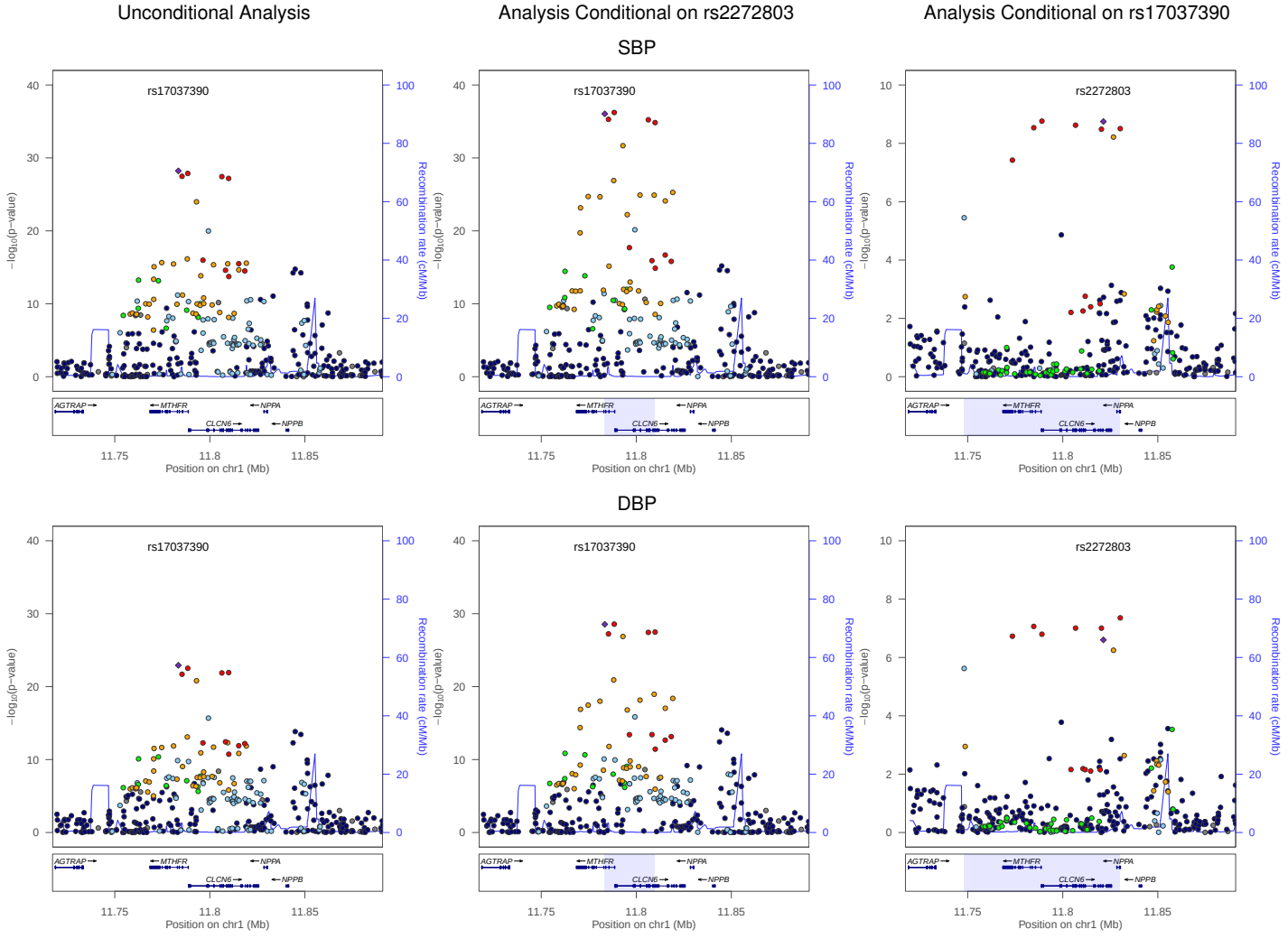


Supplementary Figure 5. Effect-size plot for each of the 66 index SNPs. The effect sizes in mm Hg per allele at each of 66 index SNPs are plotted for both phenotypes: the SBP effect size (y-axis) is plotted as a function of the DBP effect size (x-axis). Each index SNP is labeled with a different color and the corresponding locus-name is given in the legend insert.



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).

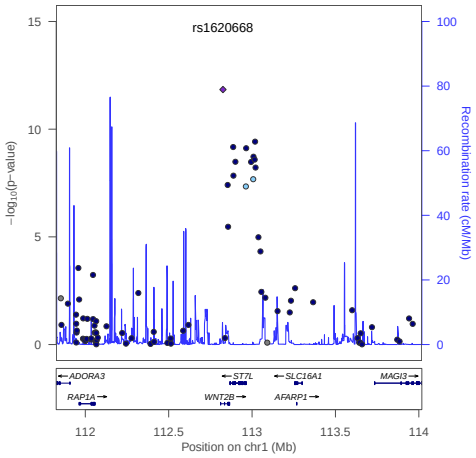
MTHFR-NPPB


Unconditional Analysis
Analysis Conditional on rs2272803
Analysis Conditional on rs17037390
SBP
DBP
rs17037390
rs2272803
−log10(p−value)
Recombination rate (cM/Mb)
AGTRAP
MTHFR
NPPA
CLCN6
NPPB
Position on chr1 (Mb)
11.75
11.8
11.85

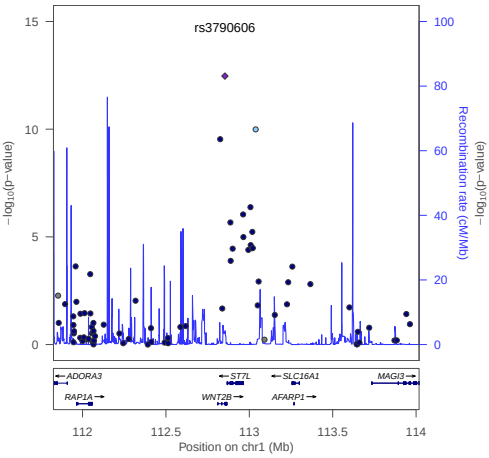
ST7L-CAPZA1-MOV10

SBP

Unconditional Analysis



Analysis Conditional on rs351370



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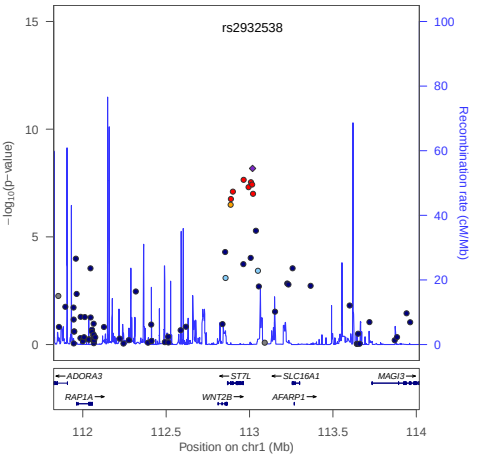

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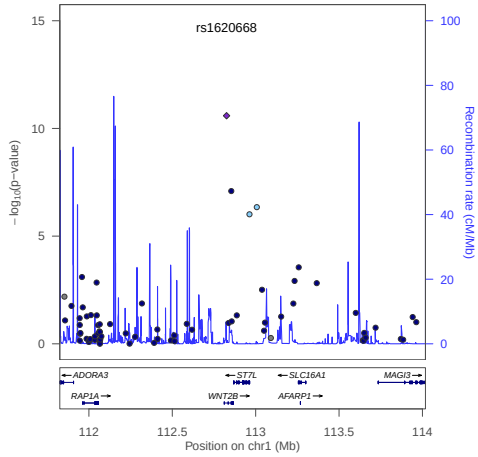
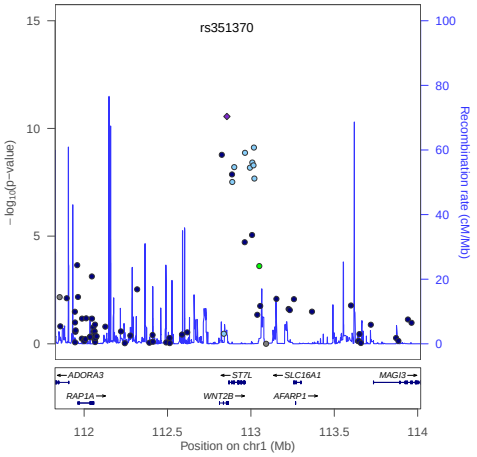
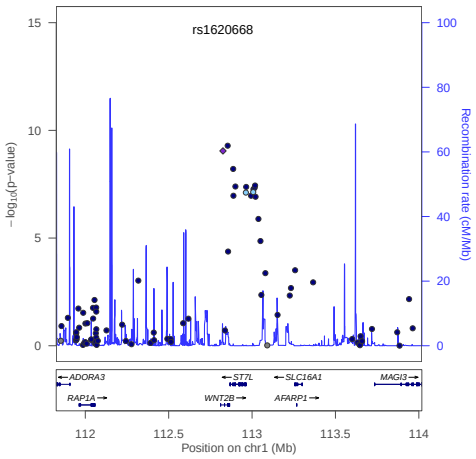


Analysis Conditional on rs3790606

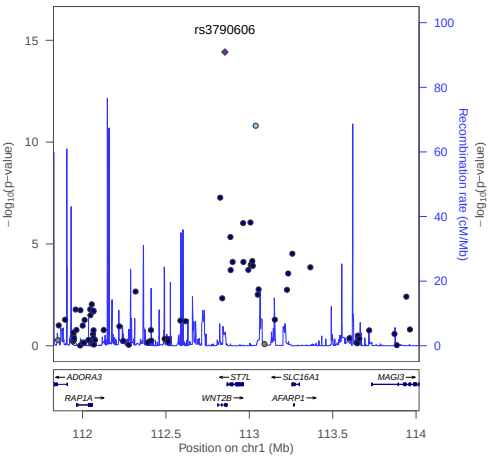


DBP

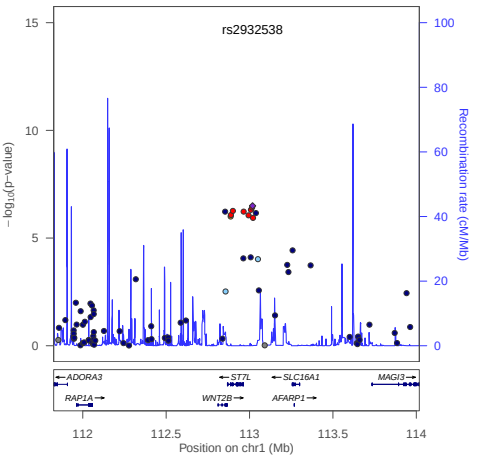
Unconditional Analysis



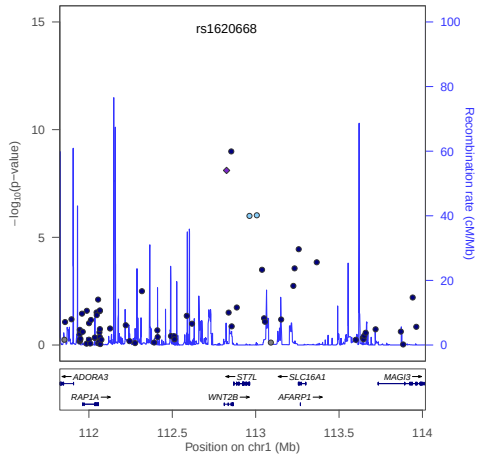
Analysis Conditional on rs351370



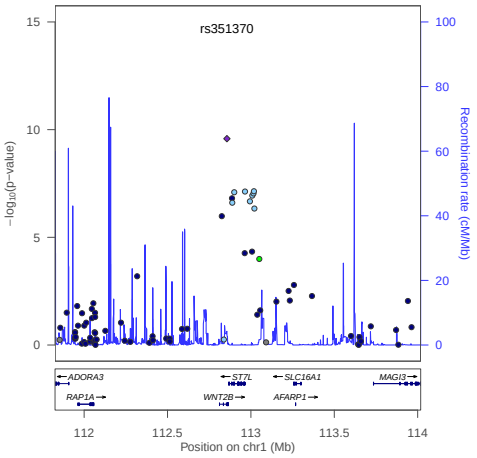
Analysis Conditional on rs1620668



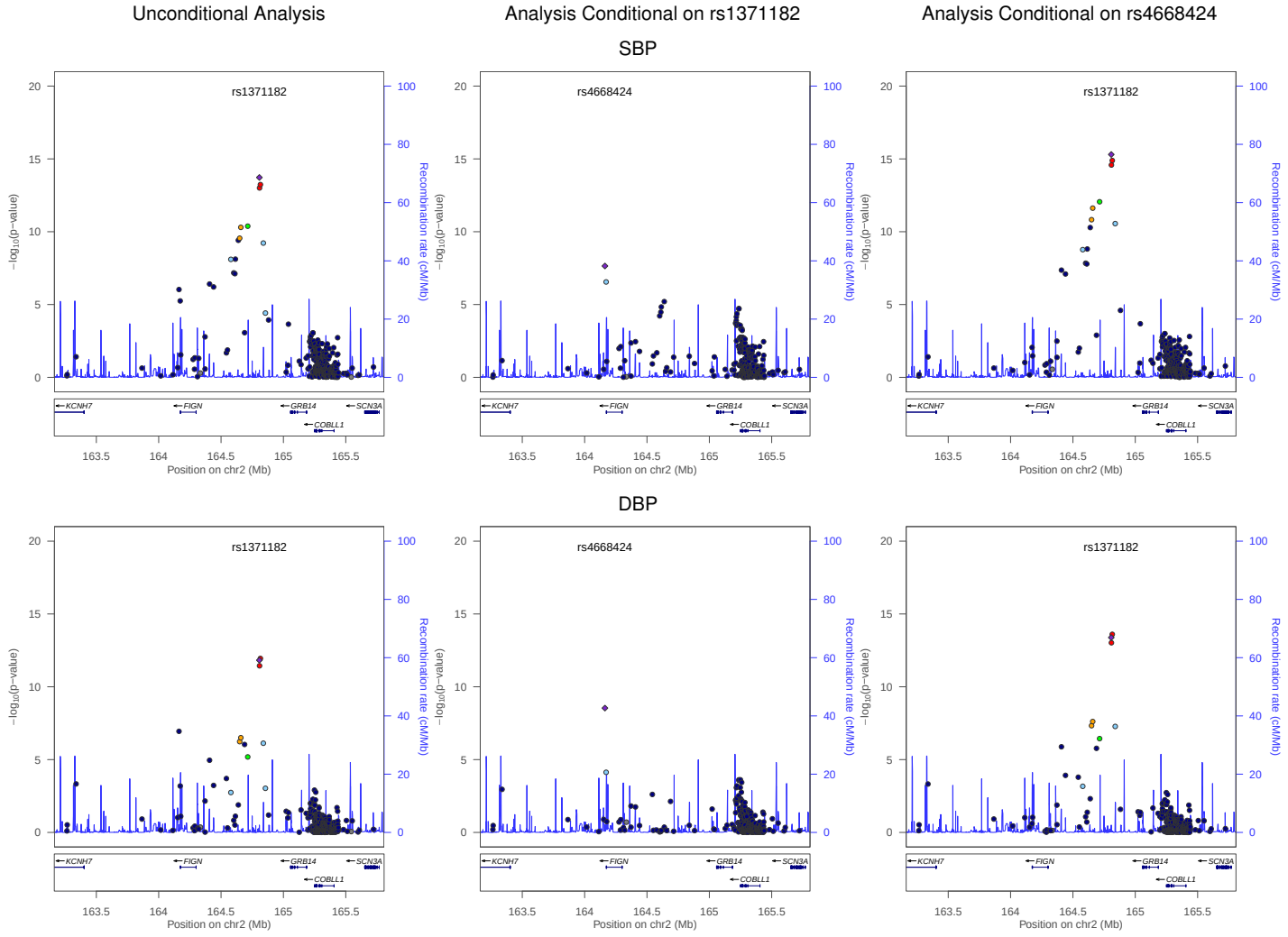
Analysis Conditional on rs2932538



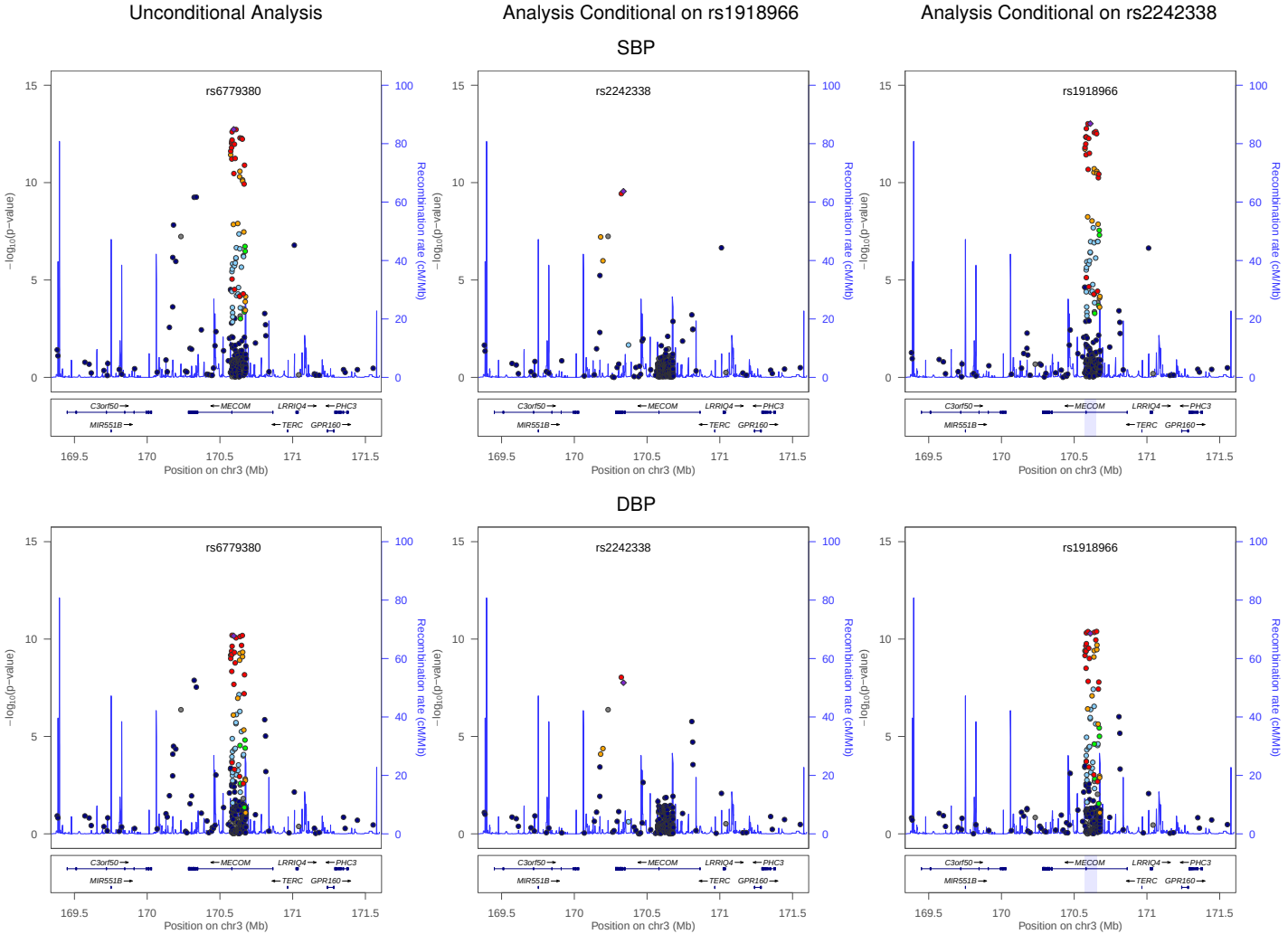
Analysis Conditional on rs3790606



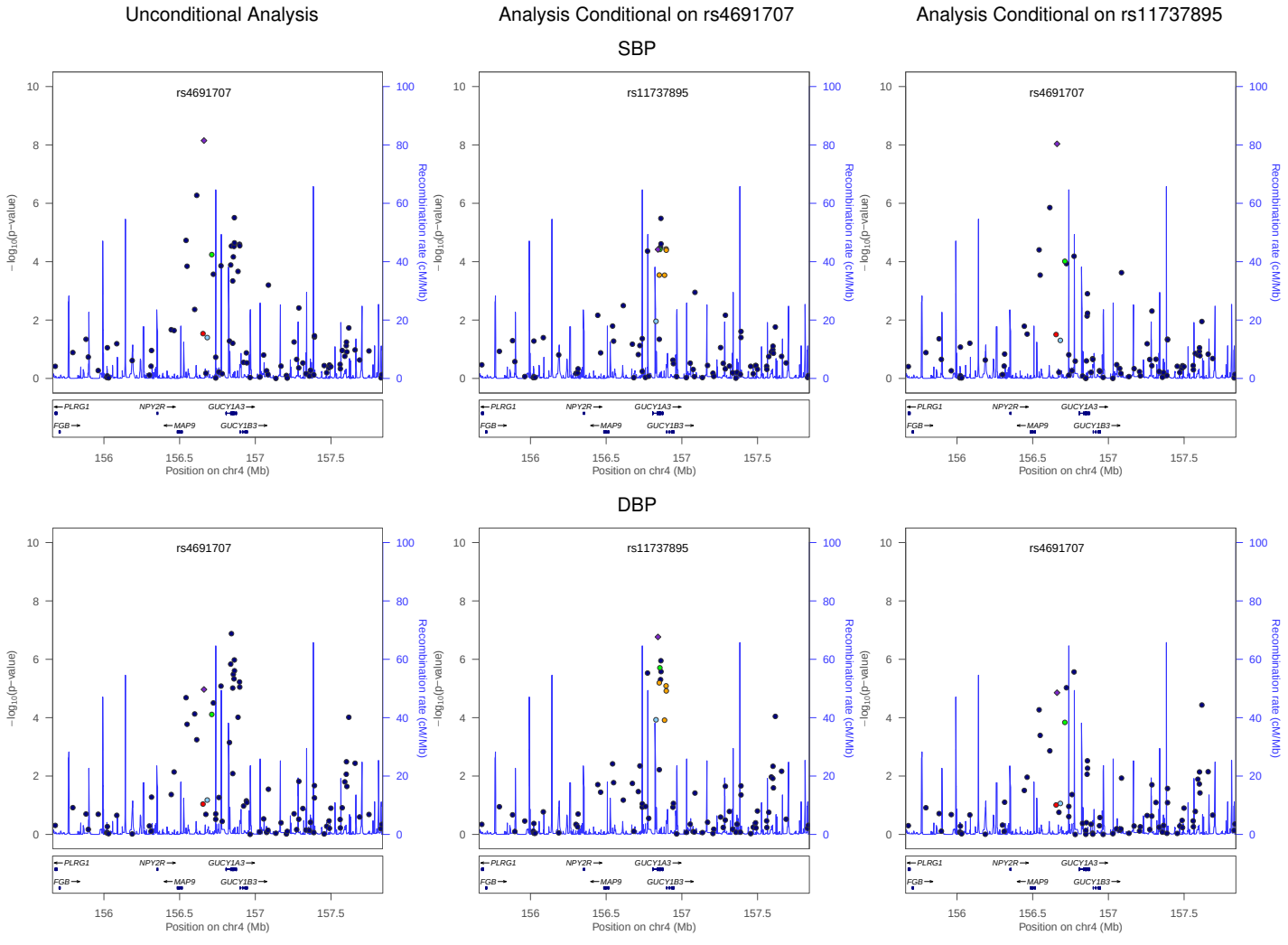
FIGN-GRB14


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)

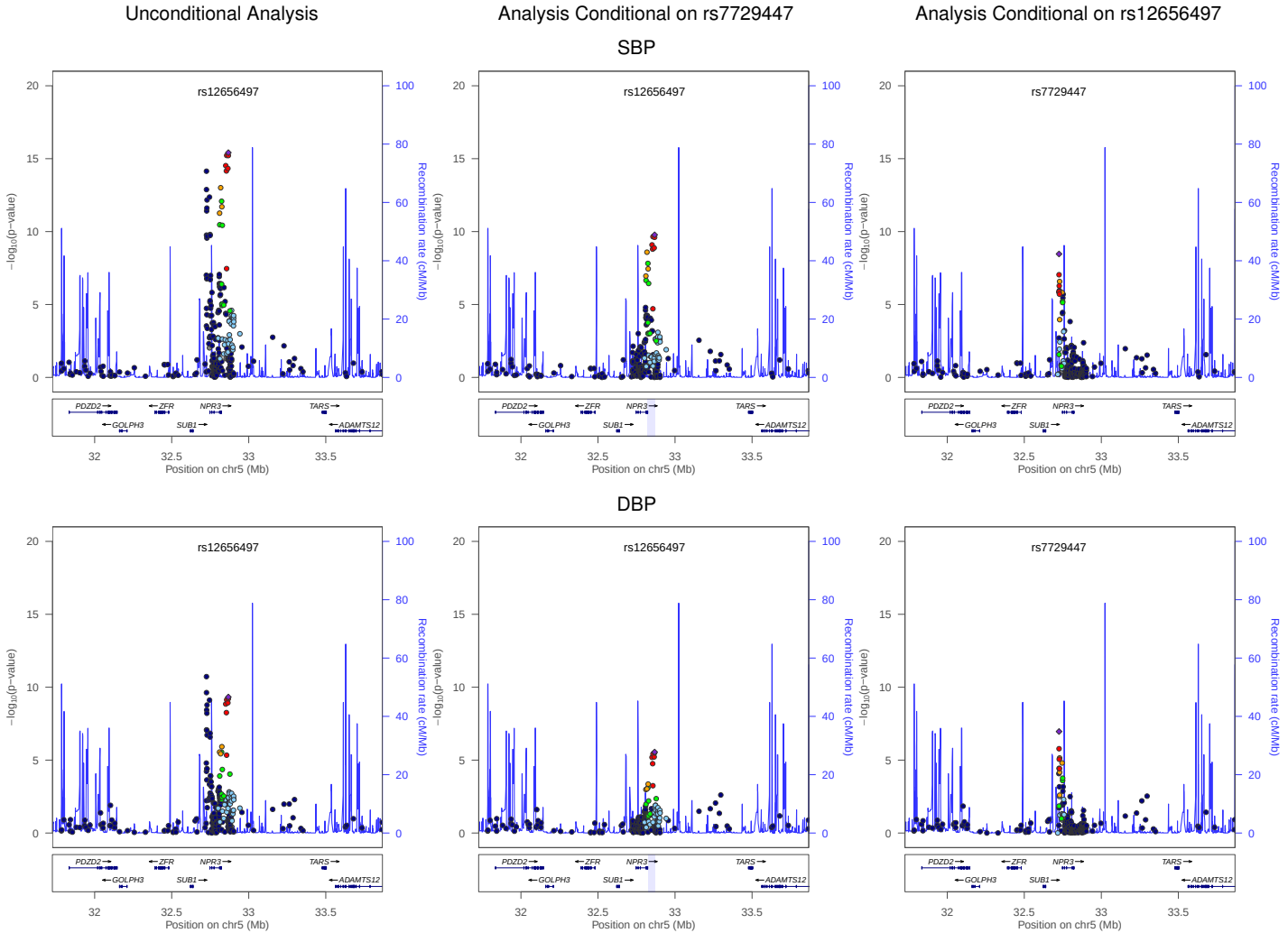
MECOM


Unconditional Analysis
Analysis Conditional on rs1918966
Analysis Conditional on rs2242338
SBP
DBP
rs6779380
rs2242338
rs1918966
−log10(p-value)
Recombination rate (cM/Mb)
C3orf50
MECOM
LRRIQ4
PHC3
MIR551B
TERC
GPR160
Position on chr3 (Mb)

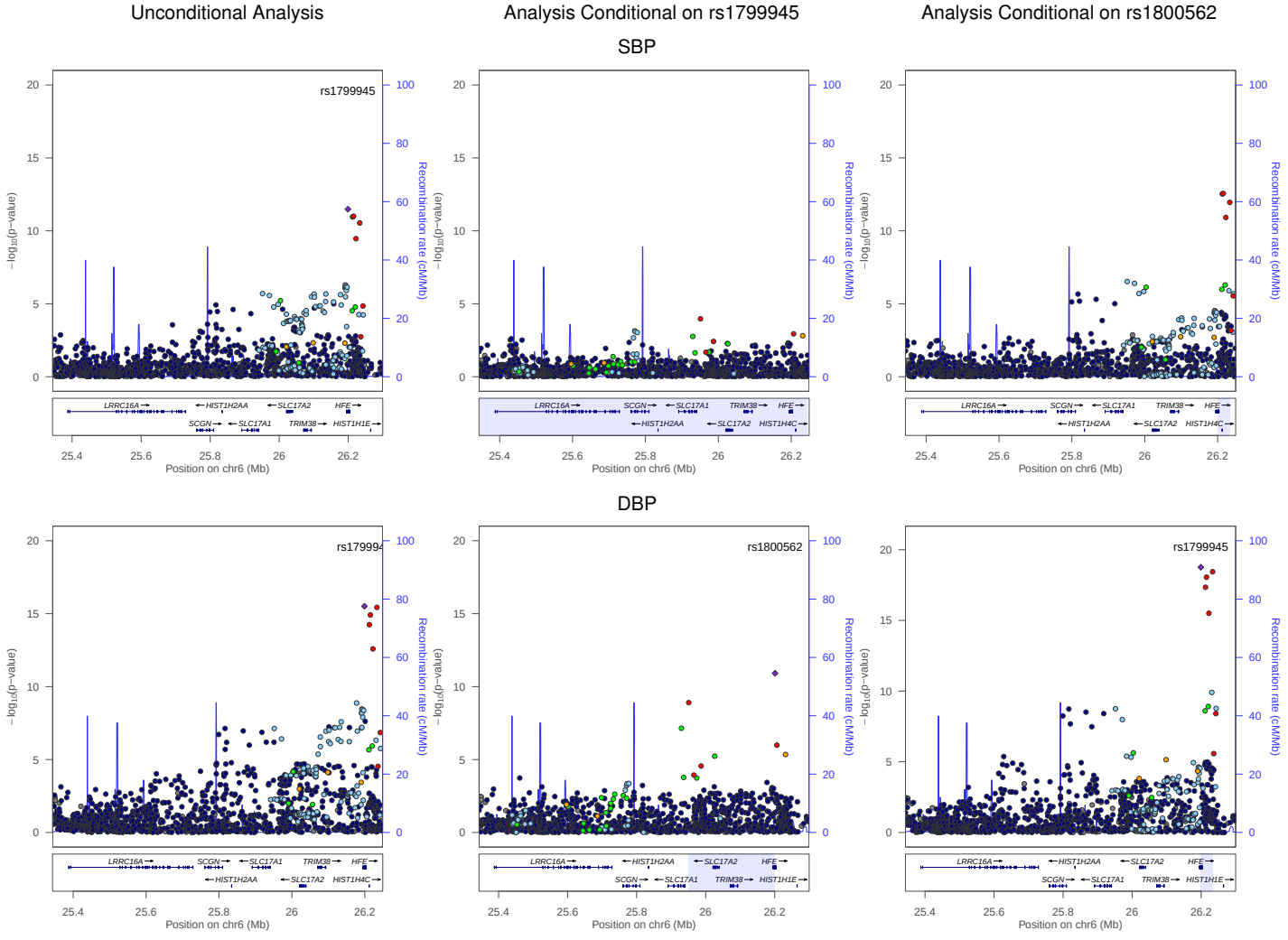
GUCY1A3


Unconditional Analysis
Analysis Conditional on rs4691707
Analysis Conditional on rs11737895
SBP
DBP
rs4691707
rs11737895
−log10(p-value)
Recombination rate (cM/Mb)
PLRG1
NPY2R
GUCY1A3
FGB
MAP9
GUCY1B3
Position on chr4 (Mb)

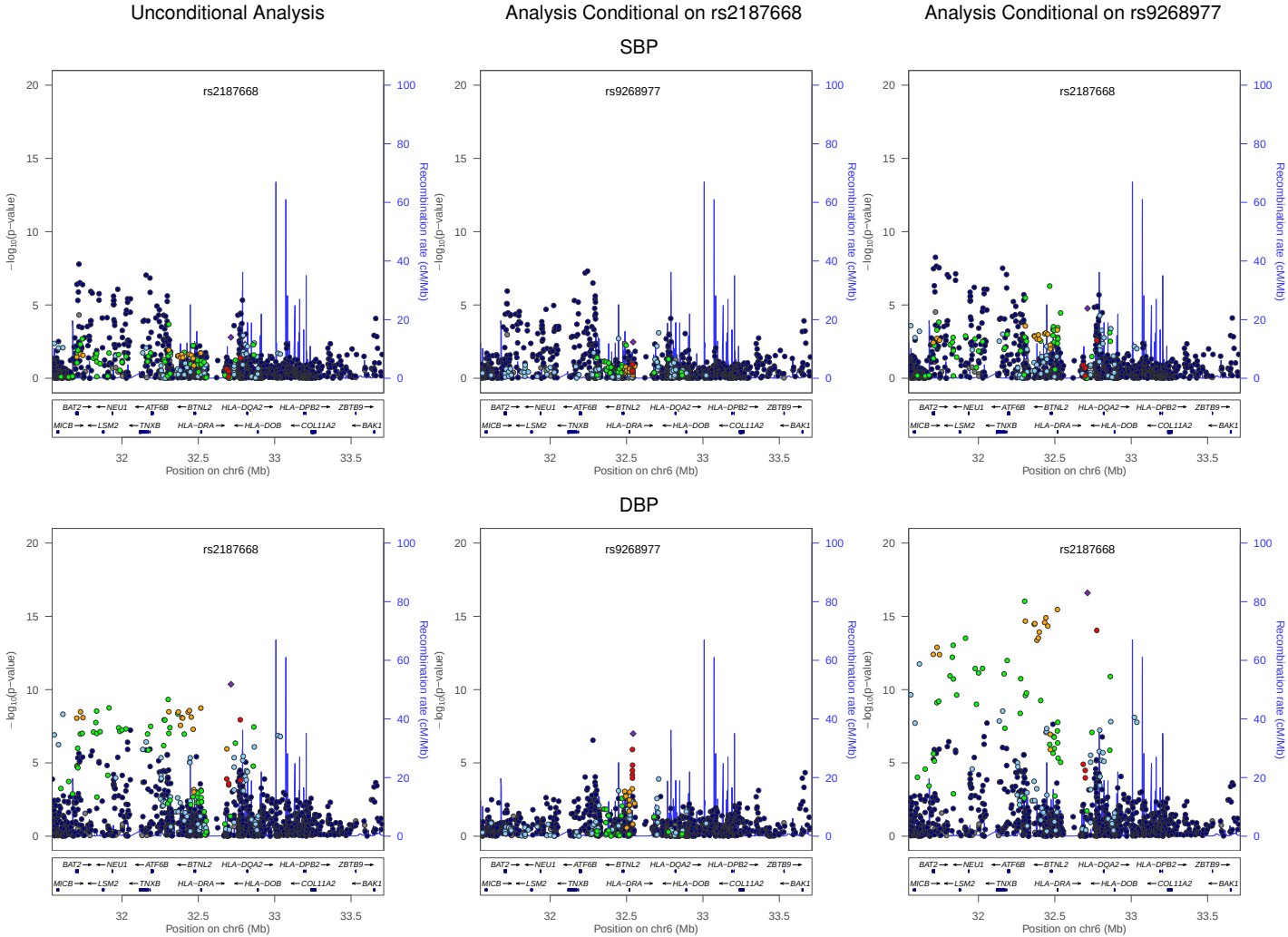
NPR3-C5orf23



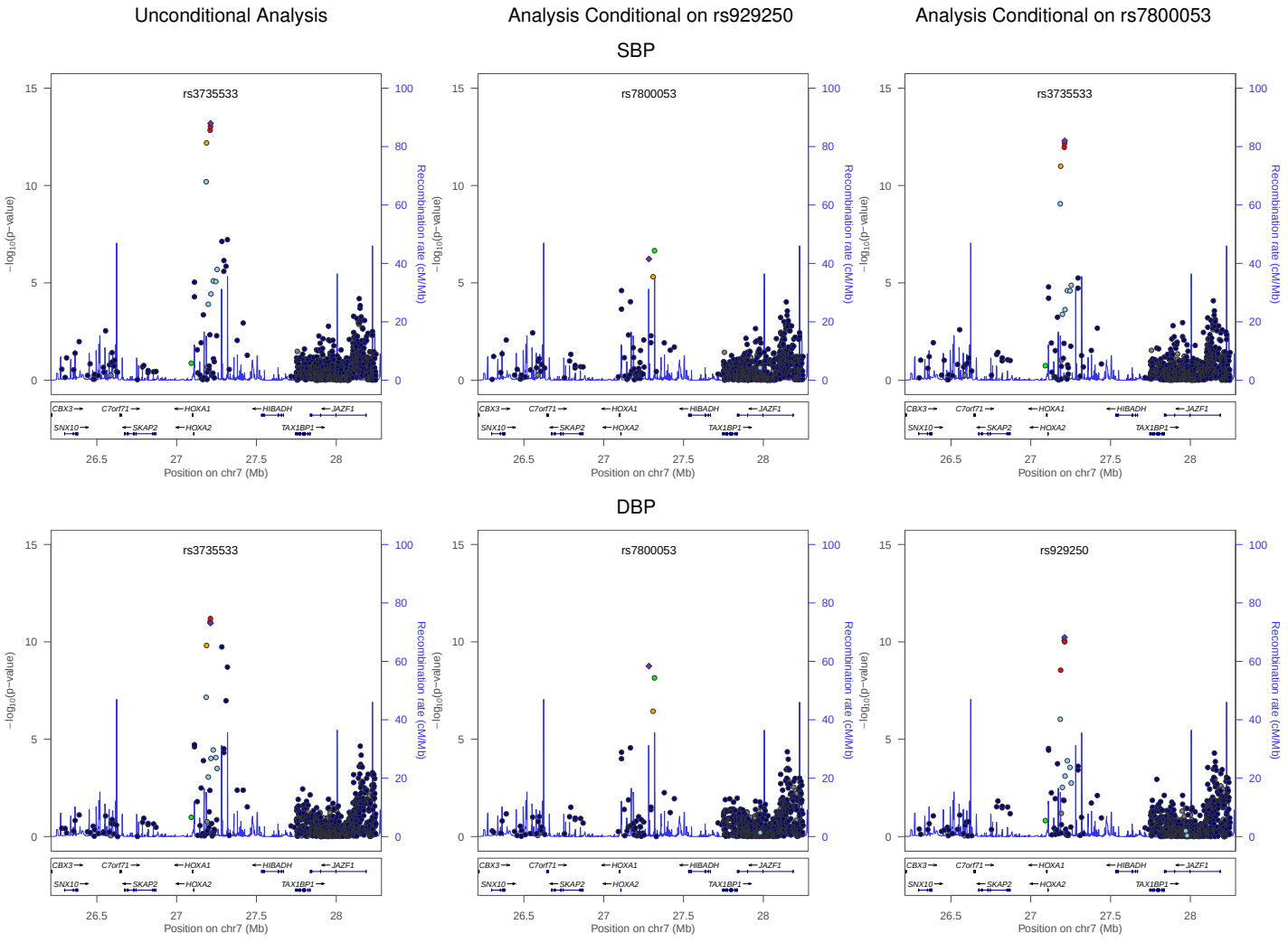
HFE


Unconditional Analysis
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

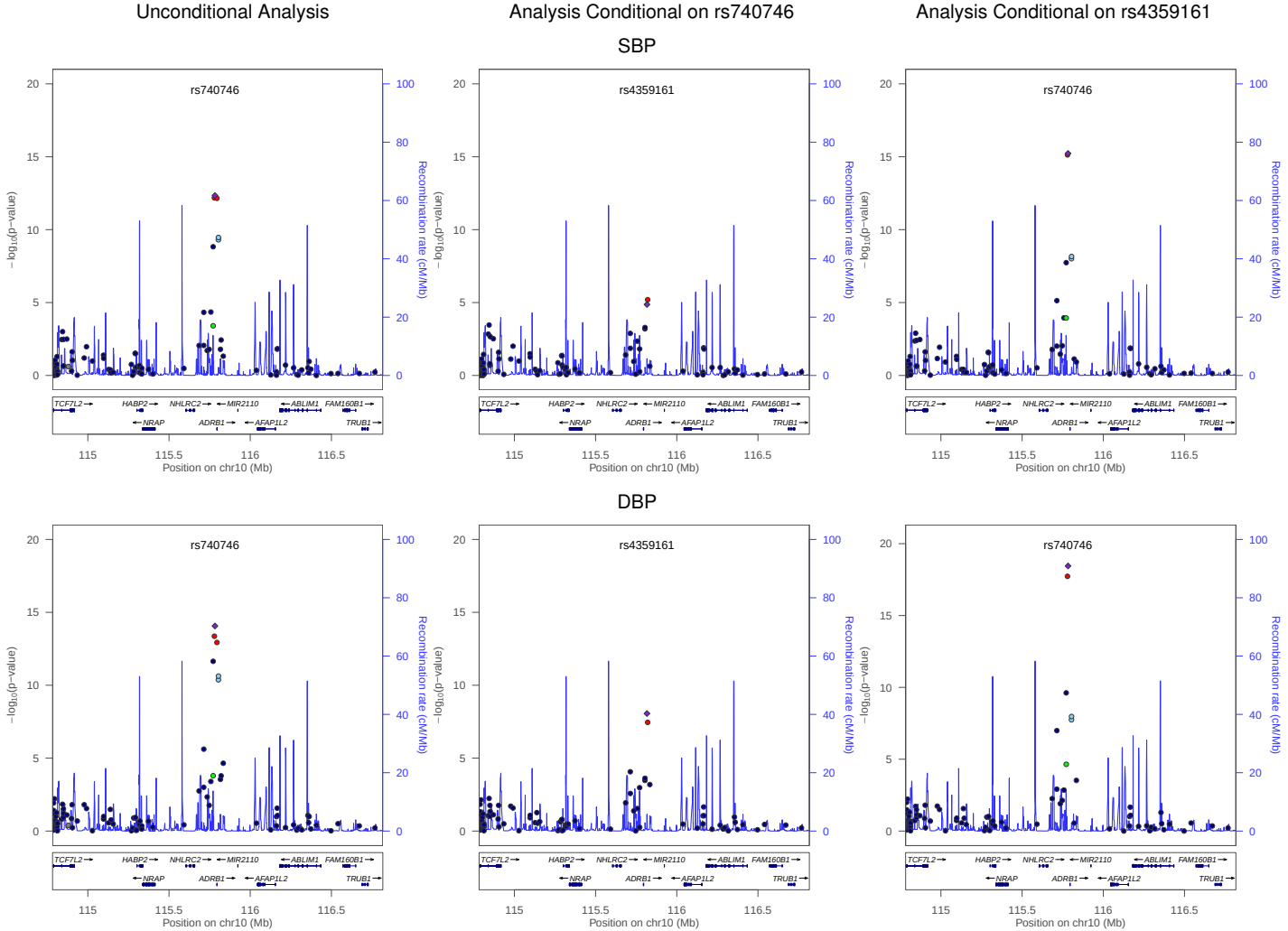
BAT2-BAT5


Unconditional Analysis
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


Unconditional Analysis
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)

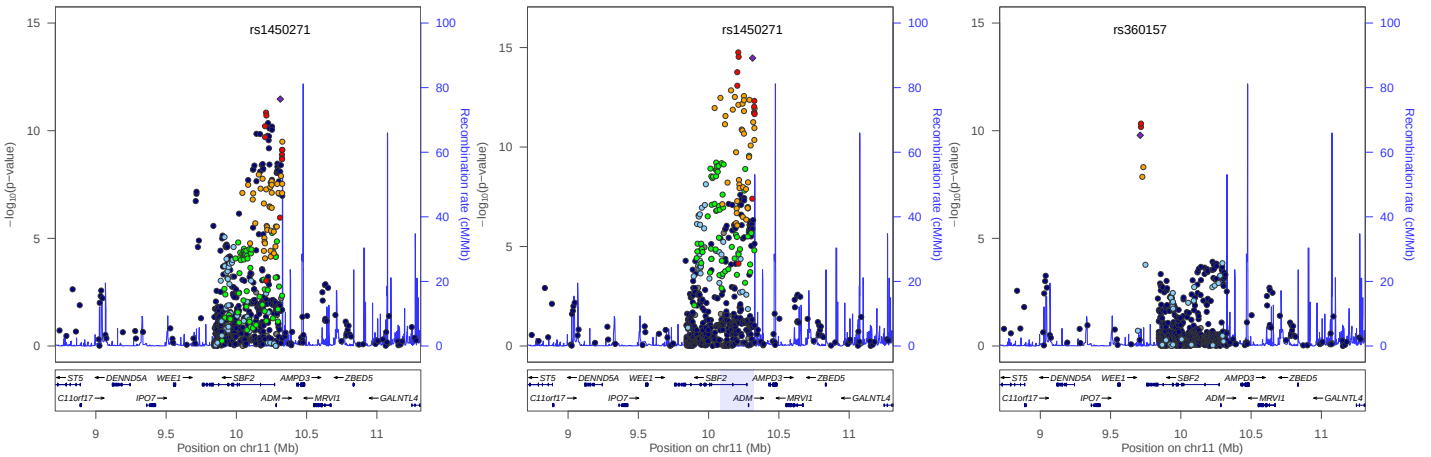
ADRB1


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)

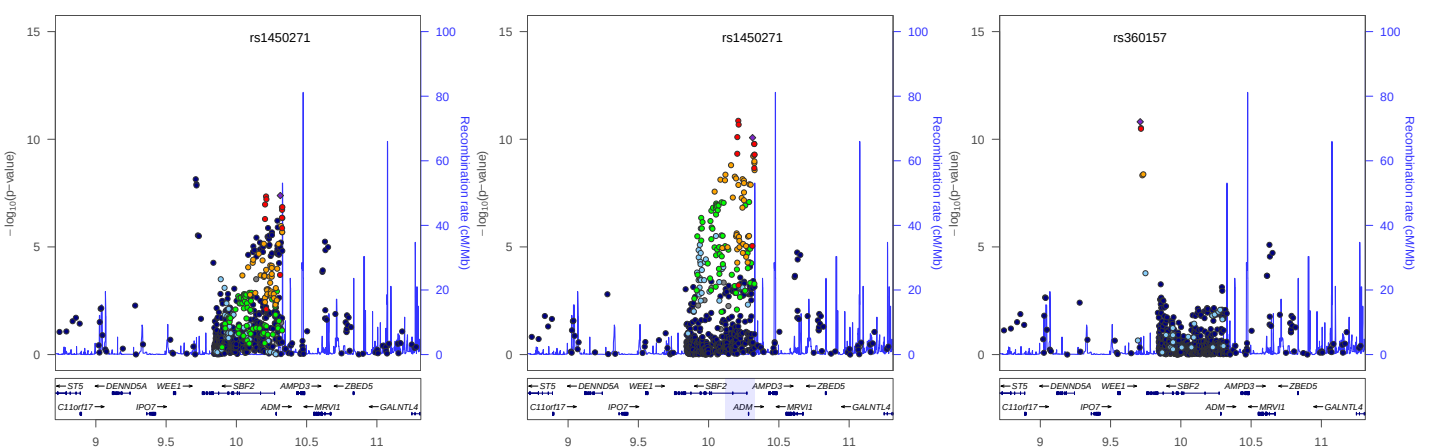
ADM

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

SBP

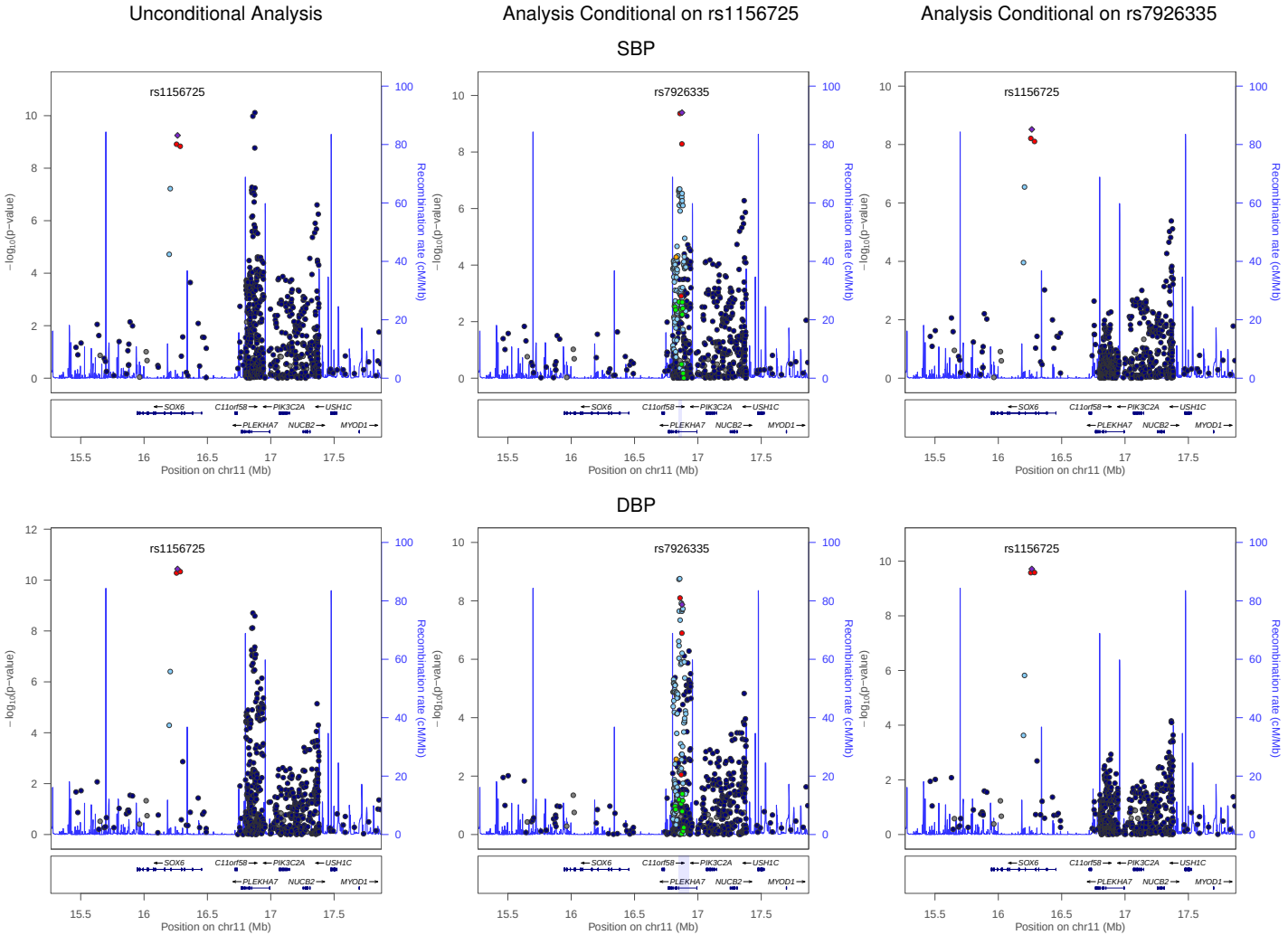


DBP

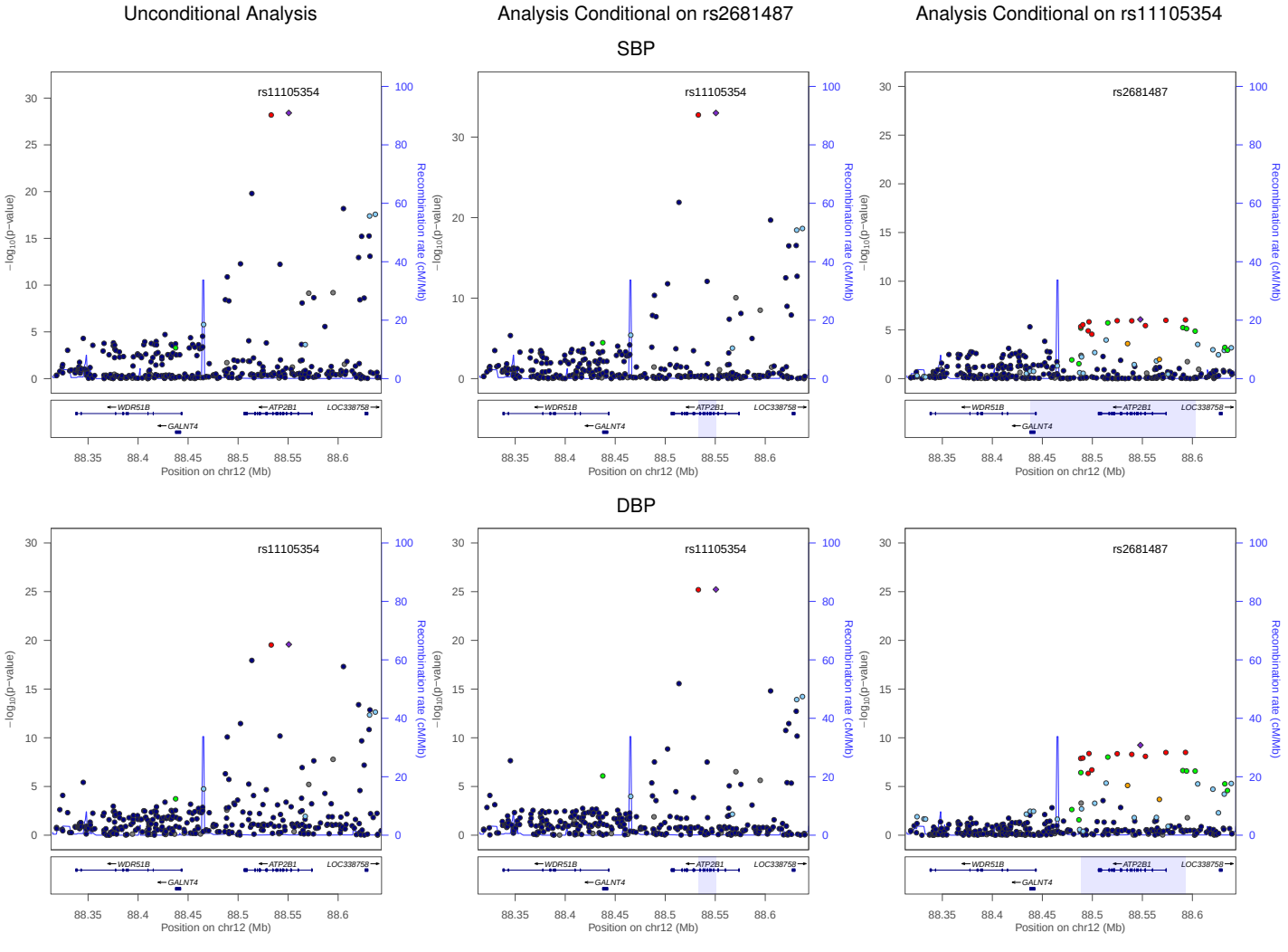


PLEKHA7

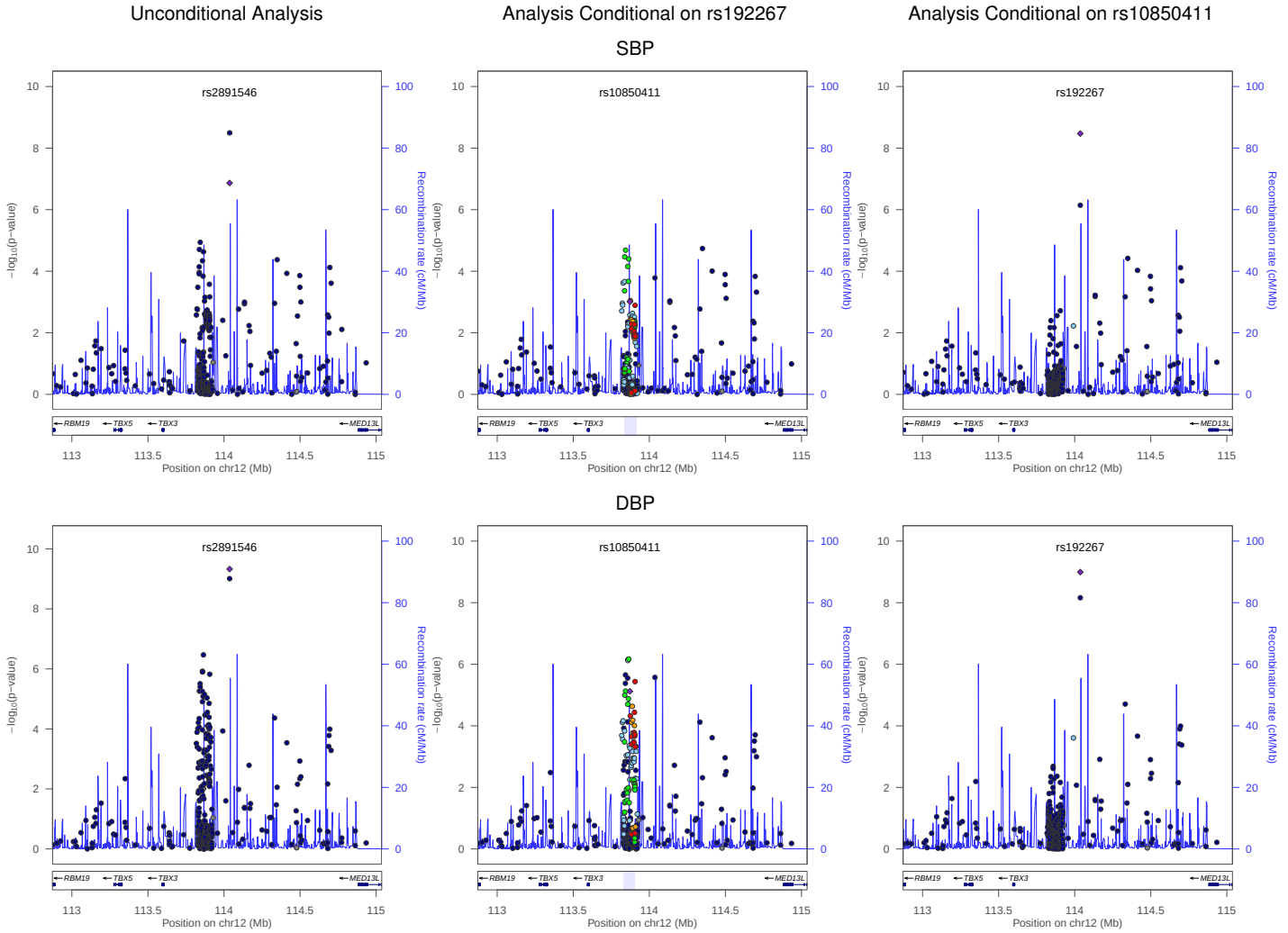
PLEKHA7

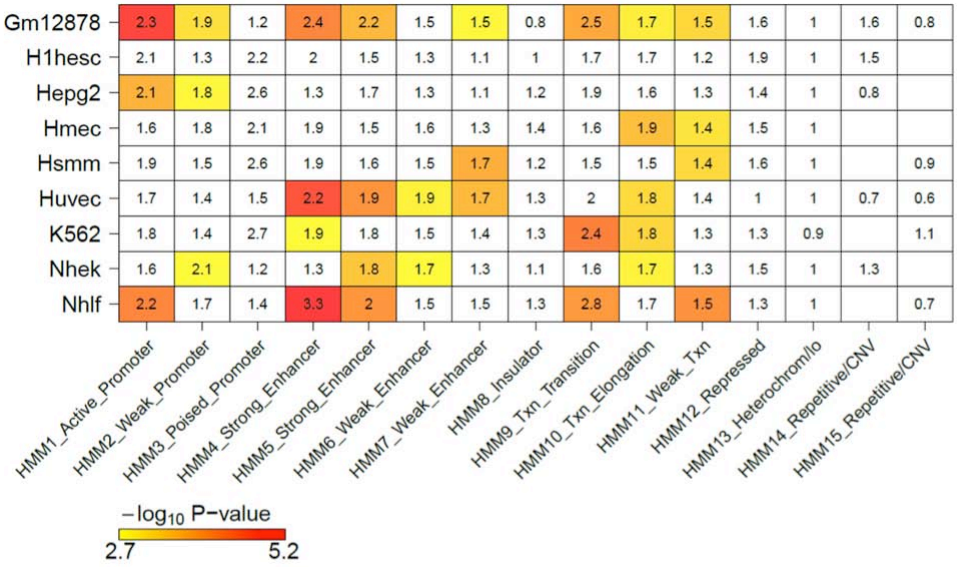

Unconditional Analysis
Analysis Conditional on rs1156725
Analysis Conditional on rs7926335
SBP
DBP
rs1156725
rs7926335
−log10(p−value)
Recombination rate (cM/Mb)
SOX6
C11orf58
PIK3C2A
USH1C
PLEKHA7
NUCB2
MYOD1
Position on chr11 (Mb)

ATP2B1

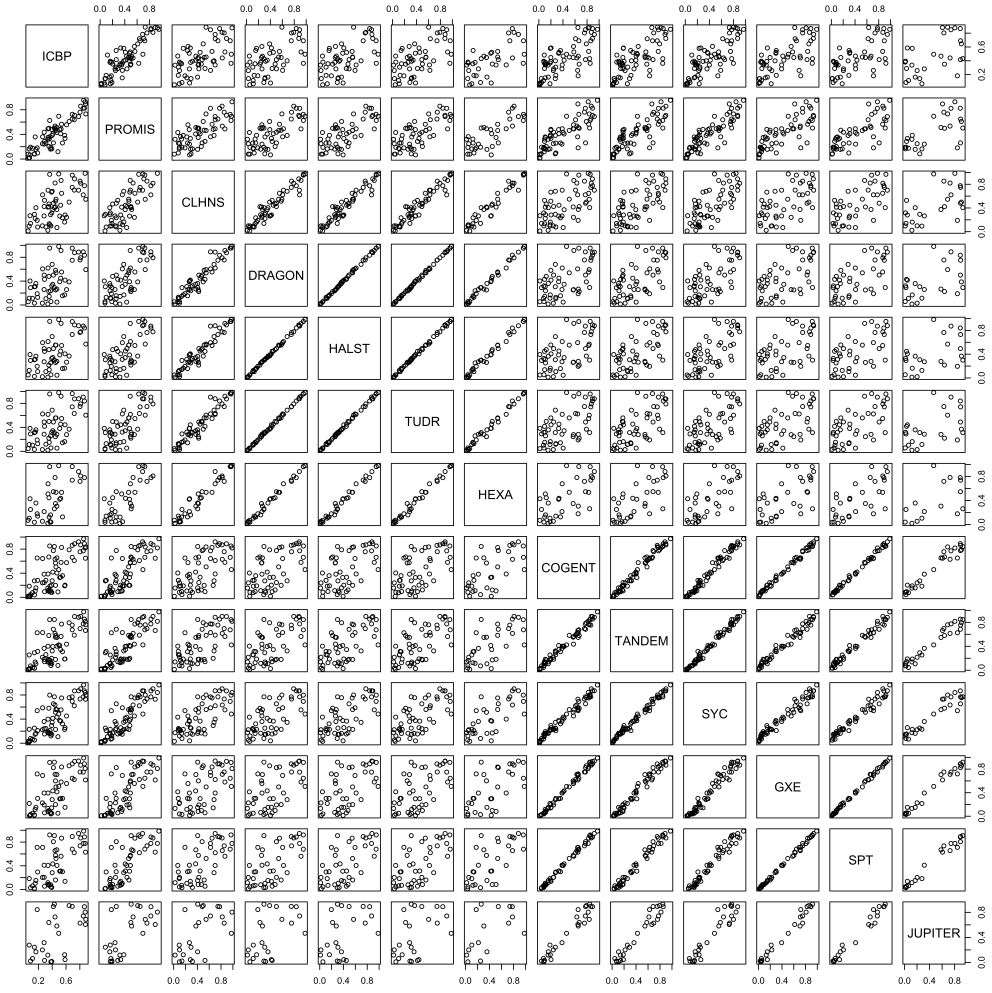

Unconditional Analysis
Analysis Conditional on rs2681487
Analysis Conditional on rs11105354
SBP
DBP
rs11105354
rs2681487
−log10(p−value)
Recombination rate (cM/Mb)
WDR51B
ATP2B1
LOC338758
GALNT4
88.35
88.4
88.45
88.5
88.55
88.6
Position on chr12 (Mb)

TBX5-TBX3

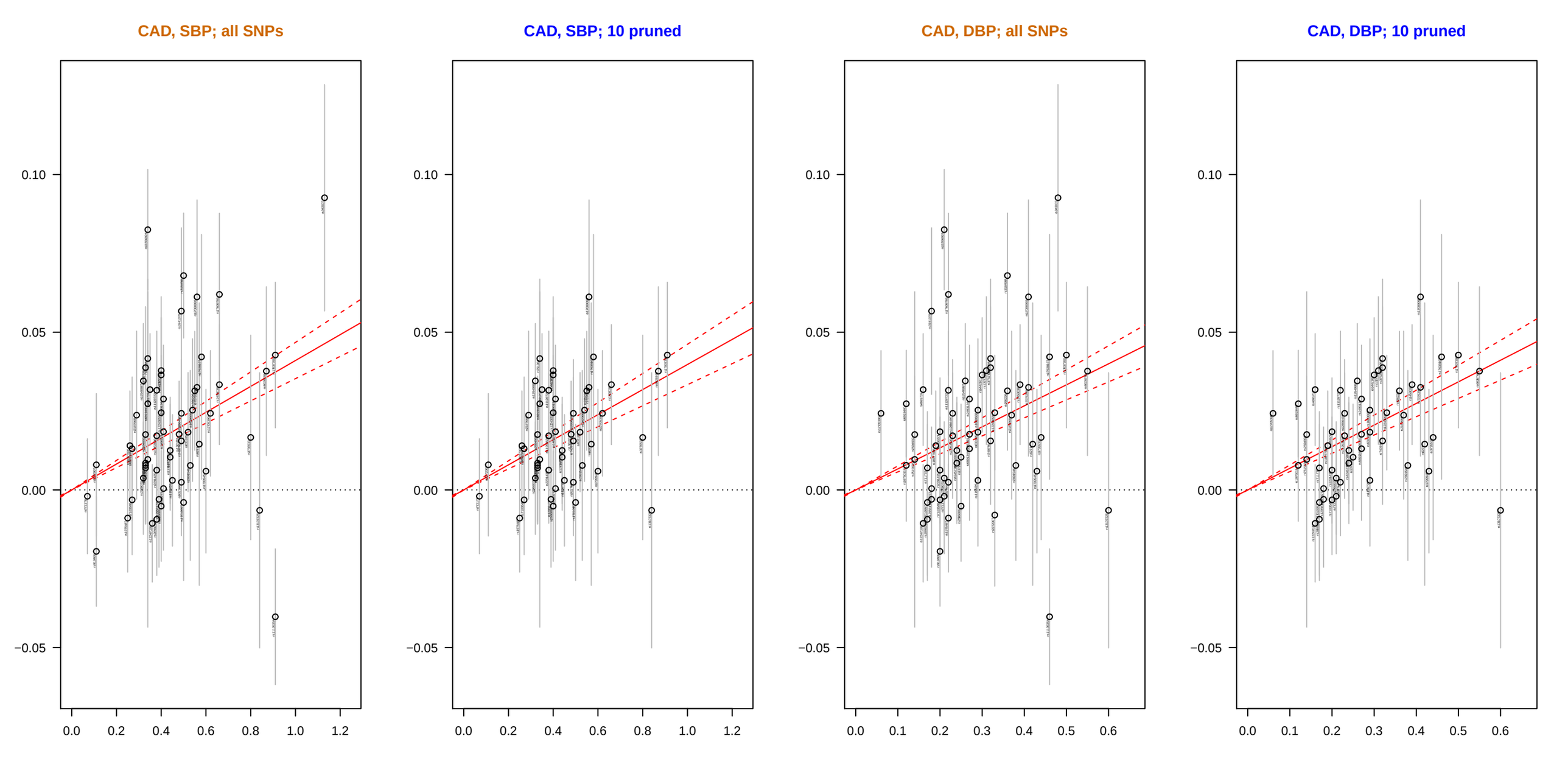

Unconditional Analysis
Analysis Conditional on rs192267
Analysis Conditional on rs10850411
SBP
DBP
rs2891546
rs10850411
rs192267
−log10(p-value)
Recombination rate (cM/Mb)
RBM19
TBX5
TBX3
MED13L
Position on chr12 (Mb)

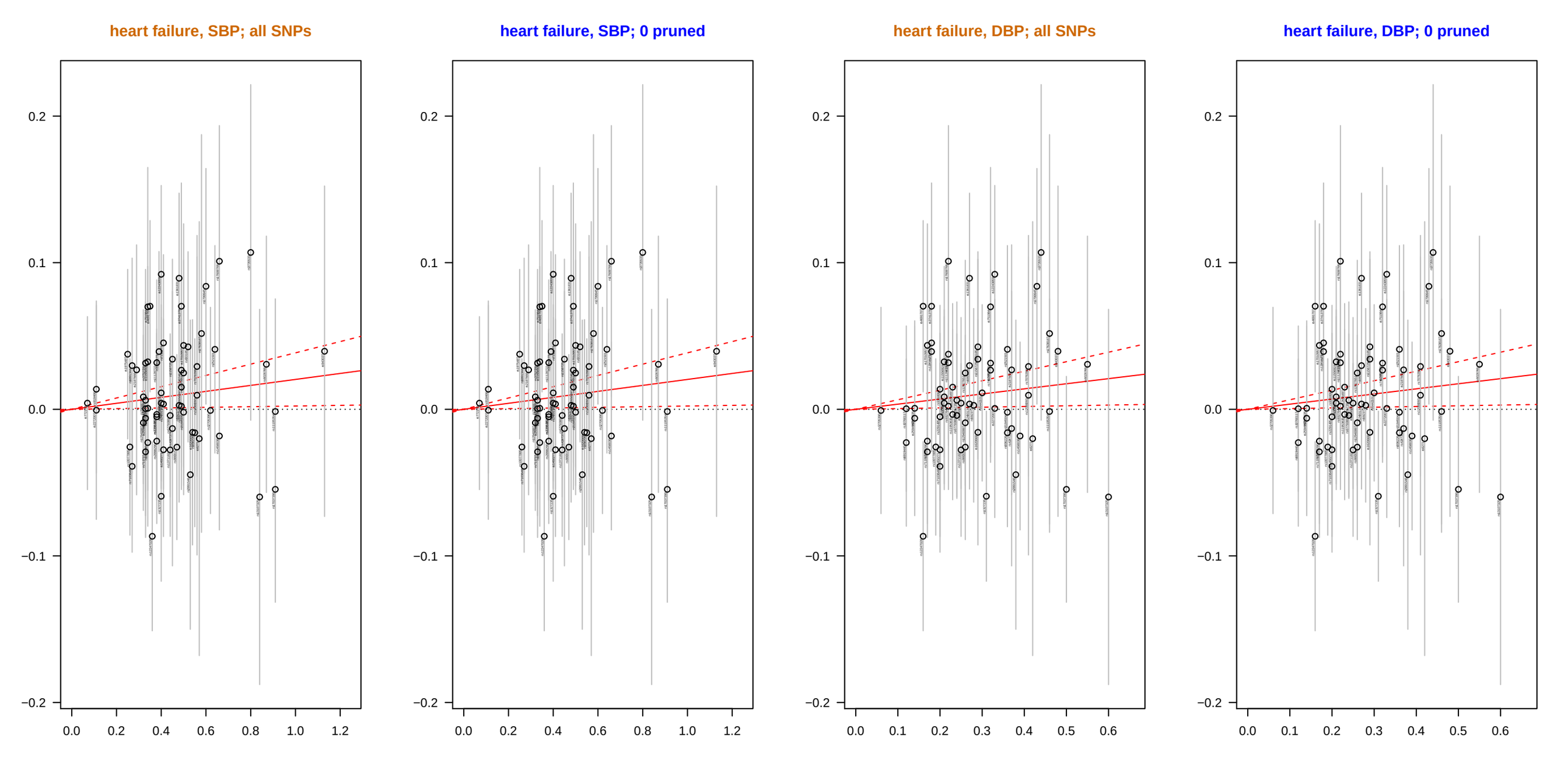


Supplementary Figure 8. Matrix of fold enrichment for BP SNPs in predicted chromatin states in nine human cell types. The boxes are colored by $-log_{10}P$ for enrichment. The white color indicates lack of significance after Bonferroni correction for 15 chromatin states and 9 tissues (see **Supplementary 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).

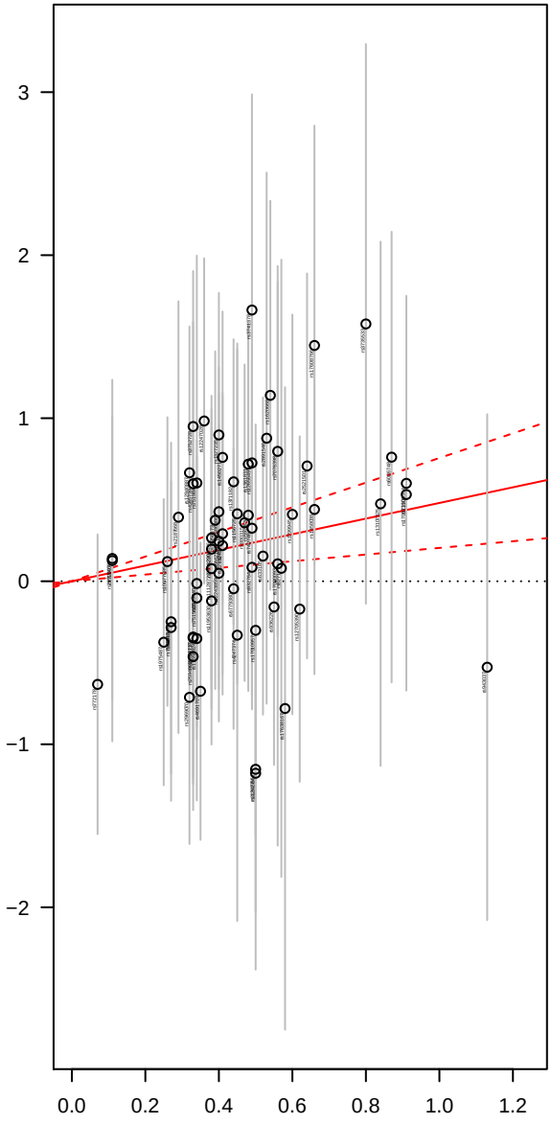


Supplementary Figure 9. Effect allele frequency plots for all samples of non-European ancestry. The effect allele frequency of each study is plotted against the effect allele frequency of every other study for all 66 index SNPs. The study names are indicated in the middle diagonal.

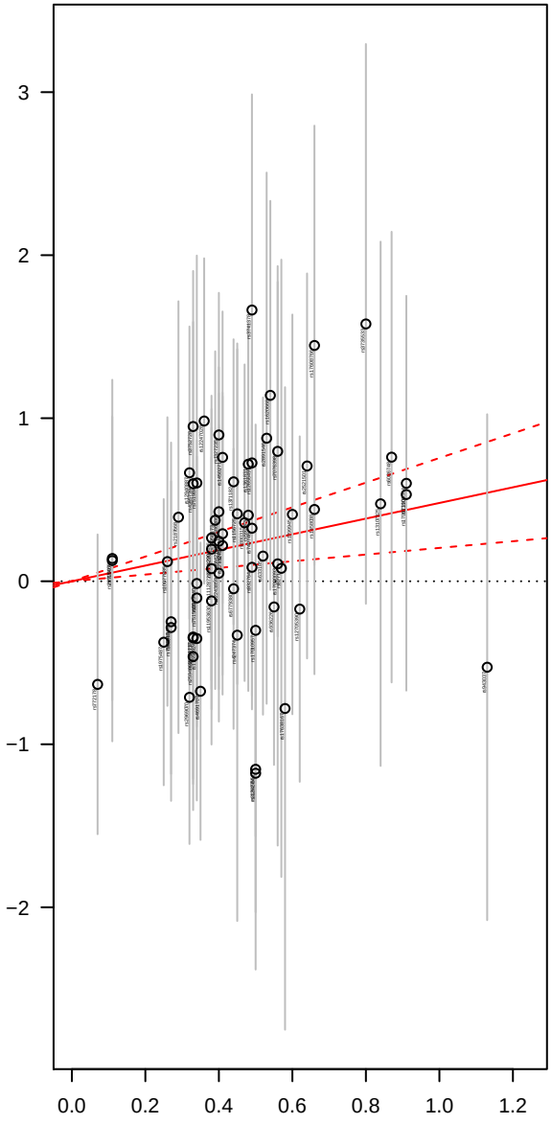

CAD, SBP; all SNPs
CAD, SBP; 10 pruned
CAD, DBP; all SNPs
CAD, DBP; 10 pruned
0.10
0.05
0.00
−0.05
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5


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

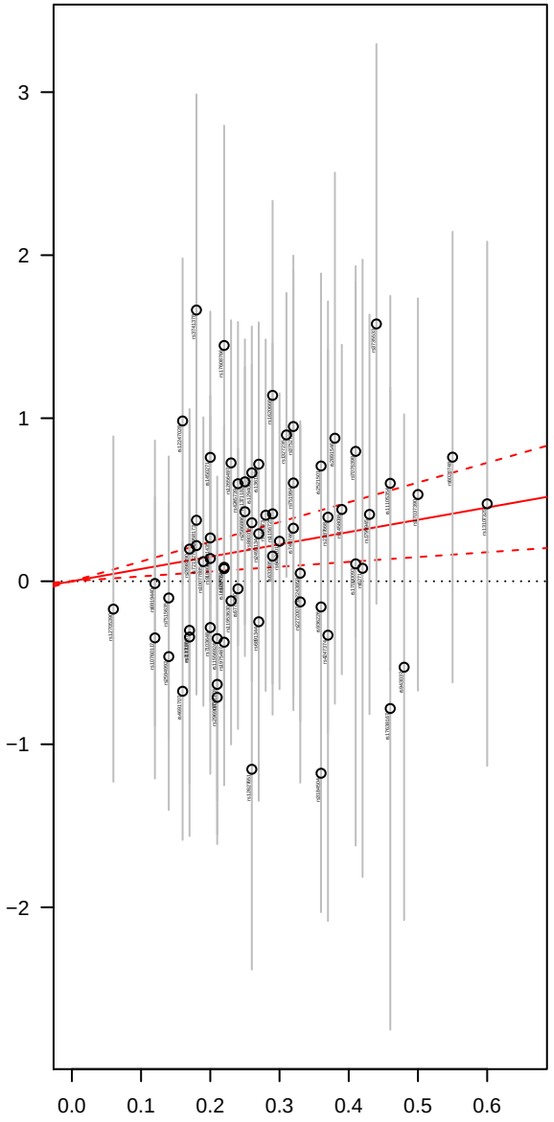
LV mass, SBP; all SNPs



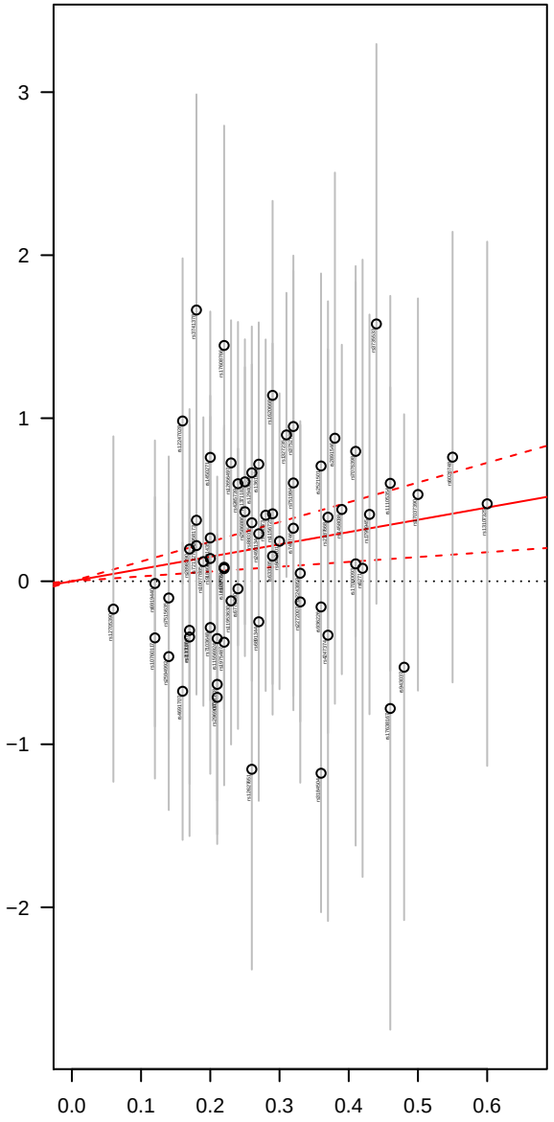
LV mass, SBP; 0 pruned

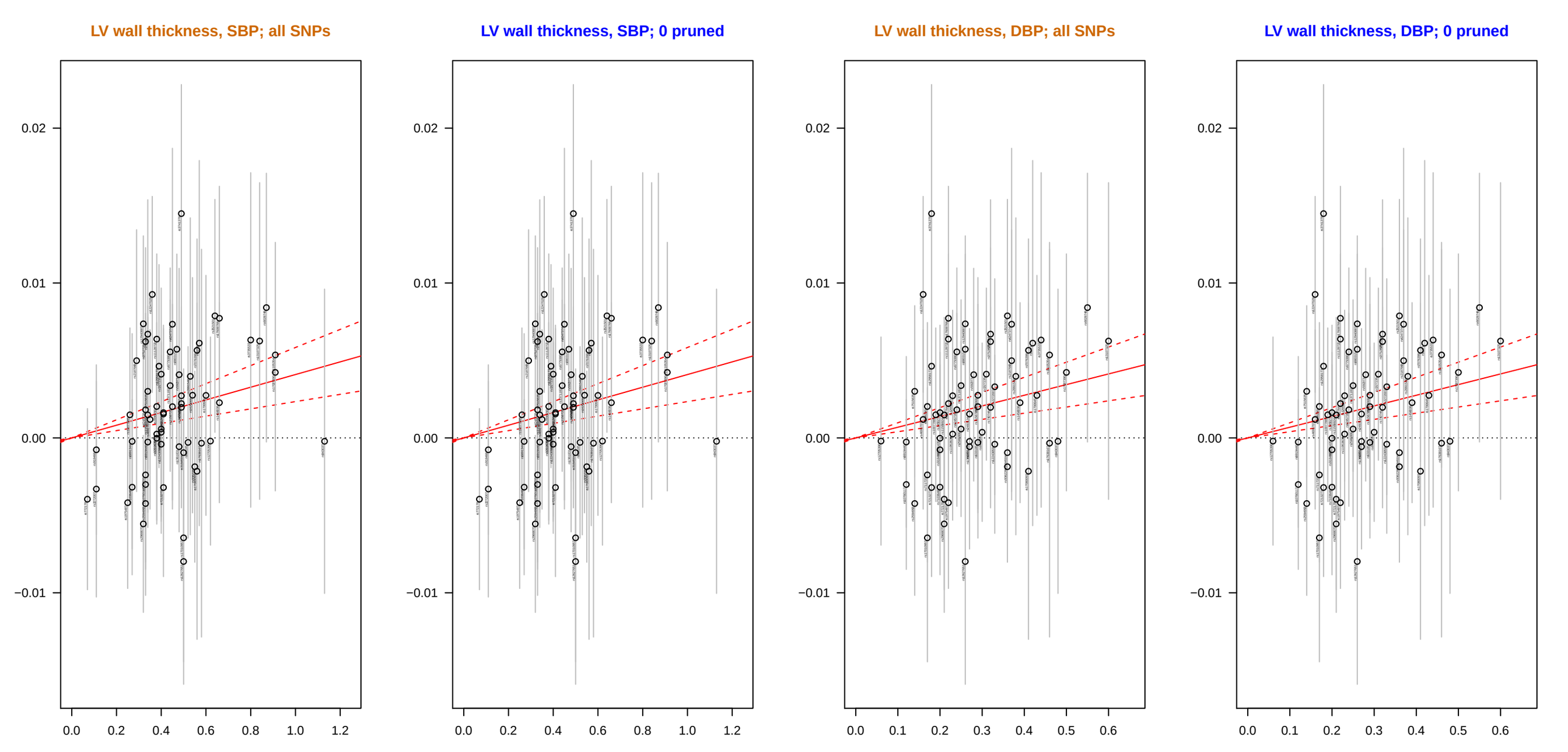


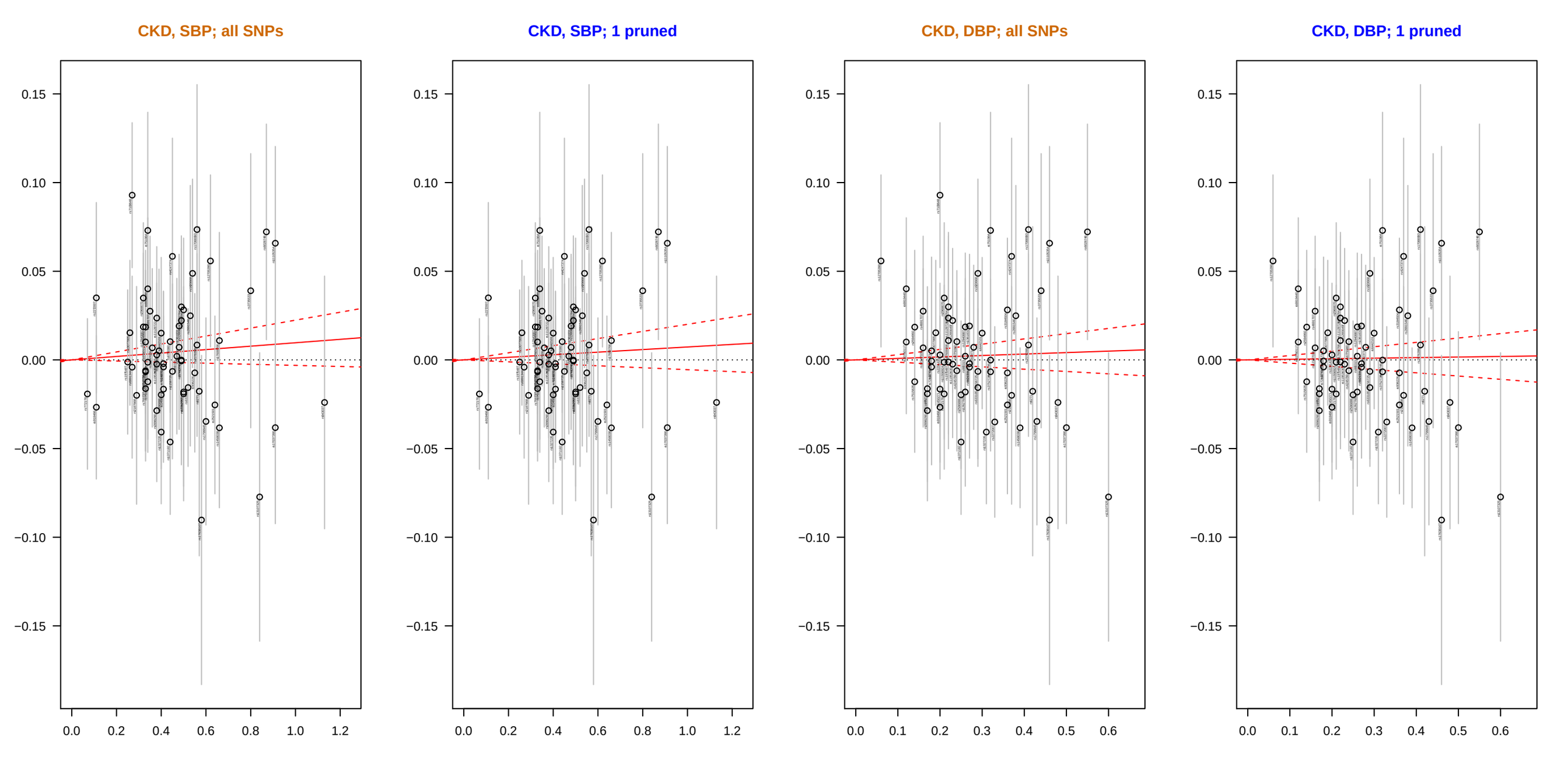
LV mass, DBP; all SNPs

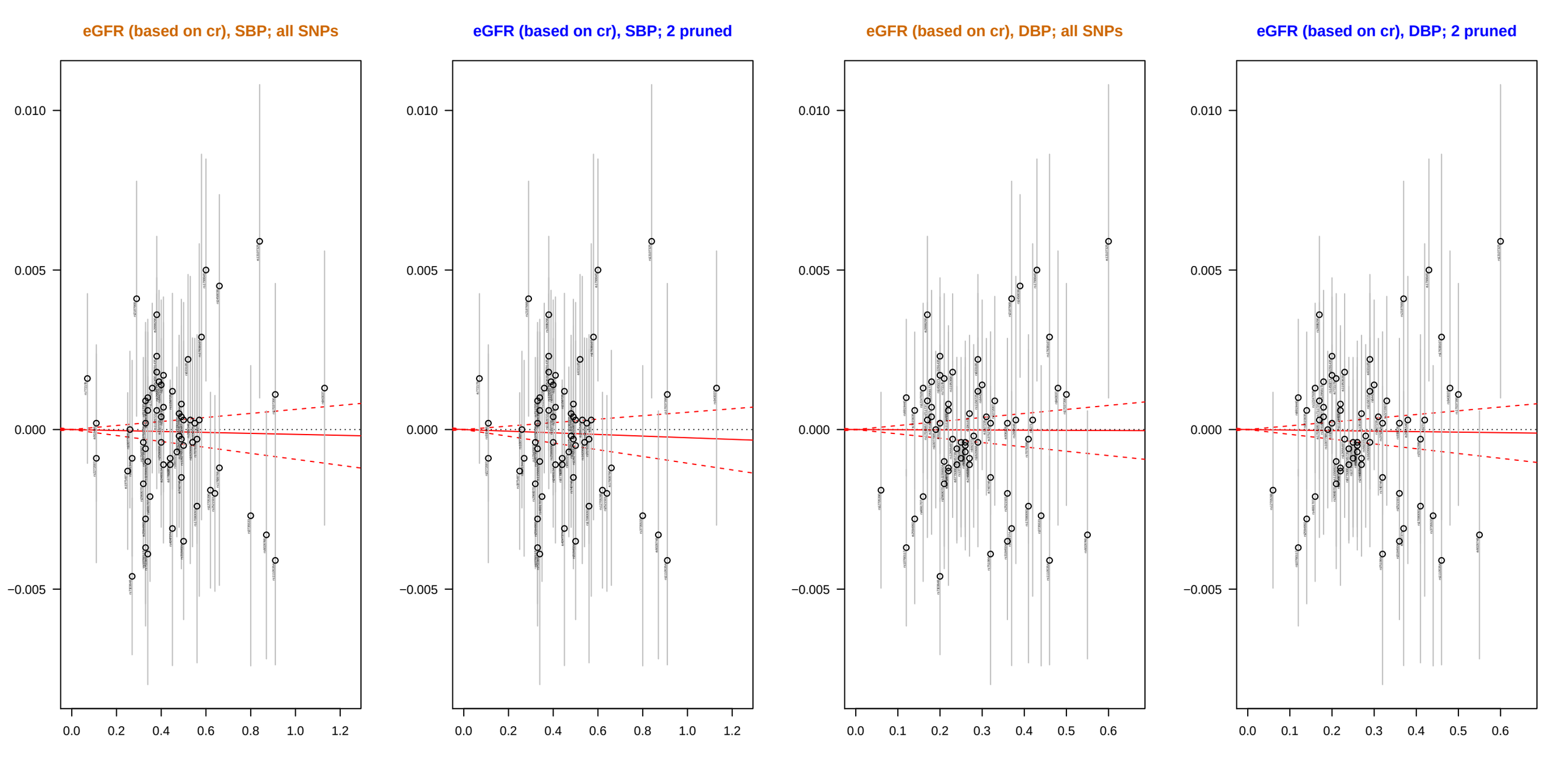


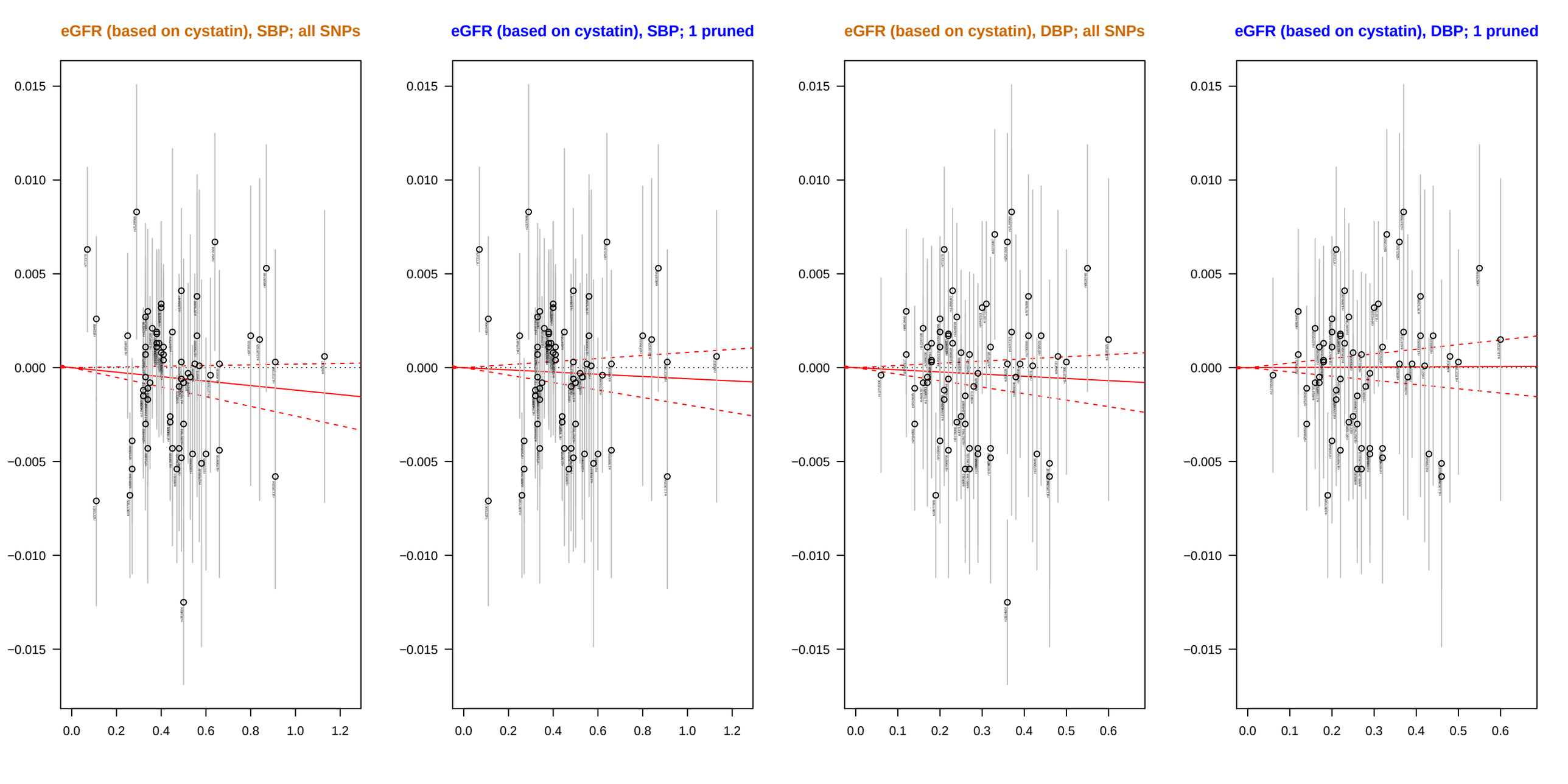
LV mass, DBP; 0 pruned

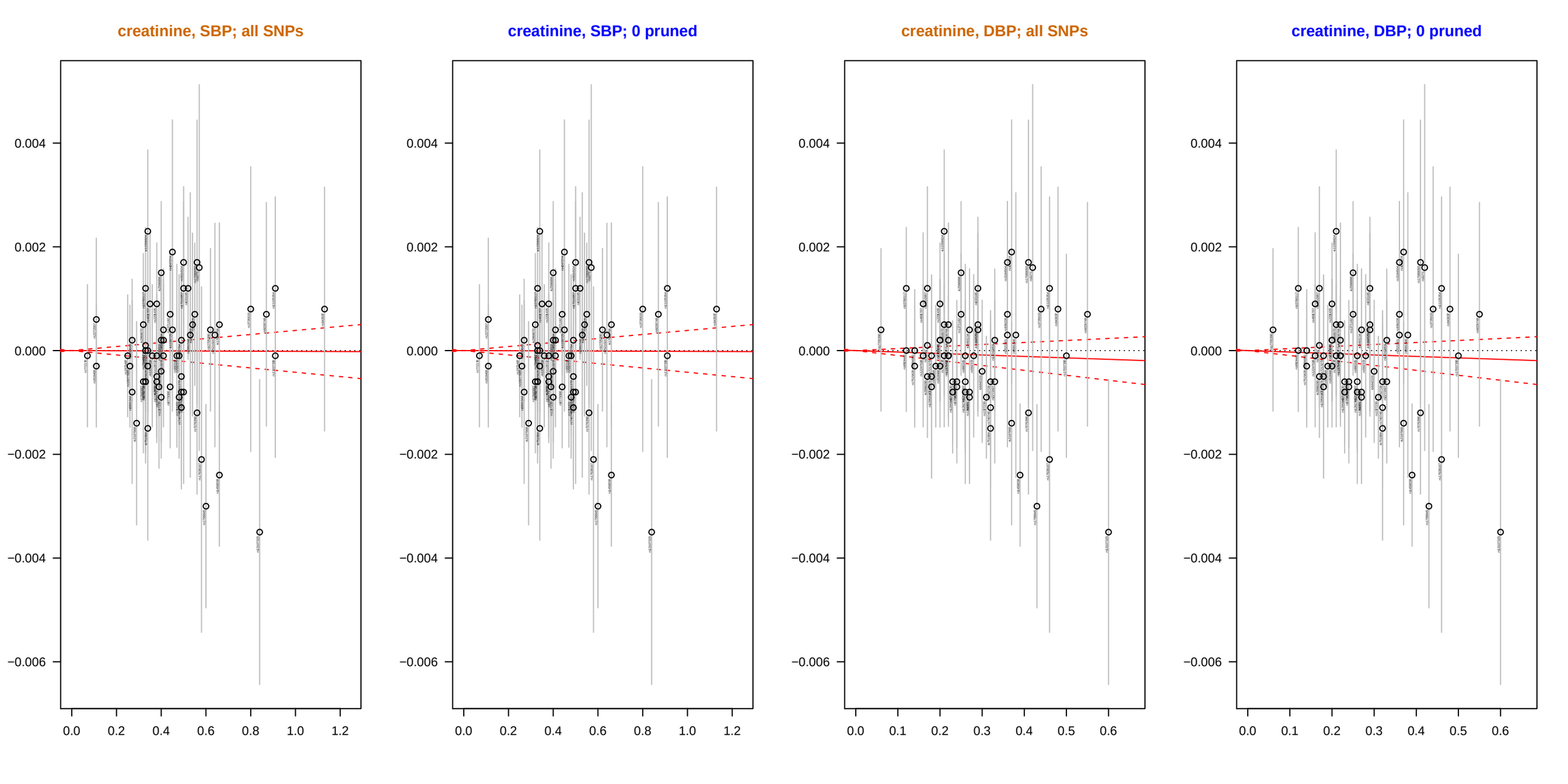


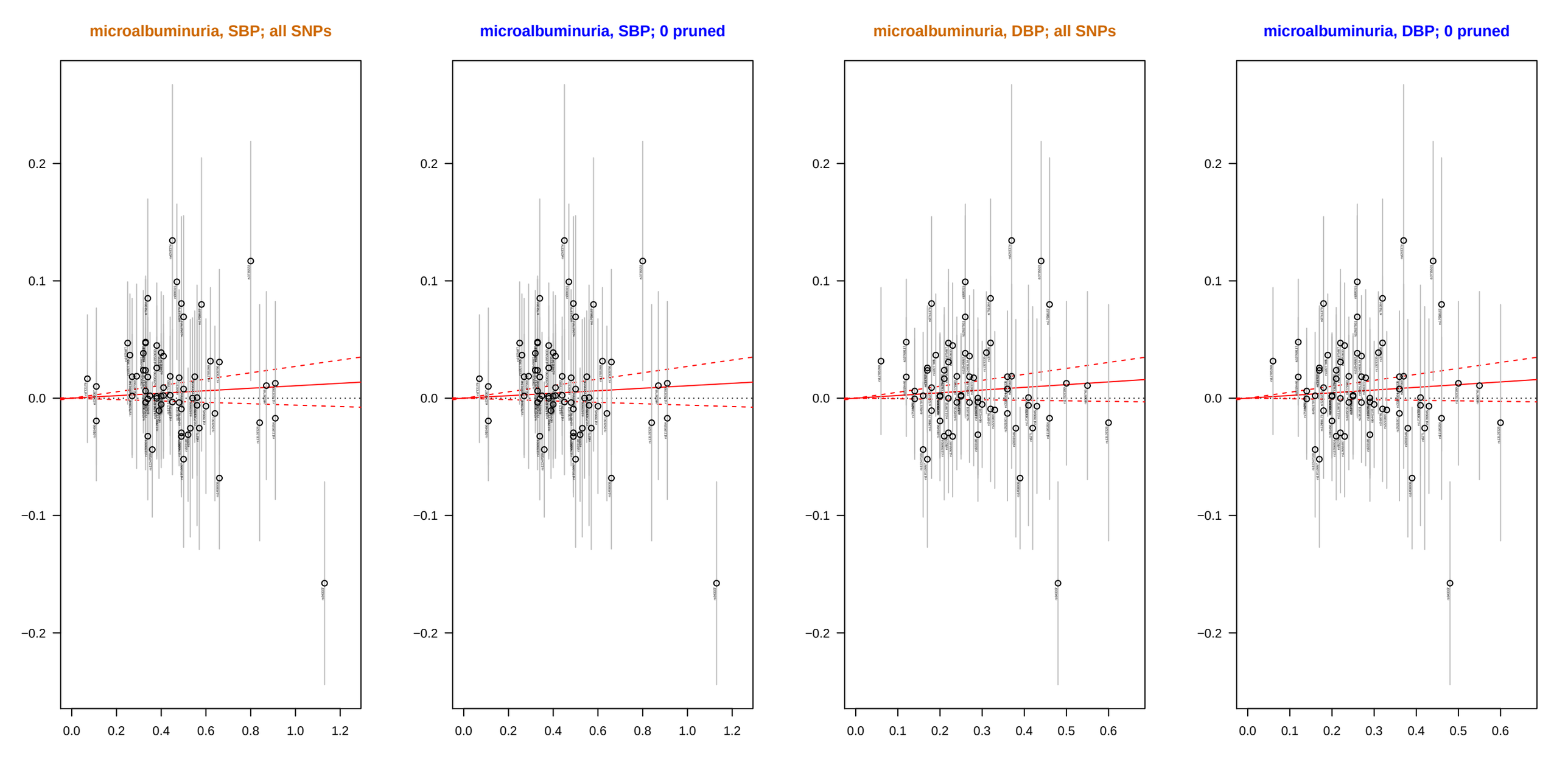

LV wall thickness, SBP; all SNPs
LV wall thickness, SBP; 0 pruned
LV wall thickness, DBP; all SNPs
LV wall thickness, DBP; 0 pruned
0.02
0.01
0.00
−0.01
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

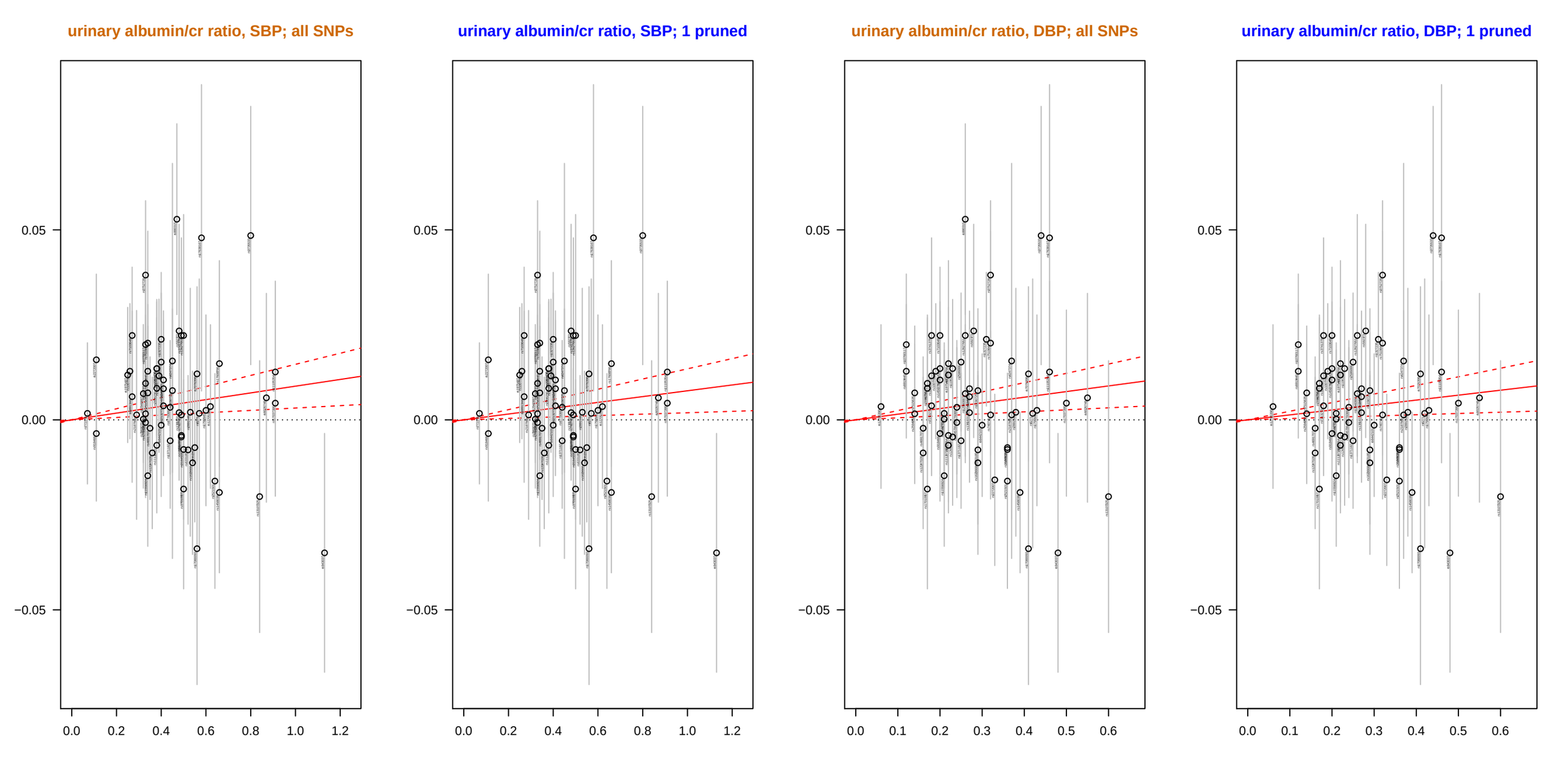

CKD, SBP; all SNPs
CKD, SBP; 1 pruned
CKD, DBP; all SNPs
CKD, DBP; 1 pruned
0.15
0.10
0.05
0.00
−0.05
−0.10
−0.15
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

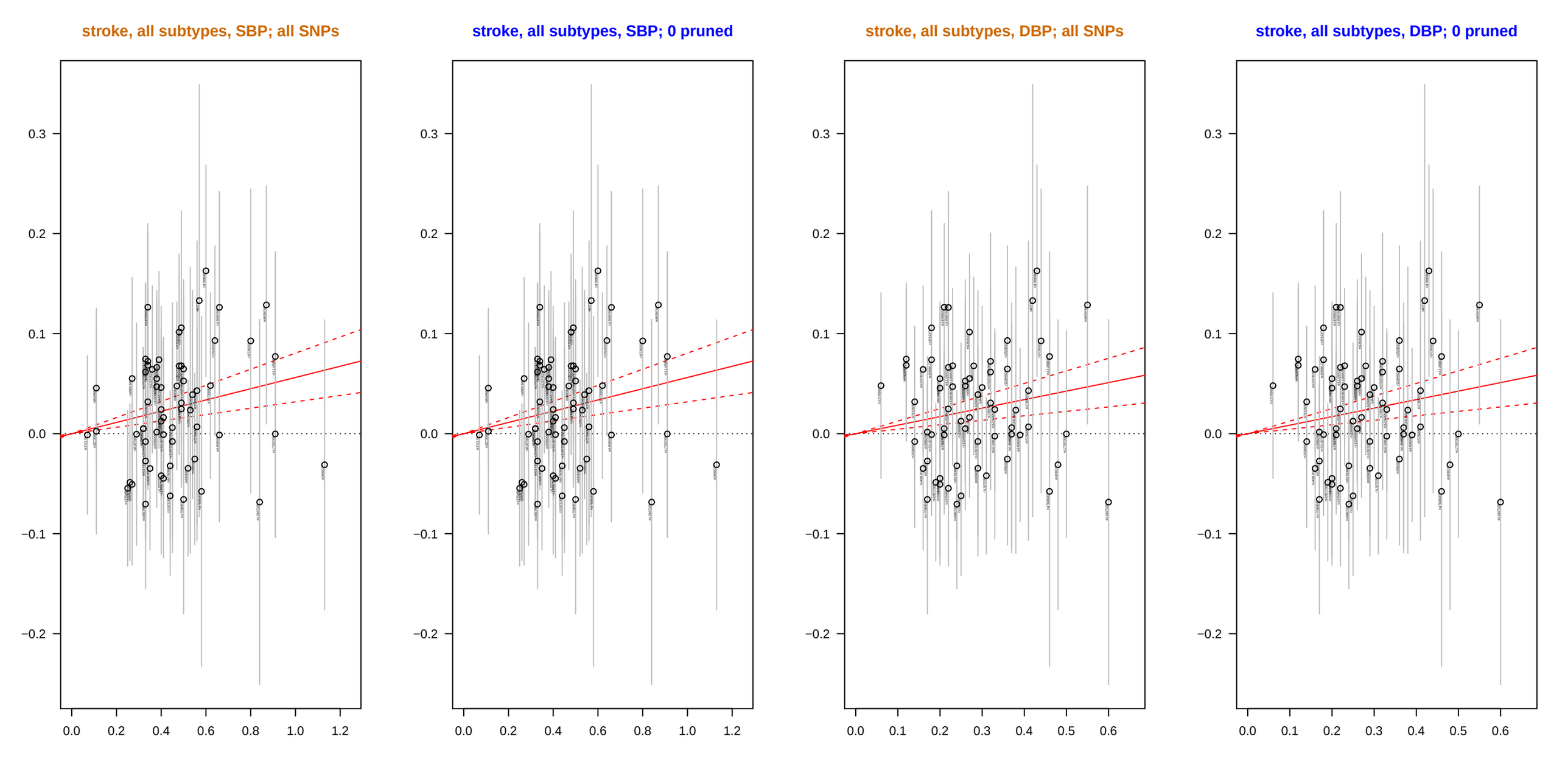

eGFR (based on cr), SBP; all SNPs
eGFR (based on cr), SBP; 2 pruned
eGFR (based on cr), DBP; all SNPs
eGFR (based on cr), DBP; 2 pruned
0.010
0.005
0.000
−0.005
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.8
1.0
1.2

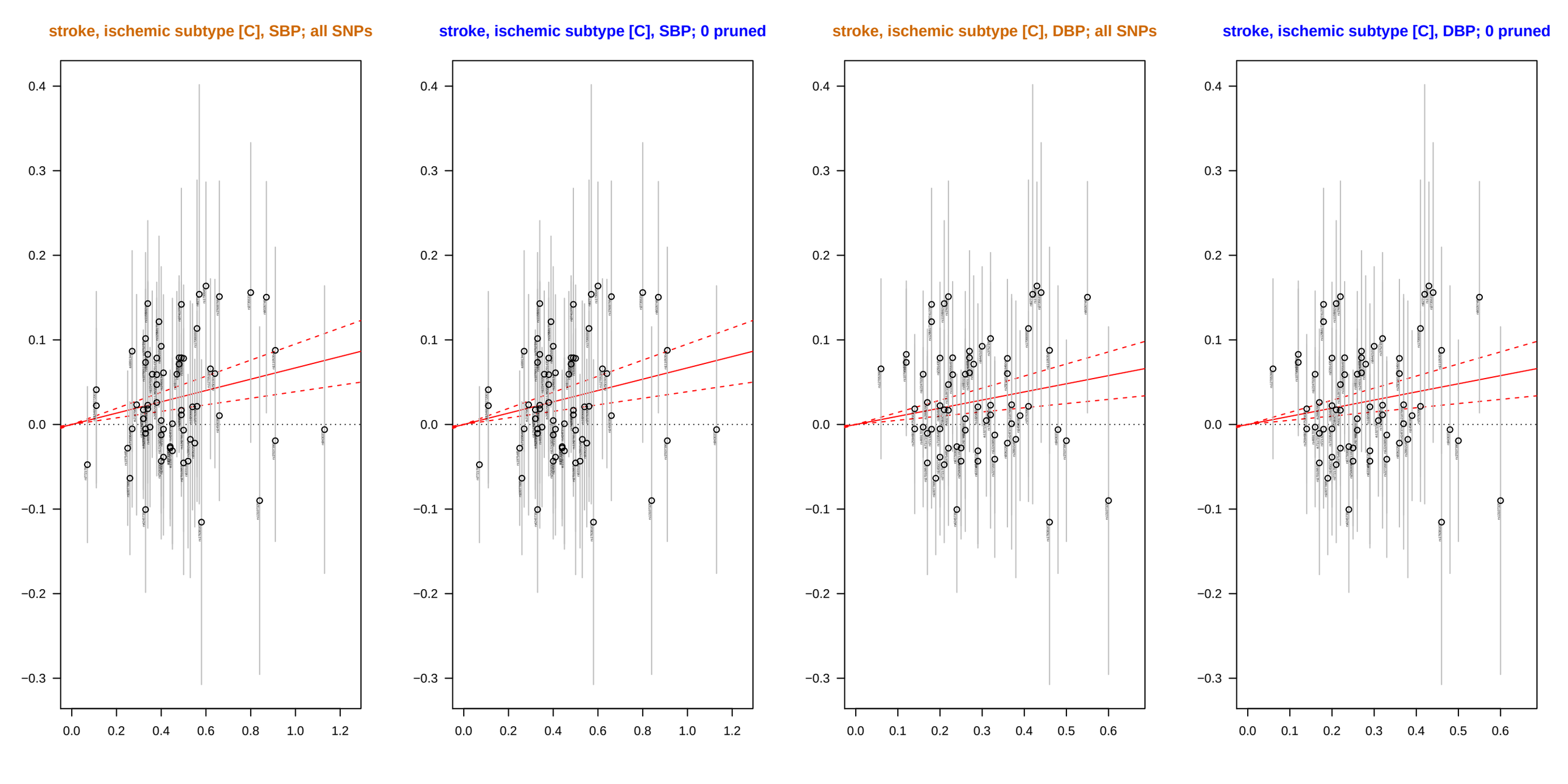

eGFR (based on cystatin), SBP; all SNPs
eGFR (based on cystatin), SBP; 1 pruned
eGFR (based on cystatin), DBP; all SNPs
eGFR (based on cystatin), DBP; 1 pruned
0.015
0.010
0.005
0.000
−0.005
−0.010
−0.015
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.8
1.0
1.2

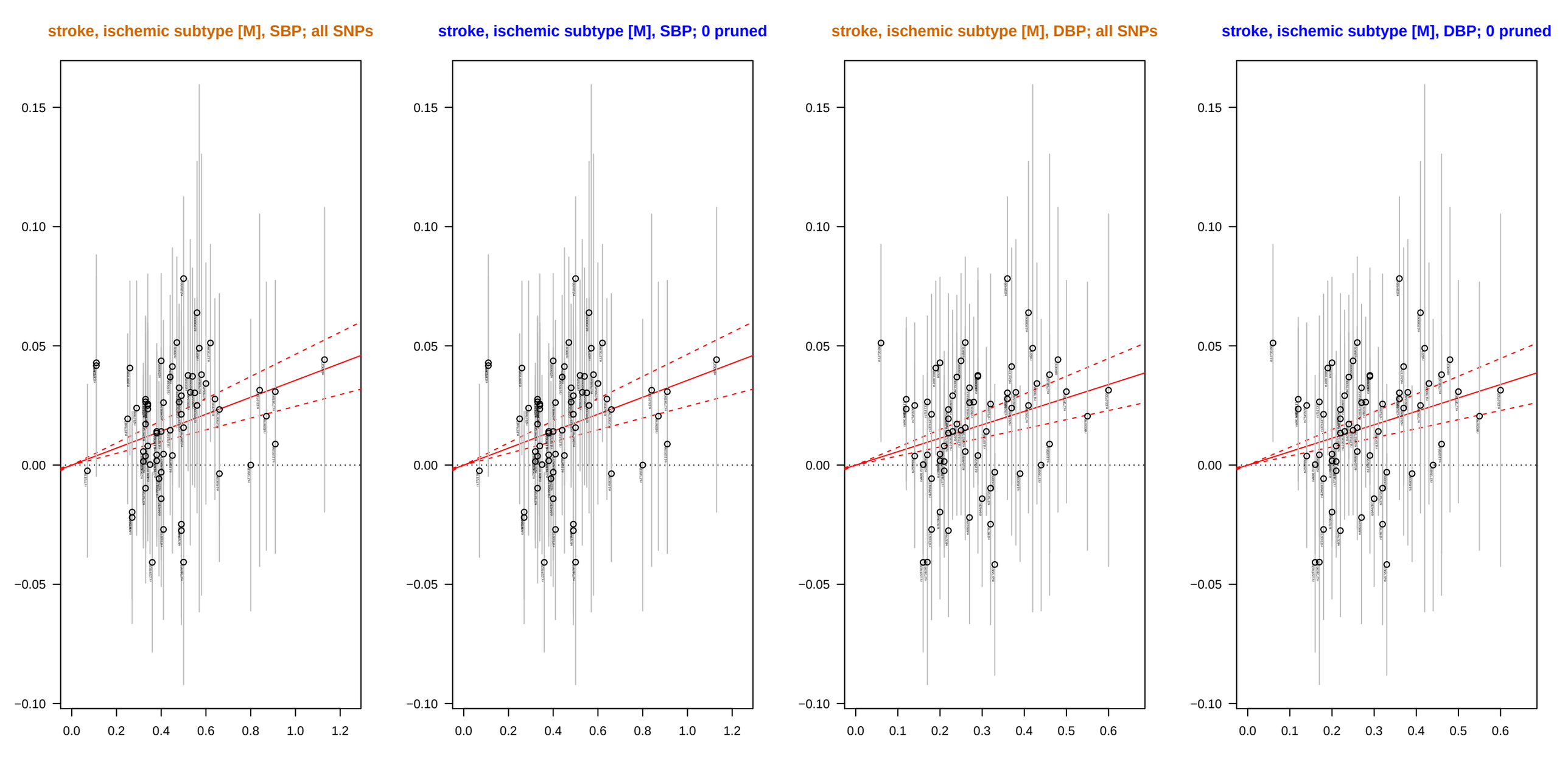

creatinine, SBP; all SNPs
creatinine, SBP; 0 pruned
creatinine, DBP; all SNPs
creatinine, DBP; 0 pruned
0.004
0.002
0.000
−0.002
−0.004
−0.006
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

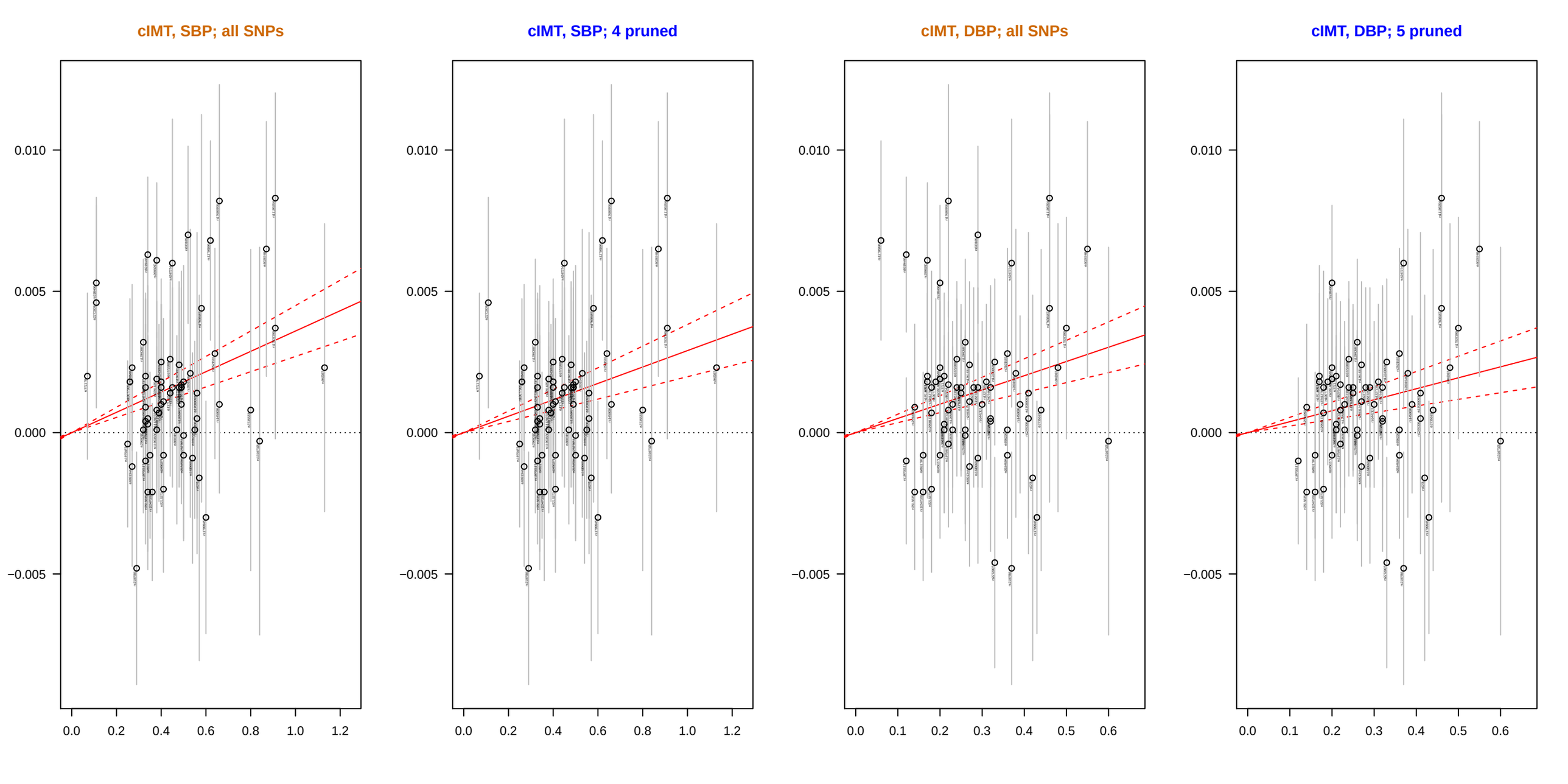

microalbuminuria, SBP; all SNPs
microalbuminuria, SBP; 0 pruned
microalbuminuria, DBP; all SNPs
microalbuminuria, DBP; 0 pruned
0.2
0.1
0.0
−0.1
−0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

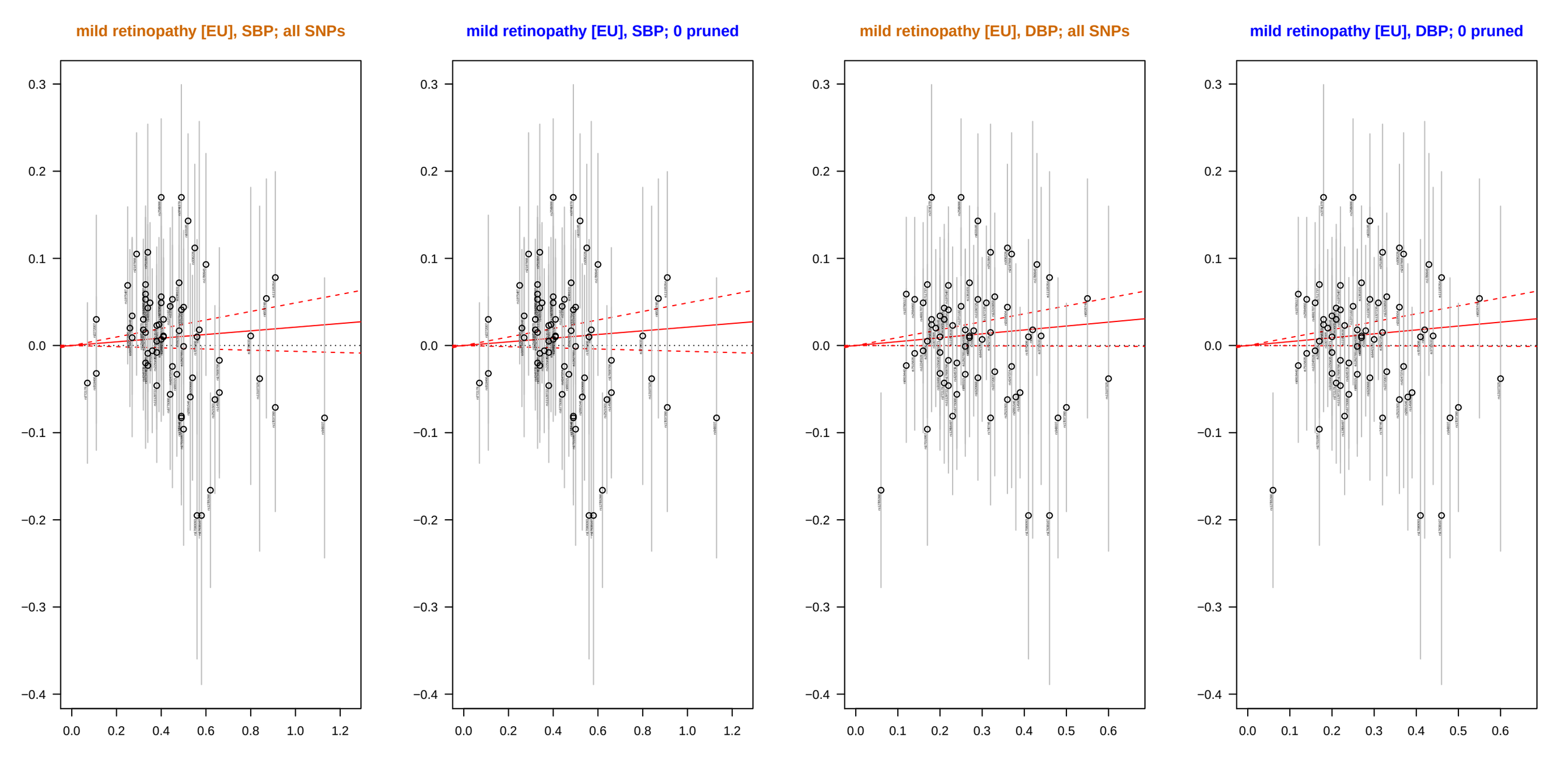

urinary albumin/cr ratio, SBP; all SNPs
urinary albumin/cr ratio, SBP; 1 pruned
urinary albumin/cr ratio, DBP; all SNPs
urinary albumin/cr ratio, DBP; 1 pruned
0.05
0.00
−0.05
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5


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

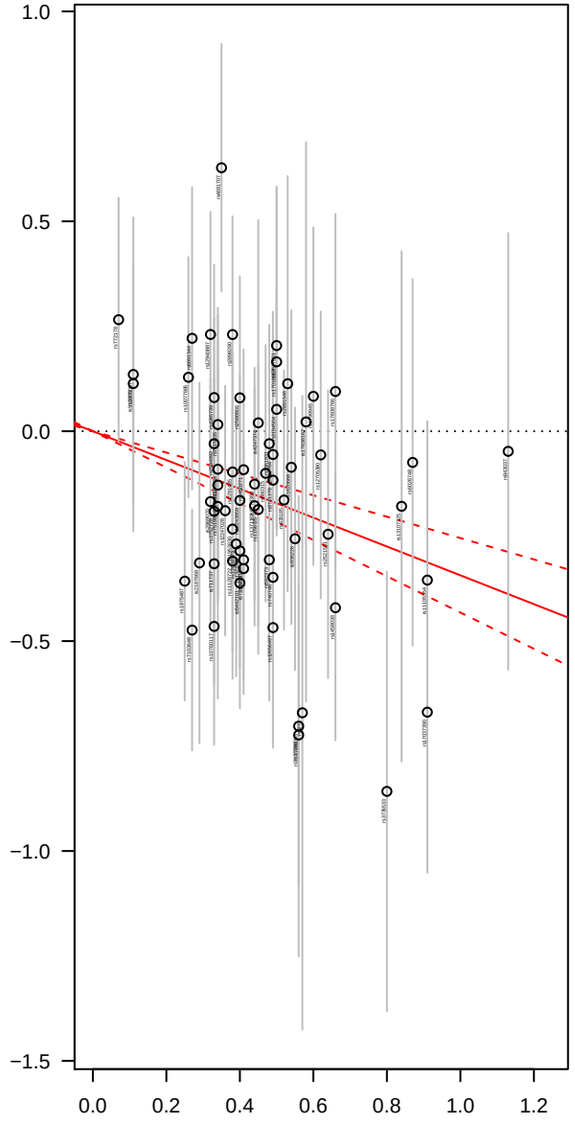

stroke, ischemic subtype [C], SBP; all SNPs
stroke, ischemic subtype [C], SBP; 0 pruned
stroke, ischemic subtype [C], DBP; all SNPs
stroke, ischemic subtype [C], DBP; 0 pruned


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

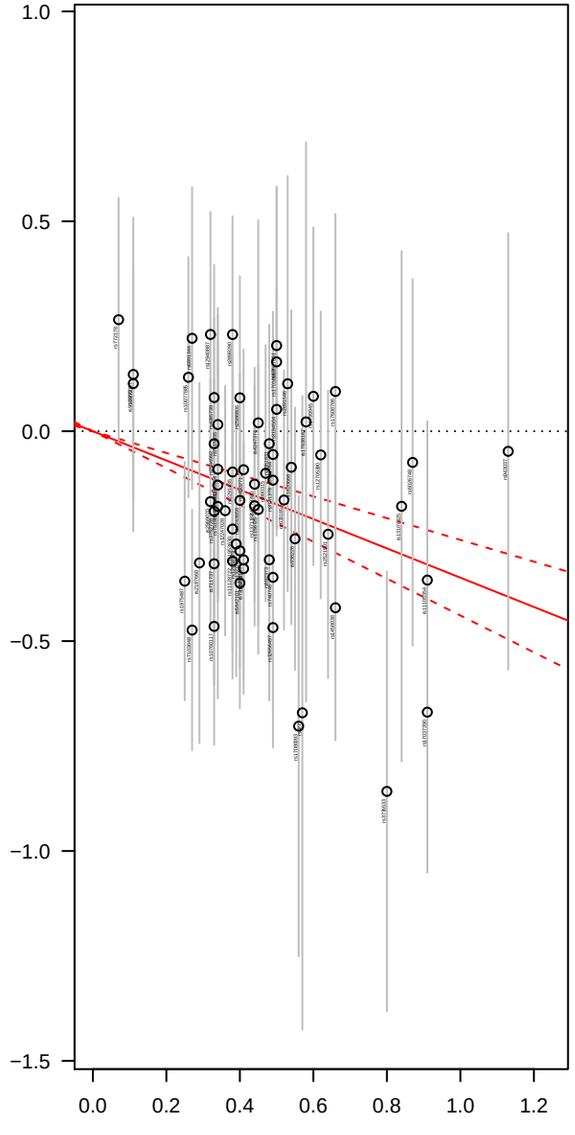

cIMT, SBP; all SNPs
cIMT, SBP; 4 pruned
cIMT, DBP; all SNPs
cIMT, DBP; 5 pruned
0.010
0.005
0.000
−0.005
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.8
1.0
1.2


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

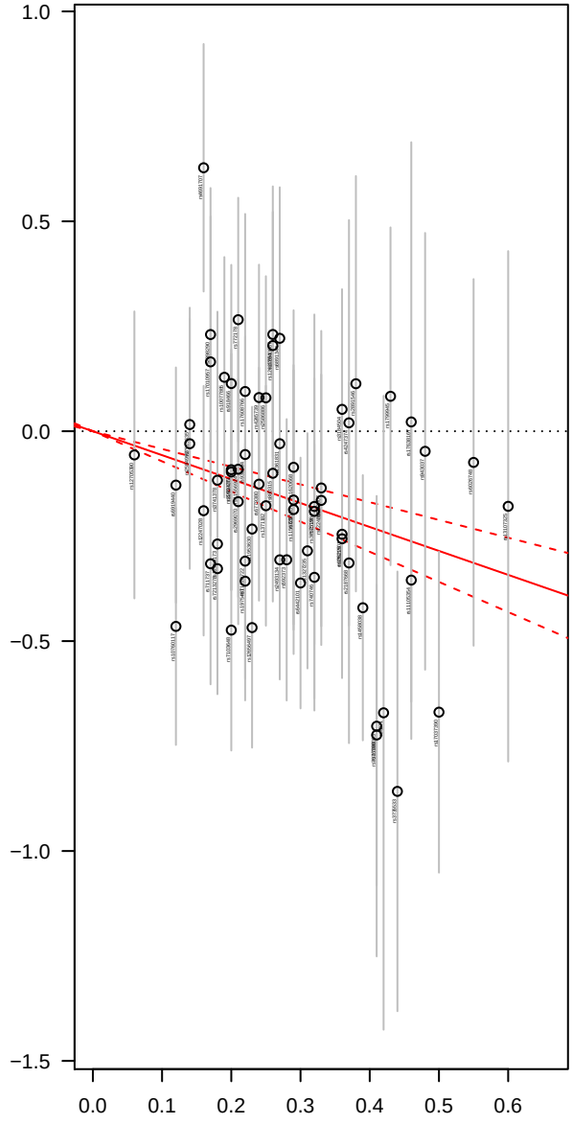
central retinal artery caliber [EU], SBP; all SNPs



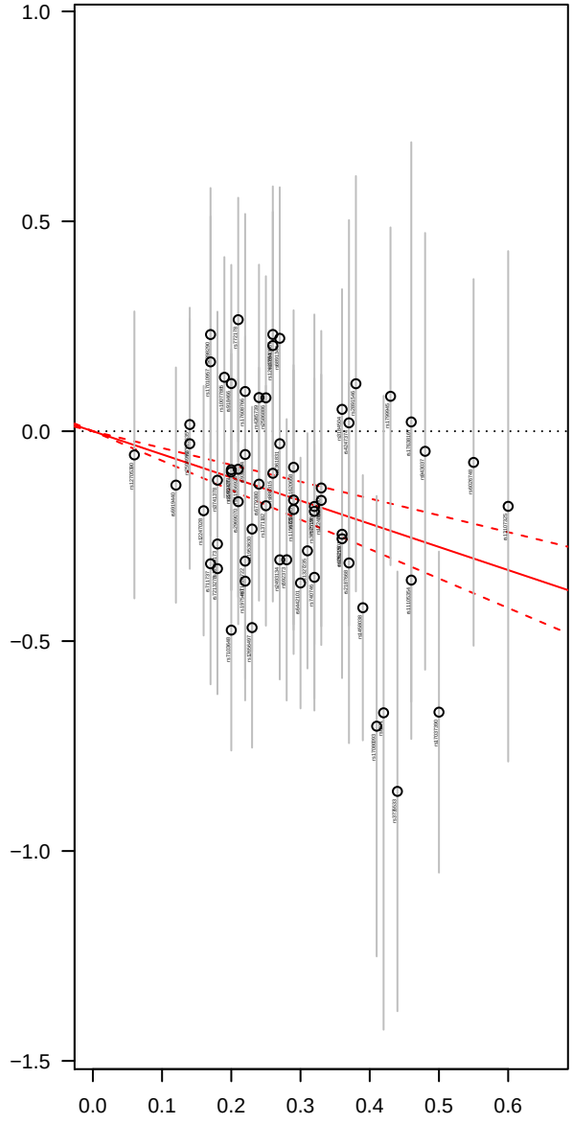
central retinal artery caliber [EU], SBP; 2 pruned

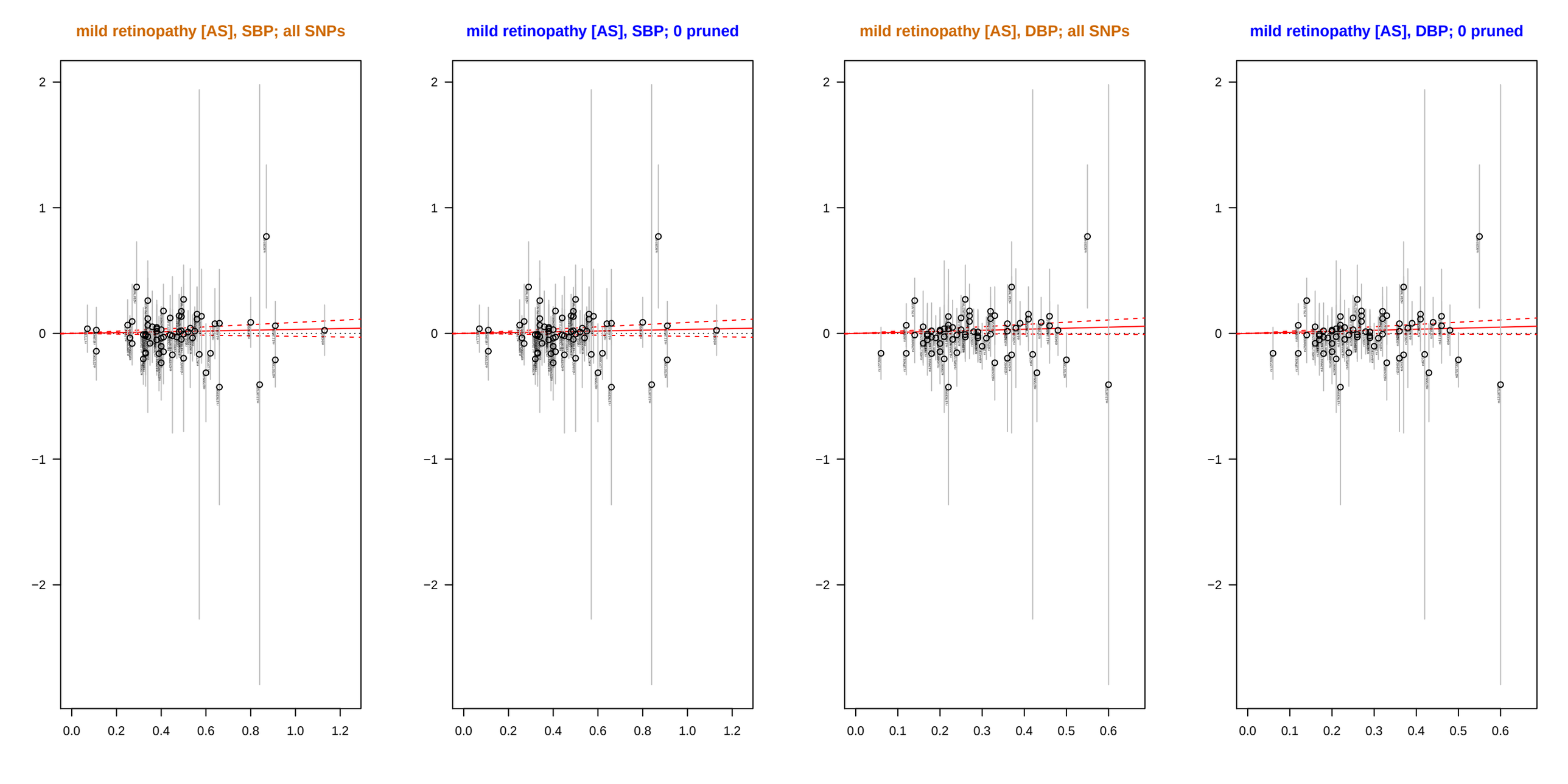


central retinal artery caliber [EU], DBP; all SNPs

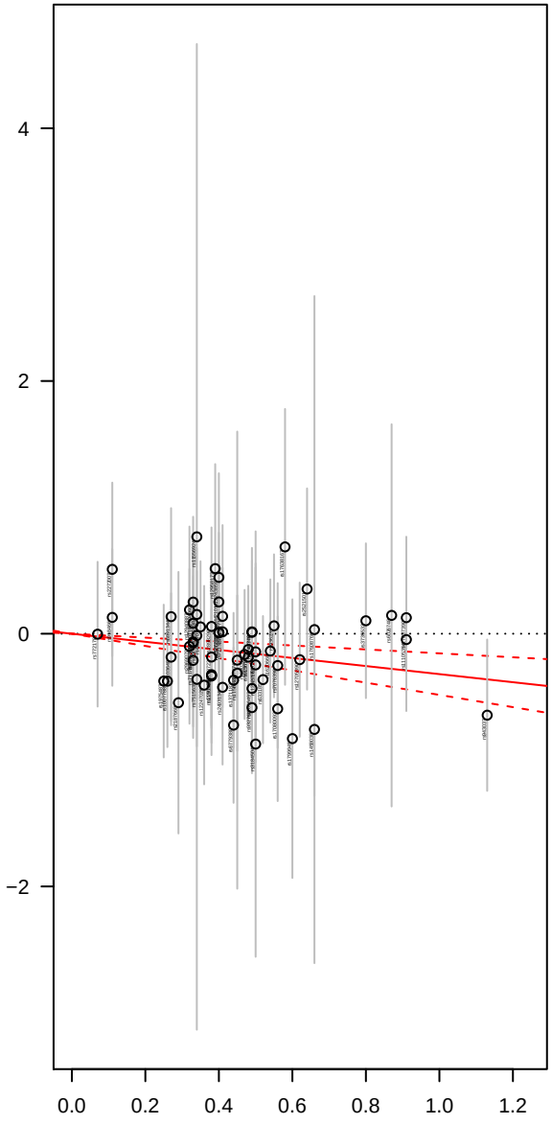


central retinal artery caliber [EU], DBP; 3 pruned

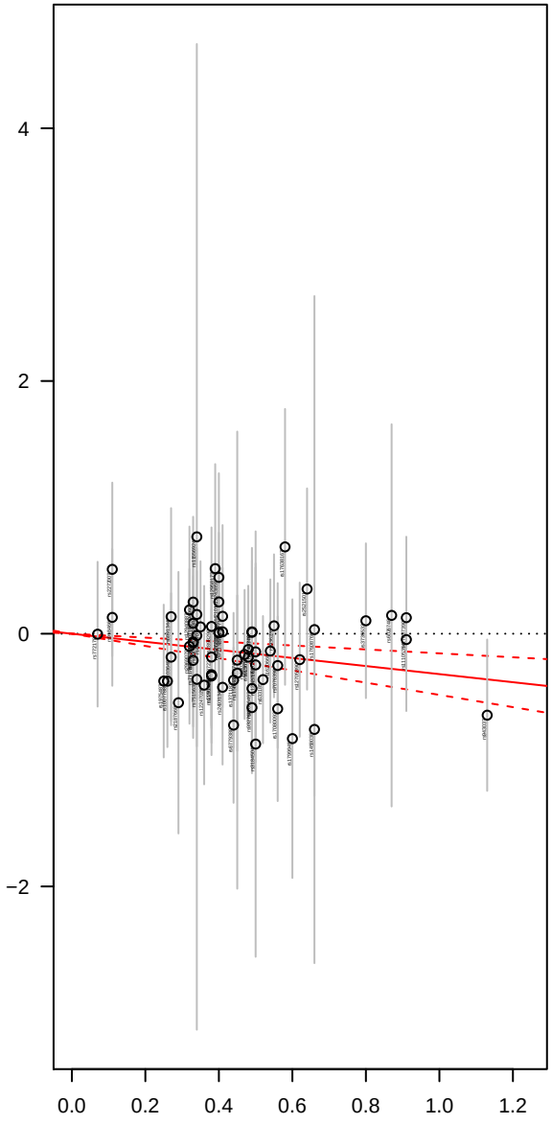



mild retinopathy [AS], SBP; all SNPs
mild retinopathy [AS], SBP; 0 pruned
mild retinopathy [AS], DBP; all SNPs
mild retinopathy [AS], DBP; 0 pruned
2
1
0
−1
−2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

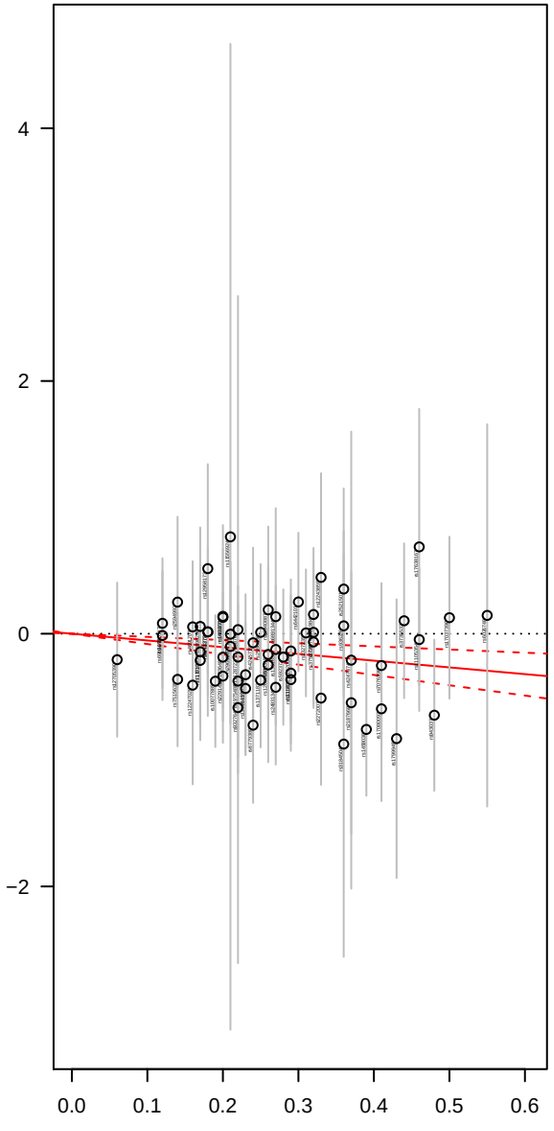
central retinal artery caliber [AS], SBP; all SNPs



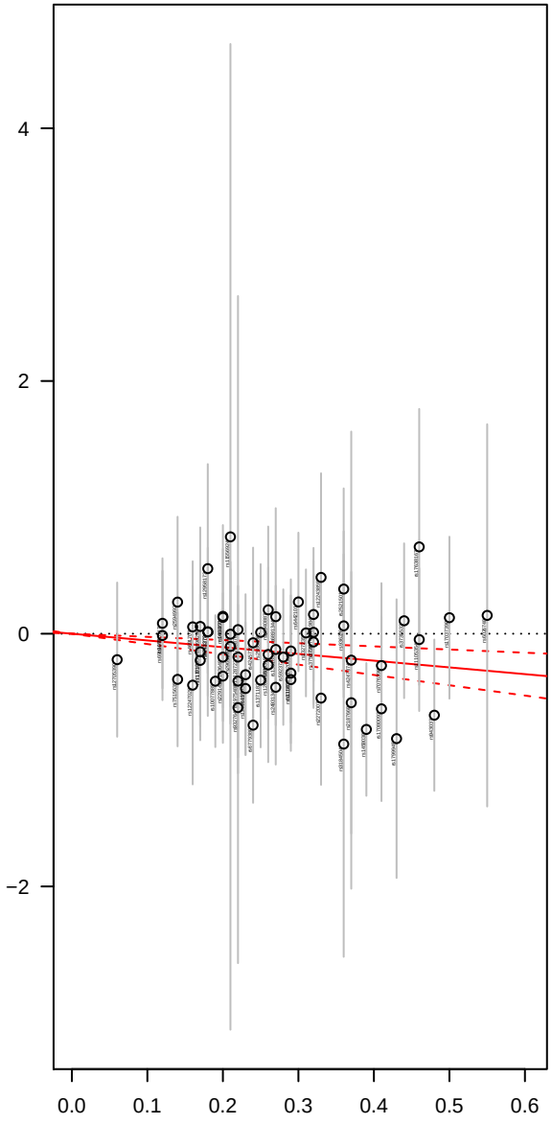
central retinal artery caliber [AS], SBP; 0 pruned

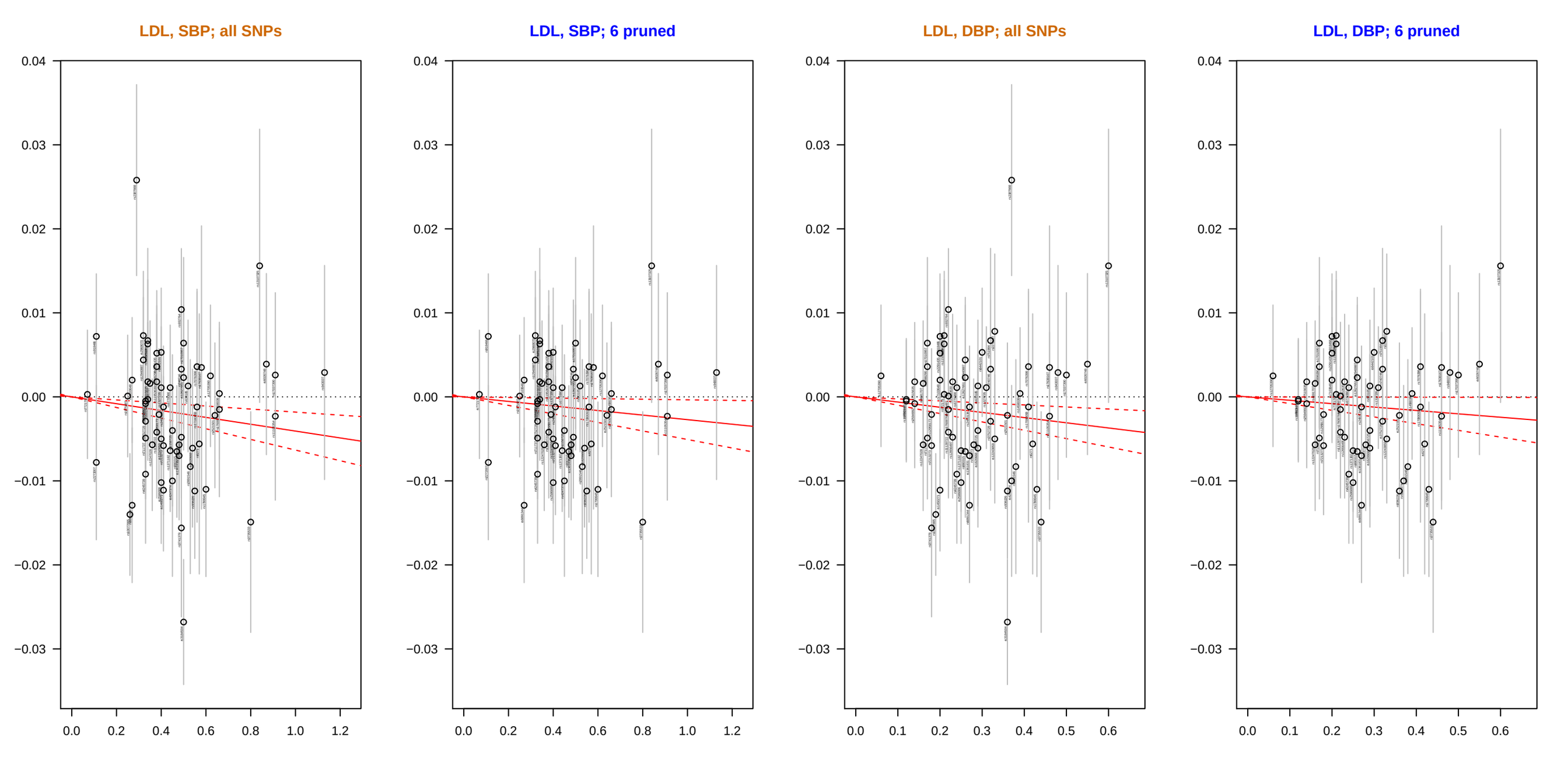


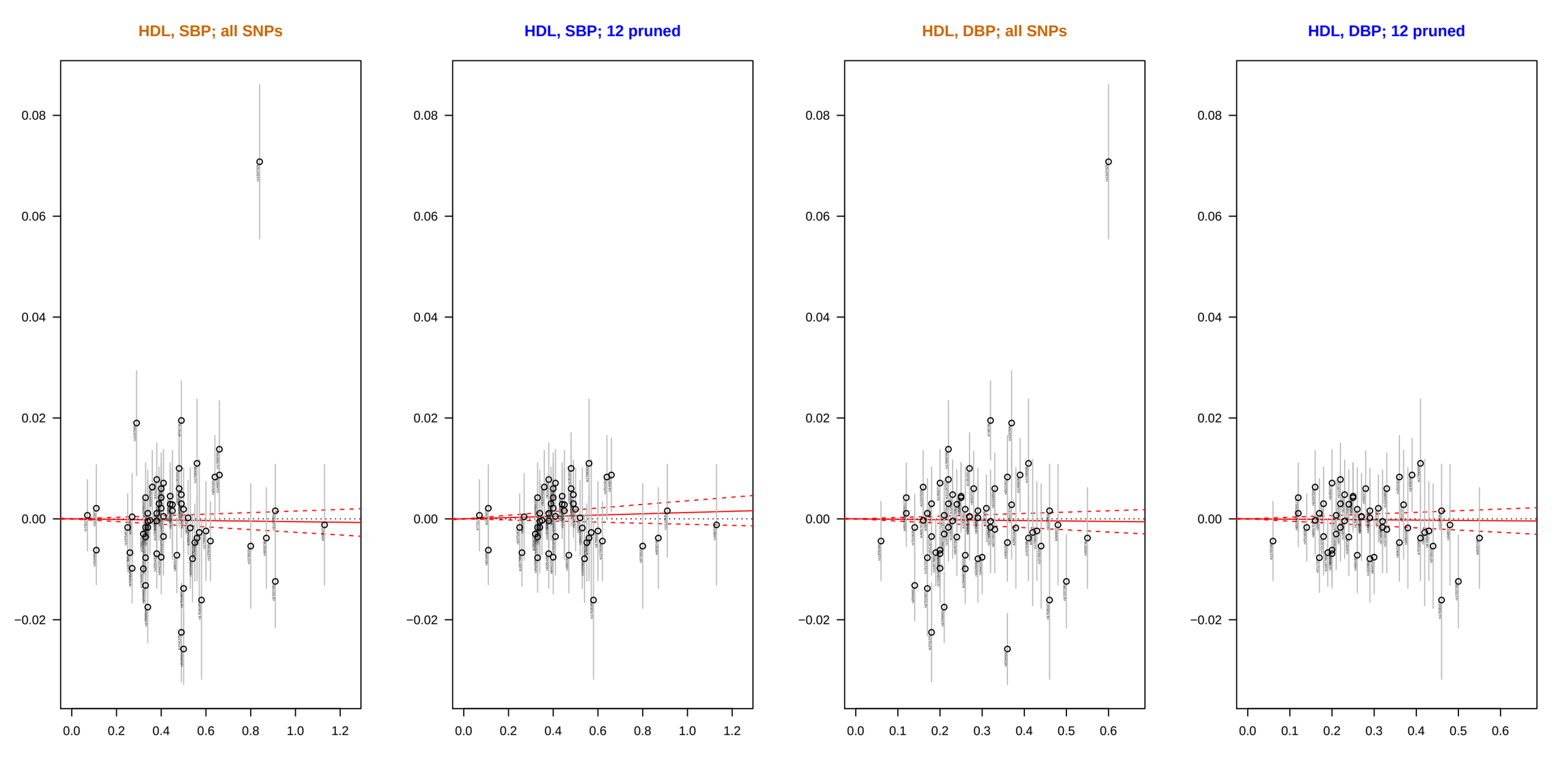
central retinal artery caliber [AS], DBP; all SNPs

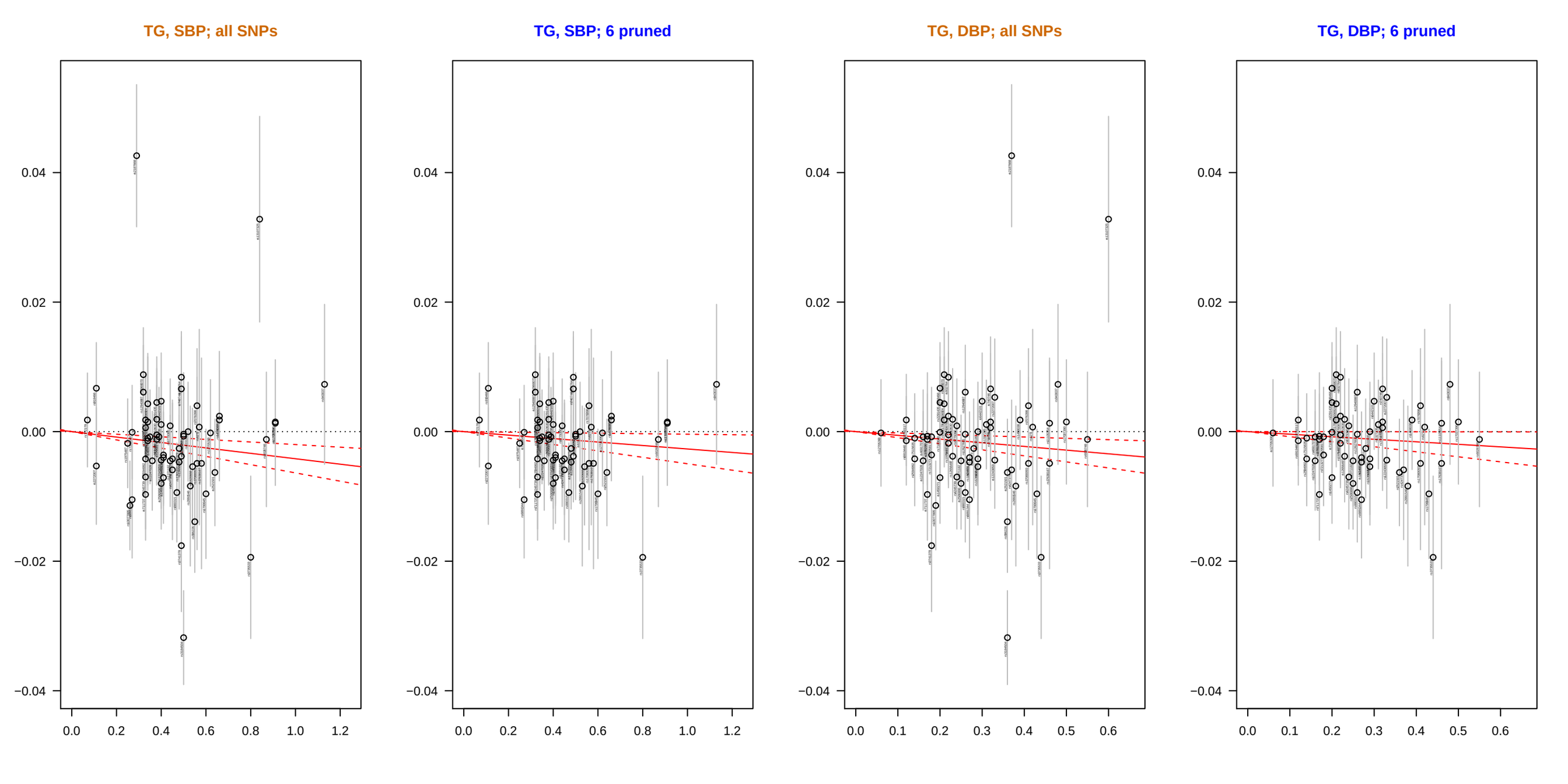


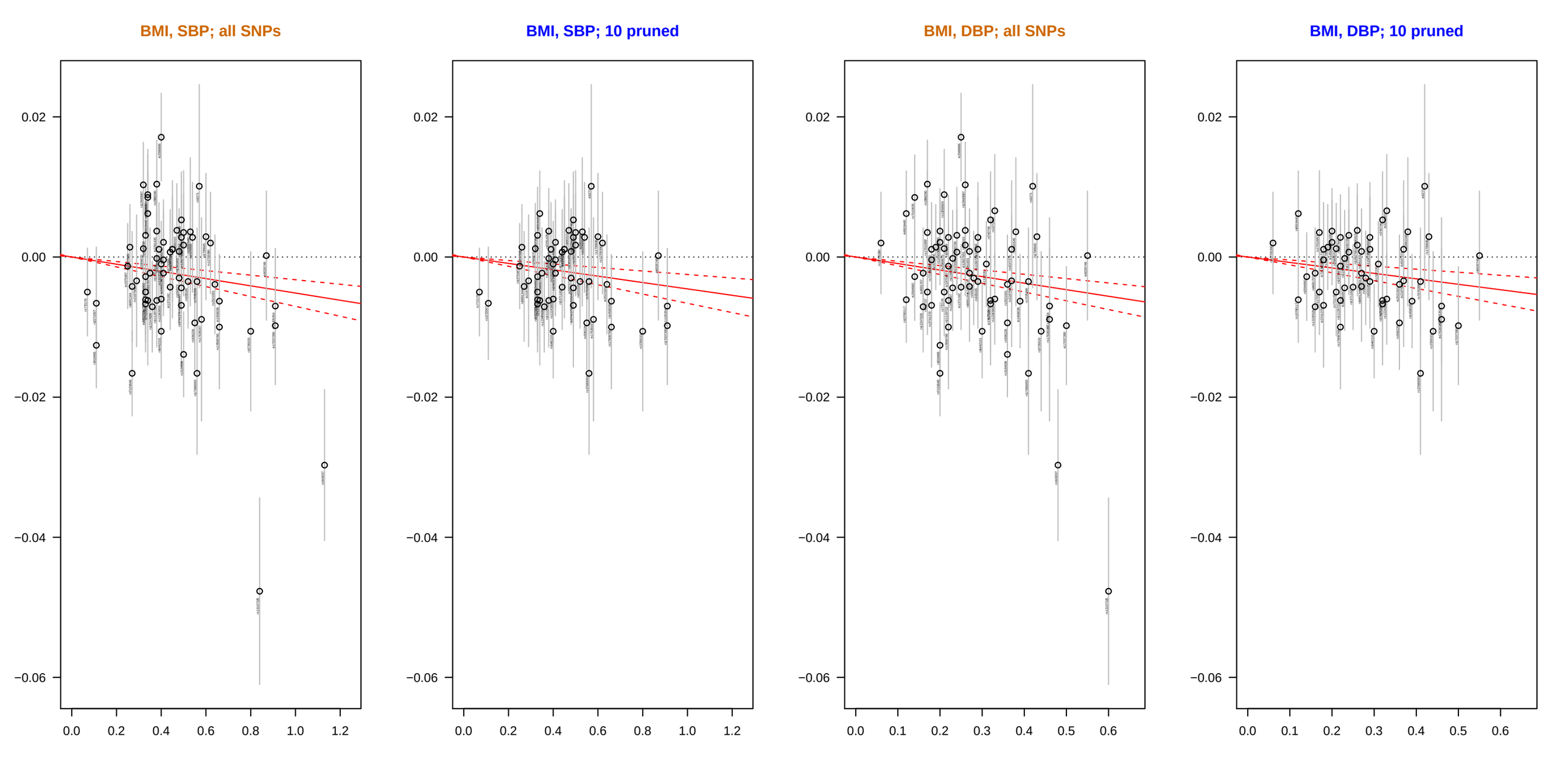
central retinal artery caliber [AS], DBP; 0 pruned

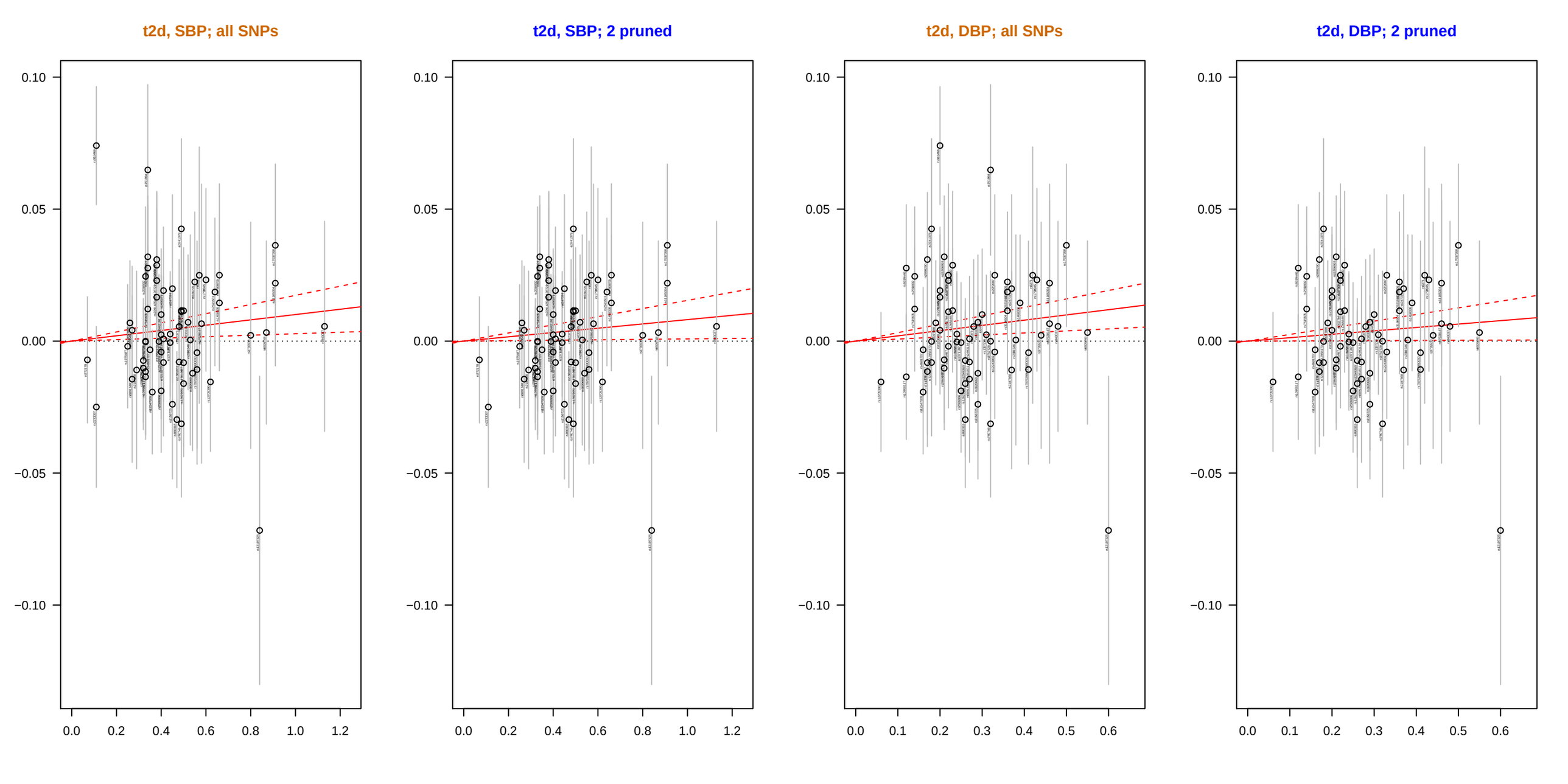


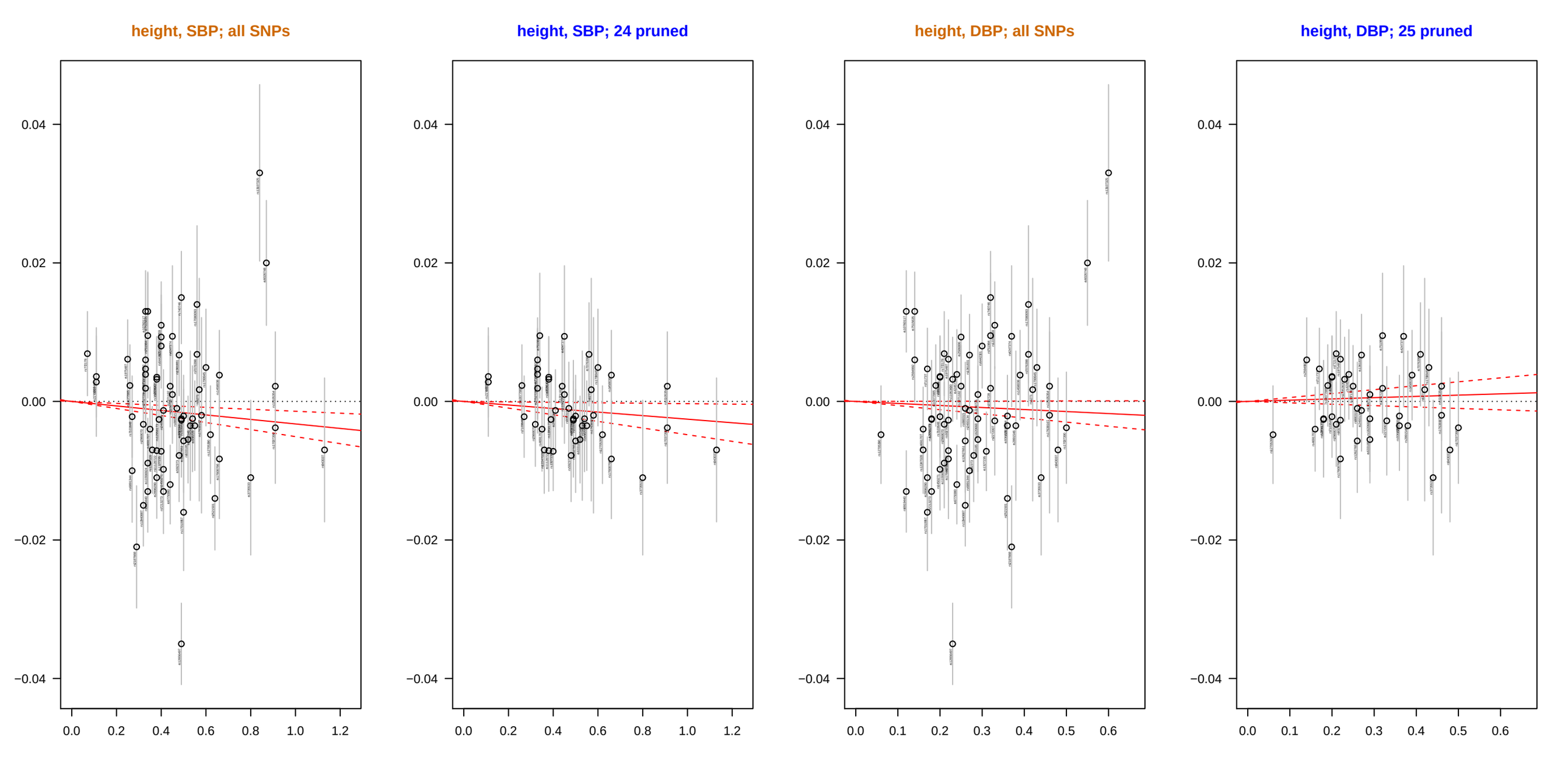

LDL, SBP; all SNPs
LDL, SBP; 6 pruned
LDL, DBP; all SNPs
LDL, DBP; 6 pruned
0.04
0.03
0.02
0.01
0.00
−0.01
−0.02
−0.03
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5


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
0.2
0.4
0.6
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
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.3
0.5

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16 Author contributions

Analysis group

Design of secondary analyses: G.B.E., T.Ferreira, T.J., A.P.M., P.B.M., C.N.-C. Computation of secondary analyses: G.B.E., T.Ferreira, T.J., A.P.M., P.B.M., C.N.-C.

Paper writing: A.C., G.B.E., T.Ferreira, T.J., A.P.M., P.B.M., C.N.-C. Study management: P.B.M., C.N.-C.

Cardio-MetaboChip or new GWAS

WGHS Study phenotyping: P.M.R., D.I.C., L.M.R. Genotyping or analysis: P.M.R., D.I.C., L.M.R., F.Giulianini Study PI: P.M.R.

JUPITER Study phenotyping: P.M.R., D.I.C., L.M.R. Genotyping or analysis: D.I.C., L.M.R., F.Giulianini Study PI: P.M.R., D.I.C.

deCODE Study phenotyping: G.B. Genotyping or analysis: G.T. Study PI: K.S., U.T.

GoDARTS Study phenotyping: C.N.A.P., L.A.D., A.D.M., A.S.F.D. Genotyping or analysis: C.N.A.P., L.A.D., A.D.M., M.I.M., C.G., N.W.W.R.R. Study PI: C.N.A.P., A.D.M.

KORA F3/F4 Study phenotyping: A.D., H.Schunkert, J.E. Genotyping or analysis: A.-K.P., M.M.-N., N.K., T.I. Study PI: H.-E.W., A.Peters

GLACIER Study phenotyping: F.R., G.H. Genotyping or analysis: P.W.F., D.Shungin, I.B., S.Edkins, F.R. Study PI: P.W.F.

B58C Genotyping or analysis: S.Kanoni, K.E.S., Wellcome Trust Case Control Consortium, E.M., T.Ferreira, T.J. Study PI: P.D.

MORGAM Study phenotyping: K.Kuulasmaa, F.Gianfagna, A.Wagner, J.Dallongeville Genotyping or analysis: M.F.H., F.Gianfagna Study PI: J.V., J.F., A.E.

SardiNIA Study phenotyping: E.G.L. Genotyping or analysis: E.G.L., O.Meirelles, S.Sanna, R.N., A.Mulas, K.V.T.

NFBC1986 Study phenotyping: M.R.J., S.Sebert, K.H.H., A.L.H. Genotyping or analysis: M.Kaakinen, A.L.H. Study PI: M.R.J.

DESIR Genotyping or analysis: N.B.-N., L.Y., S.L. Study PI: P.F., N.B.-N., B.B.

DILGOM Study phenotyping: S.M. Genotyping or analysis: K.Kristiansson, M.P., A.S.H. Study PI: V.S.

IMPROVE Study phenotyping: D.B. Genotyping or analysis: R.J.S., K.G. Study PI: A.Hamsten, E.Tremoli

HyperGEN Study phenotyping: S.C.H., D.C.R. Genotyping or analysis: A.C., V.P., G.B.E. Study PI: S.C.H.

FENLAND (MetaboChip) Study phenotyping: R.J.F.L., J.a.L., N.J.W., K.K.O. Genotyping or analysis: R.J.F.L., J.a.L., N.J.W., K.K.O. Study PI: N.J.W.

Whitehall II Study phenotyping: M.Kumari Genotyping or analysis: M.Kumari, S.Shah, C.L. Study PI: A.Hingorani, M.Kivimaki

LURIC Genotyping or analysis: M.E.K., G.Delgado Study PI: W.M.

MESA Study phenotyping: W.P. Genotyping or analysis: W.P., X.G., J.Y., V.D., K.D.T., J.I.R., Y.-D.C. Study PI: W.P.

HUNT2 Study phenotyping: K.Kvaløy, J.H., O.L.H. Genotyping or analysis: A.U.J. Study PI: K.H.

FINCAVAS Genotyping or analysis: T.L., L.-P.L., K.N., M.Kähönen Study PI: T.L., M.Kähönen

GenNet Study phenotyping: R.S.C., A.B.W. Genotyping or analysis: A.C., V.P., M.X.S., D.E.A., G.B.E. Study PI: A.C., R.S.C., A.B.W.

SCARFSHEEP Study phenotyping: B.G. Genotyping or analysis: R.J.S. Study PI: A.Hamsten, U.d.F.

DPS Study phenotyping: J.L. Genotyping or analysis: A.U.J., P.S.C. Study PI: J.T., M.U.

DR's EXTRA Study phenotyping: P.K. Genotyping or analysis: A.U.J., M.H. Study PI: R.Rauramaa, T.A.L.

FIN-D2D 2007 Genotyping or analysis: A.U.J., L.L.B. Study PI: J.Saltevo, L.M.

METSIM Study phenotyping: H.M.S. Genotyping or analysis: A.U.J., A.Stančáková Study PI: M.L., J.K.
MDC-CVA Study phenotyping: O.Melander Genotyping or analysis: O.Melander, C.F. Study PI: O.Melander
BRIGHT Study phenotyping: A.F.D., M.J.B., N.J.S., J.M.C. Genotyping or analysis: T.J., P.B.M. Study PI: M.J.C., A.F.D., M.J.B., N.J.S., J.M.C., P.B.M.
NESDA Study phenotyping: J.H.S. Genotyping or analysis: H.Snieder, I.M.N. Study PI: B.W.P.
EPIC (MetaboChip) Study phenotyping: R.J.F.L., J.a.L., N.J.W. Genotyping or analysis: J.a.L., N.J.W. Study PI: N.J.W., K.-T.K.
ELY Study phenotyping: C.L., J.a.L., N.J.W. Genotyping or analysis: C.L., J.a.L., N.J.W. Study PI: N.J.W.
DIAGEN Study phenotyping: J.G., G.M. Genotyping or analysis: A.U.J., G.M. Study PI: P.E.S., S.R.B.
GOSH Study phenotyping: P.K.M., N.L.P. Genotyping or analysis: E.I., P.K.M., N.L.P., T.Fall Study PI: E.I.
Tromsø Study phenotyping: T.W. Genotyping or analysis: A.U.J., A.J.S., N. Study PI: I.N.
ADVANCE Study phenotyping: T.L.A., C.I. Genotyping or analysis: T.L.A., E.L.S., T.Q. Study PI: T.L.A., T.Q., C.I.
ULSAM Study phenotyping: E.I., J.Sundstrom Genotyping or analysis: E.I., N.E., J.Sundstrom, A.-C.S. Study PI: J.Sundstrom
PIVUS Study phenotyping: L.Lind, J.Sundstrom Genotyping or analysis: L.Lind, N.E., J.Sundstrom, T.A. Study PI: L.Lind, J.Sundstrom
MRC NSHD Study phenotyping: D.K. Genotyping or analysis: A.Wong, J.a.L., D.K., K.K.O. Study PI: D.K.
ASCOT Study phenotyping: A.Stanton, N.P. Genotyping or analysis: T.J., M.J.C., P.B.M. Study PI: P.S., M.J.C.
THISEAS Genotyping or analysis: L.S.R., S.Kanoni, E.M., G.Kolovou Study PI: G.Dedoussis, P.D.
PARC Study phenotyping: R.M.K. Genotyping or analysis: K.D.T., E.Theusch, J.I.R., X.L., M.O.G., Y.D.I.C. Study PI: R.M.K.
AMC-PAS Genotyping or analysis: G.K.H., P.D. Study PI: G.K.H.
CARDIOGENICS Genotyping or analysis: S.Kanoni, A.H.G. Study PI: P.D., A.H.G., J.E., N.J.S., H.Schunkert

Secondary analyses

allele-specific FAIRE Design of secondary analysis: A.J.P.S. Computation of secondary analysis: A.J.P.S., F.D., P.H.
ASAP eQTL Design of secondary analysis: A.F.C. Computation of secondary analysis: L.Folkersen, P.Eriksson
CARDIOGENICS eQTL Computation of secondary analysis: L.Lataniotis
CM design Design of secondary analysis: P.B.M., C.N.-C., T.J., B.F.V. Computation of secondary analysis: P.B.M., C.N.-C., T.J., B.F.V.
Comprehensive literature review Design of secondary analysis: P.B.M. Computation of secondary analysis: K.W., P.B.M.
DEPICT Design of secondary analysis: L.Franke, T.H.P., J.N.H. Computation of secondary analysis: T.H.P.
DHS and methylation analysis by tissue Design of secondary analysis: C.J.W. Computation of secondary analysis: E.M.S.
DHS and methylation by cell-line Design of secondary analysis: D.I.C. Computation of secondary analysis: D.I.C., F.Giulianini
FHS eSNP Design of secondary analysis: R.Joehanes Computation of secondary analysis: R.Joehanes

ICBP SC Design of secondary analysis: C.N.-C., M.J.C., P.B.M., A.C., K.M.R., P.-O'R., W.P., D.L., M.D.T., B.M.P., A.D.J., P.Elliott, C.M.v.D., D.I.C., A.V.S., M.Bochud, L.V.W., H.Snieder, G.B.E.
Kidney eQTL Computation of secondary analysis: H.J.G., S.K.K.
MAGENTA Design of secondary analysis: D.I.C. Computation of secondary analysis: D.I.C.
miscellaneous Computation of secondary analysis: H.Warren
MuTHER eQTL Design of secondary analysis: P.D. Computation of secondary analysis: L.Lataniotis, T.-P.Y.
NESDA eQTL Design of secondary analysis: R.Jansen Computation of secondary analysis: R.Jansen, A.V.
NTR eQTL Design of secondary analysis: R.Jansen Computation of secondary analysis: R.Jansen, J.-J.H. Study PI: D.I.B.
eQTL, EGCUT Design of secondary analysis: A.Metspalu Computation of secondary analysis: T.E., A.Metspalu
eQTL, Groningen Design of secondary analysis: L.Franke Computation of secondary analysis: H.J.W., L.Franke
public eSNP and methylation Design of secondary analysis: A.D.J., J.D.E. Computation of secondary analysis: A.D.J., J.D.E.
PubMed search Design of secondary analysis: G.B.E. Computation of secondary analysis: G.B.E., L.Lin
WGHS conditional Design of secondary analysis: D.I.C. Computation of secondary analysis: D.I.C., F.Giulianini, L.M.R.

Lookup - Cardio-MetaboChip

HEXA Genotyping or analysis: Y.J.K., Y.K.K., Y.-A.S. Study PI: J.-Y.L.
RACe Study phenotyping: D.Saleheen, W.Zhao, A.R., A.R. Genotyping or analysis: W.Zhao, A.R., A.R. Study PI: D.Saleheen
HALST Study phenotyping: C.A.H. Genotyping or analysis: J.I.R., Y.-D.C., C.A.H., R.-H.C., I.-S.C. Study PI: C.A.H.
CLHNS Study phenotyping: N.R.L., L.S.A. Genotyping or analysis: Y.W., N.R.L., L.S.A. Study PI: K.L.M., L.S.A.
GxE/Spanish Town Study phenotyping: B.O.T., C.A.M., R.W. Genotyping or analysis: C.D.P. Study PI: R.S.C., C.A.M., R.W., T.Forrester, J.N.H.
DRAGON Study phenotyping: W.-J.L., W.H.-H.S., K.-W.L., I-Te Lee Genotyping or analysis: J.I.R., Y.-D.C., E.K., D.A., K.D.T., X.G. Study PI: W.H.-H.S.
SEY Study phenotyping: P.B. Genotyping or analysis: M.Bochud, G.B.E., F.M. Study PI: P.B., M.Bochud, M.Burnier, F.P.
TUDR Study phenotyping: W.H.-H.S., I-Te Lee, W.-J.L. Genotyping or analysis: J.I.R., Y.-D.C., E.K., K.D.T., X.G. Study PI: W.H.-H.S.
TANDEM Study phenotyping: P.B., M.Bochud Genotyping or analysis: G.B.E., F.M. Study PI: P.B., M.Bochud, M.Burnier, F.P.

Imputed genotypes

FHS Study phenotyping: D.L. Genotyping or analysis: D.L. Study PI: D.L.
ARIC Study phenotyping: E.B. Genotyping or analysis: G.B.E., E.B., A.C.M., A.C., S.K.G. Study PI: E.B., A.C.
RS Genotyping or analysis: G.C.V., A.G.U. Study PI: A.Hofman, A.G.U., O.H.F.D.
CoLaus Study phenotyping: P.V. Genotyping or analysis: Z.K. Study PI: P.V.
NFBC1966 Study phenotyping: M.R.J. Genotyping or analysis: P.O.R. Study PI: M.R.J.
SHIP Study phenotyping: R.Rettig Genotyping or analysis: A.T.

CHS Study phenotyping: B.M.P. Genotyping or analysis: K.M.R. Study PI: B.M.P.
EPIC (GWAS) Study phenotyping: N.J.W., R.J.F.L., J.a.L. Genotyping or analysis: N.J.W., J.H.Z., J.a.L. Study PI: N.J.W., K.-T.K.
SU.VI.MAX Study phenotyping: S.H. Genotyping or analysis: S.H., P.M. Study PI: P.M.
Amish Genotyping or analysis: M.E.M. Study PI: A.Parsa
FENLAND (GWAS) Study phenotyping: N.J.W., J.a.L., R.J.F.L., K.K.O. Genotyping or analysis: N.J.W., J.a.L., R.J.F.L., K.K.O. Study PI: N.J.W.
DGI Study phenotyping: C.N.C. Genotyping or analysis: C.N.C., G.Kosova Study PI: C.N.C.
ERF (EUROSPAN) Genotyping or analysis: N.A. Study PI: C.M.v.D.
MIGEN Study phenotyping: S.Kathiresan, R.E. Genotyping or analysis: S.Kathiresan, R.E. Design of secondary analysis: S.Kathiresan, R.E.
MICROS Study phenotyping: P.P.P. Genotyping or analysis: A.A.H. Study PI: A.A.H., P.P.P.
FUSION Genotyping or analysis: A.U.J. Study PI: M.Boehnke, F.S.C., K.L.M., J.Saramies
TwinsUK Genotyping or analysis: C.M. Study PI: T.D.S.
PROCARDIS Genotyping or analysis: M.Farrall, A.G. Study PI: M.Farrall
BLSA Study phenotyping: L.Ferrucci Genotyping or analysis: T.T. Study PI: L.Ferrucci
ORCADES Study phenotyping: J.F.W. Study PI: J.F.W.
Croatia-Vis Genotyping or analysis: V.V., C.H. Study PI: V.V., C.H.
NSPHS Genotyping or analysis: S.Enroth Study PI: U.G.
InCHIANTI Genotyping or analysis: T.T. Study PI: S.Bandinelli
AGES Reykjavik Study phenotyping: V.G. Genotyping or analysis: A.V.S. Study PI: V.G.

Lookup

CARDIoGRAMplusC4D Genotyping or analysis: P.D. Study PI: J.Danesh, H.Schunkert, T.L.A., J.E., S.Kathiresan, R.Roberts, N.J.S., P.D.
CHARGE cIMT Genotyping or analysis: C.O'D., J.C.B.
CHARGE EYE Genotyping or analysis: T.Y.W., X.S., R.A.J. Study PI: T.Y.W.
CHARGE-HF consortium Study phenotyping: R.S.V., J.F.F. Genotyping or analysis: H.L., J.F.F. Study PI: R.S.V.
CKDGen Genotyping or analysis: M.G., V.M.
COGENT Study phenotyping: N.F., J.R. Genotyping or analysis: N.F., X.Z., B.J.K., B.O.T., J.R.
EchoGen consortium Study phenotyping: R.S.V., J.F.F. Genotyping or analysis: H.L., J.F.F. Study PI: R.S.V.
KidneyGen Consortium Study phenotyping: J.C.C., J.S.K., P.Elliott Genotyping or analysis: W.Zhang, J.C.C., J.S.K. Study PI: J.C.C., J.S.K.
MetaStroke Genotyping or analysis: S.Bevan, H.S.M.
NeuroCHARGE Genotyping or analysis: M.Fornage, M.A.I. Study PI: M.A.I.
PROMIS Study phenotyping: D.Saleheen, W.Zhao, J.Danesh Genotyping or analysis: W.Zhao Study PI: D.Saleheen
SEED Study phenotyping: T.Y.W., C.-Y.C. Genotyping or analysis: E.-S.T, C.-Y.C., C.-Y.C. Study PI: C.-Y.C., T.Y.W.
UK Biobank Study phenotyping: Mark Caulfield, P.Elliott Genotyping or analysis: M.R.B., H.Warren, Claudia Cabrera, Evangelos Evangelou, He Gao.

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