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ARTICLE

Multi-ancestry genome-wide association study accounting for gene-psychosocial factor interactions identifies novel loci for blood pressure traits

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Summary

Psychological and social factors are known to influence blood pressure (BP) and risk of hypertension and associated cardiovascular diseases. To identify novel BP loci, we carried out genome-wide association meta-analyses of systolic, diastolic, pulse, and mean arterial BP, taking into account the interaction effects of genetic variants with three psychosocial factors: depressive symptoms, anxiety symptoms, and social support. Analyses were performed using a two-stage design in a sample of up to 128,894 adults from five ancestry groups. In the combined meta-analyses of stages 1 and 2, we identified 59 loci (p value $< 5e{-}8$), including nine novel BP loci. The novel associations were observed mostly with pulse pressure, with fewer observed with mean arterial pressure. Five novel loci were identified in African ancestry, and all but one showed patterns of interaction with at least one psychosocial factor. Functional annotation of the novel loci supports a major role for genes implicated in the immune response (*PLCL2*), synaptic function and neurotransmission (*LIN7A* and *PFIA2*), as well as genes previously implicated in neuropsychiatric or stress-related disorders (*FSTL5* and *CHODL*). These findings underscore the importance of considering psychological and social factors in gene discovery for BP, especially in non-European populations.

Introduction

High blood pressure (BP), or hypertension (MIM: 145500), is a leading risk factor for stroke, cardiovascular disease, end-stage renal disease, and mortality. By 2025, the number of adults with hypertension is predicted to reach over 1.5 billion—approximately 30% of the world adult population.[1] Hypertension also contributes significantly to health disparities, with the highest age-adjusted prevalence in the world attributed to populations of African ancestry.[2]

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Both genetic and non-genetic influences have been implicated in the etiology of hypertension. In particular, genome-wide association studies (GWAS) have identified over 900 single nucleotide polymorphisms (SNPs) associated with BP traits, mostly in populations of European ancestry.[3] These explain only slightly more than a quarter of the estimated heritability of BP.[3] The remaining unexplained heritability may be due in part to gene-environment interactions (GxE).[4] Thus, incorporating GxE effects in GWAS of BP may yield novel loci and reveal new insights about the biology of BP regulation and hypertension pathophysiology. Moreover, the detection of GxE effects may allow us to more precisely predict individual disease risk in the context of potentially modifiable environmental, lifestyle, and behavioral risk factors.

The role of psychological and social factors in the etiology of hypertension is supported by several epidemiological investigations [5,6] and animal model studies.[7] For example, anxiety and depressive symptoms have been consistently

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associated with a higher risk of hypertension.[5,8] In a systematic review of 15 prospective cohort studies, individuals with a high burden of psychological symptoms (anxiety, depression, and anger) had an 8% higher risk of hypertension compared to those reporting a low burden.[9] However, few studies have investigated potential effect modifications of genetic factors on BP traits by psychosocial factors.[10] To fill this gap in knowledge, we performed genome-wide association meta-analyses of systolic, diastolic, pulse, and mean arterial BP in the context of three psychosocial factors—depressive symptomatology, anxiety symptomatology, and social support—in a sample of up to 128,894 adults from five ancestry groups.

Subjects and methods

Study design and participating studies

The study was conducted in the setting of the Gene-Lifestyle Interactions Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium.[11,12] Study participants included adult men and women aged 18–80 years from five self-reported ancestry groups: African (AFR), Asian (ASN), Brazilian admixed (BRA), European (EUR), and Hispanic (HIS). Genome-wide association analyses accounting for gene-psychosocial factor interactions were carried out using a two-stage design (Figure 1). Stage 1 comprised up to 31 cohorts, including up to 68,450 individuals from the five self-reported ancestry groups. Stage 2 comprised up to 20 cohorts, including up to 61,046 individuals from four self-reported ancestry groups: AFR, ASN, EUR, and HIS. Not all studies or participants had data on all three psychosocial factors, so the number of participating studies and sample sizes varies for each exposure analysis (Figure 1). Details about the participating studies are provided in the Supplemental subjects and methods. Procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national). Each study obtained written informed consent from the participants and approval from the appropriate institutional review boards.

To detect novel loci with potentially underlying SNP by psychosocial factor (SNP × Psy) interaction effects, we used two complementary approaches: (1) both the SNP main effect and interaction effect on BP levels were jointly assessed using a two-degrees-of-freedom (2-df) test; (2) the effect of interaction alone was assessed using a 1-df test. When both the SNP main effect and interaction effect are present, the 2-df is more powerful[13] and, thus, may help identify BP-associated loci for which the 1-df test is underpowered.

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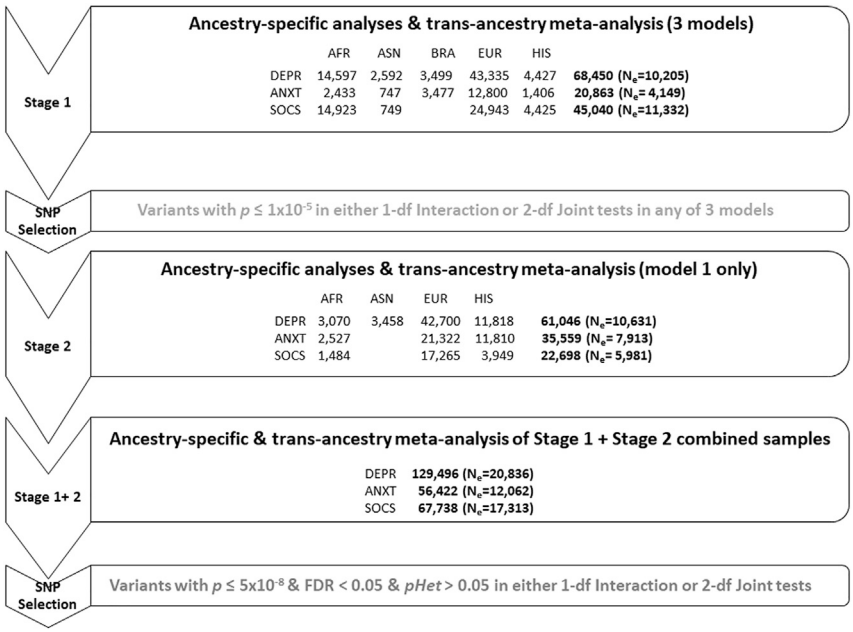

Figure 1. Overall study design
For each BP trait, association analyses were performed taking into account the interaction effects of genetic variants with each of three psychosocial factors: depressive symptoms (DEPR), anxiety (ANXT), and social support (SOCS). For each ancestry group, study-specific results were combined to perform a 1-degree of freedom (1-df) test for an interaction effect and a 2-df joint test of SNP main and interaction effects. Analyses were carried out separately in five self-reported ancestry groups: European (EUR), African (AFR), Asian (ASN), Hispanic (HIS), and Brazilian (BRA), and combined in a trans-ethnic meta-analysis. Sample sizes for each analysis are shown. N_e, number of subjects in the exposed strata (E = 1).

Blood pressure traits

Four BP measures were separately modeled: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP). SBP and DBP were adjusted for the BP-lowering effect of antihypertensive medication use by adding 15 and 10 mm Hg, respectively, to the observed BP readings.[14] After adjustment, MAP was calculated as two-thirds of DBP plus one-third of SBP. PP was calculated as the difference between SBP and DBP. Winsorizing was performed for each BP value that was more than six standard deviations away from the mean. Descriptive statistics for the four BP traits in each stage 1 and stage 2 cohort are shown in Table S1.

Psychosocial exposures

Information on depressive symptomatology, anxiety symptomatology, and social support was collected in each participating study using validated screening questionnaires (Table S2). Each measure of psychosocial exposure was dichotomized. To harmonize psychosocial exposures assessed using different screening instruments, we used recommended standard cut points specific to the screening instrument to define high depressive symptoms and high anxiety symptoms, whereas low social support was defined based on the lowest quartile of the perceived social support score in each study (all coded as E = 1). Details about the screening instruments used to measure depressive and anxiety symptomatology and social support and the cut points used to define the dichotomous variables in each study are shown in Table S2. BP readings and psychosocial questionnaires were taken at the same examination.

Genotype data

All cohorts performed genotyping on Illumina or Affymetrix arrays and imputed to the 1000 Genomes Project reference haplotypes.[15] Most studies used the Phase I Integrated Release Version 3 reference panel (2010-11 data freeze, 2012-03-14 haplotypes), which contains haplotypes for 1,092 individuals of all ethnic backgrounds.[15] Information on genotype and imputation for each study is presented in Table S3. Although we refer to the analyzed variants as SNPs, the imputed data also include indels (insertions and deletions).

Study-specific statistical analysis

We considered three statistical models to satisfy slightly different purposes:[12]

Model 1 is a joint effect model and is our primary model. It represents the joint analysis of the effects of the SNP, psychosocial exposure, and their interaction:

$$\mathrm{E[BP]} = \beta_0 + \beta_{SNP}SNP + \beta_E E + \beta_{SNP*E}SNP * E + \beta_C C$$

where E is the psychosocial variable and C represents all covariates (including age, sex, cohort-specific variables, and principal components [PCs]). PCs were derived from the directly measured genotype data and adjusted as appropriate for each study population. Information on PCs and additional study-specific covariates included in each analysis is provided in Table S3. Each SNP was coded under the assumption of an additive model. The model incorporated a SNP × Psy interaction effect. A 2-df joint test was used to simultaneously evaluate the significance of SNP and SNP × Psy effects under the null hypothesis that $\beta_{SNP} = \beta_{SNP*E} = 0$.[16] A 1-df test was also used to test for the interaction term alone under the null hypothesis that $\beta_{SNP*E} = 0$.

Model 2 is a SNP main effect model:

$$\mathrm{E[BP]} = \beta_0 + \beta_{SNP}SNP + \beta_C C$$

which was analyzed among those measured for the relevant psychosocial factor. Model 2 is used to identify SNPs with main effects only.

Model 3 is a psychosocial context-dependent SNP main effect model:

$$\mathrm{E[BP]} = \beta_0 + \beta_{SNP}SNP + \beta_E E + \beta_C C$$

which estimated the per-allele effect of the SNP on BP adjusting for an individual psychosocial factor. Model 3 is used to identify SNPs from the joint model that would be missed when the interaction term is not used.

Stage 1 cohorts performed ancestry-specific association analyses using all three models, while stage 2 cohorts performed analyses using Model 1 only. All association analyses within cohorts were

performed with various analytical software as described in Table S3.

Quality control and meta-analyses

Extensive quality control (QC) was performed for both the study-specific results and the meta-analyses results using EasyQC.[17] For each study, SNPs were filtered out if they had a minor allele frequency (MAF) less than 0.01, a low imputation quality (INFO score less than 0.5), a discrepancy in MAF compared with the 1000 Genomes reference panel greater than 0.3, or if the product of 2 * MAF *$N_{exposed}$* imputation quality score was less than 20. SNPs in the European-ancestry and multi-ancestry analyses had to be present in at least three cohorts and 3,000 participants to be reported. Due to the limited sample sizes, these criteria were relaxed for other ancestry-specific meta-analysis results, as shown in Table S4.

Inverse-variance weighted fixed-effect meta-analyses were conducted for all 3 models using METAL in stage 1.[18] Meta-analyses of the 2-df joint test and 1-df interaction test in the joint effect model (model 1) were carried out separately.[13] A 1-df Chi-square test was used to evaluate the 1-df interaction (model 1), SNP main effect (model 2), and psychosocial factor-adjusted SNP effect (model 3). A 2-df Wald test was used to jointly test the effects of both SNP and SNP × Psy interaction. Meta-analyses were conducted within each ancestry separately, then combined in a trans-ancestry meta-analysis. Genomic control correction was applied to the study-specific results and to the ancestry-specific meta-analysis results.[19] The quantile-quantile (QQ) plots and the estimated genomic control inflation factors for both 2-df and 1-df tests in stage 1 are shown in Figures S1–S6. There was mild to moderate inflation across most analyses ($\lambda \sim 1.1$). Variants with $p < 1e{-}5$ in 1-df or 2-df tests in any meta-analysis and any of the three models were selected for stage 2 analyses.

In the focused discovery stage 2, only ~20,000 variants were investigated, and we used the same approaches as in stage 1 to perform ancestry-specific and trans-ancestry meta-analyses but without genomic control correction or variant filtering. The ~20,000 variants were examined for association with the 4 BP traits, in the context of the 3 psychosocial factors and in each of the 5 ancestry groups using the joint effect model (model 1).

Finally, we performed ancestry-specific and trans-ancestry meta-analyses of all the cohort-level data from stage 1 and stage 2 together (model 1 only). There was no variant filtering at that stage, and all available data from stage 1 and stage 2 were used. We computed false discovery rate (FDR) adjusted p values (q-values) for the 2-df test using the p.adjust function in R, correcting for the number of analyses performed in stage 1 (4 BP traits, 3 psychosocial factors, and 5 + 1 ancestry/trans-ancestry groups). SNPs with $p < 5e{-}8$ and $q < 0.05$ and without any evidence of heterogeneity ($p_{Het} > 0.05$) in ancestry-specific meta-analyses for either the 1-df or 2-df test were considered statistically significant.

We defined a locus as the ±1 Mbp region surrounding an index SNP and a novel locus as ±1 Mbp away from an index SNP previously reported in the GWAS catalog and in Evangelou et al.[3]

Proportion of variance explained

We used the VarExp R package[20] to estimate the proportion of variance in each BP trait explained by previously reported BP variants and newly identified SNPs. The pruning threshold was set at $r^2 = 0.2$ to trim off redundant contribution from SNPs in high linkage disequilibrium (LD). Summary statistics and BP-SNP association estimates were derived from the meta-analyses of stages 1 and 2.

Bioinformatics and functional annotation

We assessed the functional potential of identified SNPs in the meta-analyses using multiple tools. We first used HaploReg v4.1[21] and the Functional Mapping and Annotation (FUMA)[22] to annotate the functional features of our novel BP loci. Haploreg was used to evaluate the effect of the identified SNPs on transcription factor binding site motifs and to perform enhancer enrichment analysis. Specifically, we assessed the overlap of our novel BP-associated SNPs with predicted enhancers using the ChromHMM 15-state core model and a binomial test of enrichment relative to the background frequencies of all common variants in 127 cell types. FUMA was used to prioritize candidate genes at each of the novel BP loci by incorporating three mapping strategies (positional, expression Quantitative Trait Locus (eQTL), and chromatin interaction mappings), MAGMA gene-set analyses, and several other annotation tools, such as the Combined Annotation Dependent Depletion (CADD) score.[23] We also used the PhenoScanner v2[24] database to evaluate our novel BP-associated SNPs for association with diseases and traits, metabolites (metabolite quantitative trait loci, mQTL), gene expression (eQTL), proteins (protein quantitative trait loci, pQTL), and DNA methylation (methylation quantitative trait loci, methQTL). Finally, we carried out protein-protein interaction networks and pathways enrichment analyses using STRING v.11.[25]

Results

Stage 1 analyses comprised up to 68,450 participants from five ancestry groups (Figure 1). Descriptive statistics of the studies participating in stage 1 are shown in Table S1. The proportion of individuals with psychological symptoms varied by cohort and ancestry group. On average, 16% (range: 5%–41%) of individuals reported depressive symptoms and 24% (range: 6%–75%) reported anxiety symptoms.

In stage 1 genome-wide interaction meta-analyses, we identified 20,323 unique variants with suggestive evidence ($p < 1e{-}5$) of any BP trait association with at least one of the three models tested. These were then evaluated for BP association in stage 2 in an independent sample of up to 61,046 individuals from four race/ethnicity groups (AFR, ASN, EUR, and HIS) (Figure 1).

In meta-analyses combining stage 1 and 2 cohorts, we identified 1,624 SNPs in 59 loci with genome-wide significant BP associations ($p < 5e{-}8$) (Table S5). A total of 597 SNPs in 28 loci were associated with SBP, 1,261 SNPs in 26 loci were associated with DBP, 570 SNPs in 26 loci were associated with MAP, and 150 SNPs in 19 loci were associated with PP. There were 604 SNPs associated with more than one BP trait (Figure S7). Almost all (1,614) SNPs were identified through the 2-df joint test only. Additionally, six SNPs in four loci were identified through the 1-df interaction test only, and 4 SNPs in 3 loci were identified through both. A total of 1,316 SNPs reached genome-wide significance in more than one association test (Table S5).

Novel BP loci

Among the 59 genome-wide significant loci, 15 SNPs in 9 loci were at least 1 Mbp away from any previously reported BP locus and therefore considered novel (Table 1; Table S6). All of them reached genome-wide significance in the 2-df

Table 1. Novel loci associated with BP traits discovered in the combined analysis of stages 1 and 2

Locus	Nearest gene	rsID	CHR: position	EA	EAF	MAF AA/EA/HIS/BR/ASN	Effect[a]	SE	IntEffect[a]	IntSE	P.2 df	Q.2 df	P.1 df	HetPVal[b]	Most significant 2-df model	n
1	*CSF3R*	rs77010007	1:37049595	C	0.97	0.03/0/0/0/0	1.721	0.672	3.920	1.167	2.34E−08	4.81E−04	7.82E−04	0.338	AA-MAP-DEPR	14,865
	CSF3R	rs112421395	1:37056662	A	0.03	0.03/0/0/0/0	−1.864	0.664	−3.712	1.166	2.05E−08	4.24E−04	1.45E−03	0.364	AA-MAP-DEPR	14,865
2	*PLCL2*	rs60884297	3:17115469	A	0.98	0.02/0/0/0/0	−0.106	0.638	5.125	1.049	1.39E−08	2.96E−04	1.03E−06	0.794	AA-PP-SOCS	16,406
	PLCL2	rs111333873	3:17123818	T	0.97	0.03/0/0/0/0	−0.004	0.587	4.970	0.986	3.01E−09	7.16E−05	4.58E−07	0.753	AA-PP-SOCS	16,406
	PLCL2	rs73153364	3:17135437	T	0.03	0.03/0/0/0/0	−0.005	0.533	−4.720	0.941	9.11E−09	1.99E−04	5.26E−07	0.576	AA-PP-SOCS	16,406
3	*FSTL5*	rs138187213	4:162397256	D	0.90	0.10/0.16/0.26/0.19/0.41	0.105	0.301	3.311	0.652	3.63E−08	7.08E−04	3.75E−07	0.665	AA-PP-DEPR	14,534
	FSTL5	rs5863461	4:162403550	D	0.89	0.11/0.16/0.26/0.19/0.41	0.074	0.306	3.321	0.646	2.87E−08	5.78E−04	2.72E−07	0.675	AA-PP-DEPR	14,534
4	*CASP8AP2*	rs9342214	6:90593029	A	0.91	0.01/0.01/0.12/0.05/0.42	0.055	0.234	2.430	0.453	4.72E−09	4.31E−05	7.97E−08	0.000	TRANS-PP-ANXT	23,157
5	*ACA59*	rs201673188	11:115004812	D	0.06	0.06/0.25/0.07/0.18/0	0.249	0.440	−3.570	0.708	3.86E−08	7.48E−04	4.53E−07	0.169	AA-PP-DEPR	12,882
6	*ACSS3*	rs140203359	12:81590456	A	0.99	0.01/0.01/0.11/0/0	0.400	0.578	4.444	0.969	3.23E−09	3.27E−05	4.46E−06	0.575	EA-PP-SOCS	32,600
7	*SNORD38*	rs142313940	13:90434805	A	0.02	0.20/0.02/0.06/0.05/0.25	−0.405	0.279	−2.586	0.552	4.01E−09	3.90E−05	2.75E−06	0.792	EA-PP-DEPR	76,812
	SNORD38	rs150161168	13:90434806	A	0.02	0.21/0.02/0.06/0.05/0.25	−0.401	0.279	−2.594	0.551	3.87E−09	3.80E−05	2.55E−06	0.787	EA-PP-DEPR	76,812
8	*7SK*	rs202048896	18:36191432	D	0.96	0.04/0.04/0/0.02/0	0.926	0.520	4.393	0.936	9.86E−11	2.81E−06	2.67E−06	0.241	AA-MAP-DEPR	14,534
9	*CHODL*	rs73321585	21:19312167	T	0.96	0.08/0/0.02/0.01/0	0.025	0.289	2.670	0.532	1.19E−08	9.51E−05	5.17E−07	0.003	TRANS-MAP-DEPR	37,392
	CHODL	rs73321586	21:19312525	T	0.04	0.08/0/0.02/0.01/0	0.101	0.300	−2.773	0.548	3.67E−08	2.46E−04	4.25E−07	0.002	TRANSC-MAP-DEPR	34,421

SNPs with $p < 5 \times 10^{-8}$ in the 2-df test or 1-df interaction test and at least 1 Mbp away from any previously reported BP locus are shown. EA, effect allele; EAF, effect allele frequency; MAF, minor allele frequency; SE, standard error; HetPVal, heterogeneity p value, AA, African ancestry; EUR, European ancestry; HIS, Hispanic ancestry; BR, Brazilian ancestry; ASN, Asian ancestry; df, degrees of freedom; P.2df, P value of the joint test of SNP main effect and interaction effect with 2 df; Q.2df, false discovery rate q value of the joint test with 2 df; P.1 df, P value of the interaction test with 1 df; TRANS, transethnic meta-analysis; DEPR, depressive symptomatology; ANXT, anxiety symptomatology; SOCS, social support; PP, pulse pressure; MAP, mean arterial pressure; n, total sample size.

[a]SNP main (Effect) and interaction (IntEffect) effects estimated in the joint model. Effect is in mm Hg.

[b]p Value for heterogeneity in the stage 1 + 2 in the most significant 2-df model.

test, and all but one showed suggestive evidence of interaction (1-df $p < 0.05/59 = 8.5e{-}4$). Indeed, as shown in forest plots (Figures S8–S12), associations at these novel loci were predominantly driven by interaction effects. Ten of the newly identified variants were discovered through modeling of interaction effects with depressive symptomatology, another four with social support, and only one with anxiety. Except for the two variants in the *FSTL5* gene on chromosome 4, the novel variants were of low frequency (MAF, 0.01–0.05) in the population in which they were identified. Nine of the 15 variants were discovered in analyses of populations of AFR ancestry. The enhanced discovery of novel loci in AFR ancestry may be due to differences in allele frequencies among ancestry groups. Indeed, five of the nine variants discovered in analyses of populations of AFR ancestry were not observed in any other ancestry. Seven of the 15 novel variants were not observed in individuals of EUR ancestry. Alternatively, SNP × Psy interaction effect sizes may be greater in AFR ancestry. For example, while rs201673188 is more common in EUR than AFR, the interaction of SNP with depressive symptomatology was associated with a decrease in PP of 3.57 mm Hg compared to 0.00 mm Hg in EUR (Table S5). The two low-frequency variants on chromosome 13 identified in EUR ancestry showed some evidence of BP association in AFR ancestry, where they were more common (MAF = 0.20) (2-df $p = 3.5e{-}3$; 1-df $p = 2.3e{-}3$). Three novel SNPs were identified in the trans-ancestry meta-analyses. However, these exhibited significant heterogeneity by ancestry ($p_{Het} < 0.016$), with significance being driven by results from a single ancestry group comprising stage 1 cohorts only (Table S7). Further replication of the association of these 3 SNPs with BP is therefore warranted.

Known BP loci

The remaining 1,609 SNPs reaching genome-wide significance mapped within 1 Mbp of 50 previously reported BP SNPs. These were mostly identified in European ancestry samples. Of the 1,609 SNPs, 117 showed nominally significant interaction effects (1-df $p < 0.05$), and these were mostly observed in African ancestry samples or trans-ancestry meta-analyses (Table S5).

We further assessed gene-psychosocial factor interactions on BP at previously known loci[3] in our dataset. Of 983 previously reported BP loci, 976 were present in our meta-analyses of stages 1 and 2. After harmonization of risk alleles against the previously published results, we tested for interaction in the 976 index SNPs. A Bonferroni-corrected p value threshold controlling for the number of SNPs tested (976), the number of BP traits (4), the number of Psy traits (3), and the number of ancestry groups (5) was used. There was evidence of gene-psychosocial interaction for 14 known independent SNPs (1-df $p < 0.05/976 \times 4 \times 3 \times 5 = 8.5e{-}7$), including 9 SNPs reaching genome-wide significance (Table S8). Notably, while these BP loci were identified from populations of EUR ancestry, the most significant evidence of interaction with psychosocial factors was obtained in samples of non-EUR ancestry.

Proportion of variance explained

We used ancestry-specific LD-pruned ($r^2 < 0.2$) known and novel BP SNPs to calculate the percent variance explained by the SNP main effect and the SNP-psychosocial factor interaction effect. The highest percent variance explained was 10.4% for DBP among Asian individuals when the SNP main effect and anxiety symptoms interactive effects were jointly modeled (Table S9). Notably, except for populations of EUR ancestry, the percent variance explained by interaction effects at the identified SNPs was at least equal to or greater than that explained by the SNP main effects. This was especially striking in the AFR ancestry group. Consistently, the percent variance explained by the joint effects of SNPs and psychosocial factors was 1.3- to 3.7-fold greater than that of the SNP main effects across the 4 BP traits, with the greatest difference observed for the joint effect of SNP × depressive symptoms (DEPR) in AFR ancestry (Table S9).

Functional annotation and gene prioritization

Most newly identified SNPs were annotated as either intronic or intergenic. This suggests evidence of regulatory mechanisms by which the identified SNPs may influence BP. Indeed, functional annotation using HaploReg v.4.1[21] and FUMA[22] showed evidence of regulatory motif disruption and overlap with predicted enhancers in major tissue types for the identified SNPs (Table S10). Enhancer enrichment analysis in HaploReg v.4.1[21] showed that the strongest signal was in primary natural killer cells from peripheral blood ($p = 0.01$), suggesting a possible role of innate immunity as a mechanism underlying these novel associations. Functional annotation was also conducted on all SNPs in moderate LD ($r^2 > 0.6$) with the identified novel SNPs (Table S11). Among the 125 SNPs that encompass the index SNPs and variants in LD, only two were exonic. These include a stop-loss variant (rs60111091) in *PLCL2* in high LD with the index variant rs111333873 on chromosome 3 (Locus #2). Several SNPs in LD with the novel index SNPs exhibited high CADD scores, suggesting that they are likely pathogenic. One SNP with a CADD score of 16.2 and in complete LD with rs140203359 (Locus #6) was located in an intron of *LIN7A* (MIM: 603380). Interestingly, rs140203359 was also identified as an eQTL for *LIN7A* in whole blood (Table S12). Two SNPs with similarly high CADD scores and in moderately high LD with rs73321585 (Locus #9) were located in an intron of *CHODL*. Chromatin interaction mapping showed significant evidence of long-range interactions of rs60884297 and nearby SNPs (Locus #2) with the promoter of *ANKRD28* (MIM: 611122), *DAZL* (MIM: 601486), and *PLCL2* (MIM: 614276) in aortic and left ventricular tissues (Table S13). These three genes were predicted to be highly intolerant to a loss-of-function mutation (probability of loss-of-function intolerance (pLI) score > 0.9).

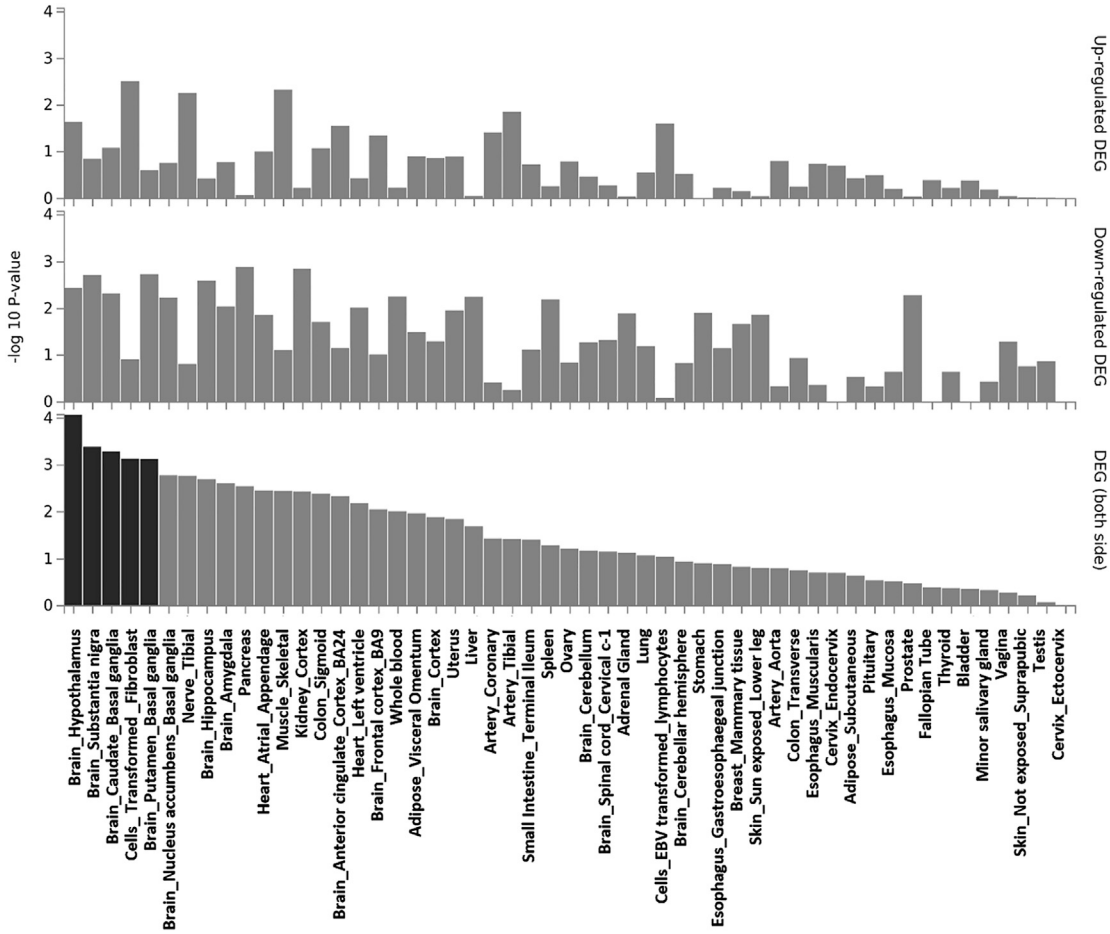

Figure 2. Enrichment of the prioritized genes mapped to the novel loci in Differentially Expressed Gene (DEG) sets from GTEx v7 data from 53 tissue types
Significantly enriched DEG sets (Bonferroni-corrected $p < 0.05$) are highlighted in red.

A total of 72 genes were prioritized by FUMA based on their physical position and their potential role in 3D chromatin interactions (Table S14). Two additional genes were prioritized via eQTL analysis using PhenoScanner v2 (Table S12). The 74 prioritized genes showed gene expression enrichment in brain tissue, notably the hypothalamus (Figure 2), and enrichment in 12 Gene Ontology terms, including several related to synaptic function (Table S15). We also used STRING v.11[25] to investigate protein-protein interaction networks and pathway enrichment analyses among the 74 prioritized genes. There was significant evidence of protein-protein interaction among the prioritized genes ($p = 2.5e{-}12$). A total of 46 protein-protein interactions were predicted. These showed enrichment in 4 major Reactome Pathways, including Neuronal System, Transmission across Chemical Synapses, Dopamine Neurotransmitter Release, and Protein-protein Interactions at Synapses (Table S15).

Discussion

This genome-wide association study systematically evaluated the joint effect of SNPs and SNP × Psy interactions on BP in a large and diverse sample and identified 59 genome-wide significant loci, of which nine were novel. Most novel loci were identified in non-European ancestry, and all but one showed patterns of interaction with at least one psychosocial factor. The enhanced discovery of novel loci in non-EUR ancestry was due to population differences in allele frequencies, with multiple novel variants not observed in EUR, and/or to population differences in SNP × Psy interaction effect sizes.

PP estimates the pulsatile component of BP and is influenced by the stiffness of large arteries and the pattern of wave reflections.[26] In a recent meta-analysis comprising 5,060 white and 3,225 African American healthy adults from 11 studies, measures of arterial stiffness and wave reflection were consistently higher in African Americans than in whites.[27] Intriguingly, the majority of the newly discovered loci were identified from analyses of African ancestry, with several of the identified variants not observed in European ancestry. The burden of hypertension in populations of African ancestry is among the highest in the world and is a primary cause of disparities in cardiovascular health and life expectancy between African Americans and whites.[28] Psychological and social stressors have been

associated with hypertension and are thought to play a major role in racial/ethnic differences in hypertension.[29] In particular, several lines of evidence indicate that psychosocial stressors may uniquely impact heart rate variability among African Americans.[29] The findings reported here underscore the value of including diverse populations in discovery of novel BP loci and may provide clues about possible biological mechanisms underlying the relationships between genes, psychosocial factors, and BP.

Functional annotation of the newly identified loci provides support for a major role of genes implicated in synaptic function, neurotransmission, and innate immunity. One of the newly identified loci for PP mapped to the *PLCL2* gene region on chromosome 3p24. Three variants in moderately high LD and polymorphic in samples of African ancestry only were associated at the genome-wide significance level with PP in the context of social support and at nominal significance level ($p < 0.05$) with SBP and MAP in the context of social support and anxiety. These variants are in strong LD with a rare stop-loss variant in the *PLCL2* gene and map to a region of long-range chromatin interaction with the *PLCL2* promoter in aortic and left ventricular tissues. *PLCL2* encodes a phospholipase C-like protein that lacks phospholipase catalytic activity.[30] *PLCL2* is expressed in hematopoietic cells, including B cells and T cells, and is a negative regulator of B cell receptor signaling and immune responses.[31] Genetic variants in the *PLCL2* gene have been associated with several auto-immune disorders[32–34] and myocardial infarction[35] in GWAS. The newly identified associations are consistent with the well-documented role of inflammation and the immune system in hypertension.[36,37]

Another newly identified association for PP mapped to a region on chromosome 12q21 that harbors several genes involved in synaptic function and plasticity. Lin-7 homolog A (*LIN7A*) is part of a family of scaffolding proteins that function as part of a tripartite complex and play a major role in synaptic function.[38] This evolutionarily conserved complex couples synaptic vesicle exocytosis to cell adhesion in the brain[39] and participates in NMDA receptor-containing vesicle transport.[40] *PPFIA2* (MIM: 603143) encodes liprin α2, which organizes presynaptic ultrastructure and controls synaptic output by regulating synaptic vesicle release.[41] *SYT1* (MIM: 185605) encodes synaptotagmin 1. The synaptotagmins are integral membrane proteins of synaptic vesicles thought to serve as calcium sensors in the process of vesicular trafficking and exocytosis.[42]

The newly identified locus on chromosome 4 associated with PP through depressive symptomatology mapped to an intronic region of the follistatin-like 5 (*FSTL5*) gene. This gene encodes a secretory glycoprotein with calcium-binding function. Gene expression analysis of mouse brain tissue shows that *Fstl5* is expressed in the olfactory system, hippocampal CA3 area, and granular cell layer of the cerebellum.[43] Variants in or near this gene have been associated with alcohol-related life events,[44] schizophrenia,[45] and the clustering of bipolar disorder, major depression, and schizophrenia.[46]

The locus on chromosome 21 mapped to an intronic region of the *CHODL* gene (MIM: 607247), which encodes a membrane-bound C-type lectin expressed in heart and skeletal muscle and is involved in muscle organ development. Rare copy number variants in this gene have been implicated in stress cardiomyopathy, also known as "broken heart syndrome," a sporadic condition precipitated by psychological or physical stress.[47]

Strengths of our study include a large sample of community-based cohorts with diverse ancestral backgrounds. Several limitations must also be acknowledged. First, while sample size was relatively balanced in the two analysis stages for populations of European and Asian ancestry, this was not the case for the other populations. Moreover, Asian and Brazilian populations were underrepresented in the overall sample. A more balanced population representation across stages 1 and 2 and a more diverse sample may have identified additional loci. Second, not all studies used the same validated instrument to capture depressive symptomatology, anxiety symptoms, and social support. This may have introduced some degree of heterogeneity and thus reduced power of our study. Finally, numerous studies show that psychological and social stressors are associated with poor health behaviors, such as cigarette smoking, excess alcohol consumption, low physical activity, and poor diet.[48–50] Thus, it is possible that the associations identified here were mediated at least in part by these factors. Indeed, although none of the nine novel loci identified here overlap with loci reported in previous GWAS of gene-by-alcohol or gene-by-smoking interaction on BP,[51,52] several known loci show such an overlap (Table S16).

In conclusion, we identified nine novel loci associated with BP traits, which harbor genes implicated in the neuronal system, synaptic function, and the immune response. Associations of these loci with BP were driven by interaction effects with at least one of three psychosocial factors. Moreover, our data highlight the potential for psychosocial factors to modify genetic associations of BP traits at previously reported loci. These findings underscore the importance of considering psychological and social factors in gene discovery for BP, especially in African ancestry.

Data and code availability

The summary statistics of the meta-analyses generated in this project are available at the CHARGE Consortium Summary Results at the database of Genotypes and Phenotypes (dbGaP) under accession number dbGaP: phs000930 or directly from the authors upon request.

Supplemental Information

Supplemental Information can be found online at https://doi.org/10.1016/j.xhgg.2020.100013.

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Declaration of Interests

The authors declare no competing interests.

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Web resources

OMIM, https://www.omim.org/
FUMA GWAS, https://fuma.ctglab.nl/
HaploReg v4.1, https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php
PhenoScnner V2, http://www.phenoscanner.medschl.cam.ac.uk/
STRING V11, https://string-db.org/
dbGaP, https://www.ncbi.nlm.nih.gov/gap/

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Supplemental Information

Multi-ancestry genome-wide association study accounting for gene-psychosocial factor interactions identifies novel loci for blood pressure traits

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STUDY DESCRIPTIONS

Stage 1 cohorts

AGES (Age Gene/Environment Susceptibility Reykjavik Study): The AGES Reykjavik study originally comprised a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967. A total of 19,381 people attended, resulting in a 71% recruitment rate. The study sample was divided into six groups by birth year and birth date within month. One group was designated for longitudinal follow up and was examined in all stages; another was designated as a control group and was not included in examinations until 1991. Other groups were invited to participate in specific stages of the study. Between 2002 and 2006, the AGES Reykjavik study re-examined 5,764 survivors of the original cohort who had participated before in the Reykjavik Study. The midlife data blood pressure measurement was taken from stage 3 of the Reykjavik Study (1974-1979), if available. Half of the cohort attended during this period. Otherwise an observation was selected closest in time to the stage 3 visit. The supine blood pressure was measured twice by a nurse using a mercury sphygmomanometer after 5 minutes rest following World Health Organization recommendations.

ARIC (Atherosclerosis Risk in Communities Study): The ARIC study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792 individuals, predominantly European American and African American, aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed three additional triennial follow-up examinations and three additional examinations in 2011-2013 (visit 5), 2016-2017 (visit 6), and 2018-2019 (visit 7). The ARIC study has been described in detail previously (The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: Design and objectives. Am J Epidemiol. 1989; 129:687-702). Blood pressure was measured using a standardized Hawksley random-zero mercury column sphygmomanometer with participants in a sitting position after a resting period of 5 minutes. The size of the cuff was chosen according to the arm circumference. Three sequential recordings for systolic and diastolic blood pressure were obtained; the mean of the last two measurements was used in this analysis, discarding the first reading. Blood pressure lowering medication use was recorded from the medication history.

Baependi Heart Study (Brazil): The Baependi Heart Study is an ongoing family-based cohort conducted in a rural town of the state of Minas Gerais. The study has enrolled approximate 2,200 individuals (over 10% of the town's adult population) and 10-year follow up period of longitudinal data. Briefly, probands were selected at random across 11 out of the 12 census districts in Baependi. After enrolment, the proband's first-degree (parents, siblings, and

offspring), second-degree (half-siblings, grandparents/grandchildren, uncles/aunts, nephews/nieces, and double cousins), and third-degree (first cousins, great uncles/aunts, and great nephews/nieces) relatives, and his/her respective spouse's relatives resident both within Baependi (municipal and rural area) and surrounding towns were invited to participate. Only individuals age 18 and older were eligible to participate in the study. The study is conducted from a clinic/office in an easily accessible sector of the town, where the questionnaires were completed. A broad range of phenotypes ranging from cardiovascular, neurocognitive, psychiatric, imaging, physiologic and several layers of endophenotypes like metabolomics and lipidomics have been collected throughout the years Details about follow-up visits and available data can be found in the cohort profile paper (PMID: 18430212). DNA samples were genotyped using the Affymetrix 6.0 genechip. After quality control, the data were prephased using SHAPEIT and imputed using IMPUTE2 based on 1000 Genomes haplotypes.

CARDIA (Coronary Artery Risk Development in Young Adults): CARDIA is a prospective multicenter study with 5,115 adults Caucasian and African American participants of the age group 18-30 years, recruited from four centers at the baseline examination in 1985-1986. The recruitment was done from the total community in Birmingham, AL, from selected census tracts in Chicago, IL and Minneapolis, MN; and from the Kaiser Permanente health plan membership in Oakland, CA. The details of the study design for the CARDIA study have been previously published. Nine examinations have been completed since initiation of the study, respectively in the years 0, 2, 5, 7, 10, 15, 20, 25 and 30. Written informed consent was obtained from participants at each examination and all study protocols were approved by the institutional review boards of the participating institutions. Systolic and diastolic blood pressure was measured in triplicate on the right arm using a random-zero sphygmomanometer with the participant seated and following a 5-minutes rest. The average of the second and third measurements was taken as the blood pressure value. Blood pressure medication use was obtained by questionnaire.

CHS (Cardiovascular Health Study): CHS is a population-based cohort study of risk factors for cardiovascular disease in adults 65 years of age or older conducted across four field centers [PMID: 1669507]. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists and an additional predominately African-American cohort of 687 persons was enrolled in 1992-93 for a total sample of 5,888. Research staff with central training in blood pressure measurement assessed repeated right-arm seated systolic and diastolic blood pressure levels at baseline with a Hawksley random-zero sphygmomanometer. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. European ancestry participants were excluded from the GWAS study sample due to prevalent coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke, or transient ischemic attack at baseline. After QC, genotyping was successful for 3271 European ancestry and 823 African-American participants. CHS was approved by institutional review committees at each site and individuals in the present analysis gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

ERF (Erasmus Rucphen Family study): Erasmus Rucphen Family is a family based study that includes inhabitants of a genetically isolated community in the South-West of the Netherlands, studied as part of the Genetic Research in Isolated Population (GRIP) program. [Aulchenko YS, Heutink P, Mackay I et al: Linkage disequilibrium in young genetically isolated Dutch population. Eur J Hum Genet 2004; 12: 527–534; Pardo LM, MacKay I, Oostra B, van Duijn CM, Aulchenko YS: The effect of genetic drift in a young genetically isolated population. Ann Hum Genet 2005; 69: 288–295].The goal of the study is to identify the risk factors in the development of complex disorders. Study population includes approximately 3,000 individuals who are living descendants of 22 couples who lived in the isolate between 1850 and 1900 and had at least six children baptized in the community church. All data were collected between 2002 and 2005. All participants gave informed consent, and the Medical Ethics Committee of the Erasmus University Medical Centre approved the study.

FHS (Framingham Heart Study): FHS began in 1948 with the recruitment of an original cohort of 5,209 men and women (mean age 44 years; 55 percent women). In 1971 a second generation of study participants was enrolled; this cohort (mean age 37 years; 52% women) consisted of 5,124 children and spouses of children of the original cohort. A third generation cohort of 4,095 children of offspring cohort participants (mean age 40 years; 53 percent women) was enrolled in 2002-2005 and are seen every 4 to 8 years. Details of study designs for the three cohorts are summarized elsewhere. At each clinic visit, a medical history was obtained with a focus on cardiovascular content, and participants underwent a physical examination including measurement of height and weight from which BMI was calculated. Systolic and diastolic blood pressures were measured twice by a physician on the left arm of the resting and seated participant using a mercury column sphygmomanometer. Blood pressures were recorded to the nearest even number. The means of two separate systolic and diastolic blood pressure readings at each clinic examination were used for statistical analyses.

GENOA (Genetic Epidemiology Network of Arteriopathy): GENOA is one of four networks in the NHLBI Family-Blood Pressure Program (FBPP). [The FBPP Investigators. Multi-center genetic study of hypertension: The Family Blood Pressure Program (FBPP). [Hypertension 2002;39:3-9.; Daniels PR, Kardia SL, Hanis CL, Brown CA, Hutchinson R, Boerwinkle E, Turner ST; Genetic Epidemiology Network of Arteriopathy study. Familial aggregation of hypertension treatment and control in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. Am J Med. 2004 May 15;116(10):676-81. PMID: 15121494.] GENOA's long-term objective is to elucidate the genetics of target organ complications of hypertension, including both atherosclerotic and arteriosclerotic complications involving the heart, brain, kidneys, and peripheral arteries. The longitudinal GENOA Study recruited European-American and African-American sibships with at least 2 individuals with clinically diagnosed essential hypertension before age 60 years. All other members of the sibships were invited to participate regardless of their hypertension status. Participants were diagnosed with hypertension if they had either 1) a previous clinical diagnosis of hypertension by a physician with current anti-hypertensive treatment, or 2) an average systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg based on the second and third readings at the time of their clinic visit. Exclusion criteria were secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes mellitus, or active malignancy. During the first exam (1995-2000), 1,583

European Americans from Rochester, MN and 1,854 African Americans from Jackson, MS were examined. Between 2000 and 2005, 1,241 of the European Americans and 1,482 of the African Americans returned for a second examination. Because African-American probands for GENOA were recruited through the Atherosclerosis Risk in Communities (ARIC) Jackson field center participants, we excluded ARIC participants from analyses.

HANDLS (Healthy Aging in Neighborhoods of Diversity across the Life Span): HANDLS is a community-based, longitudinal epidemiologic study examining the influences of race and socioeconomic status (SES) on the development of age-related health disparities among a sample of socioeconomically diverse African Americans and whites. This unique study will assess over a 20-year period physical parameters and also evaluate genetic, biologic, demographic, and psychosocial, parameters of African American and white participants in higher and lower SES to understand the driving factors behind persistent black-white health disparities in overall longevity, cardiovascular disease, and cognitive decline. The study recruited 3,722 participants from Baltimore, MD with a mean age of 47.7 years, 2,200 African Americans and 1,522 whites, with 41% reporting household incomes below the 125% poverty delimiter. Genotyping was done on a subset of self-reporting African American participants by the Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health (NIH). A larger genotyping effort included a small subset of self-reporting European ancestry samples. This research was supported by the Intramural Research Program of the NIH, NIA and the National Center on Minority Health and Health Disparities.

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

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

HyperGEN (Hypertension Genetic Epidemiology Network): HyperGEN is a family-based study that looks at the genetic causes of hypertension and related conditions in EA and AA subjects. HyperGEN recruited hypertensive sibships, along with their normotensive adult

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

JHS (Jackson Heart Study): The Jackson Heart Study is a longitudinal, community-based observational cohort study investigating the role of environmental and genetic factors in the development of cardiovascular disease in African Americans. Between 2000 and 2004, a total of 5301 participants were recruited from a tri-county area (Hinds, Madison, and Rankin Counties) that encompasses Jackson, MS. Details of the design and recruitment for the Jackson Heart Study cohort has been previously published. Briefly, approximately 30% of participants were former members of the Atherosclerosis Risk in Communities (ARIC) study. The remainder were recruited by either 1) random selection from the Accudata list, 2) commercial listing, 3) a constrained volunteer sample, in which recruitment was distributed among defined demographic cells in proportions designed to mirror those in the overall population, or through the Jackson Heart Study Family Study.

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

NEO (The Netherlands Epidemiology of Obesity study): The NEO was designed for extensive phenotyping to investigate pathways that lead to obesity-related diseases. The NEO study is a population-based, prospective cohort study that includes 6,671 individuals aged 45–65 years, with an oversampling of individuals with overweight or obesity. At baseline, information on demography, lifestyle, and medical history have been collected by questionnaires. In addition, samples of 24-h urine, fasting and postprandial blood plasma and serum, and DNA were collected. Genotyping was performed using the Illumina HumanCoreExome chip, which was subsequently imputed to the 1000 genome

reference panel. Participants underwent an extensive physical examination, including anthropometry, electrocardiography, spirometry, and measurement of the carotid artery intima-media thickness by ultrasonography. In random subsamples of participants, magnetic resonance

imaging of abdominal fat, pulse wave velocity of the aorta, heart, and brain, magnetic resonance spectroscopy of the liver, indirect calorimetry, dual energy X-ray absorptiometry, or accelerometry measurements were performed. The collection of data started in September 2008 and completed at the end of September 2012. Participants are currently being followed for the incidence of obesity-related diseases and mortality.

Pelotas Birth Cohort Study (The 1982 Pelotas Birth Cohort Study, Brazil): The maternity hospitals in Pelotas, a southern Brazilian city (current population ~330,000), were visited daily in the year of 1982. The 5,914 liveborns whose families lived in the urban area were examined and their mothers interviewed. Information was obtained for more than 99% of the livebirths. These subjects have been followed-up at the following mean ages: 11.3 months (all children born from January to Abril 1982; n=1457), 19.4 months (entire cohort; n=4934), 43.1 months (entire cohort; n=4742), 13.1 years (random subsample; n=715), 14.7 years (systematic subsample; n=1076); 18.2 (male cohorts attending to compulsory Army recruitment examination; n=2250), 18.9 (systematic subsample; n=1031), 22.8 years (entire cohort; n=4297) and 30.2 years (entire cohort; n=3701). Details about follow-up visits and available data can be found in the two Cohort Profile papers (PMID: 16373375 and 25733577). DNA samples (collected at the mean age of 22.8 years) were genotyped for ~2.5 million of SNPs using the Illumina HumanOmni2.5-8v1 array (which includes autosomal, X and Y chromosomes, and mitochondrial variants). After quality control, the data were prephased using SHAPEIT and imputed using IMPUTE2 based on 1000 Genomes haplotypes.

RS (Rotterdam Study): The Rotterdam Study is a prospective, population-based cohort study among individuals living in the well-defined Ommoord district in the city of Rotterdam in The Netherlands [Ikram, M.A. et al. The Rotterdam Study: 2018 update on objectives, design and main results. Eur J Epidemiol 2017, 32:807-850]. The aim of the study is to determine the occurrence of cardiovascular, neurological, ophthalmic, endocrine, hepatic, respiratory, and psychiatric diseases in elderly people. The cohort was initially defined in 1990 among approximately 7,900 persons, aged 55 years and older, who underwent a home interview and extensive physical examination at the baseline and during follow-up rounds every 3-4 years (RS-I). Cohort was extended in 2000/2001 (RS-II, 3,011 individuals aged 55 years and older) and 2006/2008 (RS-III, 3,932 subjects, aged 45 and older). Written informed consent was obtained from all participants and the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the study.

SP2 (Singapore Prospective Study Program): The SP2 is a population-based study of diabetes and cardiovascular disease in Singapore. It first surveyed subjects (Chinese, Malay and Indian) from four cross-sectional studies that were conducted in Singapore between 1982 and 1998. Subjects were between the ages of 24-95 years and represented a random sample of the Singapore population. Subjects were re-visited between 2003 and 2007. Among the 10,747 individuals who were eligible, 5,157 subjects completed a questionnaire and the subsequent clinical examinations. Data from this revisit were utilized for this study. Two readings of blood pressure were taken from participants after 5 min of rest, seated, using an automated blood pressure monitor (Dinamap Pro100V2; Criticon, Norderstedt, Germany) by trained observers.

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

WHI (Women's Health Initiative): WHI is a long-term national health study that focuses on strategies for preventing common diseases such as heart disease, cancer and fracture in postmenopausal women. A total of 161,838 women aged 50–79 years old were recruited from 40 clinical centers in the US between 1993 and 1998. WHI consists of an observational study, two clinical trials of postmenopausal hormone therapy (HT, estrogen alone or estrogen plus progestin), a calcium and vitamin D supplement trial, and a dietary modification trial 1. Study recruitment and exclusion criteria have been described previously 1. Recruitment was done through mass mailing to age-eligible women obtained from voter registration, driver's license and Health Care Financing Administration or other insurance list, with emphasis on recruitment of minorities and older women 2. Exclusions included participation in other randomized trials, predicted survival < 3 years, alcoholism, drug dependency, mental illness and dementia. For the CT, women were ineligible if they had a systolic BP > 200 mm Hg or diastolic BP > 105 mm Hg, a history of hypertriglyceridemia or breast cancer. Study protocols and consent forms were approved by the IRB at all participating institutions. Socio-demographic characteristics, lifestyle, medical history and self-reported medications were collected using standardized questionnaires at the screening visit. Physical measures of height, weight and blood pressure were measured at a baseline clinical visit 2. BP was measured by certified staff using standardized procedures and instruments 3. Two BP measures were recorded after 5 minutes rest using a mercury sphygmomanometer. Appropriate cuff bladder size was determined at each visit based on arm circumference. Diastolic BP was taken from the phase V Korotkoff measures. The average of the two measurements, obtained 30 seconds apart, was used in analyses. The genome wide association study (GWAS) non-overlapping samples are composed of a case-control study (WHI Genomics and Randomized Trials Network – GARNET, which included all coronary heart disease, stroke, venous thromboembolic events and selected diabetes cases that happened during the active intervention phase in the WHI HT clinical trials and aged matched controls), women selected to be "representative" of the HT trial (mostly younger white HT subjects that were also enrolled in the WHI memory study - WHIMS) and the WHI SNP Health Association Resource (WHI SHARe), a randomly selected sample of 8,515 African American and 3,642 Hispanic women from WHI. GWAS was performed using Affymetrix 6.0 (WHI-SHARe), HumanOmniExpressExome-8v1_B (WHIMS), Illumina HumanOmni1-Quad v1-0 B (GARNET). Extensive quality control (QC) of the GWAS data included alignment ("flipping") to the same reference panel, imputation to the 1000G data (using the recent reference panel - v3.20101123), identification of genetically related individuals, and computations of principal components (PCs) using methods developed by Price et al. (using EIGENSOFT software 53),

and finally the comparison with self-reported ethnicity. After QC and exclusions from analysis protocol, the number of women included in analysis is 4,423 whites for GARNET, 5,202 white for WHIMS, 7,919 for SHARe African American and 3,377 for SHARe Hispanics.

Stage 2 cohorts

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

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

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

GeneSTAR (Genetic Studies of Atherosclerosis Risk): GeneSTAR is a family-based prospective study of more than 4000 participants begun in 1983 to determine phenotypic and genetic causes of premature cardiovascular disease. Families were identified from 1983-2006 from probands with a premature coronary disease event prior to 60 years of age who were identified at the time of hospitalization in any of 10 hospitals in the Baltimore, Maryland area. Their apparently healthy 30-59 year old siblings without known coronary disease were recruited and screened between 1983 and 2006. From 2003-2006, adult offspring over 21 years of age of

all participating siblings and probands, as well as the co-parents of the offspring were recruited and screened. Genotyping was performed in 3,232 participants on the Illumina 1Mv1_c platform.

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

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

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

LBC1921 (Lothian Birth Cohort 1921): LBC1921 (http://www.lothianbirthcohort.ed.ac.uk/) consists of 550 (234 male) relatively healthy individuals, assessed on cognitive and medical traits at a mean age of 79.1 years (SD = 0.6). They were born in 1921, most took part in the Scottish Mental Survey of 1932, and almost all lived independently in the Lothian region (Edinburgh City and surrounding area) of Scotland.

LBC1936 (Lothian Birth Cohort 1936): LBC1936 (http://www.lothianbirthcohort.ed.ac.uk/) consists of 1091 (548 male) relatively healthy individuals who underwent cognitive and medical testing at a mean age of 69.6 years (SD = 0.8). They were born in 1936, most took part in the Scottish Mental Survey of 1947, and almost all lived independently in the Lothian region of Scotland.

Lifelines (Netherlands Biobank): Lifelines (https://lifelines.nl/) is a multi-disciplinary prospective population-based cohort study using a unique three-generation design to examine the health and health-related behaviors of 165,000 persons living in the North East region of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity. In addition, the Lifelines project comprises a number of cross-sectional sub-studies which investigate specific age-related conditions. These include investigations into metabolic and hormonal diseases, including obesity, cardiovascular and renal diseases, pulmonary diseases and allergy, cognitive function and depression, and musculoskeletal conditions. All survey participants are between 18 and 90 years old at the time of enrollment. Recruitment has been going on since the end of 2006, and over 130,000 participants had been included by April 2013. At the baseline examination, the participants in the study were asked to fill in a questionnaire (on paper or online) before the first visit. During the first and second visit, the first or second part of the questionnaire, respectively, are checked for completeness, a number of investigations are conducted, and blood and urine samples are taken. Lifelines is a facility that is open for all researchers. Information on application and data access procedure is summarized on www.lifelines.nl.

NESDA (Netherlands Study of Depression and Anxiety): NESDA is a multi-center study designed to examine the long-term course and consequences of depressive and anxiety disorders (http://www.nesda.nl). NESDA included both individuals with depressive and/or anxiety disorders and controls without psychiatric conditions. Inclusion criteria were age 18-65 years and self-reported western European ancestry while exclusion criteria were not being fluent in Dutch and having a primary diagnosis of another psychiatric condition (psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe substance use disorder).

SHIP (Study of Health in Pomerania): The Study of Health In Pomerania (SHIP) is a prospective longitudinal population-based cohort study in Mecklenburg-West Pomerania assessing the prevalence and incidence of common diseases and their risk factors (PMID: 20167617). SHIP encompasses the two independent cohorts SHIP and SHIP-TREND.

Participants aged 20 to 79 with German citizenship and principal residency in the study area were recruited from a random sample of residents living in the three local cities, 12 towns as well as 17 randomly selected smaller towns. Individuals were randomly selected stratified by age and sex in proportion to population size of the city, town or small towns, respectively. A total of 4,308 participants were recruited between 1997 and 2001 in the SHIP cohort. Between 2008 and 2012 a total of 4,420 participants were recruited in the SHIP-TREND cohort. Individuals were invited to the SHIP study center for a computer-assisted personal interviews and extensive physical examinations. The study protocol was approved by the medical ethics committee of the University of Greifswald. Oral and written informed consents was obtained from each of the study participants

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

The blood pressure were measured by trained interviewers (retired nurses) with a conventional mercury sphygmomanometer according to a standard protocol, after the participants sat quietly for 5 min at the study recruitment. Included in the current project were 2970 women who had GWAS data and blood pressure measurements at the baseline interview or 892 women who had GWAS data and lipids data. The Shanghai Men's Health Study (SMHS) is an ongoing population-based cohort study of 61,480 Chinese men who were aged between 40 and 74 years, were free of cancer at enrollment, and lived in urban Shanghai, China; 45,766 (74.4%) provided a blood samples. Recruitment for the SMHS was initiated in 2002 and completed in 2006. The self-administered questionnaire includes information on demographic characteristics, disease and surgery histories, personal habits (such as cigarette smoking, alcohol consumption, tea drinking, and ginseng use), residential history, occupational history, and family history of cancer. The blood pressure were measured by trained interviewers (retired nurses) with a conventional mercury sphygmomanometer according to a standard protocol, after the participants sat quietly for 5 min at the study recruitment. Included in the current project were 892 men who had GWAS data and blood pressure measurements at the baseline interview or 298 men who had GWAS data and lipids data.

TRAILS (Tracking Adolescents' Individual Lives Survey): TRAILS is a prospective cohort study of Dutch adolescents and young adults, with bi- or triennial measurements from age 11 onwards, which started in 2001. TRAILS consists of a general population and a clinical cohort (https://www.trails.nl/en/home). In the population cohort, six assessment waves have been completed to date, at mean ages 11.1 (SD = 0.6), 13.6 (SD = 0.5), 16.3 (SD = 0.7), 19.1 (SD = 0.6), 22.3 (SD = 0.6), and 25.8 (SD = 0.6). Data for the present study were collected in the population cohort only, during the third assessment wave. The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

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

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Stage 1 cohorts

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Stage 2 cohorts

BES (Beijing Eye Study): BES was supported by the National Key Laboratory Fund, Beijing, China.

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

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HCHS/SOL (Hispanic Community Health Study/ Study of Latinos): The baseline examination of HCHS/SOL was supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (N01-HC65233), University of Miami (N01-HC65234), Albert Einstein College of Medicine (N01-HC65235), Northwestern University (N01-HC65236), and San Diego State University (N01-HC65237). The National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Neurological Disorders and Stroke, and NIH Office of Dietary Supplements additionally contributed funding to HCHS/SOL. The Genetic Analysis Center at the University of Washington was supported by NHLBI and NIDCR contracts (HHSN268201300005C AM03 and MOD03). Additional analysis support was provided by 1R01DK101855-01 and 13GRNT16490017. Genotyping was also supported by National Center for Advancing Translational Sciences UL1TR000124 and NIDDK DK063491 to the Southern California Diabetes Endocrinology Research Center. This research was also supported in part by the Intramural Research Program of the NIDDK, contract no. HHSB268201200054C, and Illumina.

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KORA (Cooperative Health Research in the Augsburg Region): The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.

LBC1921 (Lothian Birth Cohort 1921): We thank the LBC1921 cohort participants and team members who contributed to these studies. Phenotype collection was supported by the UK's Biotechnology and Biological Sciences Research Council (BBSRC), The Royal Society, and The Chief Scientist Office of the Scottish Government. Genotyping was funded by the BBSRC (BB/F019394/1). The work was undertaken by The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1). Funding from the BBSRC and Medical Research Council (MRC) is gratefully acknowledged. We gratefully acknowledge the contribution of LBC1921 co-author Professor John M. Starr, who died prior to the publication of this manuscript.

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Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003) along with a supplement from the Dutch Brain Foundation.

SHIP (Study of Health in Pomerania): SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network 'Greifswald Approach to Individualized Medicine (GANI_MED)' funded by the Federal Ministry of Education and Research (grant 03IS2061A). Genome-wide data were supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthineers, Erlangen, Germany and the Federal State of Mecklenburg-West Pomerania.

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TRAILS (Tracking Adolescents' Individual Lives Survey): TRAILS is a collaborative project involving various departments of the University Medical Center and University of Groningen, the University of Utrecht, the Radboud Medical Center Nijmegen, and the Parnassia Group, all in the Netherlands. TRAILS has been financially supported by various grants from the Netherlands Organization for Scientific Research NWO (Medical Research Council program grant GB-MW 940-38-011; ZonMW Brainpower grant 100-001-004; ZonMw Risk Behavior and Dependence grants 60-60600-97-118; ZonMw Culture and Health grant 261-98-710; Social Sciences Council medium-sized investment grants GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council project grants GB-MaGW 452-04-314 and GB-MaGW 452-06-004; NWO large-sized investment grant 175.010.2003.005; NWO Longitudinal Survey and Panel Funding 481-08-013 and 481-11-001; NWO Vici 016.130.002 and 453-16-007/2735; NWO Gravitation 024.001.003), the Dutch Ministry of Justice (WODC), the European Science Foundation (EuroSTRESS project FP-006), the European Research Council (ERC-2017-STG-757364 en ERC-CoG-2015-681466), Biobanking and Biomolecular Resources Research Infrastructure BBMRI-NL (CP 32), the Gratama foundation, the Jan Dekker foundation, the participating universities, and Accare Centre for Child and Adolescent Psychiatry. Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003) along with a supplement from the Dutch Brain Foundation. We are grateful to everyone who participated in this research or worked on this project to make it possible.

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121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Kuopio, Tampere and Turku University Hospital Medical Funds (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research ; Finnish Cultural Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; and Diabetes Research Foundation of Finnish Diabetes Association. The expert technical assistance in the statistical analyses by Leo-Pekka Lyytikäinen and Irina Lisinen is gratefully acknowledged.

Figure S1. Quantile-quantile (QQ) plots for each of the BP-Psychosocial factor combinations for Stage 1 studies of African ancestry. The observed -log10(P-values) are plotted against the expected -log10(P-values). The joint 2-df test p-values are shown in black. The 1-df interaction p-values are shown in red.

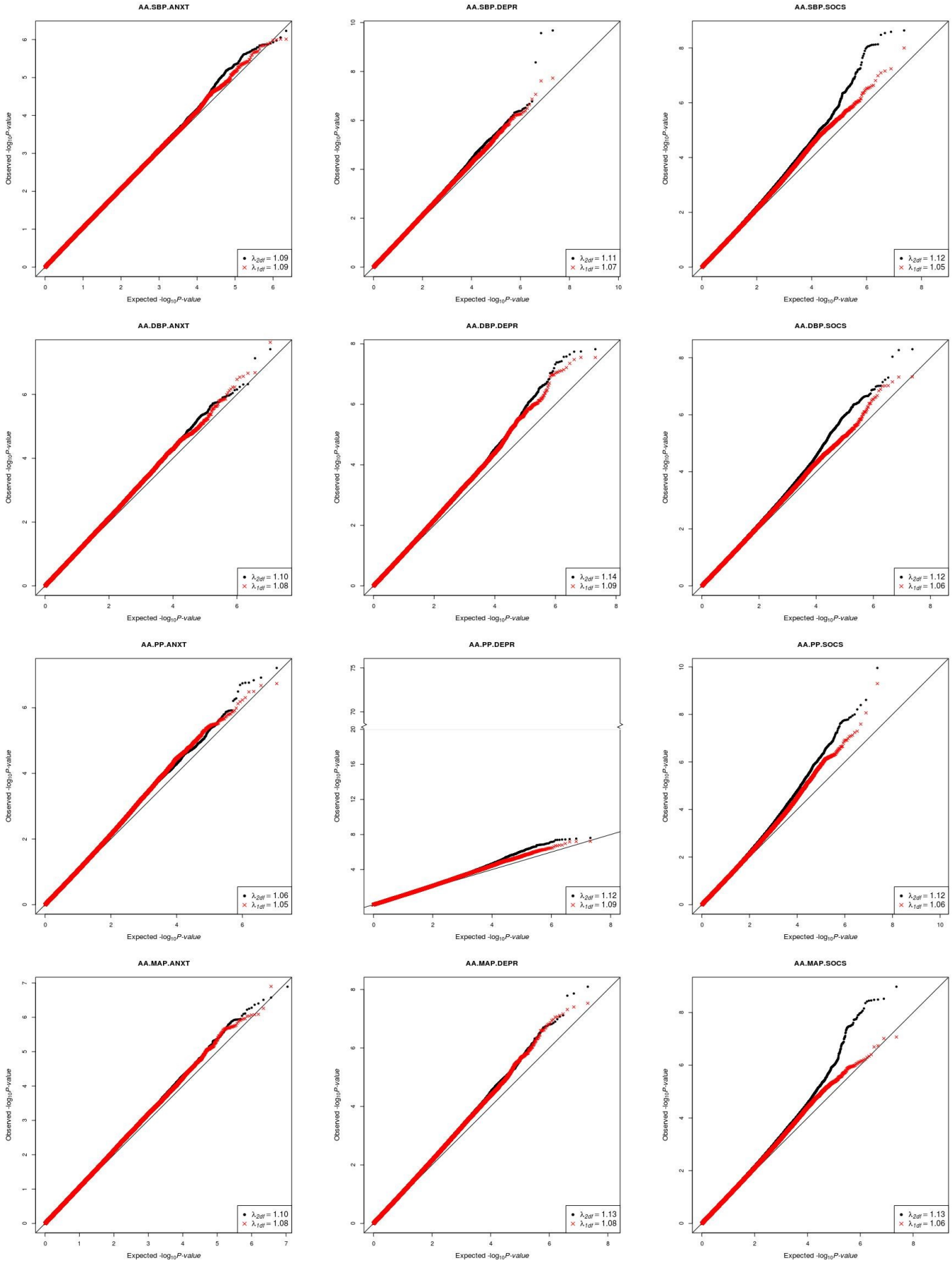


Figure S2. Quantile-quantile (QQ) plots for each of the BP-Psychosocial factor combinations for Stage 1 studies of European ancestry. The observed -log10(P-values) are plotted against the expected -log10(P-values). The joint 2-df test p-values are shown in black. The 1-df interaction p-values are shown in red.

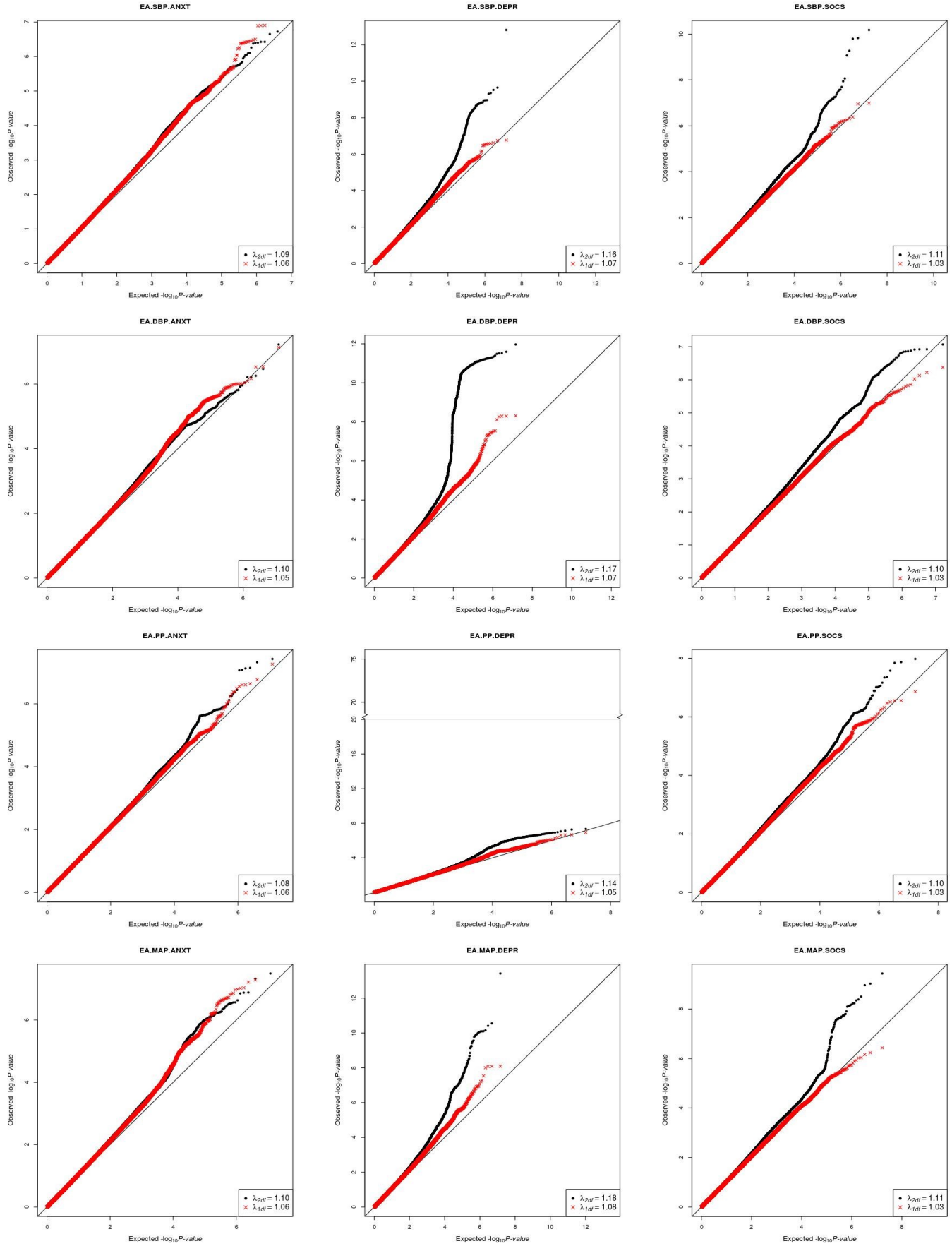


Figure S3. Quantile-quantile (QQ) plots for each of the BP-Psychosocial factor combinations for Stage 1 Brazilian cohorts. The observed -log10(P-values) are plotted against the expected -log10(P-values). The joint 2-df test p-values are shown in black. The 1-df interaction p-values are shown in red.

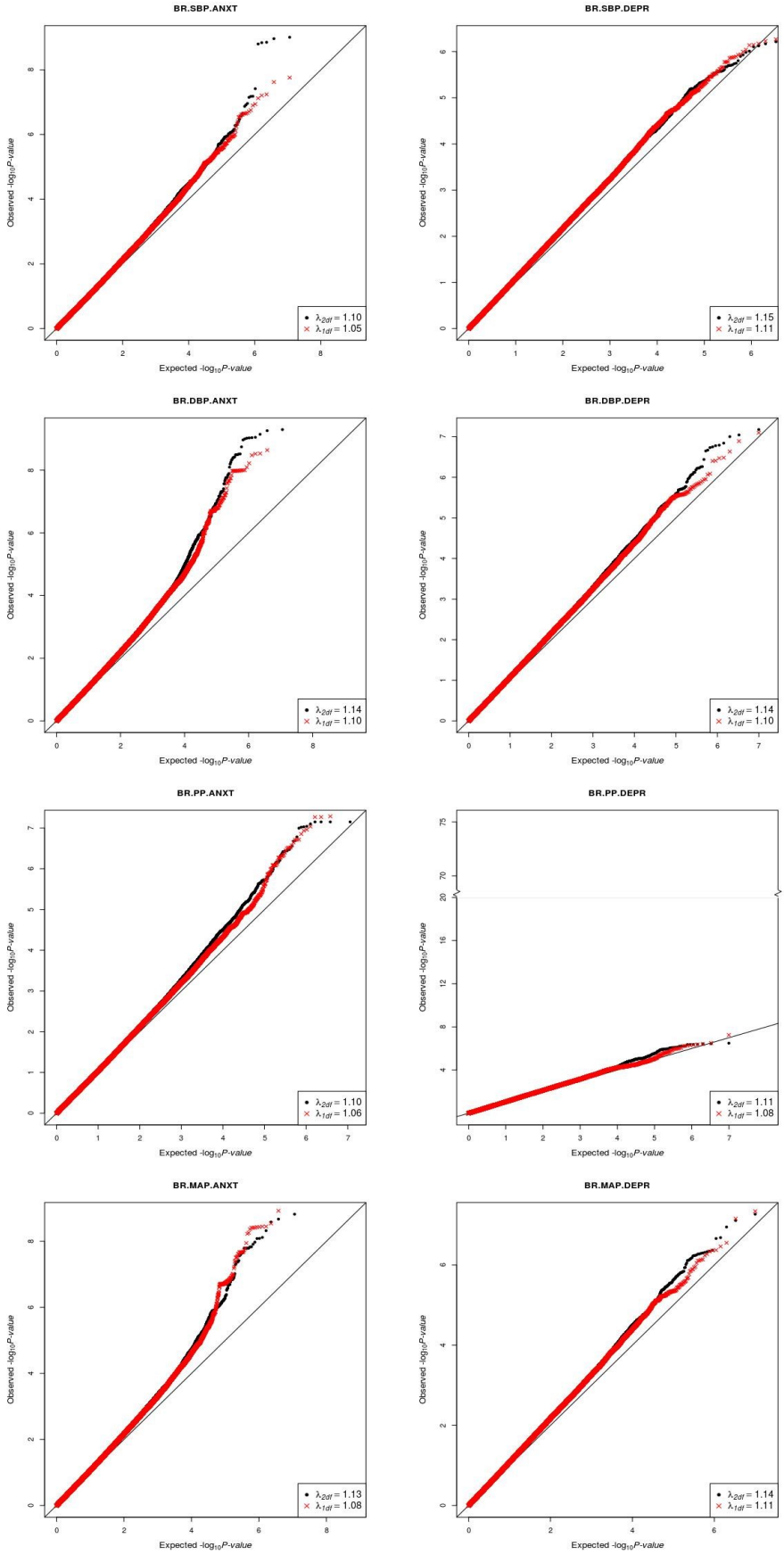


Figure S4. Quantile-quantile (QQ) plots for each of the BP-Psychosocial factor combinations for Stage 1 studies of Hispanic ancestry. The observed -log10(P-values) are plotted against the expected -log10(P-values). The joint 2-df test p-values are shown in black. The 1-df interaction p-values are shown in red.

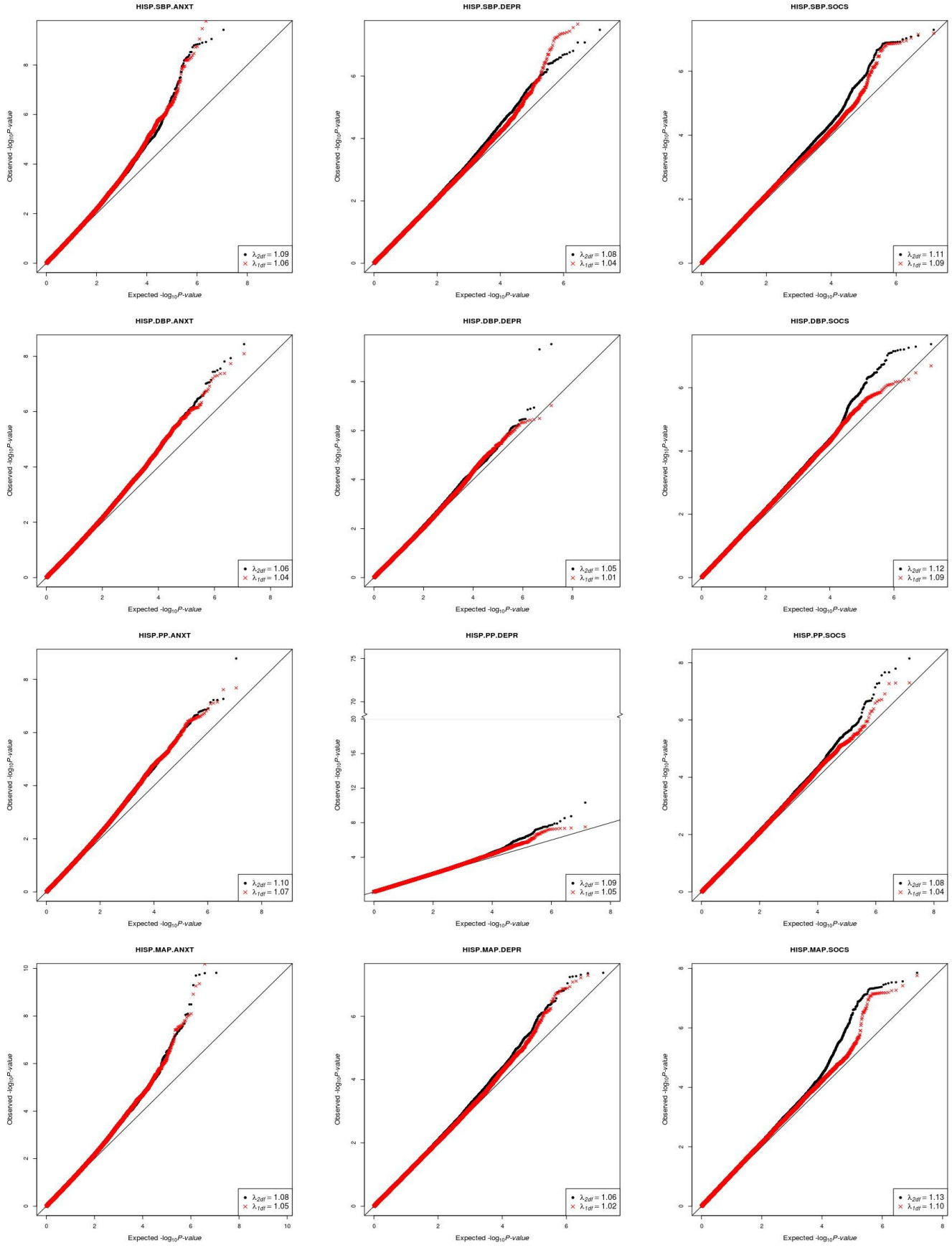


Figure S5. Quantile-quantile (QQ) plots for each of the BP-Psychosocial factor combinations for Stage 1 studies of Asian ancestry. The observed -log10(P-values) are plotted against the expected -log10(P-values). The joint 2-df test p-values are shown in black. The 1-df interaction p-values are shown in red.

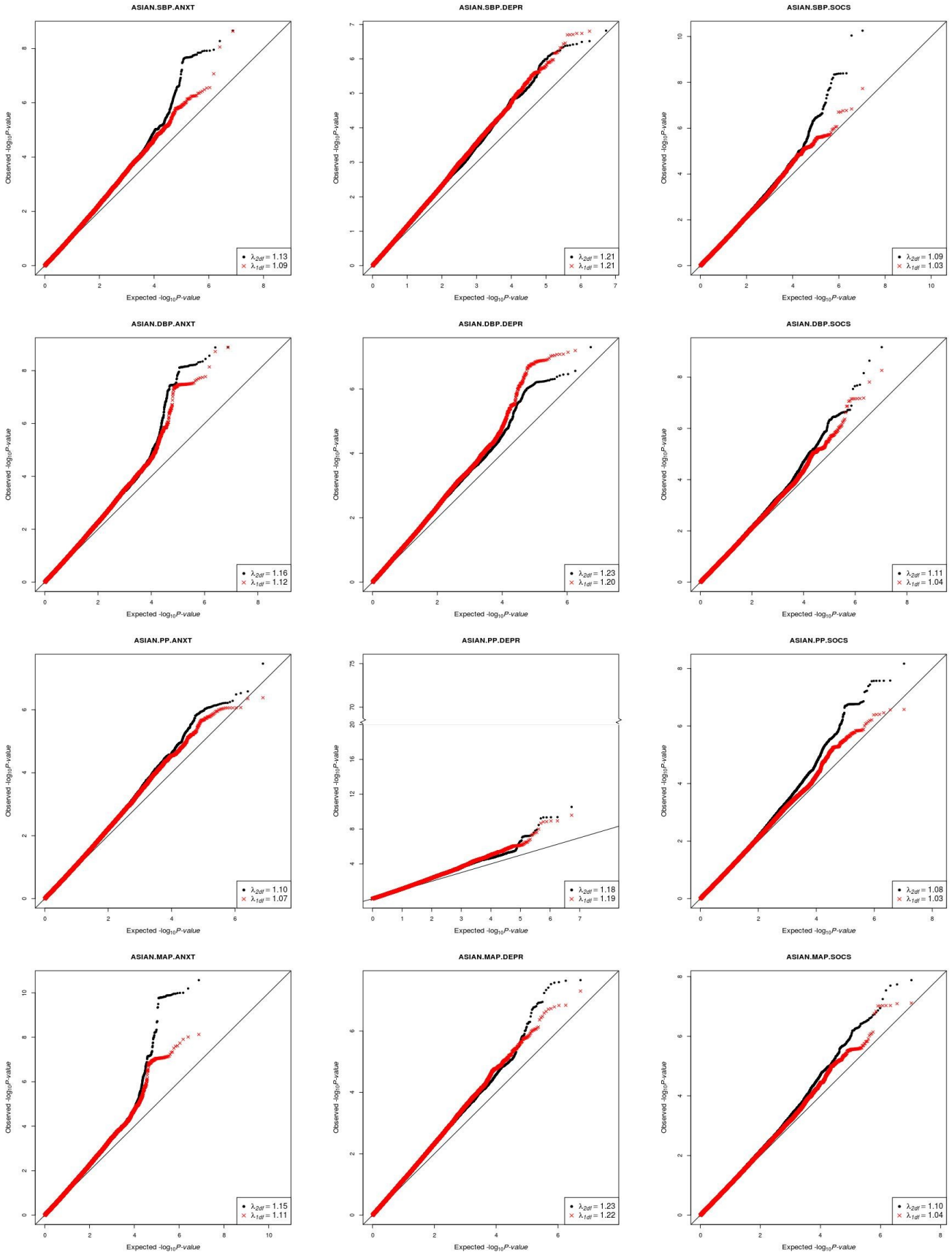


Figure S6. Quantile-quantile (QQ) plots for each of the BP-Psychosocial factor combinations for the transethnic meta-analysis of Stage 1 cohorts. The observed -log10(P-values) are plotted against the expected -log10(P-values). The joint 2-df test p-values are shown in black. The 1-df interaction p-values are shown in red.

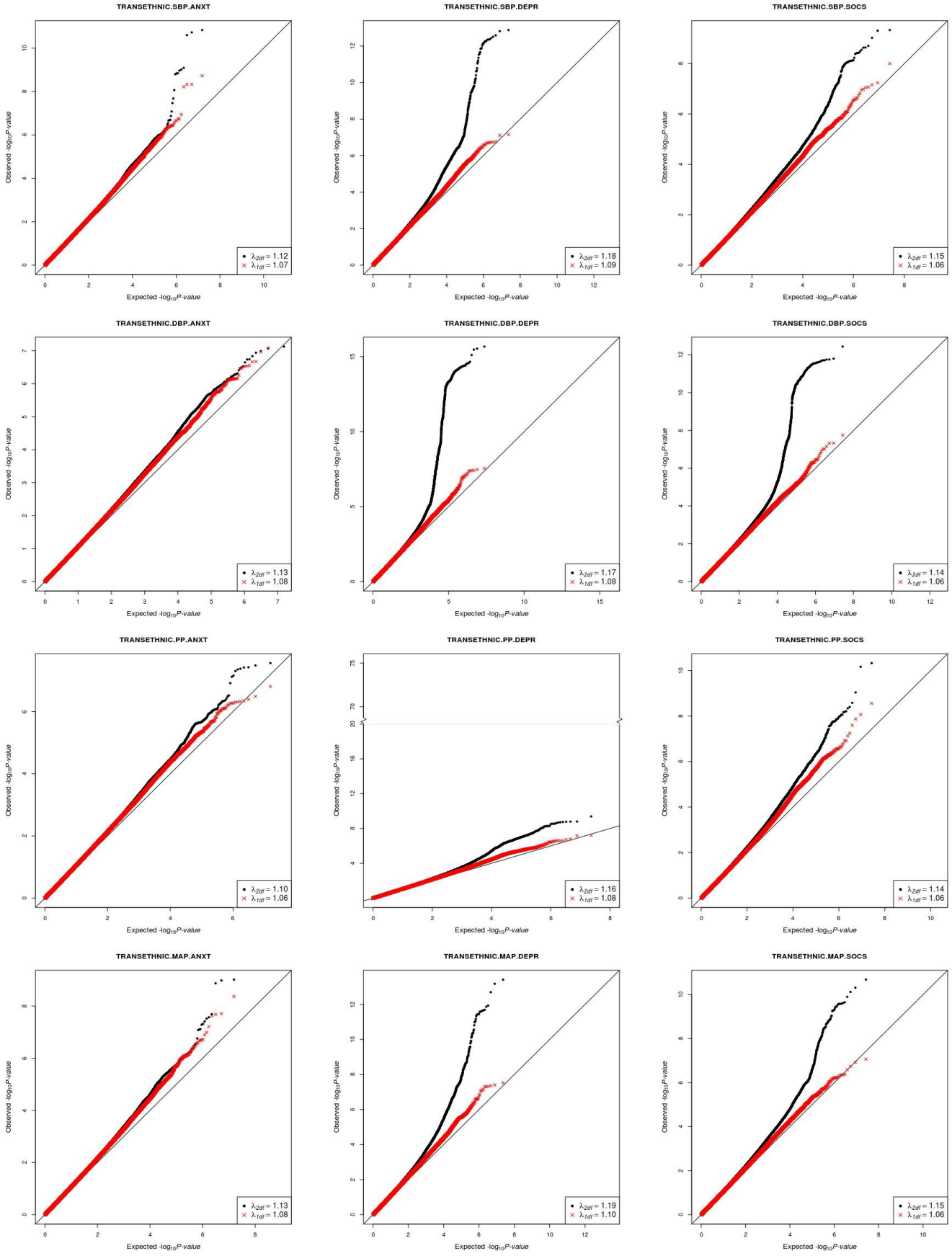


Figure S7. Venn diagram showing the distribution of genome-wide significant associations among the 1624 identified SNPs across BP traits.

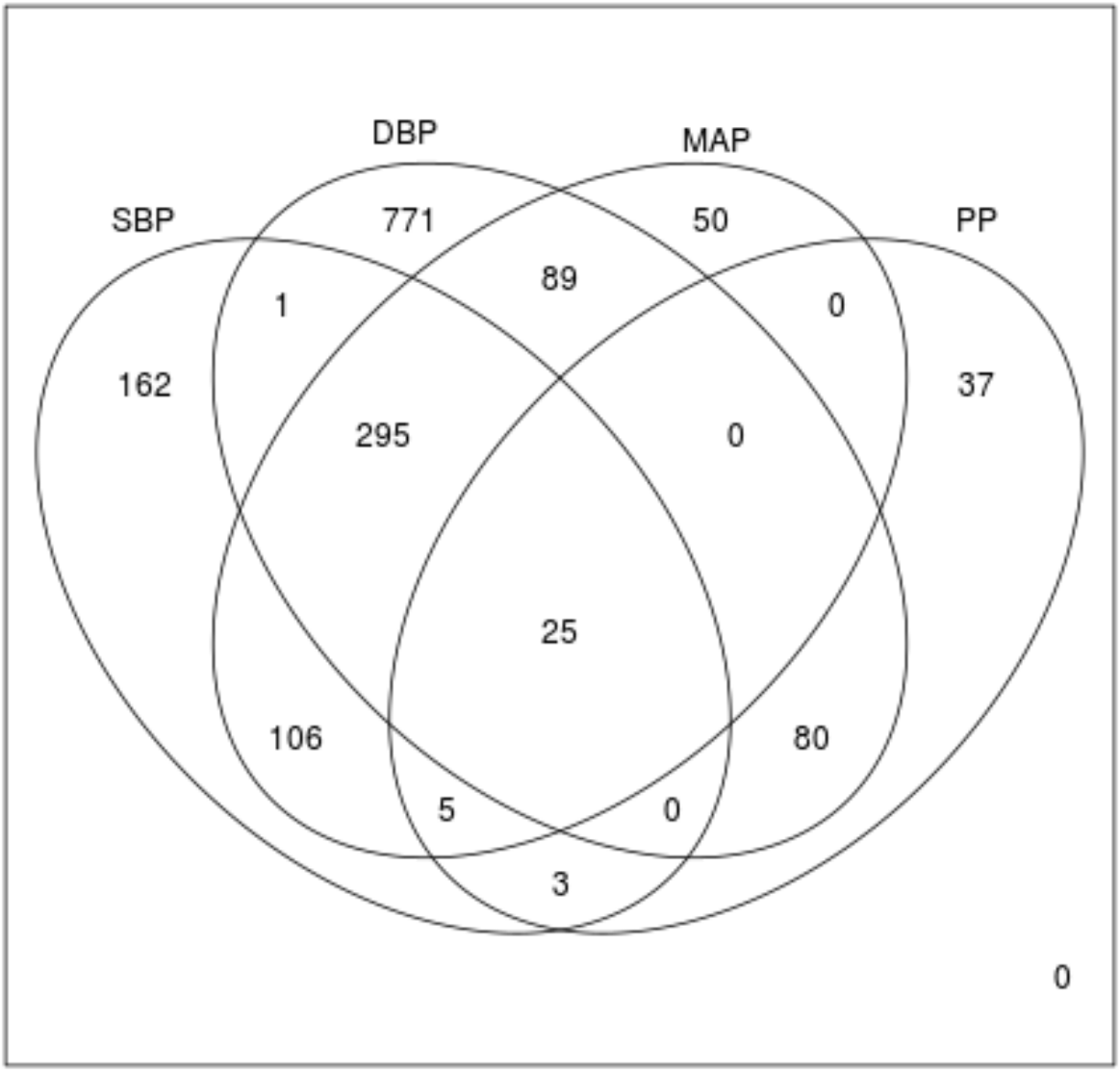


Figure S8. Forest plots of the novel SNPs associated with MAP in AA in the context of DEPR. SNP main effects (black) and interaction effects (red) are shown for stage 1, stage 2, and stage 1+ 2 combined. Note that the meta-analysis of Stage 1 and Stage 2 cohorts did not include the stringent variant filtering strategy used for Stage 1. Rather it uses all available data. As a result, the N of Stage 1+2 is always larger than that of N of the individual meta-analyses at each Stage.

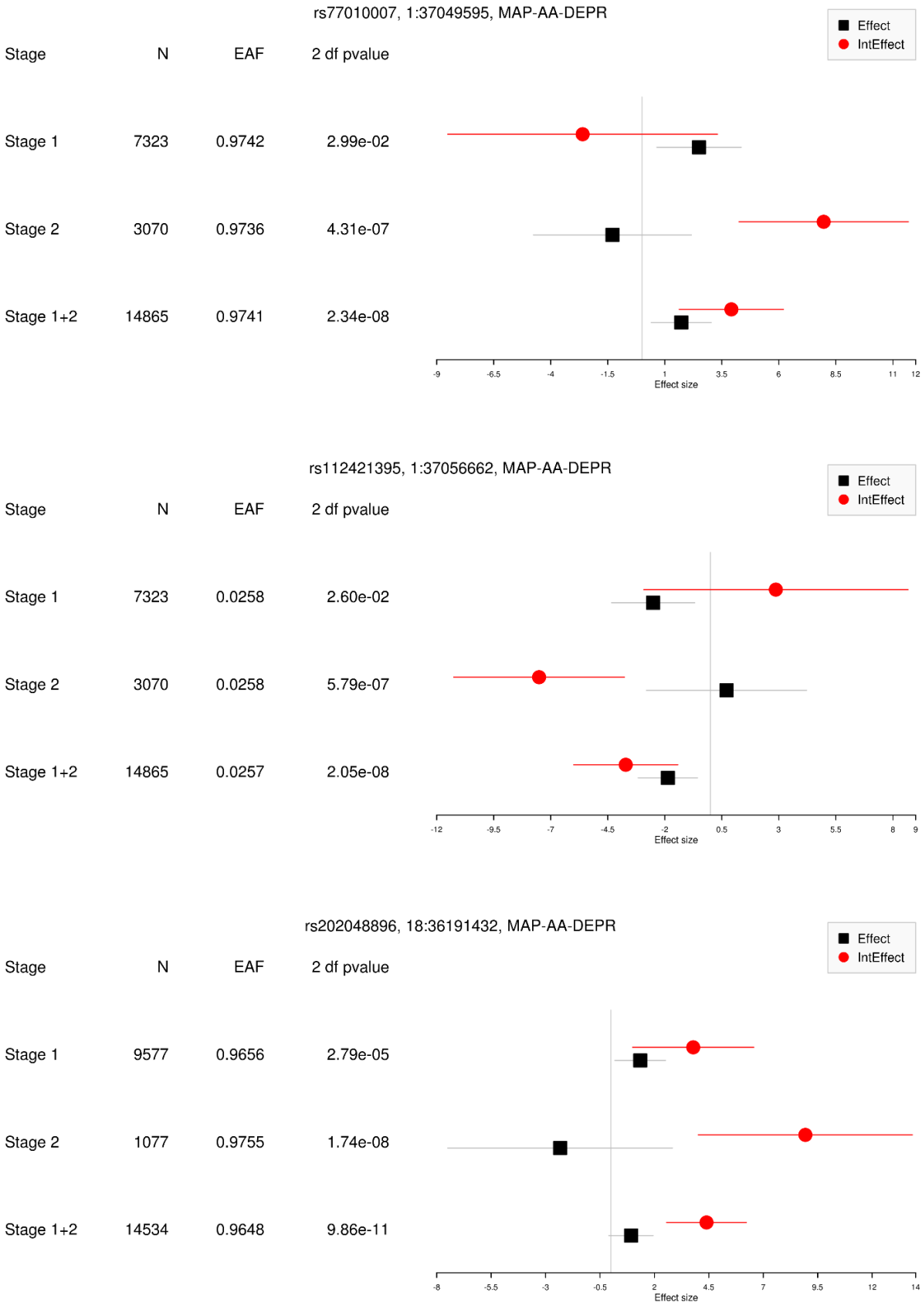


Figure S9. Forest plots of the novel SNPs associated with PP in AA in the context of SOCS. SNP main effects (black) and interaction effects (red) are shown for stage 1, stage 2, and stage 1+ 2 combined. Note that the meta-analysis of Stage 1 and Stage 2 cohorts did not include the stringent variant filtering strategy used for Stage 1. Rather it uses all available data. As a result, the N of Stage 1+2 is always larger than that of N of the individual meta-analyses at each Stage.

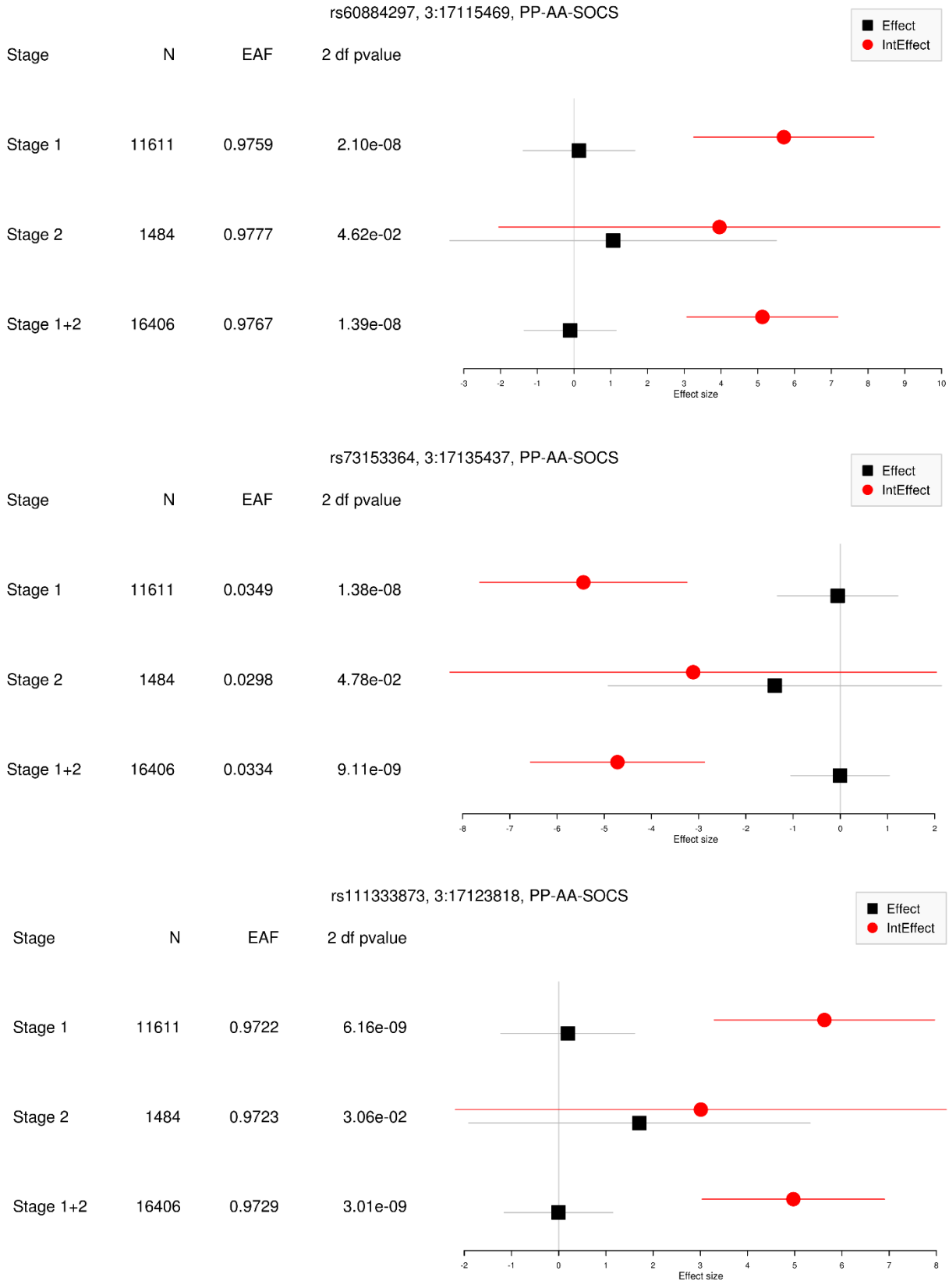
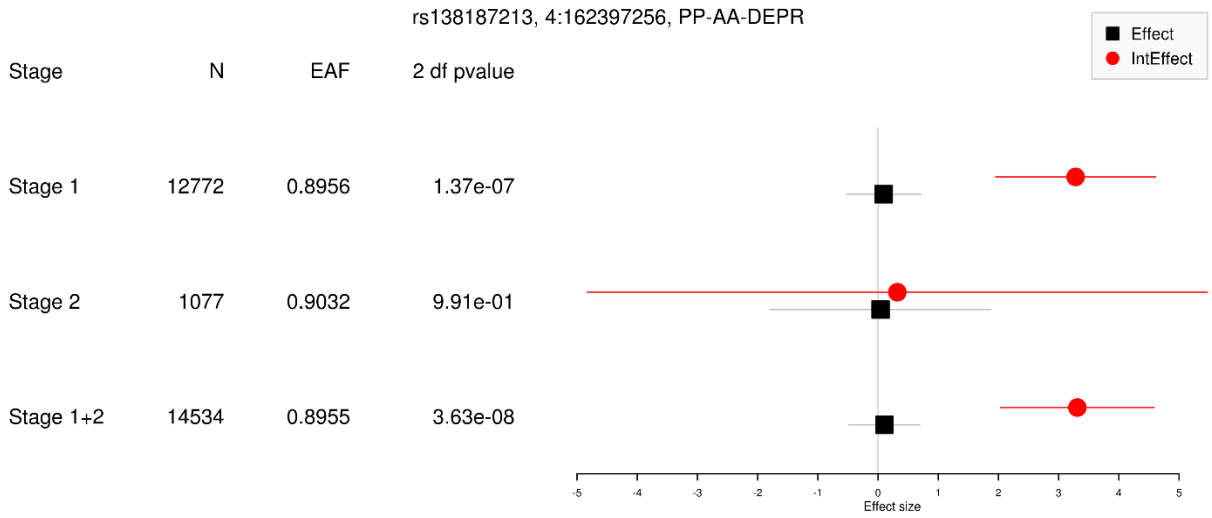
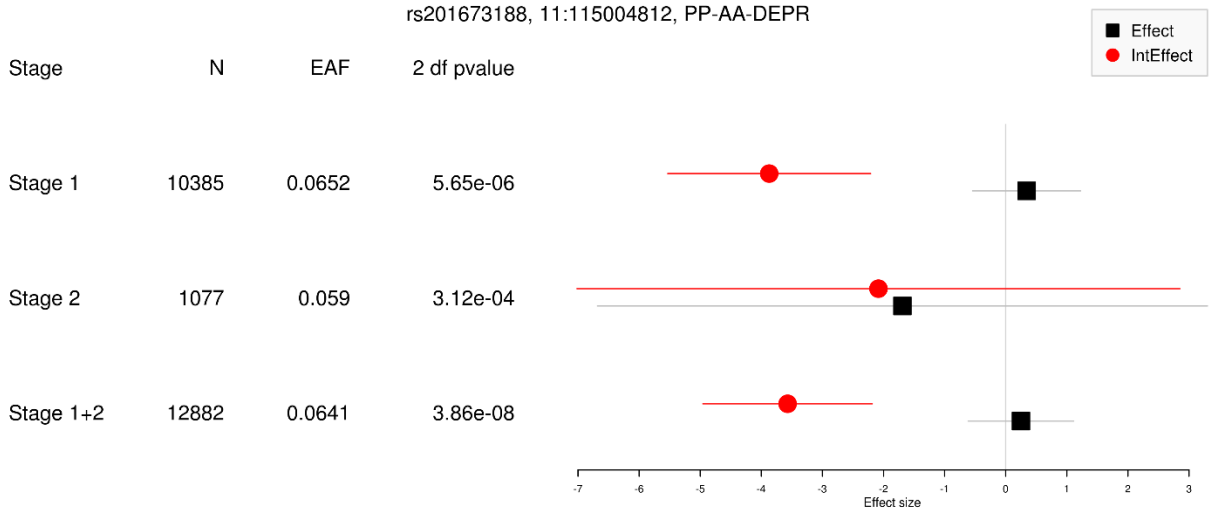


Figure S10. Forest plots of the novel SNPs associated with PP in AA in the context of DEPR. SNP main effects (black) and interaction effects (red) are shown for stage 1, stage 2, and stage 1+ 2 combined. Note that the meta-analysis of Stage 1 and Stage 2 cohorts did not include the stringent variant filtering strategy used for Stage 1. Rather it uses all available data. As a result, the N of Stage 1+2 is always larger than that of N of the individual meta-analyses at each Stage.





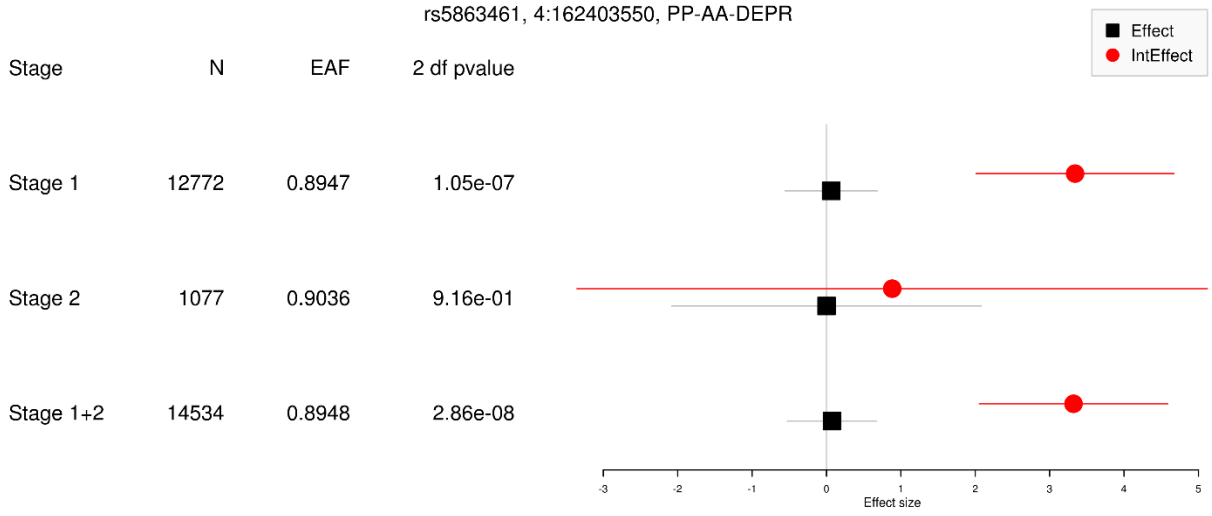
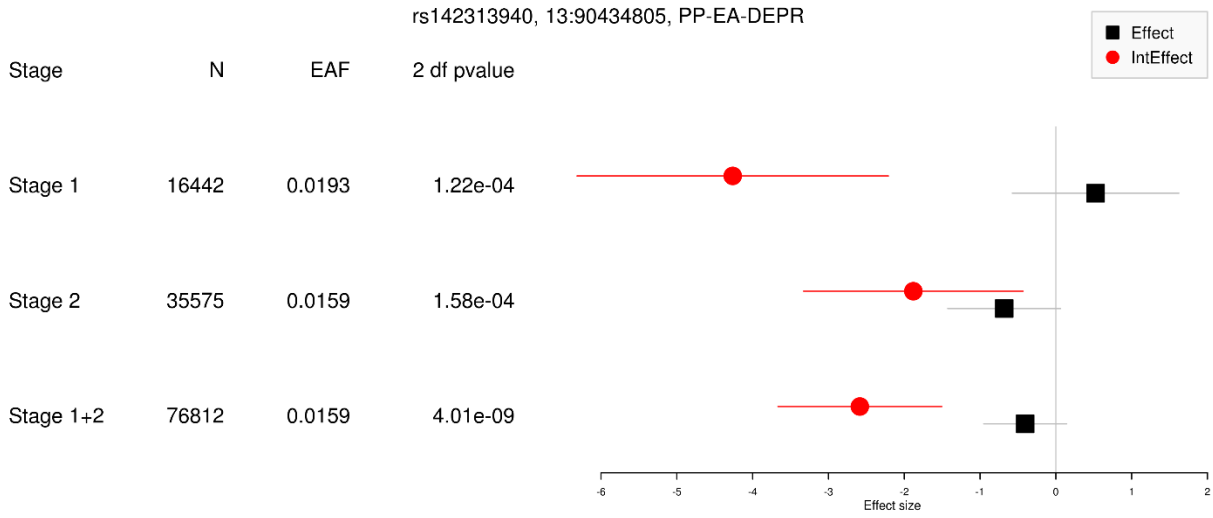
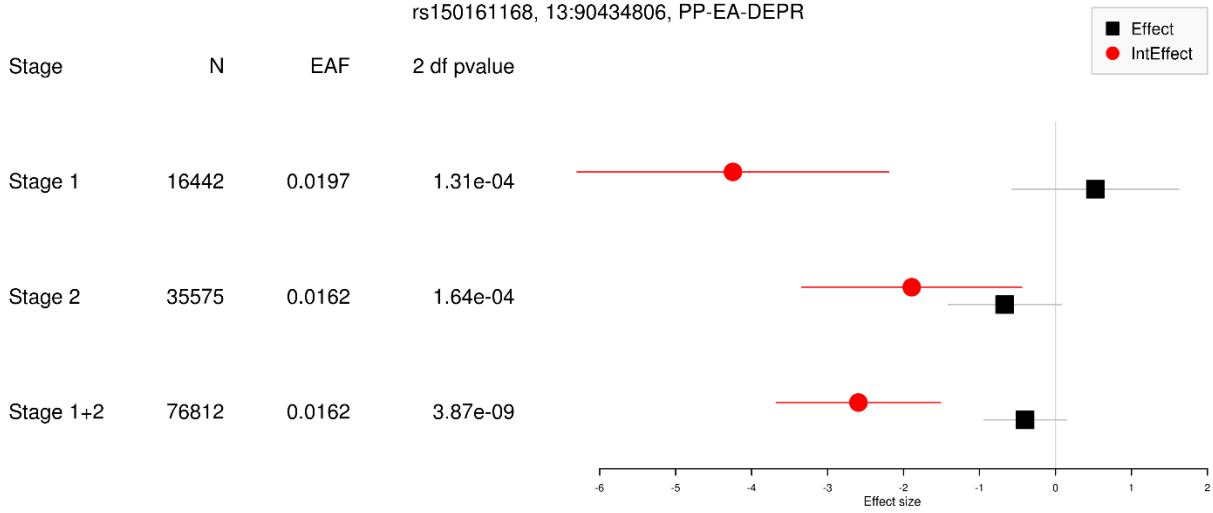


Figure S11. Forest plots of the novel SNPs associated with PP in EA in the context of DEPR or SOCS. SNP main effects (black) and interaction effects (red) are shown for stage 1, stage 2, and stage 1+ 2 combined. Note that the meta-analysis of Stage 1 and Stage 2 cohorts did not include the stringent variant filtering strategy used for Stage 1. Rather it uses all available data. As a result, the N of Stage 1+2 is always larger than that of N of the individual meta-analyses at each Stage.





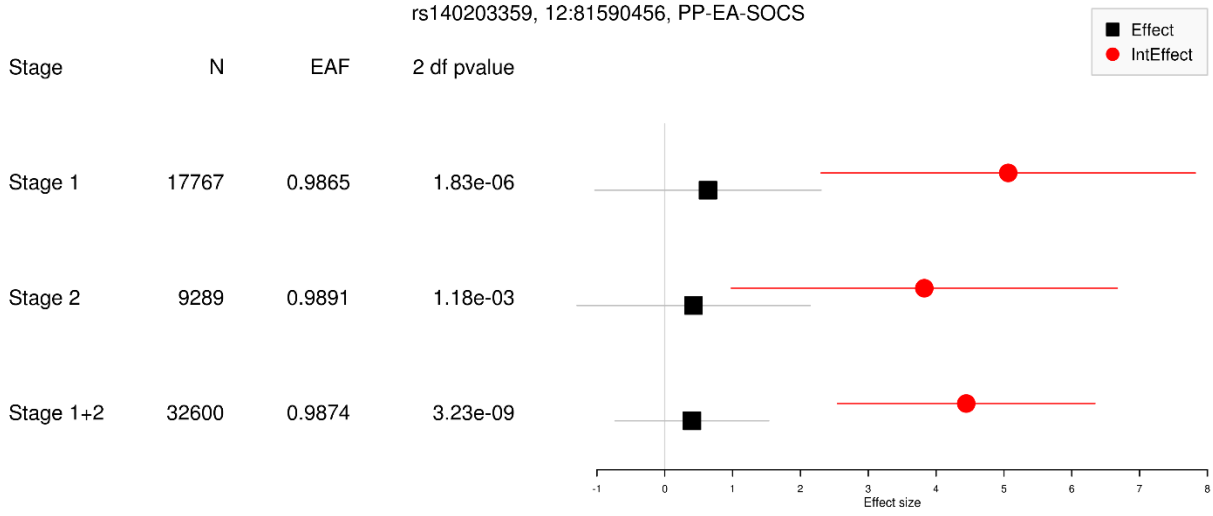


Figure S12. Forest plots of the novel SNPs associated with PP or MAP in the transethnic meta-analysis. SNP main effects (black) and interaction effects (red) are shown for stage 1, stage 2, and stage 1+ 2 combined. Note that the meta-analysis of Stage 1 and Stage 2 cohorts did not include the stringent variant filtering strategy used for Stage 1. Rather it uses all available data. As a result, the N of Stage 1+2 is always larger than that of N of the individual meta-analyses at each Stage.