

SUPPLEMENTARY NOTE

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

2 The cohorts contributing to the discovery meta-analysis for individuals of European ancestry comprise of
3 studies that were directly genotyped using Cardio-MetaboChip, studies in the published ICBP-GWAS
4 dataset¹, and new GWAS studies. The total sample size is N=201,529. The validation dataset comprised
5 individuals of European ancestry from UK Biobank, N=140,886. A targeted lookup of 66 SNPs was
6 performed in studies of non-European ancestry (East Asian N= 9,637, South Asian N= 20,875, and African
7 and African-American ancestry N= 33,909). Details on each of the studies including study design and BP
8 measurement are provided in **Supplementary Table 1**, genotyping information in **Supplementary Table**
9 **2**, and participant characteristics in **Supplementary Table 3**.

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

12 **2 Consortia and studies providing association results for cardiovascular outcomes**

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

17 **2.1 CHARGE - Heart Failure Working Group**

18 We obtained association summary statistics for SNPs of interest from the meta-analysis of 4 cohorts of
19 European ancestry with a total of 20,926 participants free of clinical heart failure at baseline, in whom
20 2,526 incident heart failure events occurred during follow-up². All cohorts included in the heart failure
21 analysis are included in the published ICBP-GWAS discovery dataset¹.

22 **2.2 EchoGen (LM mass and LV weight)**

23 Association summary statistics for left ventricular (LV) mass and LV wall thickness were obtained from
24 the discovery meta-analysis described previously³. The discovery analysis for this study combined data
25 from 5 cohorts of European ancestry with a total sample size of N = 12,612. Four of the cohorts (CHS,
26 RS, KORA F3, FHS) with total N = 9,312, overlap the studies which are included in the published ICBP-
27 GWAS discovery dataset¹.

28 **2.3 NEURO-CHARGE (stroke)**

29 Association summary statistics for risk of incident stroke were obtained from the discovery meta-
30 analysis of the CHARGE consortium, described previously⁴. 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 dataset¹.

2.4 *MetaStroke (stroke)*

Association summary statistics for ischemic risk stroke were obtained from the discovery meta-analysis of the MetaStroke consortium, described previously⁵. 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 ancestry⁶. 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 previously⁷. 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 published¹. Association summary statistics for dichotomous chronic kidney disease (CKD) were obtained by querying the same datasets⁷. 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 dataset¹. 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 dataset¹. Microalbuminuria was defined as UACR > 25 mg/g in women or > 17 mg/g in men⁸.

2.7 *KidneyGen (creatinine)*

Association summary statistics for serum creatinine were obtained from the discovery meta-analysis of the KidneyGen consortium, described previously⁹. 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 dataset¹.

2.8 *CHARGE (cIMT)*

Association summary statistics for carotid intimal thickness (cIMT) were obtained from the discovery meta-analysis of the CHARGE consortium¹⁰. 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 dataset¹.

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 hemorrhages¹¹. 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 system¹². 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 dataset¹.

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 array¹³. Sample and SNP quality control (QC) were undertaken by each study separately. All SNPs with minor allele frequency (MAF) > 1%, Hardy-Weinberg Equilibrium (HWE) $P > 1 \times 10^{-7}$ 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 medications¹⁴. 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 Consortium¹⁶ 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 ($\lambda_{GC} = 1.02/1.01$ 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 studies¹ (**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 Consortium¹⁷ 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 implemented¹. 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 ($\lambda_{GC} = 1.12/1.11$ 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 ($\lambda_{GC} = 1.00/0.99$ 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 software¹⁸ and b) scripting using the R

1 statistical language¹⁹ respectively. We sought independent validation of newly discovered BP loci using
2 summary association results from an analysis of UK Biobank participants (**Supplementary Tables 1-3**).
3 The analysis was restricted to Caucasians according to PCA based on a clustering algorithm, and
4 unrelated individuals. The mean of two BP recordings was used, and medication-adjusted SBP and DBP
5 variables were obtained by +10/15 mmHg for those on BP lowering treatment. All SNPs were tested for
6 association with SBP and DBP in a linear regression framework assuming an additive model. The
7 association analyses included sex, age, age², BMI, genotyping array, and the top 10 PCs.

9 **3.4 Systematic PubMed search +/- 100kb of each newly discovered index SNP**

10 To systematically assess whether genes near the index SNPs have been previously described to be
11 involved in BP regulation or hypertension, we performed a systematic PubMed search. All genes with
12 any overlap with a 200kb region centered around each of the 17 newly discovered index SNPs were
13 identified using the UCSC Genome Browser²⁰. Two loci did not contain any genes within their genomic
14 spans (*TBC1D1-FLJ13197*, *CSNK1G3*), the remaining 15 loci overlapped with a total of 64 genes (1-11
15 genes per locus). A search term was constructed for each gene including the short and long gene name
16 and the terms “blood pressure” and “hypertension” (e.g. for *NPPA* on chr 1: “*NPPA* OR natriuretic
17 peptide A AND (blood pressure OR hypertension)”) and the search results of each search term from
18 PubMed were individually reviewed. Of the 17 newly discovered loci, 6 contained genes within the
19 200kb interval that were previously described to be related to blood pressure or hypertension (*ELAVL3*,
20 *CHST12-LFNG*, *RAPSN-PSMC3-SLC39A13*, *DBH*, *CRYAA-SIK1*, *INSR*). Among the 49 known loci there are 3
21 genes in gene-poor regions without any UCSC Gene in the 200kb interval (*FIGN-GRB14*, *EBF1*, *TBX5-
22 TBX3*). The same search on previous knowledge based on molecular biology could not be performed in a
23 meaningful way for the known loci as here molecular biology experiments could have been carried out
24 with the knowledge of a BP GWAS signal.

25 **3.5 Trait variance explained**

26 The trait variance explained by all 66 SNPs at novel and known loci was evaluated in one study that had
27 also been used for the discovery effort (the Atherosclerosis Risk in Communities (ARIC) study. We
28 constructed a linear regression model with all 66 or the subset of 49 known SNPs in the model,
29 regressing in the residual from the covariate-adjusted treatment-corrected BP phenotype (SBP or DBP).
30 R^2 from the regression model was used as trait variance explained. Some over-fitting of these estimates
31 may exist due to the sample overlap between the individual cohorts and the overall meta-analysis
32 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, age², 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-analysis²¹.

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 $P < 5 \times 10^{-8}$ (**Supplementary Tables 6-8**) using the stage 4 combined European GWAS+ Cardio-MetaboChip meta-analysis.

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

set given its larger sample size. **Supplementary Figure 7** present locus zoom plots²³ 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 BMI¹⁹. 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' factor²⁴ 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 $\varepsilon = 0.2$ 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' factors²⁶,

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

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 design¹³. 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 association²⁴, 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 R¹⁹. The residuals resulting from the linear regression analysis of the probe set intensity values onto the covariates sex, age, body mass index (kg/m²), 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 previously³¹ 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 zygotity (in the case of twins) as random effects to account for family and twin relations³².

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 1×10^{-4} , and for *trans*-eQTL analysis 1×10^{-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 array³³. 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 array³⁴. 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 array³⁵. 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. 2004³⁶, 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 cells³⁹, left ventricle of the heart⁴⁰, CD41+ monocytes⁴¹ and the brain⁴². 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 tissues⁴³ (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 PLINK⁴⁴ 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, 2013⁴⁶. 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 examined⁴⁷.

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 ($\pm 1\%$), and 3) distance to nearest gene ($\pm 11,655$ 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 i th 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 i th control set. The second parameter p_i is calculated as the number of variants in the i th control set or their LD proxies that overlaps with the feature, divided by the total number of variants in the i th 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 method⁴⁸. 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, 2010⁴⁹. 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 DEPICT⁵⁰ 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 ($P < 1 \times 10^{-5}$) from the Cardio-MetaboChip stage 4 combined meta-analyses of SBP and the DBP. DEPICT assigned genes to associated regions if they overlapped or resided within associated LD blocks defined $r^2 > 0.5$ to a given associated SNP. After merging overlapping regions and discarding regions that mapped within the extended major

histocompatibility complex locus (we excluded chromosome 6, 20-40Mb), we were left with 76, 120, and 131 non-overlapping regions that covered 226, 292, and 329 genes for BP, SBP and DBP respectively. The gene counts differed from the loci used for manual lookups because DEPICT only included genes which passed quality control on Affymetrix gene expression microarrays (platforms U133 Plus 2.0, Human Genome U133 A, Mouse 430 2.0, and Rat 230 2.0). We used DEPICT to test enrichment at these regions for a total of 14,461 reconstituted gene sets, and for 209 tissue and cell type annotations. DEPICT relies on random loci to adjust for biases such as gene length and expression properties. In this work, we restricted the random loci construction to autosomal SNPs that were present on the Cardio-MetaboChip as well as in the 1000 Genomes data, which resulted in a total of 120,972 SNPs that covered >11,800 genes. To ensure that DEPICT worked well for the Cardio-MetaboChip-based analysis we performed 100 meta-analyses that were limited to the 120,972 Cardio-MetaboChip SNPs that passed quality control. Each simulated study comprised ~65 independent regions, which were subjected to DEPICT. Plotting of the gene set enrichment and tissue/cell type enrichment *P* values did not indicate any elevated type 1 error. We did, however, observe a slightly elevated type 1 error (data not shown) for the gene prioritization analyses and decided not to include this part of the DEPICT analysis in the results presented here. DEPICT was run using default settings, that is using 500 permutations for bias adjustment, 50 replications for false discovery rate estimation, normalized expression data from 77,840 Affymetrix microarrays for gene set reconstitution⁵¹, assessing 14,461 reconstituted gene sets for enrichment (5,984 protein complexes that were derived from 169,810 high-confidence experimentally-derived protein-protein interactions⁵²; 2,473 phenotypic gene sets derived from 211,882 gene-phenotype pairs from the Mouse Genetics Initiative⁵³; 737 Reactome database pathways⁵⁴; 184 KEGG database pathways⁵⁵; and 5,083 Gene Ontology database terms⁵⁶), 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, age², 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 language¹⁹. The heterogeneity statistics were calculated using the software package GWAMA⁵⁷.

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 package⁵⁹ for the R statistical programming language was used to estimate the effect of the SNP-risk score on the response variable in a regression model. The effect sizes are expressed as incremental change in the phenotype for quantitative traits and natural logarithm of the OR for binary traits, per 1 mmHg predicted increase in SBP or DBP (**Table 3**). Some SNPs may be related to more than one risk factor for cardiovascular disease and such pleiotropic effects could potentially lead to increased or reduced association on the cardiovascular outcome than the BP effect would be expected to cause. Such confounding by pleiotropy would be expected to lead to a decrease in the goodness of fit of the regression model described above. We tested each model for such homogeneity of outcome/BP effects as implemented in the gtx package for R statistical computing language⁵⁹ 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 ($\sim 0.05/\text{number of phenotypes}$), see results in **Table 3**. The per-SNP results for each outcome are summarized in **Supplementary Table 25**. A graphical presentation of the relationship between predictor and response variable, before and after outlier removal is given in **Supplementary Figures 10**.

12 Literature review for genes at the newly discovered loci

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

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

12.1 *FGD5*

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 arteries⁶⁰. *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 activation⁶¹.

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 testis⁶². The gene product is an F-box protein that is an interchangeable part of the SCF ubiquitin E3 ligase complex and, as such, its function is 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 events⁶³. Recently, the same non-synonymous variant (rs11556924) in *ZC3HC1* has been reported to be associated with coronary disease³⁴.

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 endings⁶⁴. 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 QTL⁶⁵ and GWAS⁶⁶.

analyses. Genetic variation in *DBH* has been associated with hypertension and cardiovascular disease. To date, three SNPs in the *DBH* promoter region (rs161115⁶⁷, rs1989787⁶⁸, 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 traits⁶⁶.

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 disease⁶⁹. 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 risk⁷⁰. Insulin's tissue-specific effects on vascular endothelium⁷¹ and smooth muscle⁷² as well as cardiomyocytes⁷³ 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 modulators⁷⁴.

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 manner⁷⁵. They are relatively large proteins containing zinc-fingers. *HIVEP3* was initially described to undergo alternate splicing, leading to functional diversity of its isoforms⁷⁶. Today, Schnurri 3 is best recognised for its role in adult osteoblast function and bone mass regulation⁷⁷ via involvement of Wnt and ERK pathways⁷⁸. 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 homeostasis⁷⁹.

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 cancer⁸³.

12.7 CSNK1G3

CSNK1G3 encodes for casein kinase 1 (CK 1/CK I) isoform γ 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 phosphoproteins⁸⁴.

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 aggregates⁸⁵. Exome sequencing approaches have identified *de novo* mutations in this gene’s SKI homology domain as an underlying cause for Schinzel-Giedion syndrome⁸⁶, 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 domain⁸⁸, 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

balance⁹¹. 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 pools⁹². In this tissue, blocking SIK1 activity prevents the hypertensive cell phenotype induced by hypertension-linked non-synonymous polymorphisms in α -adducin gene⁹³. 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 confirmed⁹². 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 differentiation⁹⁴.

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 young⁹⁵. 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 tissue⁹⁶. 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 component⁹⁶. Animal model studies have also shown that expression of MyBP-C is important for determining diastolic function of the heart, independent of hypertrophy⁹⁸.

13 Supplementary table list and legends

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

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

Supplementary Table 2: Genotyping methods.

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

Supplementary Table 4: Meta-analysis stage 4 results

Supplementary Table 5: UK Biobank validation

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

Supplementary Table 7: All SNPs selected by GCTA as independently associated with SBP.

Supplementary Table 8: All SNPs selected by GCTA as independently associated with DBP.

Supplementary Table 9: SNPs at 66 genome-wide significant CM loci or in the literature for conditional analysis in WGHS, annotation in eSNP analyses or inclusion in pathway analyses.

Supplementary Table 10: Conditional analysis using the WGHS dataset.

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

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

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

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

Supplementary Table 15: eSNP analysis for whole blood.

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

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

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

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

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

Supplementary Table 21: MAGENTA analysis.

Supplementary Table 22: DEPICT analysis.

Supplementary Table 23: FAIRE analysis.

Supplementary Table 24: Non-European meta-analysis.

Supplementary Table 25: Detailed results of risk score analyses for each SNP.

Supplementary Table 26: Genetic BP risk-score analysis applied to related cardiovascular phenotypes.

Supplementary Table 27: Genes at new BP loci using DEPICT.

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

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

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

Supplementary Table 2: Genotyping methods.

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

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

Demographic data including BP are indicated for all studies (European-, South-Asian, East-Asian, and African-Ancestry). The general demographic information includes the number of participants analyzed (N) and genotyping platform used (CM indicates Cardio-MetaboChip, and ICBP 2011 indicates if this dataset was included in the published ICBP-GWAS dataset). The basic description includes the percentage of categorical values and the mean and SD of continuous measurements. The BP values presented are after applying the treatment correction of +15/10mmHg to individuals on any anti-hypertensive medication (see Supplemental Text). The standard deviation (SD) of the residual from a linear regression on age, age², 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 in 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 $P < 5 \times 10^{-8}$. 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 $P < 5 \times 10^{-8}$ 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 $P < 5 \times 10^{-8}$. 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 al¹³. 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 is 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, 2013⁴⁶. 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 $\leq 5\%$ 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 (r^2), 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

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

6 **Supplementary Table 25:** Detailed results of risk score analyses for each SNP per outcome.

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

11 **Supplementary Table 26:** Genetic BP risk-score analysis applied to related cardiovascular phenotypes.

12 The BP genetic risk score was applied to related cardiovascular phenotypes using public databases (T2D:

13 <http://diagram-consortium.org/about.html>; BMI and height:

14 https://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files;

15 lipids: <http://csg.sph.umich.edu//abecasis/public/lipids2013/>). Pt = phenotype investigated, noSNPs =

16 number of SNPs used in the analysis, SBPeffect/DBPeffect = effect size of the genetic BP risk score,

17 SBPpval/DBPpval = *p*-value of the genetic risk score analysis. Information is provided on candidate

18 genes per new locus using the definition described in **Section 12** of this document.

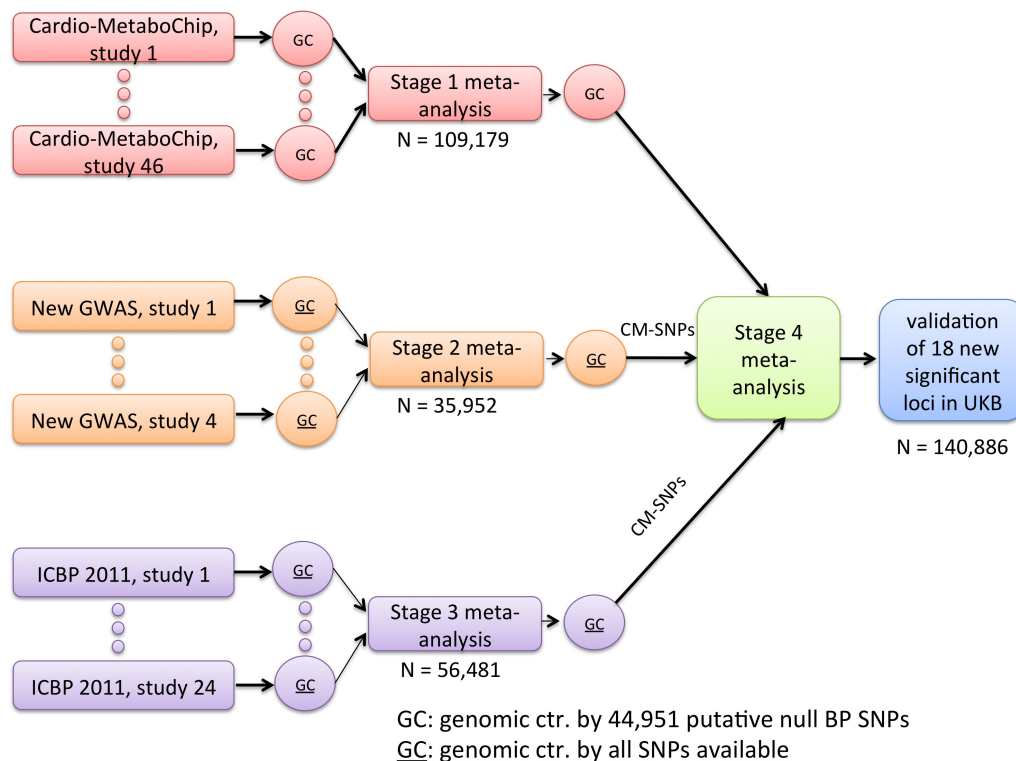
19 **Supplementary Table 27:** Genes at new BP loci using DEPICT.

20 Information is provided on candidate genes per new locus using the definition described in **Section 12** of

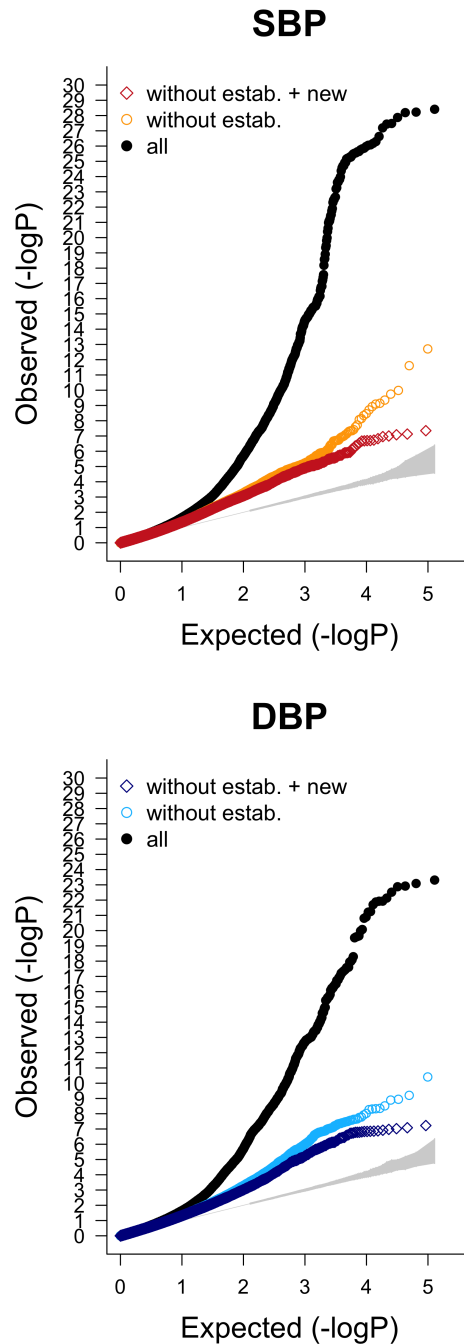
21 this document.

22

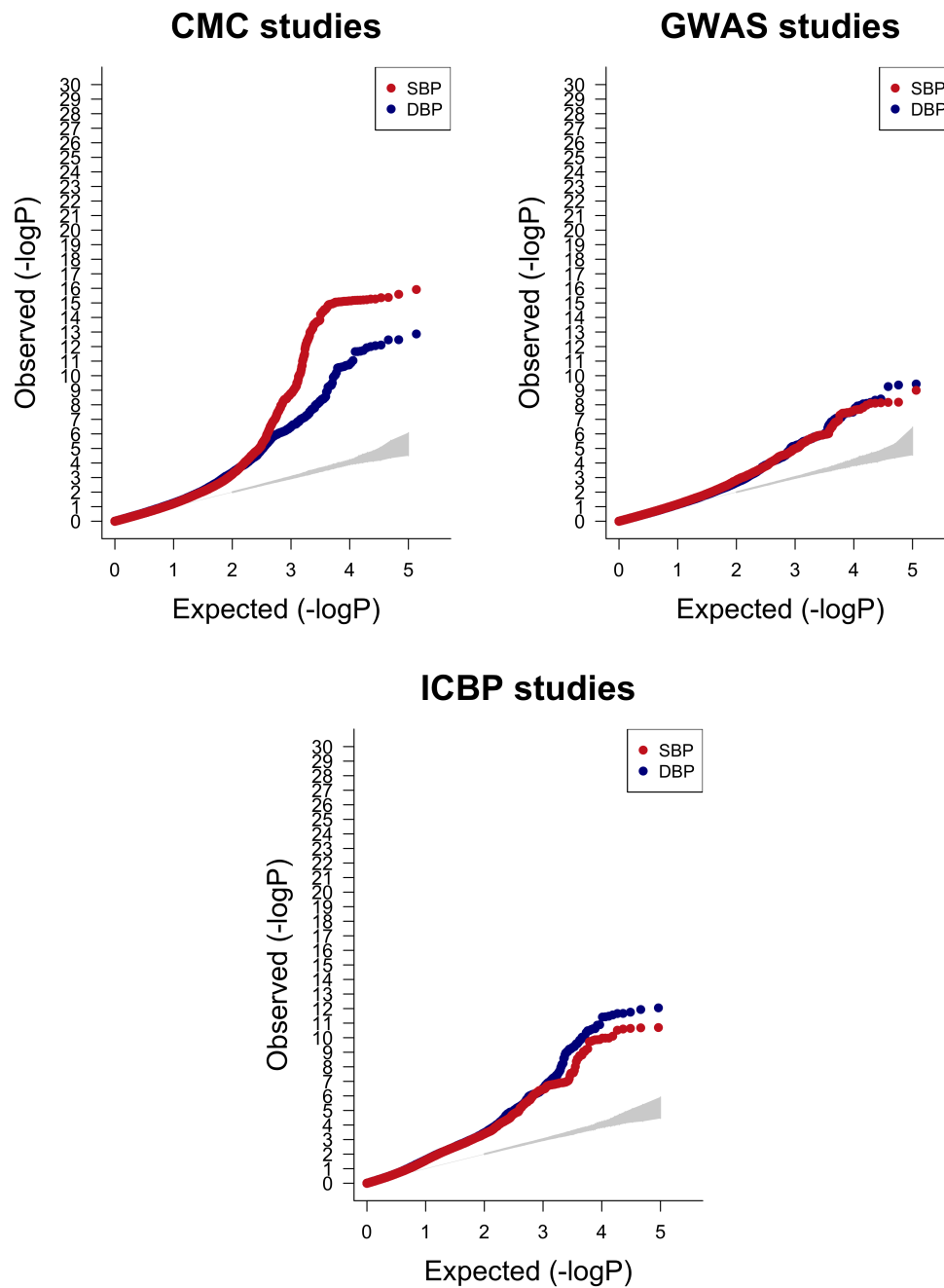
1 14 Supplementary figures



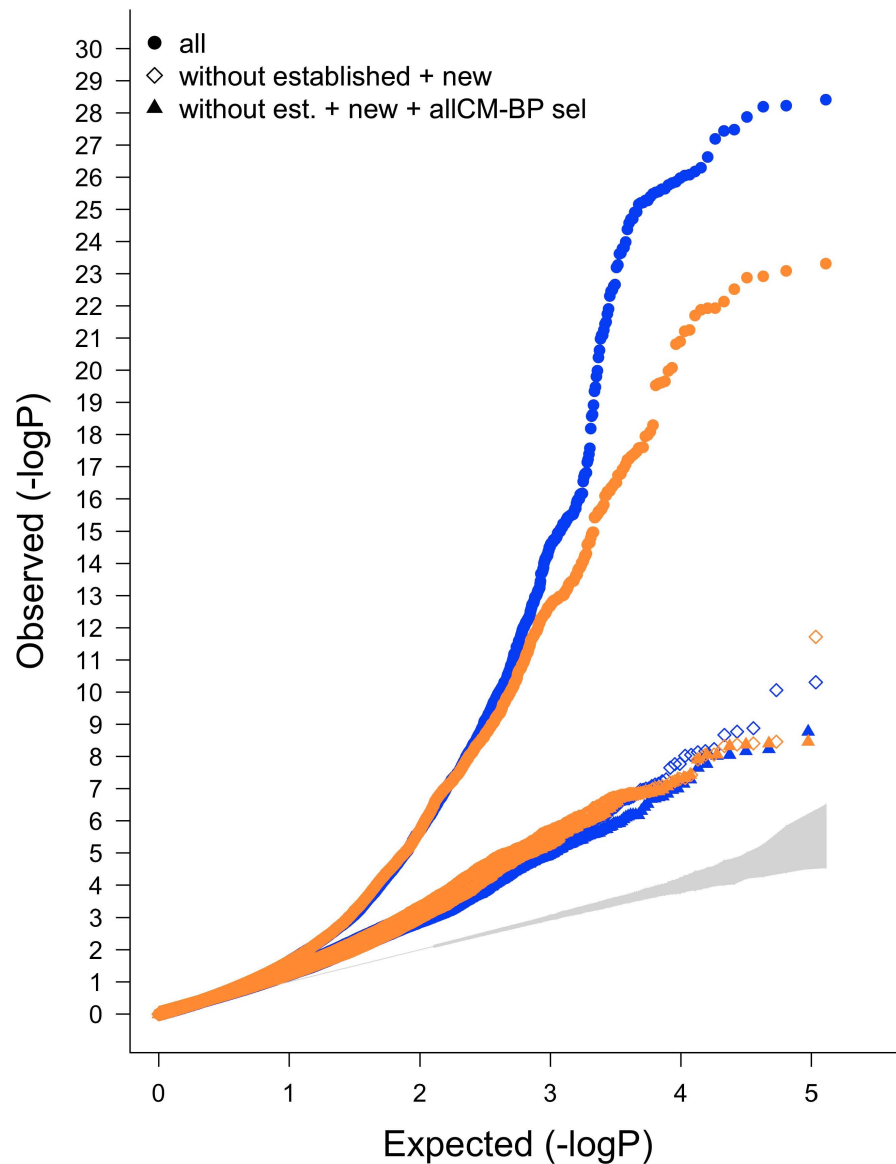
Supplementary Figure 1. Schematic of the experimental design of the meta-analyses. Meta-analyses were carried out in 4 stages (see **Supplementary Information**). Stage 1: results from 46 studies genotyped using Cardio-MetaboChip; Stage 2: unpublished results based on imputed genotypes from genome-wide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



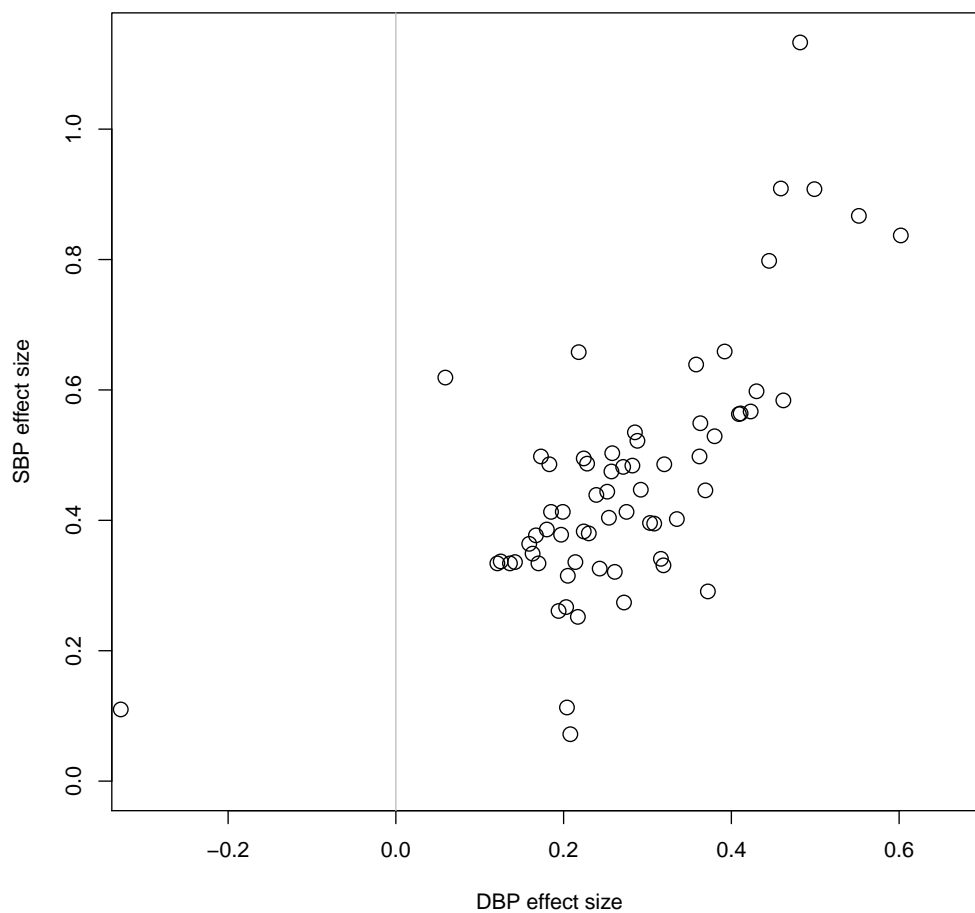
Supplementary Figure 2. Quantile-quantile-plots of the p-values from the Stage 4 Cardio-MetaboChip-wide meta-analysis for SBP and DBP. Observed $-\log_{10}P$ are plotted against expected $-\log_{10}P$ for three datasets: in black the entire dataset; in orange (SBP) and light blue (DBP) results after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



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

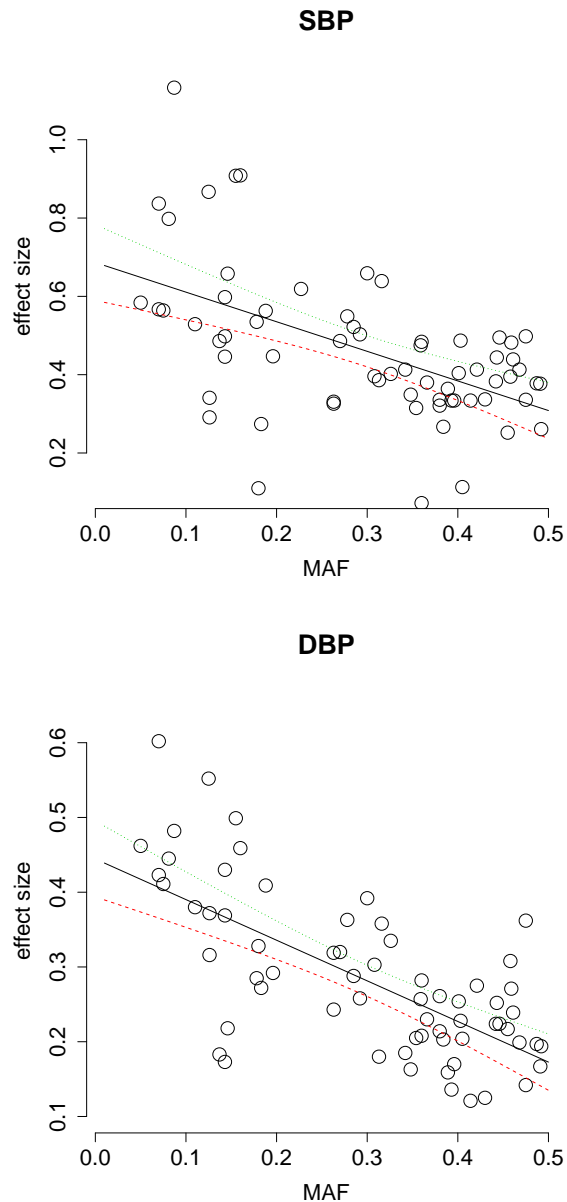


Supplementary Figure 4. Quantile-quantile-plots of the P values of final meta-analysis results after subtracting new, known, and all BP related SNPs contained on the Cardio-MetaboChip. In addition to the 5,000 SNPs selected from previous studies, the Cardio-MetaboChip contains additional SNPs selected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



Supplementary Figure 5. Effect-size plot for each of the 66 index SNPs.

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



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

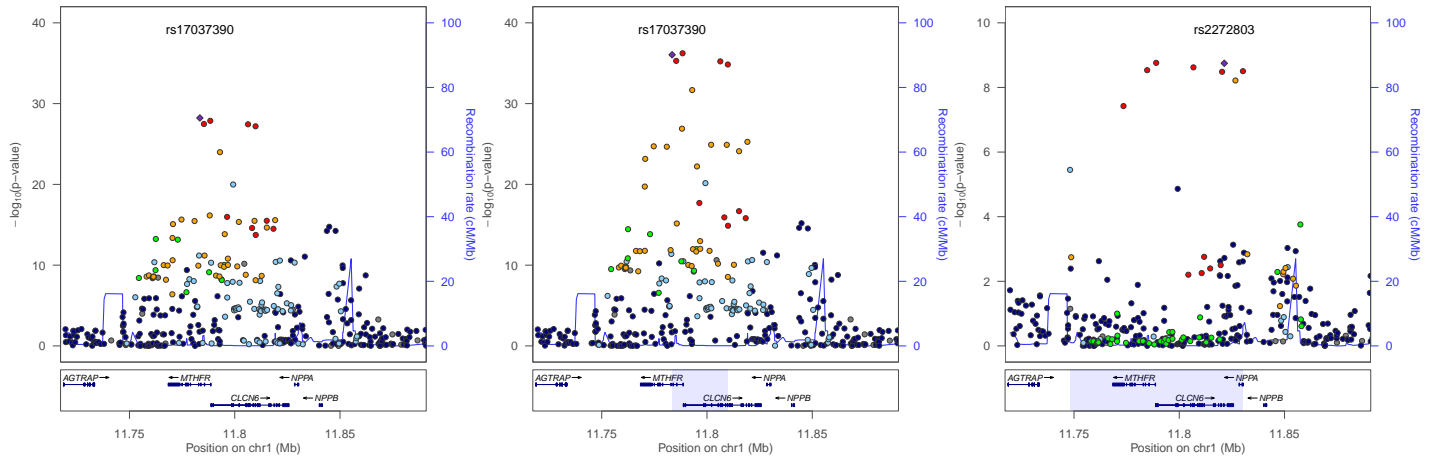
MTHFR-NPPB

Unconditional Analysis

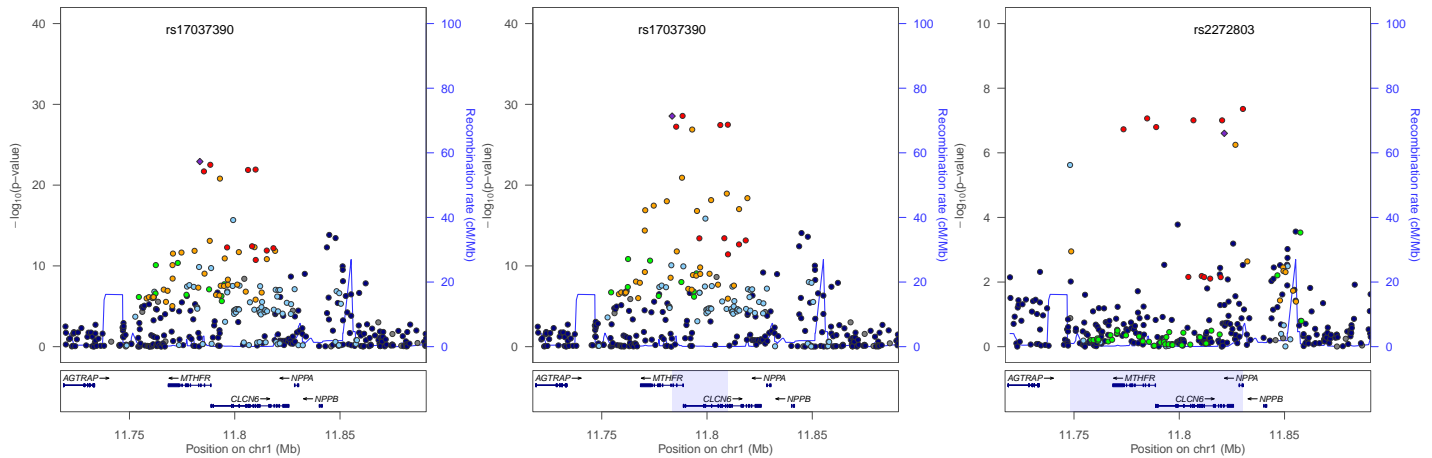
Analysis Conditional on rs2272803

Analysis Conditional on rs17037390

SBP



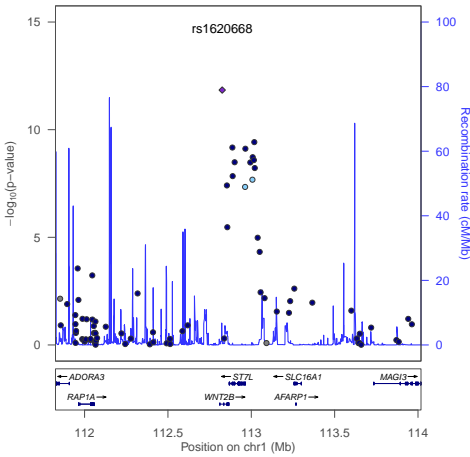
DBP



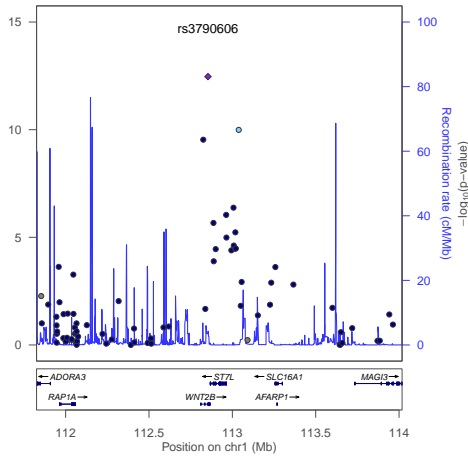
Supplementary Figures 7: Locus Zoom plots of BP loci. The unconditional analyses are shown to the left conditionals in the figures to the right.

ST7L-CAPZA1-MOV10

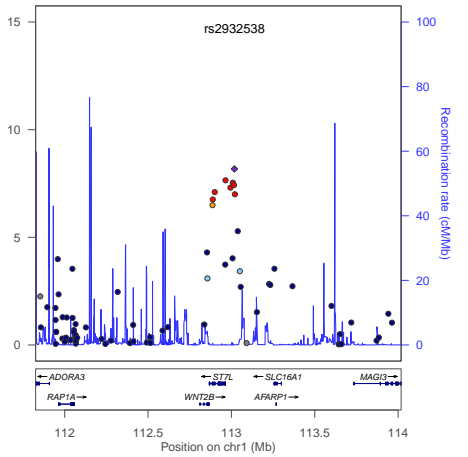
Unconditional Analysis



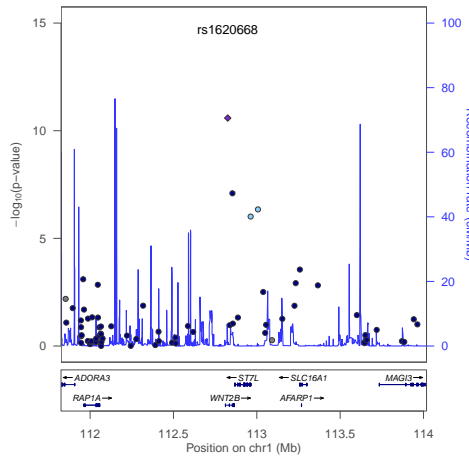
Analysis Conditional on rs351370



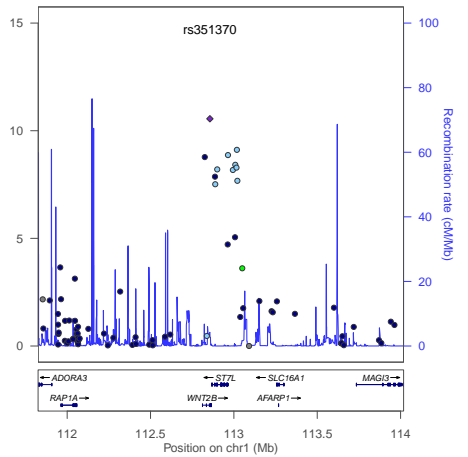
Analysis Conditional on rs1620668



Analysis Conditional on rs2932538

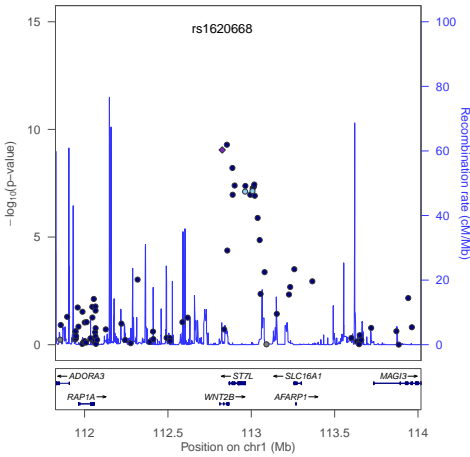


Analysis Conditional on rs3790606

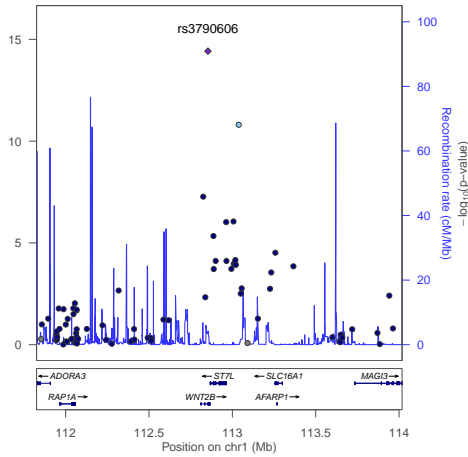


DBP

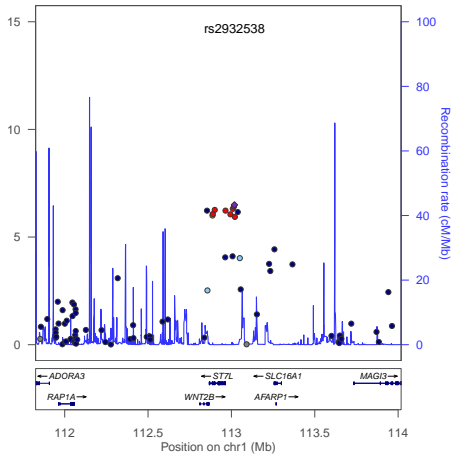
Unconditional Analysis



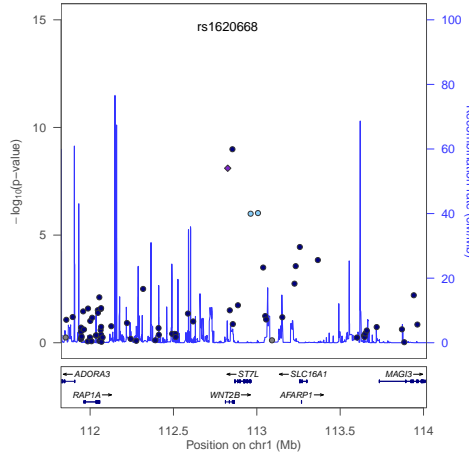
Analysis Conditional on rs351370



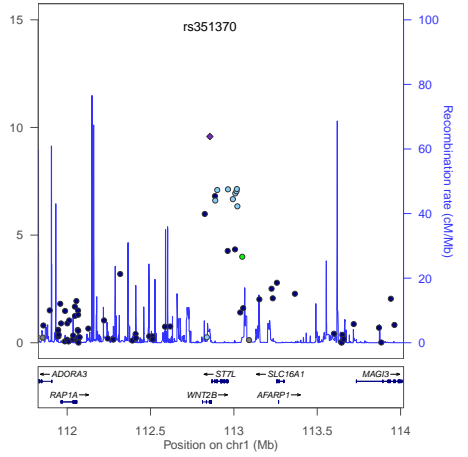
Analysis Conditional on rs1620668



Analysis Conditional on rs2932538

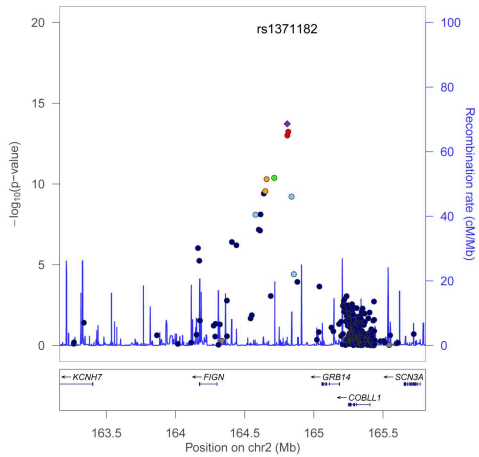


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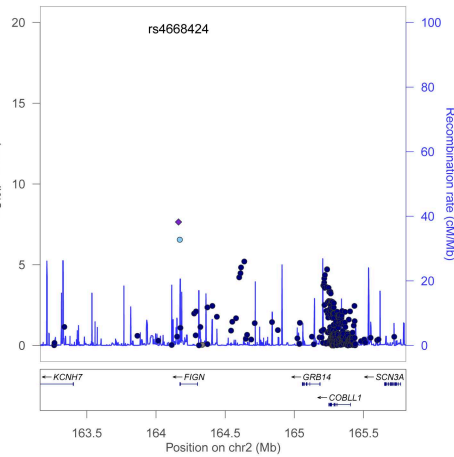


FIGN-GRB14

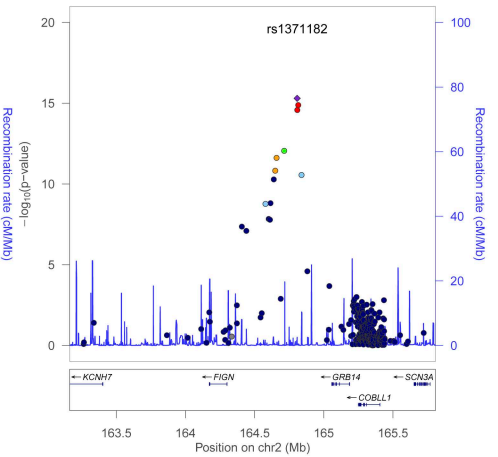
Unconditional Analysis



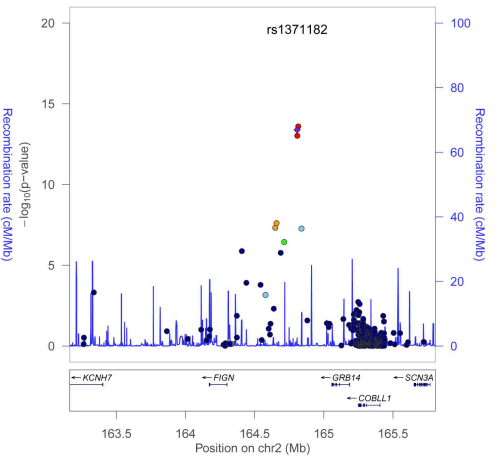
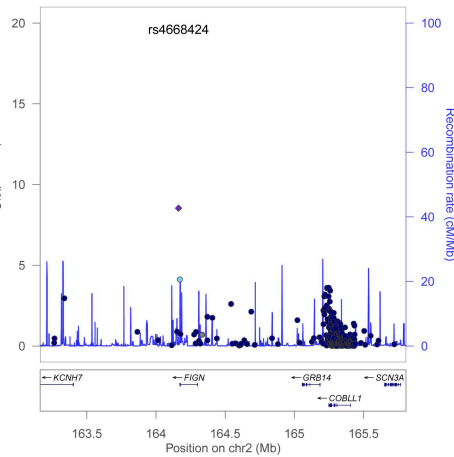
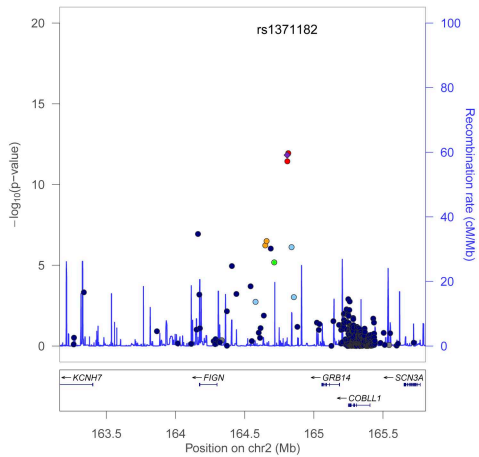
Analysis Conditional on rs1371182
SBP



Analysis Conditional on rs4668424

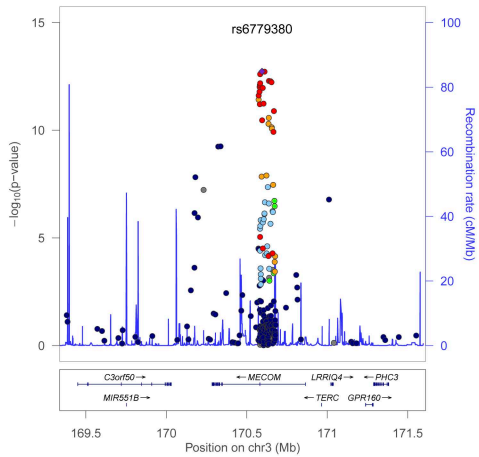


DBP



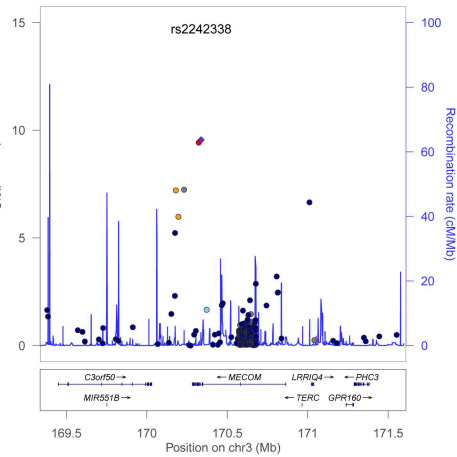
MECOM

Unconditional Analysis

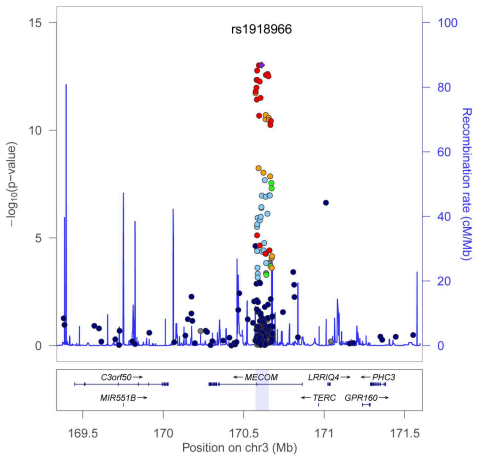


Analysis Conditional on rs1918966

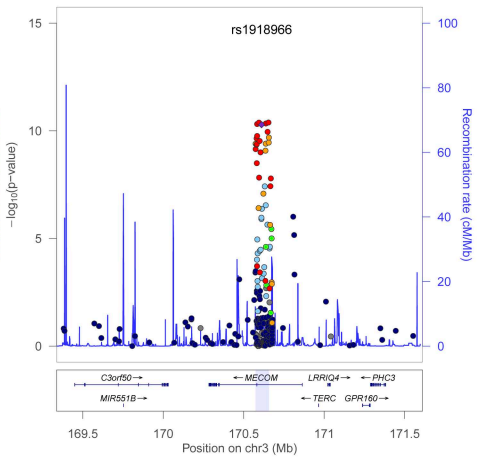
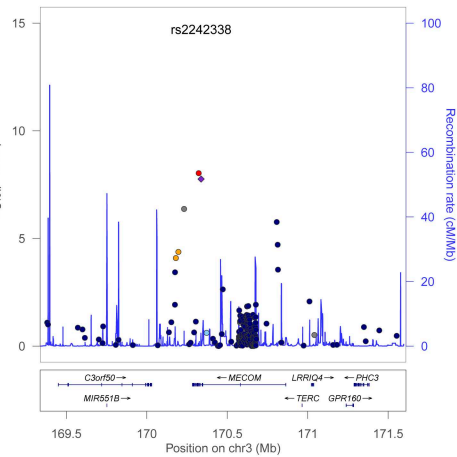
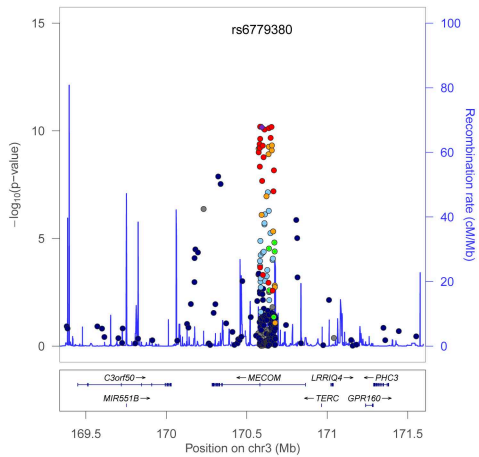
SBP



Analysis Conditional on rs2242338

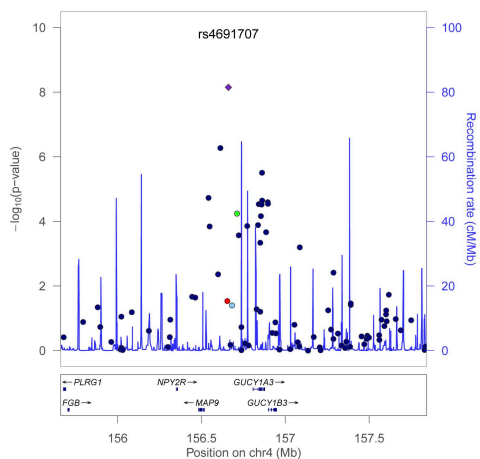


DBP



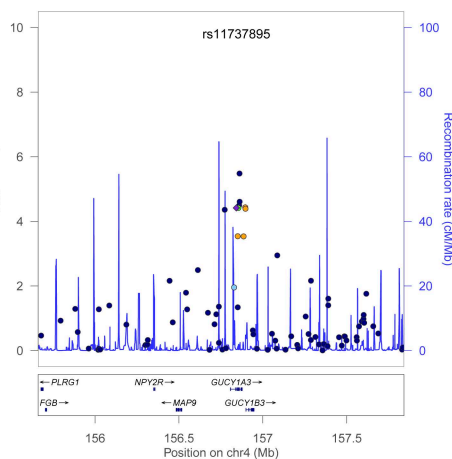
GUCY1A3

Unconditional Analysis

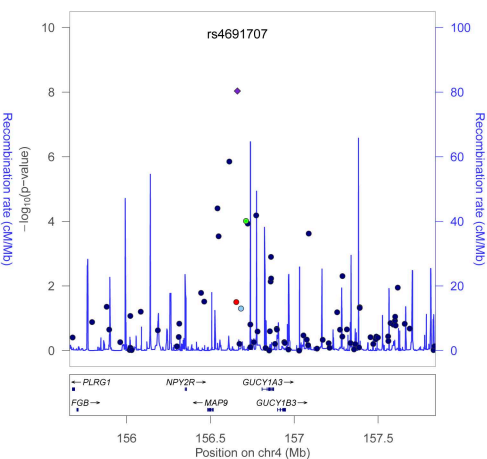


Analysis Conditional on rs4691707

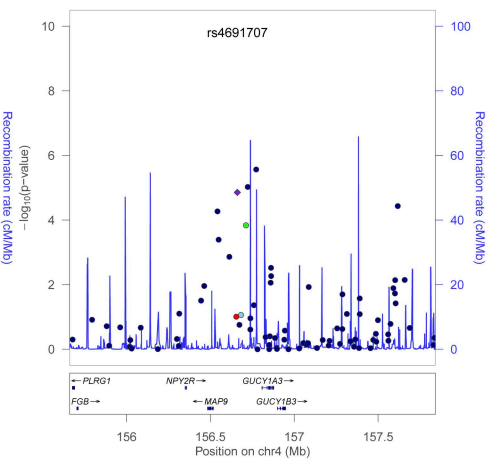
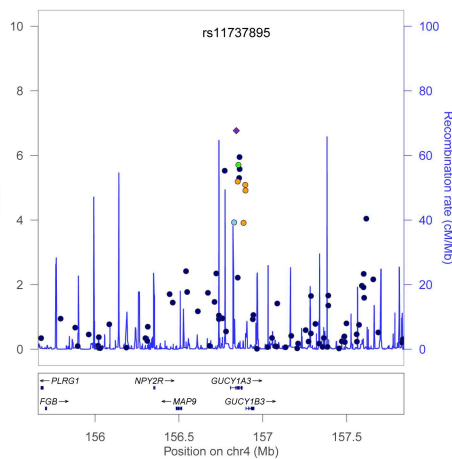
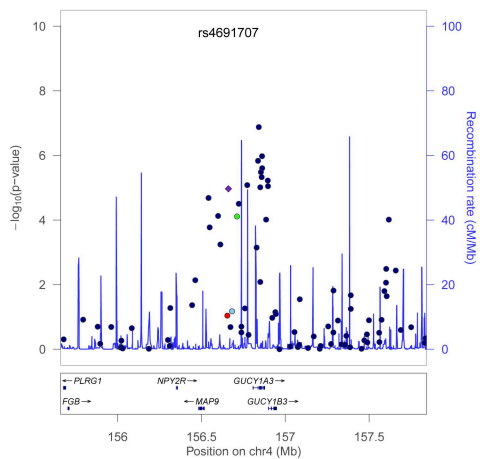
SBP



Analysis Conditional on rs11737895

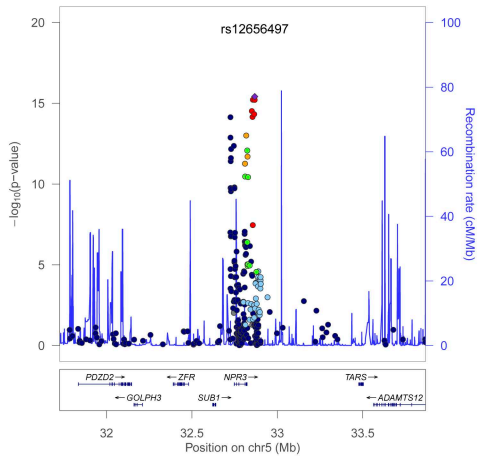


DBP



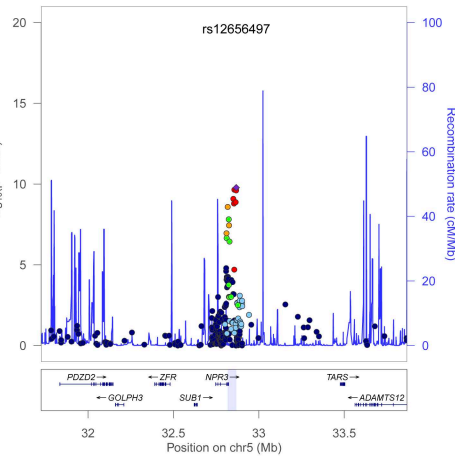
NPR3-C5orf23

Unconditional Analysis

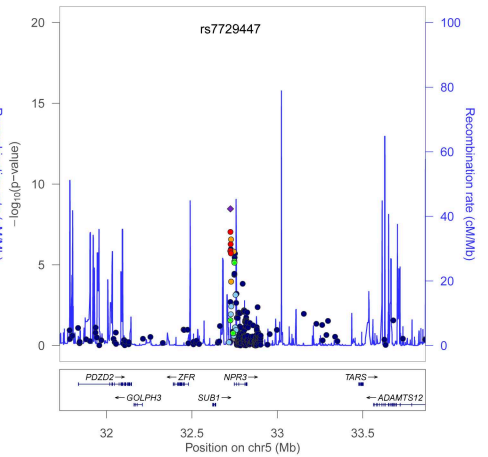


Analysis Conditional on rs7729447

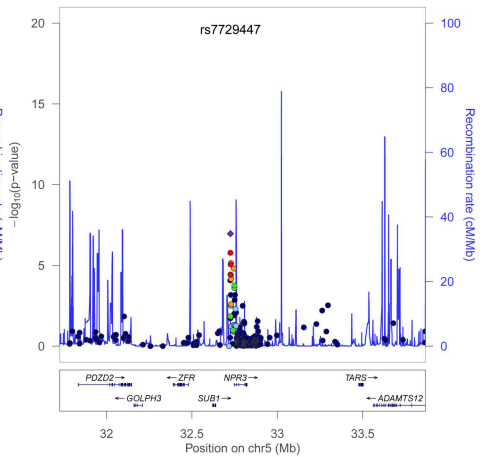
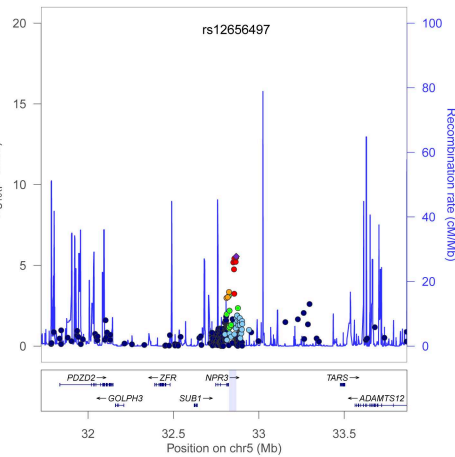
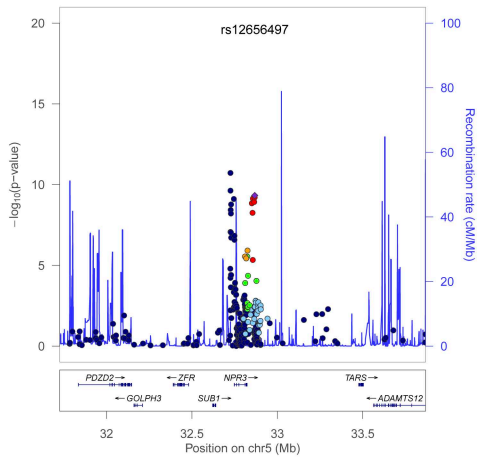
SBP



Analysis Conditional on rs12656497



DBP



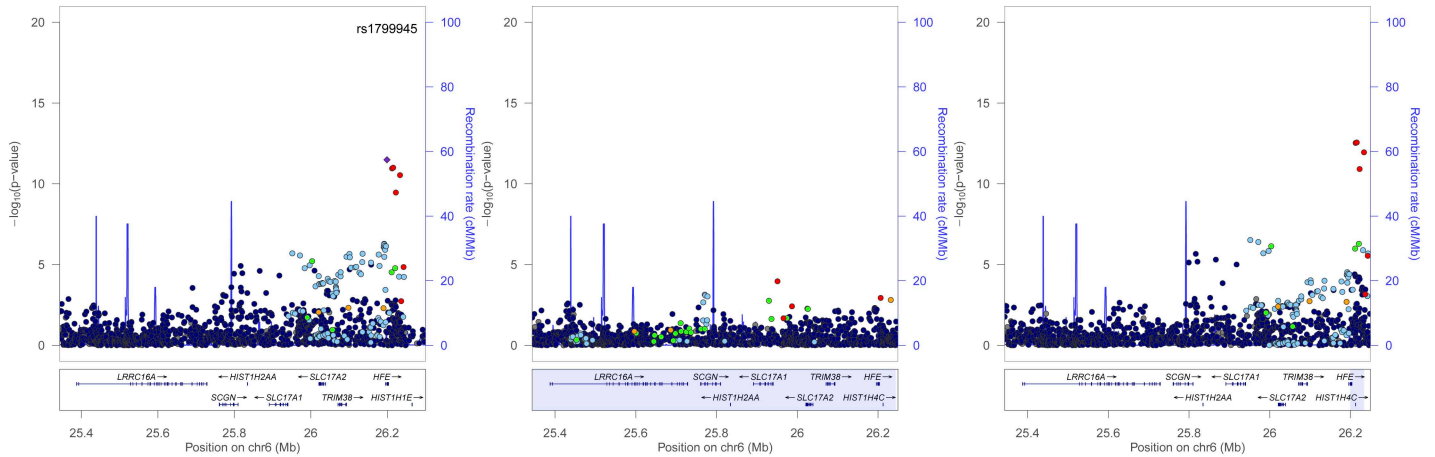
HFE

Unconditional Analysis

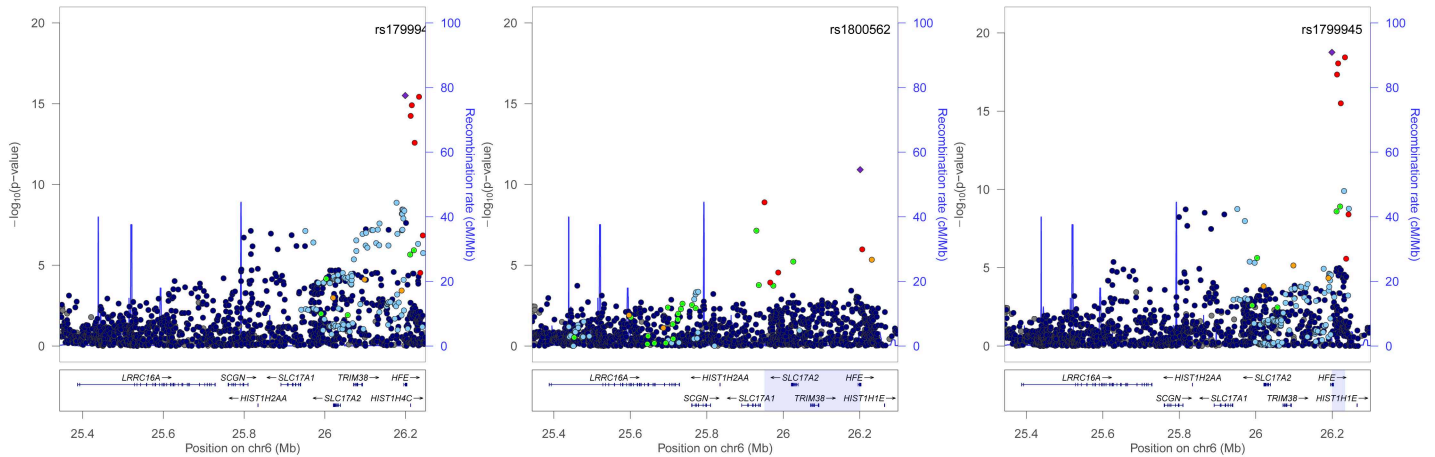
Analysis Conditional on rs1799945

Analysis Conditional on rs1800562

SBP



DBP



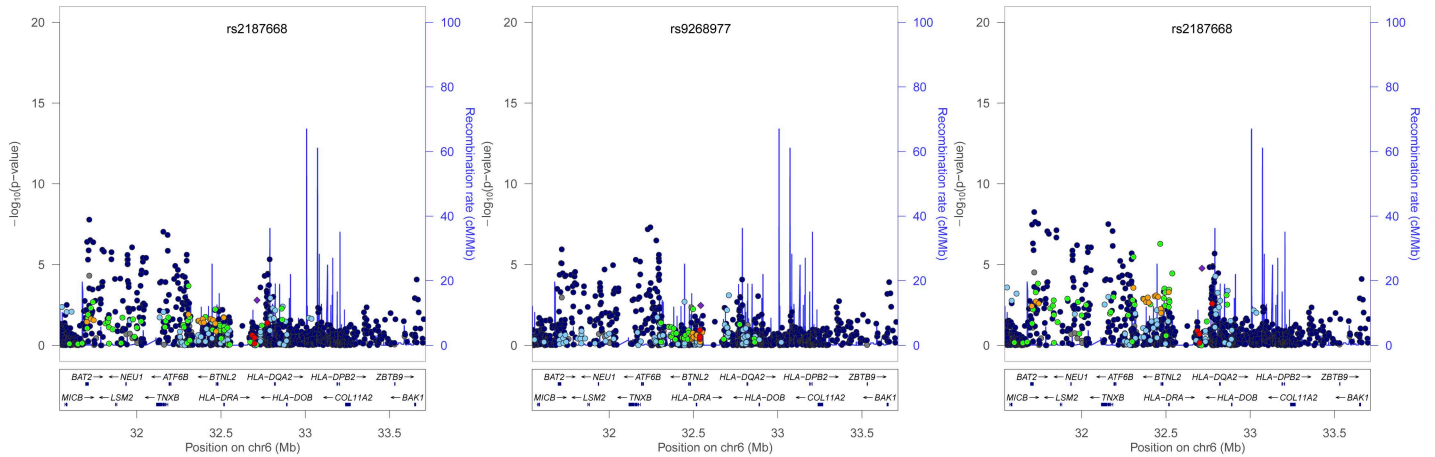
BAT2-BAT5

Unconditional Analysis

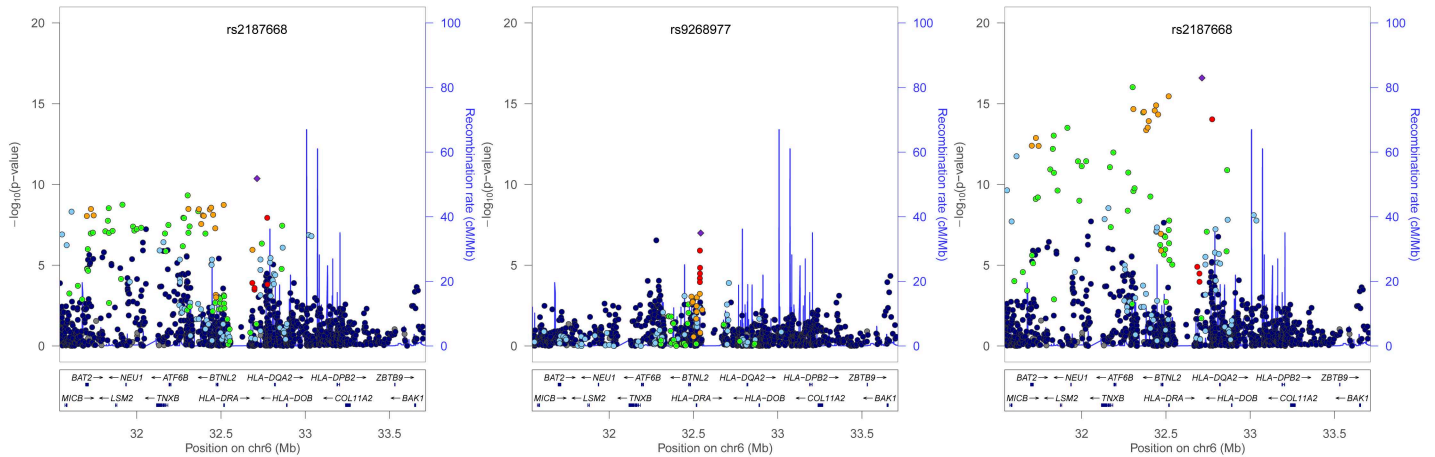
Analysis Conditional on rs2187668

Analysis Conditional on rs9268977

SBP

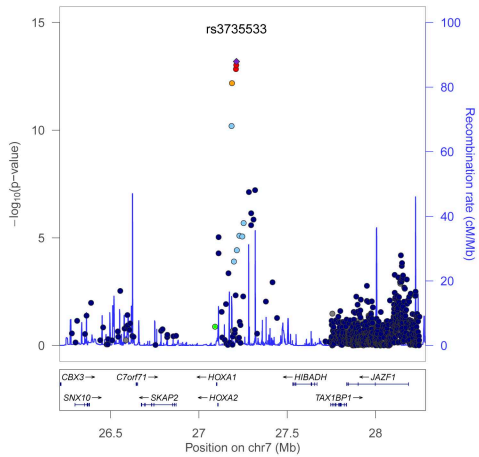


DBP



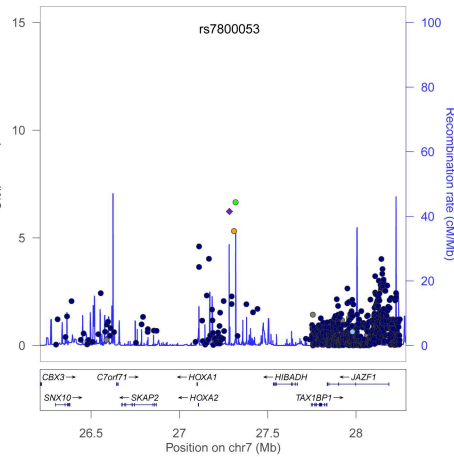
HOTTIP-EVX

Unconditional Analysis

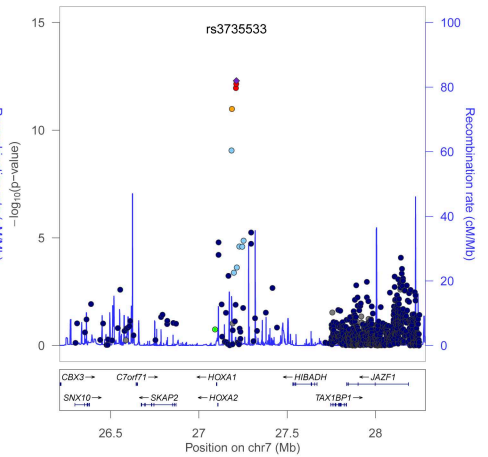


Analysis Conditional on rs929250

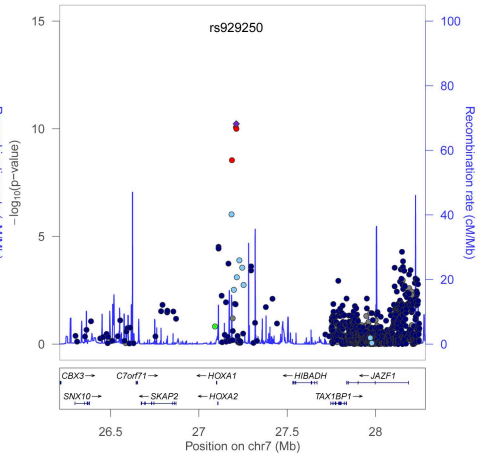
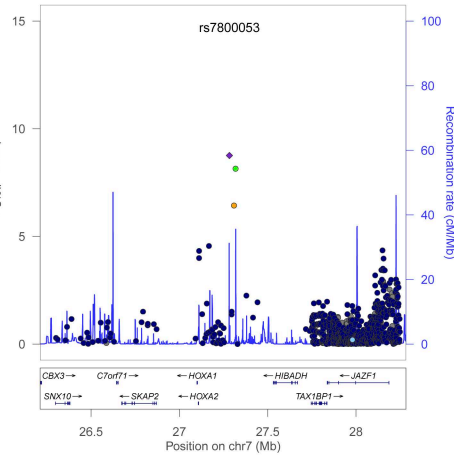
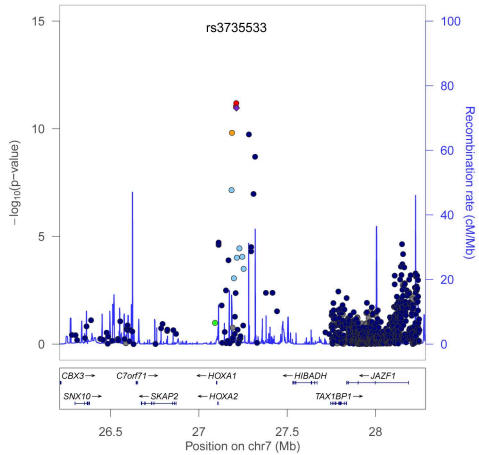
SBP



Analysis Conditional on rs7800053

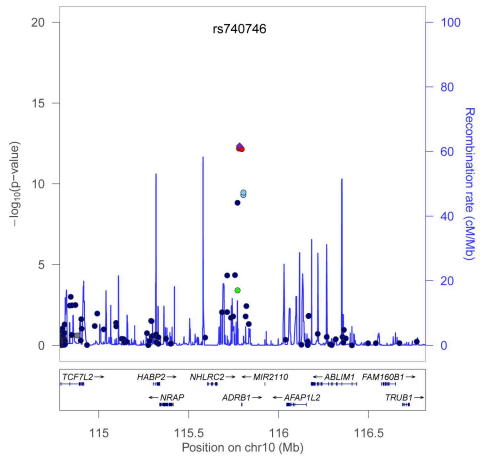


DBP



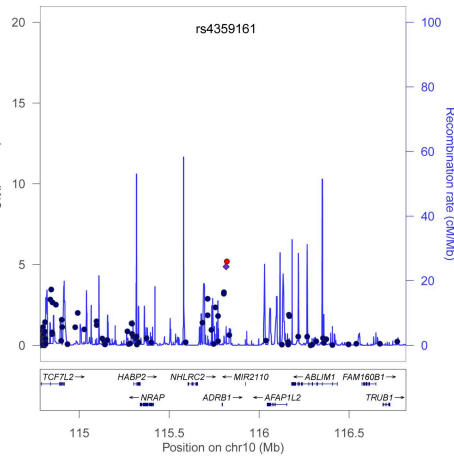
ADRB1

Unconditional Analysis

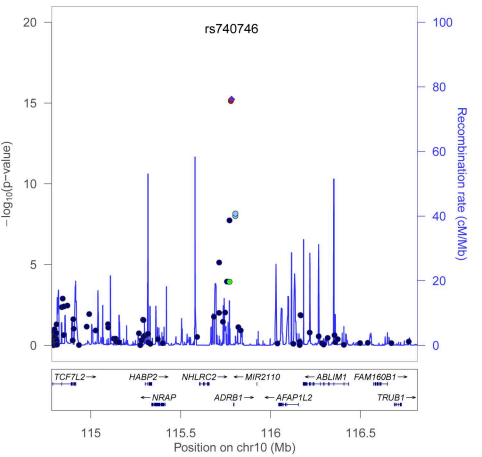


Analysis Conditional on rs740746

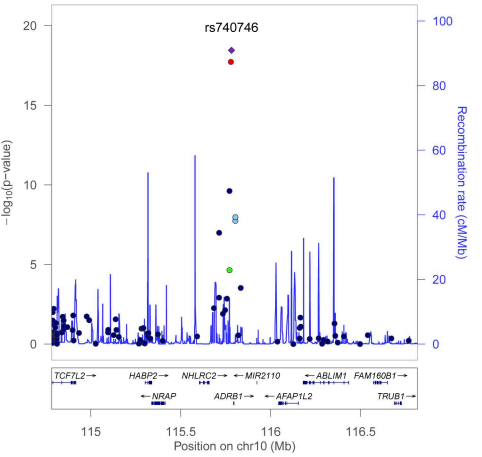
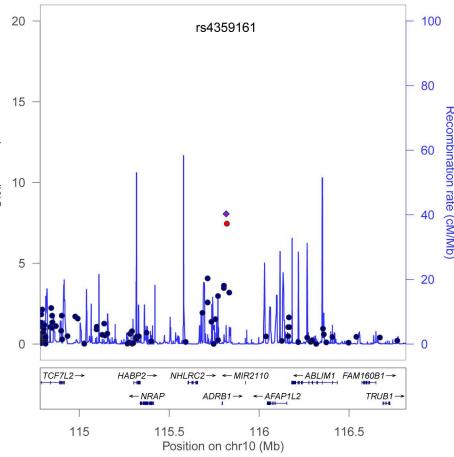
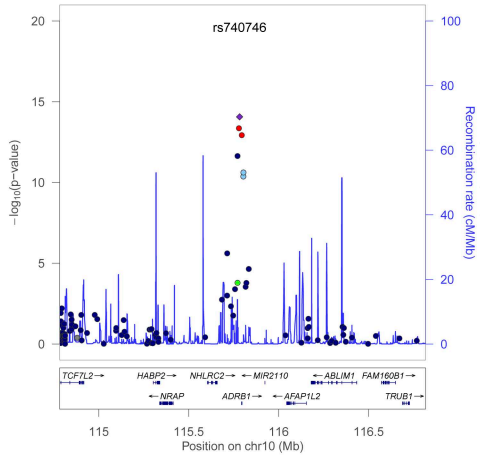
SBP



Analysis Conditional on rs4359161



DBP



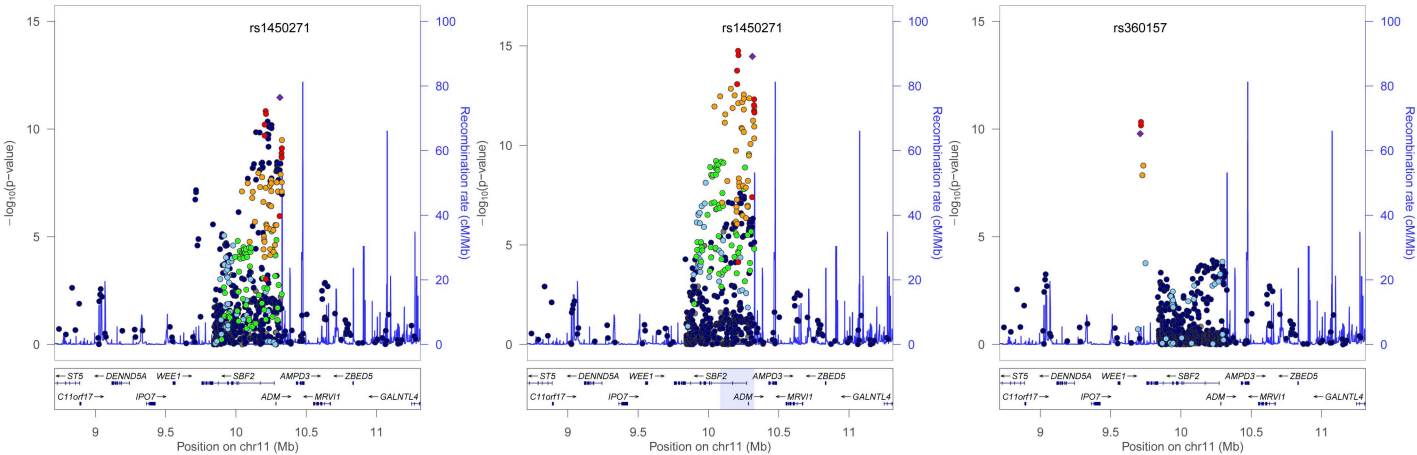
ADM

Unconditional Analysis

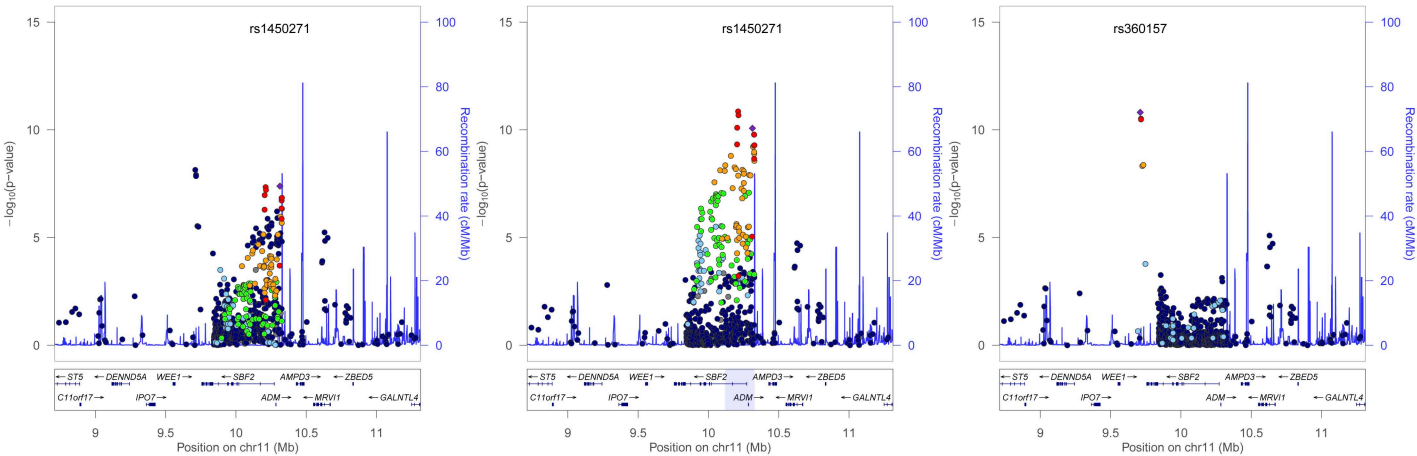
Analysis Conditional on rs360157

Analysis Conditional on rs1450271

SBP



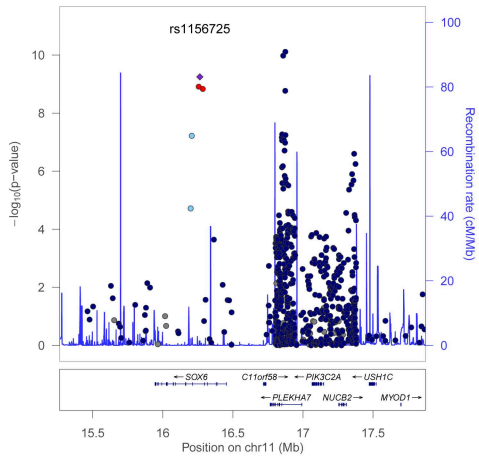
DBP



PLEKHA7

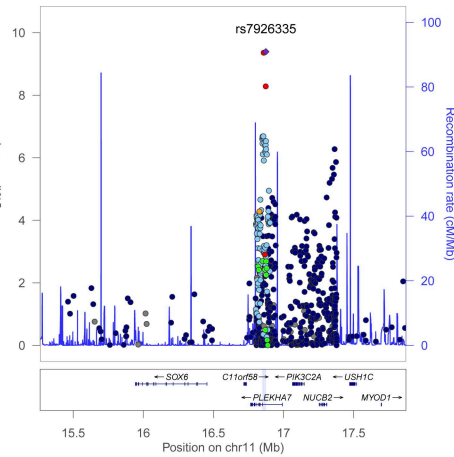
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Unconditional Analysis

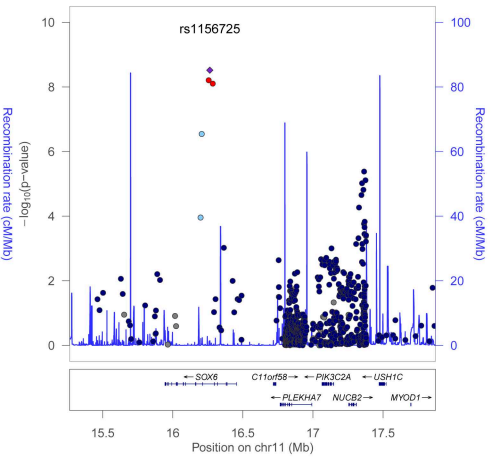


Analysis Conditional on rs1156725

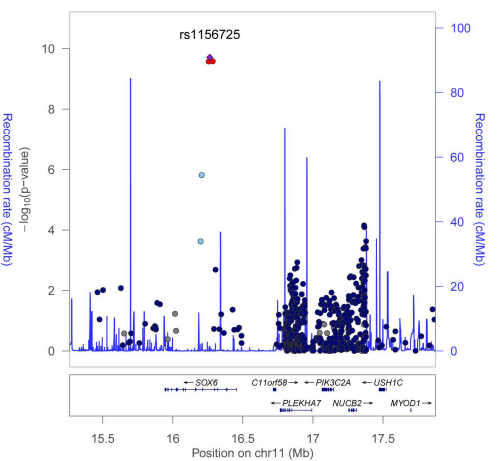
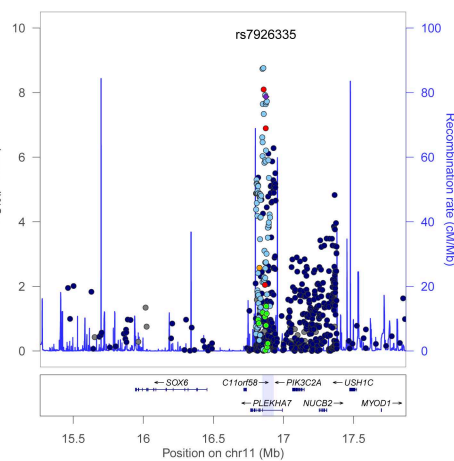
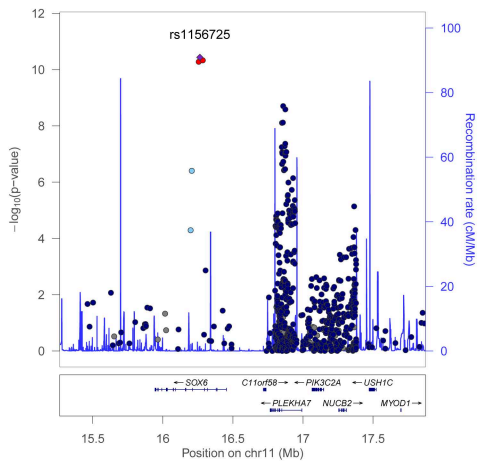
SBP



Analysis Conditional on rs7926335

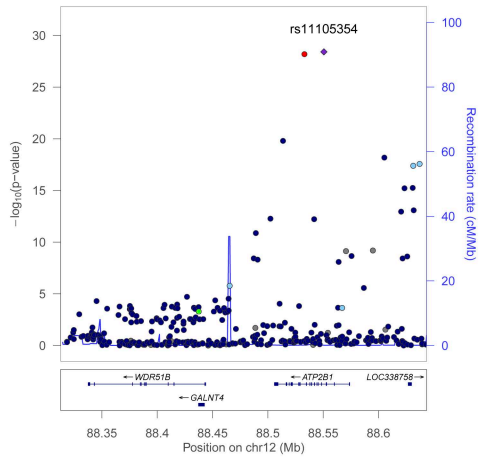


DBP



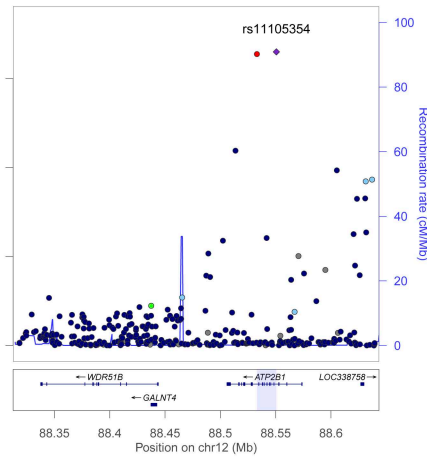
ATP2B1

Unconditional Analysis

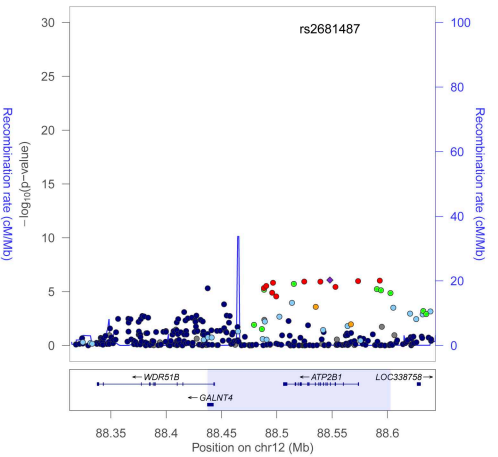


Analysis Conditional on rs2681487

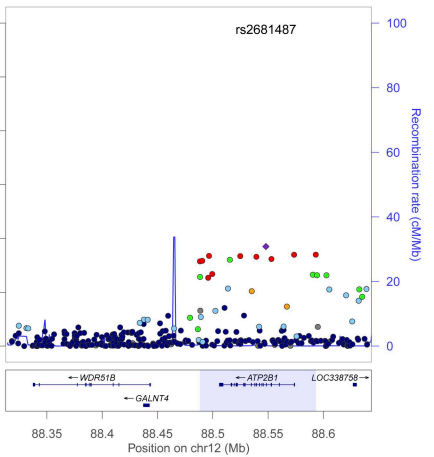
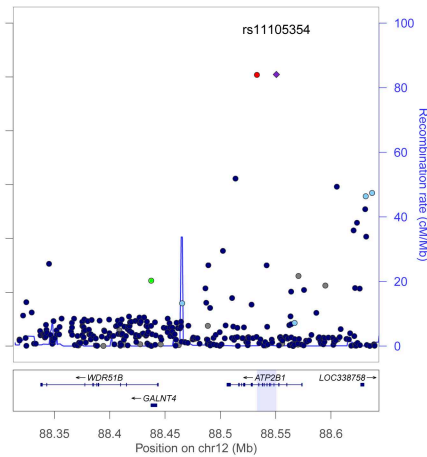
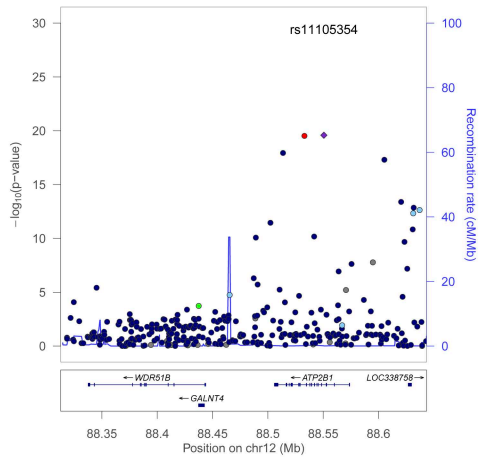
SBP



Analysis Conditional on rs11105354

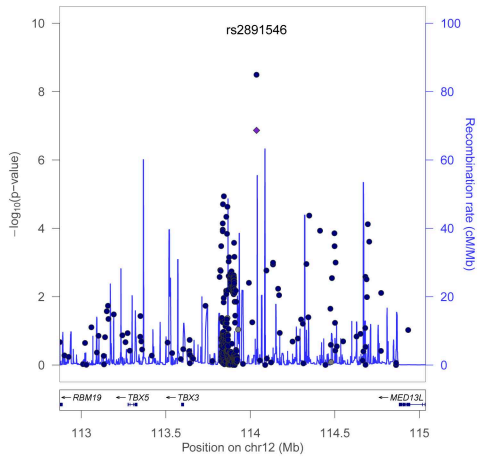


DBP



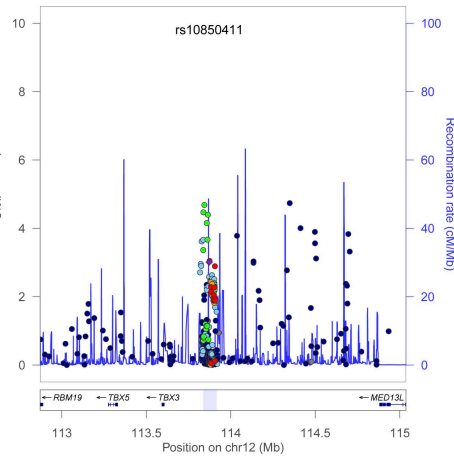
TBX5-TBX3

Unconditional Analysis

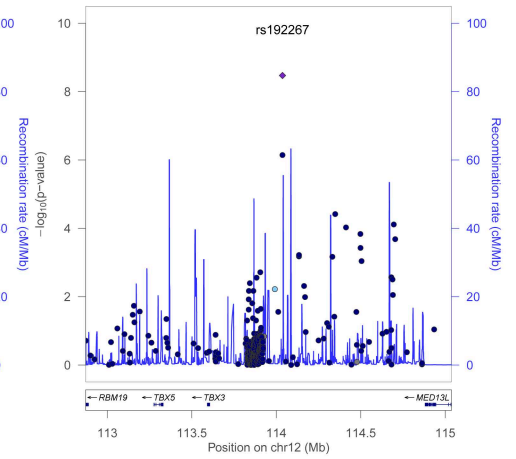


Analysis Conditional on rs192267

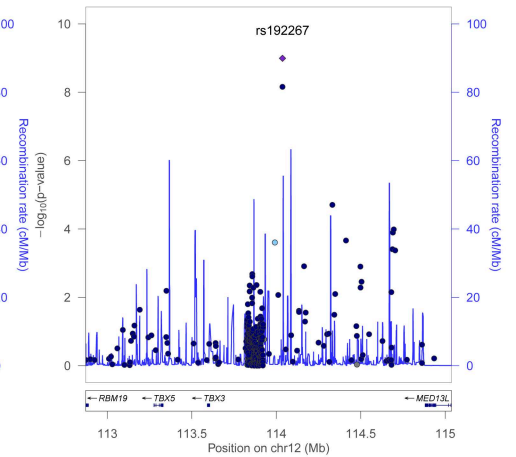
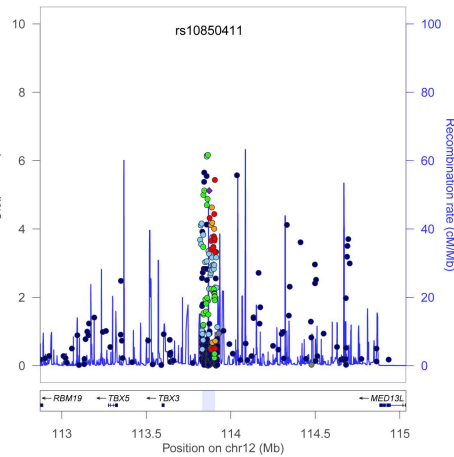
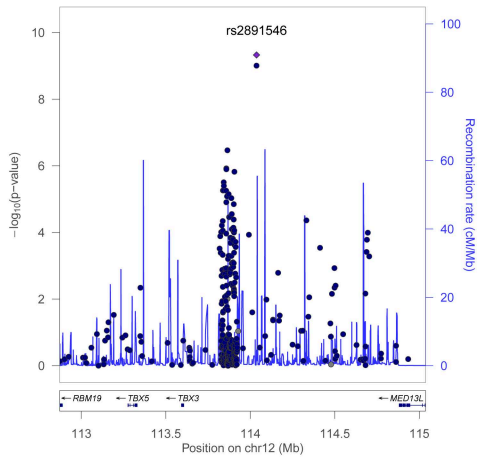
SBP

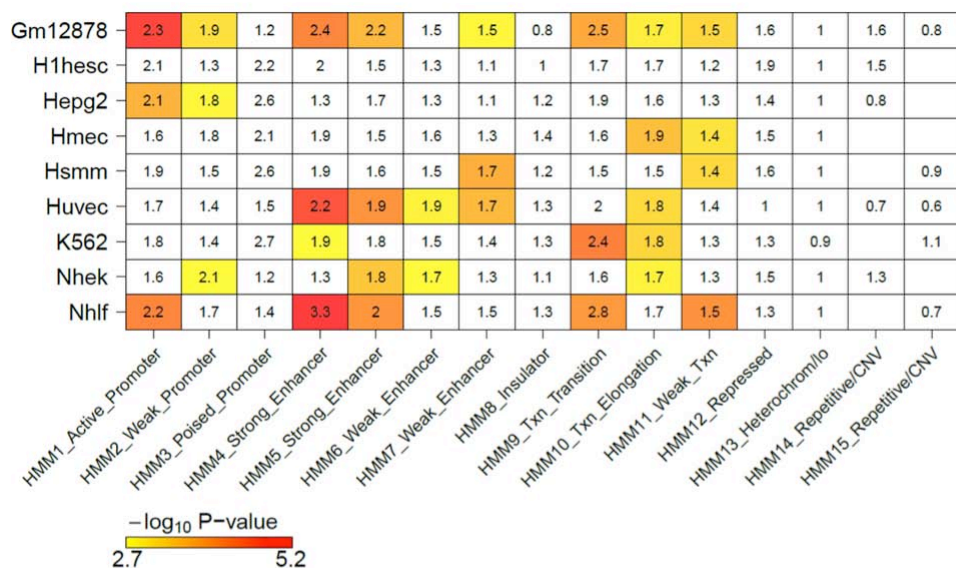


Analysis Conditional on rs10850411



DBP



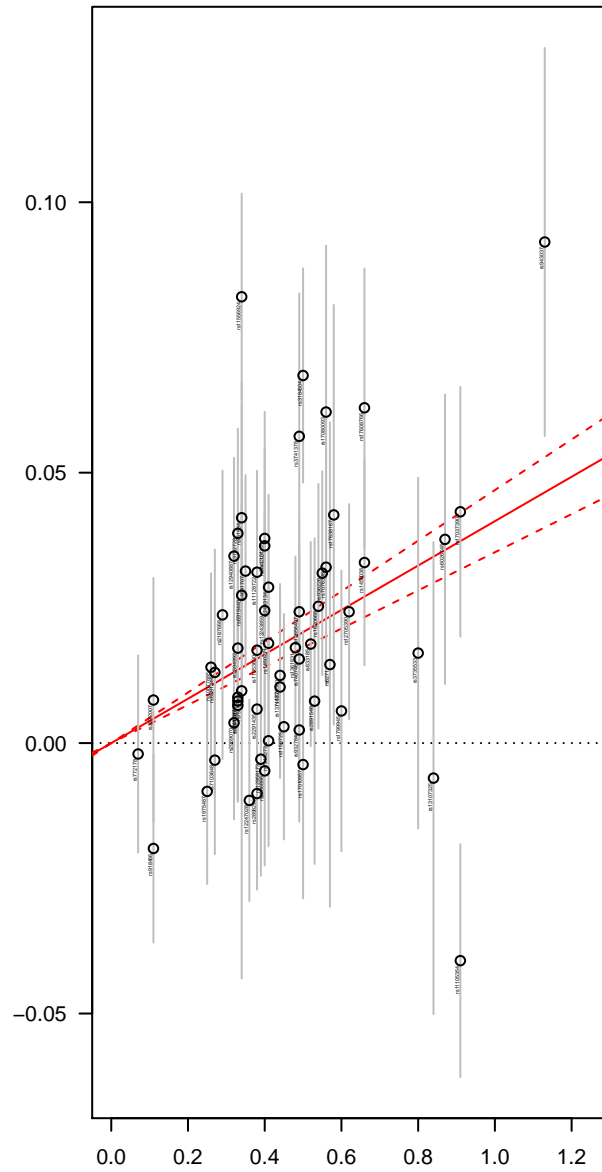


Supplementary Figure 8. Matrix of fold enrichment for BP SNPs in predicted chromatin states in nine human cell types. The boxes are colored by $-\log_{10}P$ for enrichment. The white color indicates lack of significance after Bonferroni correction for 15 chromatin states and 9 tissues (see **Supplementary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

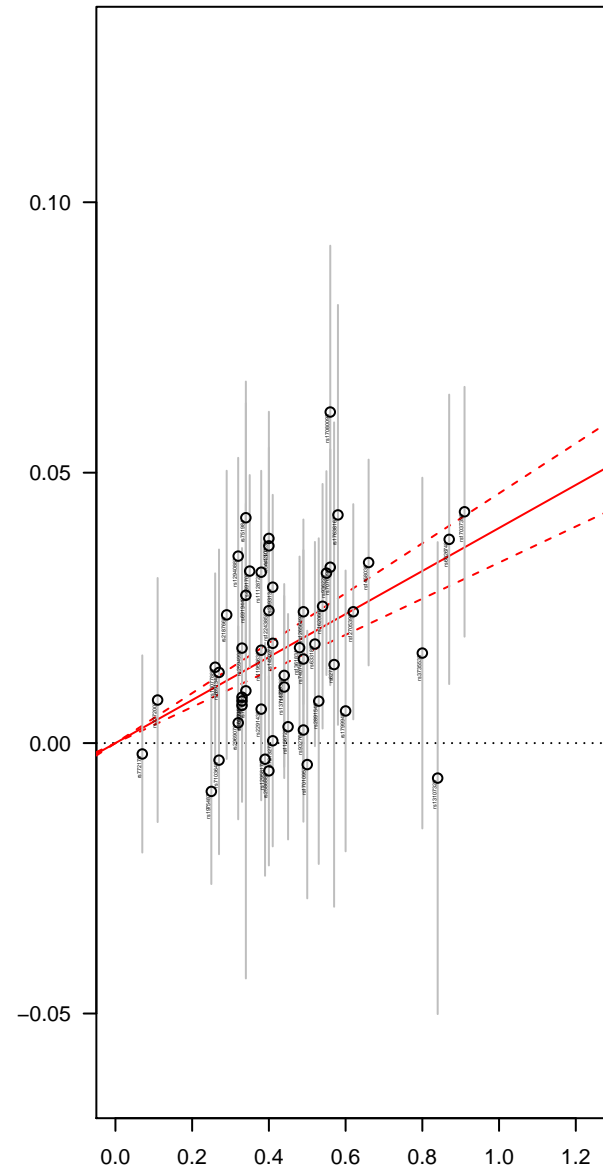


Supplementary Figure 9. Effect allele frequency plots for all samples of non-European ancestry. The effect allele frequency of each study is plotted against the effect allele frequency of every other study for all 66 index SNPs. The study names are indicated in the middle diagonal.

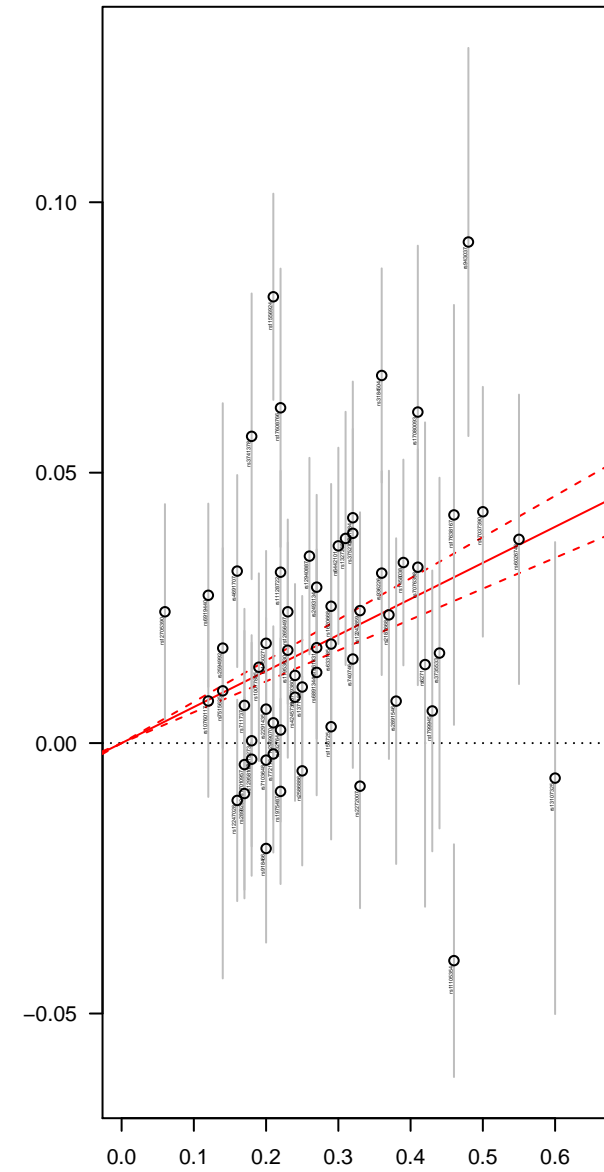
CAD, SBP; all SNPs



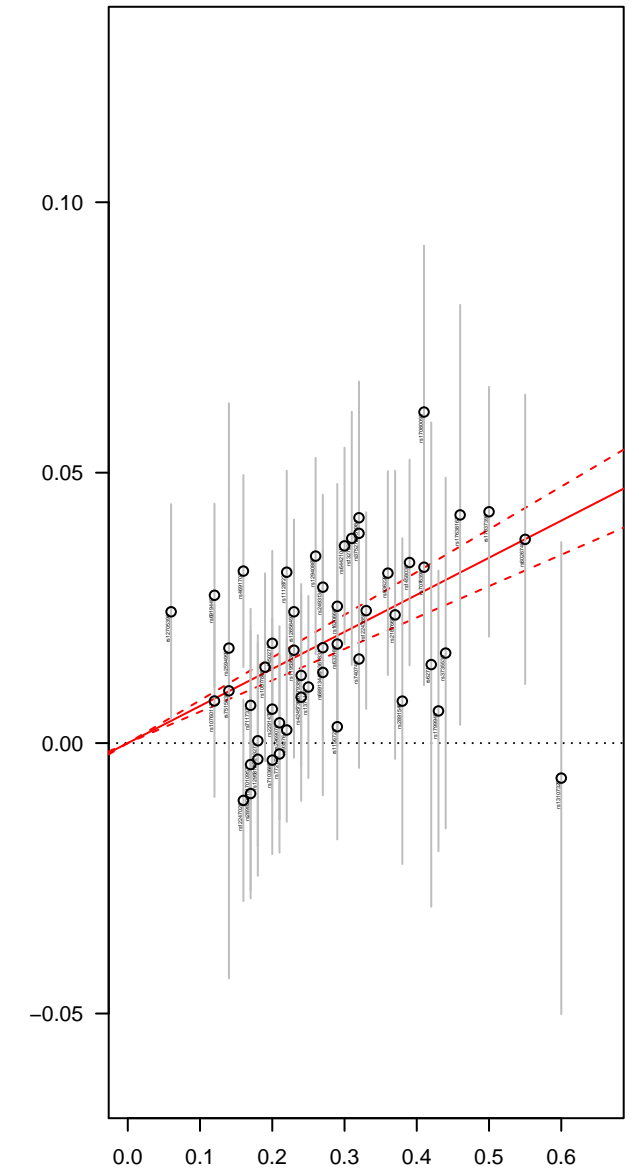
CAD, SBP; 10 pruned



CAD, DBP; all SNPs

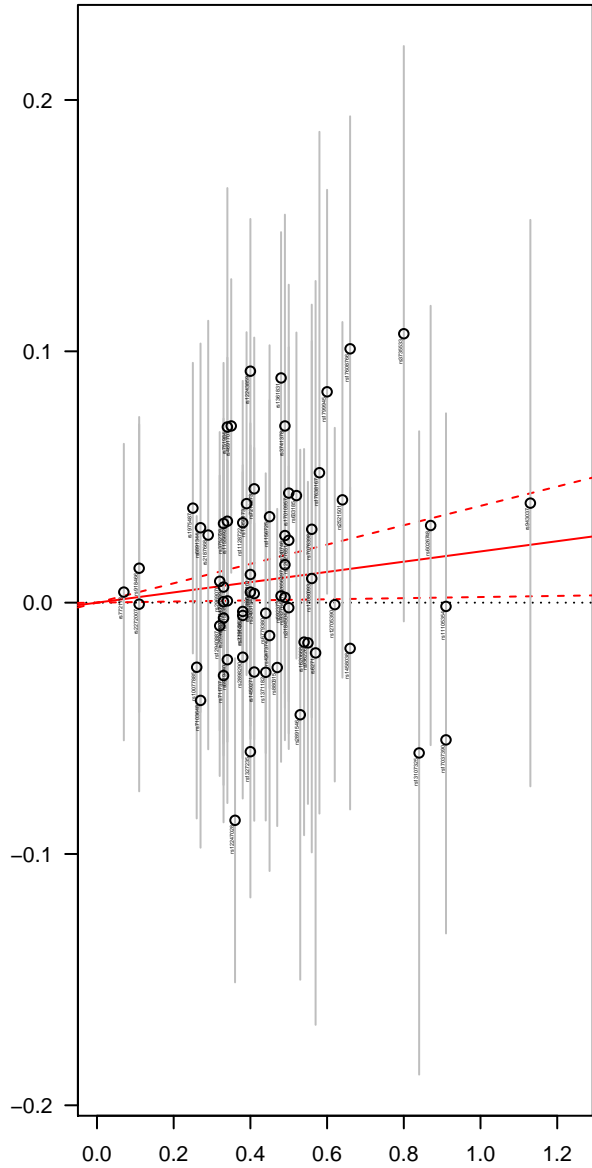


CAD, DBP; 10 pruned

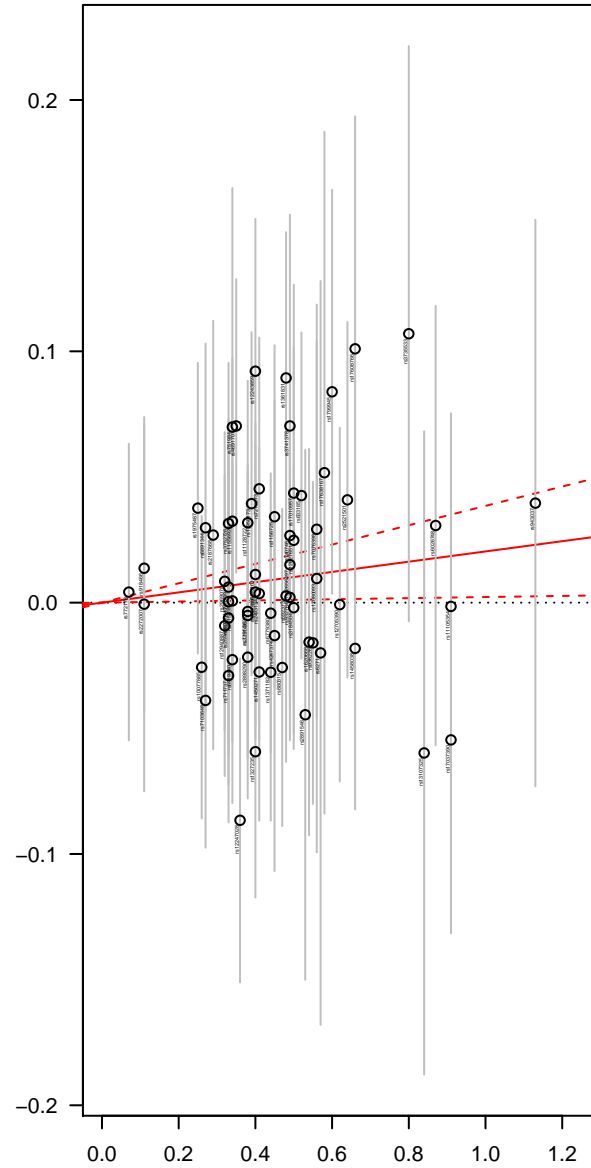


Supplementary Figures 10. Risk score analyses results for each SNP. The BP effect is on the x-axis, the outcome effect on the y-axis.

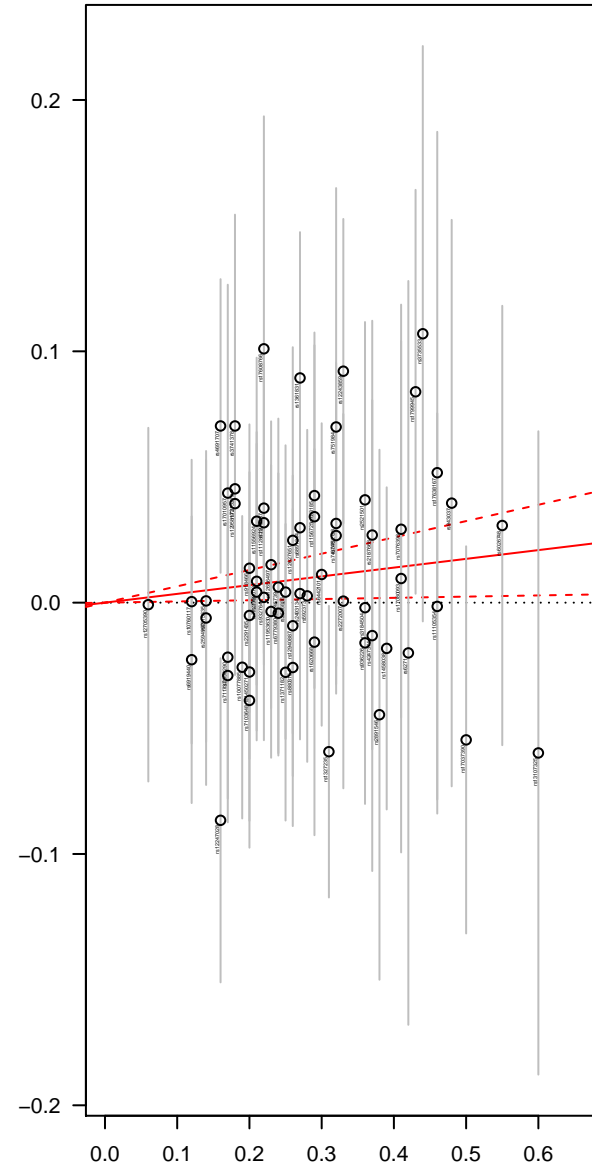
heart failure, SBP; all SNPs



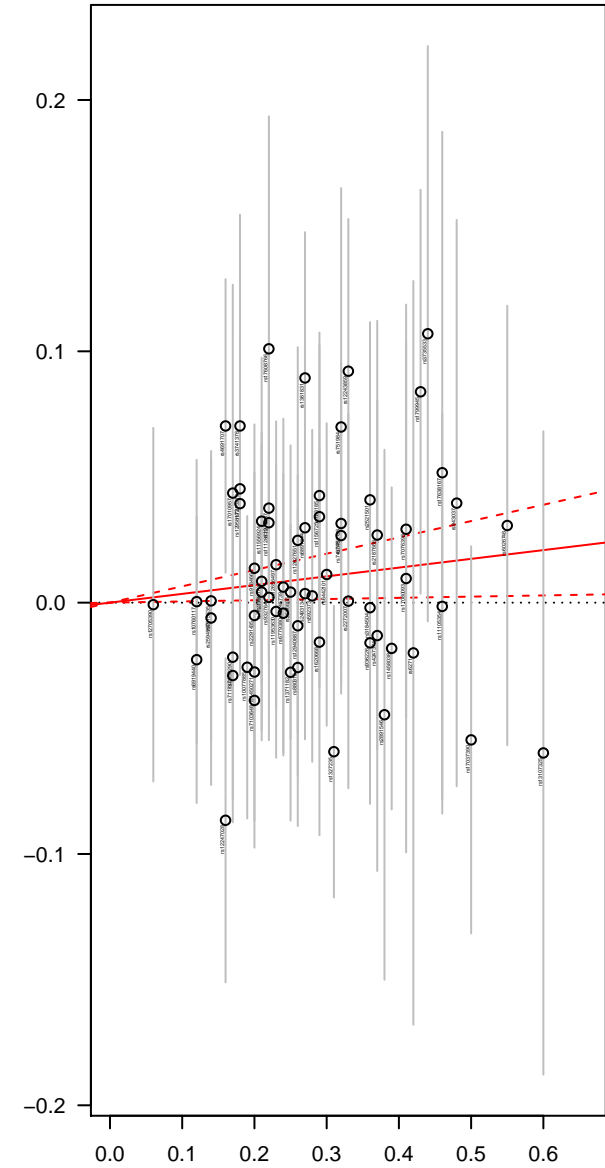
heart failure, SBP; 0 pruned



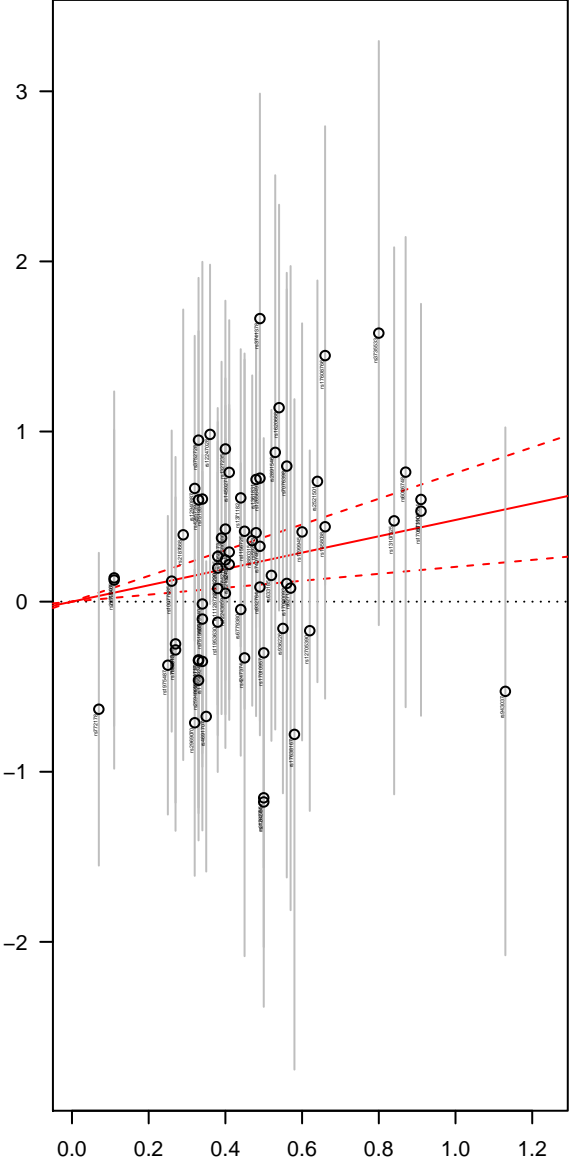
heart failure, DBP; all SNPs



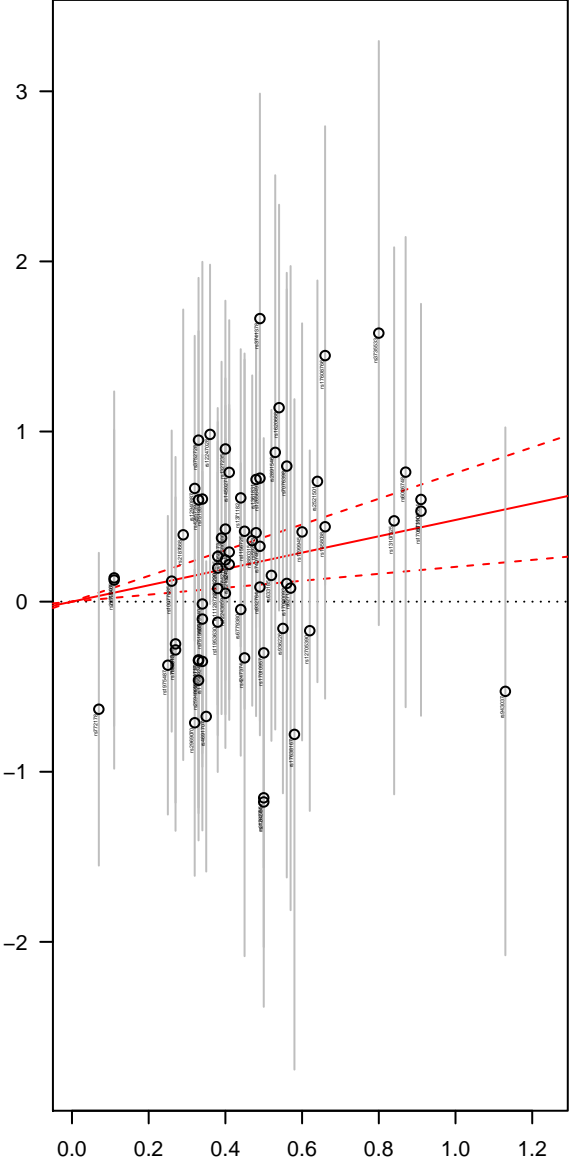
heart failure, DBP; 0 pruned



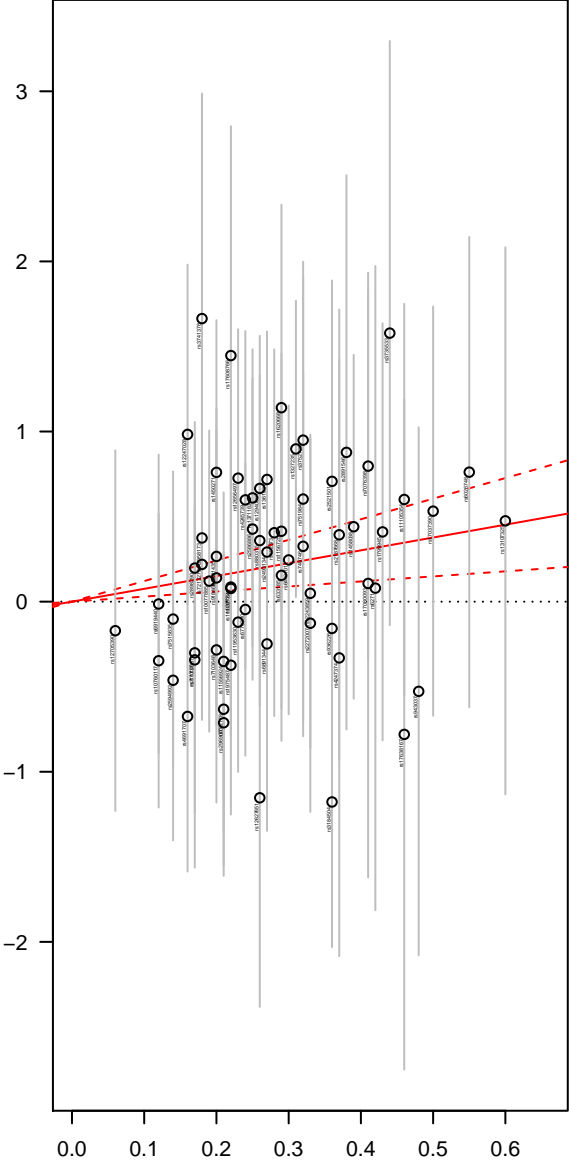
LV mass, SBP; all SNPs



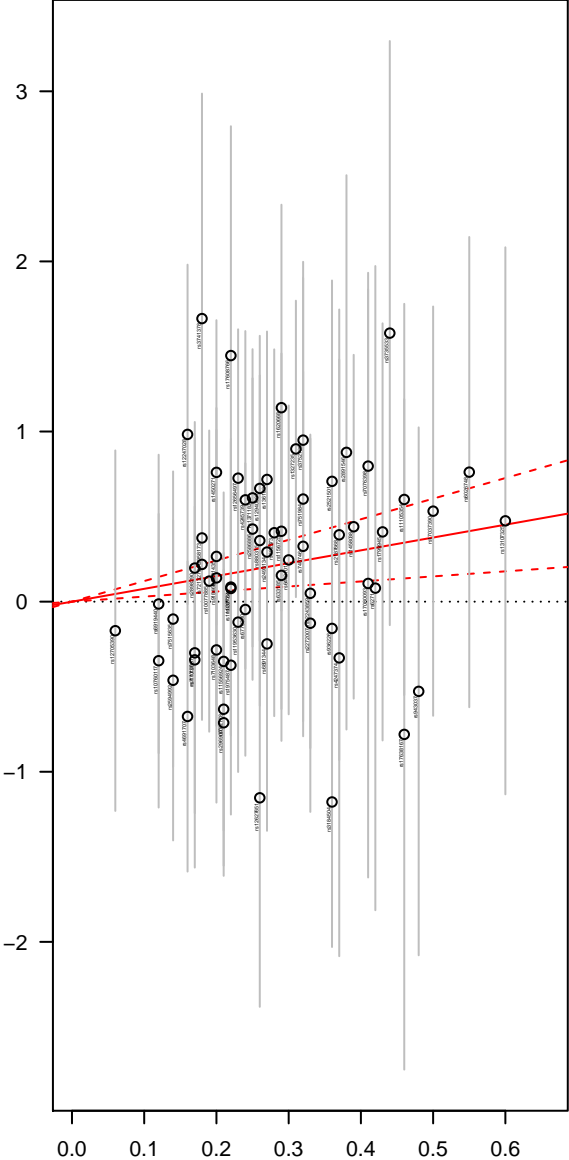
LV mass, SBP; 0 pruned



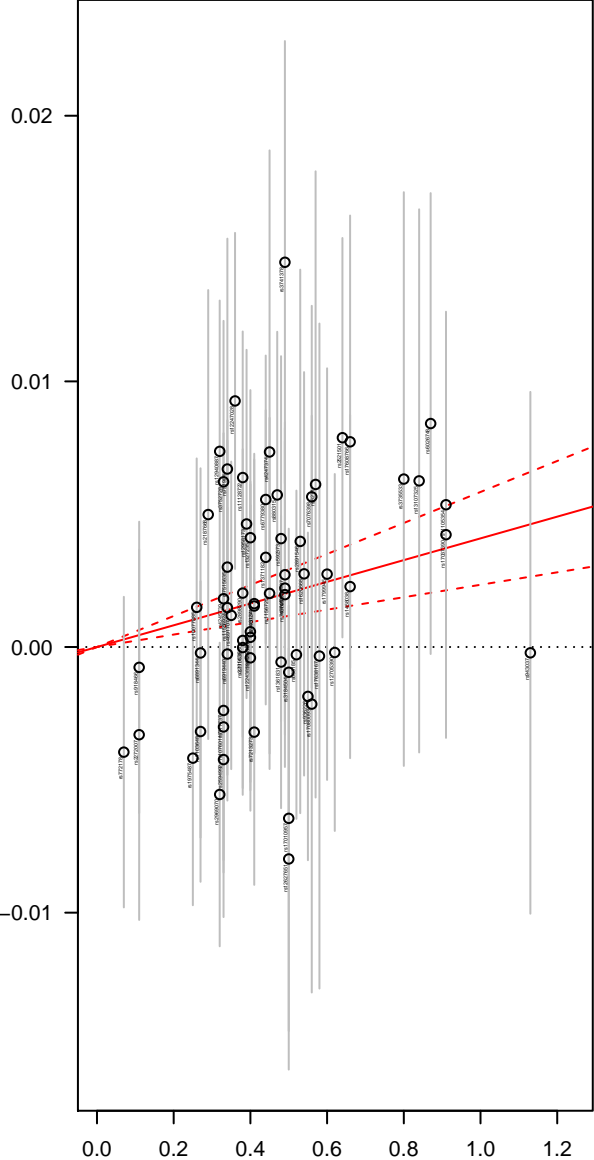
LV mass, DBP; all SNPs



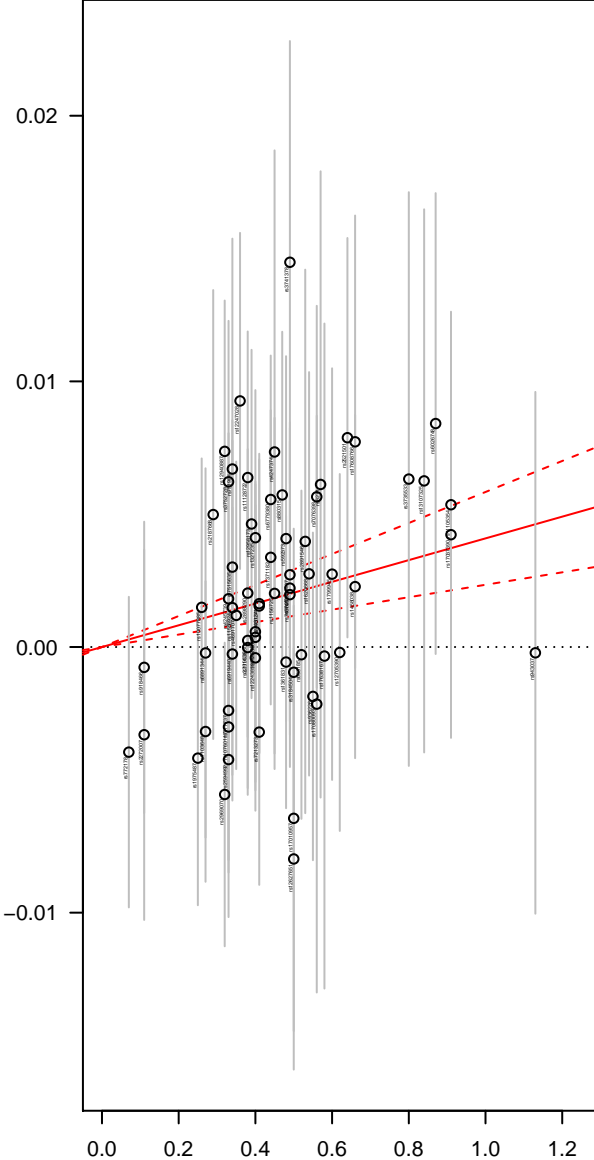
LV mass, DBP; 0 pruned



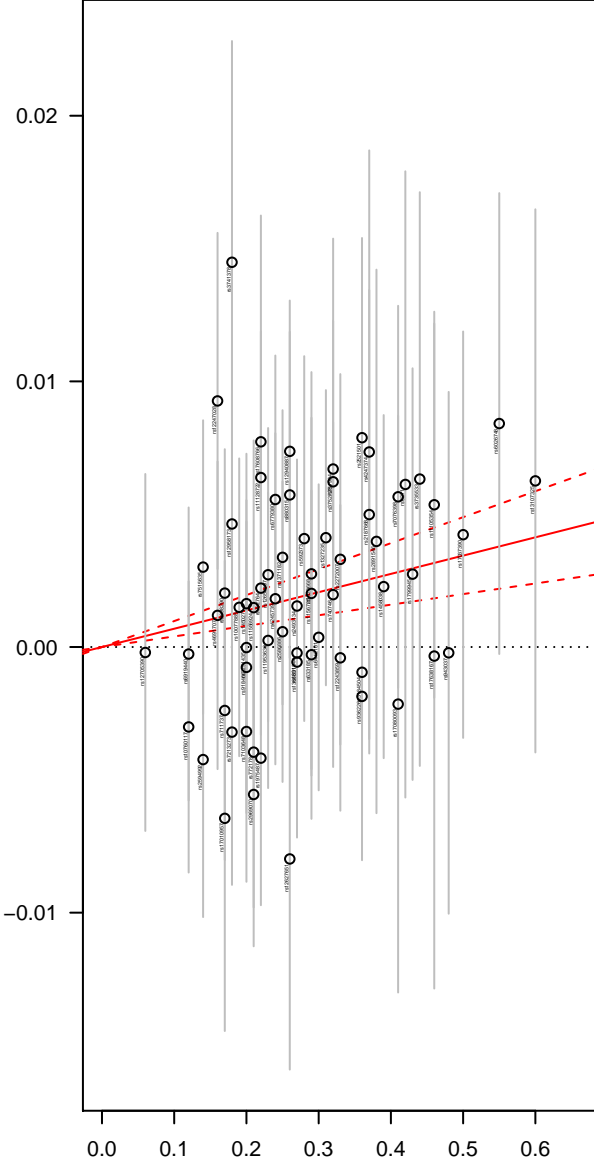
LV wall thickness, SBP; all SNPs



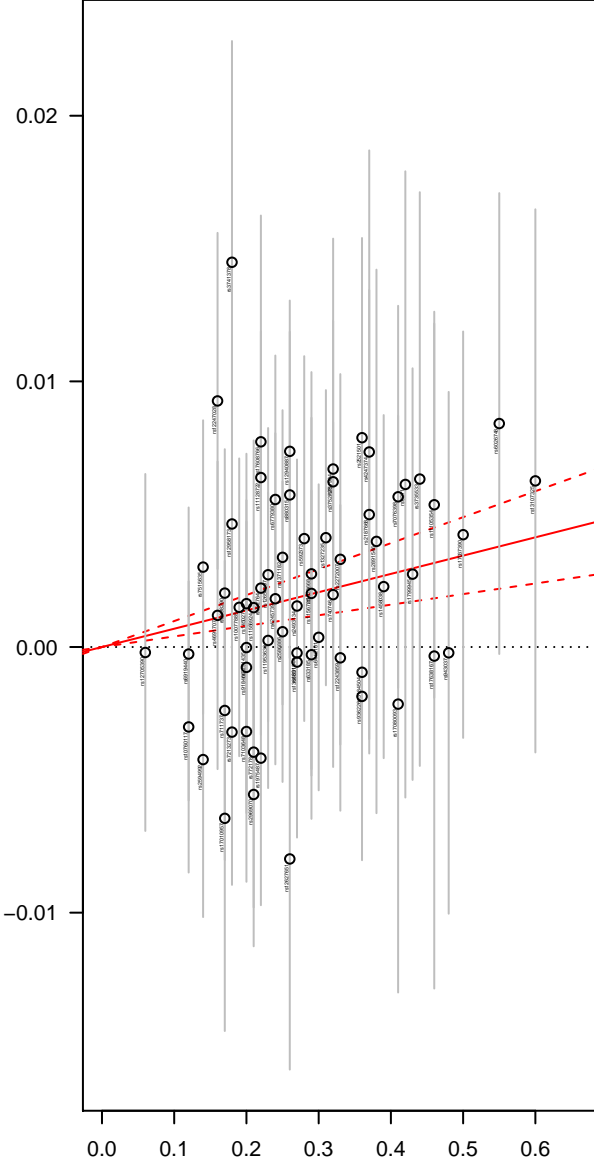
LV wall thickness, SBP; 0 pruned



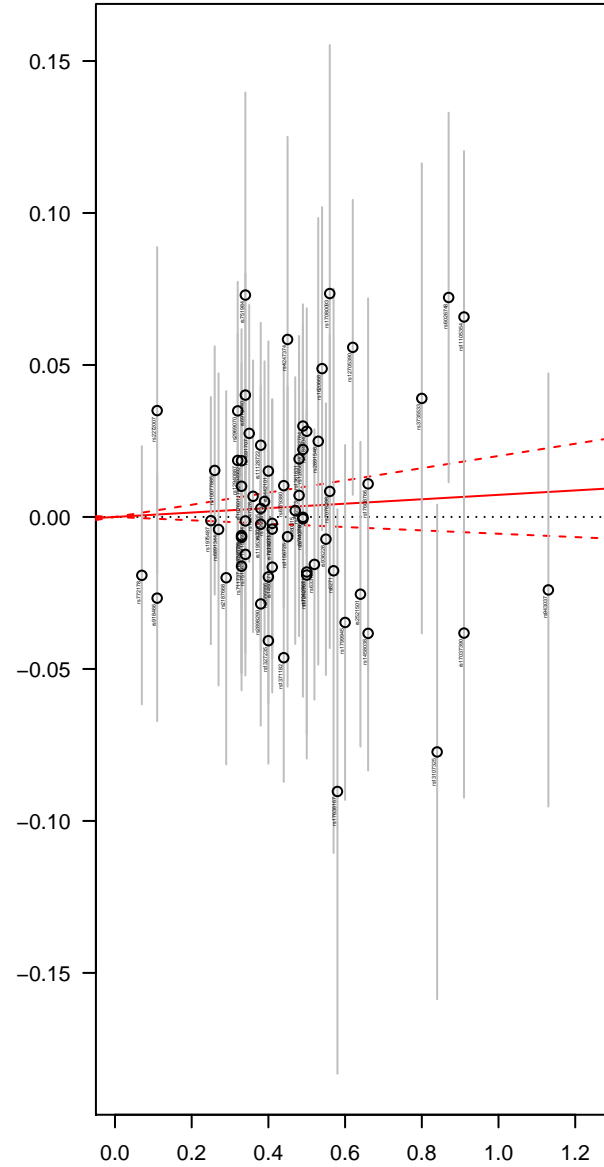
LV wall thickness, DBP; all SNPs



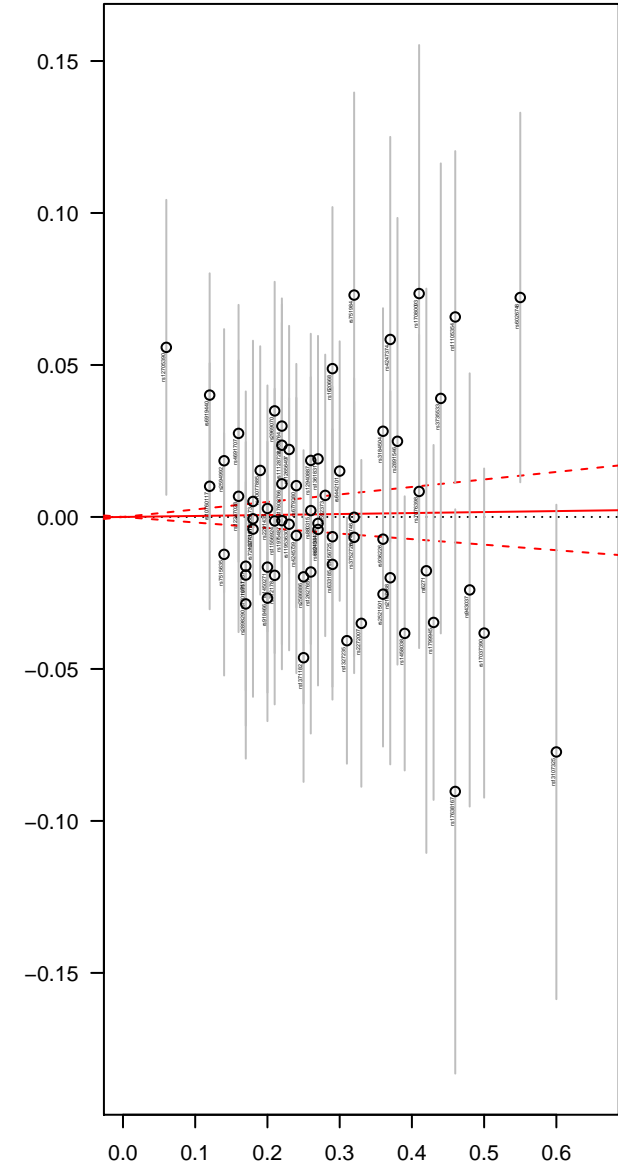
LV wall thickness, DBP; 0 pruned



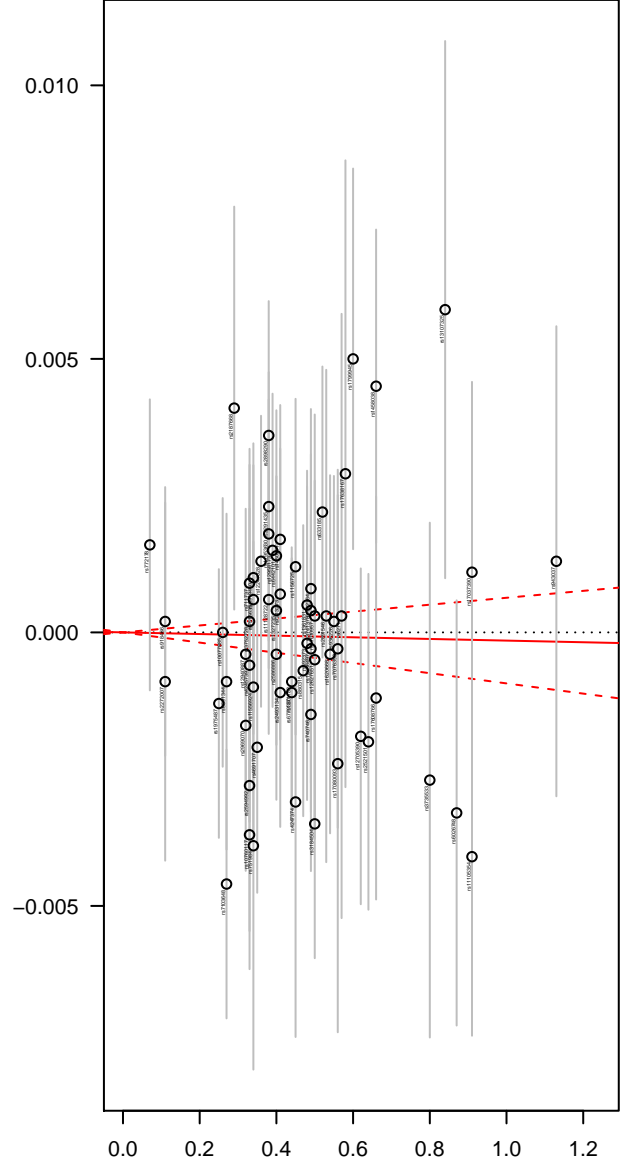
CKD, SBP; 1 pruned



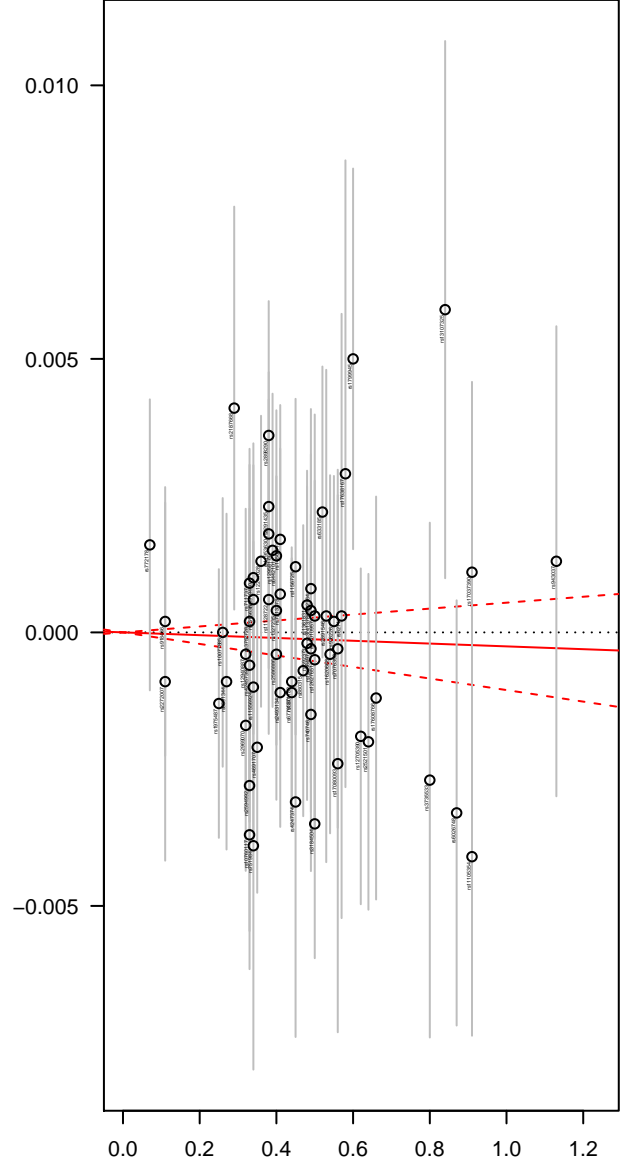
CKD, DBP; 1 pruned



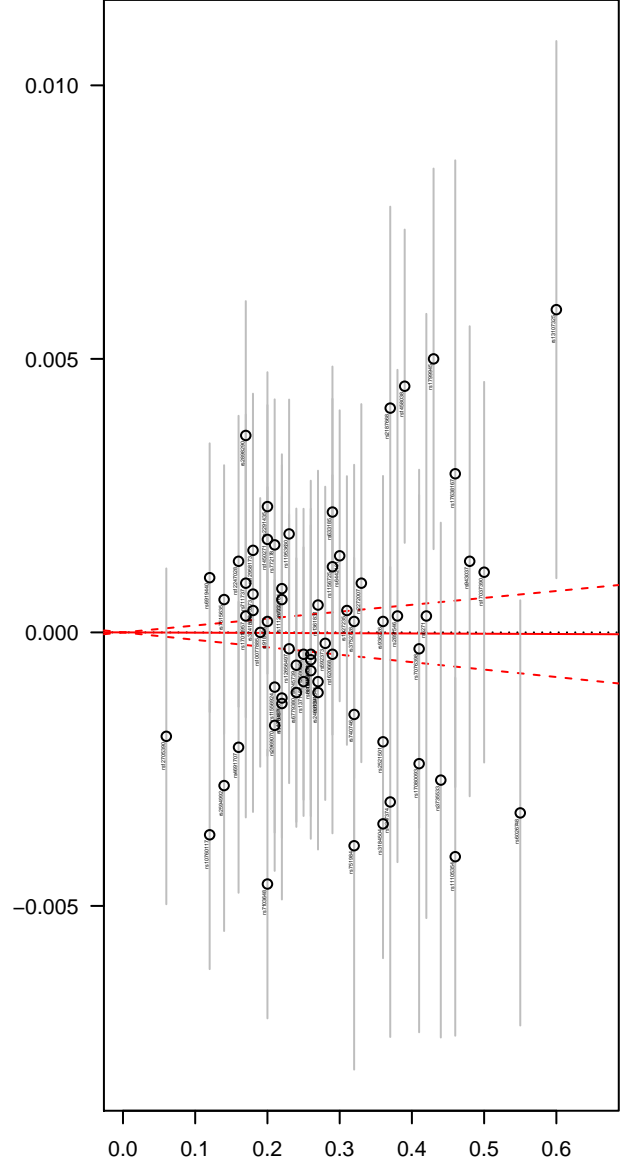
eGFR (based on cr), SBP; all SNPs



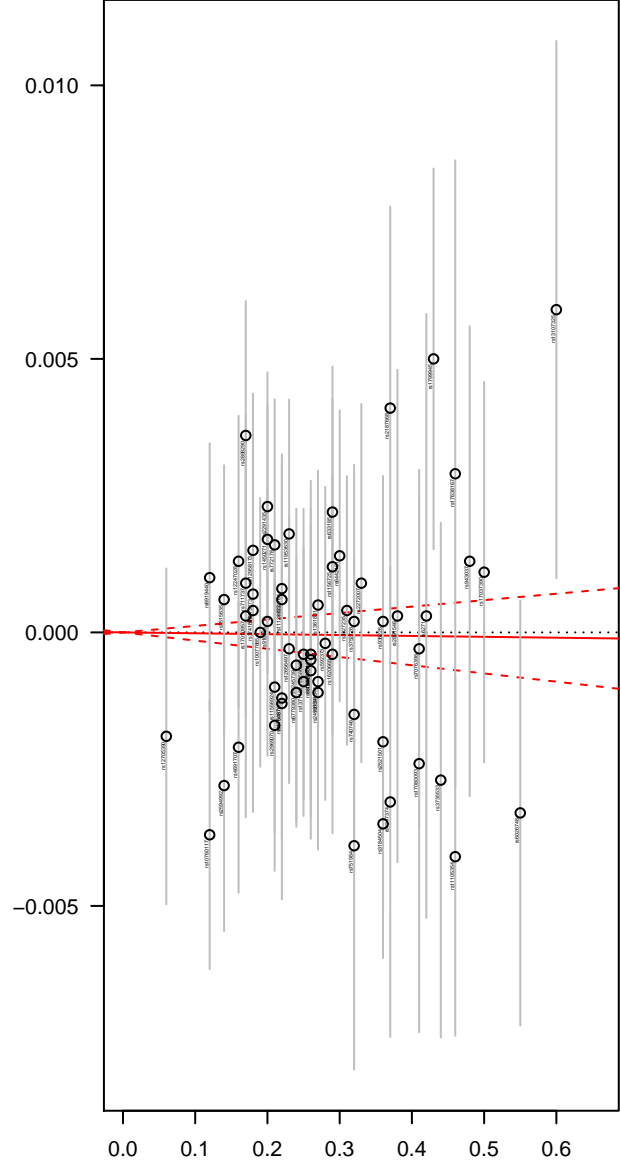
eGFR (based on cr), SBP; 2 pruned



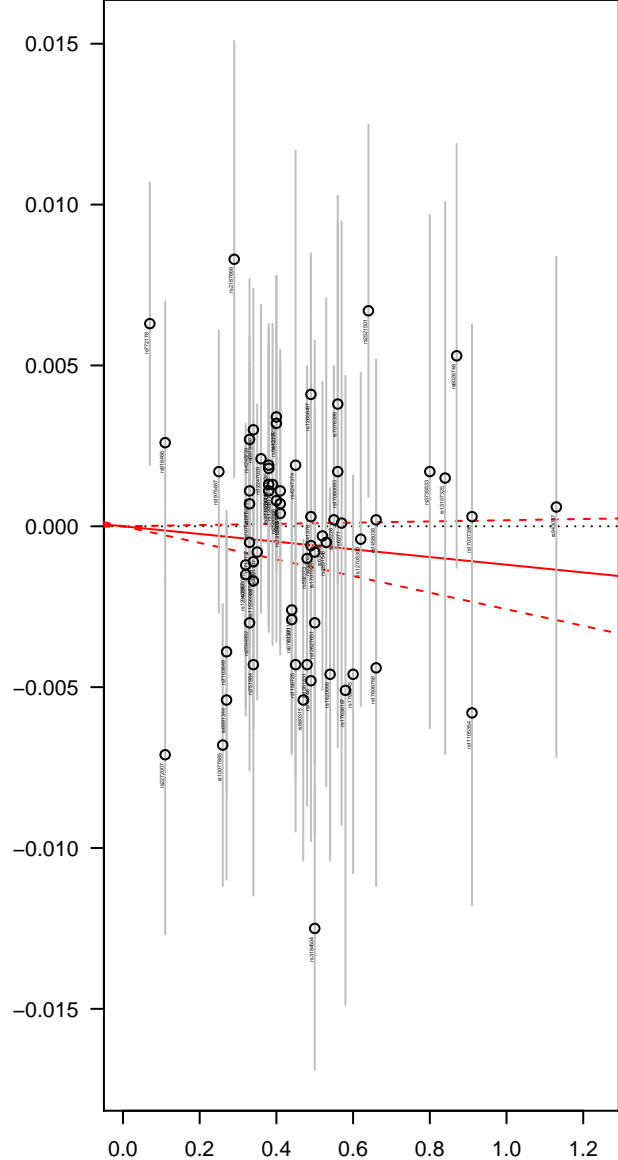
eGFR (based on cr), DBP; all SNPs



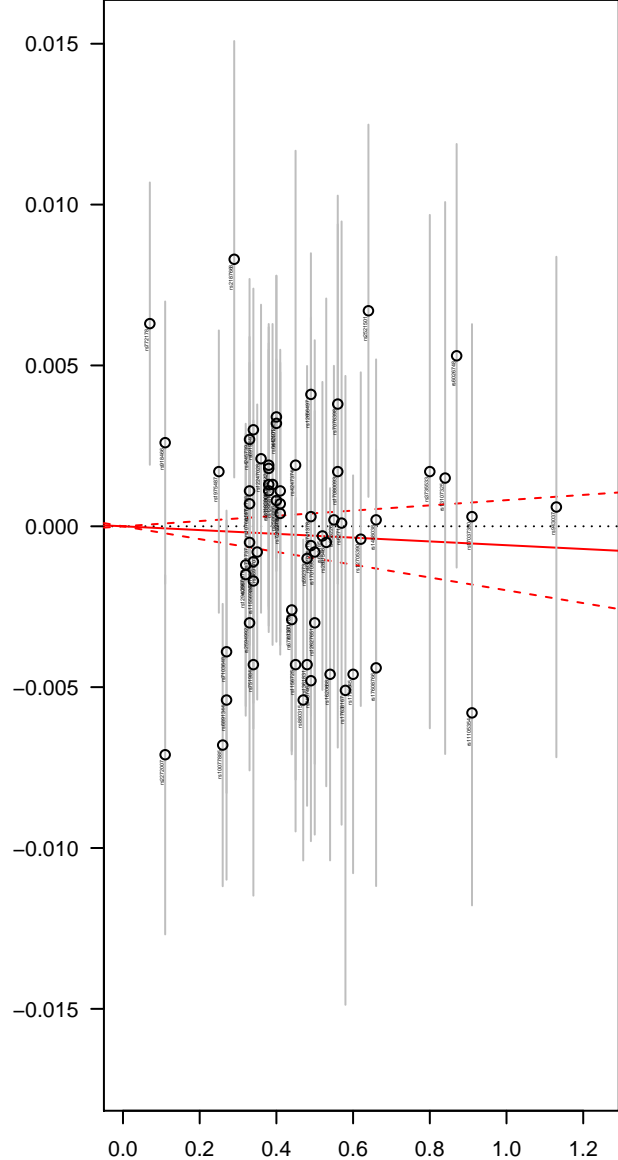
eGFR (based on cr), DBP; 2 pruned



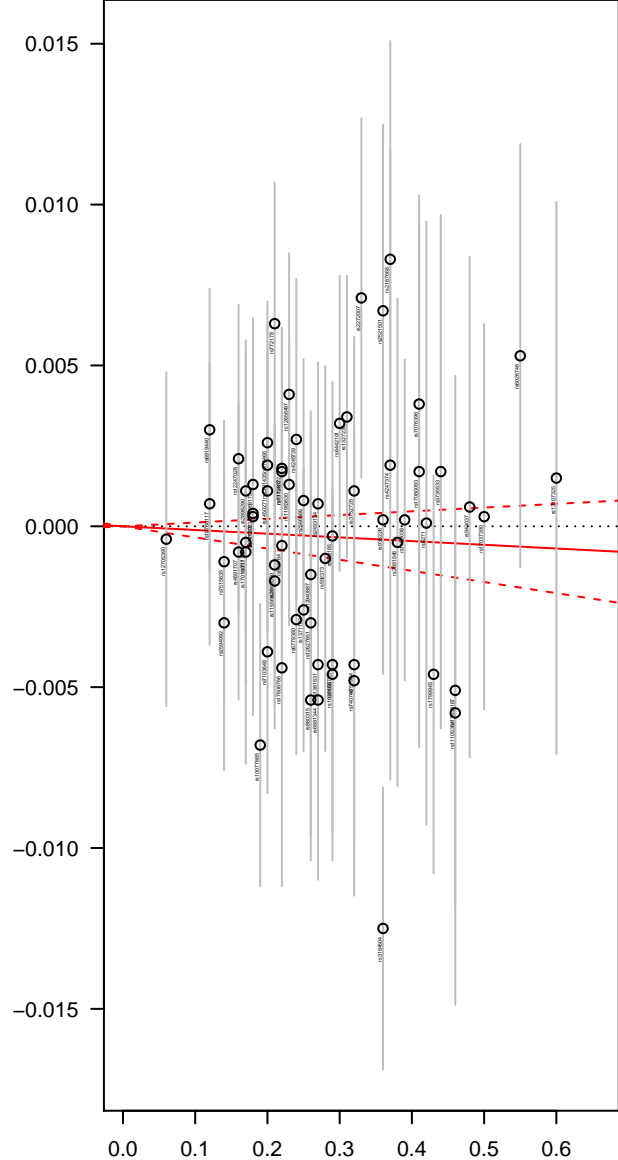
eGFR (based on cystatin), SBP; all SNPs



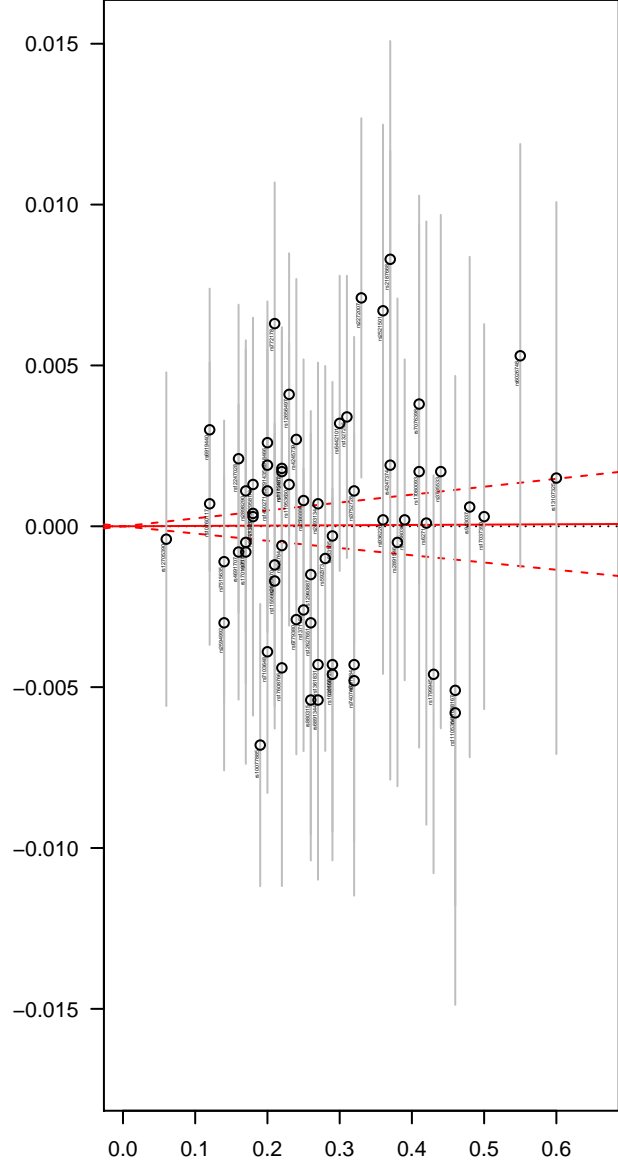
eGFR (based on cystatin), SBP; 1 pruned



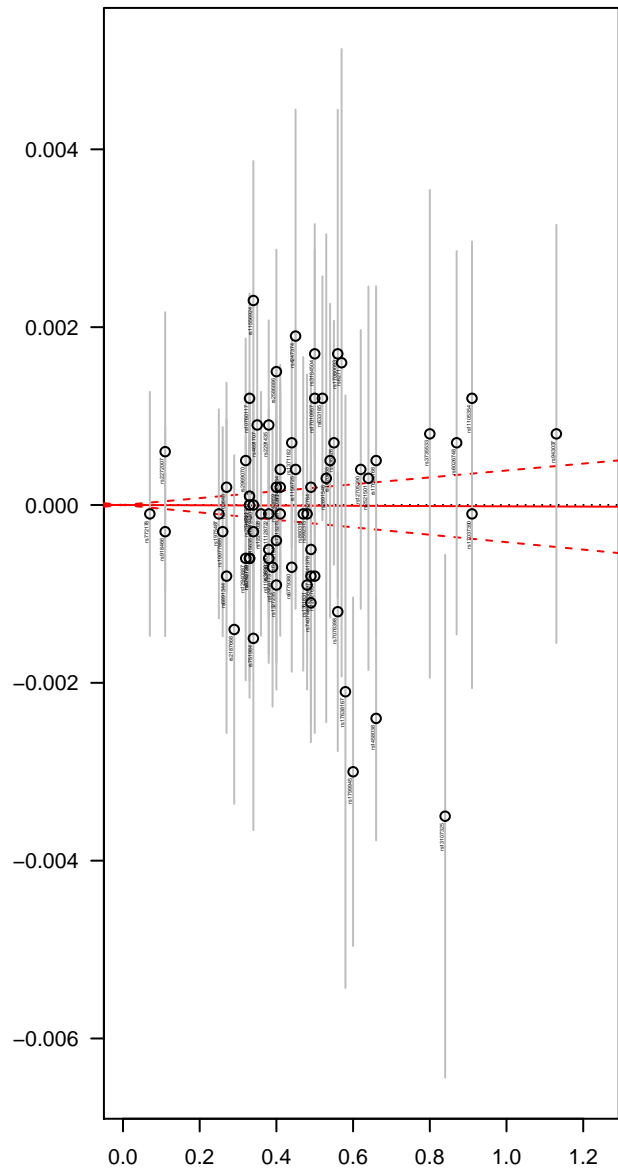
eGFR (based on cystatin), DBP; all SNPs



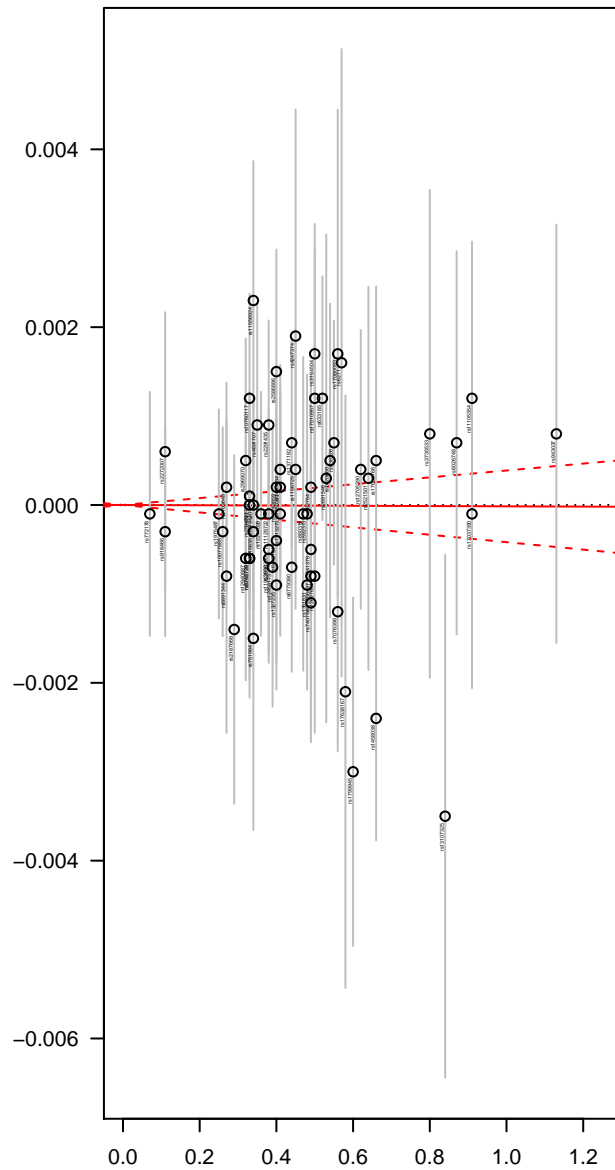
eGFR (based on cystatin), DBP; 1 pruned



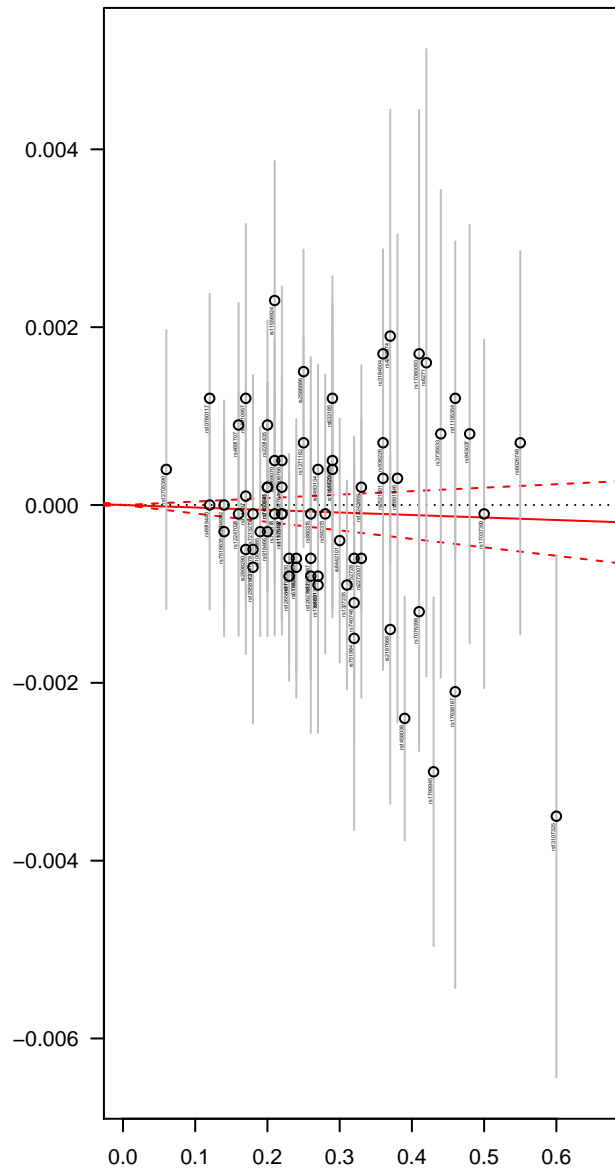
creatinine, SBP; all SNPs



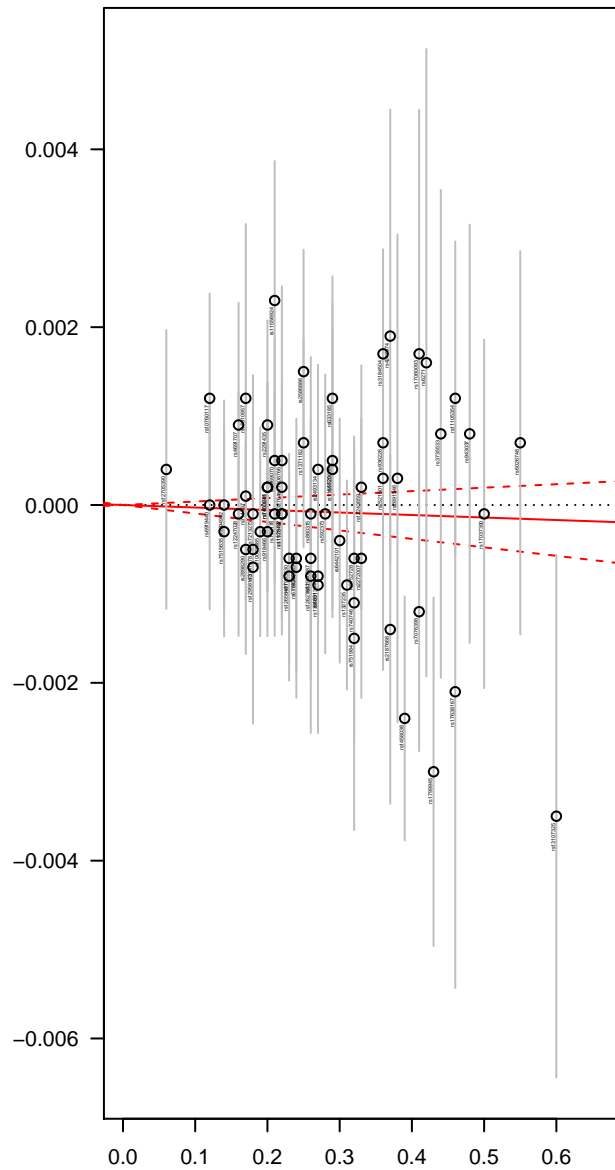
creatinine, SBP; 0 pruned



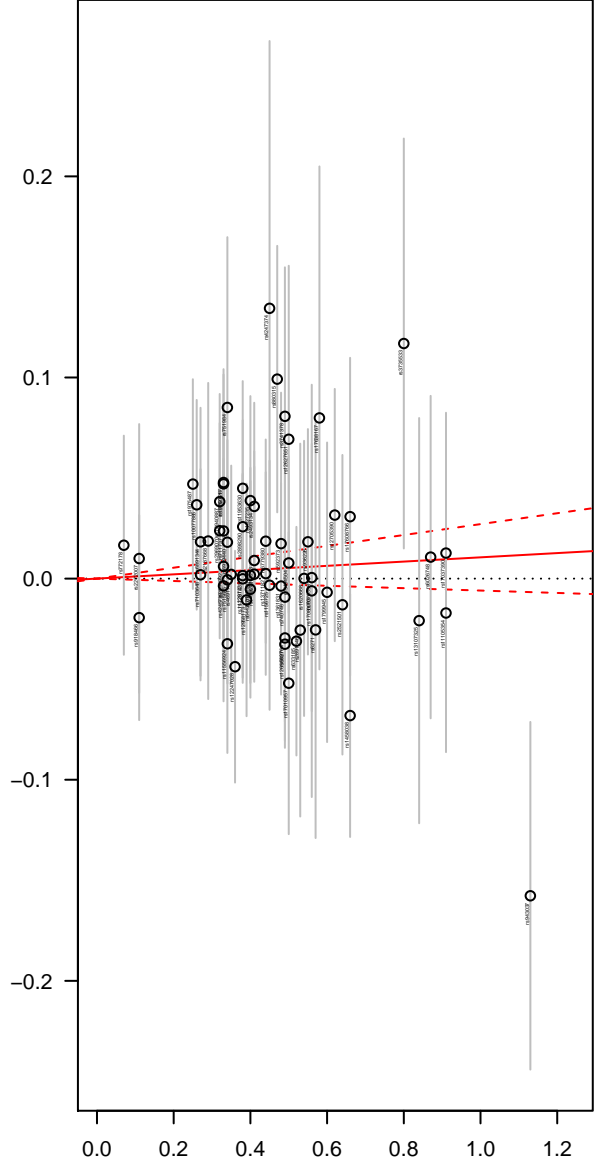
creatinine, DBP; all SNPs



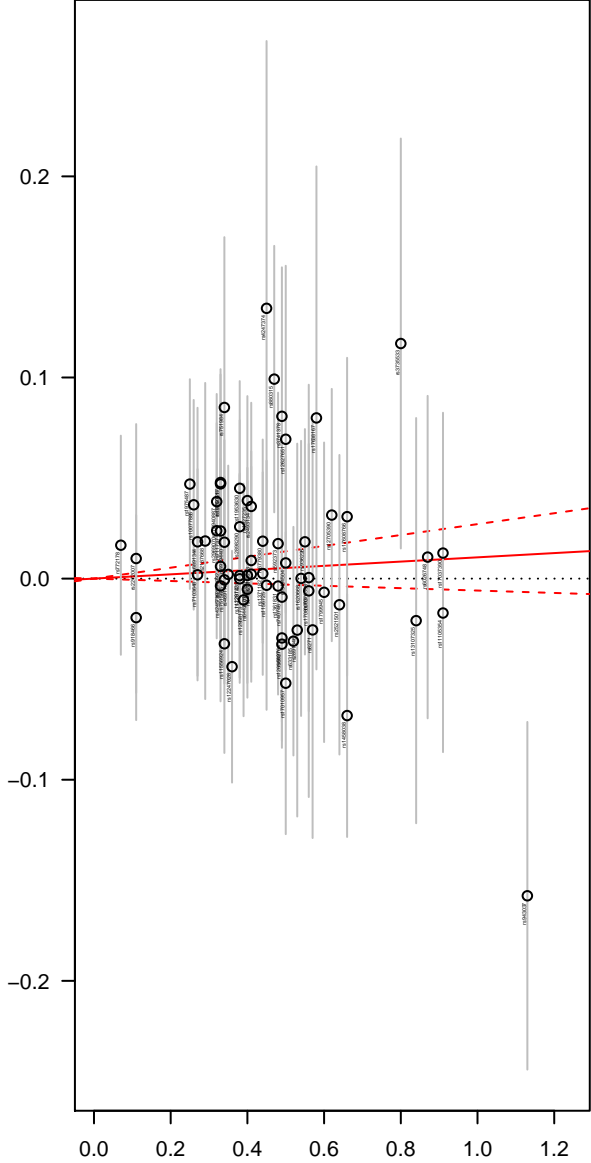
creatinine, DBP; 0 pruned



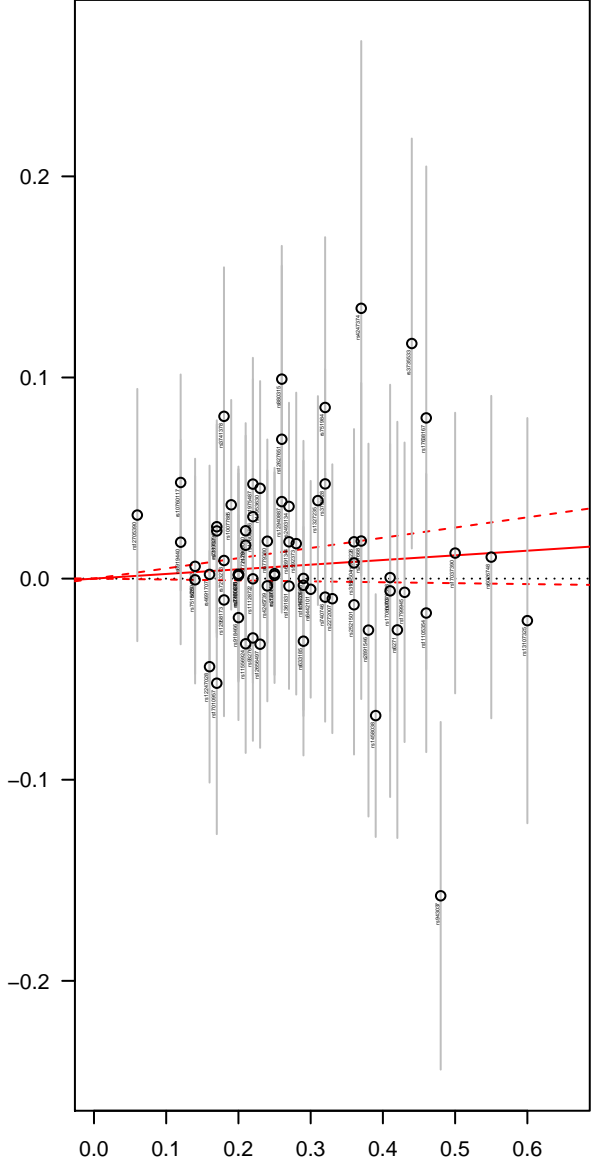
microalbuminuria, SBP; all SNPs



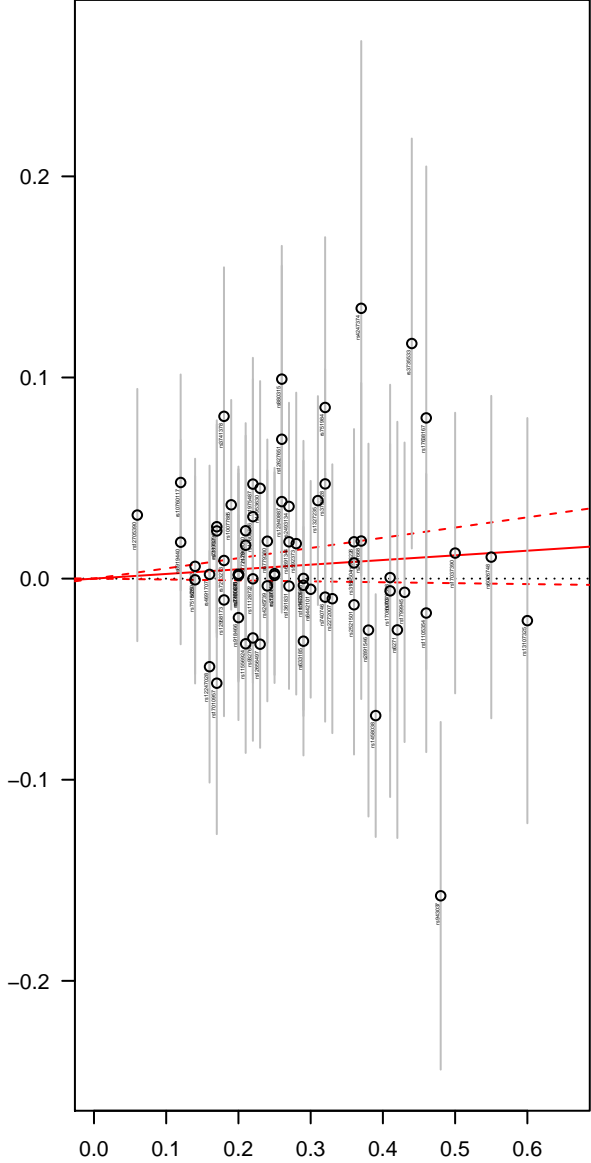
microalbuminuria, SBP; 0 pruned



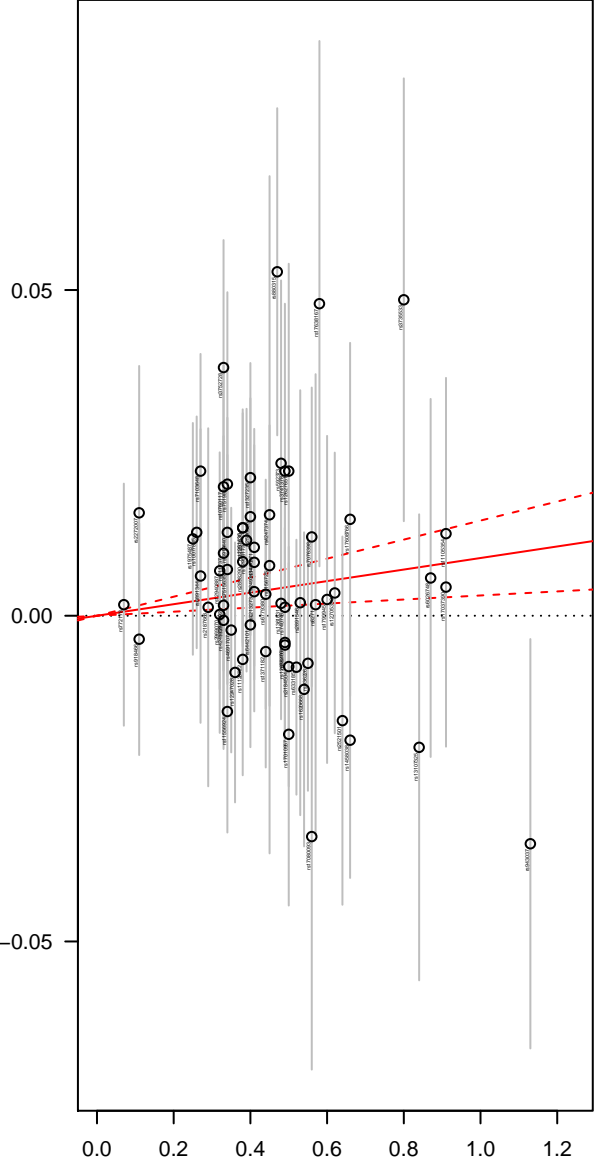
microalbuminuria, DBP; all SNPs



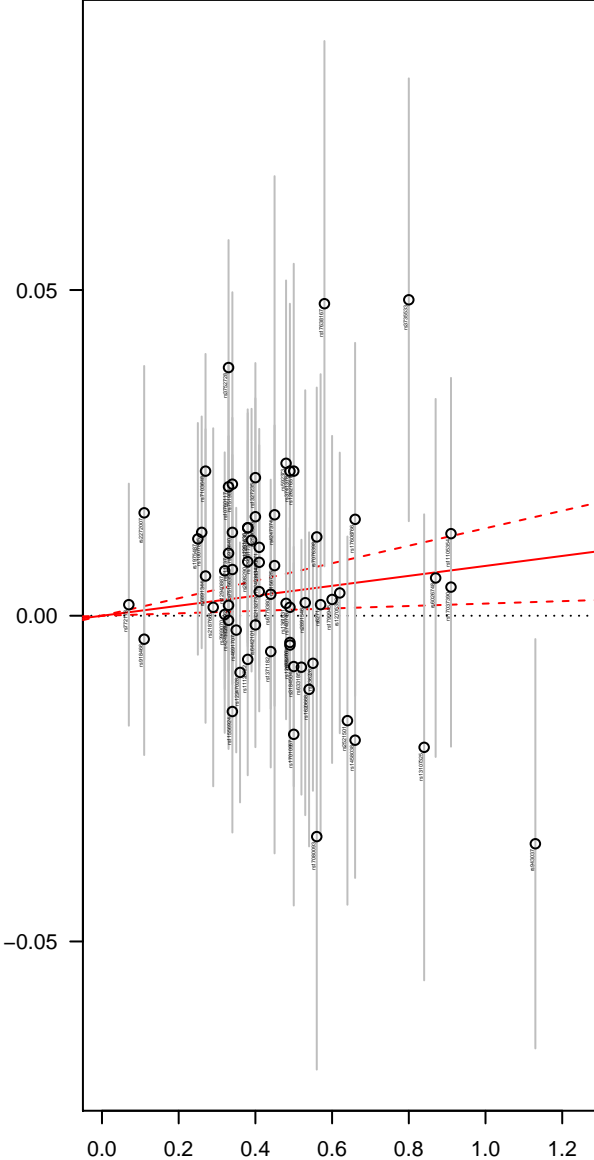
microalbuminuria, DBP; 0 pruned



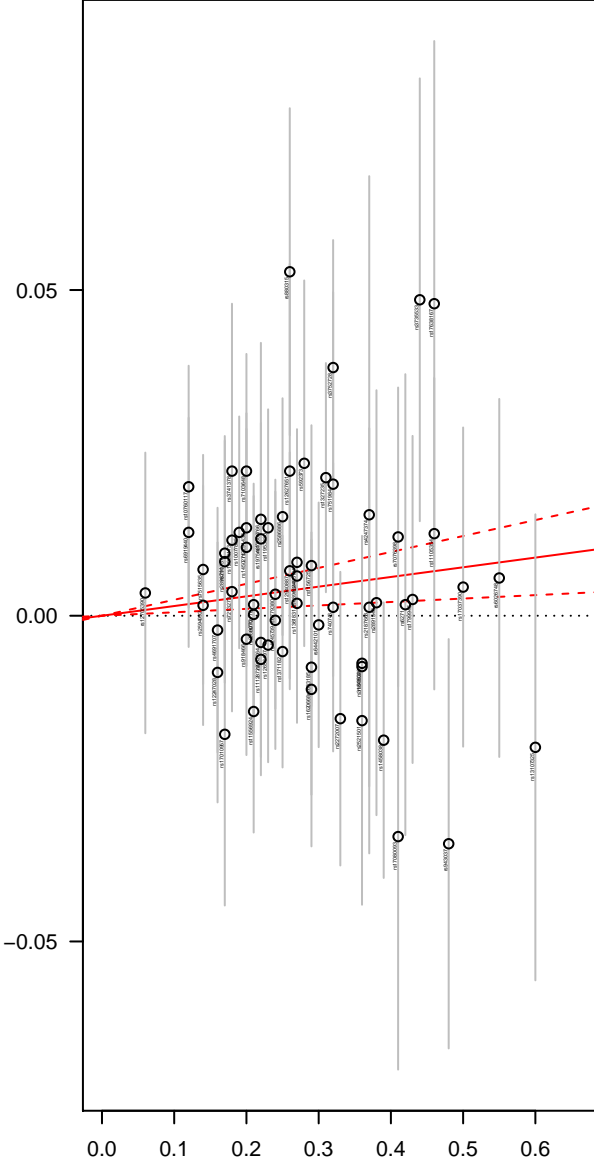
urinary albumin/cr ratio, SBP; all SNPs



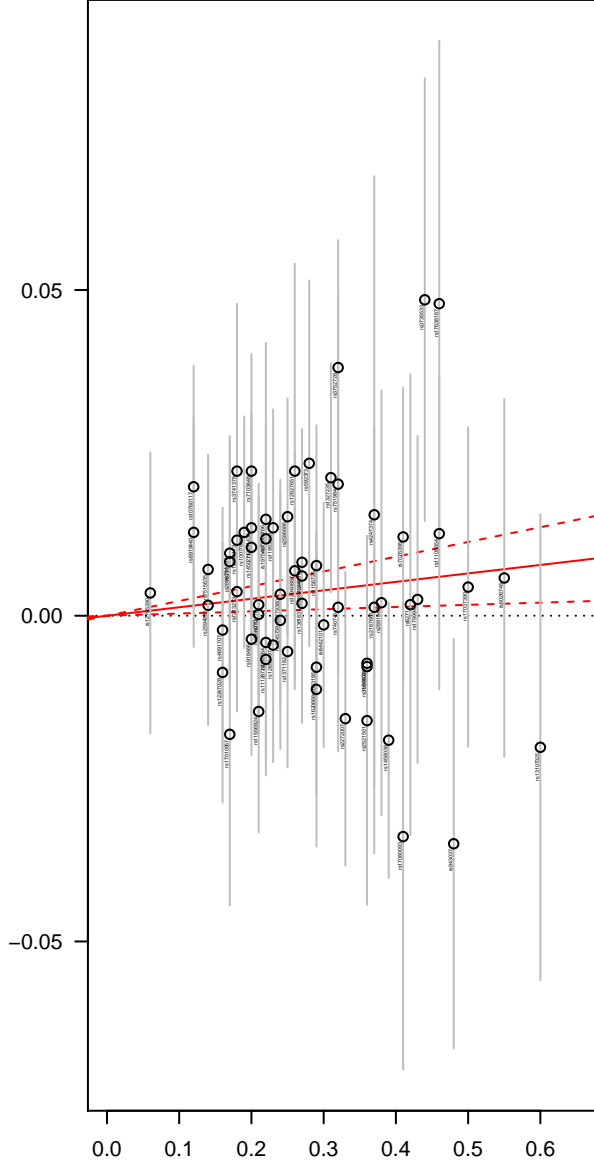
urinary albumin/cr ratio, SBP; 1 pruned



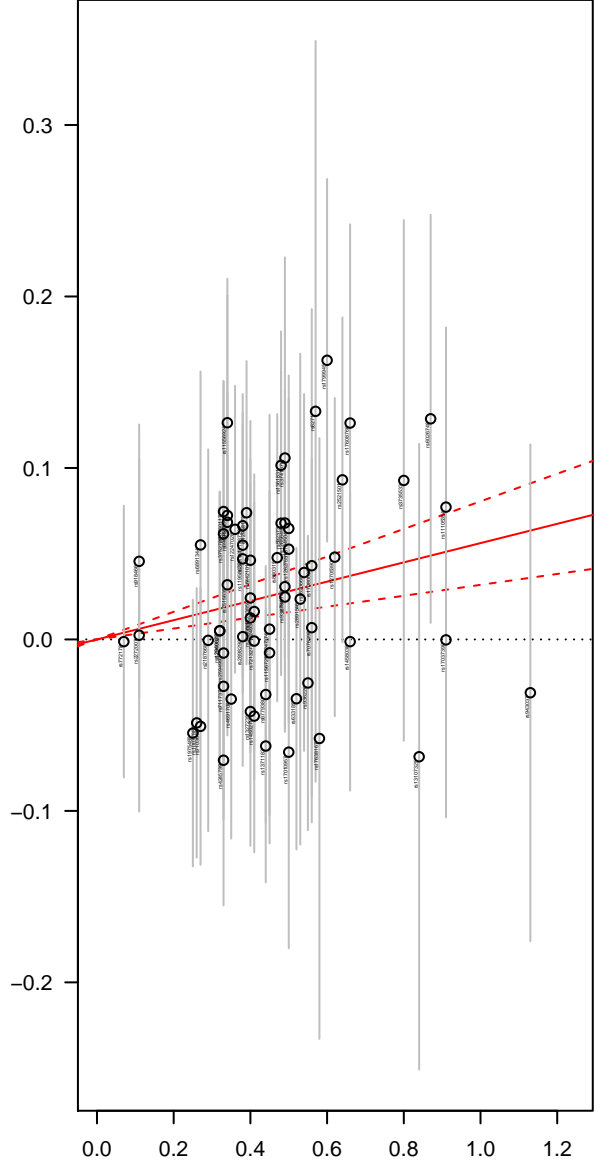
urinary albumin/cr ratio, DBP; all SNPs



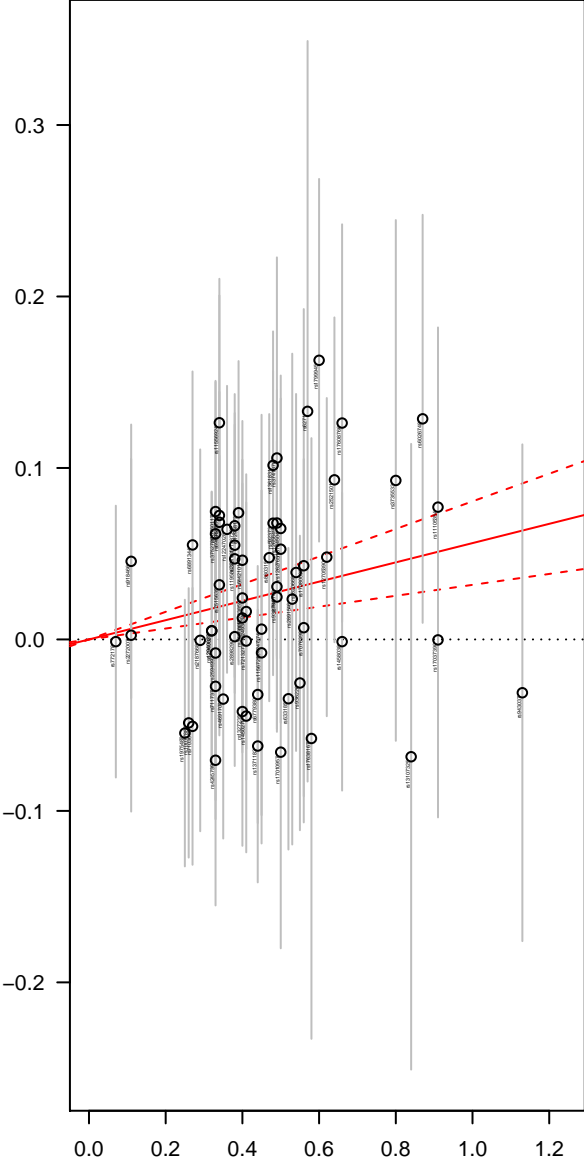
urinary albumin/cr ratio, DBP; 1 pruned



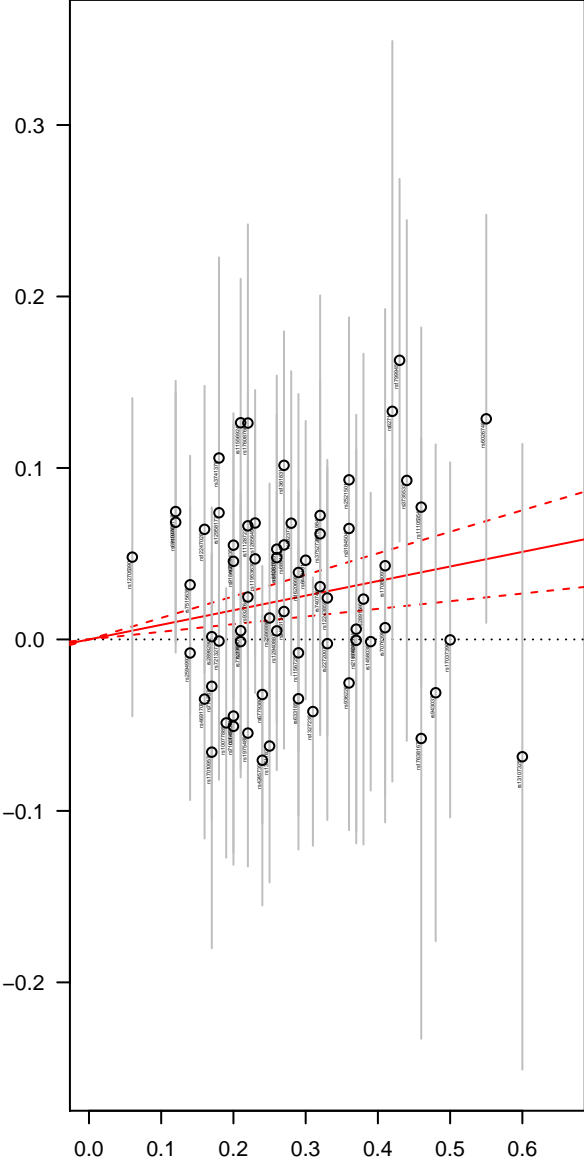
stroke, all subtypes, SBP; all SNPs



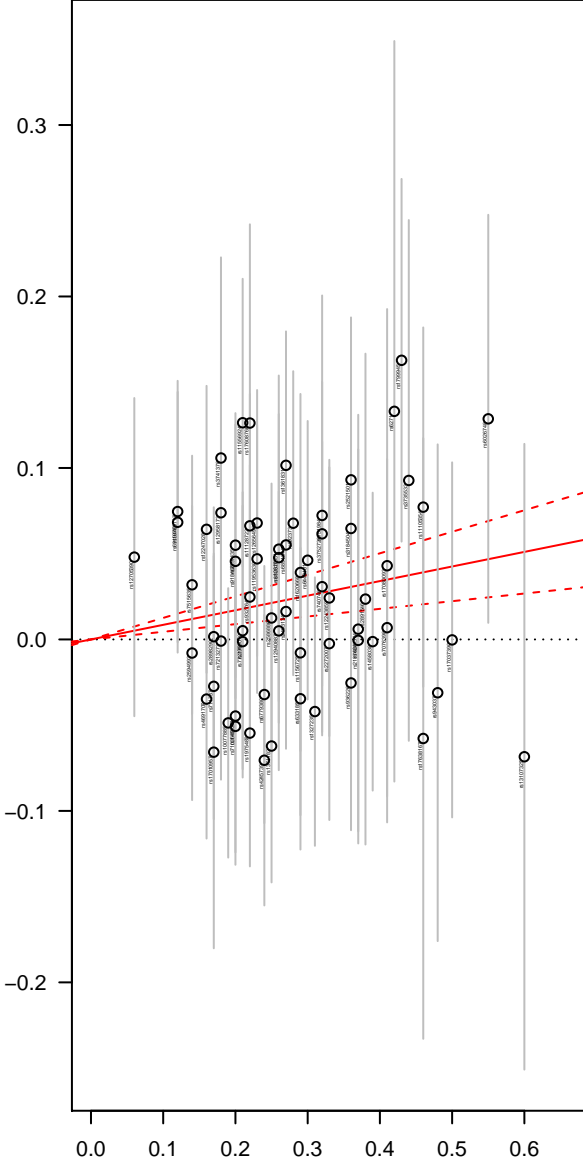
stroke, all subtypes, SBP; 0 pruned



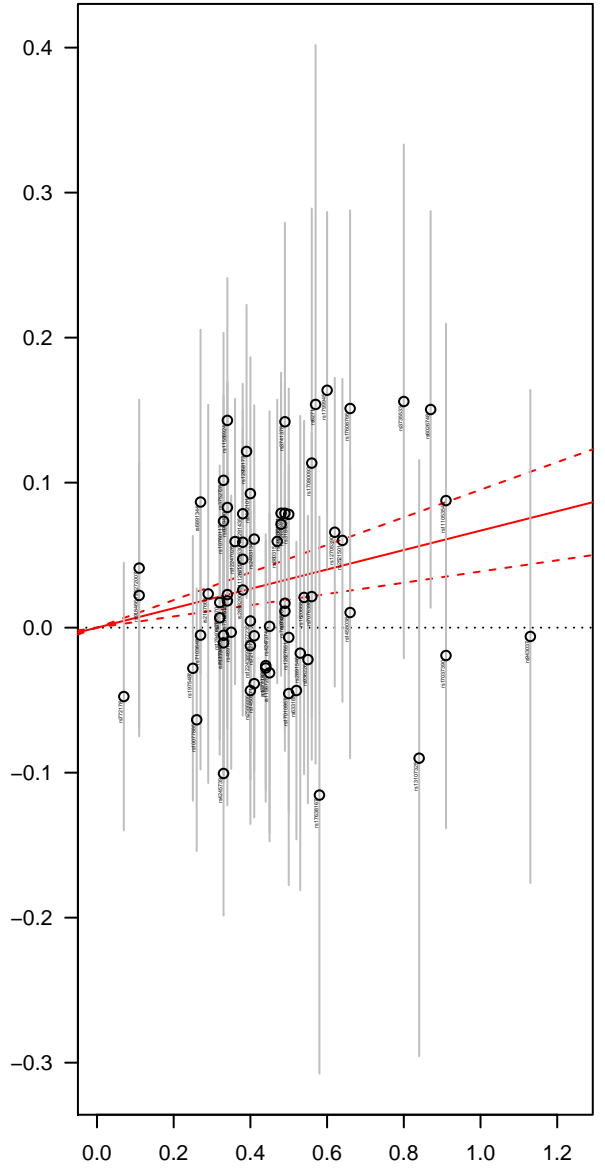
stroke, all subtypes, DBP; all SNPs



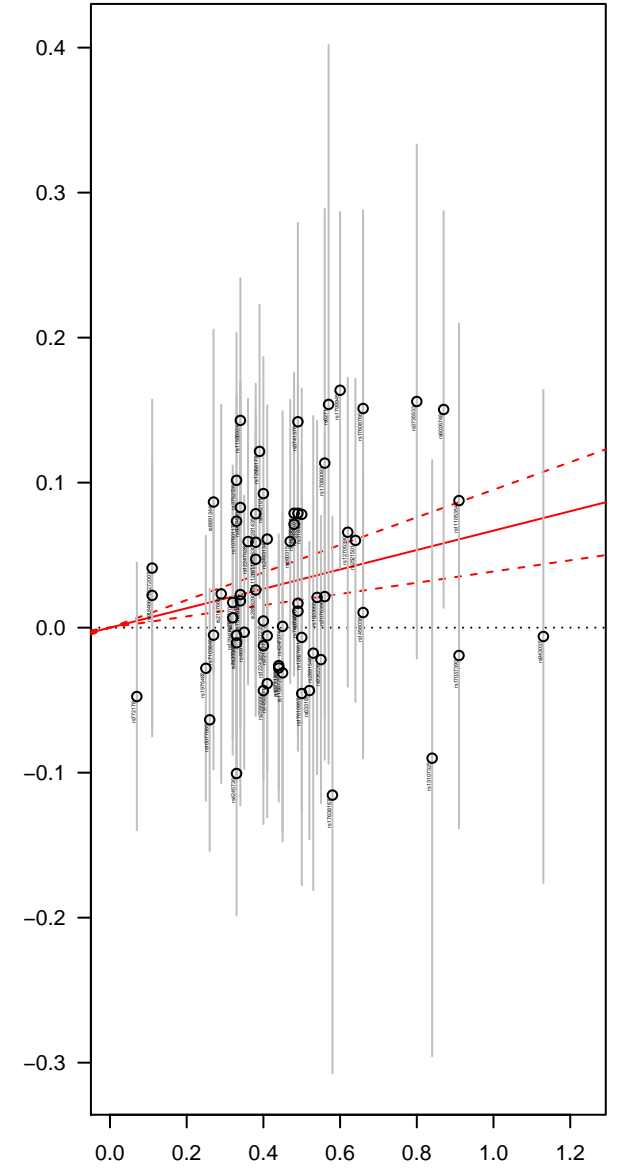
stroke, all subtypes, DBP; 0 pruned



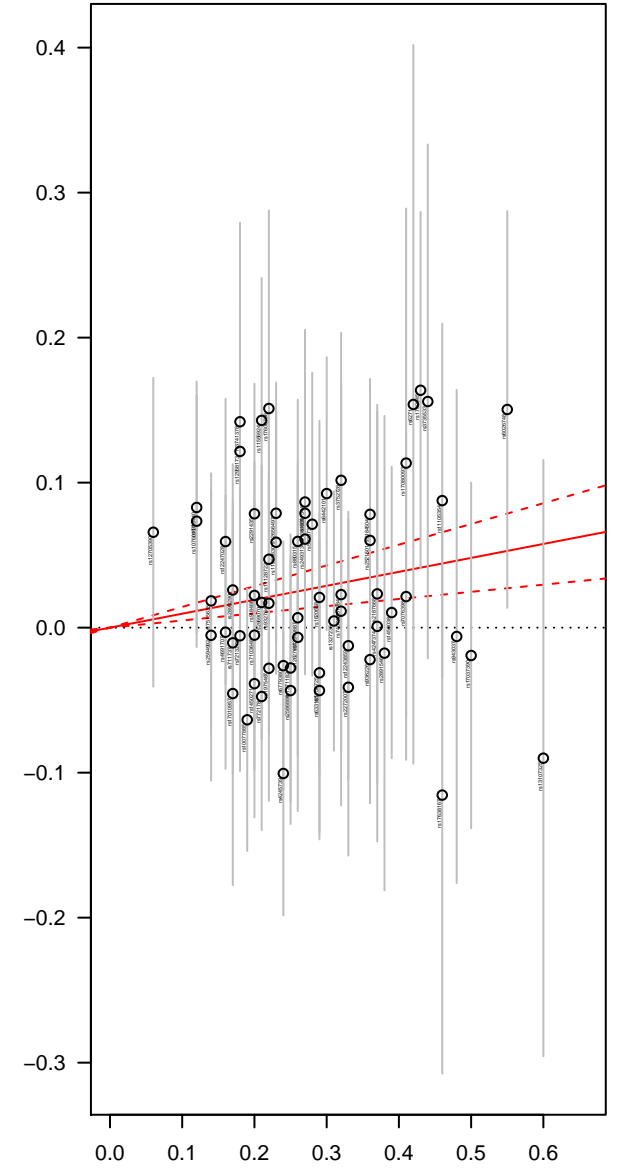
stroke, ischemic subtype [C], SBP; all SNPs



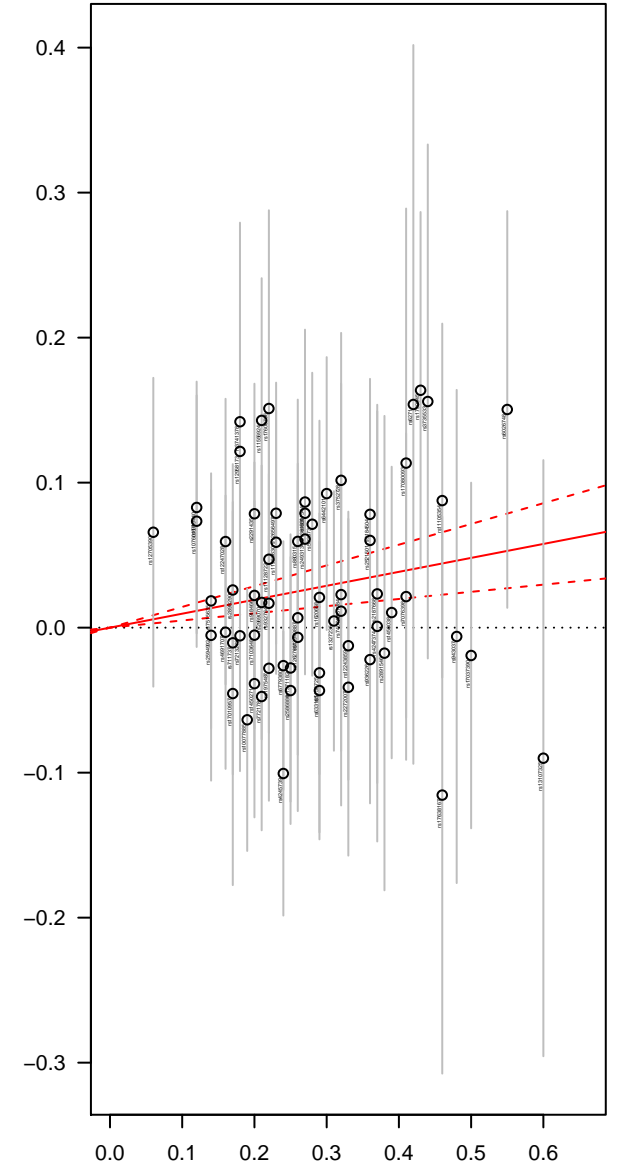
stroke, ischemic subtype [C], SBP; 0 pruned



stroke, ischemic subtype [C], DBP; all SNPs



stroke, ischemic subtype [C], DBP; 0 pruned

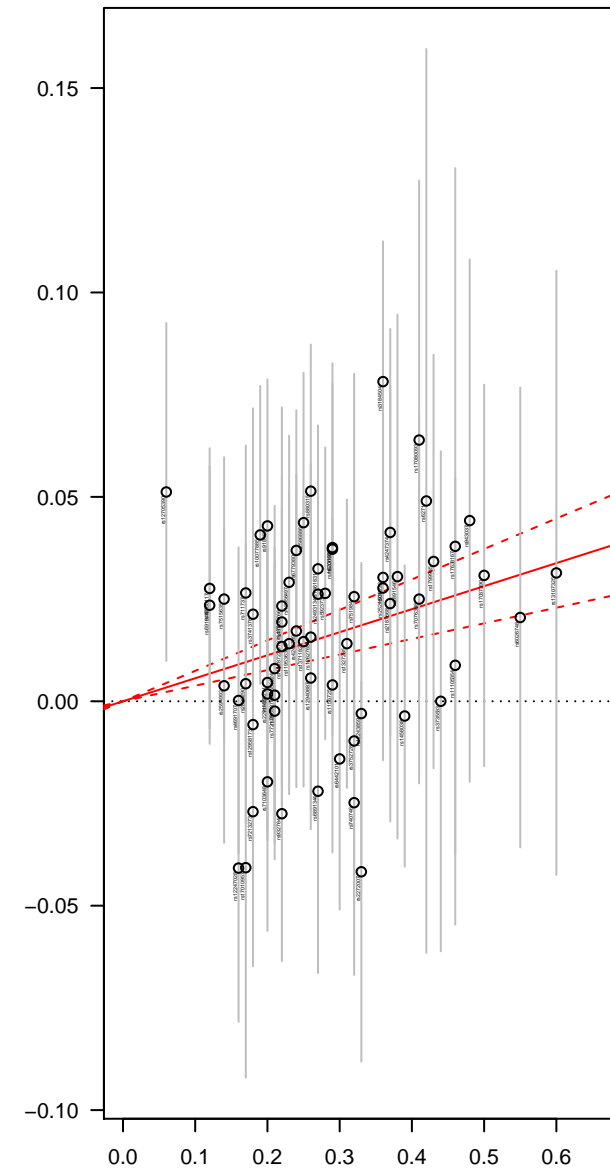
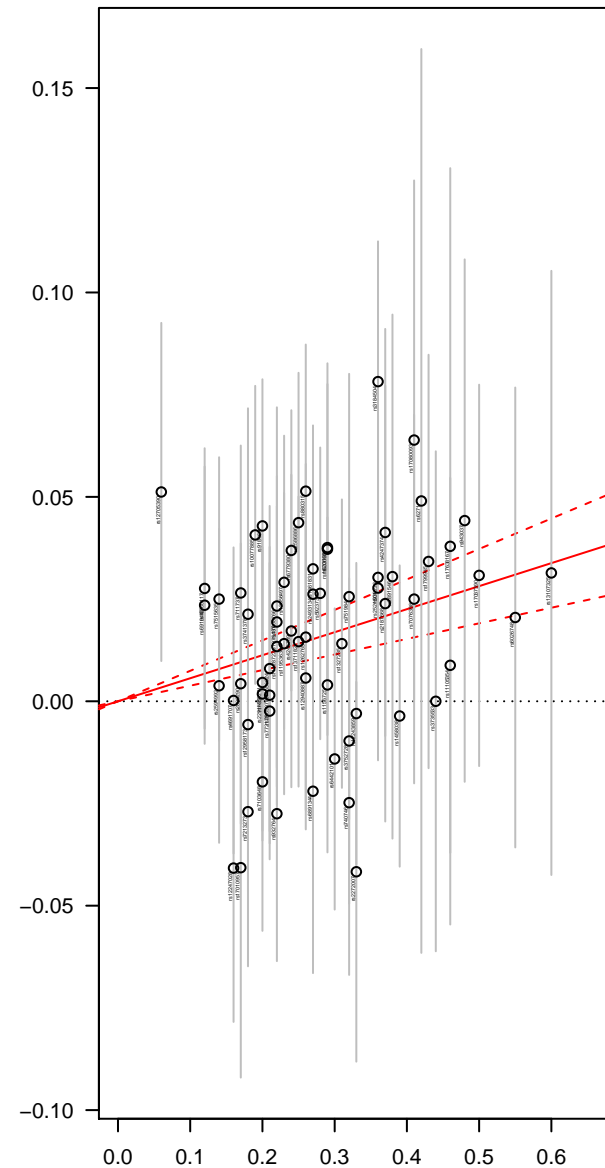
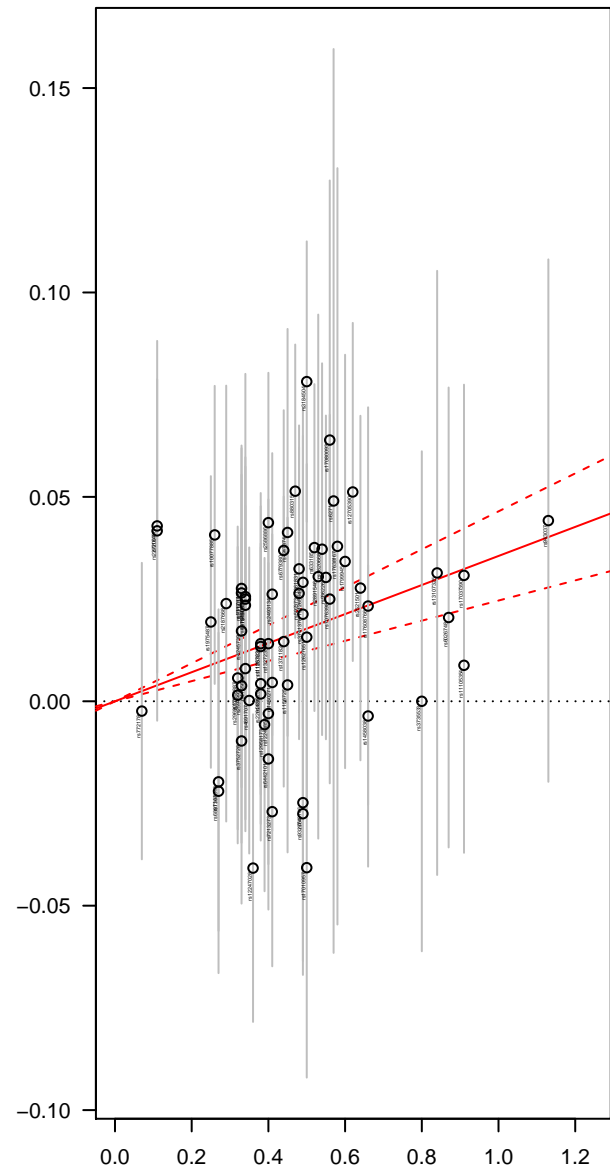
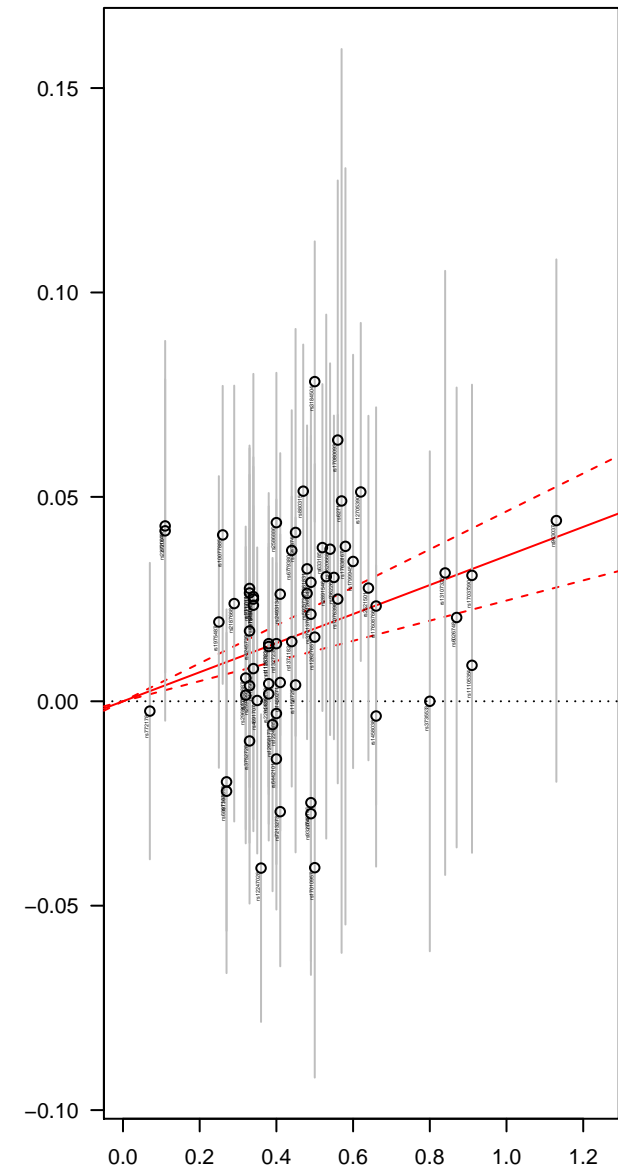


stroke, ischemic subtype [M], SBP; all SNPs

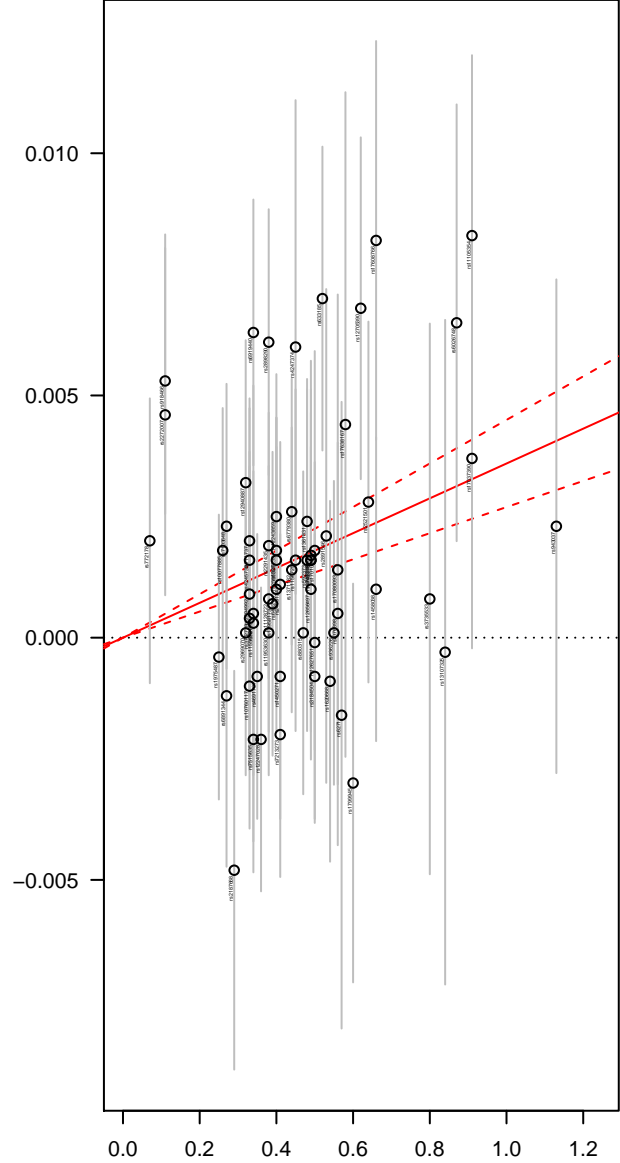
stroke, ischemic subtype [M], SBP; 0 pruned

stroke, ischemic subtype [M], DBP; all SNPs

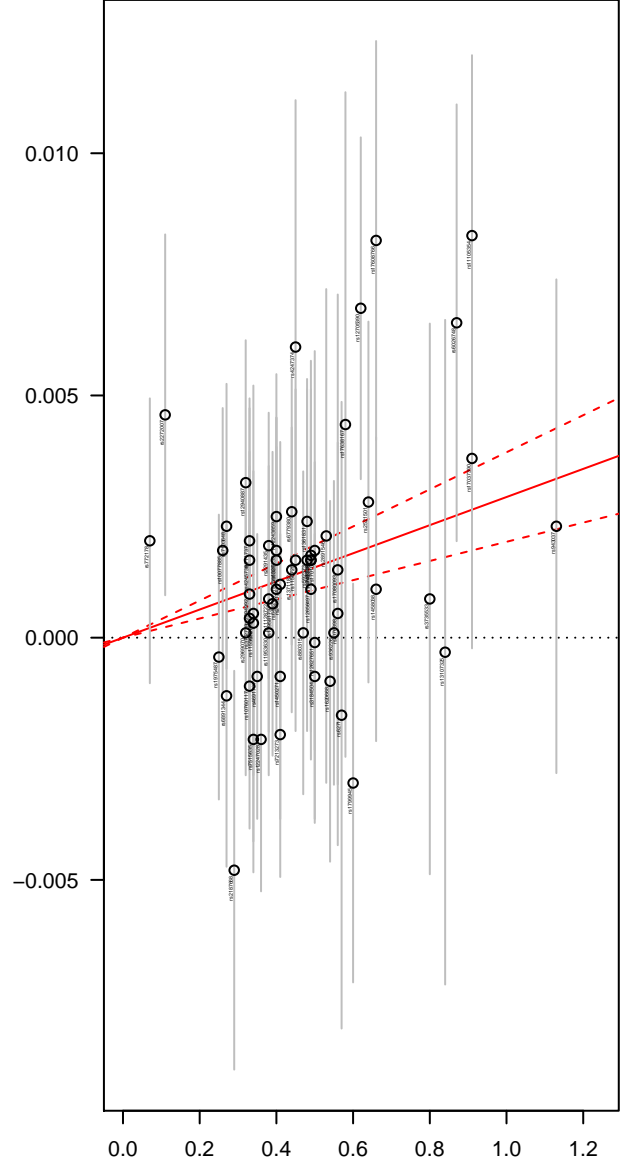
stroke, ischemic subtype [M], DBP; 0 pruned



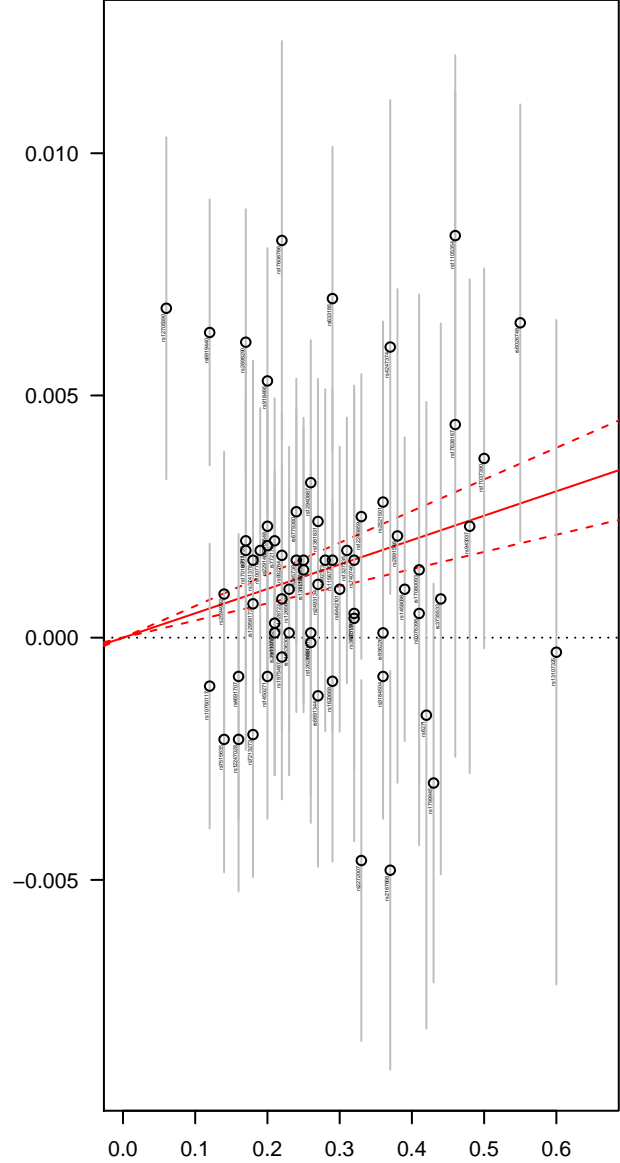
cIMT, SBP; all SNPs



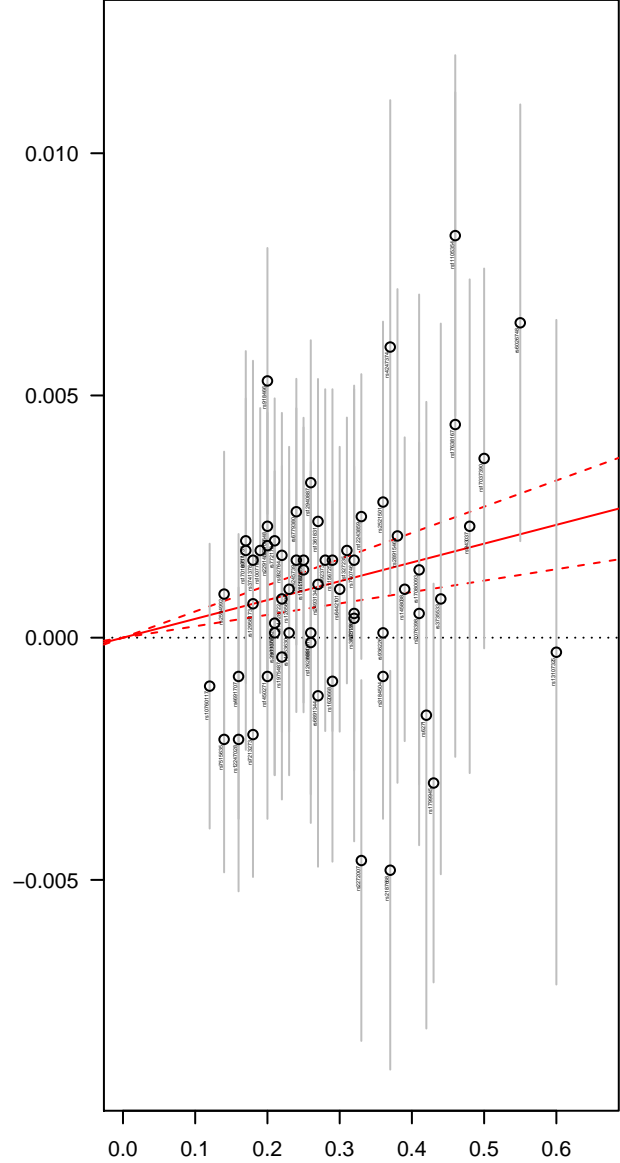
cIMT, SBP; 4 pruned



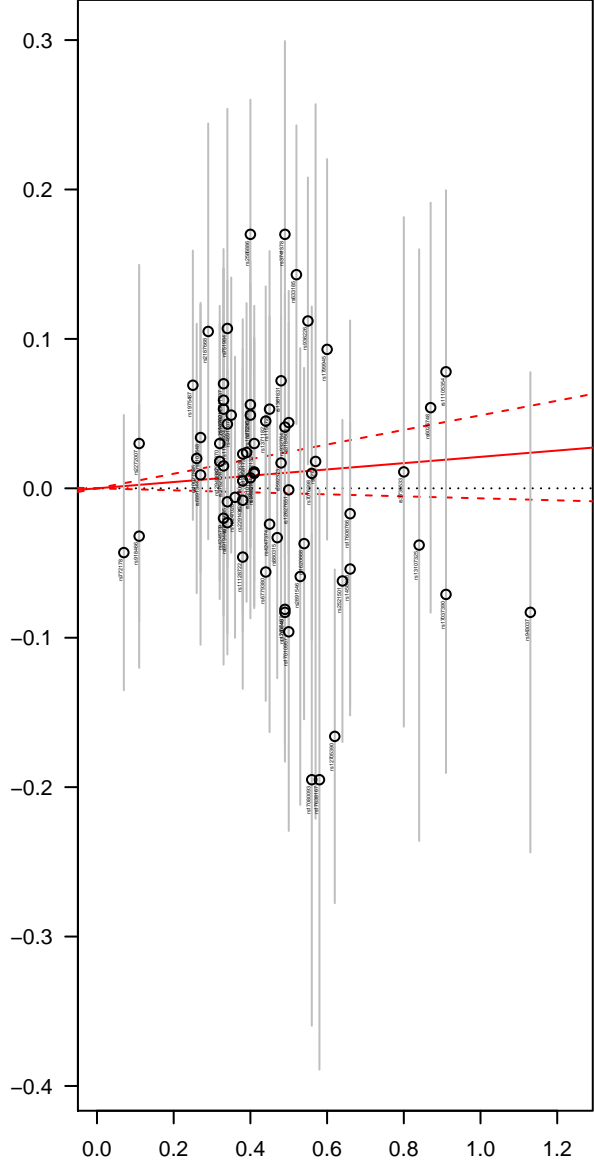
cIMT, DBP; all SNPs



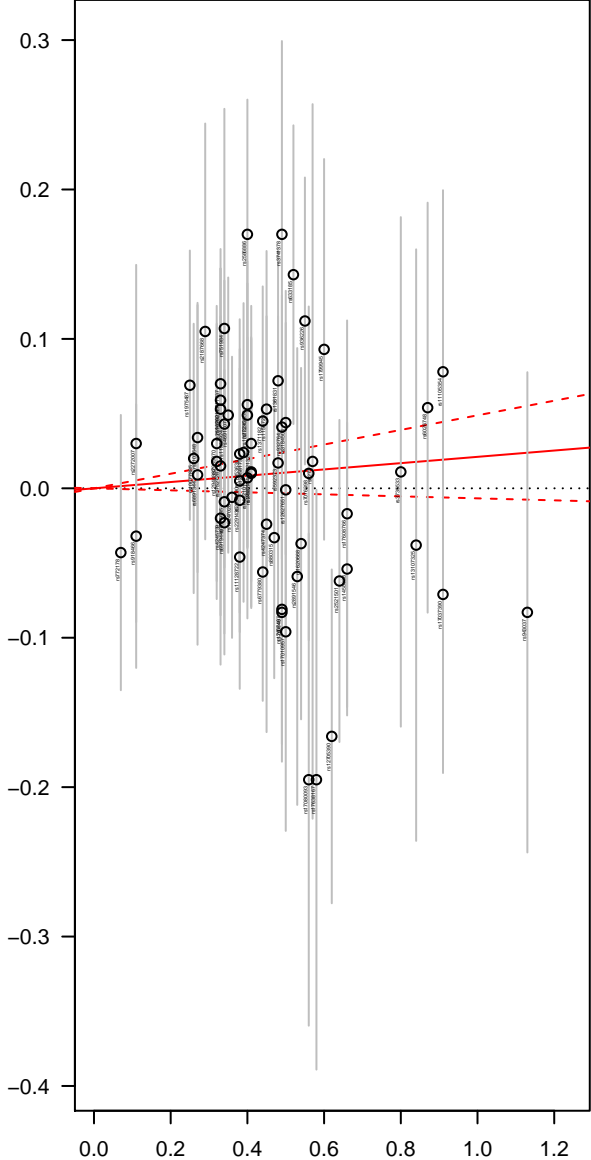
cIMT, DBP; 5 pruned



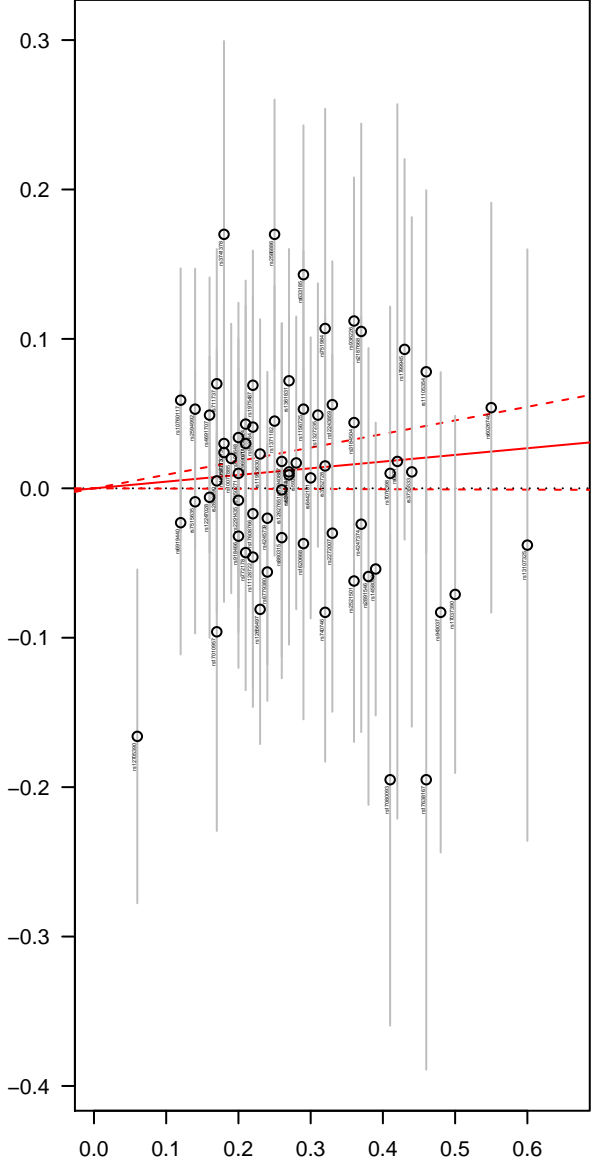
mild retinopathy [EU], SBP; all SNPs



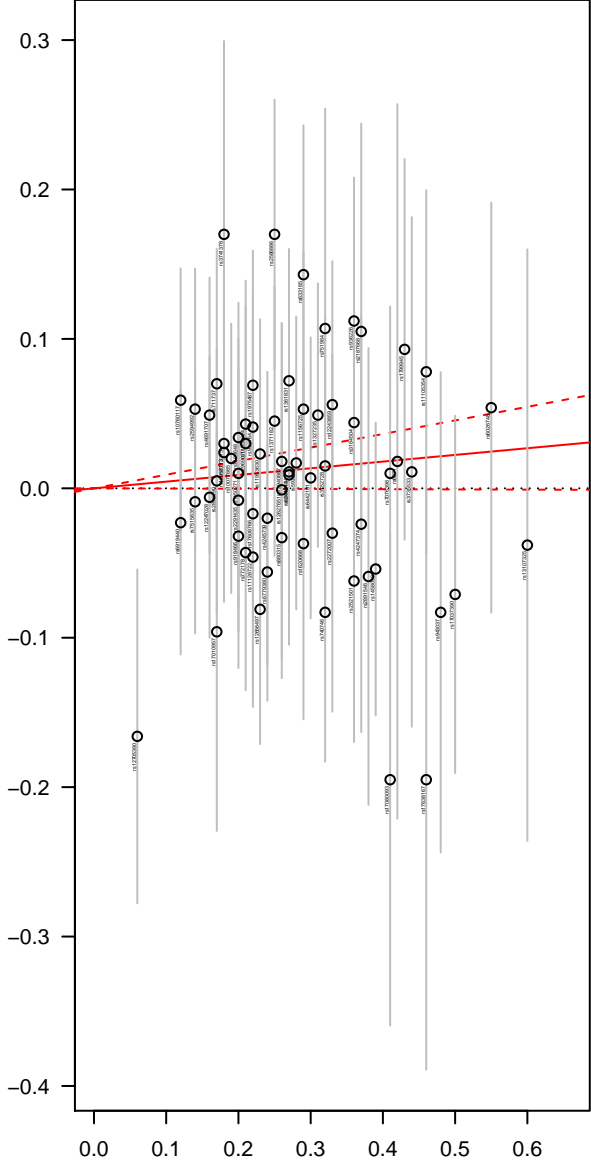
mild retinopathy [EU], SBP; 0 pruned



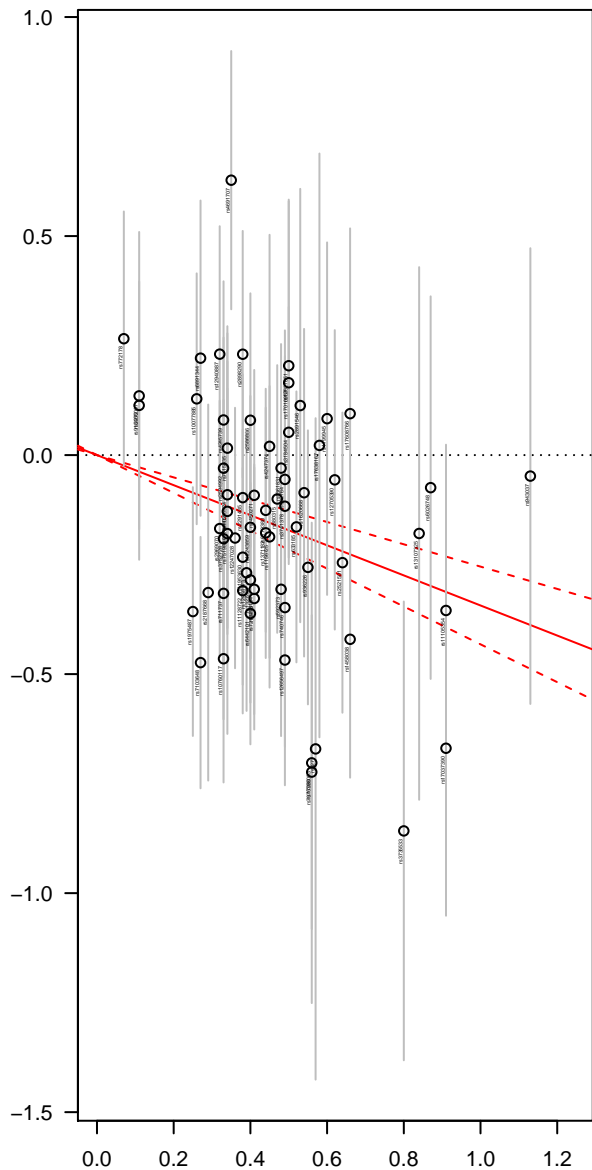
mild retinopathy [EU], DBP; all SNPs



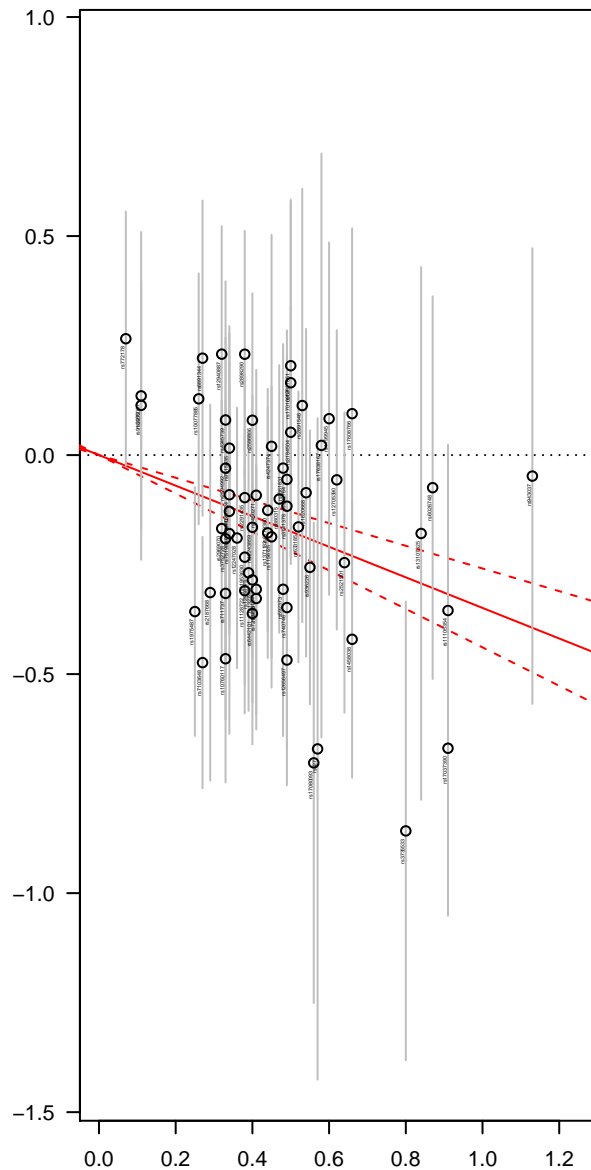
mild retinopathy [EU], DBP; 0 pruned



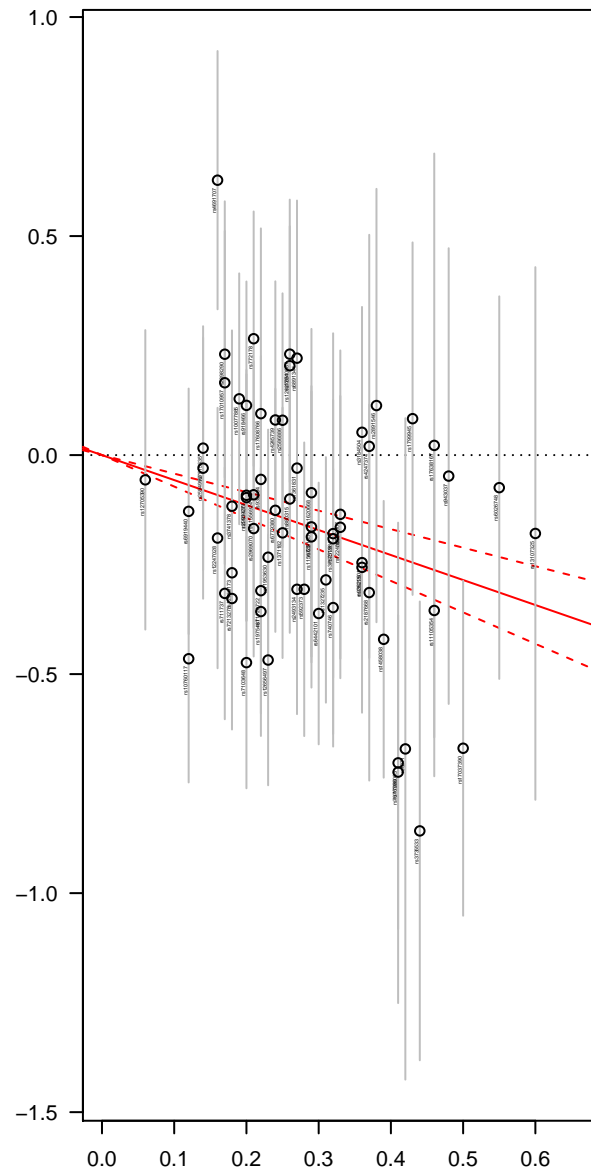
central retinal artery caliber [EU], SBP; all SNPs



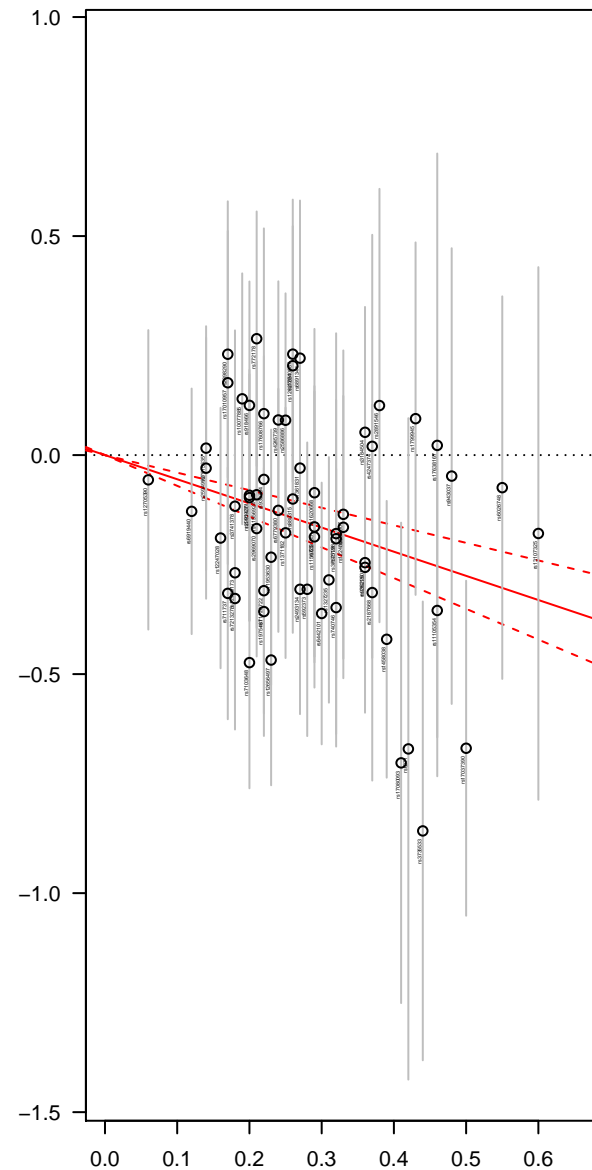
central retinal artery caliber [EU], SBP; 2 pruned



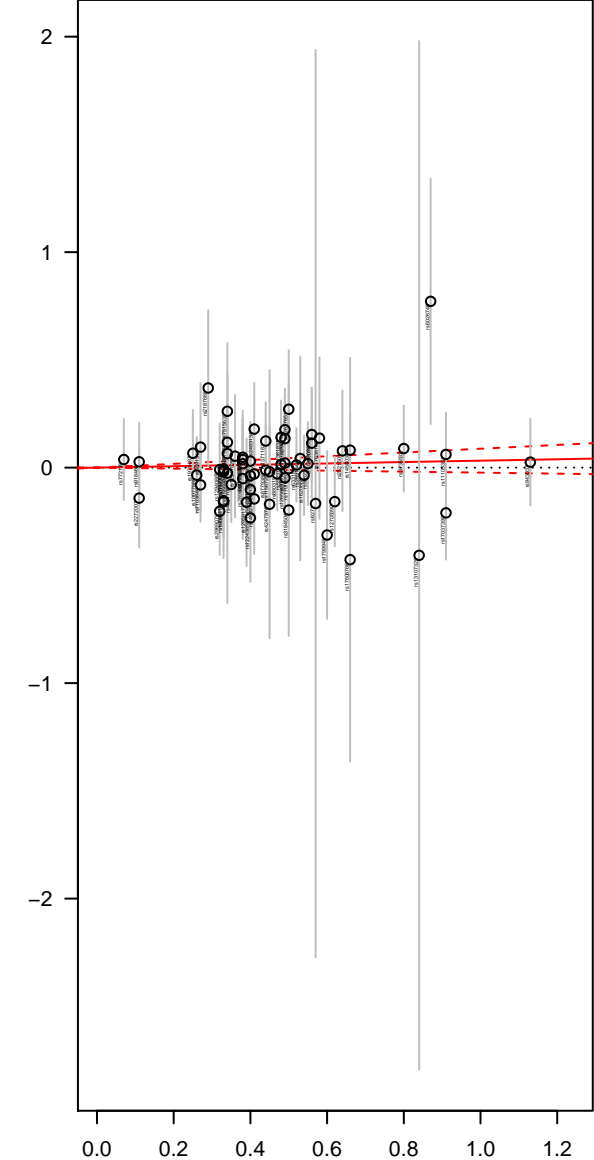
central retinal artery caliber [EU], DBP; all SNPs



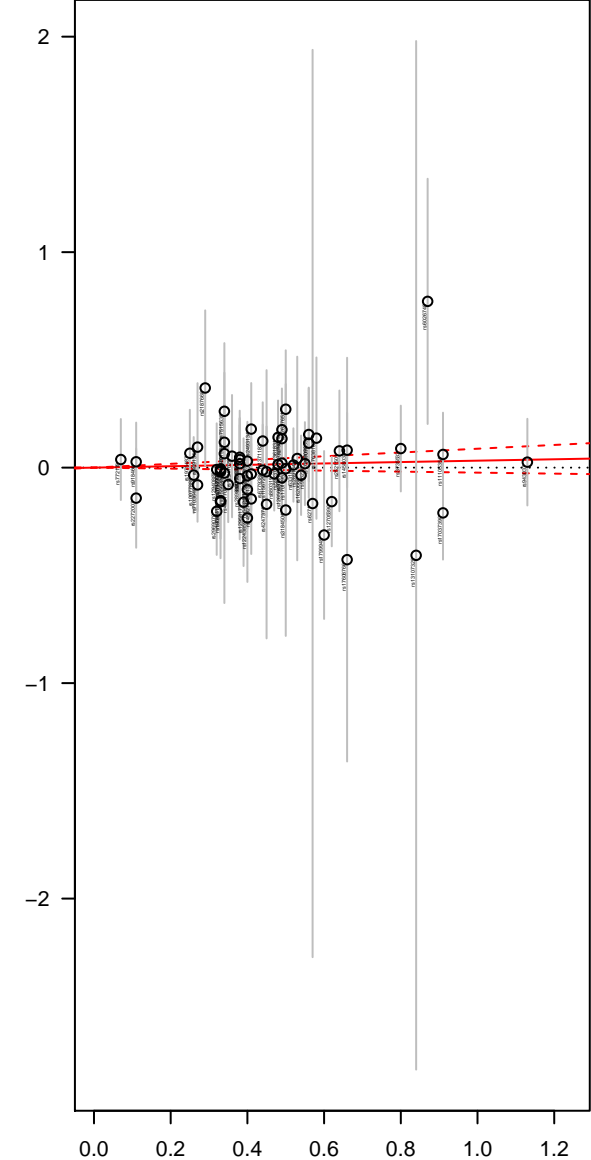
central retinal artery caliber [EU], DBP; 3 pruned



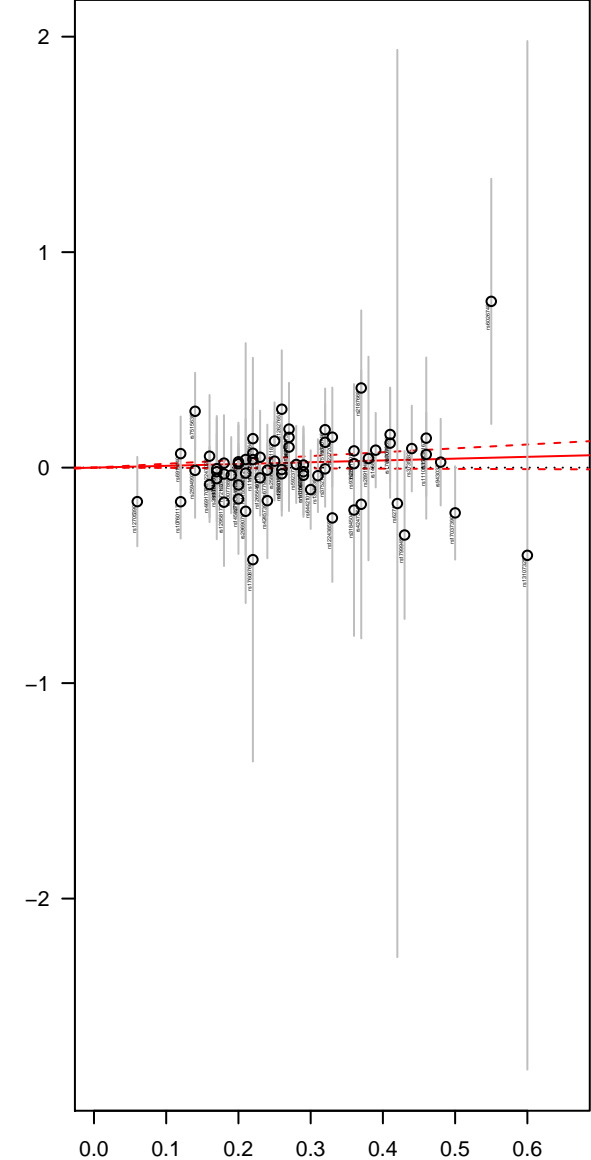
mild retinopathy [AS], SBP; all SNPs



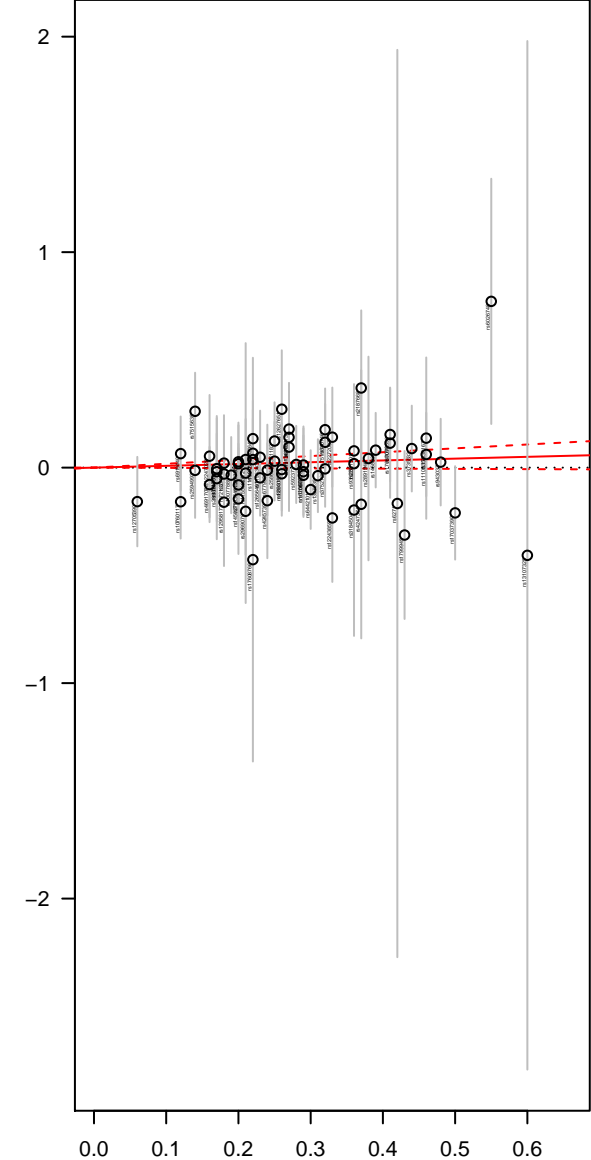
mild retinopathy [AS], SBP; 0 pruned



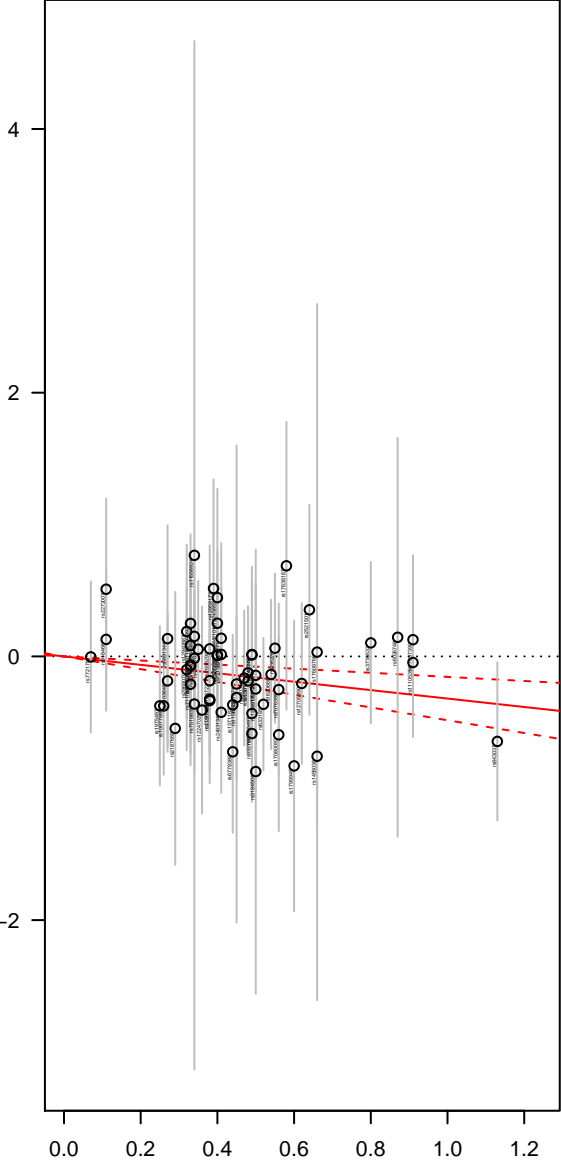
mild retinopathy [AS], DBP; all SNPs



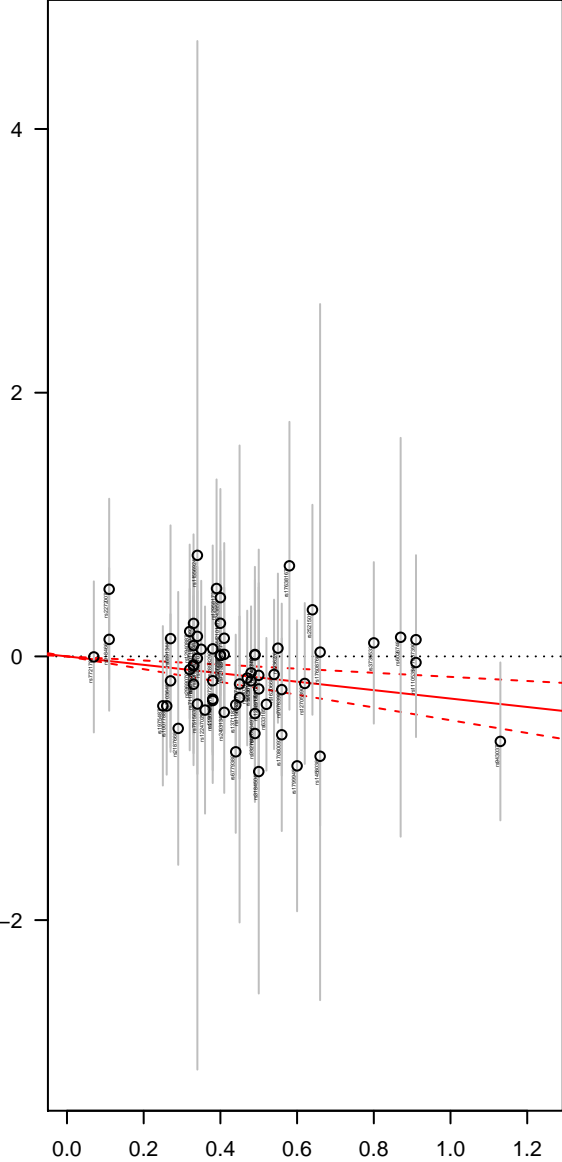
mild retinopathy [AS], DBP; 0 pruned



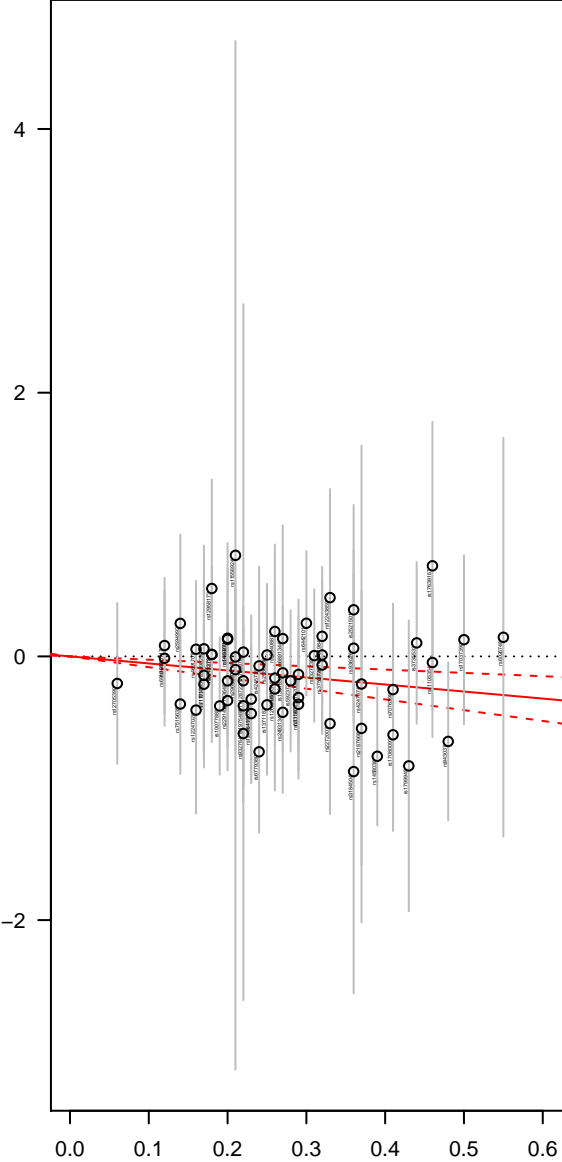
central retinal artery caliber [AS], SBP; all SNPs



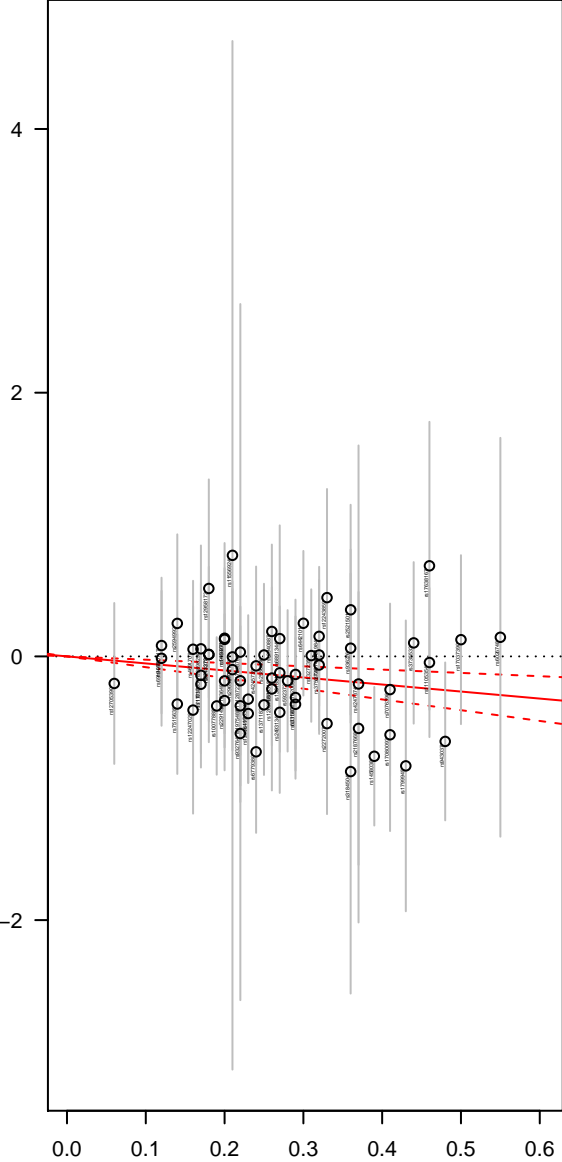
central retinal artery caliber [AS], SBP; 0 pruned



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



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

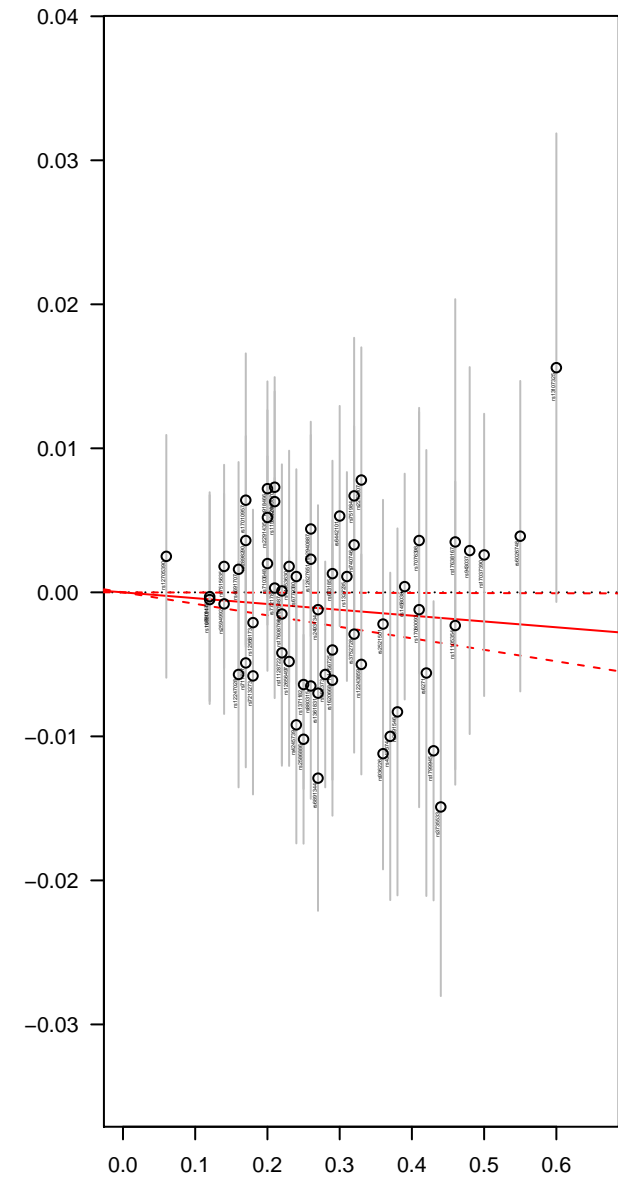
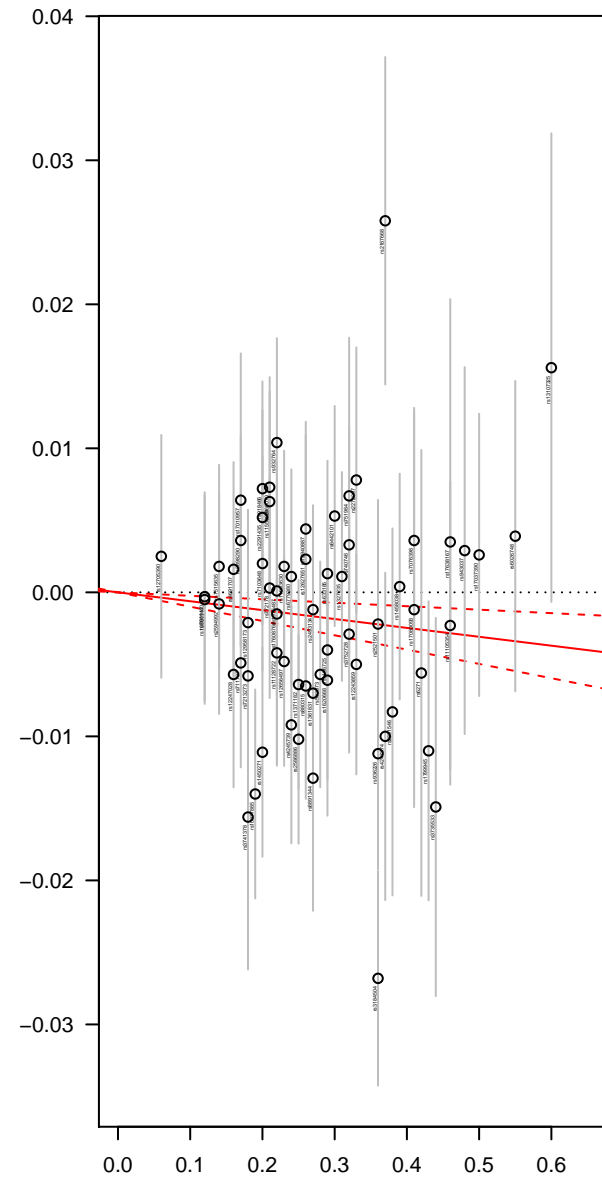
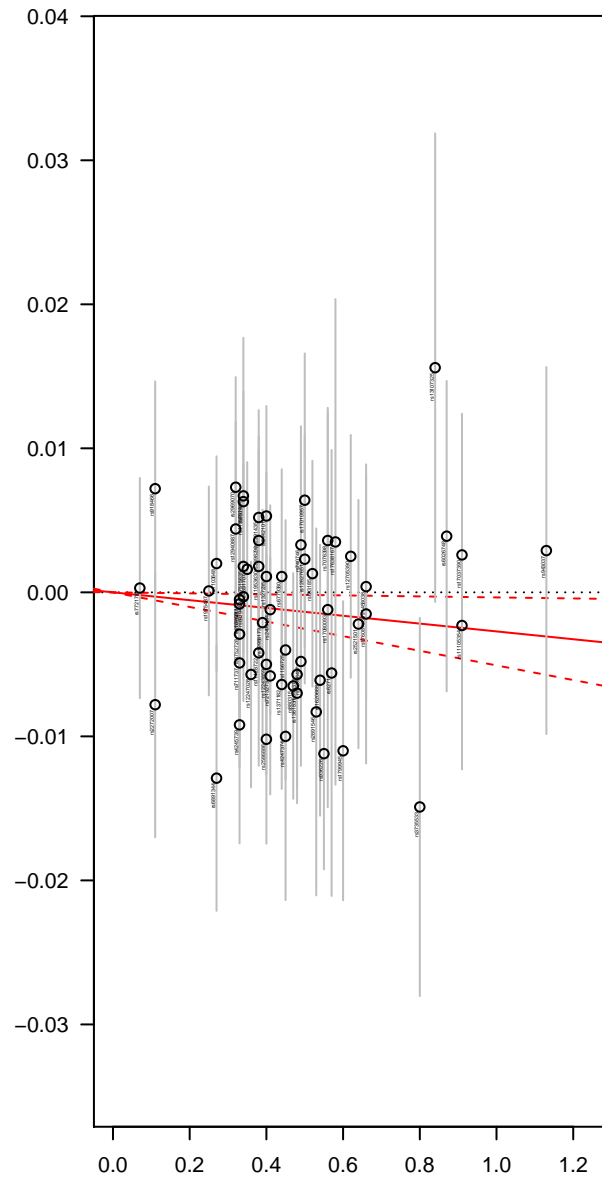
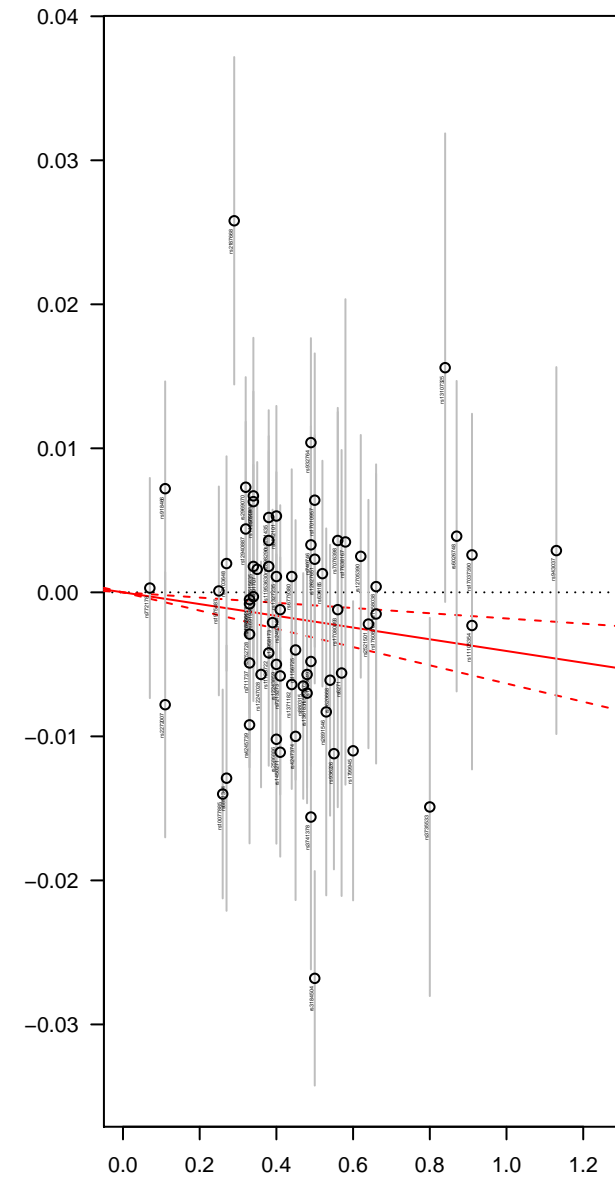


LDL, SBP; all SNPs

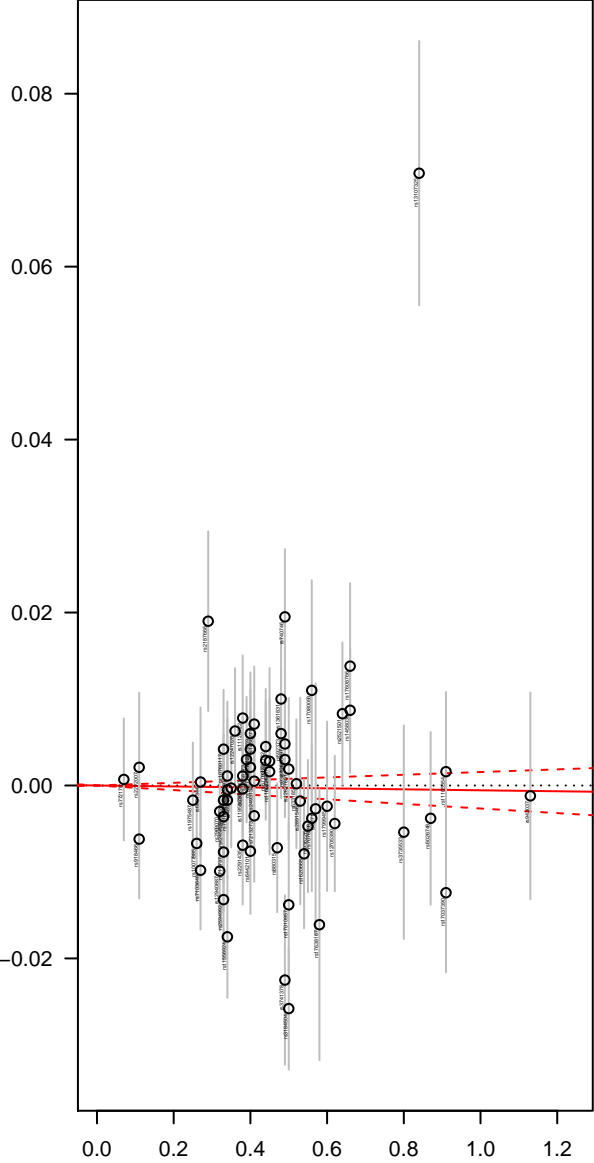
LDL, SBP; 6 pruned

LDL, DBP; all SNPs

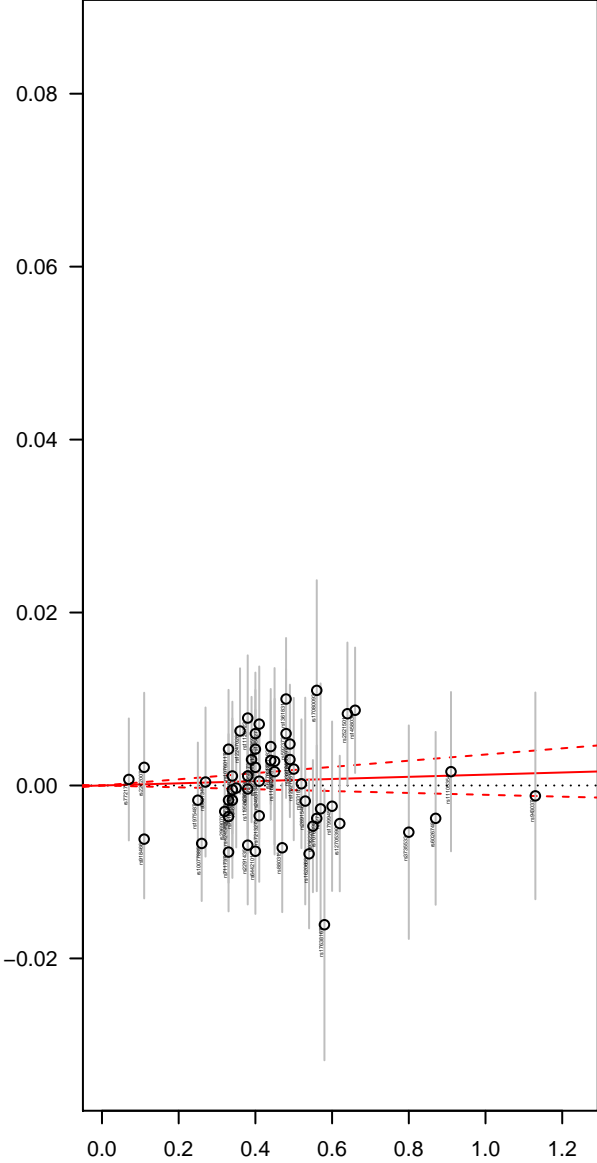
LDL, DBP; 6 pruned



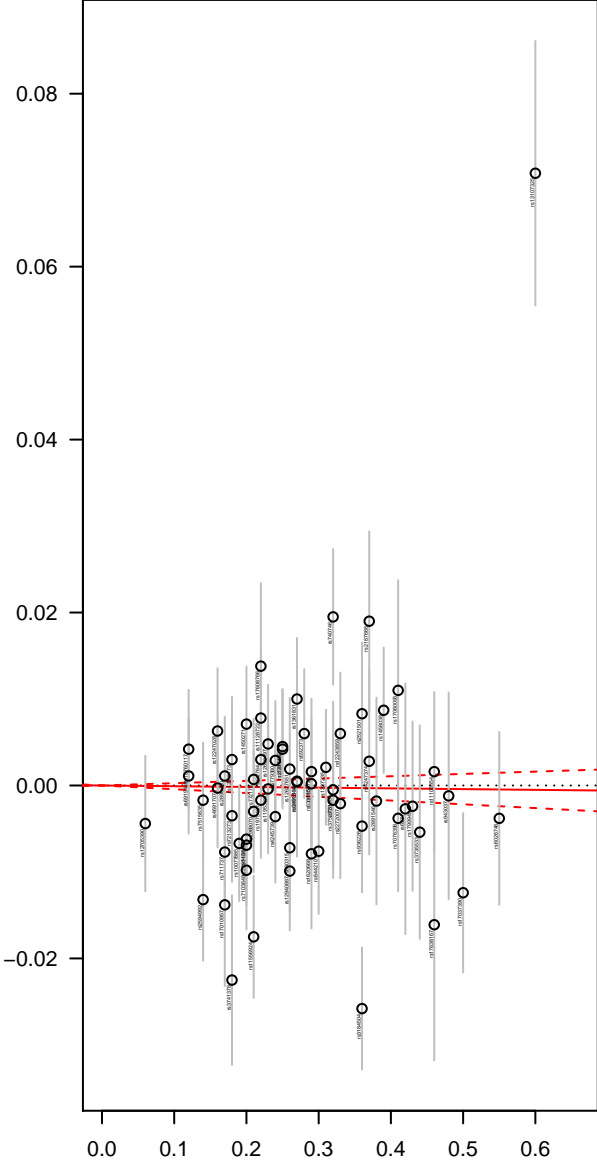
HDL, SBP; all SNPs



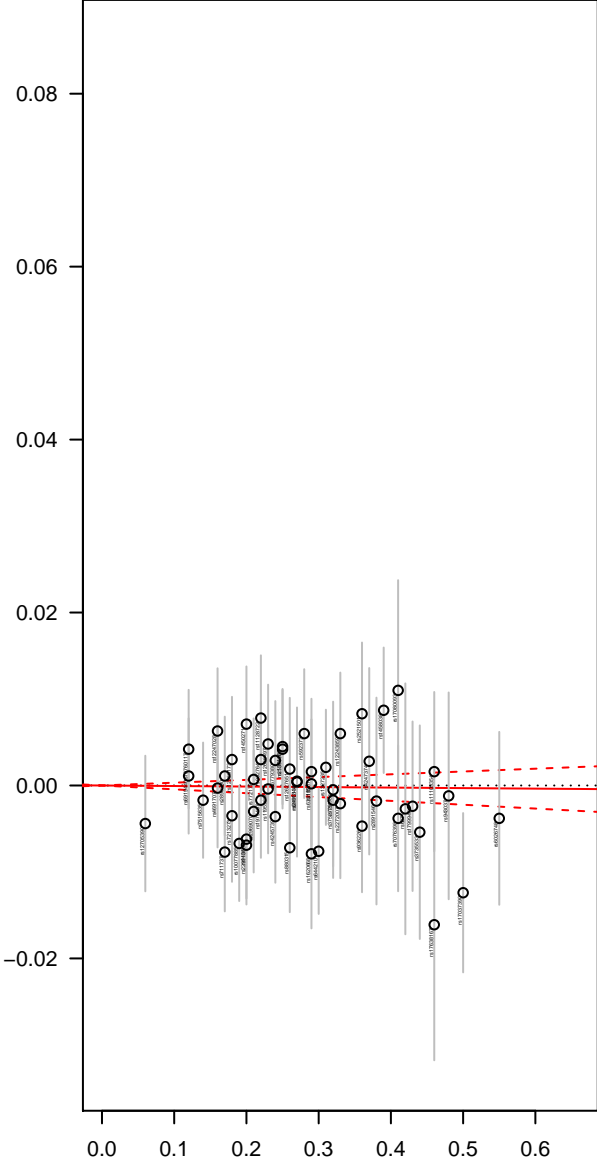
HDL, SBP; 12 pruned



HDL, DBP; all SNPs



HDL, DBP; 12 pruned

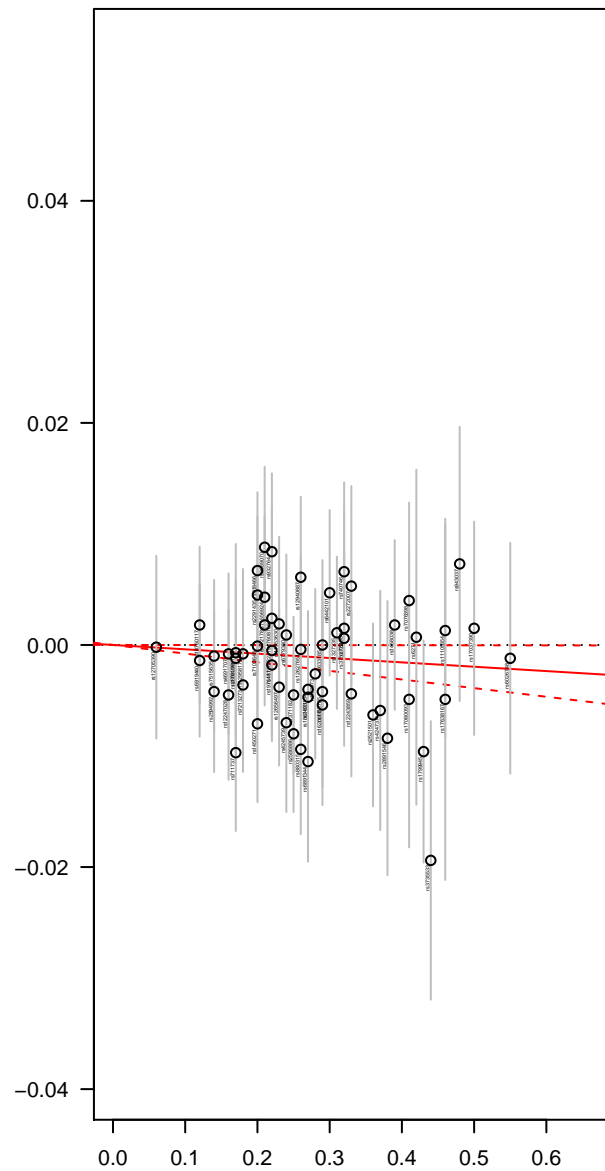
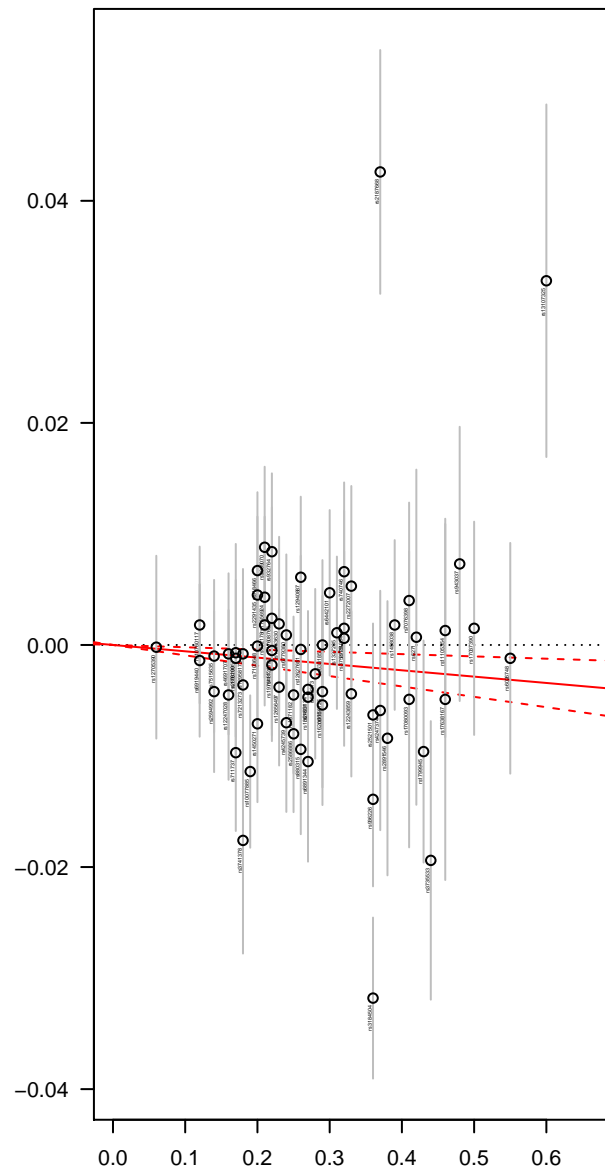
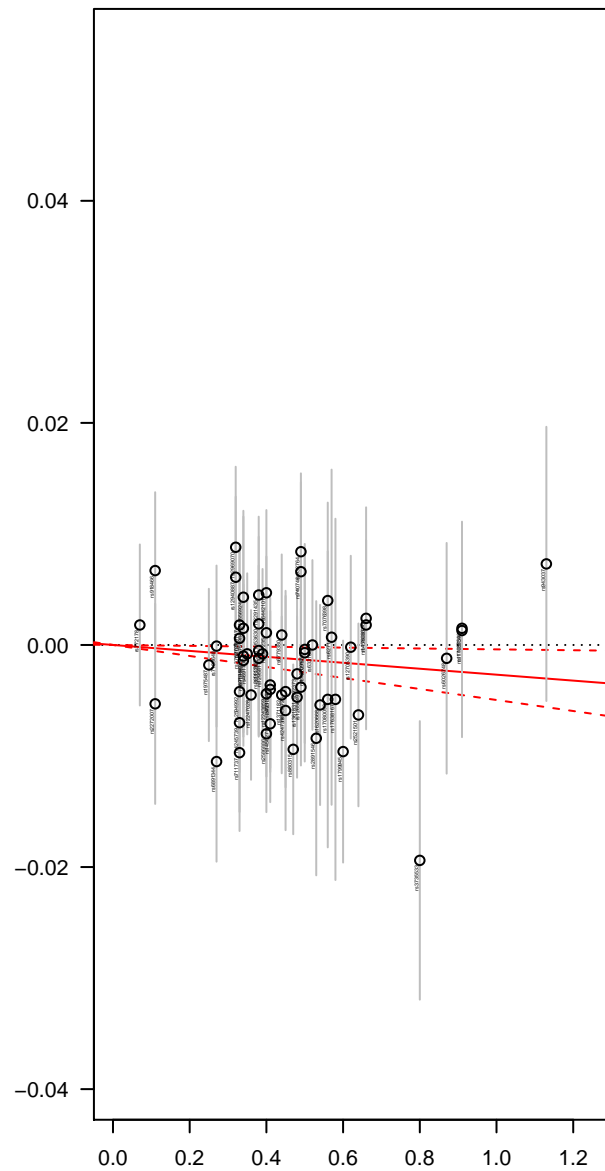
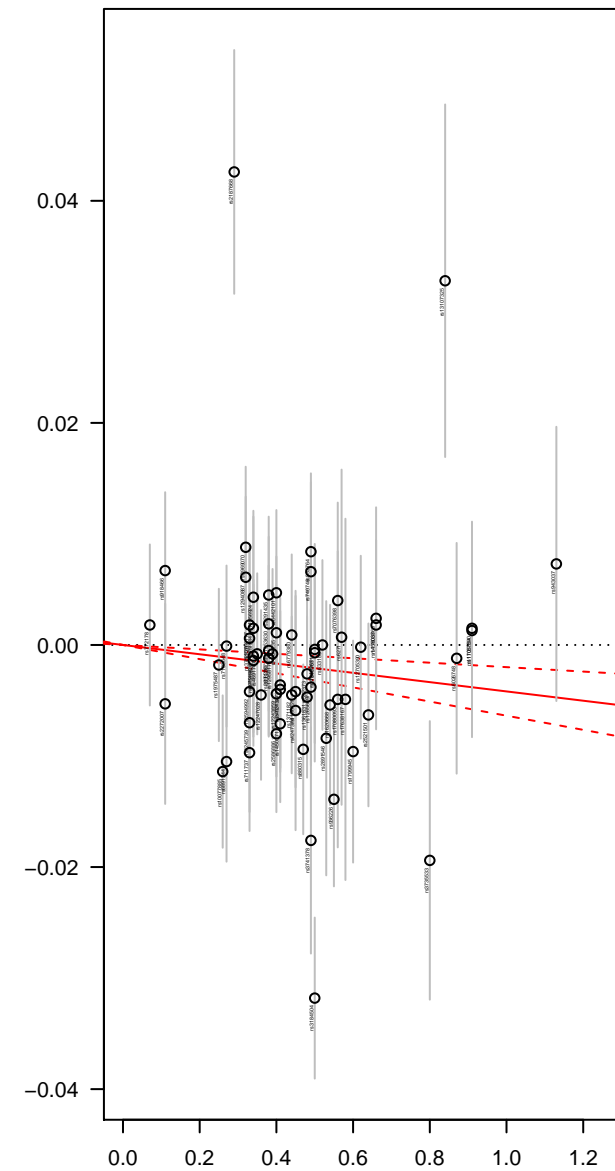


TG, SBP; all SNPs

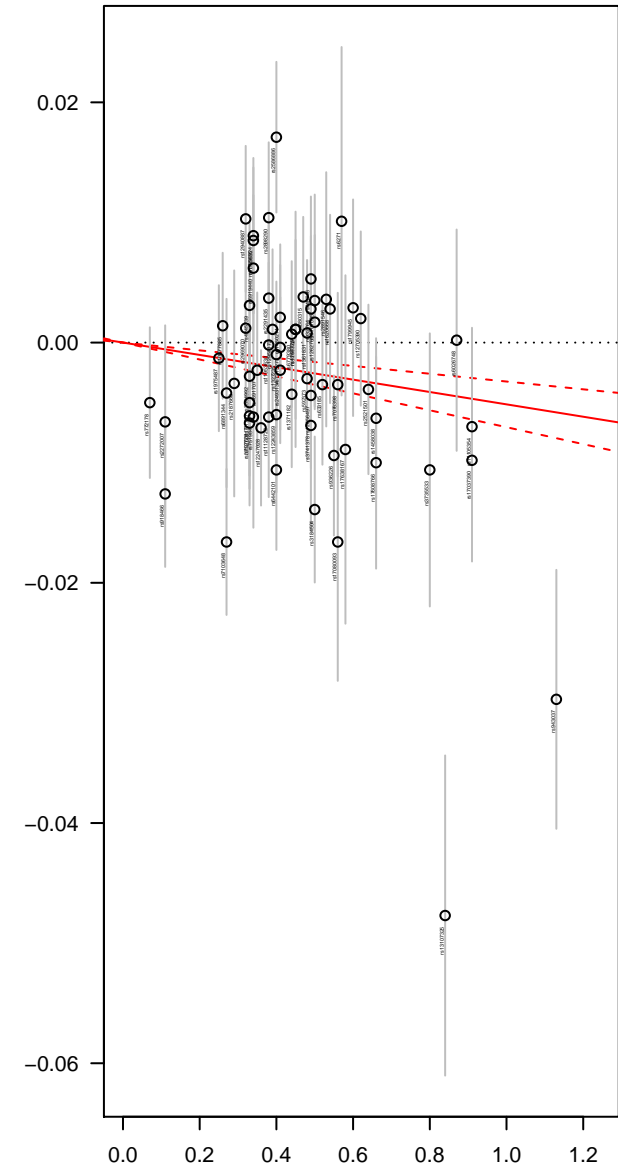
TG, SBP; 6 pruned

TG, DBP; all SNPs

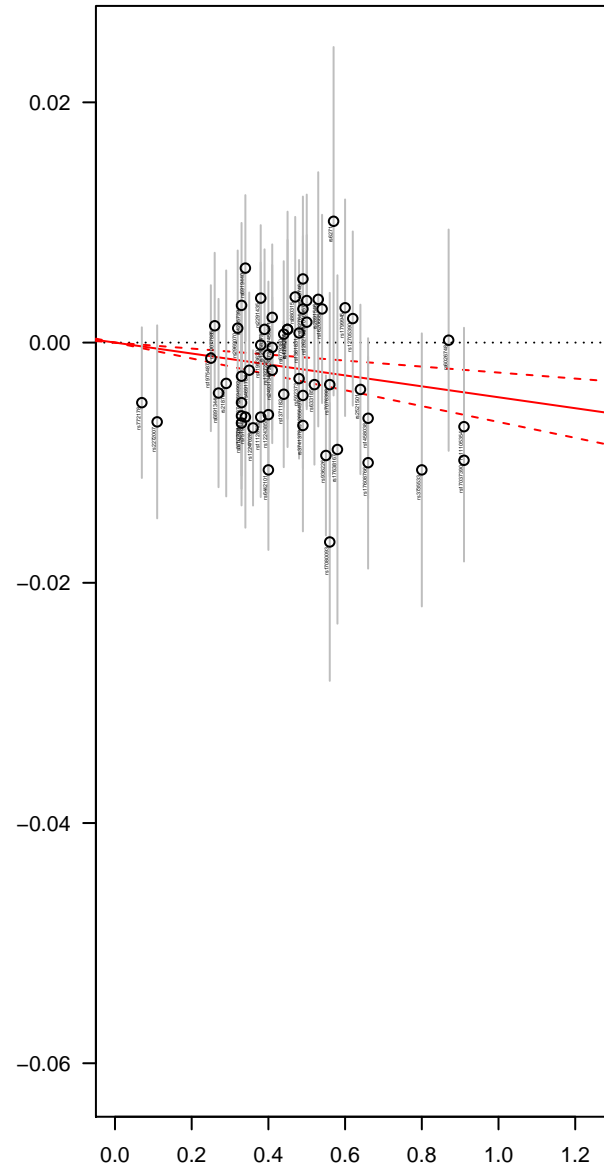
TG, DBP; 6 pruned



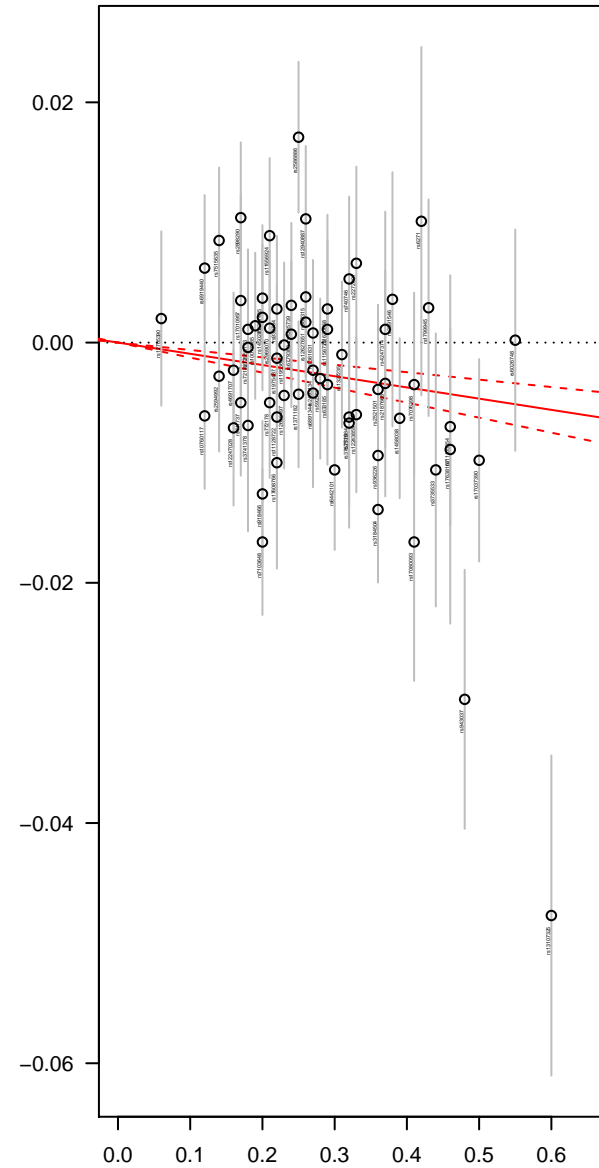
BMI, SBP; all SNPs



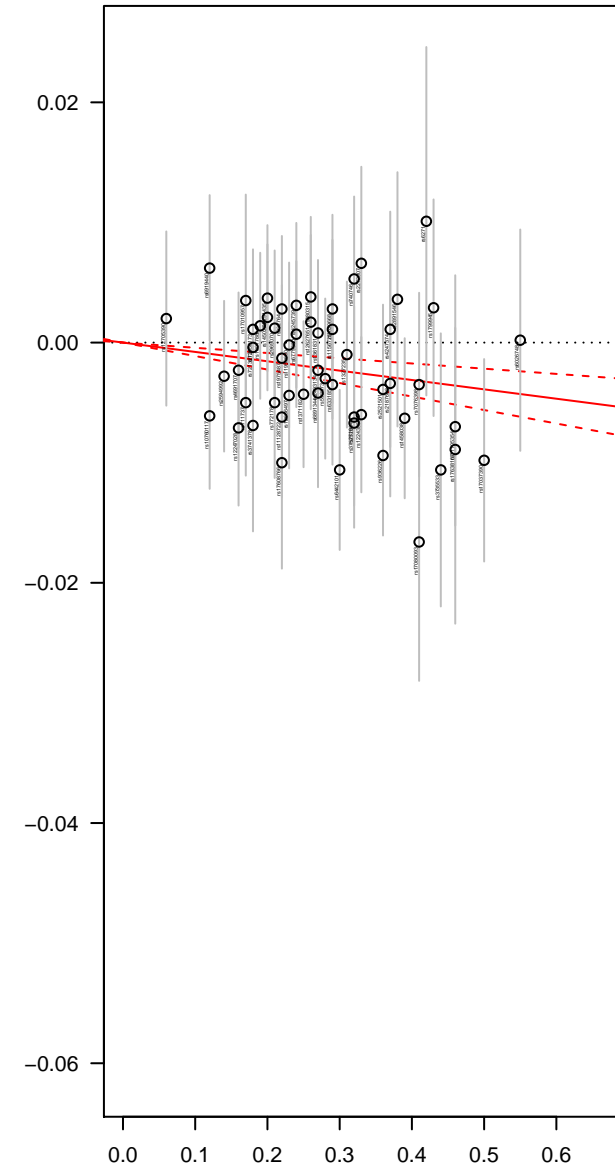
BMI, SBP; 10 pruned



BMI, DBP; all SNPs



BMI, DBP; 10 pruned

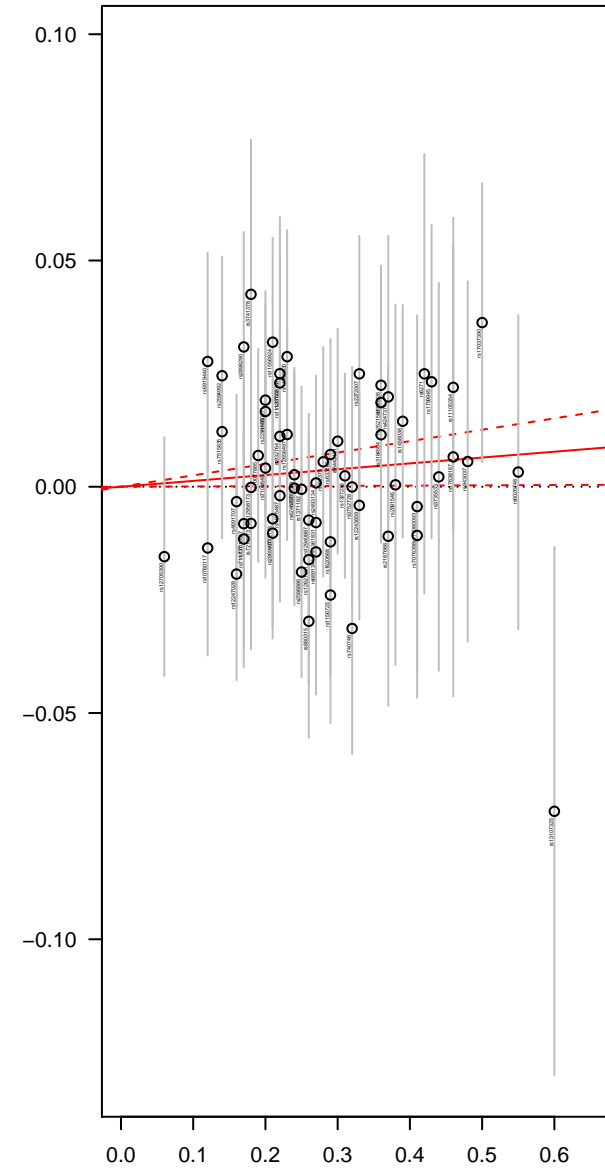
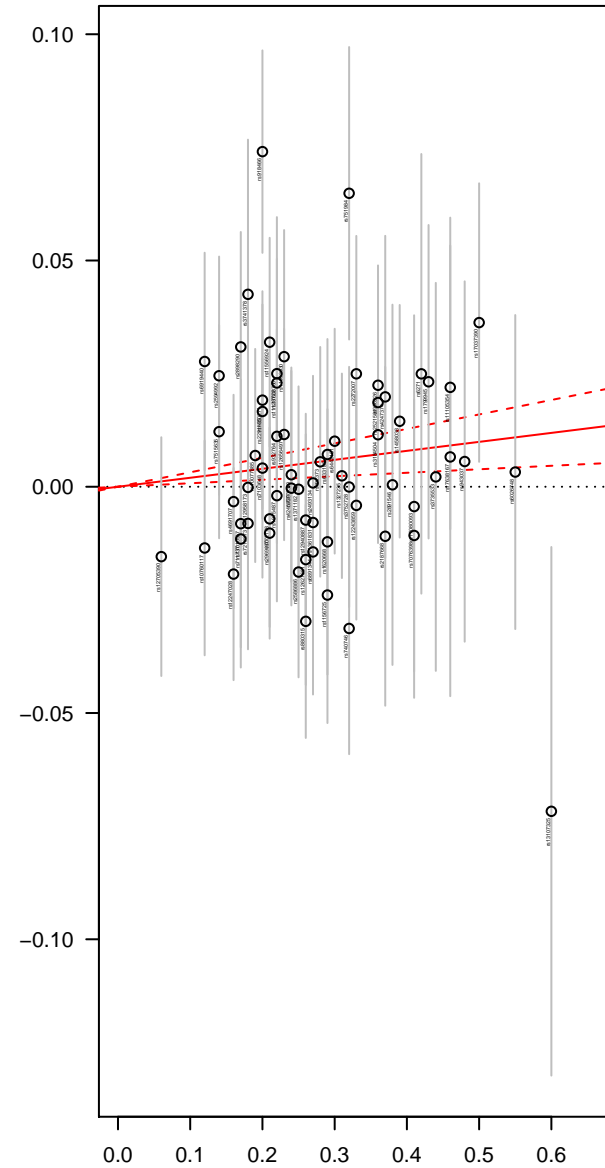
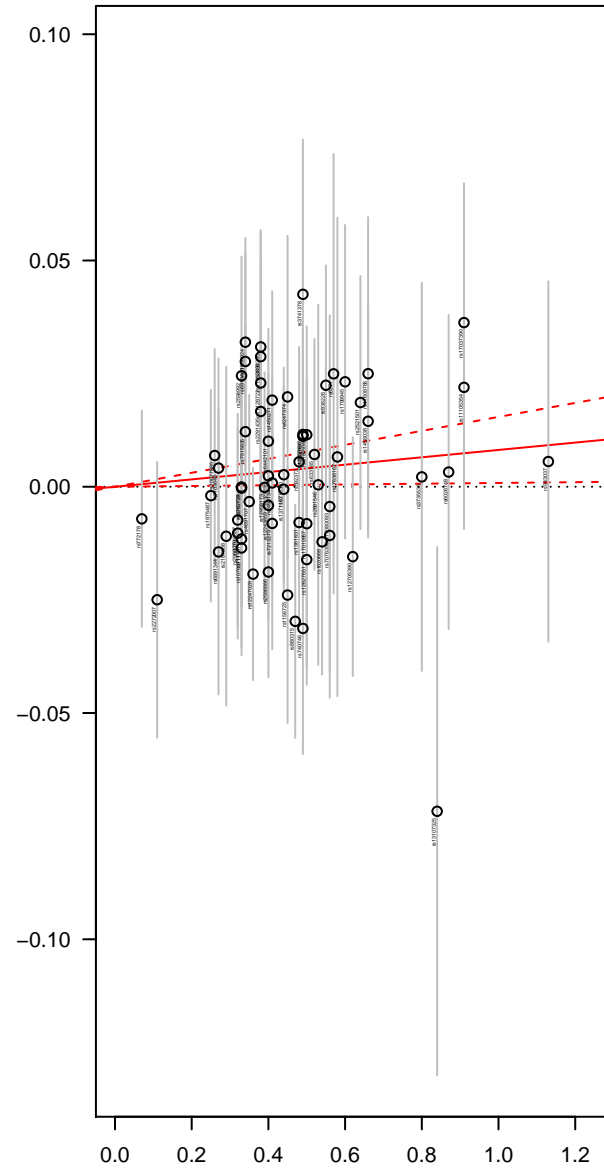
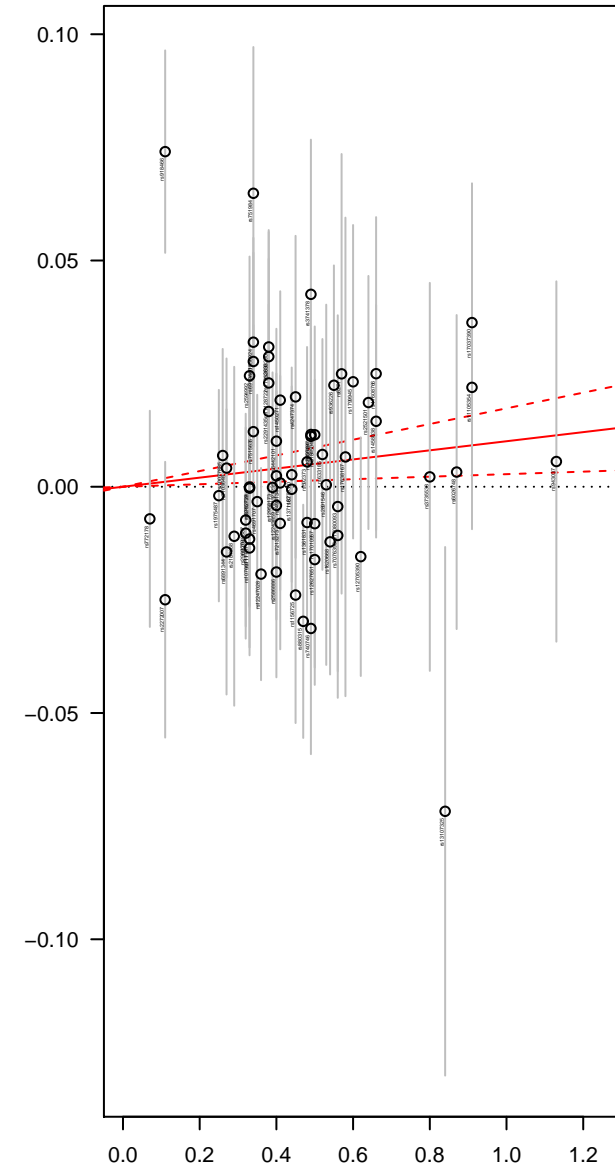


t2d, SBP; all SNPs

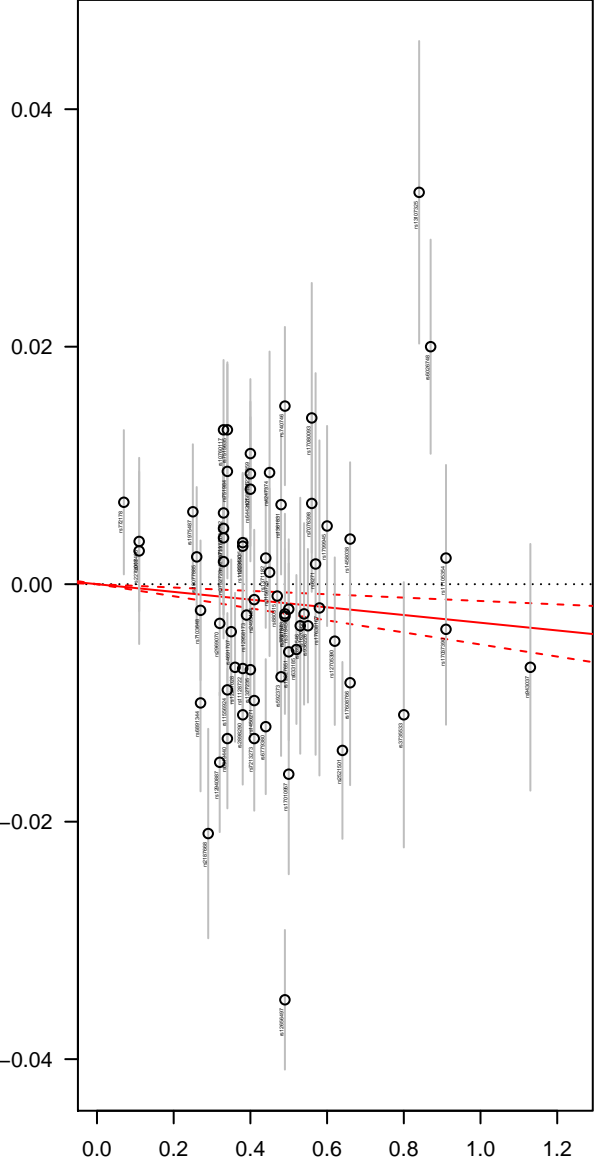
t2d, SBP; 2 pruned

t2d, DBP; all SNPs

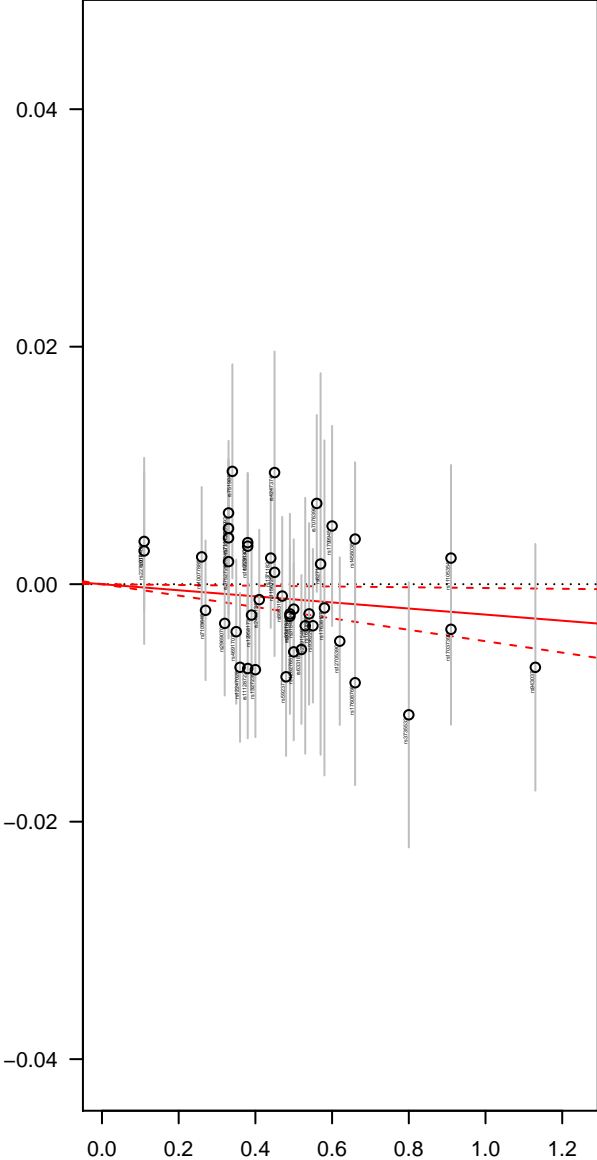
t2d, DBP; 2 pruned



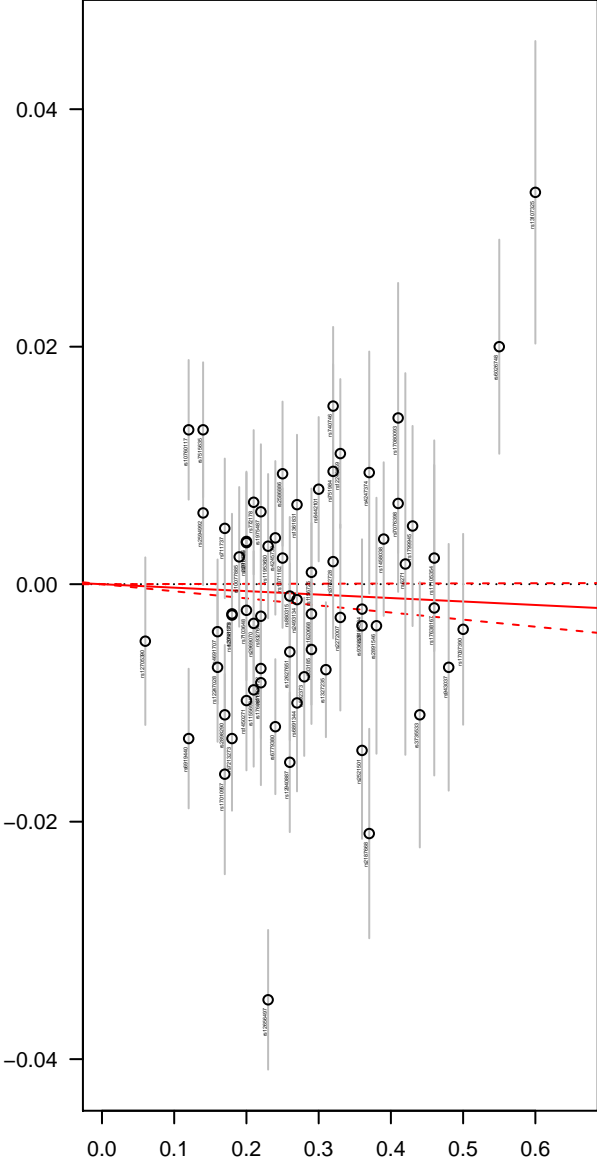
height, SBP; all SNPs



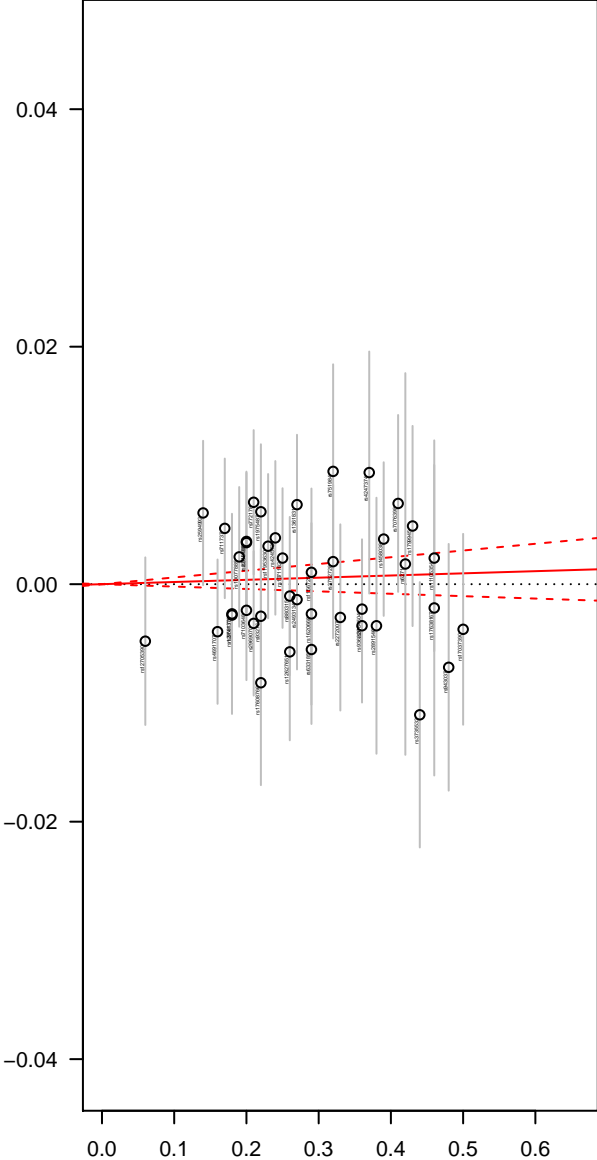
height, SBP; 24 pruned



height, DBP; all SNPs



height, DBP; 25 pruned



15 References

1. Ehret, G.B. *et al.* Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* **478**, 103-109 (2011).
2. Smith, N.L. *et al.* Association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the cohorts for heart and aging research in genomic epidemiology (CHARGE) consortium. *Circ Cardiovasc Genet* **3**, 256-66 (2010).
3. Vasan, R.S. *et al.* Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data. *JAMA* **302**, 168-78 (2009).
4. Ikram, M.A. *et al.* Genomewide association studies of stroke. *N Engl J Med* **360**, 1718-28 (2009).
5. Traylor, M. *et al.* Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. *Lancet Neurol* **11**, 951-62 (2012).
6. Deloukas, P. *et al.* Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet* (2012).
7. Pattaro, C. *et al.* Genome-wide association and functional follow-up reveals new loci for kidney function. *PLoS Genet* **8**, e1002584 (2012).
8. Boger, C.A. *et al.* CUBN is a gene locus for albuminuria. *J Am Soc Nephrol* **22**, 555-70 (2011).
9. Chambers, J.C. *et al.* Genetic loci influencing kidney function and chronic kidney disease. *Nat Genet* **42**, 373-5 (2010).
10. Bis, J.C. *et al.* Meta-analysis of genome-wide association studies from the CHARGE consortium identifies common variants associated with carotid intima media thickness and plaque. *Nat Genet* **43**, 940-947 (2011).
11. Jensen, R.A. *et al.* Genome-Wide Association Study of Retinopathy in Individuals without Diabetes. *PLoS One* **8**, e54232 (2013).
12. Sim, X. *et al.* Genetic loci for retinal arteriolar microcirculation. *PLoS One* **8**, e65804 (2013).
13. Voight, B.F. *et al.* The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. *PLoS Genet* **8**, e1002793 (2012).
14. Tobin, M.D., Sheehan, N.A., Scurrah, K.J. & Burton, P.R. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. *Stat Med* **24**, 2911-35 (2005).
15. Devlin, B. & Roeder, K. Genomic control for association studies. *Biometrics* **55**, 997-1004 (1999).
16. Abecasis, G.R. *et al.* An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56-65 (2012).
17. Consortium, I.H. The International HapMap Project. *Nature* **426**, 789-96 (2003).
18. Willer, C.J., Li, Y. & Abecasis, G.R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190-1 (2010).
19. R Development Core Team. R: A Language and Environment for Statistical Computing. (R Foundation for Statistical Computing, Vienna, Austria).
20. Kent, W.J. *et al.* The human genome browser at UCSC. *Genome Res* **12**, 996-1006 (2002).
21. Yang, J., Lee, S.H., Goddard, M.E. & Visscher, P.M. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet* **88**, 76-82 (2011).
22. Yang, J. *et al.* Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat Genet* **44**, 369-75, S1-3 (2012).

- 1 23. Pruim, R.J. *et al.* LocusZoom: regional visualization of genome-wide association scan results.
2 *Bioinformatics* **26**, 2336-7 (2010).
- 3 24. Wakefield, J. A Bayesian measure of the probability of false discovery in genetic epidemiology studies. *Am*
4 *J Hum Genet* **81**, 208-27 (2007).
- 5 25. Marchini, J., Howie, B., Myers, S., McVean, G. & Donnelly, P. A new multipoint method for genome-wide
6 association studies by imputation of genotypes. *Nat. Genet* **39**, 906-913 (2007).
- 7 26. Wellcome Trust Case Control, C. *et al.* Bayesian refinement of association signals for 14 loci in 3 common
8 diseases. *Nat Genet* **44**, 1294-301 (2012).
- 9 27. Penninx, B.W. *et al.* The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and
10 methods. *Int J Methods Psychiatr Res* **17**, 121-40 (2008).
- 11 28. Boomsma, D.I. *et al.* Netherlands Twin Register: from twins to twin families. *Twin Res Hum Genet* **9**, 849-
12 57 (2006).
- 13 29. Jansen, R. *et al.* Sex differences in the human peripheral blood transcriptome. *BMC Genomics* **15**, 33
14 (2014).
- 15 30. Wright, F.A. *et al.* Heritability and genomics of gene expression in peripheral blood. *Nat Genet* **46**, 430-7
16 (2014).
- 17 31. Nivard, M.G. *et al.* Further confirmation of the association between anxiety and CTNND2: replication in
18 humans. *Genes Brain Behav* **13**, 195-201 (2014).
- 19 32. Visscher, P.M., Benyamin, B. & White, I. The use of linear mixed models to estimate variance components
20 from data on twin pairs by maximum likelihood. *Twin Res* **7**, 670-4 (2004).
- 21 33. Grundberg, E. *et al.* Mapping cis- and trans-regulatory effects across multiple tissues in twins. *Nat Genet*
22 **44**, 1084-9 (2012).
- 23 34. Schunkert, H. *et al.* Large-scale association analysis identifies 13 new susceptibility loci for coronary artery
24 disease. *Nat Genet* **43**, 333-8 (2011).
- 25 35. Folkersen, L. *et al.* Association of genetic risk variants with expression of proximal genes identifies novel
26 susceptibility genes for cardiovascular disease. *Circ Cardiovasc Genet* **3**, 365-73 (2010).
- 27 36. Rodwell, G.E. *et al.* A transcriptional profile of aging in the human kidney. *PLoS Biol* **2**, e427 (2004).
- 28 37. Wheeler, H.E. *et al.* Sequential use of transcriptional profiling, expression quantitative trait mapping, and
29 gene association implicates MMP20 in human kidney aging. *PLoS Genet* **5**, e1000685 (2009).
- 30 38. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the
31 feasibility phase. The DCCT Research Group. *Diabetes* **35**, 530-45 (1986).
- 32 39. Romanoski, C.E. *et al.* Network for activation of human endothelial cells by oxidized phospholipids: a
33 critical role of heme oxygenase 1. *Circ Res* **109**, e27-41 (2011).
- 34 40. Koopmann, T.T. *et al.* Genome-wide identification of expression quantitative trait loci (eQTLs) in human
35 heart. *PLoS One* **9**, e97380 (2014).
- 36 41. Fairfax, B.P. *et al.* Innate immune activity conditions the effect of regulatory variants upon monocyte gene
37 expression. *Science* **343**, 1246949 (2014).
- 38 42. Ramasamy, A. *et al.* Genetic variability in the regulation of gene expression in ten regions of the human
39 brain. *Nat Neurosci* **17**, 1418-28 (2014).
- 40 43. Maurano, M.T. *et al.* Systematic localization of common disease-associated variation in regulatory DNA.
41 *Science* **337**, 1190-5 (2012).
- 42 44. Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses.
43 *Am J Hum Genet* **81**, 559-75 (2007).

- 1 45. Welter, D. *et al.* The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic Acids Res*
2 **42**, D1001-6 (2014).
- 3 46. Trynka, G. *et al.* Chromatin marks identify critical cell types for fine mapping complex trait variants. *Nat*
4 *Genet* **45**, 124-30 (2013).
- 5 47. Ernst, J. *et al.* Mapping and analysis of chromatin state dynamics in nine human cell types. *Nature* **473**, 43-
6 9 (2011).
- 7 48. Te Grotenhuis, M., Eisinga, R. & Pelzer, B. Saddlepoint approximations for the sum of independent non-
8 identically distributed binomial random variables. *Statistica Neerlandica* **67**, 190-201 (2013).
- 9 49. Segre, A.V. *et al.* Common inherited variation in mitochondrial genes is not enriched for associations with
10 type 2 diabetes or related glycemic traits. *PLoS Genet* **6**(2010).
- 11 50. Pers, T.H. *et al.* Biological interpretation of genome-wide association studies using predicted gene
12 functions. *Nat Commun* **6**, 5890 (2015).
- 13 51. Fehrmann, R.S. *et al.* Gene expression analysis identifies global gene dosage sensitivity in cancer. *Nat*
14 *Genet* **47**, 115-25 (2015).
- 15 52. Lage, K. *et al.* A human phenome-interactome network of protein complexes implicated in genetic
16 disorders. *Nat Biotechnol* **25**, 309-16 (2007).
- 17 53. Bult CJ, R.J., Blake JA, Kadin JA, Ringwald M, Eppig JT, and the Mouse Genome Database Group. . Mouse
18 genome informatics in a new age of biological inquiry. in *Proceedings of the IEEE International Symposium*
19 *on Bio-Informatics and Biomedical Engineering* 29-32 (2000.).
- 20 54. Croft, D. *et al.* Reactome: a database of reactions, pathways and biological processes. *Nucleic Acids Res*
21 **39**, D691-7 (2011).
- 22 55. Kanehisa, M., Goto, S., Sato, Y., Furumichi, M. & Tanabe, M. KEGG for integration and interpretation of
23 large-scale molecular data sets. *Nucleic Acids Res* **40**, D109-14 (2012).
- 24 56. Ashburner, M. *et al.* Gene ontology: tool for the unification of biology. The Gene Ontology Consortium.
25 *Nat Genet* **25**, 25-9 (2000).
- 26 57. Magi, R. & Morris, A.P. GWAMA: software for genome-wide association meta-analysis. *BMC*
27 *Bioinformatics* **11**, 288 (2010).
- 28 58. Dastani, Z. *et al.* Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic
29 traits: a multi-ethnic meta-analysis of 45,891 individuals. *PLoS Genet* **8**, e1002607 (2012).
- 30 59. Johnson, T. Efficient Calculation for Multi-SNP Genetic Risk Scores. in *American Society of Human Genetics*
31 (2012).
- 32 60. Kurogane, Y. *et al.* FGD5 mediates proangiogenic action of vascular endothelial growth factor in human
33 vascular endothelial cells. *Arterioscler Thromb Vasc Biol* **32**, 988-96 (2012).
- 34 61. Korn, C. & Augustin, H.G. Born to die: blood vessel regression research coming of age. *Circulation* **125**,
35 3063-5 (2012).
- 36 62. Ouyang, T. *et al.* Identification and characterization of a nuclear interacting partner of anaplastic
37 lymphoma kinase (NIPA). *J Biol Chem* **278**, 30028-36 (2003).
- 38 63. Bassermann, F. *et al.* NIPA defines an SCF-type mammalian E3 ligase that regulates mitotic entry. *Cell* **122**,
39 45-57 (2005).
- 40 64. Cubells, J.F. & Zabetian, C.P. Human genetics of plasma dopamine beta-hydroxylase activity: applications
41 to research in psychiatry and neurology. *Psychopharmacology (Berl)* **174**, 463-76 (2004).
- 42 65. Zabetian, C.P. *et al.* A quantitative-trait analysis of human plasma-dopamine beta-hydroxylase activity:
43 evidence for a major functional polymorphism at the DBH locus. *Am J Hum Genet* **68**, 515-22 (2001).

- 1 66. Mustapic, M. *et al.* The catecholamine biosynthetic enzyme dopamine beta-hydroxylase (DBH): first
2 genome-wide search positions trait-determining variants acting additively in the proximal promoter. *Hum*
3 *Mol Genet* (2014).
- 4 67. Chen, Y. *et al.* Human dopamine beta-hydroxylase (DBH) regulatory polymorphism that influences
5 enzymatic activity, autonomic function, and blood pressure. *J Hypertens* **28**, 76-86 (2010).
- 6 68. Chen, Y. *et al.* Human dopamine beta-hydroxylase promoter variant alters transcription in chromaffin
7 cells, enzyme secretion, and blood pressure. *Am J Hypertens* **24**, 24-32 (2011).
- 8 69. Rask-Madsen, C. & Kahn, C.R. Tissue-specific insulin signaling, metabolic syndrome, and cardiovascular
9 disease. *Arterioscler Thromb Vasc Biol* **32**, 2052-9 (2012).
- 10 70. Asselbergs, F.W. *et al.* Large-scale gene-centric meta-analysis across 32 studies identifies multiple lipid
11 loci. *Am J Hum Genet* **91**, 823-38 (2012).
- 12 71. Duncan, E.R. *et al.* Effect of endothelium-specific insulin resistance on endothelial function in vivo.
13 *Diabetes* **57**, 3307-14 (2008).
- 14 72. Manrique, C., Lastra, G. & Sowers, J.R. New insights into insulin action and resistance in the vasculature.
15 *Ann N Y Acad Sci* **1311**, 138-50 (2014).
- 16 73. Symons, J.D. *et al.* Knockout of insulin receptors in cardiomyocytes attenuates coronary arterial
17 dysfunction induced by pressure overload. *Am J Physiol Heart Circ Physiol* **300**, H374-81 (2011).
- 18 74. Guo, S. Insulin signaling, resistance, and the metabolic syndrome: insights from mouse models into
19 disease mechanisms. *J Endocrinol* **220**, T1-T23 (2014).
- 20 75. Wu, L.C. *et al.* The mouse DNA binding protein Rc for the kappa B motif of transcription and for the V(D)J
21 recombination signal sequences contains composite DNA-protein interaction domains and belongs to a
22 new family of large transcriptional proteins. *Genomics* **35**, 415-24 (1996).
- 23 76. Hicar, M.D., Liu, Y., Allen, C.E. & Wu, L.C. Structure of the human zinc finger protein HIVP3: molecular
24 cloning, expression, exon-intron structure, and comparison with paralogous genes HIVP1 and HIVP2.
25 *Genomics* **71**, 89-100 (2001).
- 26 77. Jones, D.C. *et al.* Regulation of adult bone mass by the zinc finger adapter protein Schnurri-3. *Science* **312**,
27 1223-7 (2006).
- 28 78. Shim, J.H. *et al.* Schnurri-3 regulates ERK downstream of WNT signaling in osteoblasts. *J Clin Invest* **123**,
29 4010-22 (2013).
- 30 79. Leung, A. *et al.* Novel long noncoding RNAs are regulated by angiotensin II in vascular smooth muscle
31 cells. *Circ Res* **113**, 266-78 (2013).
- 32 80. Balint, I., Muller, A., Nagy, A. & Kovacs, G. Cloning and characterisation of the RBCC728/TRIM36 zinc-
33 binding protein from the tumor suppressor gene region at chromosome 5q22.3. *Gene* **332**, 45-50 (2004).
- 34 81. Hatakeyama, S. TRIM proteins and cancer. *Nat Rev Cancer* **11**, 792-804 (2011).
- 35 82. Miyajima, N., Maruyama, S., Nonomura, K. & Hatakeyama, S. TRIM36 interacts with the kinetochore
36 protein CENP-H and delays cell cycle progression. *Biochem Biophys Res Commun* **381**, 383-7 (2009).
- 37 83. Takayama, K. *et al.* Integration of cap analysis of gene expression and chromatin immunoprecipitation
38 analysis on array reveals genome-wide androgen receptor signaling in prostate cancer cells. *Oncogene* **30**,
39 619-30 (2011).
- 40 84. Venerando, A., Ruzzene, M. & Pinna, L.A. Casein kinase: the triple meaning of a misnomer. *Biochem J* **460**,
41 141-56 (2014).
- 42 85. Minakuchi, M. *et al.* Identification and characterization of SEB, a novel protein that binds to the acute
43 undifferentiated leukemia-associated protein SET. *Eur J Biochem* **268**, 1340-51 (2001).
- 44 86. Hoischen, A. *et al.* De novo mutations of SETBP1 cause Schinzel-Giedion syndrome. *Nat Genet* **42**, 483-5
45 (2010).

- 1 87. Sakaguchi, H. *et al.* Exome sequencing identifies secondary mutations of SETBP1 and JAK3 in juvenile
2 myelomonocytic leukemia. *Nat Genet* **45**, 937-41 (2013).
- 3 88. Horike, N., Takemori, H., Katoh, Y., Doi, J. & Okamoto, M. Roles of several domains identified in the
4 primary structure of salt-inducible kinase (SIK). *Endocrine research* **28**, 291-4 (2002).
- 5 89. Lizcano, J.M. *et al.* LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including
6 MARK/PAR-1. *The EMBO journal* **23**, 833-43 (2004).
- 7 90. Hashimoto, Y.K., Satoh, T., Okamoto, M. & Takemori, H. Importance of autophosphorylation at Ser186 in
8 the A-loop of salt inducible kinase 1 for its sustained kinase activity. *Journal of cellular biochemistry* **104**,
9 1724-39 (2008).
- 10 91. Stenstro, K. *et al.* SIK1 is part of a cell sodium-sensing network that regulates active sodium transport
11 through a calcium-dependent process. (2007).
- 12 92. Jaitovich, A. & Bertorello, A.M. Intracellular sodium sensing: SIK1 network, hormone action and high blood
13 pressure. *Biochimica et biophysica acta* **1802**, 1140-9 (2010).
- 14 93. Stenström, K., Takemori, H., Bianchi, G., Katz, A.I. & Bertorello, A.M. Blocking the salt-inducible kinase 1
15 network prevents the increases in cell sodium transport caused by a hypertension-linked mutation in
16 human alpha-adducin. *Journal of hypertension* **27**, 2452-7 (2009).
- 17 94. Romito, A. *et al.* Lack of sik1 in mouse embryonic stem cells impairs cardiomyogenesis by down-regulating
18 the cyclin-dependent kinase inhibitor p57kip2. *PLoS one* **5**, e9029 (2010).
- 19 95. Watkins, H. *et al.* Mutations in the cardiac myosin binding protein-C gene on chromosome 11 cause
20 familial hypertrophic cardiomyopathy. *Nature genetics* **11**, 434-7 (1995).
- 21 96. Sadayappan, S. & de Tombe, P.P. Cardiac myosin binding protein-C as a central target of cardiac
22 sarcomere signaling: a special mini review series. *Pflügers Archiv : European journal of physiology* **466**,
23 195-200 (2014).
- 24 97. Bonne, G. *et al.* Cardiac myosin binding protein-C gene splice acceptor site mutation is associated with
25 familial hypertrophic cardiomyopathy. *Nature genetics* **11**, 438-40 (1995).
- 26 98. Tong, C.W., Nair, N.a., Doersch, K.M., Liu, Y. & Rosas, P.C. Cardiac myosin-binding protein-C is a critical
27 mediator of diastolic function. *Pflügers Archiv : European journal of physiology* **466**, 451-7 (2014).
- 28 99. Ho, J.E. *et al.* Discovery and replication of novel blood pressure genetic loci in the Women's Genome
29 Health Study. *J Hypertens* **29**, 62-9 (2011).
- 30 100. Padmanabhan, S. *et al.* Genome-Wide Association Study of Blood Pressure Extremes Identifies Variant
31 near UMOD Associated with Hypertension. *PLoS Genet* **6**, e1001177 (2010).
- 32 101. Takeuchi, F. *et al.* Blood pressure and hypertension are associated with 7 loci in the Japanese population.
33 *Circulation* **121**, 2302-9 (2010).
- 34 102. Johnson, A.D. *et al.* Association of hypertension drug target genes with blood pressure and hypertension
35 in 86,588 individuals. *Hypertension* **57**, 903-10 (2011).
- 36 103. Johnson, T. *et al.* Blood pressure loci identified with a gene-centric array. *The American Journal of Human*
37 *Genetics* (2011).
- 38 104. Kato, N. *et al.* Meta-analysis of genome-wide association studies identifies common variants associated
39 with blood pressure variation in east Asians. *Nat Genet* **43**, 531-8 (2011).
- 40 105. Salvi, E. *et al.* Genomewide association study using a high-density single nucleotide polymorphism array
41 and case-control design identifies a novel essential hypertension susceptibility locus in the promoter
42 region of endothelial NO synthase. *Hypertension* **59**, 248-255 (2012).
- 43 106. Wain, L.V. *et al.* Genome-wide association study identifies six new loci influencing pulse pressure and
44 mean arterial pressure. *Nature Genetics* (2011).

- 1 107. Ganesh, S.K. *et al.* Loci influencing blood pressure identified using a cardiovascular gene-centric array.
2 *Hum Mol Genet* (2013).
- 3 108. Kato, N. *et al.* Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood
4 pressure and implicates a role for DNA methylation. *Nat Genet* **47**, 1282-93 (2015).
- 5

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