ARTICLE

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A large-scale genome-wide study of gene-sleep duration interactions for blood pressure in 811,405 individuals from diverse populations

Pavithra Nagarajan[1,183], Thomas W. Winkler[2,183], Amy R. Bentley[3,183], Clint L. Miller[4,5,183], Aldi T. Kraja[6,183], Karen Schwander[7,183], Songmi Lee[8], Wenyi Wang[9], Michael R. Brown[10], John L. Morrison[11], Ayush Giri[12,13], Jeffrey R. O'Connell[14], Traci M. Bartz[15,16], Lisa de las Fuentes[17,18], Valborg Gudmundsdottir[19,20], Xiuqing Guo[21], Sarah E. Harris[22], Zhijie Huang[23], Mart Kals[24], Minjung Kho[25], Christophe Lefevre[26], Jian'an Luan[27], Leo-Pekka Lyytikäinen[28,29], Massimo Mangino[30,31], Yuri Milaneschi[32,33], Nicholette D. Palmer[34], Varun Rao[35], Rainer Rauramaa[36], Botong Shen[37], Stefan Stadler[38], Quan Sun[39], Jingxian Tang[40], Sébastien Thériault[41], Adriaan van der Graaf[42], Peter J. van der Most[43], Yujie Wang[44], Stefan Weiss[45,46], Kenneth E. Westerman[47,48], Qian Yang[49,50], Tabara Yasuharu[51,52], Wei Zhao[53,54], Wanying Zhu[55], Drew Altschul[22,56], Md Abu Yusuf Ansari[57], Pramod Anugu[58], Anna D. Argoty-Pantoja[43], Michael Arzt[38], Hugues Aschard[59,60], John R. Attia[61], Lydia Bazzanno[23], Max A. Breyer[55], Jennifer A. Brody[15], Brian E. Cade[1,47], Hung-hsin Chen[55], Yii-Der Ida Chen[21], Zekai Chen[43], Paul S. de Vries[10], Latchezar M. Dimitrov[34], Anh Do[18], Jiawen Du[39], Charles T. Dupont[62], Todd L. Edwards[13,63], Michele K. Evans[37], Tariq Faquih[1,47], Stephan B. Felix[46,64], Susan P. Fisher-Hoch[65], James S. Floyd[15,66], Mariaelisa Graff[44], Charles Gu[18], Dongfeng Gu[67], Kristen G. Hairston[68], Anthony J. Hanley[69], Iris M. Heid[2], Sami Heikkinen[70], Heather M. Highland[44], Michelle M. Hood[54], Mika Kähönen[71], Carrie A. Karvonen-Gutierrez[54], Takahisa Kawaguchi[52], Setoh Kazuya[51], Tanika N. Kelly[35], Pirjo Komulainen[36], Daniel Levy[72,73], Henry J. Lin[21], Peter Y. Liu[21], Pedro Marques-Vidal[74,75], Joseph B. McCormick[65], Hao Mei[57], James B. Meigs[47,76], Cristina Menni[30], Kisung Nam[25], Ilja M. Nolte[43], Natasha L. Pacheco[37], Lauren E. Petty[55], Hannah G. Polikowsky[55], Michael A. Province[7], Bruce M. Psaty[15,66], Laura M. Raffield[77], Olli T. Raitakari[78,79,80], Stephen S. Rich[81], Renata L. Riha[82], Lorenz Risch[83,84], Martin Risch[85,86], Edward A. Ruiz-Narvaez[87], Rodney J. Scott[88], Colleen M. Sitlani[15], Jennifer A. Smith[53,54], Tamar Sofer[1,89], Maris Teder-Laving[24], Uwe Völker[45,46], Peter Vollenweider[74,75], Guanchao Wang[62], Ko Willems van Dijk[9,90], Otis D. Wilson[13,91], Rui Xia[8], Jie Yao[21], Kristin L. Young[44], Ruiyuan Zhang[92], Xiaofeng Zhu[93], Jennifer E. Below[55], Carsten A. Böger[94,95,96], David Conen[97], Simon R. Cox[22], Marcus Dörr[46,64], Mary F. Feitosa[7], Ervin R. Fox[98], Nora Franceschini[44], Sina A. Gharib[99], Vilmundur Gudnason[19,20], Sioban D. Harlow[54], Jiang He[92], Elizabeth G. Holliday[61], Zoltan Kutalik[42,100], Timo A. Lakka[70,101,102], Deborah A. Lawlor[49,50], Seunggeun Lee[25], Terho Lehtimäki[28,29], Changwei Li[92], Ching-Ti Liu[40], Reedik Mägi[24], Fumihiko Matsuda[52], Alanna C. Morrison[10], Brenda WJH Penninx[32,33], Patricia A. Peyser[54], Jerome I. Rotter[21], Harold Snieder[43], Tim D. Spector[30], Lynne E. Wagenknecht[103], Nicholas J. Wareham[27], Alan B. Zonderman[37], Kari E. North[44], Myriam Fornage[8,10], Million Veteran Program*, Adriana M. Hung[13,93], Alisa K. Manning[104,105], James Gauderman[11], Han Chen[10], Patricia B. Munroe[106,184], Dabeeru C. Rao[18,184], Diana van Heemst[107,184], Susan Redline[1,47,184], Raymond Noordam[107,184] and Heming Wang[1,47,184]✉

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Although both short and long sleep duration are associated with elevated hypertension risk, our understanding of their interplay with biological pathways governing blood pressure remains limited. To address this, we carried out genome-wide cross-population gene-by-short-sleep and long-sleep duration interaction analyses for three blood pressure traits (systolic, diastolic, and pulse pressure) in 811,405 individuals from diverse population groups. We discovered 22 novel gene-sleep duration interaction loci for blood pressure, mapped to 23 genes. Investigating these genes' functional implications shed light on neurological, thyroidal, bone metabolism, and hematopoietic pathways that necessitate future investigation for blood pressure management that caters to sleep health lifestyle. Non-overlap between short sleep (12) and long sleep (10) interactions underscores the plausible nature of distinct influences of both sleep duration extremes in cardiovascular health. Several of our loci are specific towards a particular population background or sex, emphasizing the importance of addressing heterogeneity entangled in gene-environment interactions, when considering precision medicine design approaches for blood pressure management.

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A full list of author affiliations appears at the end of the paper.

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INTRODUCTION

Abnormal sleep duration is detrimental to cardiovascular health – increasing the risk of incident cardiovascular disease (CVD) and mortality – and inherently complex, with suspected heterogeneous effects according to sex and race/ethnicity [1, 2]. Deviation from healthy sleep can impact diurnal rhythms, hormone levels (e.g. ghrelin, cortisol), autonomous nervous system balance, and even remodel vascular structure - resulting in adverse consequences, such as reduced nocturnal blood pressure (BP) dipping and sustained daytime hypertension [1, 3].

Yet the mechanistic pathways underlying the biomolecular connection between short and long sleep with cardiovascular health remain unclear. Evidence implicates heightened sympathetic tone and metabolic dysfunction in the mechanism of short sleep, but there remains a gap in clarity with the added complexity of interwoven pathways like oxidative stress and endothelial dysfunction [1, 4]. The role of long sleep is more elusive, with recent work highlighting the pertinence of inflammatory markers, underlying comorbidity burden (i.e. dyslipidemia, depression) and arterial stiffness metrics [5, 6]. This incomplete understanding of the intersection between habitual sleep duration and cardiovascular health necessitates further investigation.

Hypertension is a major risk factor for CVD, with blood pressure traits known to have a strong genetic background. Recent genome-wide association analyses (GWASs) have discovered more than 2000 loci explaining ~40% of systolic or diastolic BP heritability among individuals of European descent [7]. It is important to investigate the role of sleep health in such a polygenic landscape. This may both explain additional heritability of BP traits, as well as bring to the forefront novel genomic loci that inform perspective on sleep's influence on biomolecular pathways underlying BP. Moreover, incorporating diverse population groups is essential – as this can reveal novel gene targets specific to particular subgroups or shared across – improving downstream therapeutic designs, and offering tangible insight to counter disparities in health. Our prior work in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Gene-Lifestyle Interactions Working Group highlighted novel non-overlapping gene-sleep interactions for BP, suggesting distinct roles of influence for short and long sleep duration [8]. Our current analysis advances the field by including a 12-fold larger sample size and additional sex-stratified analyses, yielding enhanced statistical power and granularity.

MATERIALS AND METHODS

This work was approved by the Institutional Review Board of Washington University in St. Louis and complies with all relevant ethical regulations. For each of the participating cohorts, the appropriate ethics review board approved the data collection and all participants provided informed consent.

Data harmonization

Data from each cohort (Supplementary Tables S1–S2) were harmonized following a centralized protocol. In brief, data were stratified by population group, based on geographic origins or self-reported ethnicity using individual cohort definitions (AFR: African, EAS: East Asian, EUR: European, HIS: Hispanic/Latinos, SAS: South Asian), and sex (combined sex, female sex, male sex). Analyses considered 3 primary blood pressure (BP) traits as outcome variables (SBP: systolic, DBP: diastolic, PP: pulse pressure) and 2 dichotomous lifestyle exposures (LTST: long total sleep time, STST: short total sleep time). Genetic variants (G) were restricted to autosomal chromosomes 1–22 imputation quality ≥ 0.3, and minor allele frequency ≥ 0.1%. Age was restricted to ≥18 years, and reported total sleep time constrained within 3 and 14 hours. In scenarios of multiple visits, the single visit with largest sample size was utilized. If a participating study used a case-control study design (no matter the disease of interest), all analyses were run separately in cases and controls (as defined by that study team) to allow for identification of any potential biases as a result of study design.

For BP outcome measures, if multiple readings were taken in a single visit the mean was used. All BP values were winsorized at 6 standard deviations from the mean. BP values were adjusted for reported use of antihypertensive medications as follows: SBP (+15 mmHg) and DBP (+10 mmHg). PP was derived as SBP – DBP. In the case of studies with known between-sample relatedness, null model residuals (regressing BP traits on a kinship matrix/genetic covariance matrix) were denoted as the BP outcome. STST and LTST were derived from total sleep time (TST) by regressing TST on age, sex, age×sex and using the residuals' 20 and 80th percentiles as cutoffs (STST = 1 if ≤20th percentile, LTST = 1 if ≥80th percentile, STST = 0 if >20th percentile, LTST = 0 if <80th percentile). Covariates included population-group specific principal components, cohort-specific confounders (study center), age, age^2, sex, age×S/LTST, age^2 ×S/LTST, and sex×S/LTST. Samples with missing data were excluded.

Genome-wide gene-sleep interaction analysis

After data harmonization, each population-group specific cohort ran 2 regression models (M1 and M2) for 18 phenotype-exposure-sex combinations (3 phenotypes × 2 exposures × 3 sex groups: combined sex, female sex, male sex). Below E denotes the lifestyle exposure (STST or LTST), Y denotes the BP outcome (SBP, DBP, or PP), C_1 denotes the vector of covariates incorporating E (age, age^2, age×S/LTST, age^2×S/LTST, sex, sex×S/LTST), and C_2 denotes the subset without incorporating E (age, age^2, sex). Female-specific and male-specific analyses were not adjusted for sex. Specialized software included LinGxEScanR v1.0 (https://github.com/USCbiostats/LinGxEScanR), GEM v1.4.1 (https://github.com/large-scale-gxe-methods/GEM), and/or MMAP (latest version available) (https://github.com/MMAP/MMAP.github.io) with robust standard errors (SEs) enforced [9]. One degree of freedom (df) tests for the marginal effect (β_{M2_G}), the main effect (β_{M1_G}), and the interaction effect ($\beta_{M1\_G\times E}$) were conducted; alongside the 2df joint test that simultaneously assesses the main effect and the interaction effect (β_{M1_G}, $\beta_{M1\_G\times E}$) [10].

Model 1 (Primary GxE Model of Interest)

$$\mathbf{M1}: Y = \beta_{M1\_0} + \beta_E E + \beta_{M1\_G} G + \beta_{M1\_G\times E} E\times G + \beta_{M1\_C1} C_1 \quad (1)$$

Model 2 (Marginal Effect Model for Comparison)

$$\mathbf{M2}: Y = \beta_{M2\_0} + \beta_{M2\_G} G + \beta_{M2\_C2} C_2 \quad (2)$$

Summary statistics were centrally processed after individual studies submitted results. EasyQC2 software (www.genepi-regensburg.de/easyqc2) was used to perform quality control (QC) on resultant data [11]. Data were filtered for degrees of freedom ≥ 20 calculated as minor allele count × imputation quality (e.g. MAC×R^2 provided by each cohort) within the unexposed, the exposed, and the total sample. Missing or invalid/out of range values for statistics and duplicated or monomorphic variants were discarded. hg19 genomic coordinates were lifted over to hg38 genomic coordinates. Allele frequency discrepancies relative to TOPMed-imputed 1000 G reference panels (Trans-Omics for Precision Medicine imputed 1000Genomes) were assessed for each specific population group, along with genomic control (GC) lambda inflation. Meta-level quality control was conducted within groups based on population group, with evaluation of unwanted centering of the outcome variable, outlying cohorts highlighting unstable numerical computation, or alarming inflation.

Meta-analysis

Meta-analysis was designed using the following paradigm. Cross-population meta-analysis (CPMA) was designed to combine all population group results, with additional focused population-group specific and sex-specific analyses. This resulted in 18 total meta-analyses to be run: 6 population groups (CPMA, EUR, HIS, EAS, AFR, SAS) and 3 sex groups (combined sex, female sex, male sex). To accomplish this, METAL software was first used to run all meta-analyses within each specific population group for the marginal effect (β_{M2_G}), main effect (β_{M1_G}), interaction effect ($\beta_{M1\_G\times E}$), and joint effect (β_{M1_G}, $\beta_{M1\_G\times E}$) with GC correction for inflation [12]. Inverse-variance weights were used and Manning et al.'s method for the 2df joint test [13]. CPMA was subsequently executed on the resultant population-group specific METAL output results with GC correction.

Genome-wide significant loci identification

EasyStrata2 software was used to prioritize top loci from significant results identified from the 1df interaction and 2df joint tests [14]. GC correction for population-group specific results was applied. Variants found within 1 Mb

distance of the major histocompatibility complex (MHC) region were excluded. Either minimum sample size ($N > 20{,}000$) or multiple cohorts (≥3) was required as necessary criteria for processing results from a specific sex-stratified, and/or population group-stratified meta-analysis.

Significant variants were identified using the following threshold criteria: (i) *i* variants with significant interaction effect ($P_{M1\_G\times E}<5\times10^{-9}$, FDR<0.05); (ii) *j* variants with significant joint effect ($P_{M1\_G,G\times E}<5\times10^{-9}$, FDR<0.05); and (iii) *k* top variants for the interaction effect identified using a 2-step method – identifying first *z* variants by the marginal effect ($P_{M2\_G}<10^{-5}$) and then filtering these by the interaction effect ($P_{M1\_G\times E}<0.05/N_G$, $FDR_{G\times E}<0.05$) where N_G is the number of independent tests calculated using principal components analysis on the *z* variants. This 2-step method was incorporated to increase power for detecting interactions [15]. This design was executed to maintain both stringent threshold criteria and incorporate false discovery correction implemented by the Benjamini-Hochberg method.

All such *i*+*j*+*k* significant variants were narrowed down to loci based on 500 kilobase (kb) regions. Finally, within these regions independent lead variants were identified as the top significant variant within the locus, subsequently defining variants in LD as those with linkage disequilibrium (LD) r^2 threshold < 0.1 using TOPMed-imputed 1000 G reference panels. If variants were missing in the LD panels, then the most significant variant within each 500 kb region was retained for combined sex meta-analyses results.

Prioritizing novel sleep duration interaction loci

Significant independent loci were subsequently filtered to prioritize gene-sleep duration interaction loci. From the 1df interaction test, *X* interaction loci were prioritized as those not found within 1 Mb of previously identified gene-sleep duration loci for BP [8]. Loci were annotated as whether novel for BP genetic architecture, or not, by checking for overlap with 1 Mb of previous GWAS variants (Supplementary Table S3).

For the 2df test, first loci were filtered to those variants not found within 1 Mb of previous GWAS identified variants for BP traits, and with insignificant marginal effect ($P_{M2\_G}>5\times10^{-9}$, $FDR_{M2\_G} > 0.05$). From these variants, *Y* loci were prioritized as driven by interaction if they harbored a stronger interaction effect relative to the main effect ($P_{M1\_G\times E} < P_{M1\_G}$), and *Z* loci deemed as supported (but not driven) by interaction if this was not true.

Thus, collectively *X*+*Y* gene-sleep duration interaction loci were highlighted, alongside secondarily *Z* loci supported by interaction.

Heterogeneity by sex

To test for interaction effects showing evidence of heterogeneity by sex ($p < 0.05/Q$), two-sample Z-tests assuming independence, were conducted for each of the top interaction loci and adjusted for multiple testing.

Mapped protein coding genes

Gene mapping prioritized protein-coding genes for downstream interpretation. Variants directly overlapping protein-coding gene regions were top priority criteria for gene assignment. For intergenic variants nearest distance to transcription start site (TSS) or gene start/end site was queried from Open Target Genetics v22.10 [16] or MyGene.Info using Python package *mygene* v3.2.2 (https://github.com/biothings/mygene.py). Variant mapping annotations were additionally noted from Open Target Genetics, Functional Annotation of Variants – Online Resource v2.0 (FAVOR) [17], HaploReg v4.2 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php), BRAVO variant browser (https://bravo.sph.umich.edu/freeze8/hg38/), Functional Mapping and Annotation of Genome-wide Association Studies v1.5.6 (FUMA) [18], and MyGene.Info.

Variant annotations

FAVOR was queried to annotate deleteriousness or functionality scores [17], and RegulomeDB v2.2 was used to extract aggregate regulatory function evidence scores, along with chromatin state, DNA accessibility, overlap with transcription factor (TF) binding sites or TF motifs, and expression quantitative trait loci (eQTL) [19]. FUMA's SNP2GENE pipeline was used to annotate a comprehensive list of genes for each top locus, incorporating positional, chromatin interaction (FDR $<=10^{-6}$, 250 bp upstream - 500 bp downstream of TSS), and GTEXv8 eQTL evidence (agreeing with RegulomeDB) with the top variant or its variants in LD ($r^2 > 0.1$ within 500 kb) [18].

At the variant level, PheWeb, Open Target Genetics, Common Metabolic Diseases Knowledge Portal (https://hugeamp.org/), and Oxford Brain Imaging Genetics Server (BIG40) were queried for significant trait associations ($p < 5\times10^{-8}$) from past GWAS [16, 20, 21]. At the gene level, International Mouse Phenotyping Consortium release 19.1 (IMPC), Online Mendelian Inheritance in Man (OMIM; https://omim.org/), PheWeb, Phenotype-Genotype Integrator (PheGenI), and Open Target Genetics were queried for phenotypic annotations from mice knockout study results, involvement in Mendelian disorders, and significant trait associations ($p < 5\times10^{-8}$) [16, 20, 22, 23]. All STST and LTST mapped protein-coding genes were then queried using FUMA's GENE2FUNC pipeline to identify significant (adjusted *p*-value < 0.05) pathways and traits [18]. STRING v12.0 was additionally queried using medium confidence threshold (0.4) to note significantly (FDR < 0.05) enriched traits or pathways to compare and contrast LTST and STST loci [24].

Druggability analysis

The Drug-Gene Interaction database (v4.2.0) was first utilized to identify druggability potential, with genes also annotated for implicated pathways and functions using the Kyoto Encyclopedia of Genes and Genomes database. Druggability target categories were annotated and all interacting drugs queried from reports across 43 databases (BaderLabGenes, CarisMolecularIntelligence, dGene, FoundationOneGenes, GO, HingoraniCasas, HopkinsGroom, HumanProteinAtlas, IDG, MskImpact, Oncomine, Pharos, RussLampel, Tempus, CGI, CIViC, COSMIC, CancerCommons, ChemblDrugs, ChemblInteractions, ClearityFoundationBiomarkers, ClearityFoundationClinicalTrial, DTC, DoCM, DrugBank, Ensembl, Entrez, FDA, GuideToPharmacology, JACX-CKB, MyCancerGenome, MyCancerGenomeClinicalTrial, NCI, OncoKB, PharmGKB, TALC, TEND, TTD, TdgClinicalTrial, Wikidata). Protein targets for available active ligands in ChEMBL were also noted. Gene targets were looked up in the druggable genome using the most recent druggable genome list established from the NIH Illuminating the Druggable Genome Project (https://github.com/druggablegenome/IDGTargets) available through the Pharos web platform. Lastly, FDA-approved drugs, late-stage clinical trials and disease indications were queried in the DrugBank, ChEMBL, ClinicalTrials.gov databases to provide results for the top MESH and DrugBank indications and clinical trials.

RESULTS

Discovery of novel gene-sleep duration interactions

From an initial source of 37 studies, 59 population-group specific cohorts (derived from geographic origins or self-reported ethnicity) resulted in a pooled sample size of 811,405 individuals comprising of 5.9% AFR (12 cohorts), 6.0% EAS (5 cohorts), 83.4% EUR (34 cohorts), 3.7% HIS (7 cohorts), and 0.9% SAS (1 cohort) (Supplementary Tables S1–S2). The 1df test discovered seven loci and the 2-step method discovered one locus. The 2df joint test first identified 3629 significant loci, from which 18 were novel for BP (Supplementary Table S3) with insignificant marginal genetic effect – revealing 14 loci driven by the interaction effect, and four not driven by the interaction effect. Thus in total we discovered 22 gene-sleep duration interaction loci (Tables 1–2), and 4 secondary loci (Table 3) – of which 21 are novel for BP traits (Fig. 1, Supplementary Table S4). Among the 22 prioritized interaction loci, four loci exhibited cross-population effects (Table 1, Fig. 2, Supplementary Figs S1–S3) – one identified in combined sex, three in female sex-stratified analyses, and 18 identified specific to either one of the AFR, HIS, or EUR population groups (Table 2, Fig. 3, Supplementary Figs S1–S3). Specifically, AFR analysis revealed one gene-sleep duration interaction locus, HIS analysis revealed 11 gene-sleep duration interaction loci, and EUR analysis revealed six gene-sleep duration loci (Table 2). Three variants identified in combined sex meta-analyses showed evidence of heterogeneous effect by sex (Table 2). Leave-one-study-out sensitivity analysis for variants identified in at least 3 cohorts demonstrated consistent direction of interaction effects, providing additional confidence in our reported novel loci (Supplementary Fig. S4).

Table 1. Novel gene-sleep duration interaction loci identified in cross-population meta-analysis.

Exposure	Variant	Nearest gene(s)	Position (hg38)	Alleles (E/O)	AF	N	Sex	Population Groups	Trait	B_{M1_G} (se_{M1_G})	$B_{G\times E}$ ($se_{G\times E}$)	P_{M1_G}	$P_{G\times E}$	$P_{G,G\times E}$	P_{sex_diff}
Loci identified by 1df Interaction Test															
STST	rs11314421[a]	*WBP1L*	10:102808541	C/CG	0.551	279527	F	AFR, EAS, EUR, HIS, SAS	PP	0.12 (0.04)	0.40 (0.09)	1.60E-03	7.82E-06	3.54E-11	8.84E-05
LTST	rs538479553[b]	*FAM98A*	2:33903659	C/G	0.102	41814	F	AFR, EAS, EUR, HIS	SBP	1.12 (0.40)	−5.09 (0.86)	5.27E-03	3.32E-09	2.35E-08	3.59E-06
Loci identified by 2df Joint Test, Driven by Interaction Effect															
STST	rs76458410[b]	*YWHAB*	20:44851866	G/A	0.023	47678	C	AFR,HIS	PP	0.14 (0.34)	−3.65 (0.73)	6.93E-01	6.38E-07	3.88E-09	6.87E-02
LTST	rs143199695[b]	*ALG10B*	12:37297511	T/C	0.016	29473	F	EUR, HIS	PP	−0.57 (0.44)	-3.28 (0.78)	1.88E-01	2.46E-05	4.55E-09	**4.07E-04**

All results herein are from the M1 model. Supplementary Table S21 provides summary statistics according to each population group identified in cross-population results. For the sex column, C denotes combined sex, and F denotes female sex-stratified meta-analysis. For the alleles column, E denotes effect allele, and O denotes other allele used as reference. Bold denotes significance.
[a]denotes the variant was identified using the two-step approach.
[b]denotes variants novel for BP.

Prior reported gene-sleep interactions

In our current cross-population meta-analysis, rs10406644 showed interaction evidence with STST ($P_{G\times E}=2.0\times10^{-4}$ for PP), and rs7955964 with LTST ($P_{G\times E}=6.6\times10^{-3}$ for SBP, $P_{G\times E}=1.7\times10^{-2}$ for DBP) with direction of association agreeing with prior work [8], and non-significance ($P_{G\times E} > 0.05$) for the opposite sleep duration exposure (Supplementary Table S5). All 22 prioritized interaction loci in this current analysis are notably distal (>14 Mb, or on different chromosomes) and therefore most likely to be independent of our previously reported gene-sleep interaction loci for blood pressure traits based on regional association plots (Supplementary Fig. S5).

Functional potential of variants

Four variants (rs11483173, rs372262693, rs113952142, rs11314421) were marked by high transcription activity chromatin states and eight variants (rs114831731, rs372262693, rs143863772, rs533724062, rs11314421, rs1035064, rs538479553, rs13032423) were marked by accessible chromatin in heart tissue or blood (Supplementary Table S6). Six variants (rs114831731, rs542745170, rs533724062, rs11314421, rs1035064, rs538479553) reflected marked regulatory potential with RegulomeDB scores ≥ 2c (Supplementary Table S6).

Mapped protein-coding genes

All 26 variants identified were either intronic or intergenic, and mapped to a primary set of 27 protein coding genes (Supplementary Table S7). Extended gene mapping revealed 292 genes highlighted for the 12 STST interaction loci, 67 genes for the 10 LTST interaction loci, and 35 genes for the four joint 2df loci not driven by interaction (Supplementary Tables S7–S9).

Expression quantitative trait loci (eQTL)

Tissue-specific (GTEXv8) eQTL associations were observed at rs11314421, rs1035064, and rs34761985 in tissues of the heart, vasculature, or blood (Supplementary Table S8) [19]. *WBP1L*-rs11314421 and *ZNF682*-rs1035064 gene mappings were corroborated by eQTL evidence identified in venous blood or the tibial artery. Beyond these primary mapped genes, *MFSD13A*, *BORCS7*, *CALHM2*, *RPARP-AS1*, *AS3MT*, and *SFXN2* expression were mapped to rs11314421 by eQTL evidence in the ascending aorta, coronary artery, tibial artery, left ventricle myocardium, right atrium auricular region, venous blood, or lymphoblast. Similarly, *ZNF56*, *ZNF253*, *ZNF93*, *ZNF90*, and *ZNF486* were mapped by coronary artery or venous blood eQTL evidence to rs1035064. *UXS1* was mapped by rs34761985 eQTL data identified in the right atrium auricular region.

Variant-level cross-trait associations

Several variants show associations ($P < 5\times10^{-8}$) with other traits (Supplementary Table S10). Querying Open Target Genetics (https://genetics.opentargets.org) identified rs11314421 (*WBP1L)* to be associated with hypertension and testosterone levels, and rs13032423 *(VRK2)* with sleep duration and "feeling miserable" (Supplementary Table S11). Common Metabolic Diseases Knowledge Portal (https://hugeamp.org/) further identified rs13032423 *(VRK2)* to be associated with BMI and sleep duration (Supplementary Fig. S6). Querying brain imaging phenotypes through the Oxford Brain Imaging Genetics Server (BIG40) revealed rs13032423's (*VRK2)* connection to brain functional connectivity by its association with rfMRI connectivity (ICA100 edge 965) (Supplementary Table S12, Supplementary Fig. S7) [21].

Gene functional implications

Mice knockout evidence highlighted genes important for heart morphology (*BRINP3, CRBN, ALG10B, PRMT6*), and cardiac rhythm (*TG, WBP1L*) (Supplementary Table S13). Open Target Genetics, PheWeb, and PheGenI revealed genes implicated in genetic associations ($p < 5\times10^{-8}$), with OMIM (https://omim.org/)

Table 2. Novel gene-sleep duration interaction loci identified specific to certain population groups.

Exposure	Variant	Nearest gene(s)	Position (hg38)	Alleles (E/O)	Sex	AF	N	Population Groups	Trait	B_{M1_G} (se_{M1_G})	B_{GxE} (se_{GxE})	P_{M1_G}	P_{GxE}	$P_{G,GxE}$	P_{sex_diff}[b]
Loci Identified by 1df Interaction Test															
STST	rs114831731	*AHCYL1*	1:109970740	A/T	C	0.009	23897	HIS	PP	0.85 (0.64)	−6.27 (1.04)	1.87E-01	1.57E-09	7.34E-11	**5.67E-04**
	rs144229676	*ZNF521*	18:25303461	A/C	C	0.019	27119	HIS	DBP	2.32 (0.70)	−7.23 (1.18)	8.70E-04	8.10E-10	1.80E-09	5.00e-01
	rs1035064	*ZNF682*	19:19997730	T/C	M	0.019	392939	EUR	SBP	-0.27 (0.18)	2.10 (0.36)	1.62e-01	4.82E-09	5.76E-08	**1.52E-04**
	rs112958007[a]	*PAK5*	20:9805888	C/T	C	0.005	23897	HIS	PP	2.09 (0.97)	−10.83 (1.78)	3.03E-02	1.28E-09	1.23E-08	
	rs752086677[a]	*KRTAP13-2*	21:30362234	C/G	C	0.002	30009	EUR	DBP	2.12 (0.87)	−8.71 (1.23)	1.47E-02	1.46E-12	5.68E-13	
LTST	rs372262693	*TG, SLA*	8:133069499	T/C	C	0.023	23897	HIS	PP	0.62 (0.41)	−4.91 (0.82)	1.34E-01	2.33E-09	7.11E-09	2.43E-01
Loci Identified by 2df Joint Test, Driven by Interaction Effect															
STST	rs143863772[a]	*MROH7*	1:54707218	T/G	C	0.006	23902	HIS	SBP	−1.56 (1.06)	−6.99 (1.74)	1.47E-01	5.79E-05	1.84E-10	
	rs141117715[a]	*KCNJ3*	2:155446948	C/T	C	0.021	23897	HIS	PP	0.51 (0.44)	−4.29 (0.76)	2.53E-01	1.74E-08	2.45E-09	7.86E-02
	rs17011282[a]	*ZNF385D*	3:22386254	C/G	C	0.006	23897	HIS	PP	−0.01 (0.79)	−6.00 (1.20)	9.93E-01	5.86E-07	4.13E-10	1.97E-01
	rs764985249[a]	*EFNA5*	5:105713137	T/C	C	0.002	26230	EUR	PP	0.97 (1.48)	−11.78 (2.00)	5.09E-01	4.06E-09	6.45E-12	
	rs542745170[a]	*WWOX*	16:78323227	A/C	C	0.009	23897	HIS	PP	−0.36 (0.72)	−4.96 (1.19)	6.20E-01	3.14E-05	5.00E-09	**2.05E-03**
LTST	rs533724062[a]	*BRINP3*	1:190792851	TA/T	C	0.011	34442	AFR	PP	1.13 (0.60)	−4.40 (1.18)	6.03E-02	1.92E-04	3.69E-09	**3.56E-04**
	rs138288695[a]	*CRBN*	3:3295965	G/A	C	0.006	23897	HIS	DBP	0.57 (0.68)	−5.50 (1.08)	4.07E-01	3.46E-07	1.31E-09	
	rs142966182[a]	*ALCAM*	3:104791665	T/C	C	0.006	26230	EUR	DBP	−0.20 (0.62)	−5.37 (1.01)	7.50E-01	1.01E-07	1.21E-09	
	rs540041583[a]	*PAM*	5:103002447	A/G	C	0.003	26230	EUR	PP	−1.54 (1.20)	−6.50 (1.66)	1.99E-01	8.93E-05	6.93E-10	
	rs113952142[a]	*SDK1*	7:3917121	A/C	C	0.005	23902	HIS	SBP	−0.28 (1.20)	−9.07 (1.90)	8.18E-01	1.81E-06	5.49E-10	
	rs111392401[a]	*JMJD1C*	10:65029197	T/G	C	0.007	23897	HIS	DBP	0.49 (0.63)	−5.71 (1.00)	4.32E-01	1.27E-08	2.28E-10	
	rs772862932[a]	*ATP8A2*	13:25395875	T/C	C	0.002	30009	EUR	DBP	−0.11 (0.70)	−4.85 (1.00)	8.70E-01	1.31E-06	1.28E-09	

All results herein are from the M1 model. Supplementary Table S22 provides summary statistics according to each population group-specific cohort identified in these population-group specific results. For the sex column, C denotes combined sex meta-analysis, and M denotes male sex-stratified meta-analysis. For the alleles column, E denotes effect allele, and O denotes other allele used as reference. Bold denotes significance.

[a]denotes variants novel for BP.

[b]Empty cell in P_{sex_diff} indicates the variant, after quality control, was not found in both sex-stratified meta-analyses.

Table 3. Novel BP loci identified by the 2df Joint Test, not driven by the interaction effect.

Exposure	Variant	Nearest gene(s)	Position (hg38)	Alleles (E/O)	Sex	AF	N	Population Groups	Outcome	B_{M1_G} (se_{M1_G})	B_{GxE} (se_{GxE})	P_{M1_G}	P_{GxE}	$P_{G,GxE}$	P_{sex_diff}[2]
Loci identified by 2df Joint Test, Not Driven by Interaction Effect															
STST	rs59680540[1]	*PRMT6*	1:106595299	GGTGA/G	C	0.0065	23897	HIS	PP	−2.43 (0.66)	−2.59 (1.18)	2.52E-04	2.74E-02	**4.87E-09**	4.68E-01
	rs34761985[1]	*ST6GAL2*	2:106923653	T/TG	C	0.6124	731622	AFR, EAS, EUR, HIS, SAS	SBP	−0.18 (0.04)	−0.12 (0.08)	3.87E-06	1.43E-01	**2.87E-09**	1.10E-01
	rs150586434[1]	*HTR1F*	3:87648138	A/G	C	0.0057	23902	HIS	SBP	−3.49 (1.09)	−4.36 (1.77)	1.40E-03	1.37E-02	**1.31E-09**	
LTST	rs34761985[1]	*ST6GAL2*	2:106923653	T/TG	C	0.6124	731622	AFR, EAS, EUR, HIS, SAS	SBP	−0.20 (0.04)	−0.06 (0.08)	7.53E-07	4.45E-01	**4.78E-09**	1.90E-01
	rs13032423[1]	*VRK2*	2:57764977	A/G	C	0.534	799211	AFR, EAS, EUR, HIS, SAS	SBP	−0.21 (0.04)	0.20 (0.07)	2.21E-09	4.77E-03	**4.86E-09**	3.45E-01

All results herein are from the M1 model. Supplementary Tables S21–S22 provides summary statistics according to each population group-specific cohort for rs59680540 and rs150586434, and according to each population group for rs34761985 and rs13032423 below. For the sex column, C denotes combined sex meta-analysis. For the alleles column, E denotes effect allele, and O denotes other allele used as reference. Bold denotes significance.

[a]denotes variants novel for BP.

[b]Empty cell in P_{sex_diff} indicates the variant, after quality control, was not found in both sex-stratified meta-analyses.

identifying any linked Mendelian disorders (Supplementary Tables S14–S17) [16, 20, 23]. Specifically, eight genes harbored links to the cardiovascular domain through association with traits identified by genetic studies: *WBP1L*, *EFNA5, ZNF521*, *WWOX*, *ZNF385D*, *FAM98A*, *PAM*, and *JMJD1C*. *ALG10B* was identified to be implicated in the Mendelian disorder long QT syndrome. In the realm of sleep and circadian health, reported genetic associations corroborated the relevance of *EFNA5*, *ZNF52*1, *WWOX, ALG10B*, *PAM* and *SDK1* with insomnia, daytime napping, or chronotype traits. Genetic associations to other pertinent domains including kidney function, neurological health, liver function, thyroid function, metabolism, lifestyle choice, and inflammation, were also noted (Supplementary Table S10).

Gene set enrichment analysis

We performed gene set enrichment analyses on the aforementioned extended gene sets in the FUMA GENE2FUNC platform and STRING database (Supplementary Tables S18–S19) [18, 24]. STST-mapped genes highlighted pathways in antioxidant defense and neuron excitation, along with phenotypic connection to lipid levels, neurological health, cardiovascular health, metabolism and immune defense. LTST-mapped genes implicated traits involving inflammation, neurological health, and metabolism. A clearly distinctive pattern differentiating short and long sleep duration interaction loci was thus not observed.

Druggability

We investigated druggability of the primary mapped genes using an integrative approach to highlight drug repurposing potential (Supplementary Table S20) [25–28]. Identified gene candidates revealed connections to serotonergic response (*HTR1F, KCNJ3*), proteasome-mediated ubiquitination (*CRBN*), thyroid hormone synthesis (*TG*), and axon guidance (*PAK5, ALCAM*) pathways. Of these, *KCNJ3, CRBN, HTR1F, TG*, *PAK5*, and *ALCAM* harbored links to reported drug interactions and active ligand interactions in the ChEMBL database. The following genes displayed evidence of pharmacological targeting: *KCNJ3* (by small molecule inhibitors Atomoxetine and Dronedarone); *CRBN (*by thalidomide analogs Pomalidomide and Lenalidomide); *HTR1F* (by selective serotonin receptor agonists like Lasmiditan); and *ALCAM* (by chemotherapy agent Fluorouracil).

DISCUSSION

In this large-scale effort investigating the biomolecular mechanisms underpinning the intersecting roles of sleep health and blood pressure traits, we conducted genome-wide gene-by-sleep duration (short and long sleep) interaction analyses in 811,405 individuals of diverse population backgrounds (AFR, EAS, EUR, HIS, SAS) for systolic blood pressure, diastolic blood pressure, and pulse pressure. We report novel discovery of 22 gene-sleep duration interaction loci for BP traits – 12 for short sleep, and 10 for long sleep. 15 of the identified variants are rare with allele frequency <=1%, with four variants identified in sex-stratified meta-analyses, and 18 variants specific to either the AFR(1), EUR(6), or HIS (11) population groups. In line with our previous research, the identified genomic loci exhibiting interactions with short and long sleep are non-overlapping (with non-significance in the opposing sleep duration exposure), suggesting distinct mechanisms influencing cardiovascular health. Nonetheless, we did not observe a clear differentiating pattern in the biological pathways implicated when comparing short sleep and long sleep.

The functional annotation investigations of our prioritized genes point towards cardiovascular and neurological connections, along with revealing links to circadian rhythm, thyroid function, bone health, and hematopoiesis mechanisms. Our findings highlight potential pharmacological candidates and suggest

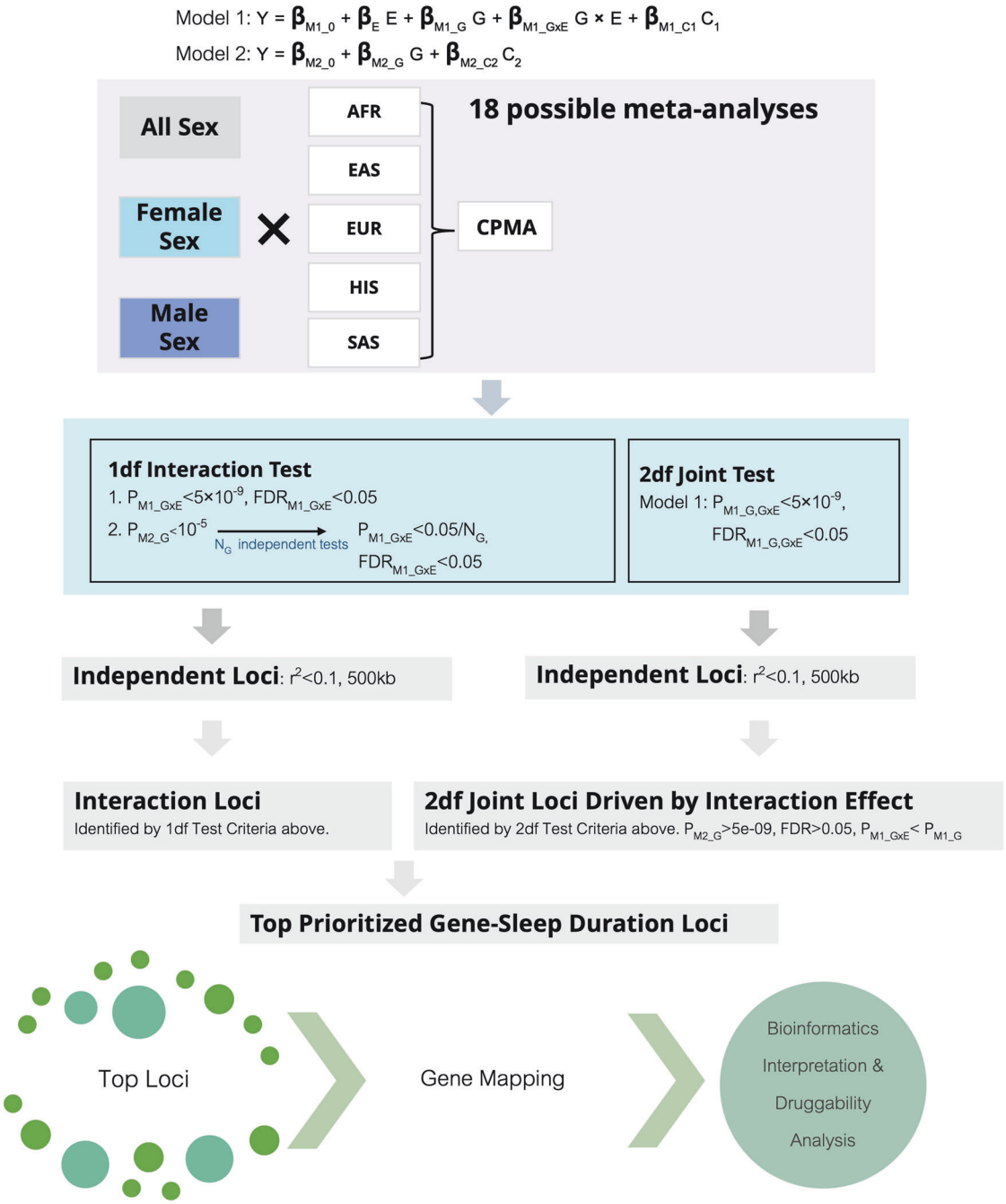

Fig. 1 Analysis workflow.

pertinent pathways to consider when designing holistic therapeutic regimens for improving blood pressure control.

Firstly, at a broad level, several identified genes are tied to neurological mechanisms. *KCNJ3* encodes Kir3.1 – the alpha subunit for the I_{KACh} potassium channel – and is interestingly implicated in bradyarrhythmia by its missense variant inducing a gain of function of I_{KACh}, as activation of this channel is tied to the negative chronotropic effect on heart rate exerted by the parasympathetic nervous system [29]. *CRBN* is linked to cognitive function [30], *SDK1* promotes synaptic connectivity [31], *ZNF521* regulates neuron cell fate [32], and *ATP8A2* is involved in both neuron vesicle transport and cardiac conduction [33]. Further, *KRTAP13-2*, *WWOX, EFNA5*, and *ALCAM* are linked to nervous system development with additional roles for *WWOX* in myelination [34] and *EFNA5* in vascular sympathetic innervation [35]. These functional connections may suggest a potential nervous system-heart connection that could be influenced by sleep or circadian disturbances.

In fact neurological pathway connections to circadian rhythm reveal themselves through two enzymes - *PAK5* and *PAM*. Given that circadian rhythm and clock gene expression is intimately connected to blood pressure patterns, of note is *PAK5* – a serine/threonine kinase protective of adult neurons from injury and ischemic stress [36]. *PAK5* has both been shown to be targeted by clock gene-regulated miRNAs in the liver and identified to strongly bind to 14-3-3 proteins – a protein family connected to light-sensitive melatonin diurnal patterns and plausibly influential for sleep behavior [37, 38]. This strong binding affinity to 14-3-3

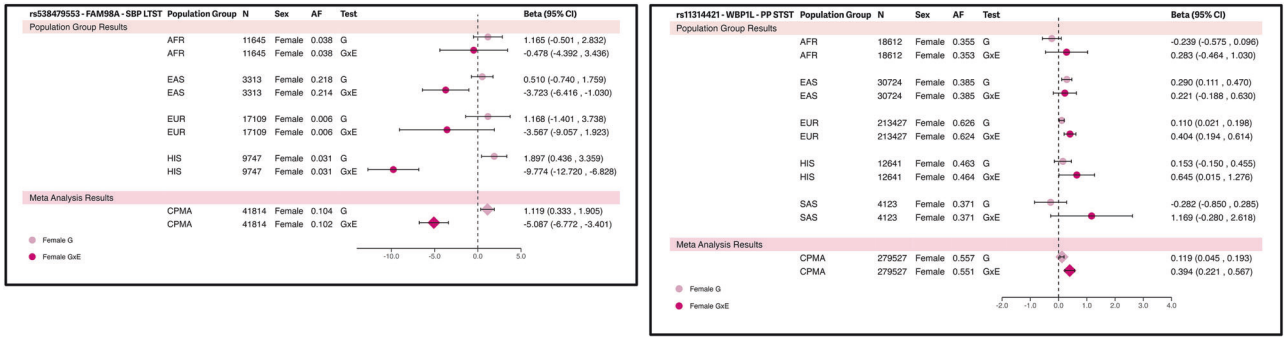

Fig. 2 Forest plots of gene-sleep duration loci identified by the 1df interaction test in female-specific cross-population meta-analyses. These are the prioritized 1df Interaction Test results from female-specific cross-population meta-analyses. Contributing female-specific population groups' (if this variant is found in the particular population group, after quality control) summary statistics are depicted here that were pooled.

proteins suggests an interesting connection, as *YWHAB* (one of this study's primary genes mapped to a STST interaction locus), is part of this protein family. Another enzyme informing the neurological-sleep axis is *PAM*, encoding a copper-dependent enzyme important for synthesizing amidated neuropeptides like NPY – which regulates sleep through noradrenergic signals [39, 40].

Further, *TG* and *JMJD1C*, both encoding proteins intrinsically tied to thyroid hormone function (thyroglobulin and thyroid receptor-interacting protein 8 respectively) – present suggestive ties to the intersection between thyroid function and circadian rhythms. *TG* mRNA and protein expression levels have shown to increase in response to melatonin, along with its genetic variants associated with autoimmune thyroid diseases [41, 42]. Gene silencing of *JMJD1C*'s paralog has shown arrhythmicity and prolonged sleep in Drosophila [43]. Given that circadian clock and thyroid function are increasingly suggested to be interconnected, and sleep deprivation can disrupt temporal hormone profiles (e.g. increased morning plasma thyroid-stimulating hormone (TSH) levels), it may be valuable to investigate further the overlapping pathways between thyroid function, healthy sleep duration, and cardiovascular morbidity [44].

Beyond thyroidal pathways, hematopoiesis presents a possible comprehensive perspective on the interconnectedness between sleep health and nervous system response. *WBP1L*, one of the primary genes identified (mapped to a STST interaction locus identified in female-specific CPMA) has suggestive connection to regulating the *CXCL12-CXCR4* signaling pathway by its inhibitory role on *CXCR4*, the receptor for ligand *CXCL12* [45]. This pathway is both influential for inflammation and hematopoietic state, reflects circadian control, and directly implicates the sympathetic nervous system response – pertinent as stressors are suspected to induce a more exacerbated response in females [46, 47]. If stress factors (e.g. sleep loss) induce noradrenaline, this can downregulate *CXCL12*, with resultant increased cell proliferation of pro-inflammatory cells from the bone marrow, incurring vascular damage [46]. For instance, fragmented sleep has shown to promote myelopoiesis and lower hypocretin release by the hypothalamus, in turn accelerating atherosclerosis progression [48]. Thus perhaps *WBP1L* can offer insight into the intersections between sympathetic activation, neurological control, and unhealthy sleep impacting cardiovascular health, especially in women.

On a similar note of addressing sex-specificity, of relevance is *FAM98A*, a gene identified in female-specific CPMA for interaction with long sleep. *FAM98A*, harboring multiple arginine demethylation sites, is a substrate of *PRMT1* - an enzyme which catalyzes the synthesis of asymmetric dimethylarginine (ADMA), a molecule associated with cardiovascular harm as it induces endothelial dysfunction [49]. Thus seeking to lower harmful ADMA levels to counter harmful effects of sleep loss may be relevant in preservation of vascular integrity [50]. *FAM98A*, encoding a microtubule-associated protein, is also functionally linked to osteoclast formation, which is key to bone resorption and involved in postmenopausal osteoporosis etiology [51]. Given that osteoporosis and CVD share pathology, the *FAM98A* locus may shed light on the importance of considering holistic treatment for hypertensive women approaching or after menopause – an example being Felodipine, an antihypertensive found to additionally discourage osteoclast differentiation [52, 53].

Apart from *FAM98A*, specific genes highlight pathway connections to offer possible avenues for enhancing treatment efficacy for hypertension. Addressing the role of inflammation, *SLA* may lend promise as an immunosuppressant, with cytoplasm-specific delivery of specific domains of *SLA* shown to inhibit the T cell receptor functional cascade [54]. *ALG10B* closely interacts with *KCNH2* to protect it from inhibition by pharmaceuticals and thus prevent acquired long QT syndrome - interesting, as past work has identified *KCNH2* genetic variation to associate with efficacy of specific antihypertensive drugs [55, 56]. *PAK5* is the effector protein of *CDC42*, vital for endothelial integrity and involved in the mechanism of Nebivolol, a third generation beta-blocker [57, 58]. *CRBN*, due to its intrinsic role in ubiquitination, is recruited as an E3 ligase ligand in protease-targeted chimeras (PROTACs), which hold promise in cardiovascular therapeutics – an example being P22A shown to reduce collateral damage of HMGCR upregulation caused by statins [59]. These findings point to the need for future preclinical and clinical studies to confirm the hypothesized mechanisms and test promising interventions.

Our druggability analysis specified genes acting as existing pharmacological targets of FDA-approved drugs, offering perspective for drug repurposing. *HTR1F* and *KCNJ3* are linked to the serotonergic pathway and are targets of approved drugs Atomoxetine (ADHD, obstructive sleep apnea) and Dronedarone (arrhythmia), respectively. This is potentially relevant given that serotonin may impact blood pressure regulation, and serotonin receptor desensitization is implicated in chronic sleep restriction [60, 61]. *HTR1F* encodes for 5-HT_{1F}, shown to function in smooth muscle and trigeminal nerves, with its selective agonists (i.e. Lasmiditan) offering greater efficacy for migraine treatment without the collateral harm of vasoconstrictive effects induced by non-selective triptans [62].

Noticeably all 22 gene-sleep duration interaction loci we identified were specific to a particular population group, a subset of population groups, or a particular sex. This may be due to substantial heterogeneity in BP architecture and sleep lifestyle as a result of cultural differences, uniquely varying stressors due to socioeconomics, and genetic risk that are both shaped by and influence lifestyle choices. For example, admixed African and Hispanic populations are more likely to have poorly controlled

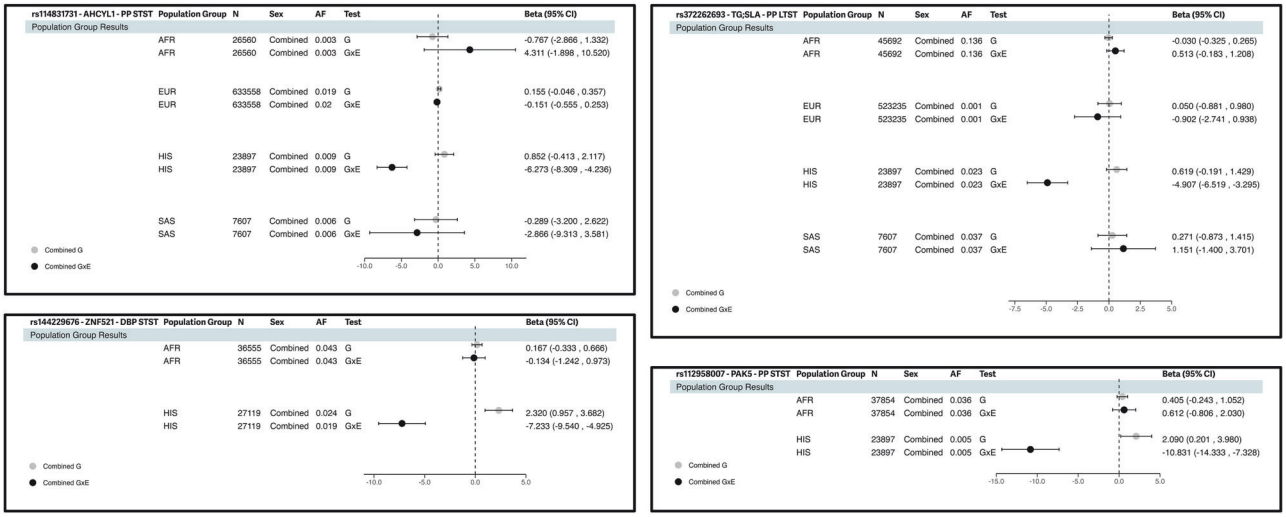

Fig. 3 Forest plots of gene-sleep duration loci identified by the 1df interaction test in combined sex HIS-specific meta-analyses. These are the prioritized 1df Interaction Test results from HIS-specific meta-analyses. Other population group data (if this variant is found in the particular population group, after quality control) are shown here to emphasize that these gene-sleep duration interaction loci were significant only in the HIS population group.

hypertension and circadian abnormalities in BP regulation, as well as higher prevalence of both short and long sleep duration relative to individuals of European ancestry [63, 64]. Females generally sleep longer, have higher prevalence of insomnia, and experience an increased proinflammatory response to sleep deprivation compared to males [65]. Such differential risk profiles are likely attributed to a myriad of social or environmental variables along with genetic and epigenetic susceptibility [8]. Therefore, it is likely that the same duration of self-reported sleep has different etiologies and physiological effects across sex and population background. Future research incorporating extensive phenotyping may help clarify whether gender-specific or population-specific findings are explained by differences in sleep-related or other lifestyle behaviors, mechanisms underlying response to sleep disturbance, or are spurious.

This study has several strengths including its large-scale nature made possible by inclusion of several international biobanks and cohort studies, rigorous data harmonization and quality control protocols, and robust statistical analysis pipelines. Our findings are reinforced by multiple lines of evidence from bioinformatics analysis. Focused druggability analysis and interpretation of drug-gene interactions offer promising insight in drug repurposing and candidate targets for future pursuits.

Limitations of this study include the risk of unidentified misclassification of self-reported sleep duration (opposed to objective measurements from actigraphy or polysomnography) due to recall bias, sleep misperception, or other psychosocial factors. Sleep health is complex, with key dimensions beyond duration (e.g., timing, quality, satisfaction, and regularity) [66]. Abnormality in these other sleep dimensions were not tested here due to lack of readily available data. Adding to the complexity, sleep duration itself reflects heterogeneous health effects influenced by genetic determinants. For example, genetic variation conducive to naturally short sleepers may even lend neuroprotection against harmful brain pathology [67]. In addition, there may be residual confounding bias due to unadjusted comorbidities or environmental factors. Lastly, despite notable diversity of our sample, our data was dominated by individuals of European ancestry. It is striking that several of our loci are HIS-specific – which may be resultant of complex admixture present in this population group. Although we were able to delve into sex-specific interpretations for *FAM98A*, and *WBP1L* – future investigation is desired to understand the reasons behind heterogeneous effects by sex. Enrichment of sample sizes in minority populations is critical for future investigations.

In conclusion this study advances our understanding of the interaction between sleep duration extremes and genetic risk factors shaping the genetic landscape of blood pressure. Our novel discovery of 22 gene-sleep duration interaction loci both accentuates the relevance of proper sleep duration in cardiovascular health and the need to be conscious of heterogeneity present in specific sex or population groups, providing valuable perspective for therapeutic intervention strategies to address cardiovascular disease burden.

DATA AVAILABILITY

Due to restrictions in the written informed consent and local regulations, individual genotype-level data from this project could not be shared. Summary statistics are available at the CHARGE (Cohorts for Heart and Ageing Research in Genomics Epidemiology) dbGaP summary site (phs000930).

CODE AVAILABILITY

All computation central to the conclusions of this meta-analysis was conducted with the following open-source software: *LinGxEScanR* (https://github.com/USCbiostats/LinGxEScanR), *GEM v1.4.1* (https://github.com/large-scale-gxe-methods/GEM), *MMAP* (https://mmap.github.io/), *EasyQC2* and *EasyStrata2* (www.genepi-regensburg.de/charge-gli), and *METAL* (https://csg.sph.umich.edu/abecasis/metal/download/, https://genome.sph.umich.edu/wiki/Meta_Analysis_of_SNPxEnvironment_Interaction).

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AUTHOR CONTRIBUTIONS

PN and HW conducted centralized project data analyses, data consolidation, meta-analyses, quality control, bioinformatics analysis, and contextual interpretation. PN, HW, ARB, ATK, CLM KS, TWW, PBM, RN, DCR, SR, and DVH were part of the writing group and participated in project workflow design, interpretation of results, and drafting the manuscript. LDLF, AD, CG, and DCR participated in centralized study coordination. ATK, JLM, JRO, TWW, HA, JB Meigs, XZ, Han Chen, JG, AKM, CLM, PBM, and PAP acted as collaborators facilitating project design, specific code scripts, or specialized analyses. All other co-authors participated in final result interpretation, cohort-level study concept and design, cohort-level phenotype data acquisition and/or quality control, cohort-level genotype data acquisition and/or quality control, and/or cohort-level data-analysis and interpretation. All authors approved the final version of the paper that was submitted to the journal.

COMPETING INTERESTS

CLM has received funding from AstraZeneca not related to the current study. BMP serves on the steering committee of the Yale Open Data Access Project funded by Johnson & Johnson. DC receives consultancy fees from Roche Diagnostics and Trimedics and speaker fees from Servier. DAL has received support from Medtronic LTD and Roche Diagnostics for biomarker research not related to the current study. HC receives consulting fees from Character Biosciences. The remaining authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Heming Wang.

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[1]Division of Sleep and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. [2]Department of Genetic Epidemiology, University of Regensburg, Regensburg, Germany. [3]Center for Research on Genomics and Global Health, National Human Genome Research Institute, US National Institutes of Health, Bethesda, MD, USA. [4]Center for Public Health Genomics, Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA. [5]Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA, USA. [6]University of Mississippi Medical Center, Jackson, MS, USA. [7]Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St. Louis, MO, USA. [8]Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center at Houston, McGovern Medical School, Houston, TX, USA. [9]Department of Human Genetics, Leiden University Medical Center, Leiden, Netherlands. [10]Human Genetics Center, Department of Epidemiology, University of Texas Health Science Center at Houston School of Public Health, Houston, TX, USA. [11]Division of Biostatistics, Department of Population and Public Health Sciences, University of Southern California, Los Angeles, CA, USA. [12]Division of Quantitative and Clinical Sciences, Department of Obstetrics & Gynecology, Vanderbilt University Medical Center, Nashville, TN, USA. [13]Biomedical Laboratory Research and Development, Tennessee Valley Healthcare System (626), Department of Veterans Affairs, Nashville, TN, USA. [14]Division of Endocrinology, Diabetes and Nutrition, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA. [15]Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA. [16]Department of Biostatistics, University of Washington, Seattle, WA, USA. [17]Cardiovascular Division, Department of Medicine, Washington University School of Medicine in St. Louis, St. Louis, MO, USA. [18]Center for Biostatistics and Data Science, Institute for Informatics, Data Science, and Biostatistics, Washington University School of Medicine in St. Louis, St. Louis, MO, USA. [19]Icelandic Heart Association, Kopavogur, Iceland. [20]Faculty of Medicine, Department of Health Sciences, University of Iceland, Reykjavik, Iceland. [21]The Institute for Translational Genomics and Population Sciences, Pediatrics, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA, USA. [22]Department of Psychology, The University of Edinburgh, Edinburgh, UK. [23]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA. [24]Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia. [25]Graduate School of Data Science, Seoul National University, Seoul, South Korea. [26]Department of Data Sciences, Hunter Medical Research Institute, New Lambton Heights, NSW, Australia. [27]MRC Epidemiology Unit, University of Cambridge, Cambridge, UK. [28]Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland. [29]Department of Clinical Chemistry, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, Tampere, Finland. [30]Department of Twin Research & Genetic Epidemiology, King's College London, London, UK. [31]National Heart & Lung Institute, Cardiovascular Genomics and Precision Medicine, Imperial College London, London, UK. [32]Department of Psychiatry, Amsterdam UMC/Vrije universiteit, Amsterdam, Netherlands. [33]GGZ inGeest, Amsterdam, Netherlands. [34]Department of Biochemistry, Wake Forest University School of Medicine, Winston-Salem, NC, USA. [35]Division of Nephrology, Department of Medicine, University of Illinois Chicago, Chicago, IL, USA. [36]Kuopio Research Institute of Exercise Medicine, Kuopio, Finland. [37]Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA. [38]Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany. [39]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [40]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA. [41]Department of Molecular Biology, Medical Biochemistry and Pathology, Université Laval, Quebec City, QC, Canada. [42]Statistical Genetics Group, Department of Computational Biology, University of Lausanne, Lausanne, Switzerland. [43]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands. [44]Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [45]Department of Functional Genomics, Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany. [46]DZHK (German Center for Cardiovascular Research), partner site Greifswald, Greifswald, Germany. [47]Department of Medicine, Harvard Medical School, Boston, MA, USA. [48]Clinical and Translational Epidemiology Unit, Mongan Institute, Massachusetts General Hospital,

Boston, MA, USA. [49]MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK. [50]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK. [51]Graduate School of Public Health, Shizuoka Graduate University of Public Health, Shizuoka, Japan. [52]Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. [53]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, USA. [54]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA. [55]Division of Genetic Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [56]School of Psychology, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom. [57]Department of Data Science, University of Mississippi Medical Center, Jackson, MS, USA. [58]Jackson Heart Study, University of Mississippi Medical Center, Jackson, MS, USA. [59]Department of Computational Biology, F-75015 Paris, France Institut Pasteur, Université Paris Cité, Paris, France. [60]Department of Epidemiology, Harvard TH School of Public Health, Boston, MA, USA. [61]School of Medicine and Public Health, College of Health Medicine and Wellbeing, University of Newcastle, New Lambton Heights, NSW, Australia. [62]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA. [63]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [64]Cardiology, Pneumology, Infectious Diseases, Intensive Care Medicine, Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany. [65]School of Public Health, The University of Texas Health Science Center at Houston (UTHealth), Brownsville, TX, USA. [66]Department of Epidemiology, University of Washington, Seattle, WA, USA. [67]Shenzhen Key Laboratory of Cardiovascular Health and Precision Medicine, Southern University of Science and Technology, Shenzhen, China. [68]Department of Endocrinology, Wake Forest University School of Medicine, Winston-Salem, NC, USA. [69]Department of Nutritional Sciences, University of Toronto, Toronto, ON, Canada. [70]Institute of Biomedicine, School of Medicine, University of Eastern Finland, Kuopio, Finland. [71]Department of Clinical Physiology, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, Tampere, Finland. [72]Population Sciences Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA. [73]Framingham Heart Study, Framingham, MA, USA. [74]Department of Medicine, Internal Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland. [75]Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland. [76]Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA. [77]Department of Genetics, University of North Carolina, Chapel Hill, NC, USA. [78]Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland. [79]Research Centre of Applied and Preventive Cardiovascular Medicine, and Department of Clinical Physiology and Nuclear Medicine, University of Turku, and Turku University Hospital, Turku, Finland. [80]Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland. [81]Department of Genome Sciences, University of Virginia, Charlottesville, VA, USA. [82]Department of Sleep Medicine, The University of Edinburgh, Edinburgh, UK. [83]Faculty of Medical Sciences, Institute for Laboratory Medicine, Private University in the Principality of Liechtenstein, Vaduz, Liechtenstein. [84]Center of Laboratory Medicine, Institute of Clinical Chemistry, University of Bern and Inselspital, Bern, Switzerland. [85]Central Laboratory, Cantonal Hospital Graubünden, Chur, Switzerland. [86]Medical Laboratory, Dr. Risch Anstalt, Vaduz, Liechtenstein. [87]Department of Nutritional Sciences, University of Michigan, Ann Arbor, MI, USA. [88]School of Biomedical Sciences and Pharmacy, College of Health Medicine and Wellbeing, University of Newcastle, New Lambton Heights, NSW, Australia. [89]CardioVascular Institute (CVI), Beth Israel Deaconess Medical Center, Boston, MA, USA. [90]Department of Internal Medicine, Division of Endocrinology, Leiden, Netherlands. [91]Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [92]Department of Epidemiology, O'Donnell School of Public Health, University of Texas Southwestern Medical Center, Dallas, TX, USA. [93]Department of Population and Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, OH, USA. [94]Department of Nephrology, University Hospital Regensburg, Regensburg, Germany. [95]Department of Nephrology and Rheumatology, Kliniken Südostbayern, Traunstein, Germany. [96]KfH Kidney Centre Traunstein, Traunstein, Germany. [97]Population Health Research Institute, Medicine, McMaster University, Hamilton, ON, Canada. [98]Jackson Heart Study, Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA. [99]Pulmonary, Critical Care and Sleep Medicine, Medicine, University of Washington, Seattle, WA, USA. [100]Center for Primary Care and Public Health, University of Lausanne, Lausanne, Switzerland. [101]Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland. [102]Foundation for Research in Health Exercise and Nutrition, Kuopio Research Institute of Exercise Medicine, Kuopio, Finland. [103]Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC, USA. [104]Clinical and Translational Epidemiology Unit, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA. [105]Metabolism Program, Broad Institute of MIT and Harvard, Cambridge, MA, USA. [106]Clinical Pharmacology and Precision Medicine, Queen Mary University of London, London, UK. [107]Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, Netherlands. [183]These authors contributed equally: Pavithra Nagarajan, Thomas W. Winkler, Amy R. Bentley, Clint L. Miller, Aldi T. Kraja, Karen Schwander. [184]These authors jointly supervised this work: Patricia B Munroe, Dabeeru C Rao, Diana van Heemst, Susan Redline, Raymond Noordam, Heming Wang. *A list of authors and their affiliations appears at the end of the paper. ✉email: hwang@bwh.harvard.edu

MILLION VETERAN PROGRAM

Sumitra Muralidhar[108], Jennifer Moser[108], Jennifer E. Deen[108], Philip S. Tsao[109], J. Michael Gaziano[110], Elizabeth Hauser[111], Amy Kilbourne[112], Michael Matheny[113], Dave Oslin[114], Lori Churby[109], Stacey B. Whitbourne[110], Jessica V. Brewer[110], Shahpoor Alex Shayan[110], Luis E. Selva[110], Saiju Pyarajan[110], Kelly Cho[110], Scott L. DuVall[115], Mary T. Brophy[110], Brady Stephens[116], Todd Connor[117], Dean P. Argyres[117], Themistocles L. Assimes[109], Adriana Hung[113], Henry Kranzler[114], Samuel Aguayo[118], Sunil Ahuja[119], Kathrina Alexander[120], Xiao M. Androulakis[121], Prakash Balasubramanian[122], Zuhair Ballas[123], Elizabeth S. Bast[124], Jean Beckham[111], Sujata Bhushan[125], Edward Boyko[126], David Cohen[127], Louis Dellitalia[128], Gerald Wayne Dryden Jr.[129], L. Christine Faulk[130], Joseph Fayad[131], Daryl Fujii[132], Saib Gappy[133], Frank Gesek[134], Jennifer Greco[135], Michael Godschalk[136], Todd W. Gress[137], Samir Gupta[138], Salvador Gutierrez[139], John Harley[140], Mark Hamner[141], Daniel J. Hogan[142], Robin Hurley[143], Pran Iruvanti[144], Frank Jacono[145], Darshana Jhala[114], Scott Kinlay[110], Michael Landry[146], Peter Liang[147], Suthat Liangpunsakul[148], Jack Lichy[149], Tze Shien Lo[150], C. Scott Mahan[151], Ronnie Marrache[152], Stephen Mastorides[153], Kristin Mattocks[154], Paul Meyer[155], Jonathan Moorman[156], Providencia Morales[157], Timothy Morgan[158], Maureen Murdoch[159], Eknath Naik[160], James Norton[161], Olaoluwa Okusaga[162], Michael K. Ong[163], Kris Ann Oursler[164], Ismene Petrakis[165], Samuel Poon[166], Emily Potter[167], Michael Rauchman[168], Amneet S. Rai[169], Richard Servatius[170], Satish Sharma[171], River Smith[172], Peruvemba Sriram[173], Patrick Strollo Jr.[174], Neeraj Tandon[175], Gerardo Villareal[117], Jessica Walsh[115], John Wells[176], Jeffrey Whittle[177], Mary Whooley[178], Peter Wilson[179], Junzhe Xu[180], Shing Shing Yeh[181] and Andrew W. Yen[182]

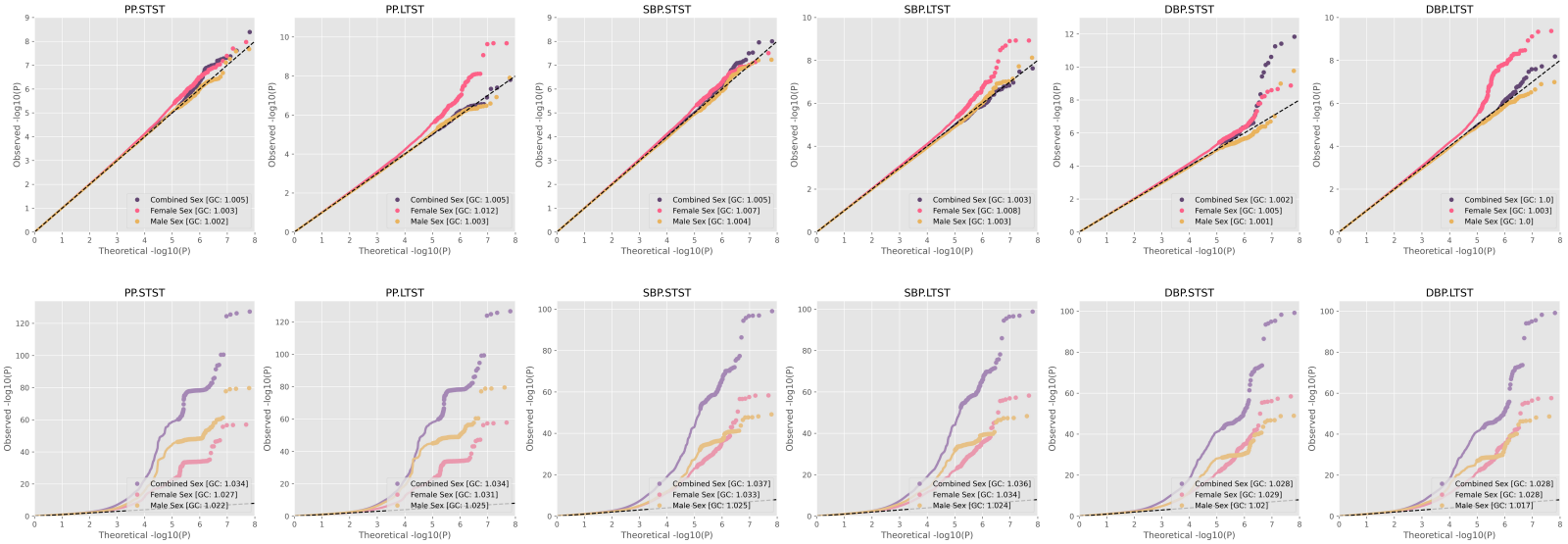
[108]US Department of Veterans Affairs, Washington, D. C., USA. [109]VA Palo Alto Health Care System, Palo Alto, CA, USA. [110]VA Boston Healthcare System, Boston, MA, USA. [111]Durham VA Medical Center, Durham, NC, USA. [112]VA HSR&D, Ann Arbor, MI, USA. [113]VA Tennessee Valley Healthcare System, Nashville, TN, USA. [114]Philadelphia VA Medical Center, Philadelphia, PA, USA. [115]VA Salt Lake City Health Care System, Salt Lake City, UT, USA. [116]Canandaigua VA Medical Center, Canandaigua, NY, USA. [117]New Mexico VA Health Care System, Albuquerque, NM, USA. [118]Phoenix VA Health Care System, Phoenix, AZ, USA. [119]South Texas Veterans Health Care System, San Antonio, TX, USA. [120]Veterans Health Care System of the Ozarks, Fayetteville, AR, USA. [121]Columbia VA Health Care System, Columbia, SC, USA. [122]William S. Middleton Memorial Veterans Hospital, Madison, WI, USA. [123]Iowa City VA Health Care System, Iowa City, IA, USA. [124]Miami VA Health Care System, Miami, FL, USA. [125]VA North Texas Health Care System, Dallas, TX, USA. [126]VA Puget Sound Health Care System, Seattle, WA, USA. [127]Portland VA Medical Center, Portland, OR, USA. [128]Birmingham VA Medical Center, Birmingham, AL, USA. [129]Louisville VA Medical Center, Louisville, KY, USA. [130]Robert J. Dole VA Medical Center, Wichita, KS, USA. [131]VA Southern Nevada Healthcare System, North Las Vegas, NV, USA. [132]VA Pacific Islands Health Care System, Honolulu, HI, USA. [133]John D. Dingell VA Medical Center, Detroit, MI, USA. [134]White River Junction VA Medical Center, White River Junction, VT, USA. [135]Sioux Falls VA Health Care System, Sioux Falls, SD, USA. [136]Richmond VA Medical Center, Richmond, VA, USA. [137]Hershel "Woody" Williams VA Medical Center, Huntington, WV, USA. [138]VA San Diego Healthcare System, San Diego, CA, USA. [139]Edward Hines, Jr. VA Medical Center, Hines, IL, USA. [140]Cincinnati VA Medical Center, Cincinnati, OH, USA. [141]Ralph H. Johnson VA Medical Center, Charleston, SC, USA. [142]Bay Pines VA Healthcare System, Bay Pines, FL, USA. [143]W.G. (Bill) Hefner VA Medical Center, Salisbury, NC, USA. [144]Hampton

VA Medical Center, Hampton, VA, USA. [145]VA Northeast Ohio Healthcare System, Cleveland, OH, USA. [146]Southeast Louisiana Veterans Health Care System, New Orleans, LA, USA. [147]VA New York Harbor Healthcare System, New York, NY, USA. [148]Richard Roudebush VA Medical Center, Indianapolis, IN, USA. [149]Washington DC VA Medical Center, Washington, D. C., USA. [150]Fargo VA Health Care System, Fargo, ND, USA. [151]Charles George VA Medical Center, Asheville, NC, USA. [152]VA Maine Healthcare System Center, Augusta, ME, USA. [153]James A. Haley Veterans' Hospital, Tampa, FL, USA. [154]Central Western Massachusetts Healthcare System, Leeds, MA, USA. [155]Southern Arizona VA Health Care System, Tucson, AZ, USA. [156]James H. Quillen VA Medical Center, Mountain Home, TN, USA. [157]Northern Arizona VA Health Care System, Prescott, AZ, USA. [158]VA Long Beach Healthcare System, Long Beach, CA, USA. [159]Minneapolis VA Health Care System, Minneapolis, MN, USA. [160]West Palm Beach VA Medical Center, West Palm Beach, FL, USA. [161]VA Health Care Upstate New York, Albany, NY, USA. [162]Michael E. DeBakey VA Medical Center, Houston, TX, USA. [163]VA Greater Los Angeles Health Care System, Los Angeles, CA, USA. [164]Salem VA Medical Center, Salem, VA, USA. [165]VA Connecticut Healthcare System, West Haven, CT, USA. [166]Manchester VA Medical Center, Manchester, NH, USA. [167]VA Eastern Kansas Health Care System, Leavenworth, KS, USA. [168]St. Louis VA Health Care System, St. Louis, MO, USA. [169]VA Sierra Nevada Health Care System, Reno, NV, USA. [170]Syracuse VA Medical Center, Syracuse, NY, USA. [171]Providence VA Medical Center, Providence, RI, USA. [172]Eastern Oklahoma VA Health Care System, Muskogee, OK, USA. [173]N. FL/S. GA Veterans Health System, Gainesville, FL, USA. [174]VA Pittsburgh Health Care System, Pittsburgh, PA, USA. [175]Overton Brooks VA Medical Center, Shreveport, LA, USA. [176]Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA, USA. [177]Clement J. Zablocki VA Medical Center, Milwaukee, WI, USA. [178]San Francisco VA Health Care System, San Francisco, CA, USA. [179]Atlanta VA Medical Center, Decatur, GA, USA. [180]VA Western New York Healthcare System, Buffalo, NY, USA. [181]Northport VA Medical Center, Northport, NY, USA. [182]VA Northern California Health Care System, Mather, CA, USA.

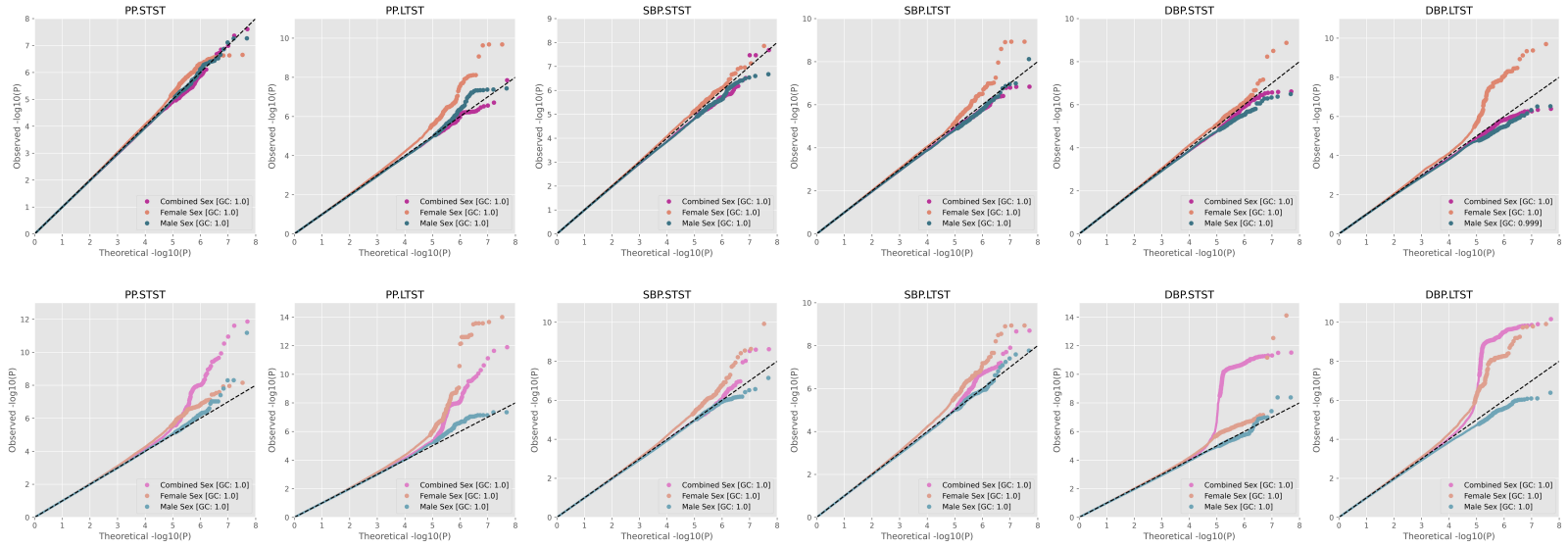
Supplementary Fig S1. Quantile-Quantile (QQ) Plots

Note: Both lifestyle exposures (E) Long Total Sleep Time (LTST) and Short Total Sleep Time (STST) are depicted. All 3 Blood Pressure (BP) outcome traits are plotted – Systolic (SBP), Diastolic (DBP), and Pulse Pressure (PP). All population-group specific results - African (AFR), East Asian (EAS), European (EUR), Hispanic/Latino (HIS), and South Asian (SAS) - are denoted along with cross population meta-analysis (CPMA). The top row of plots in each figure A-F depicts 1 degree of freedom Interaction Test results, while the bottom row depicts 2 degree of freedom Joint Test results.

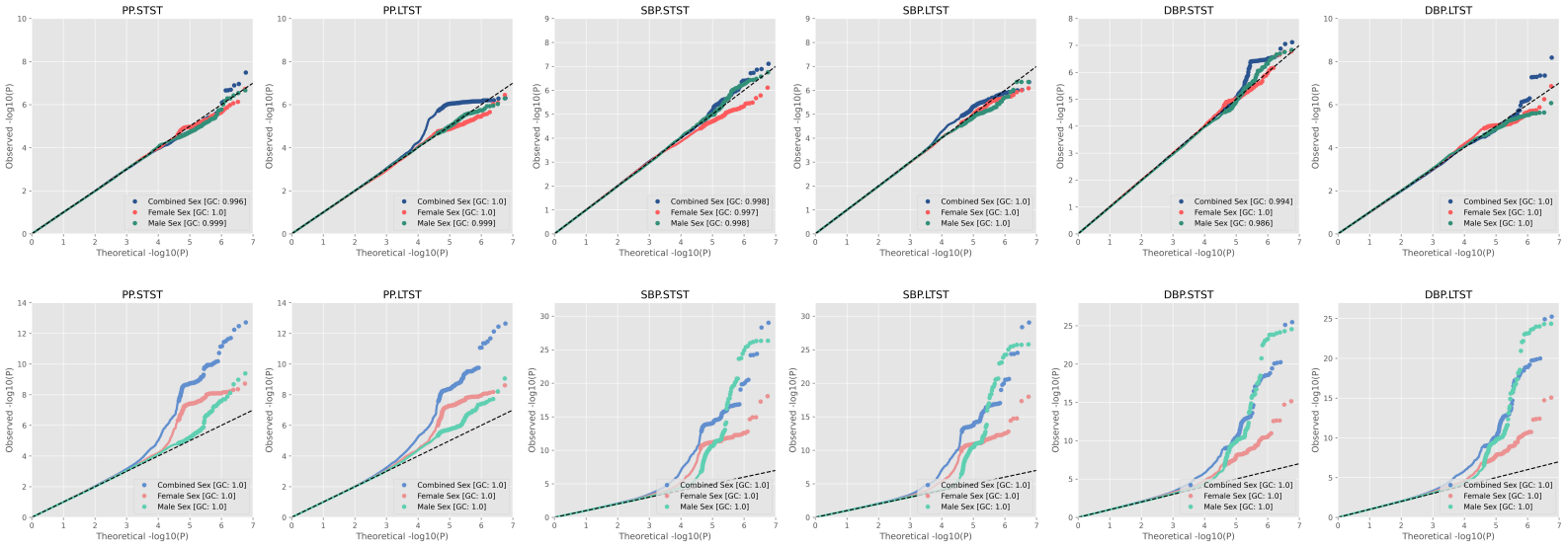
A. Cross Population Meta-Analysis



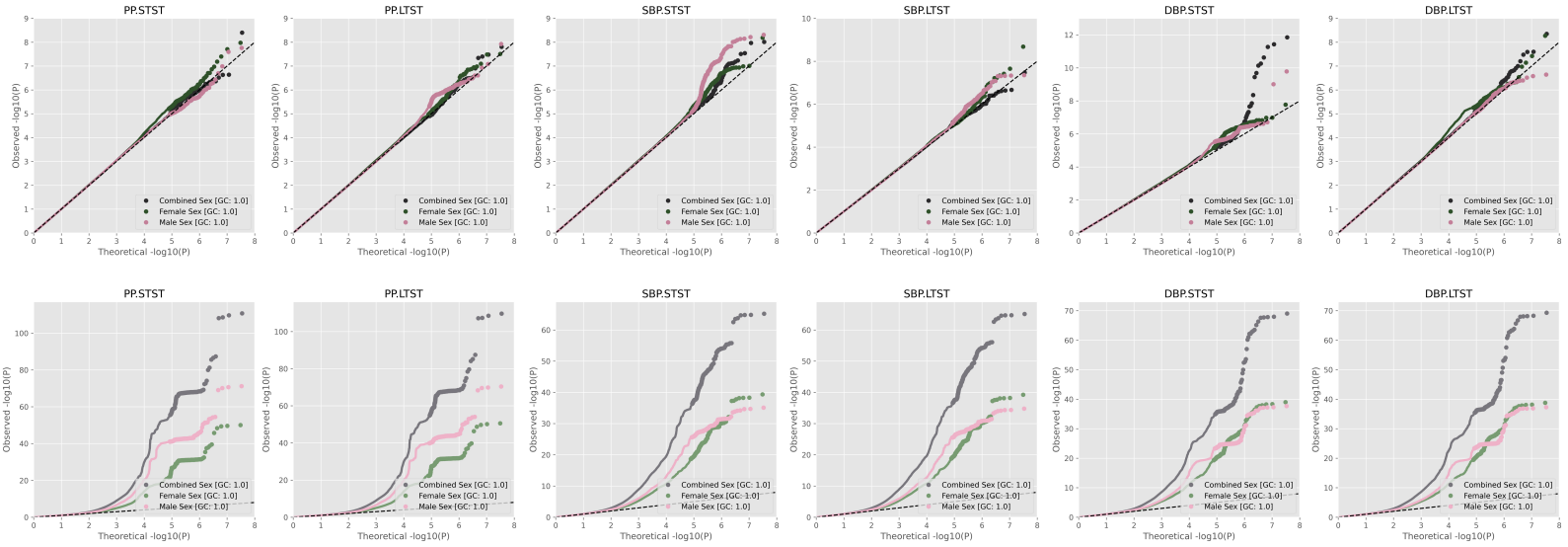
B. AFR-Specific Meta-Analysis



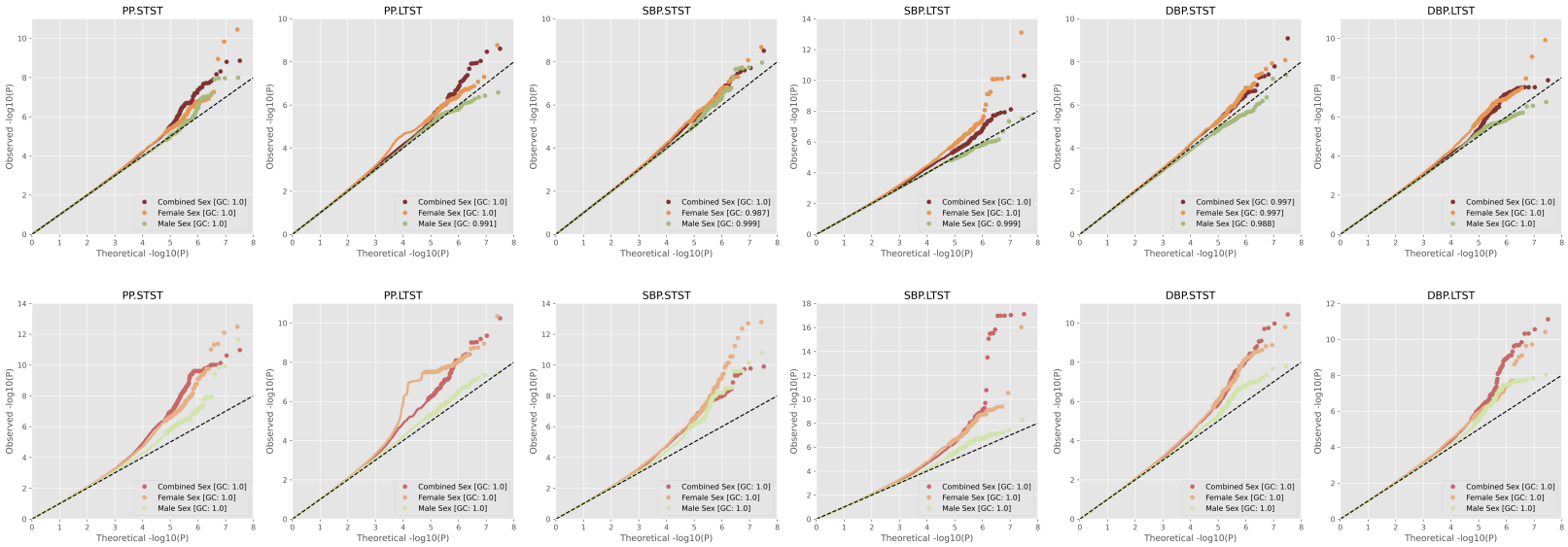
C. EAS-Specific Meta-Analysis



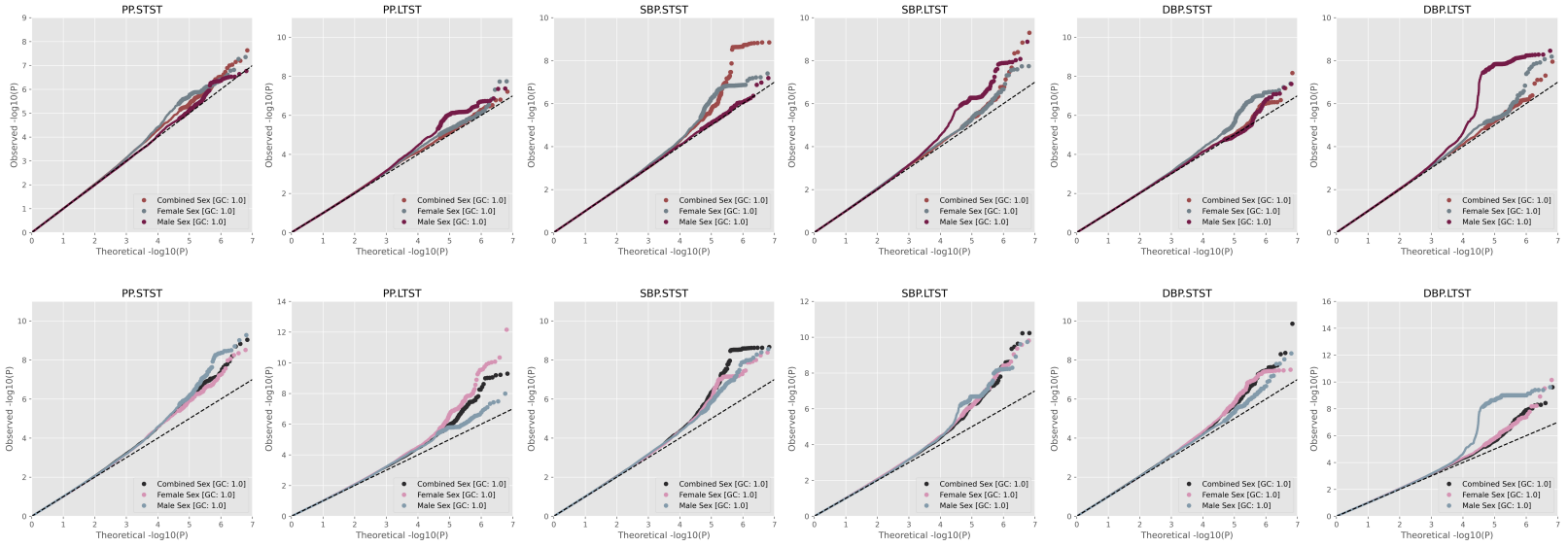
D. EUR-Specific Meta-Analysis



E. HIS-Specific Meta-Analysis



F. SAS-Specific Meta-Analysis



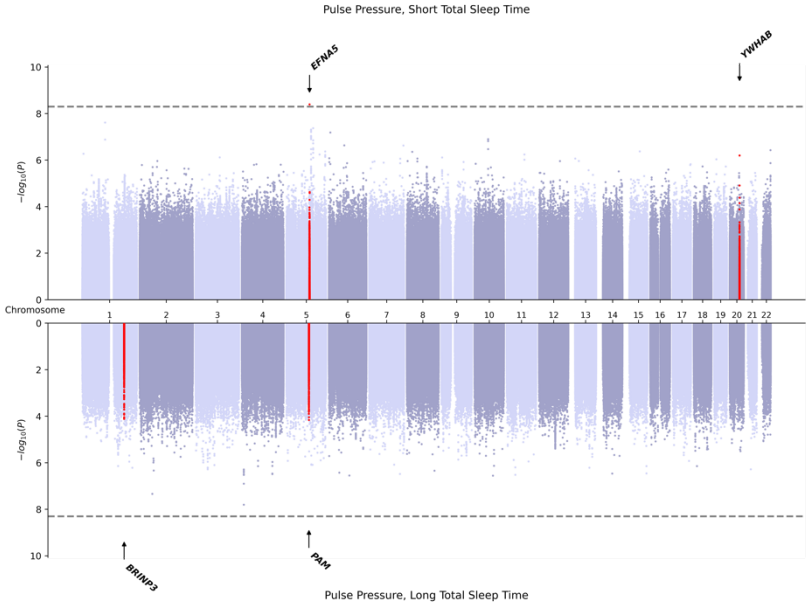
Supplementary Figure S2. Miami Plots

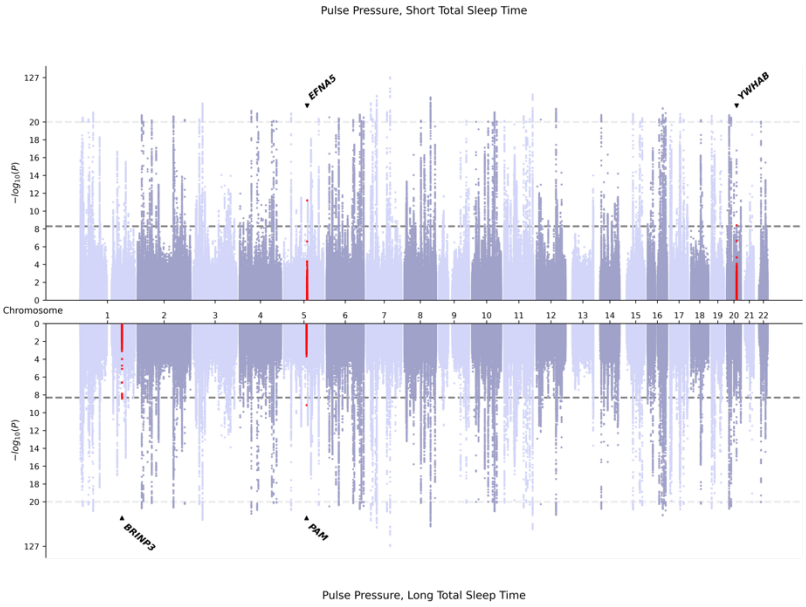
Note: Both lifestyle exposures (E) Long Total Sleep Time (LTST) and Short Total Sleep Time (STST) are depicted for each blood pressure trait specified below as the outcome variable. All population-group specific results are denoted - African (AFR), East Asian (EAS), European (EUR), Hispanic/Latino (HIS), and South Asian (SAS), along with cross population meta-analysis (CPMA). The top plot in each Miami plot depicts the STST interaction p-values with the bottom plot in each Miami Plot depicting the LTST interaction p-values. The left plot of each figure shows 1 degree of freedom GxE interaction effect p-values, with on the right, 2 degree of freedom joint effect p-values. For joint P-values, y-axis has a breakpoint at –log10(P)=20 to enable view, signified by the light grey dashed line. For all plots, genome-wide significance y=-log10(5e-09) is plotted as a dashed line in dark grey. Red loci signify top loci prioritized - those identified to be driven by the interaction effect, with orange loci signifying those supported by, but not driven by the interaction effect.

Regarding SNPs that passed the genome-wide threshold but did not end up being top prioritized loci, our Methods section details prioritization criteria and quality control criteria for independent top loci marked for prioritization. Briefly, all novel top loci required a SNP-specific sample size of N>20000 with respective thresholding criteria. For novel interaction loci prioritized by the 1df interaction test this was: p<5e-09, FDR<0.05. For novel interaction loci prioritized by the 2df joint test to be driven by the interaction effect this was: non-overlap with past GWAS BP loci (+/- 100 Mb distance), significant joint effect (p<5e-09, FDR<0.05), stronger interaction effect signal relative to the main genetic effect ($p_{M1\_GxE} < p_{M1\_G}$), and nonsignificant marginal effect (p_{M2_G}>5e-09, FDR>0.05). For secondary loci noted by the 2df joint test to be supported but not driven by the interaction effect this was: non-overlap with past GWAS BP loci (+/- 100 Mb distance), significant joint effect (p<5e-09, FDR<0.05), weaker interaction effect signal relative to the main genetic effect ($p_{M1\_GxE} > p_{M1\_G}$), and nonsignificant marginal effect (p_{M2_G}>5e-09, FDR>0.05). Variants were filtered to independent genomic loci (across 500 kb regions) using LD reference panels, with missing variants not found in panels to be reported if the variant was found to be the top most significant in a respective 500kb region in combined sex analyses.

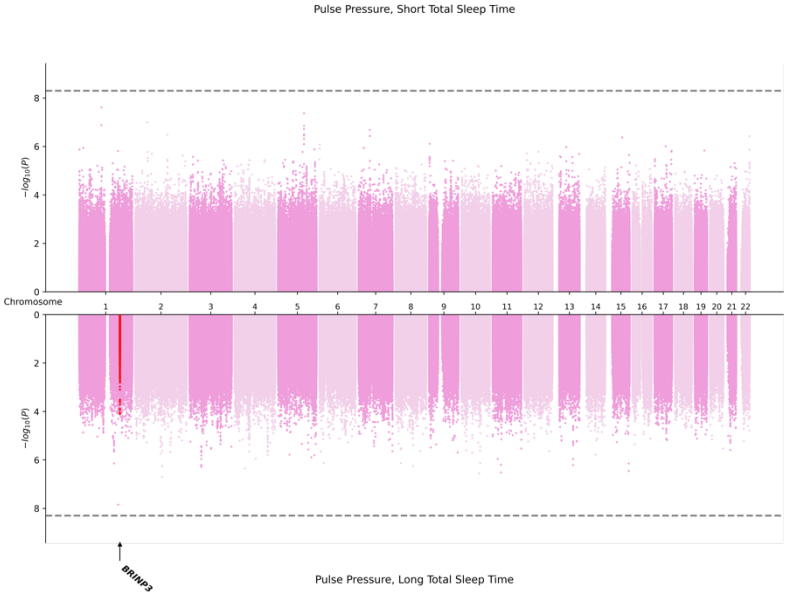
A. Miami Plots for Pulse Pressure in Combined Sex

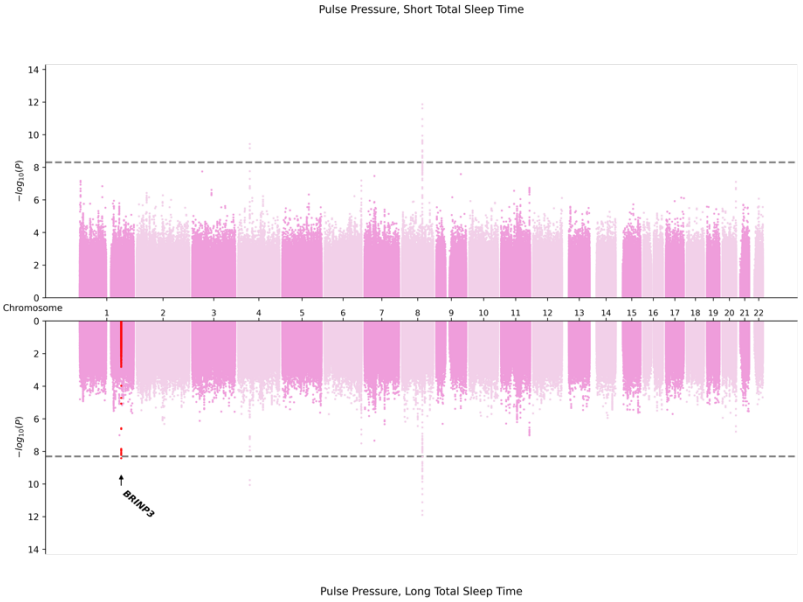
1. Cross Population Meta-Analysis



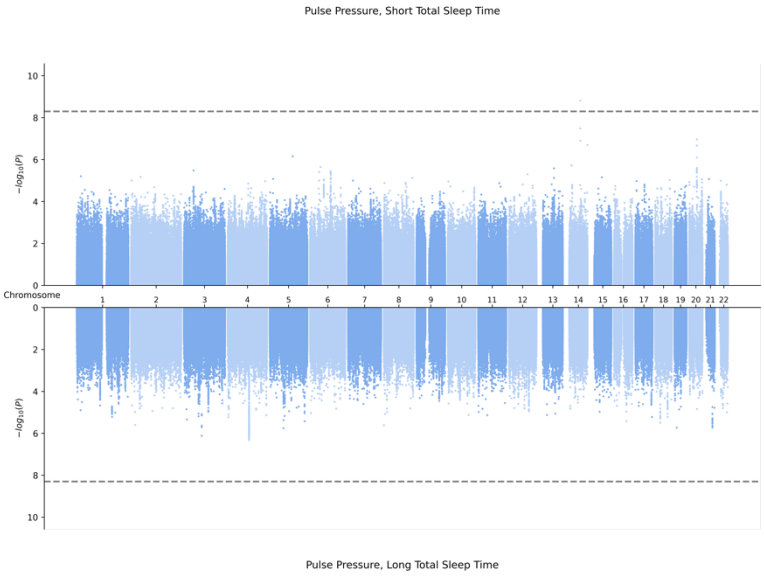


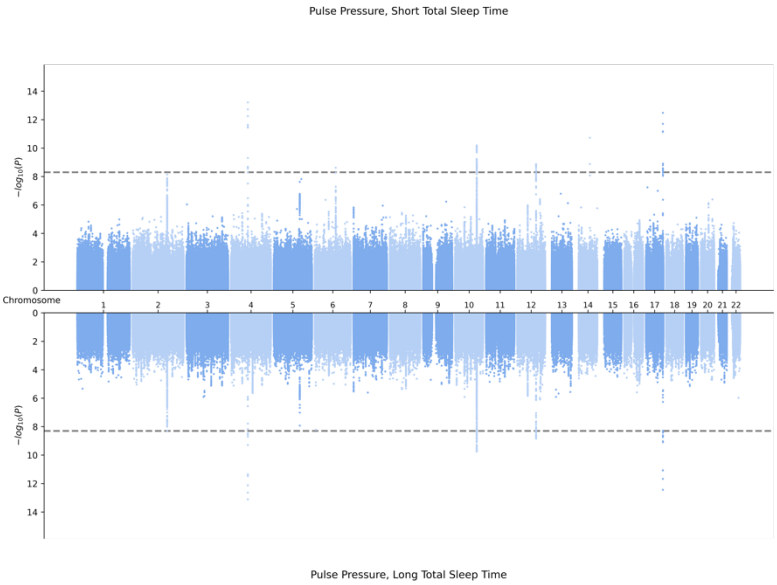
2. AFR-Specific Meta-Analysis



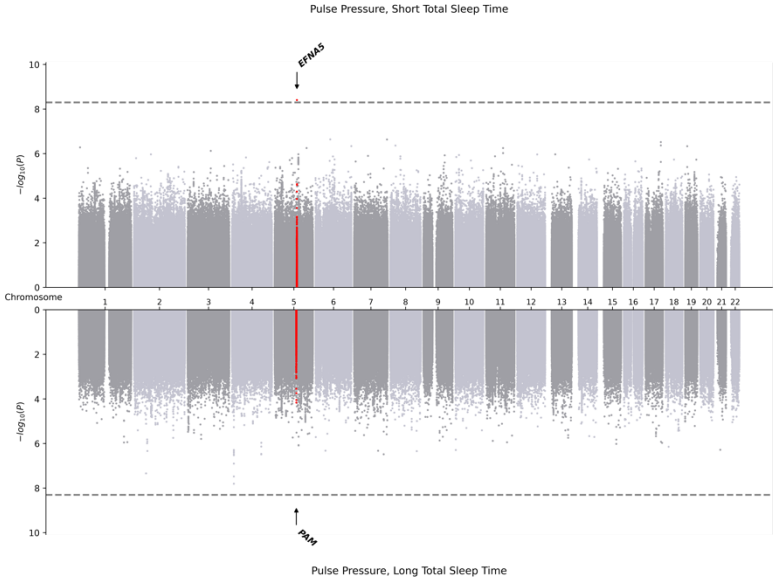


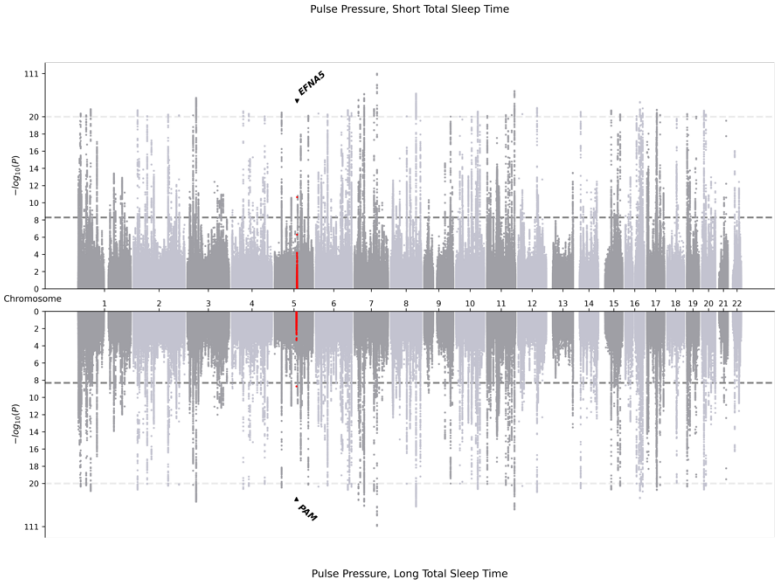
3. EAS-Specific Meta-Analysis



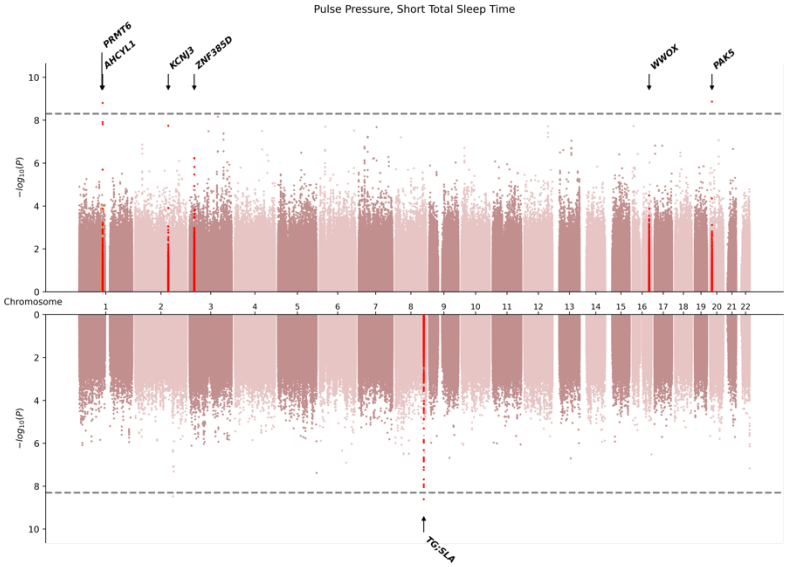


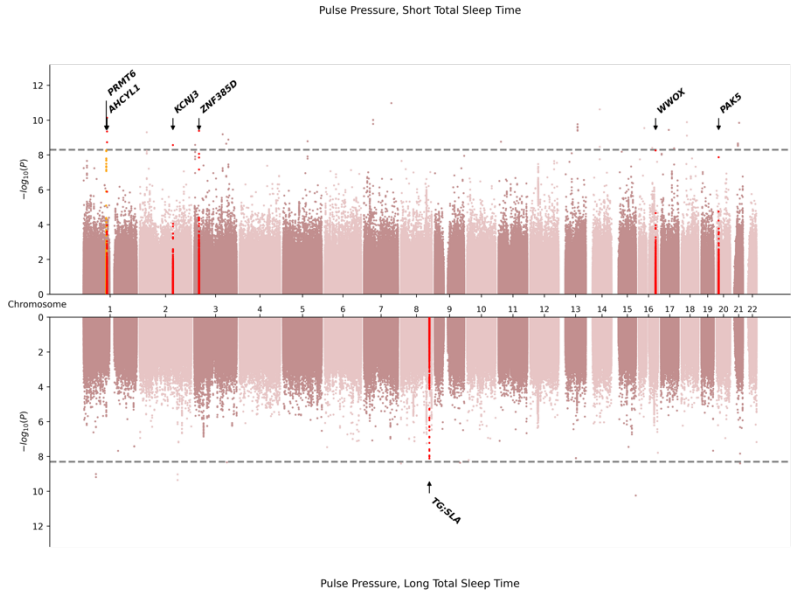
4. EUR-Specific Meta-Analysis



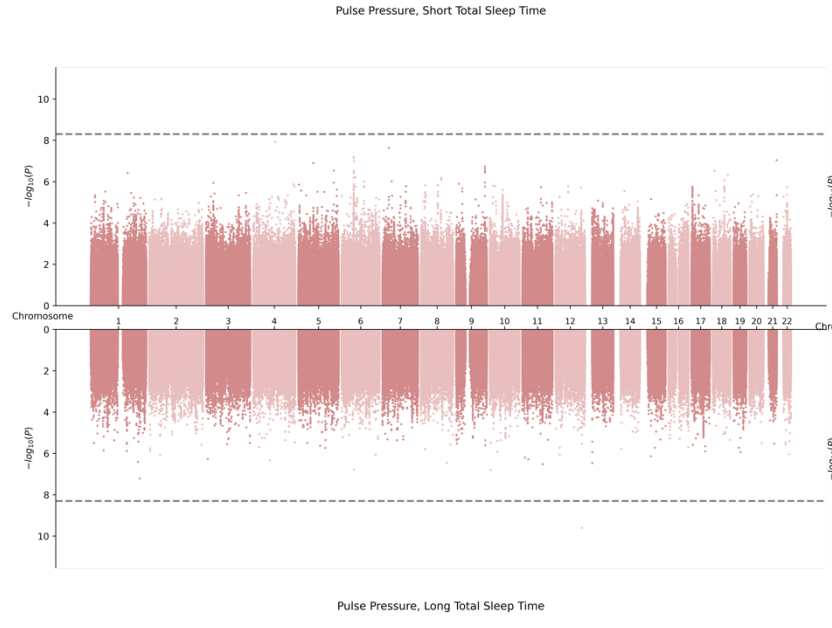


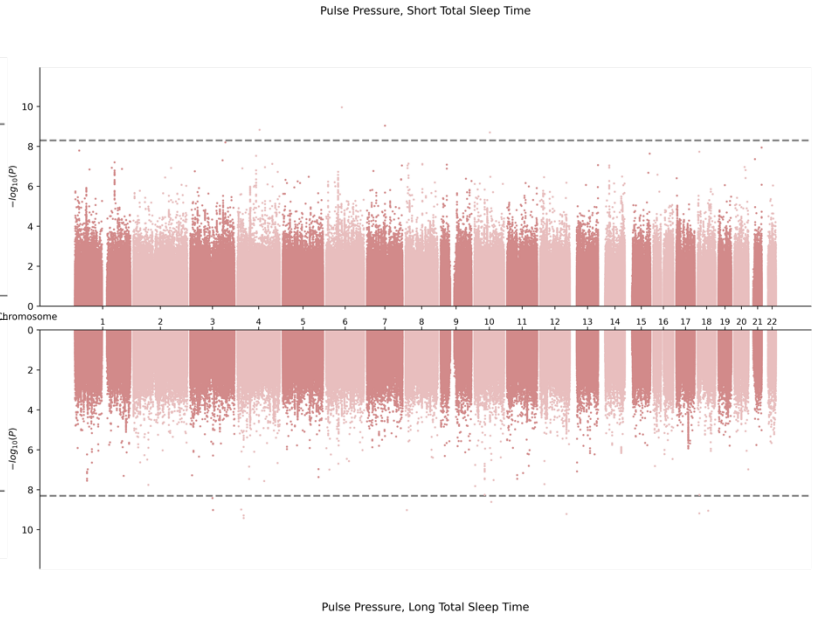
5. HIS-Specific Meta-Analysis





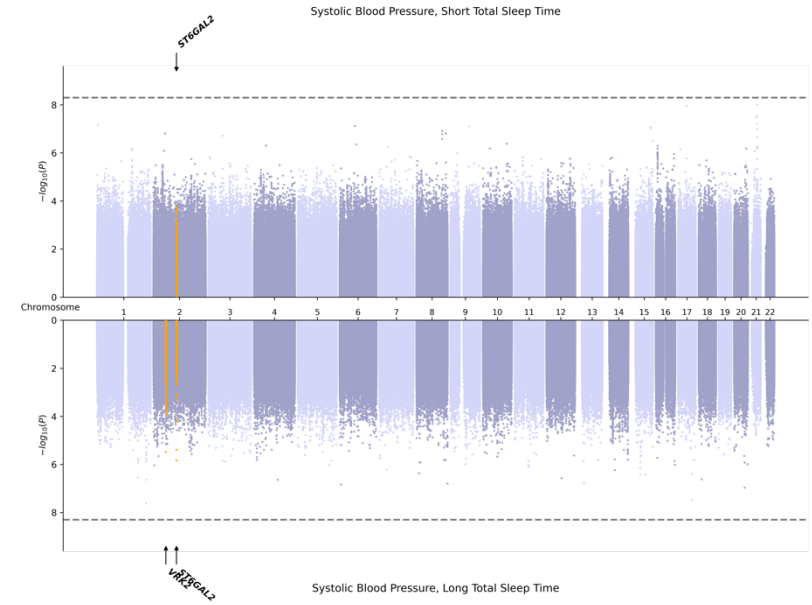
6. SAS-Specific Meta-Analysis

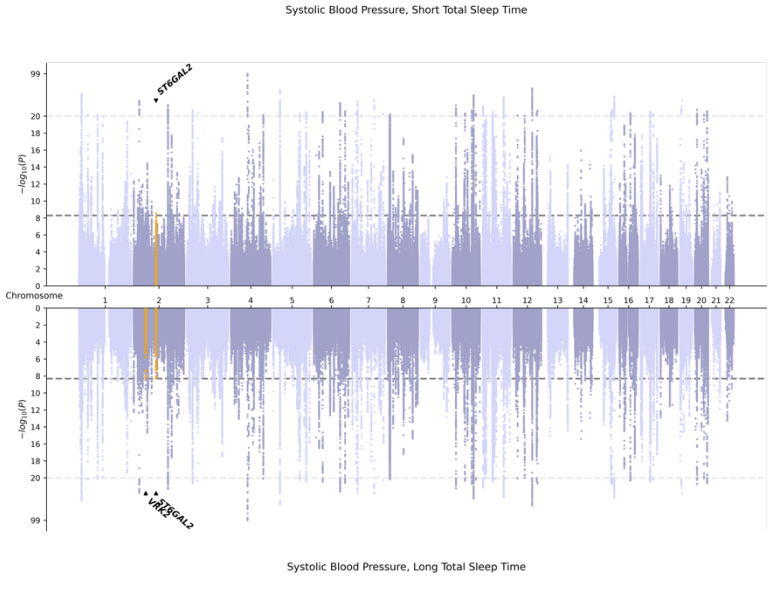




B. Miami Plots for Systolic Blood Pressure in Combined Sex

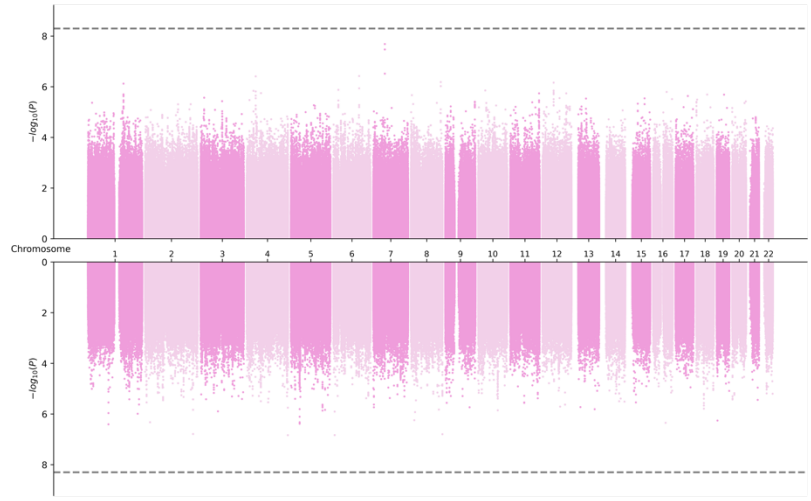
1. Cross Population Meta-Analysis



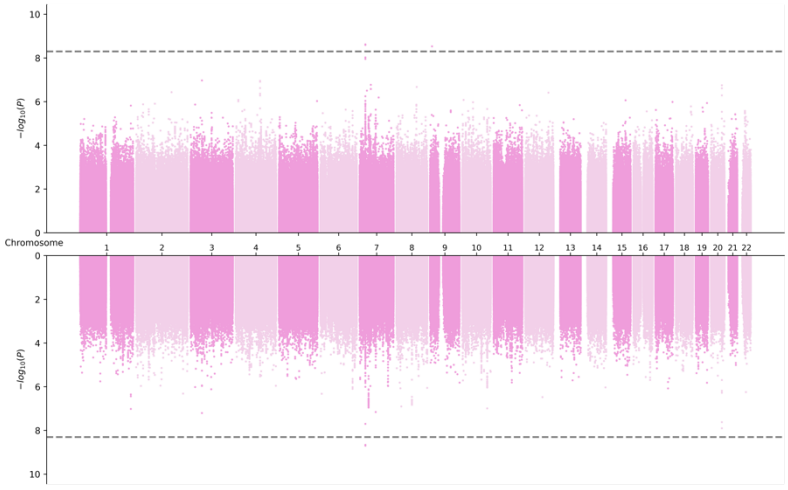


2. AFR-Specific Meta-Analysis

Systolic Blood Pressure, Short Total Sleep Time

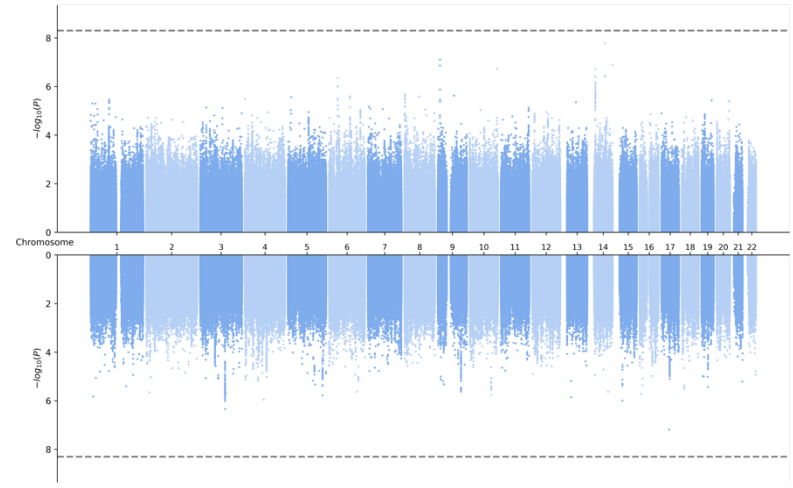


Systolic Blood Pressure, Long Total Sleep Time

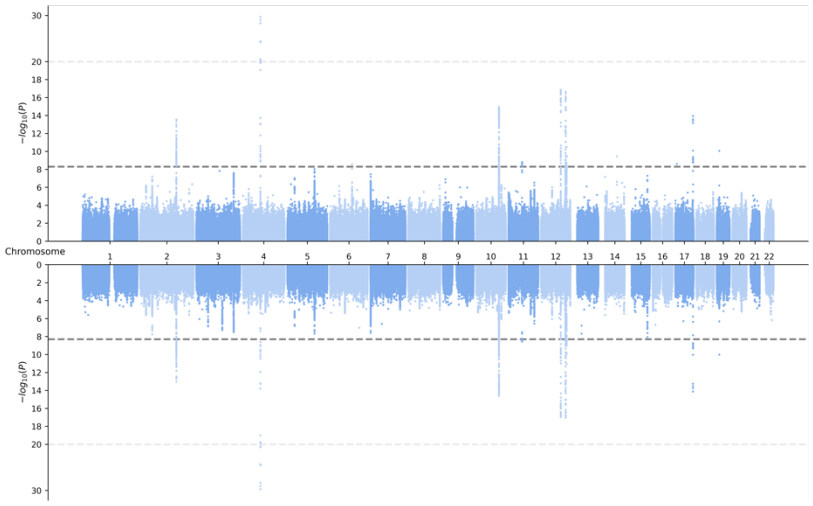


3. EAS-Specific Meta-Analysis

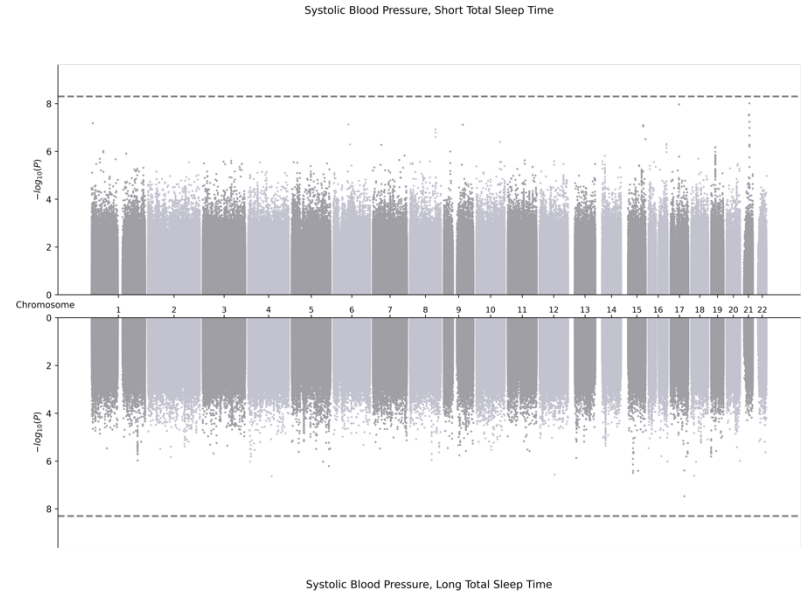
Systolic Pressure, Short Total Sleep Time

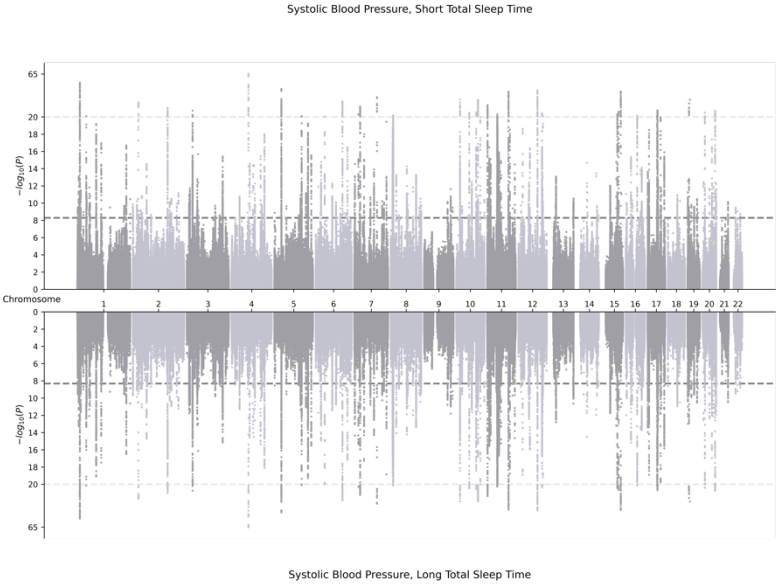


Systolic Pressure, Long Total Sleep Time

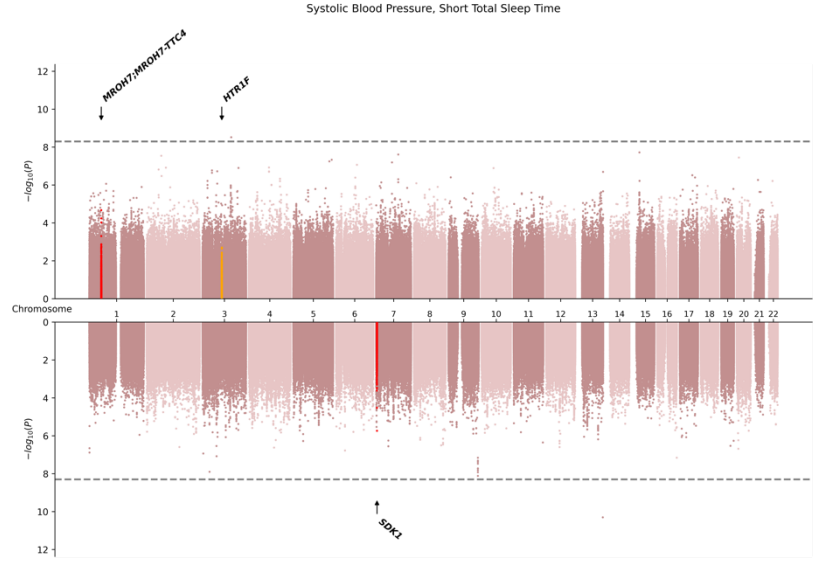


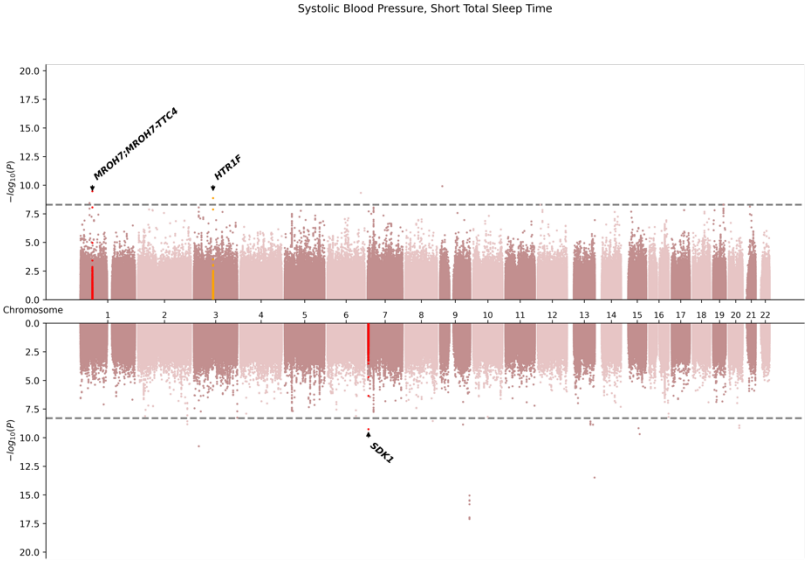
4. EUR-Specific Meta-Analysis



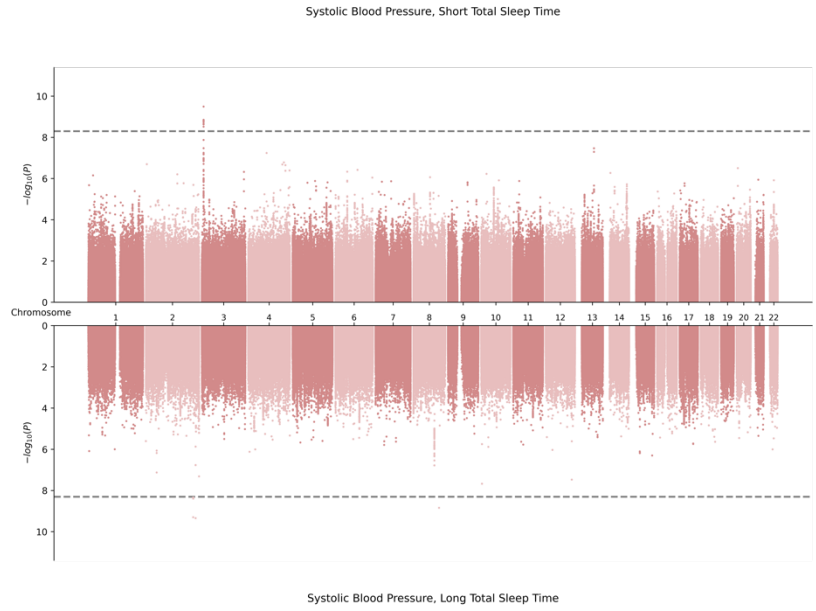


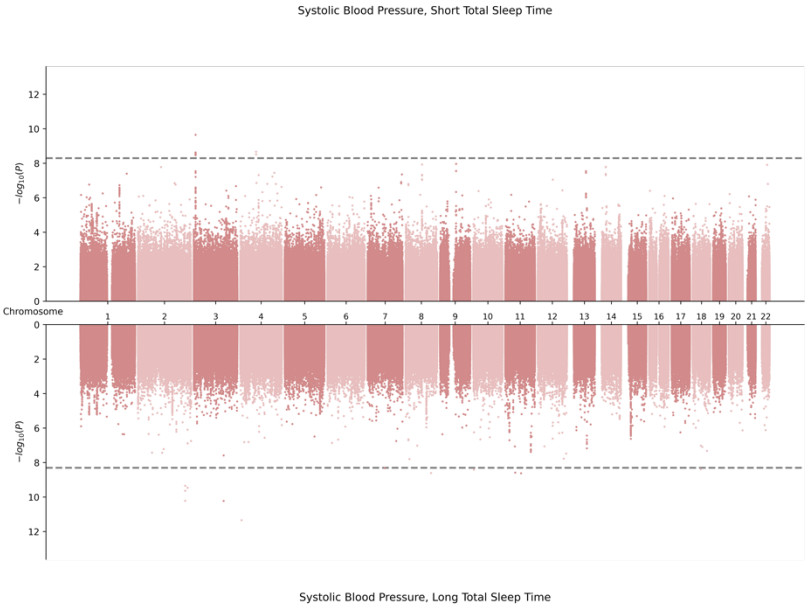
5. HIS-Specific Meta-Analysis





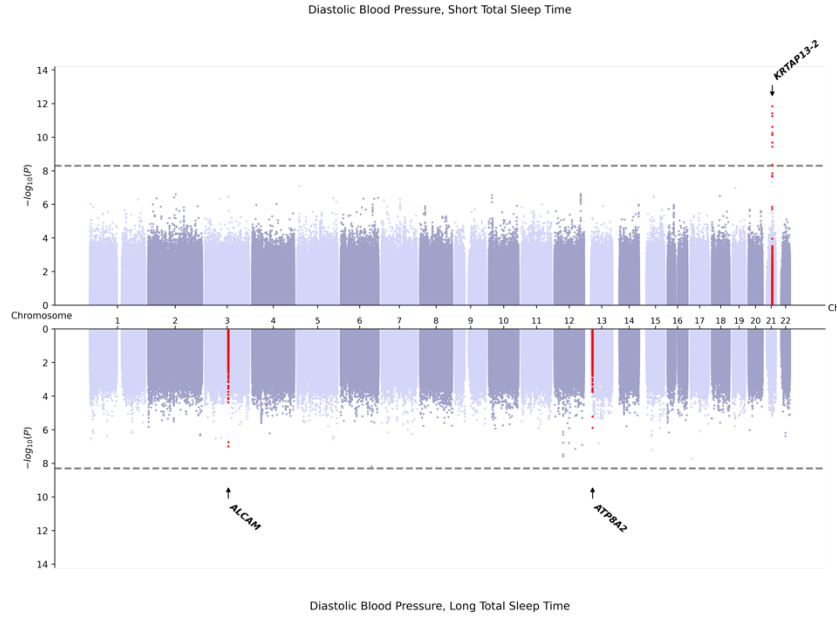
6. SAS-Specific Meta-Analysis

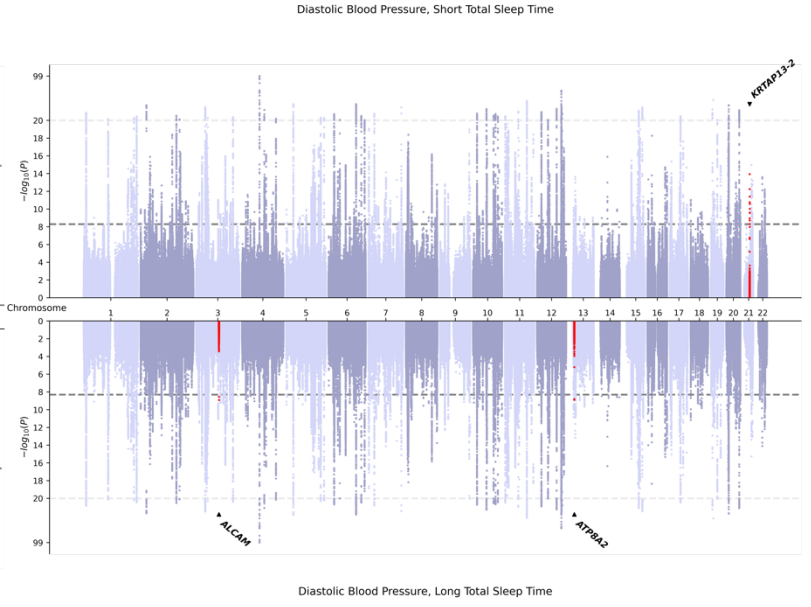




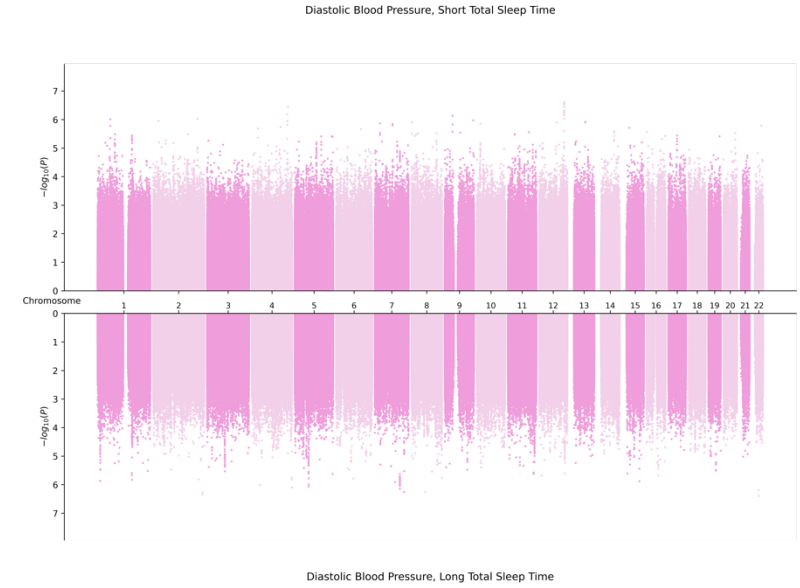
C. Miami Plots for Diastolic Pressure in Combined Sex

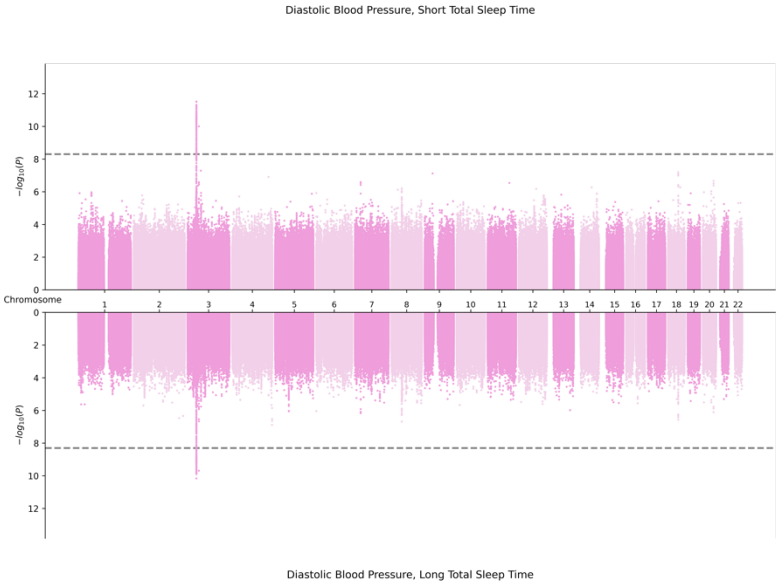
1. Cross Population Meta-Analysis



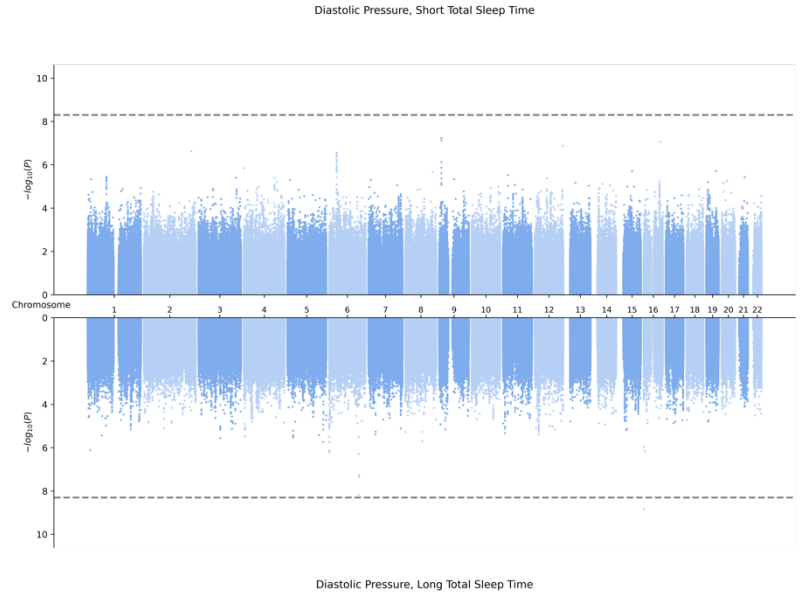


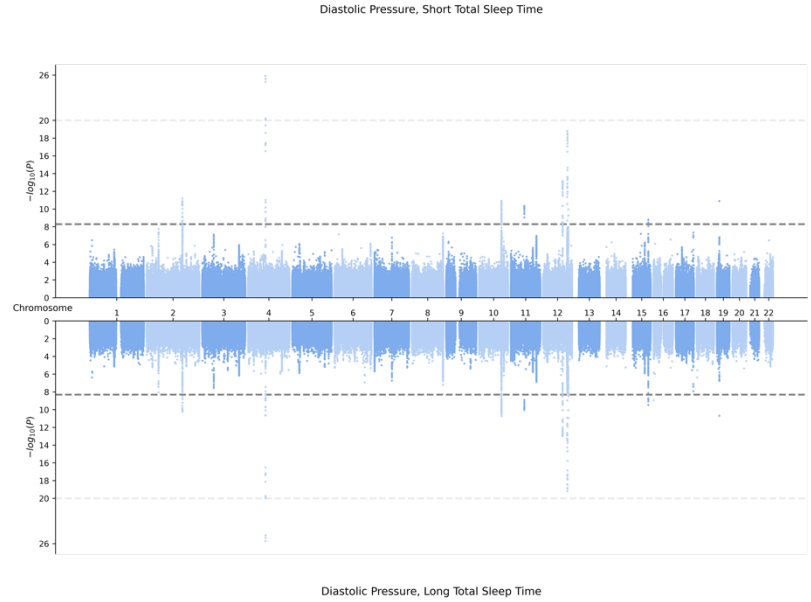
2. AFR-Specific Meta-Analysis



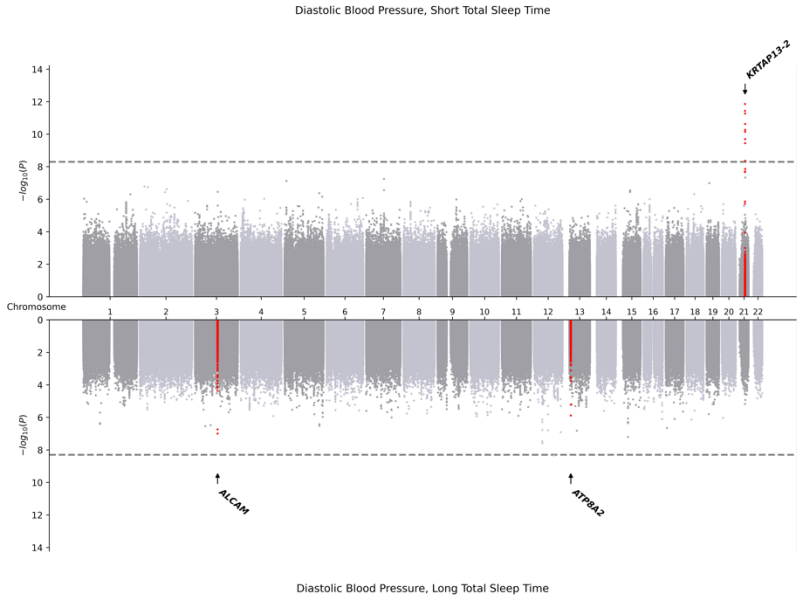


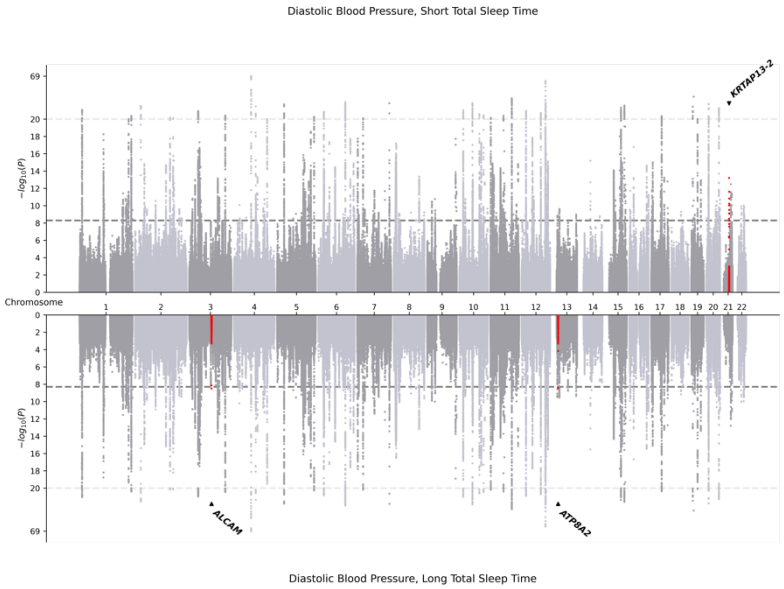
3. EAS-Specific Meta-Analysis



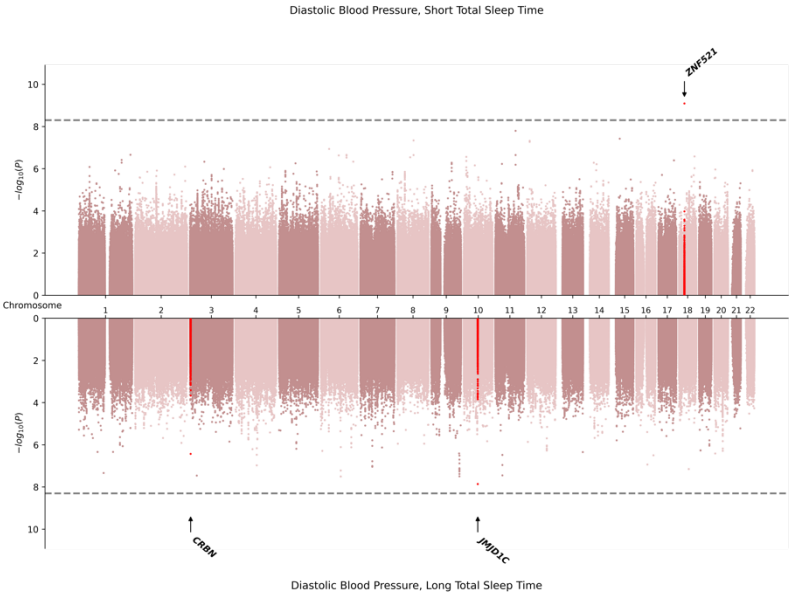


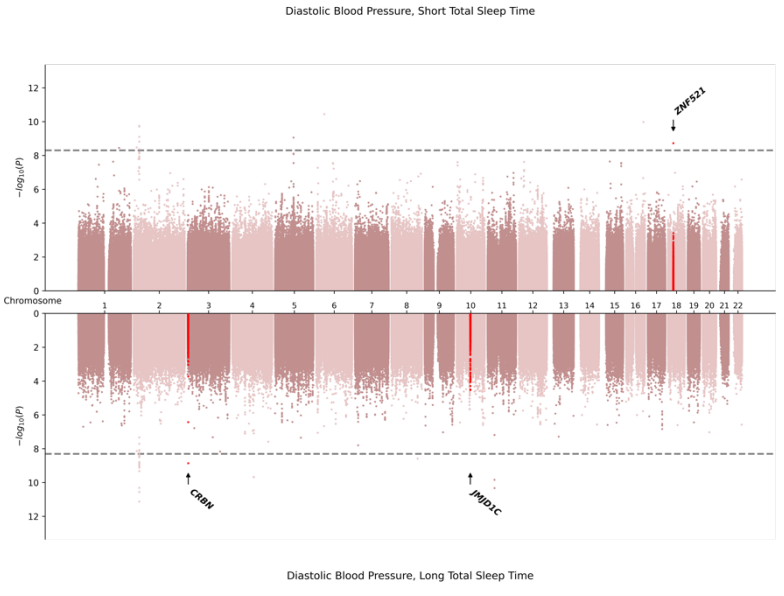
4. EUR-Specific Meta-Analysis



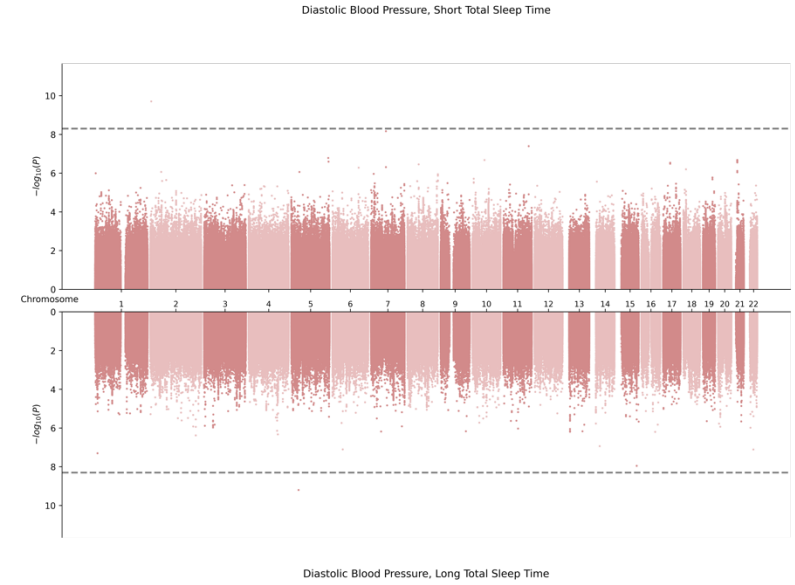


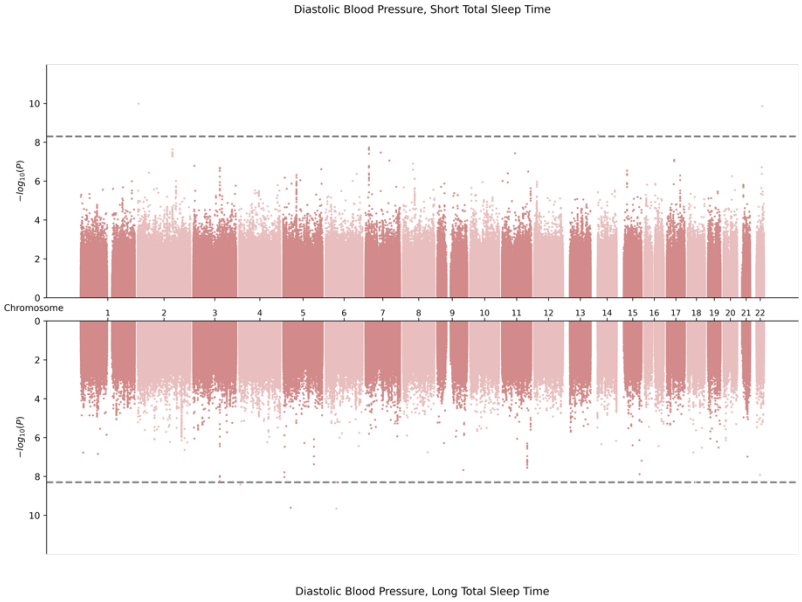
5. HIS-Specific Meta-Analysis





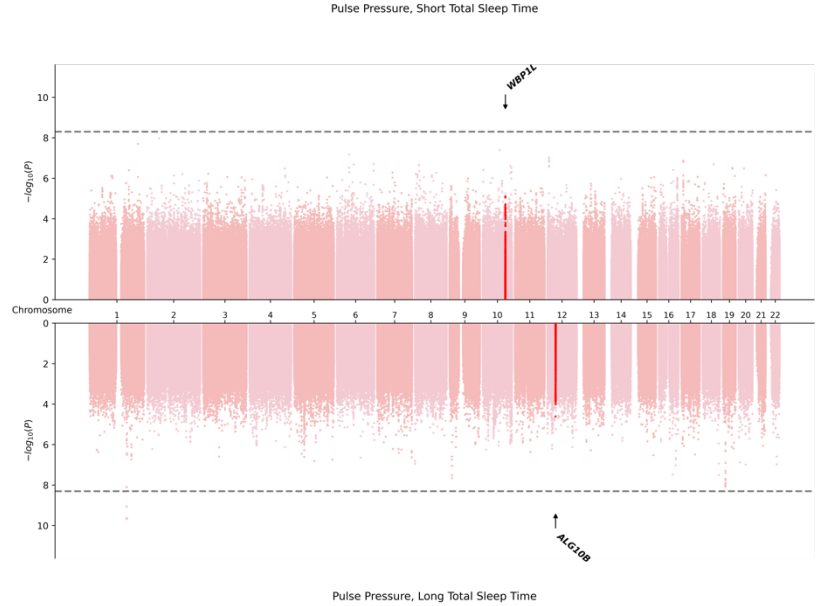
6. SAS-Specific Meta-Analysis

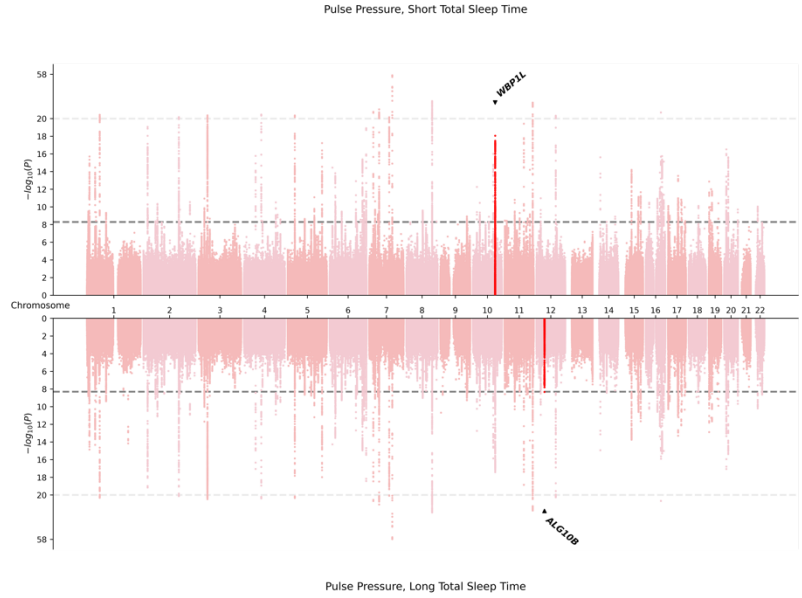




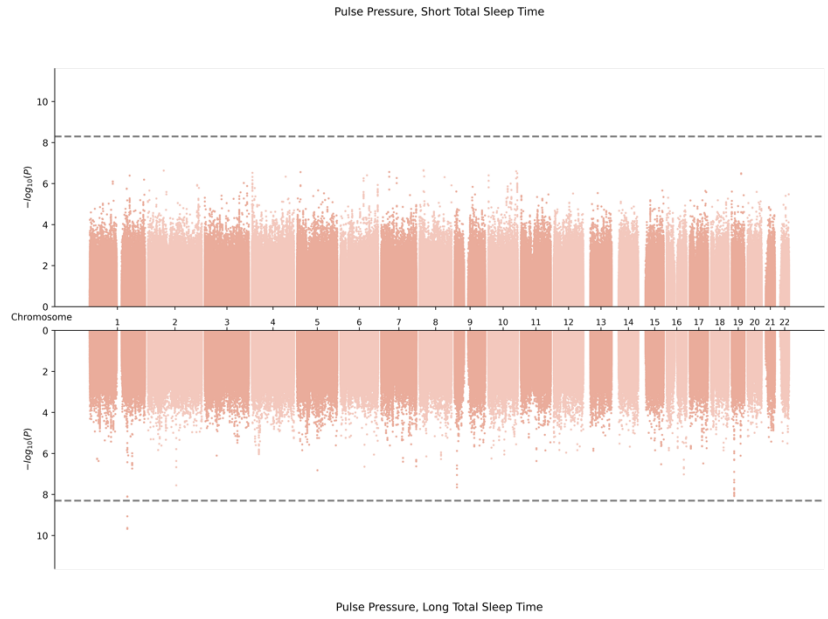
D. Miami Plots for Pulse Pressure in Female Sex

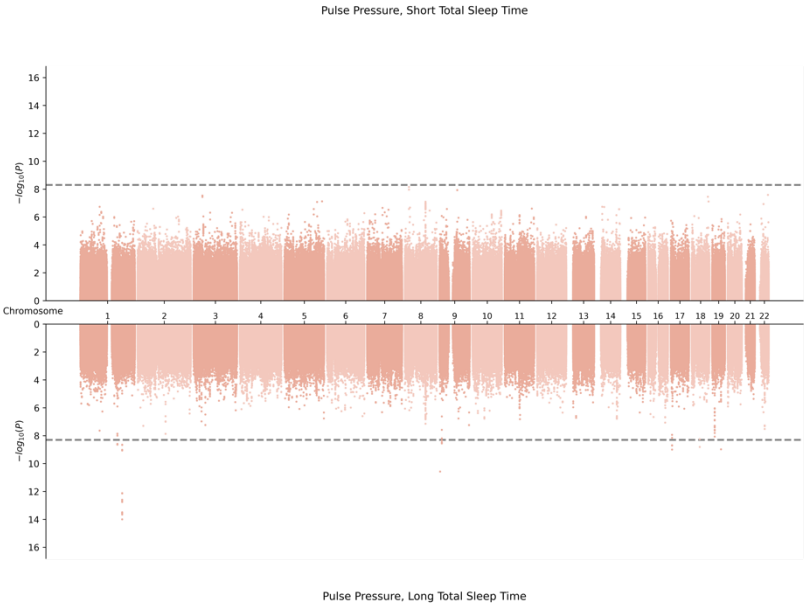
1. Cross Population-Meta Analysis



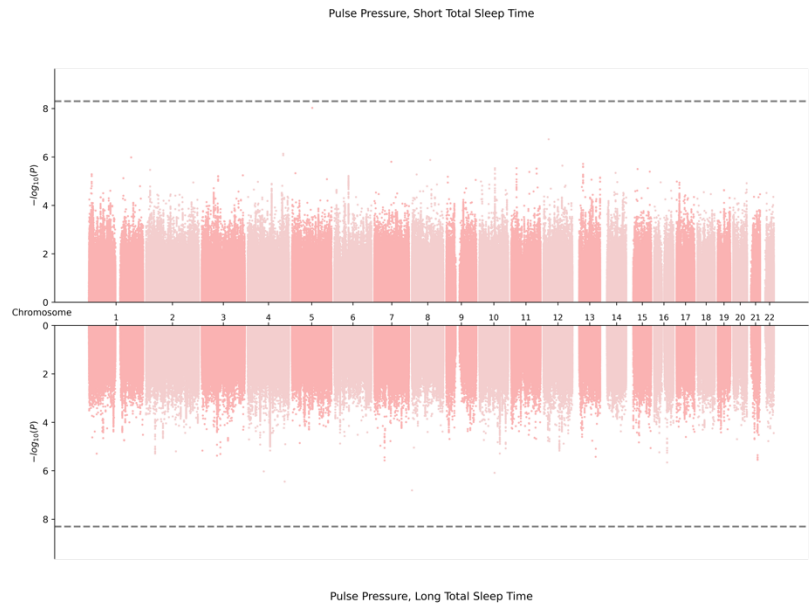


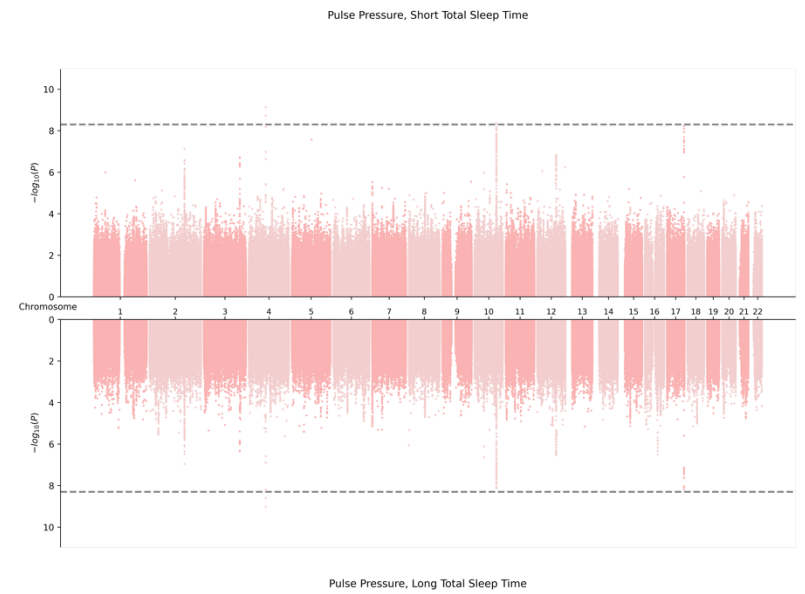
2. AFR-Specific Meta-Analysis



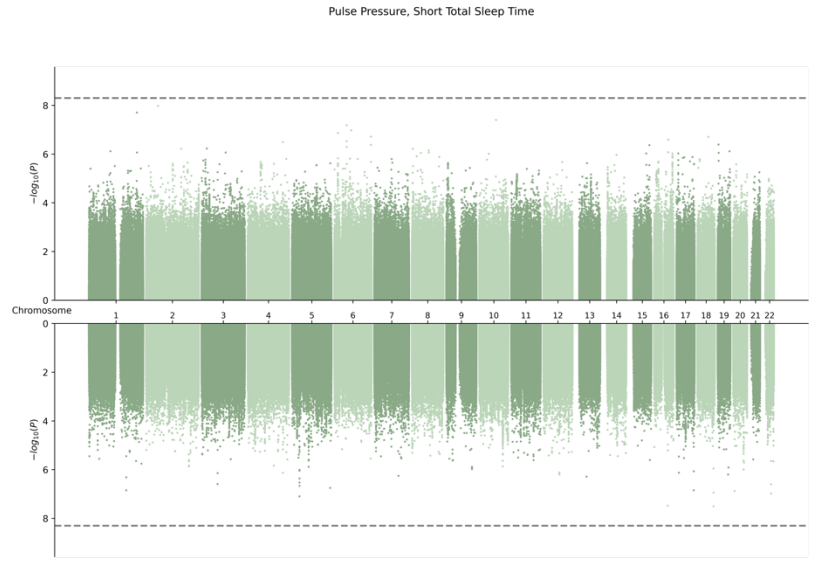


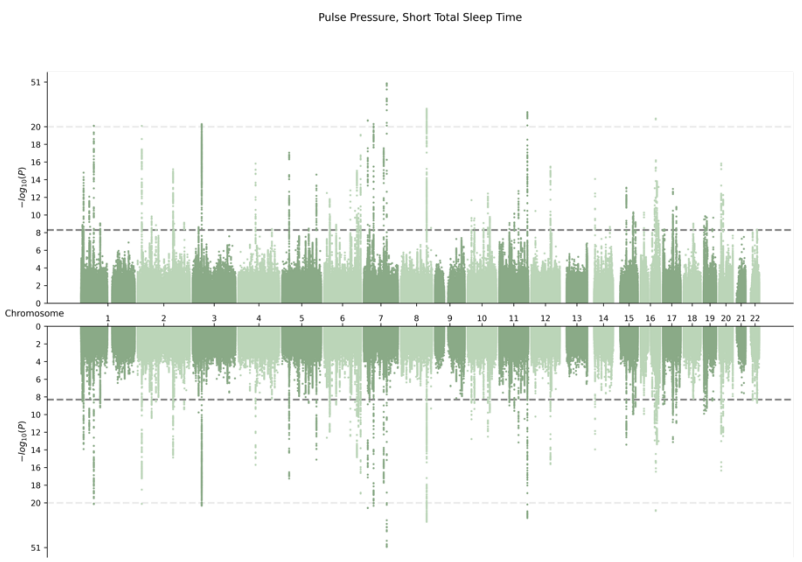
3. EAS-Specific Meta-Analysis



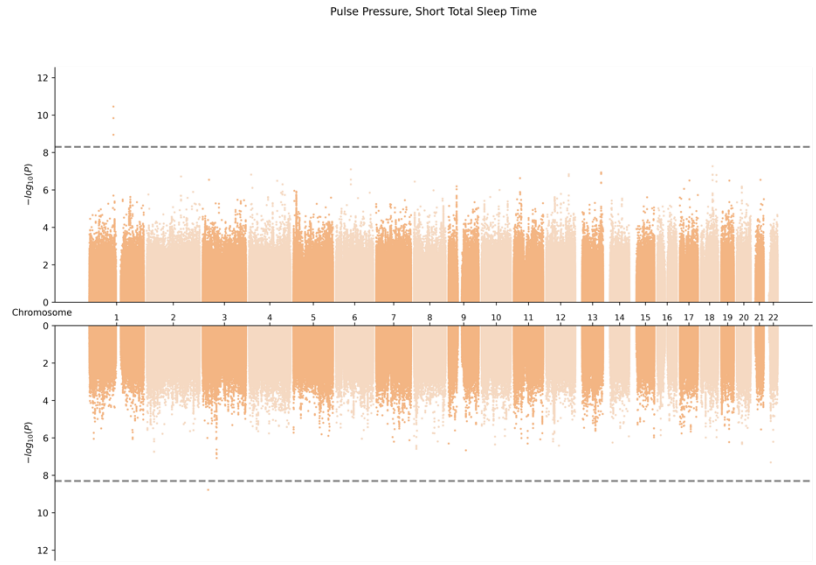


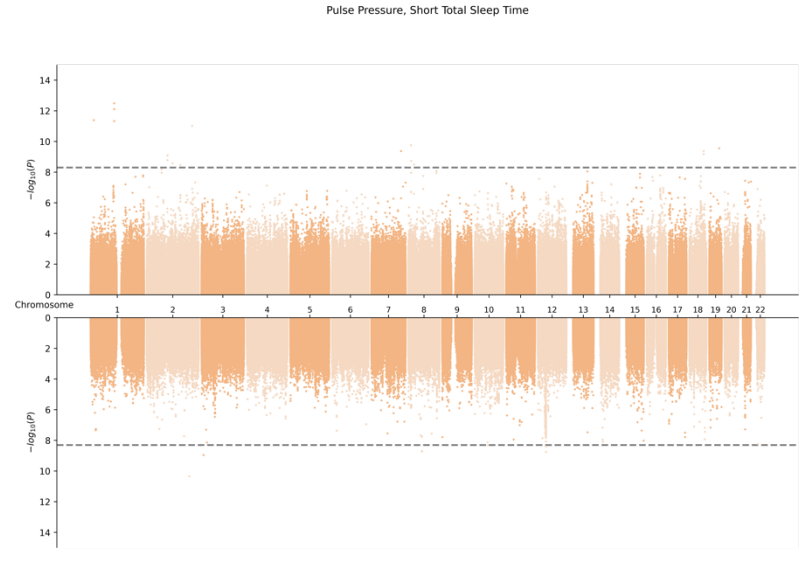
4. EUR-Specific Meta-Analysis



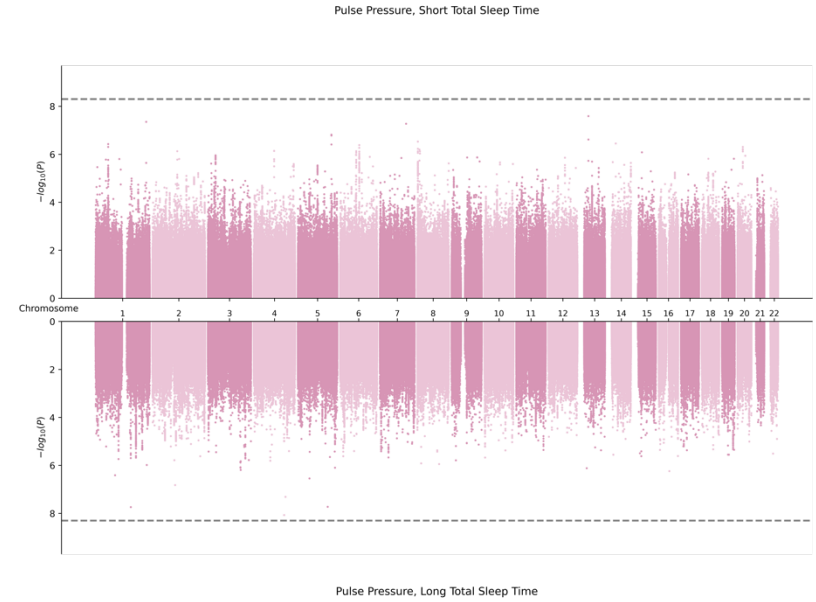


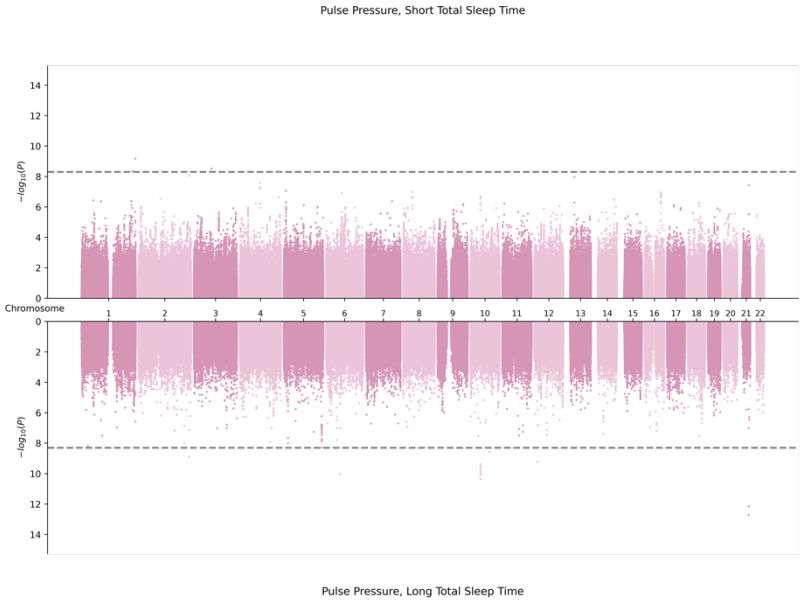
5. HIS-Specific Meta-Analysis





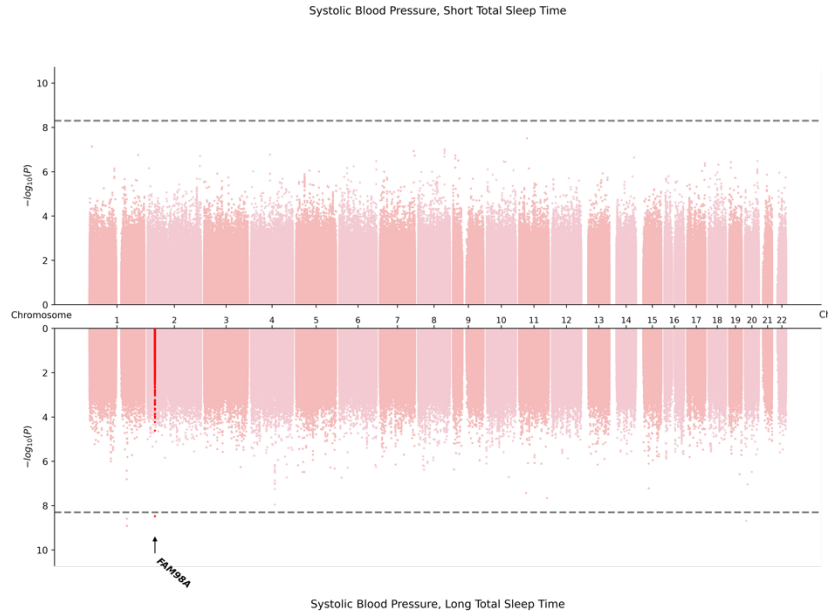
6. SAS-Specific Meta-Analysis

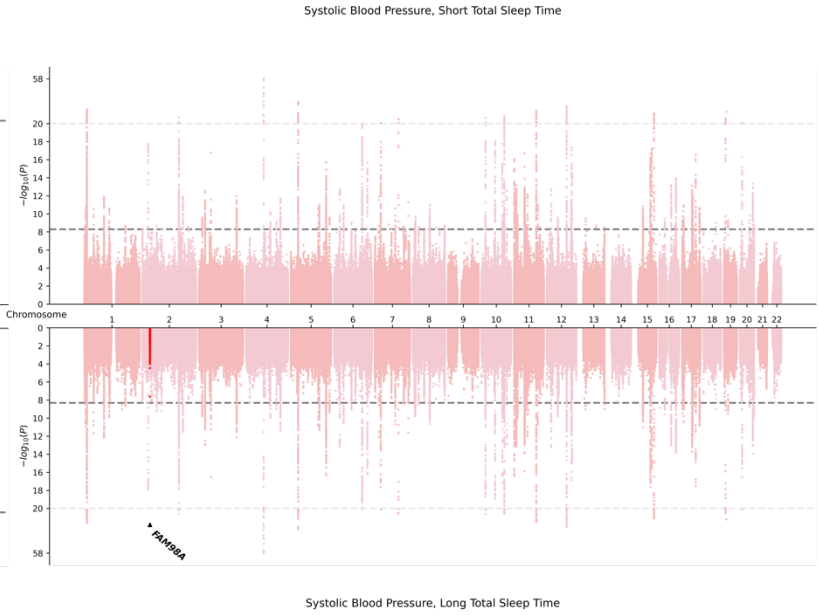




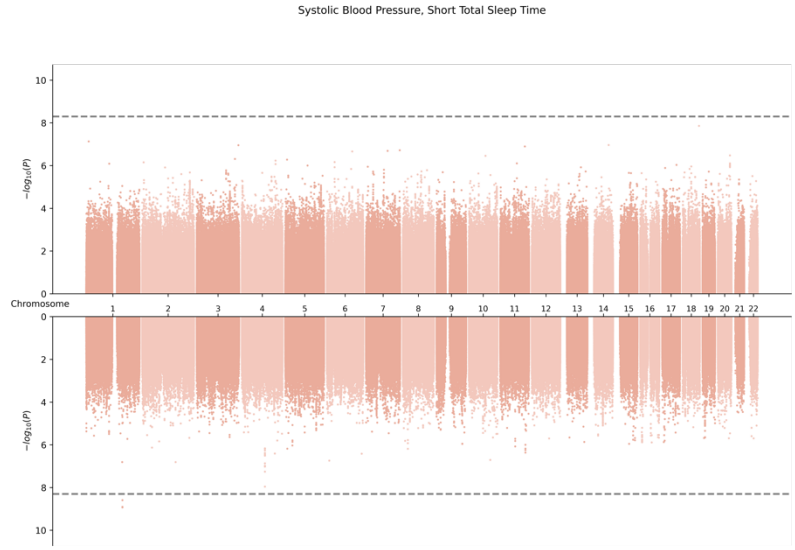
E. Miami Plots for Systolic Blood Pressure in Female Sex

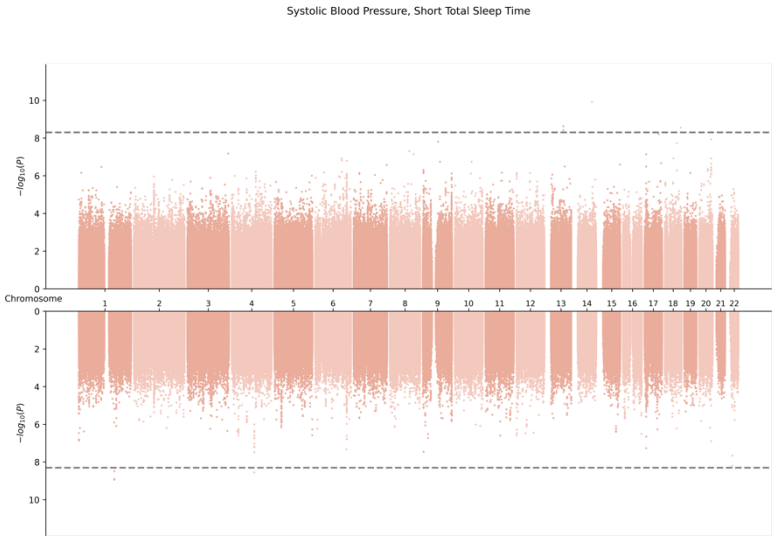
1. Cross Population Meta-Analysis



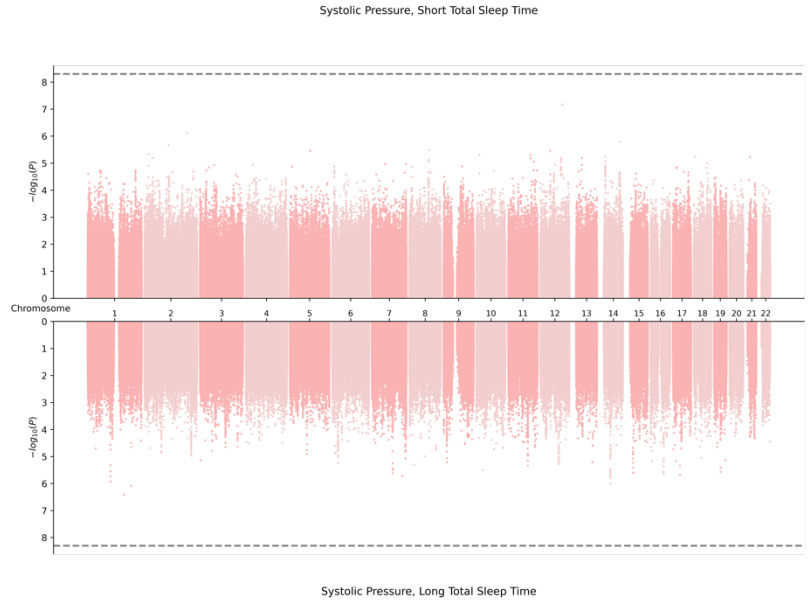


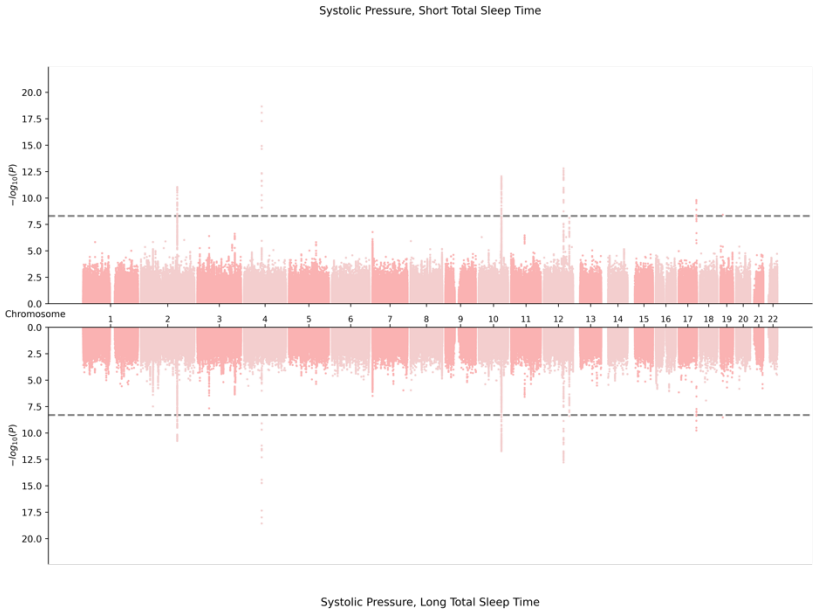
2. AFR-Specific Meta-Analysis



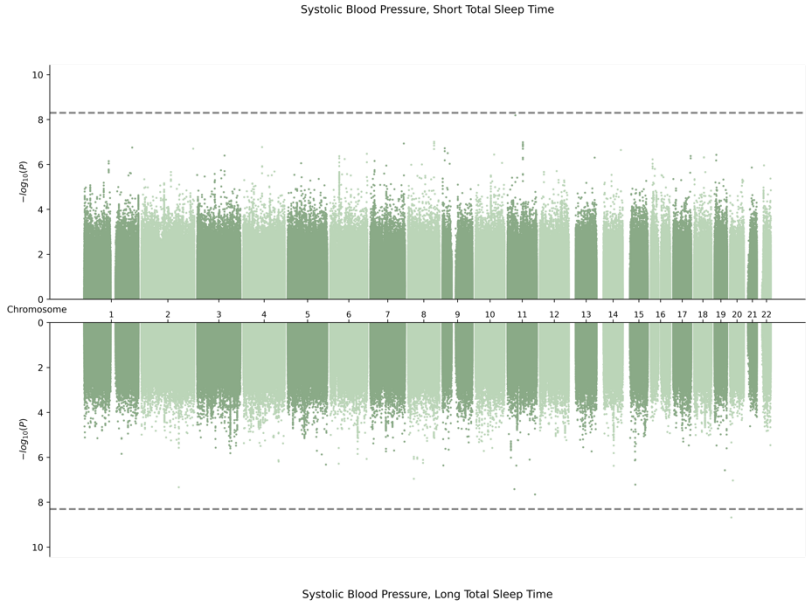


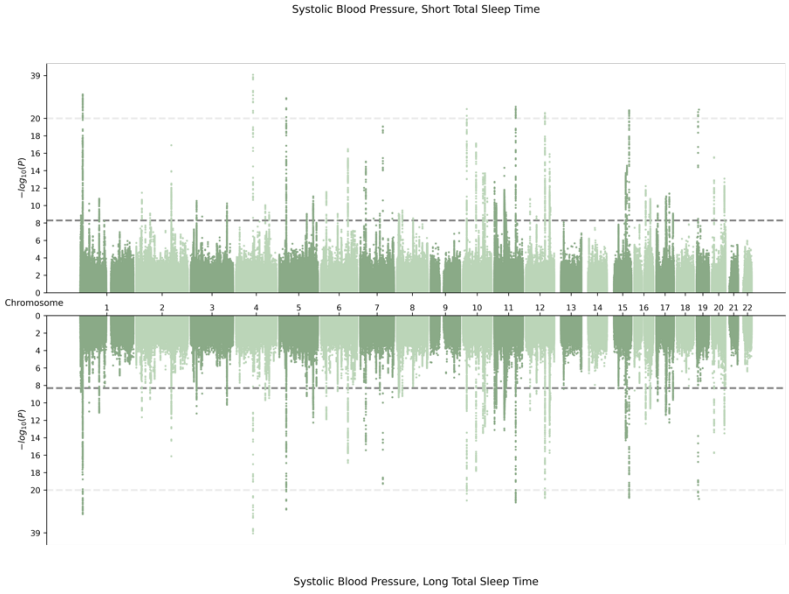
3. EAS-Specific Meta-Analysis



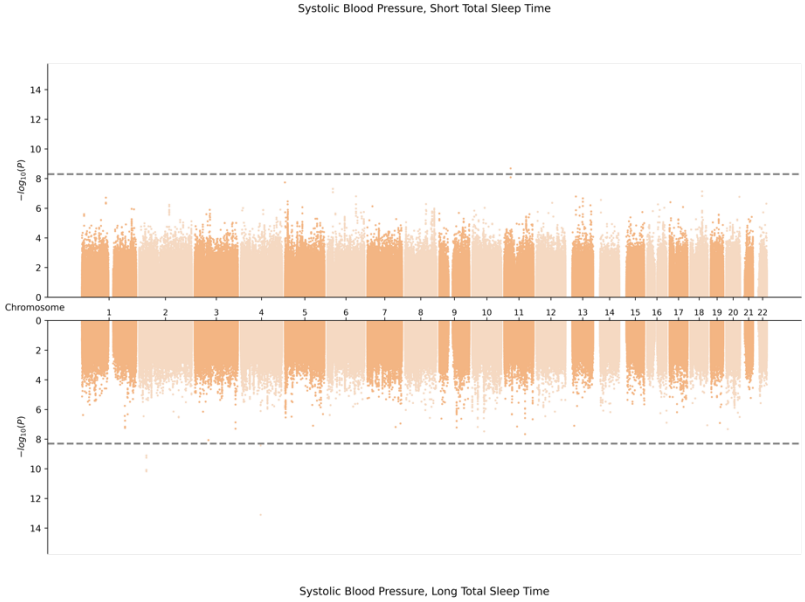


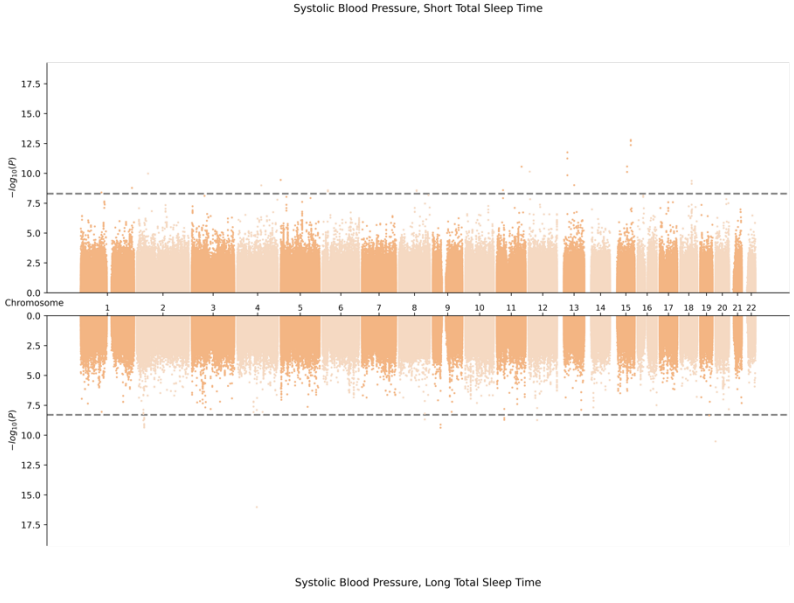
4. EUR-Specific Meta-Analysis



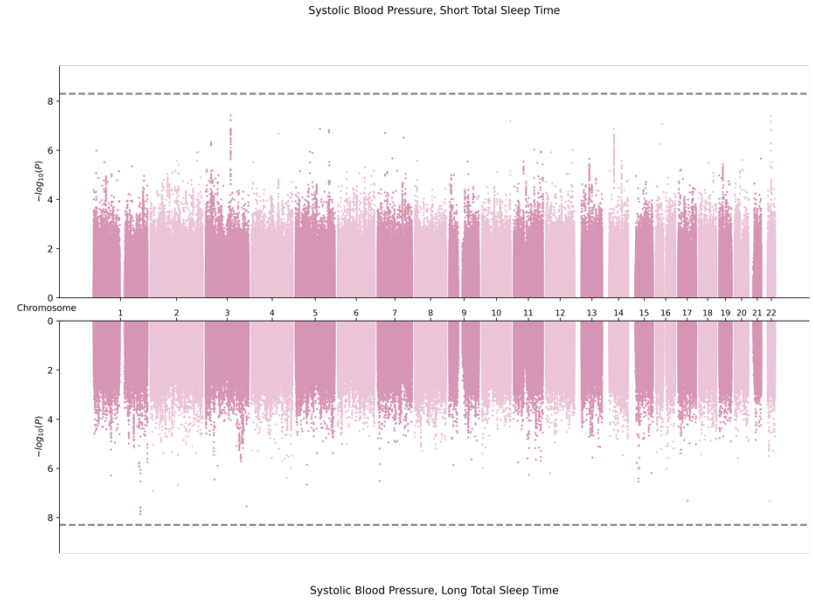


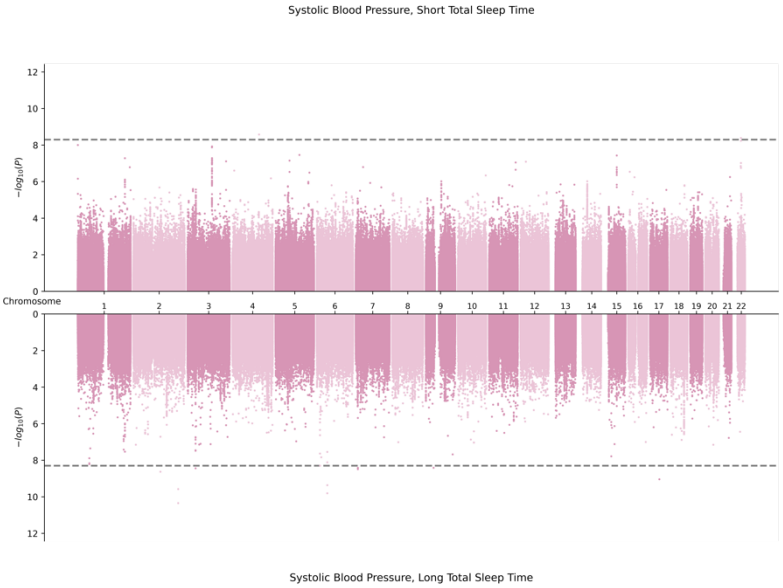
5. HIS-Specific Meta-Analysis





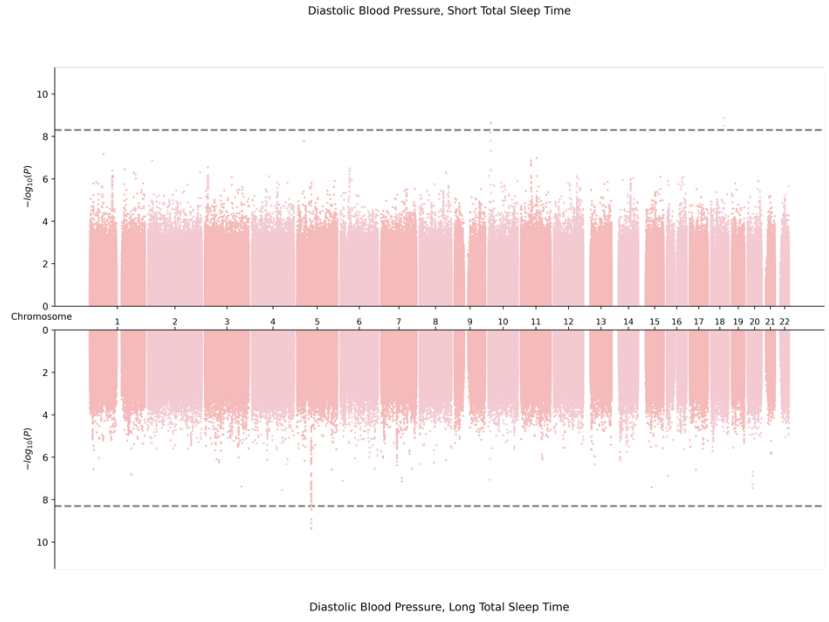
6. SAS-Specific Meta-Analysis

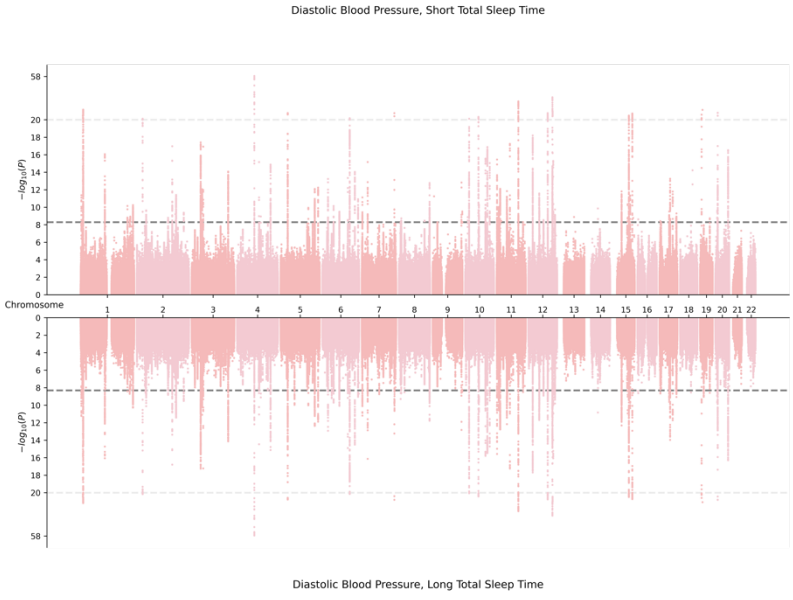




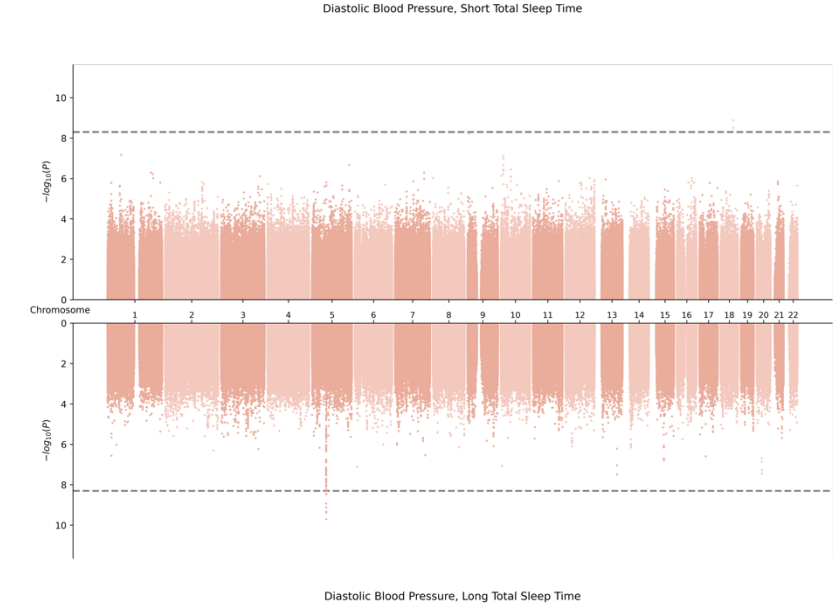
F. Miami Plots for Diastolic Blood Pressure in Female Sex

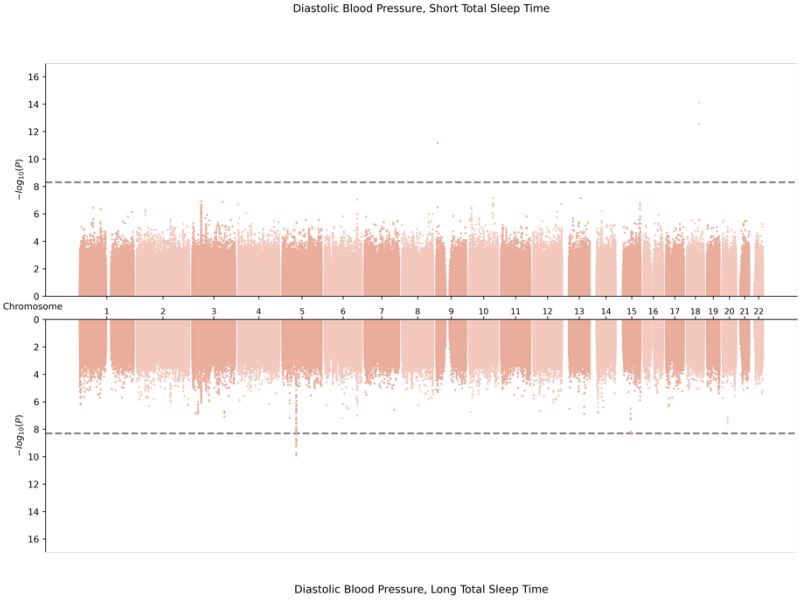
1. Cross Population Meta-Analysis



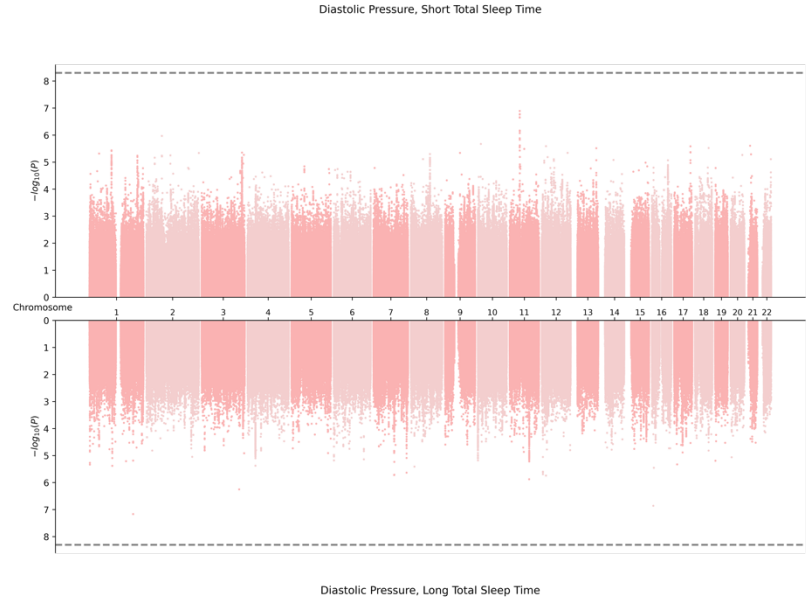


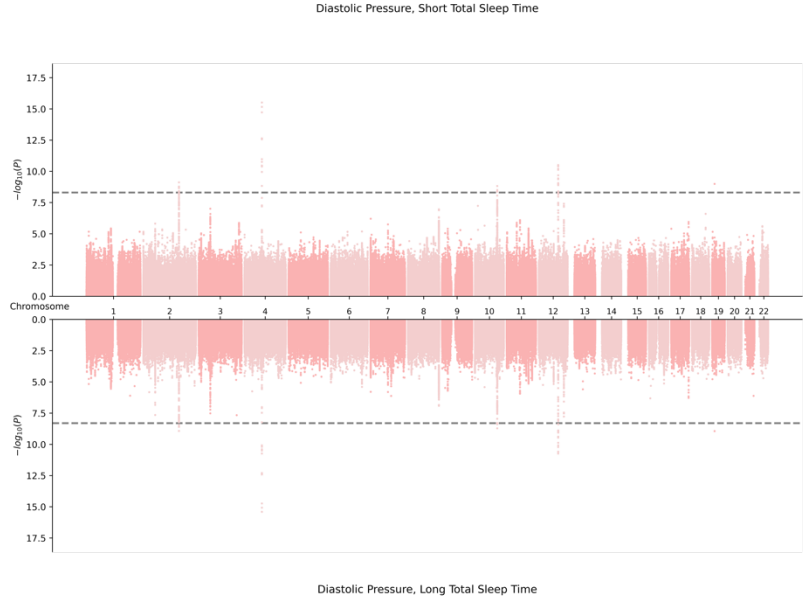
2. AFR-Specific Meta-Analysis



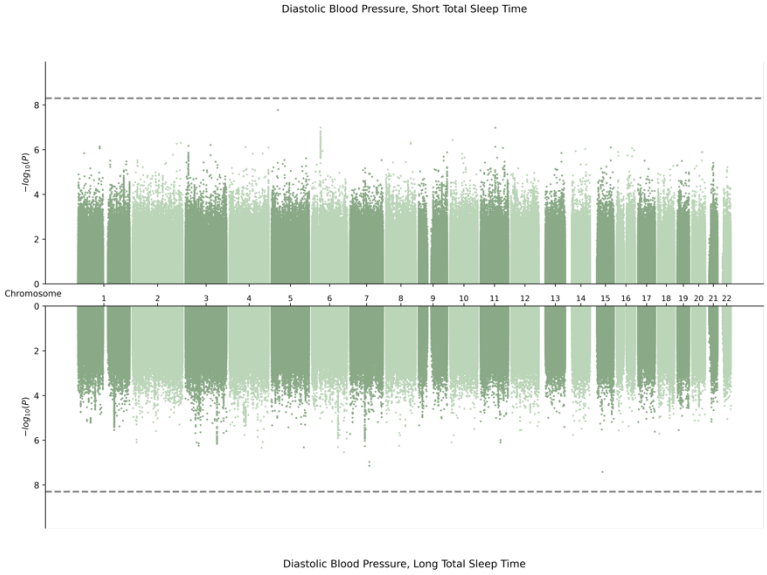


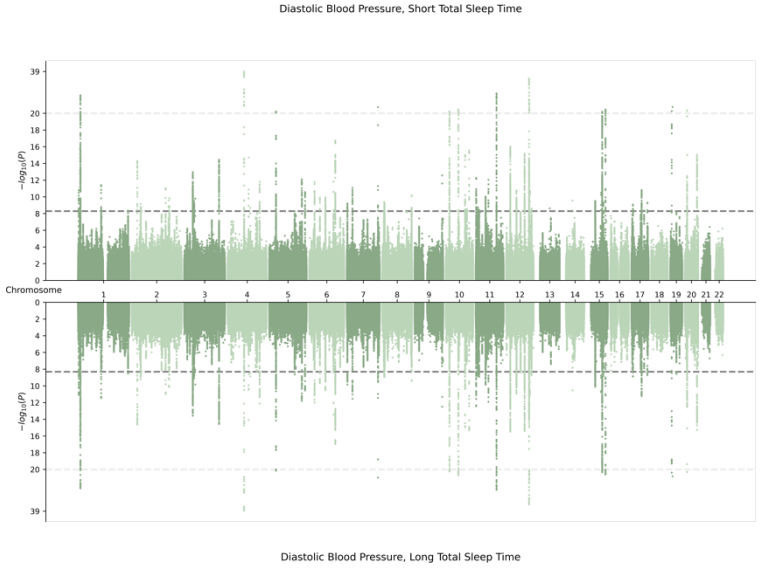
3. EAS-Specific Meta-Analysis



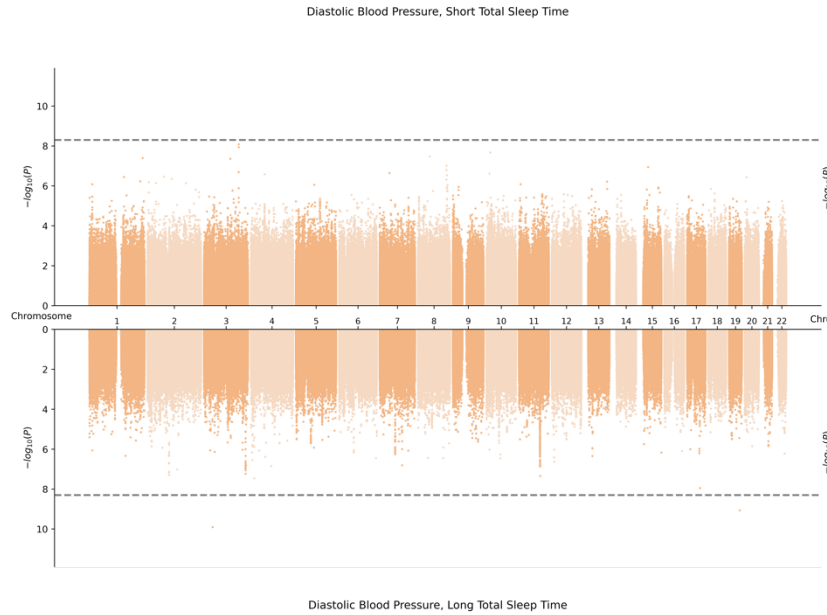


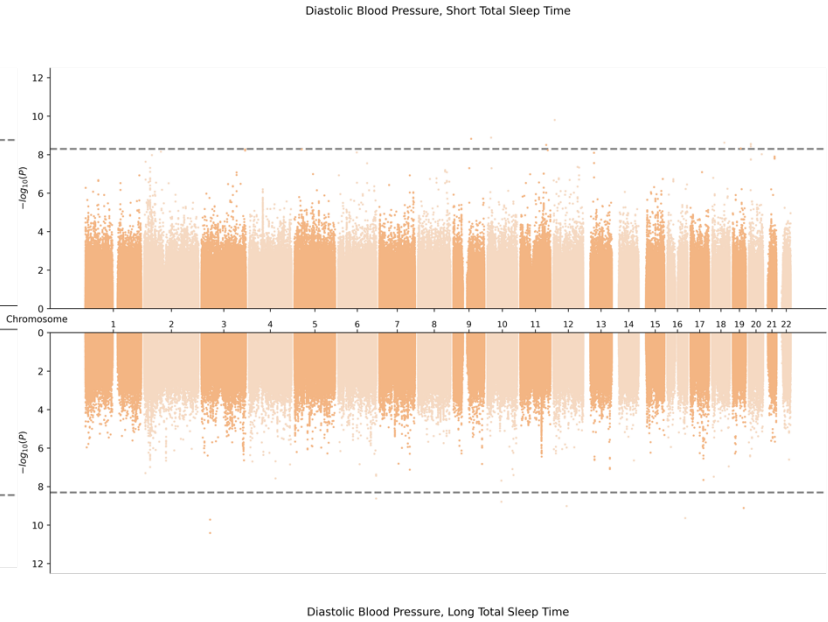
4. EUR-Specific Meta-Analysis



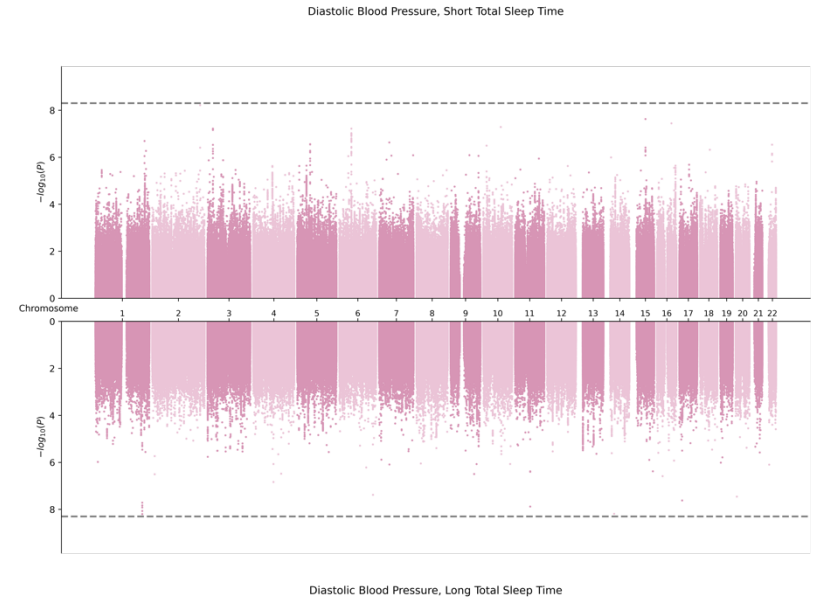


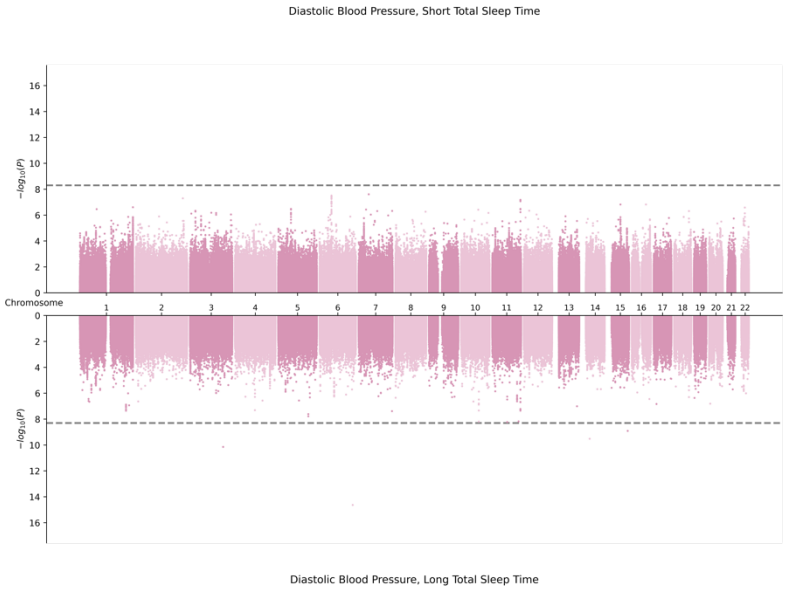
5. HIS-Specific Meta-Analysis





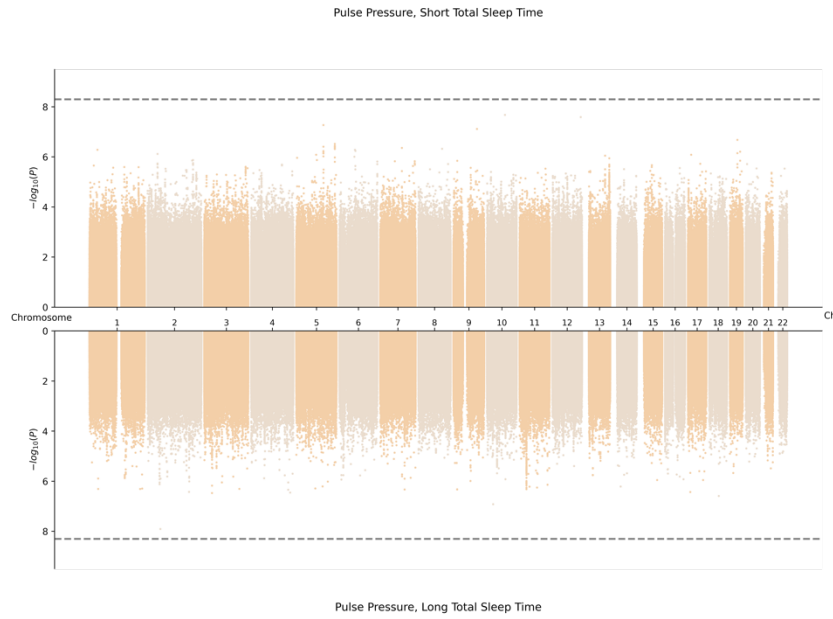
6. SAS-Specific Meta-Analysis

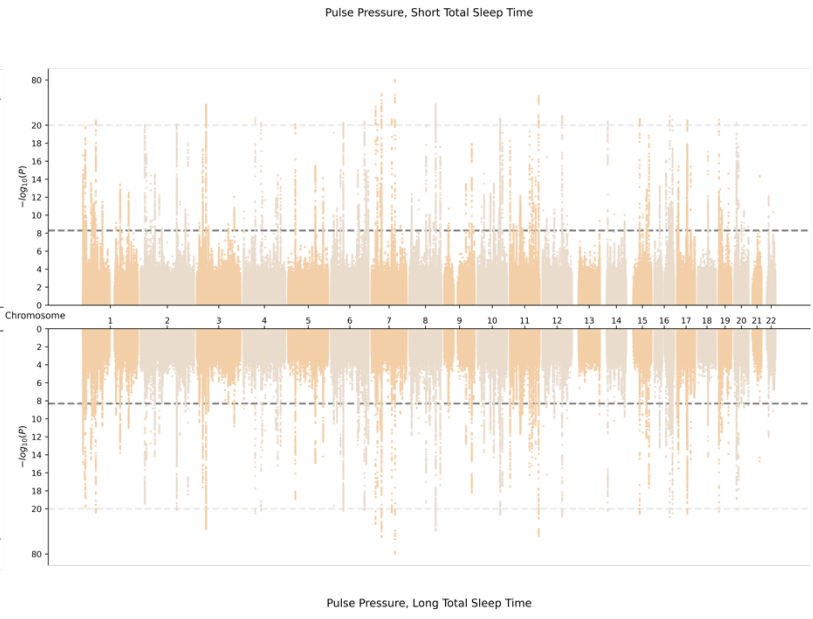




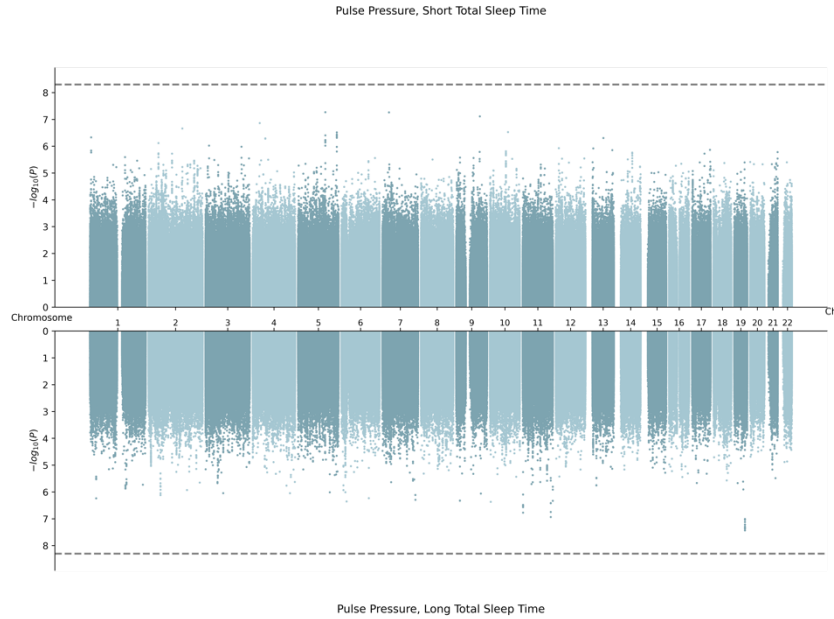
G. Miami Plots for Pulse Pressure in Male Sex

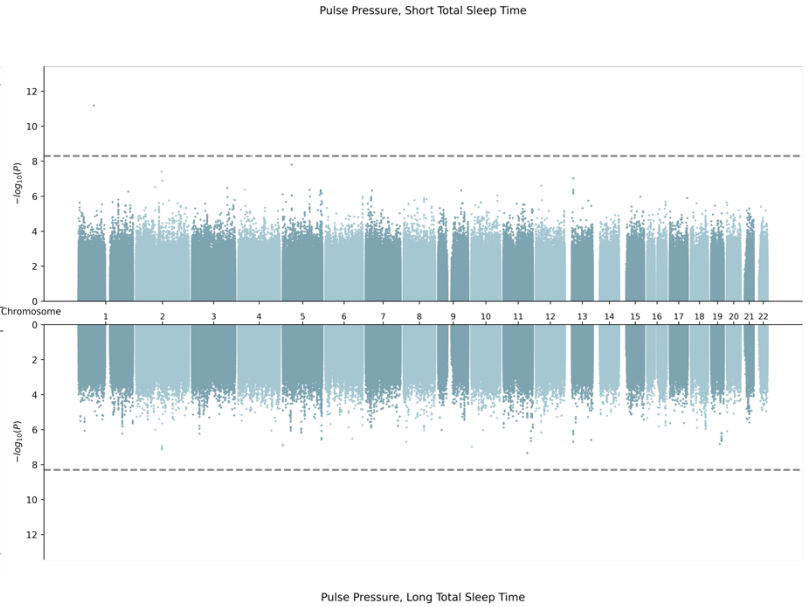
1. Cross Population Meta-Analysis



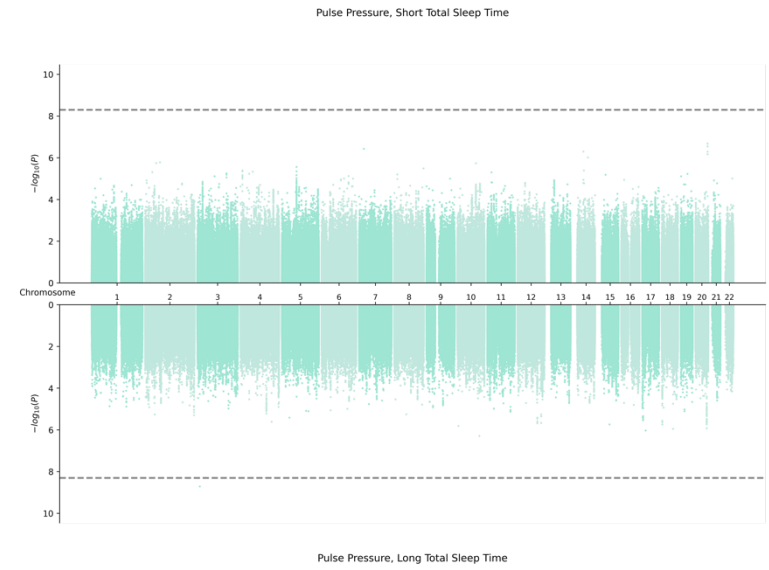


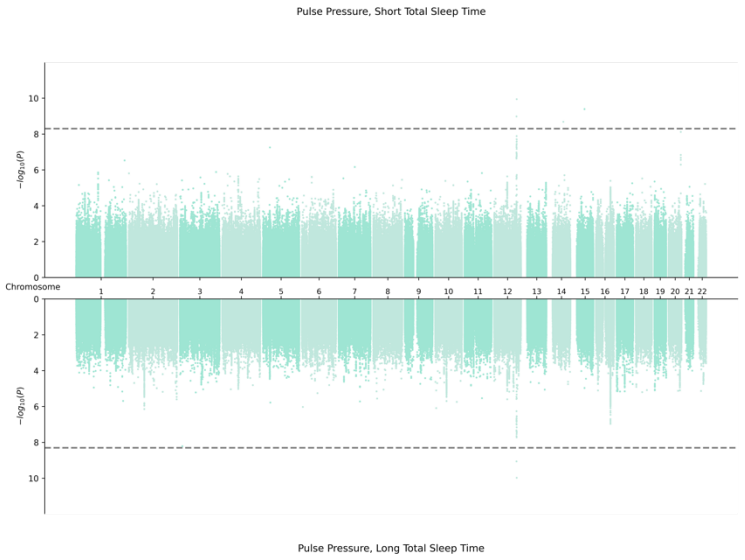
2. AFR-Specific Meta-Analysis



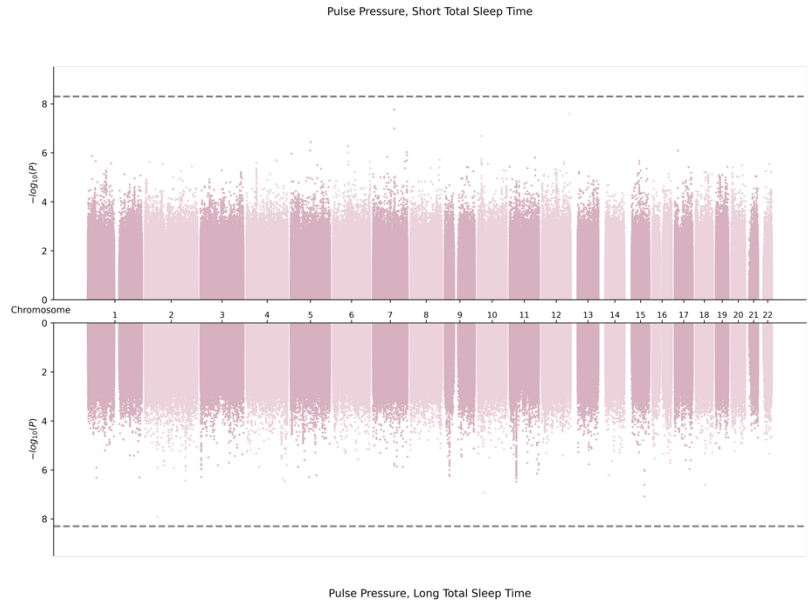


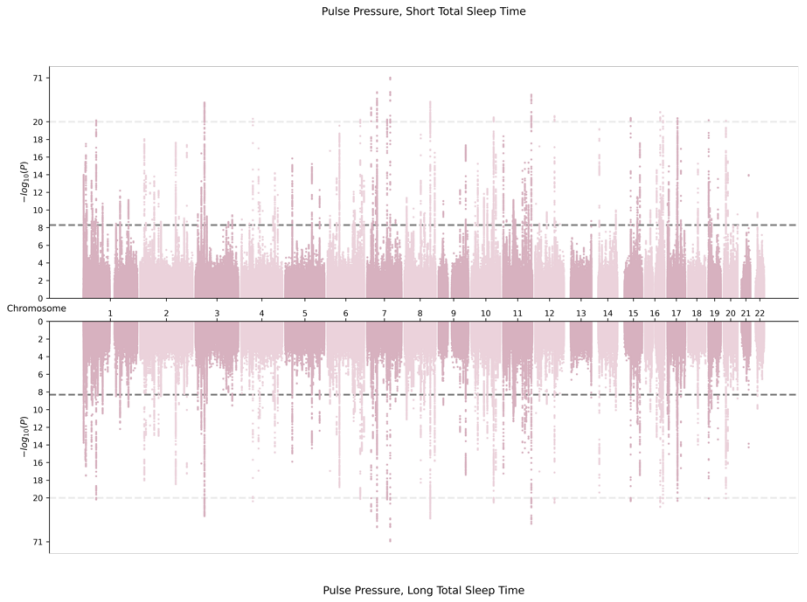
3. EAS-Specific Meta-Analysis



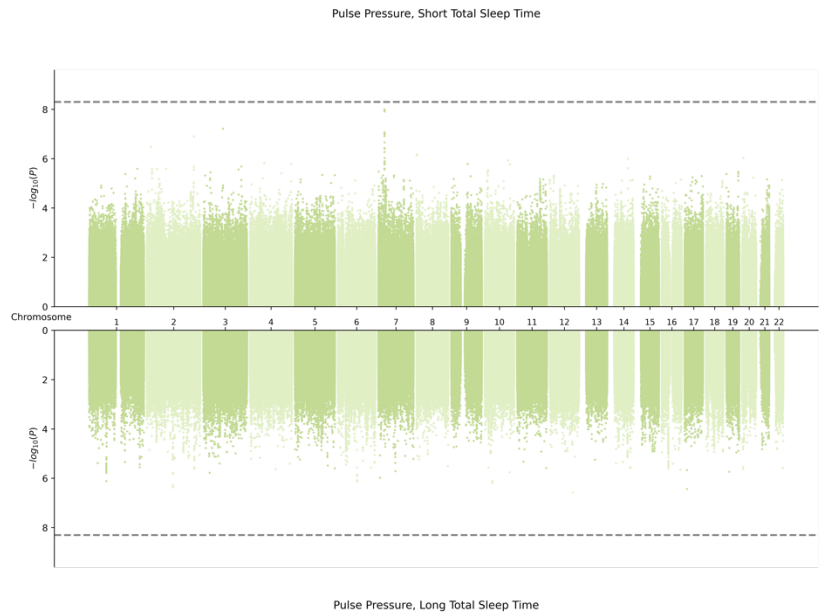


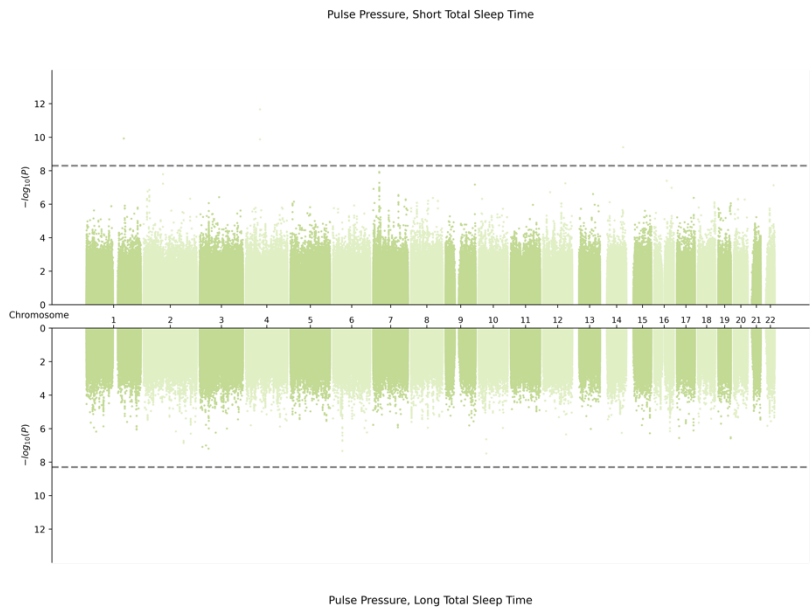
4. EUR Meta-Analysis



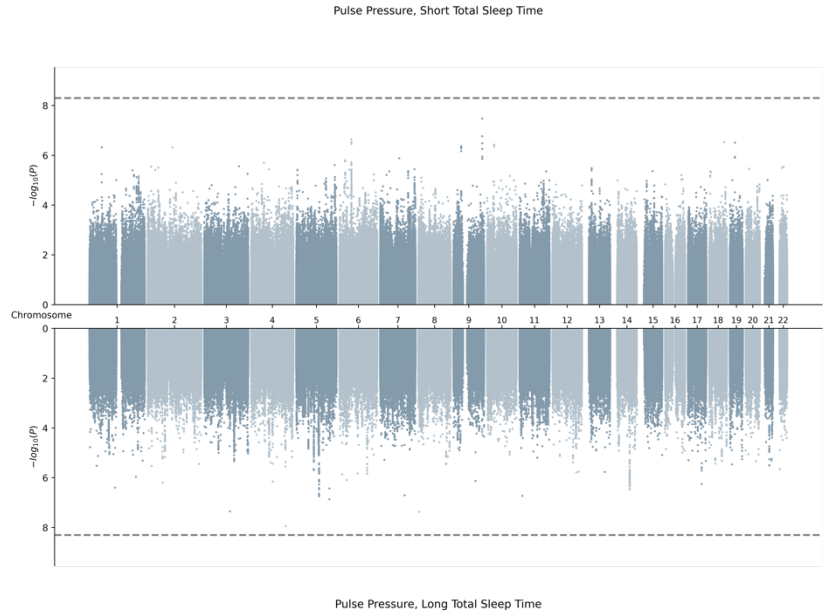


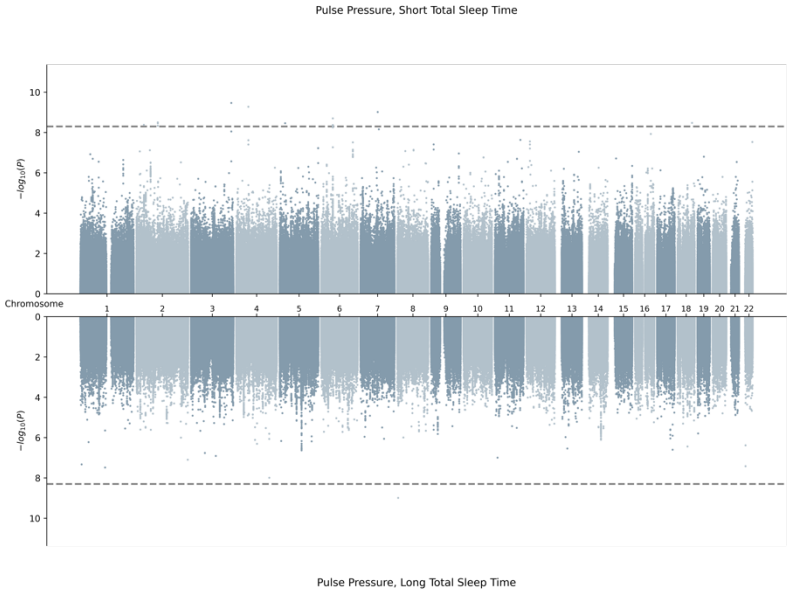
5. HIS-Specific Meta-Analysis





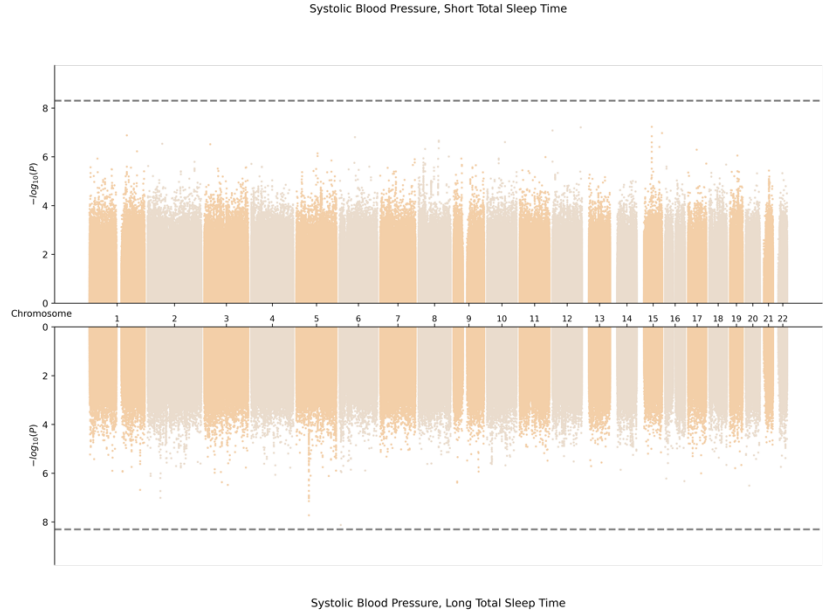
6. SAS-Specific Meta-Analysis

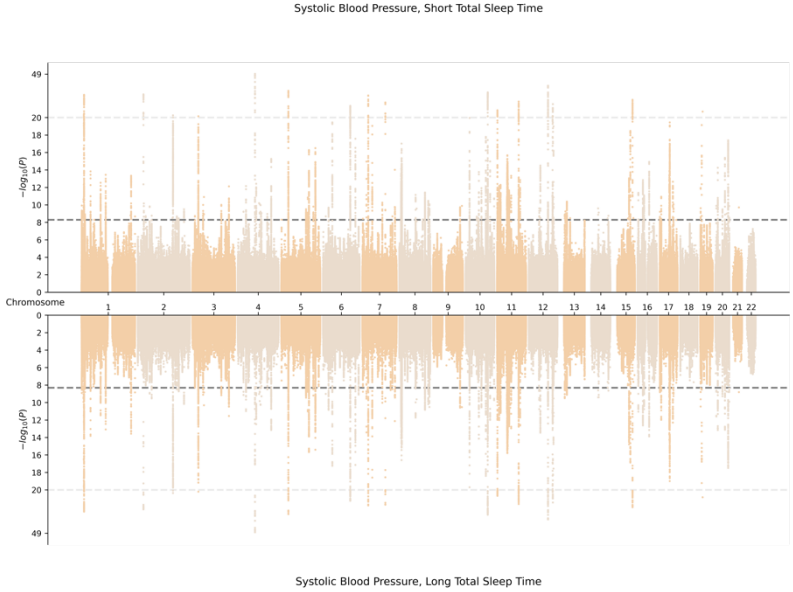




H. Miami Plots for Systolic Blood Pressure in Male Sex

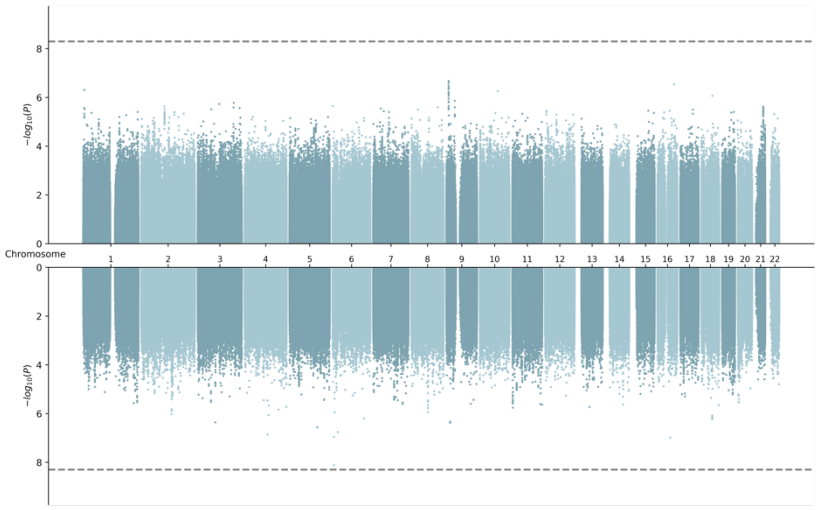
1. Cross Population Meta-Analysis



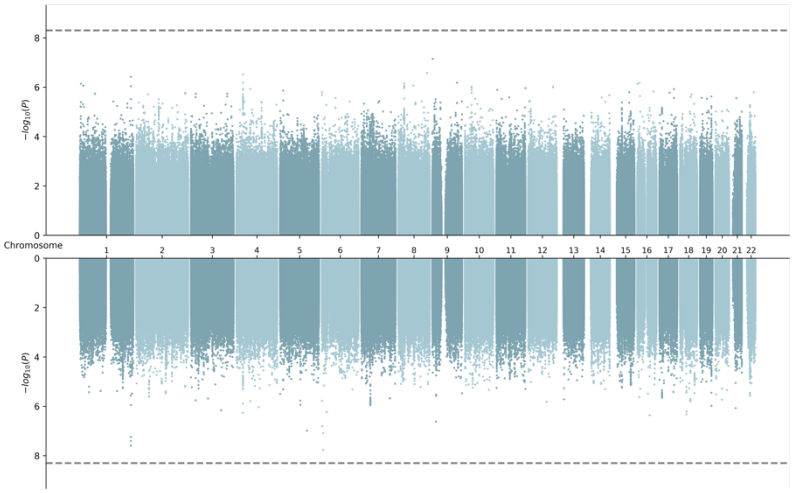


2. AFR-Specific Meta-Analysis

Systolic Blood Pressure, Short Total Sleep Time



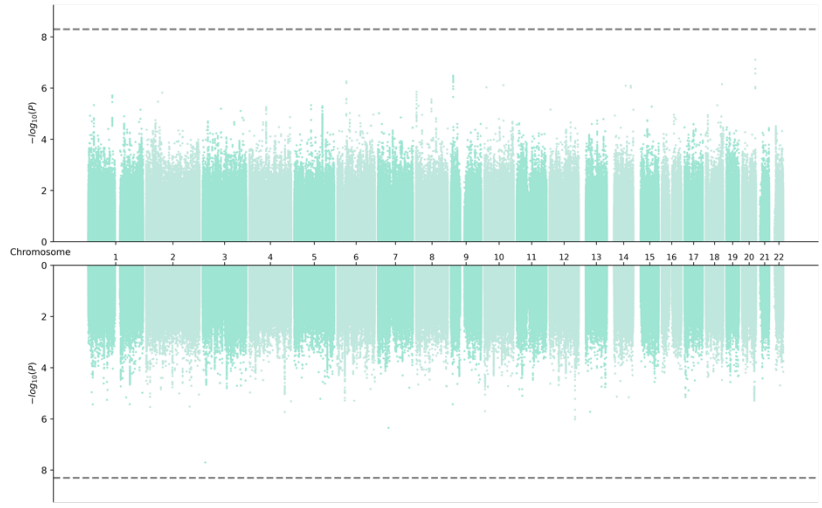
Systolic Blood Pressure, Long Total Sleep Time



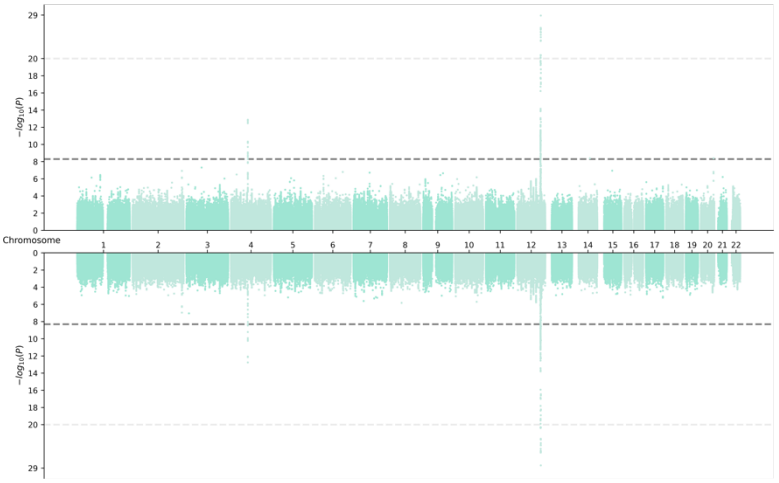
Systolic Blood Pressure, Long Total Sleep Time

3. EAS-Specific Meta-Analysis

Systolic Pressure, Short Total Sleep Time

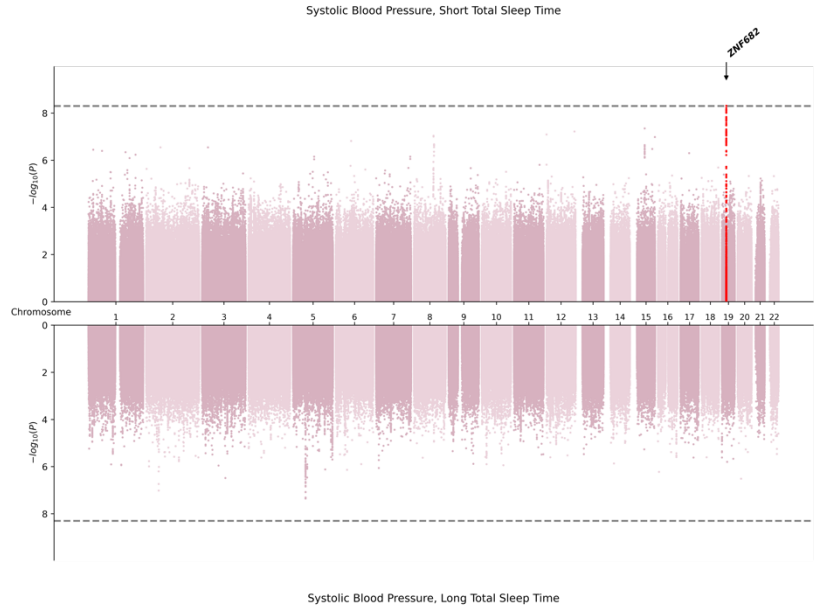


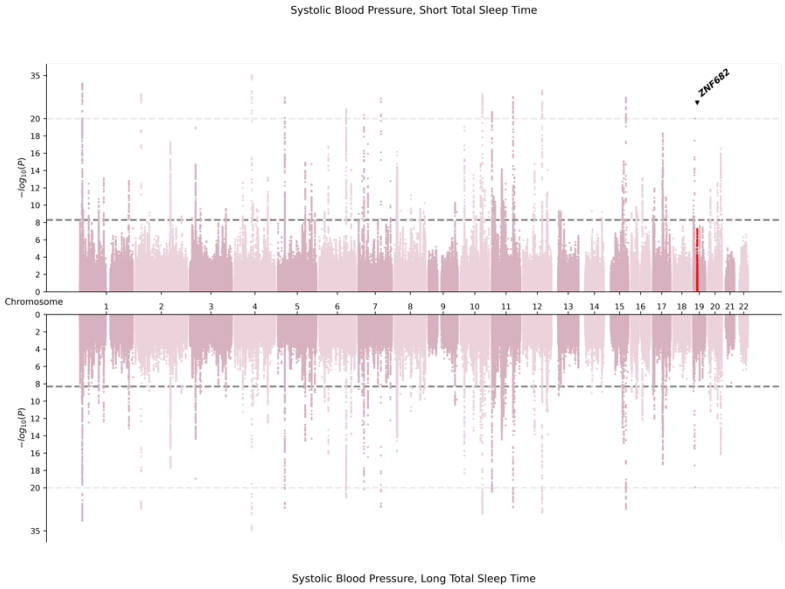
Systolic Pressure, Long Total Sleep Time



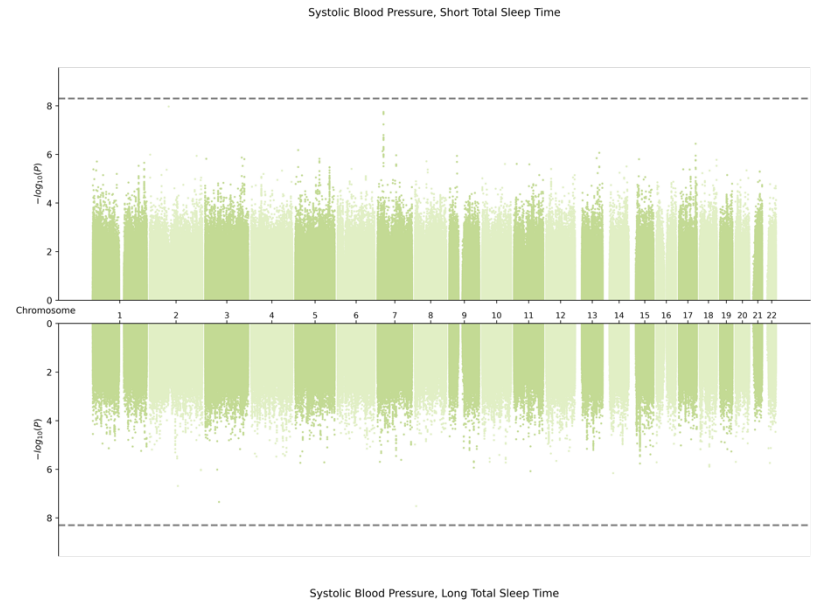
Systolic Pressure, Long Total Sleep Time

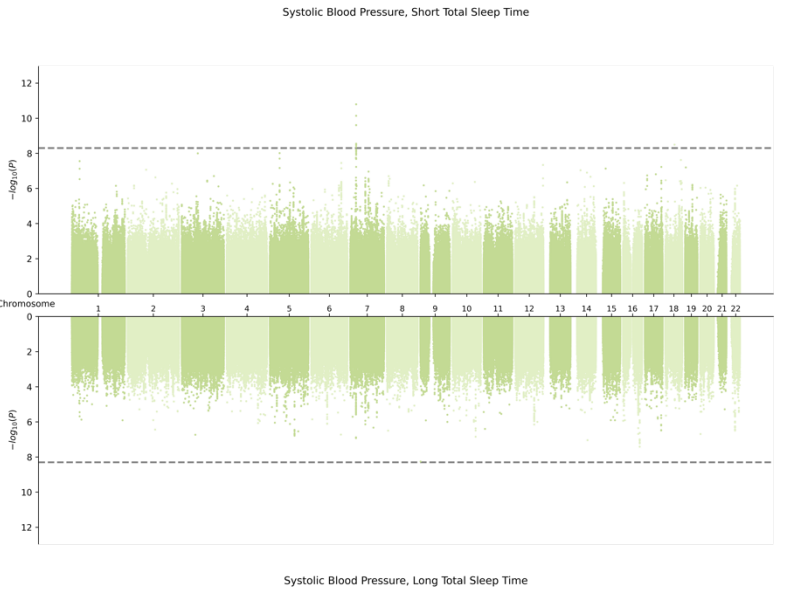
4. EUR-Specific Meta-Analysis



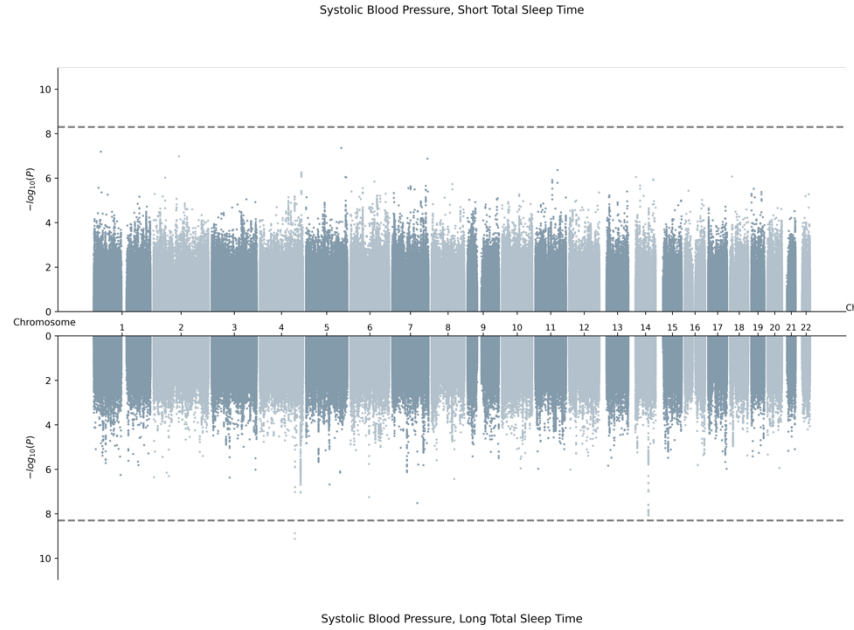


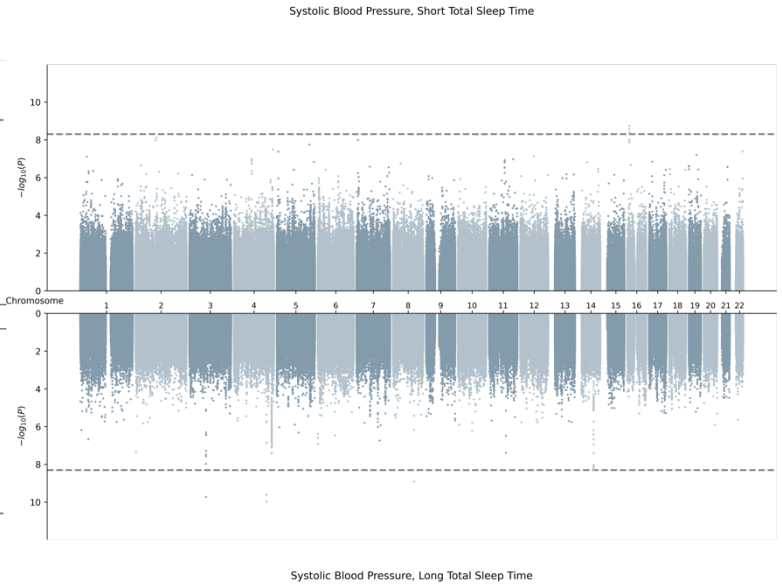
5. HIS-Specific Meta-Analysis





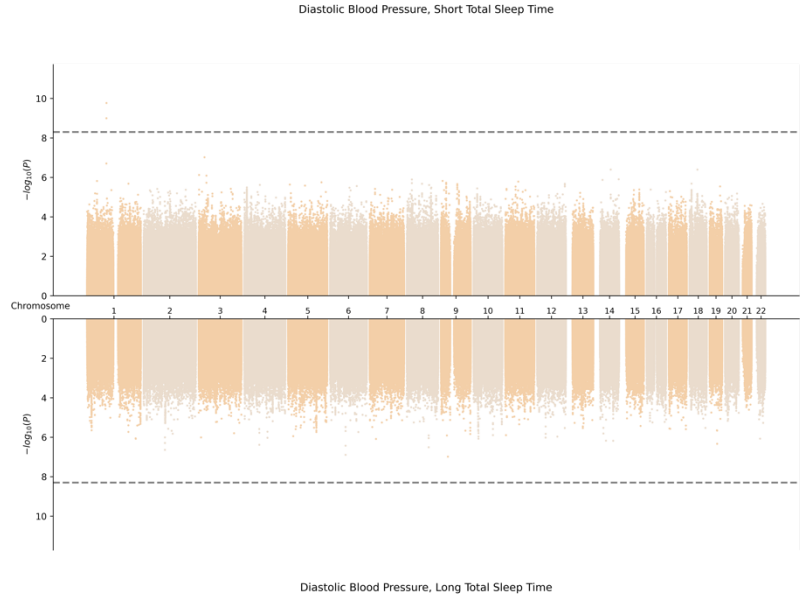
6. SAS-Specific Meta-Analysis

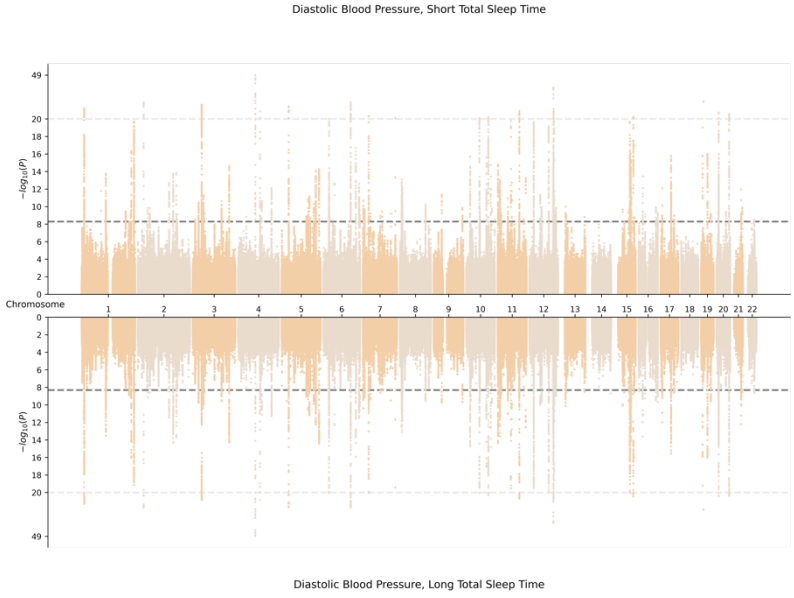




I. Miami Plots for Diastolic Blood Pressure in Male Sex

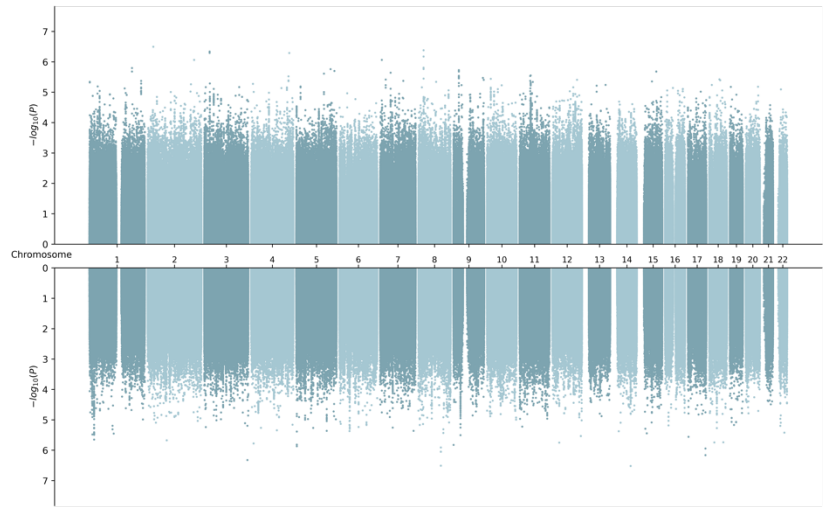
1. Cross Population Meta-Analysis





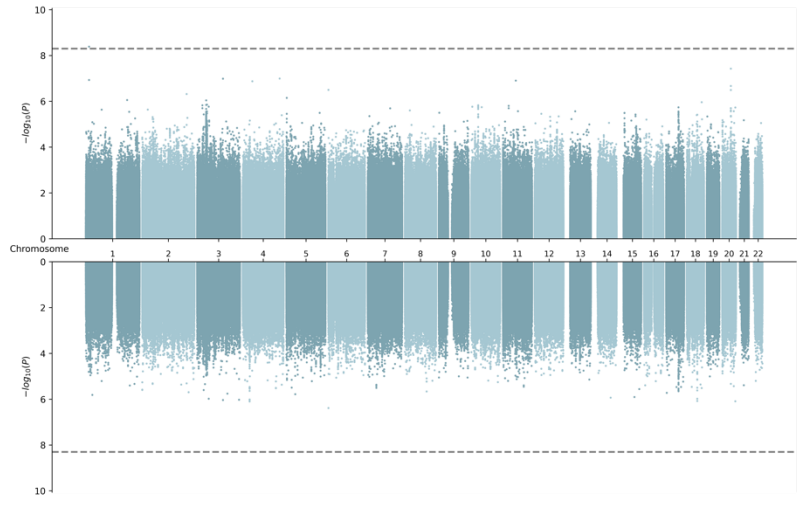
2. AFR-Specific Meta-Analysis

Diastolic Blood Pressure, Short Total Sleep Time



Diastolic Blood Pressure, Long Total Sleep Time

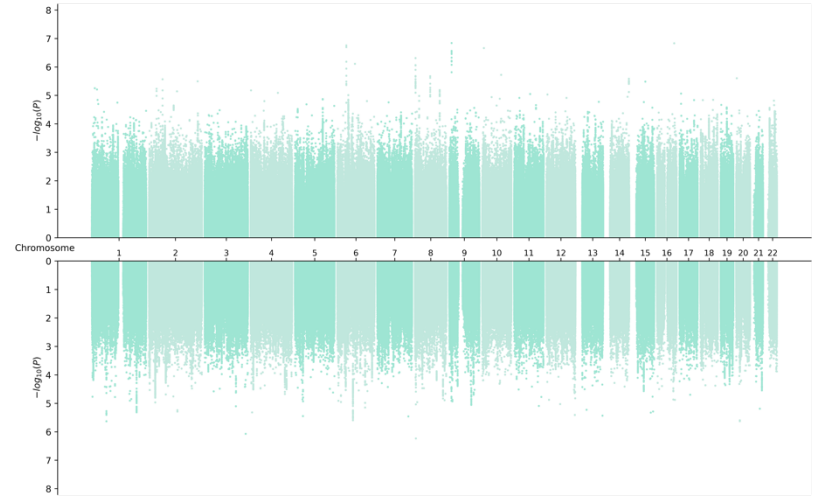
Diastolic Blood Pressure, Short Total Sleep Time



Diastolic Blood Pressure, Long Total Sleep Time

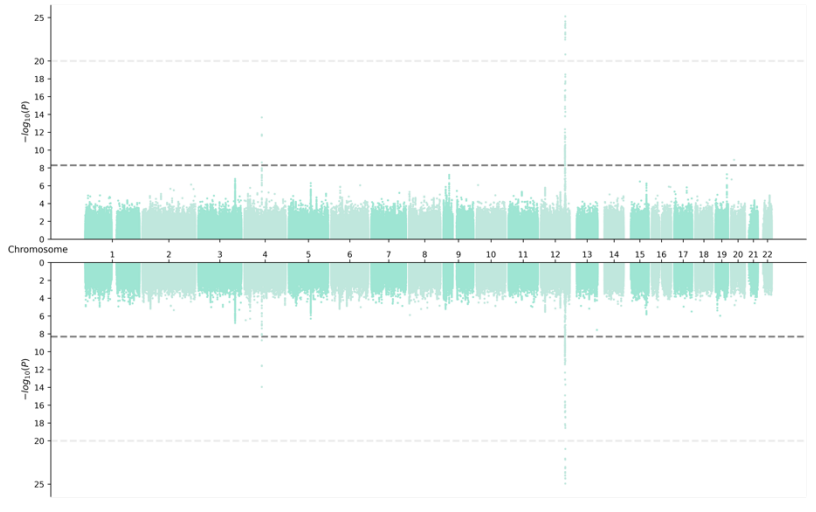
3. EAS-Specific Meta-Analysis

Diastolic Pressure, Short Total Sleep Time



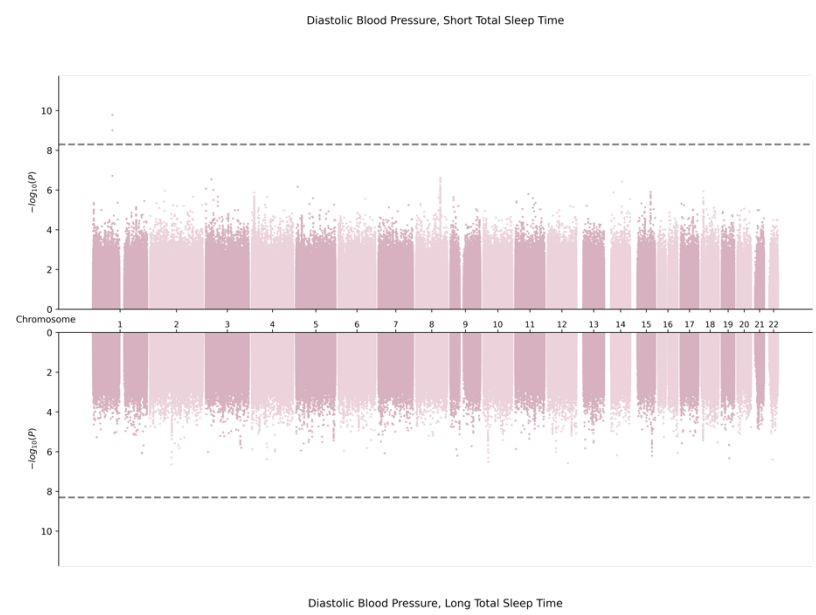
Diastolic Pressure, Long Total Sleep Time

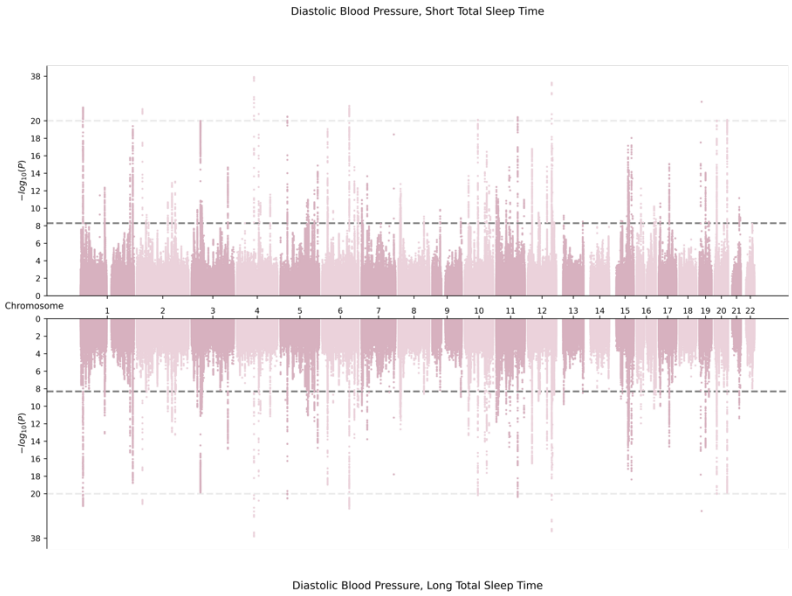
Diastolic Pressure, Short Total Sleep Time



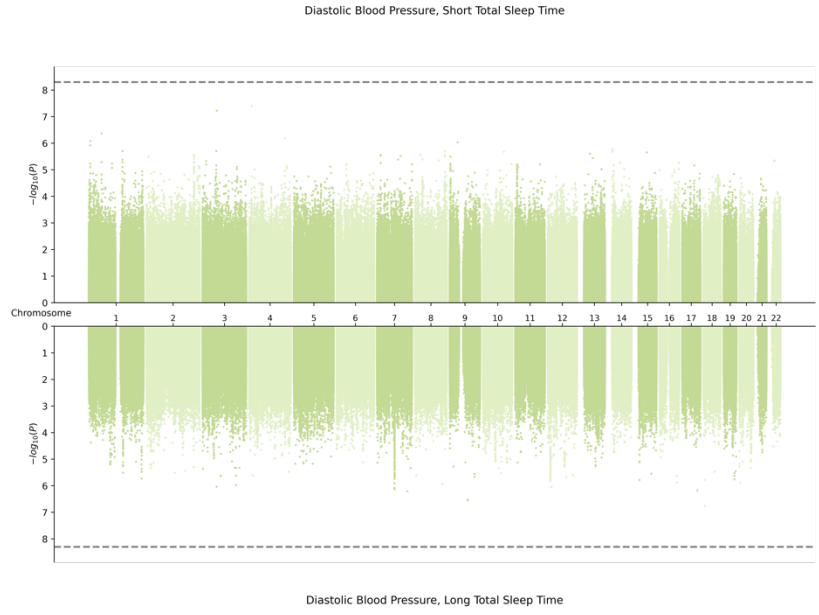
Diastolic Pressure, Long Total Sleep Time

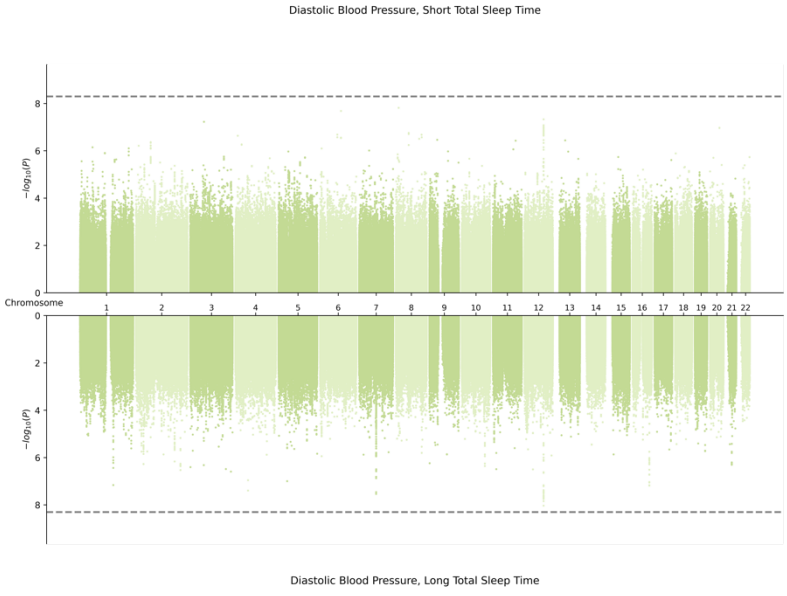
4. EUR-Specific Meta-Analysis



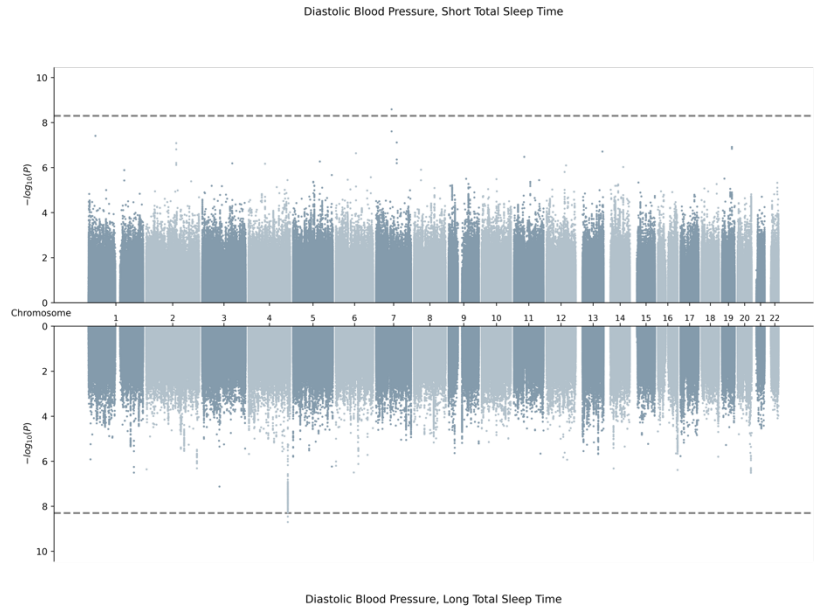


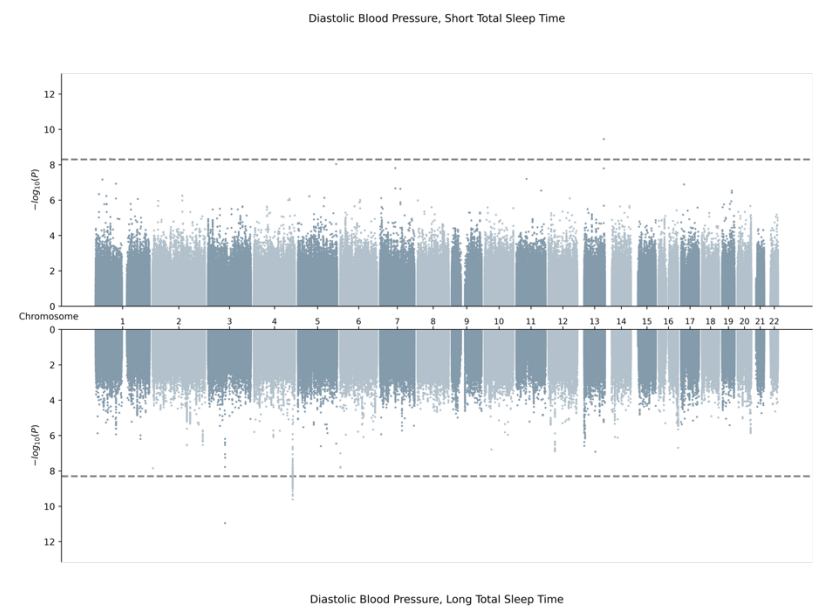
5. HIS-Specific Meta-Analysis





6. SAS-Specific Meta-Analysis Results

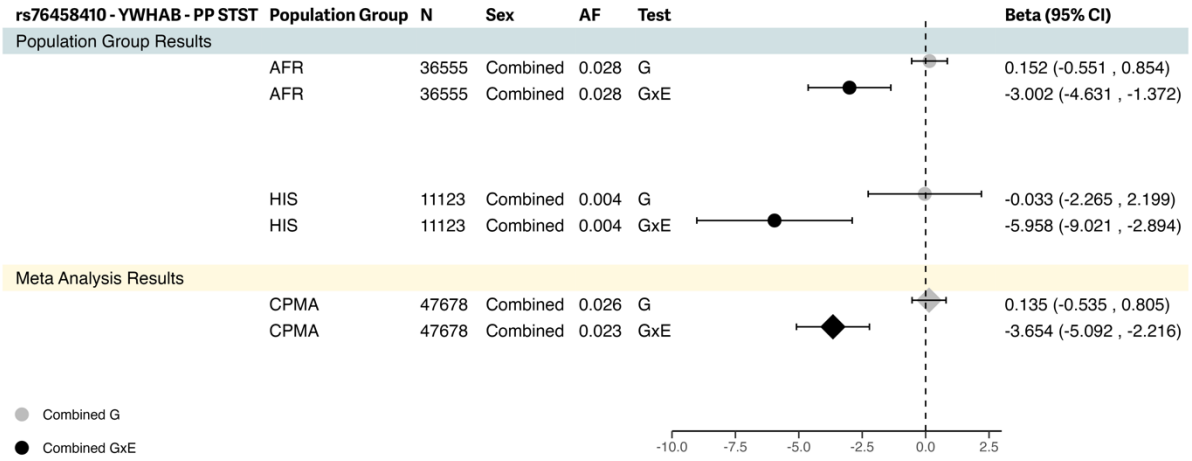




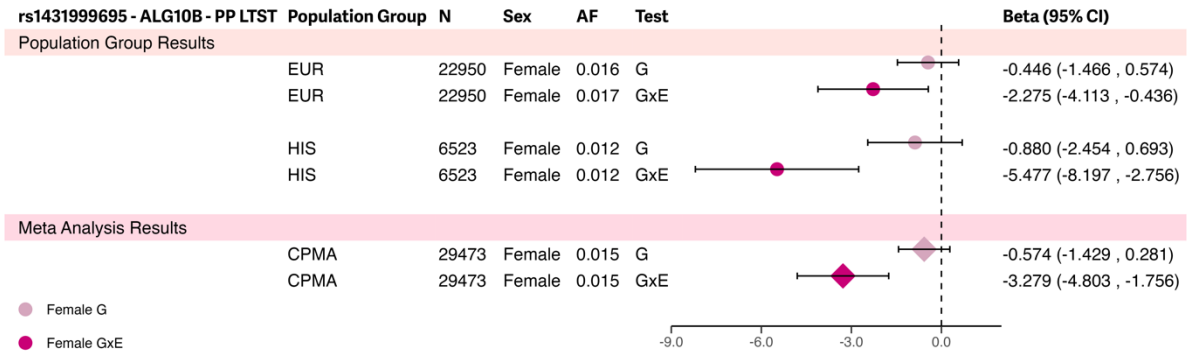
Supplementary Fig. S3. Forest Plots

A. Cross-Population Variants

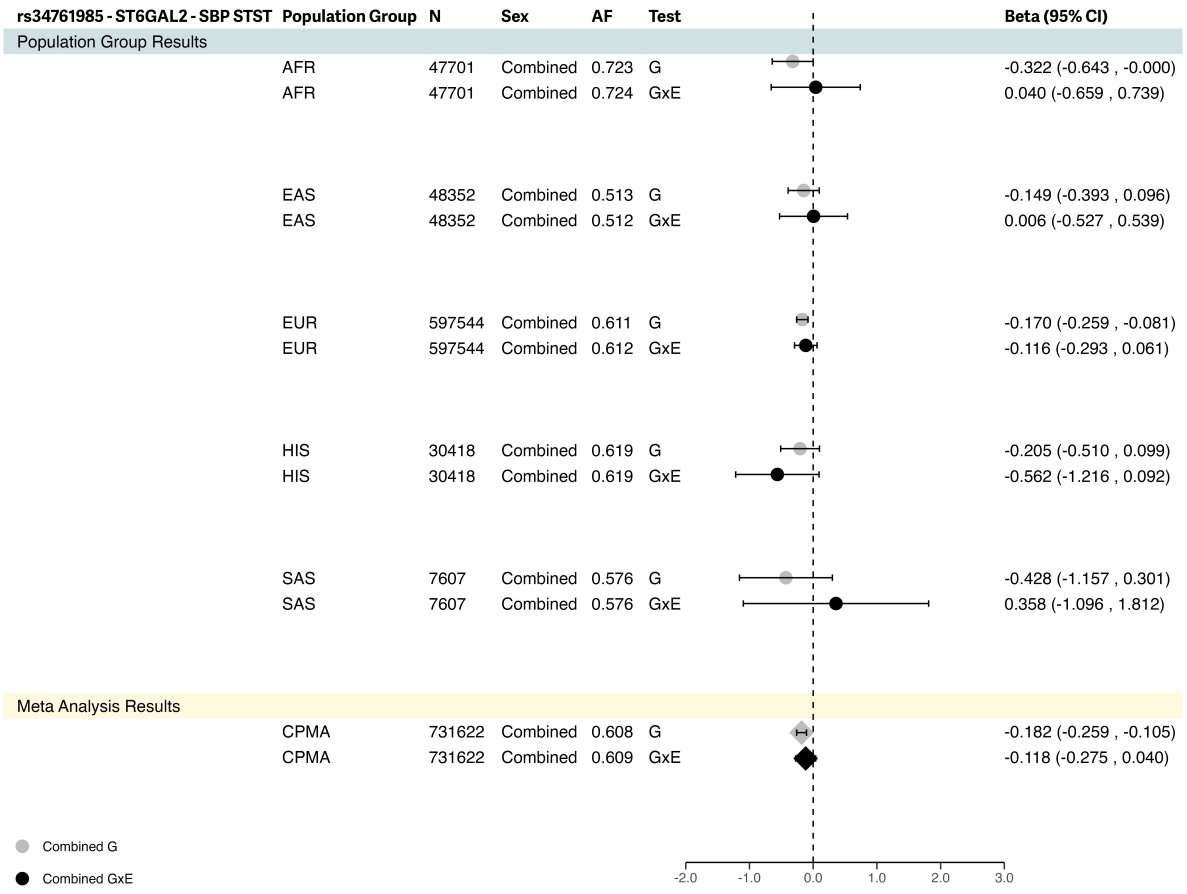
1. rs76458410 *(YWHAB)* was identified in combined sex meta-analysis by the 2df joint test for pulse pressure, found to be driven by interaction with STST.



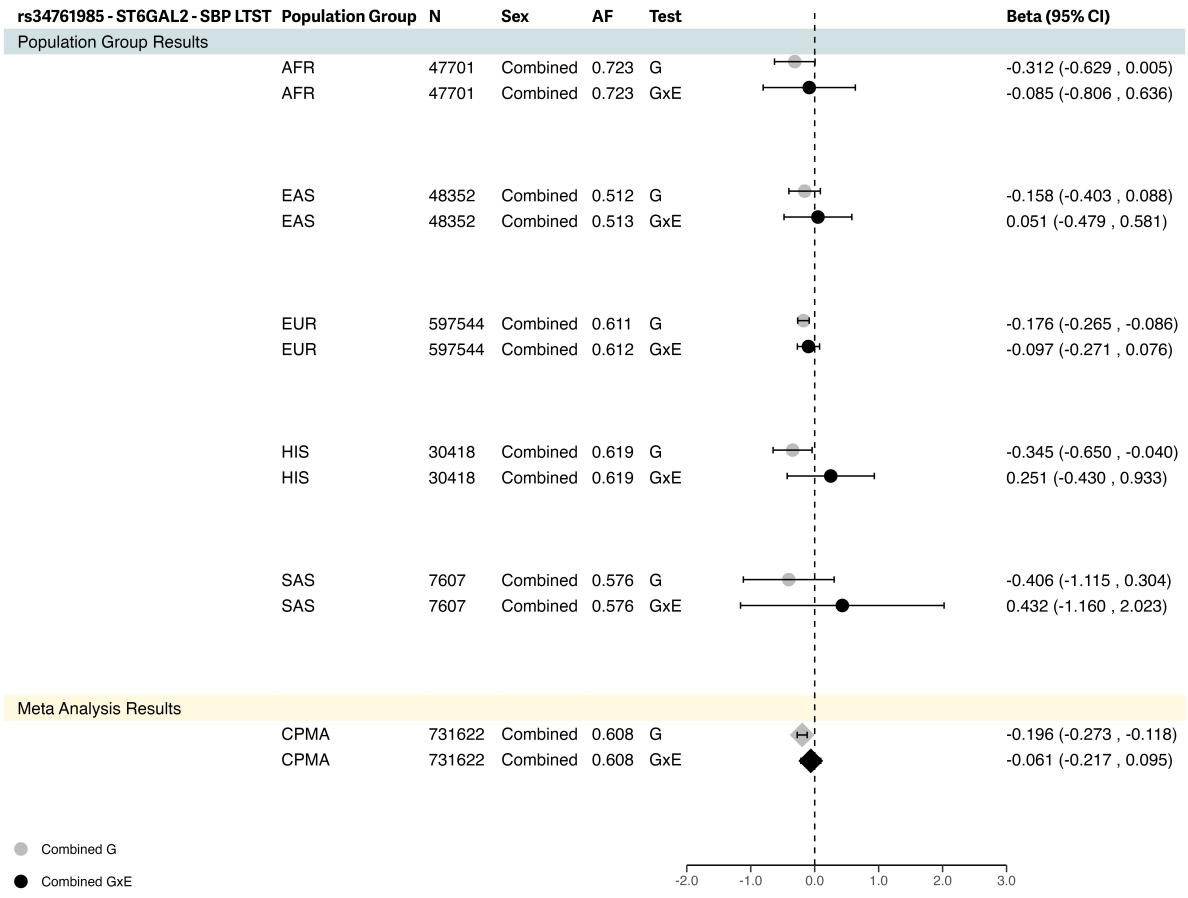
2. rs1431999695 *(ALG10B)* was identified in female-specific meta-analysis by the 2df joint test for pulse pressure found to be driven by interaction with LTST.



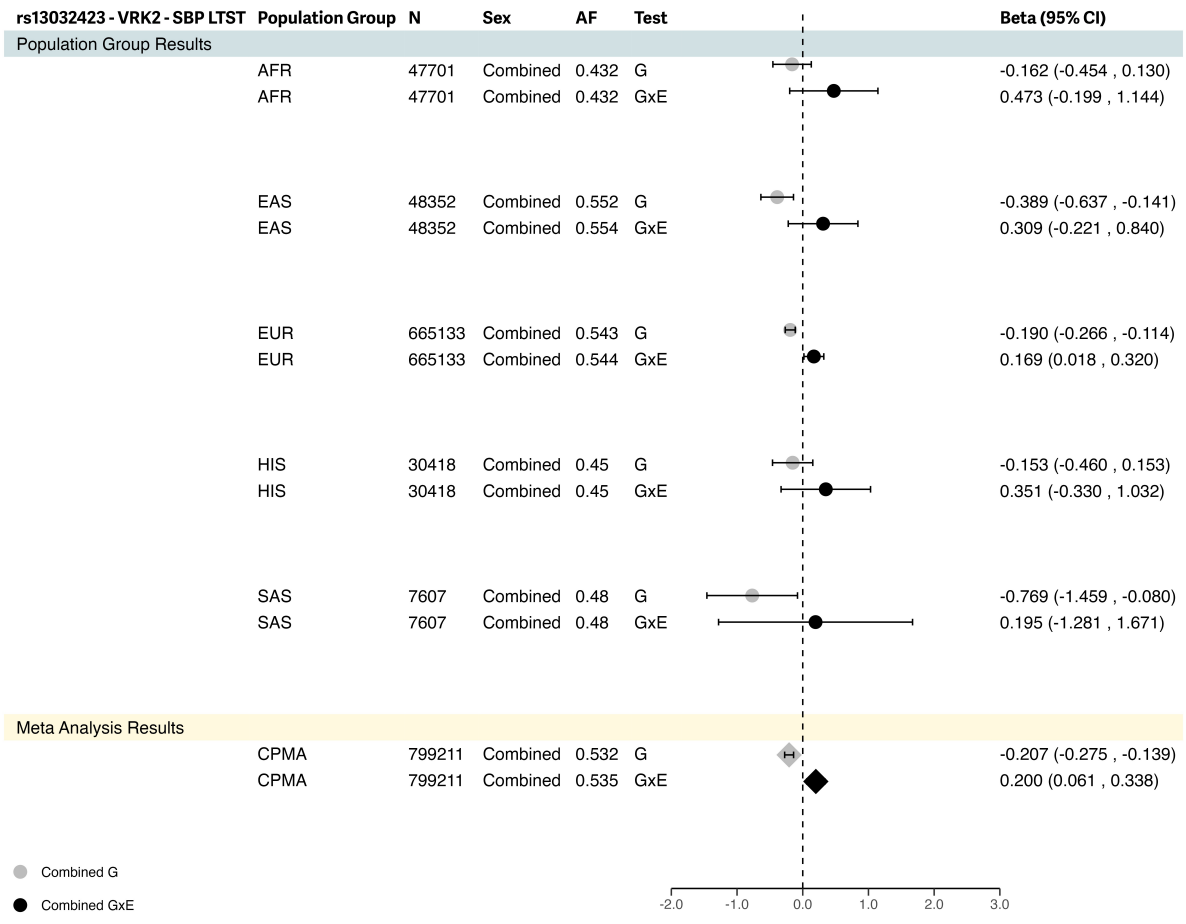
3. rs34761985 (*ST6GAL2*) was identified in combined sex meta-analysis by the 2df joint test for systolic blood pressure, found to not be driven by interaction with STST.



4. rs34761985 (*ST6GAL2*) was identified in combined sex meta-analysis by the 2df joint test for systolic blood pressure, found to not be driven by interaction with LTST.

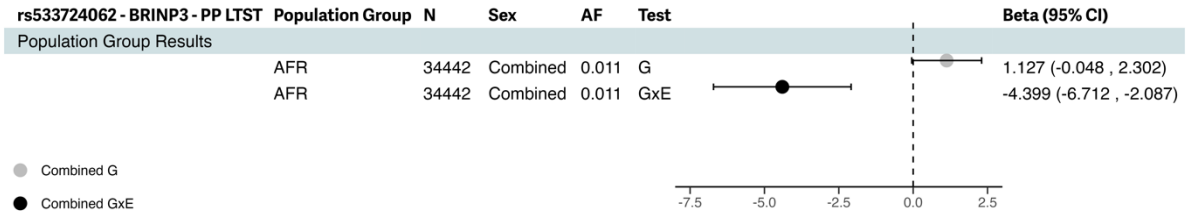


5. rs13032423 *(VRK2)* was identified in combined sex meta-analysis by the 2df joint test for systolic blood pressure, found to not be driven by interaction with LTST.



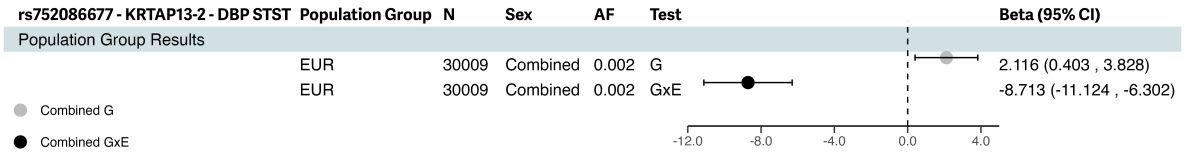
B. AFR-Specific Variant

1. rs533724062 *(BRINP3)* was identified in combined sex meta-analysis for pulse pressure, found to be driven by the interaction with LTST.

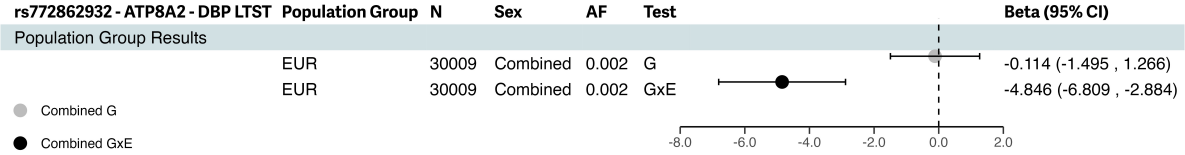


C. EUR-Specific Variants

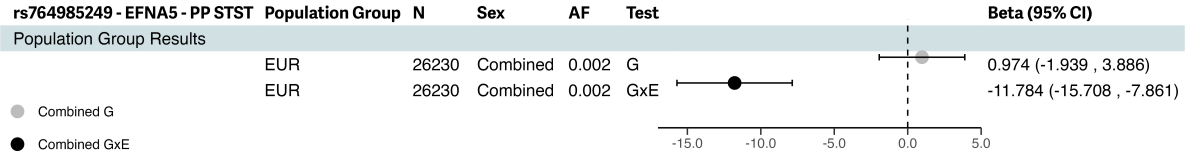
1. rs752086677 (*KRTAP13-2*) was identified in combined sex meta-analysis for diastolic blood pressure by the 1df interaction test for interaction with STST.



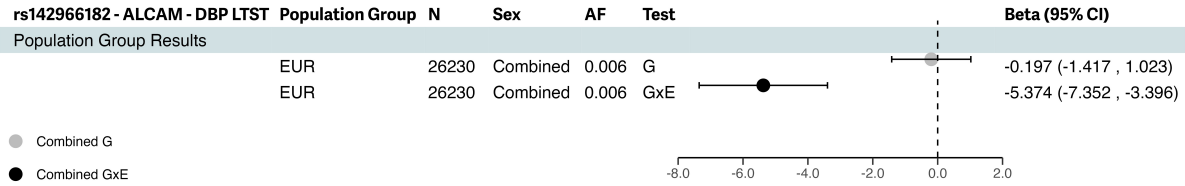
2. rs772862932 *(ATP8A2)* was identified in combined sex meta-analysis for diastolic blood pressure by the 2df joint test, found to be driven by interaction with LTST.



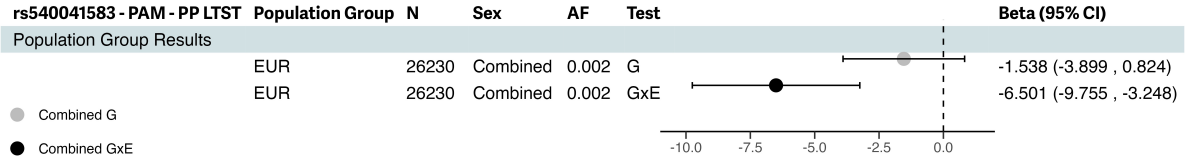
3. rs764985249 *(EFNA5)* was identified in combined sex meta-analysis for pulse pressure by the 2df joint test, found to be driven by interaction with STST.



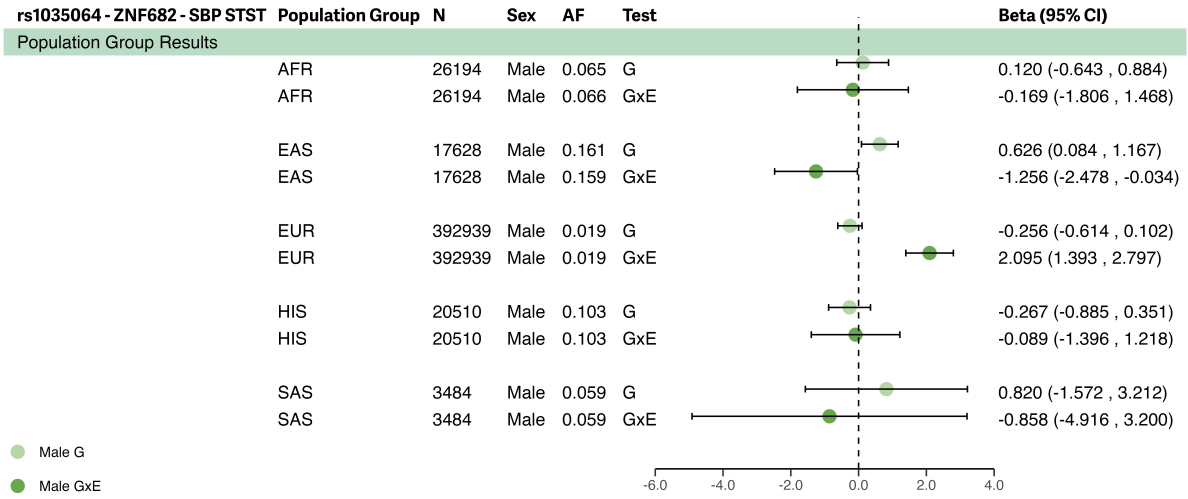
4. rs142966182 *(ALCAM)*, was identified in combined sex meta-analysis for diastolic blood pressure by the 2df joint test, found to be driven by interaction with LTST.



5. rs540041583 *(PAM*) was identified in combined sex meta-analysis for pulse pressure by the 2df joint test driven by interaction with LTST.

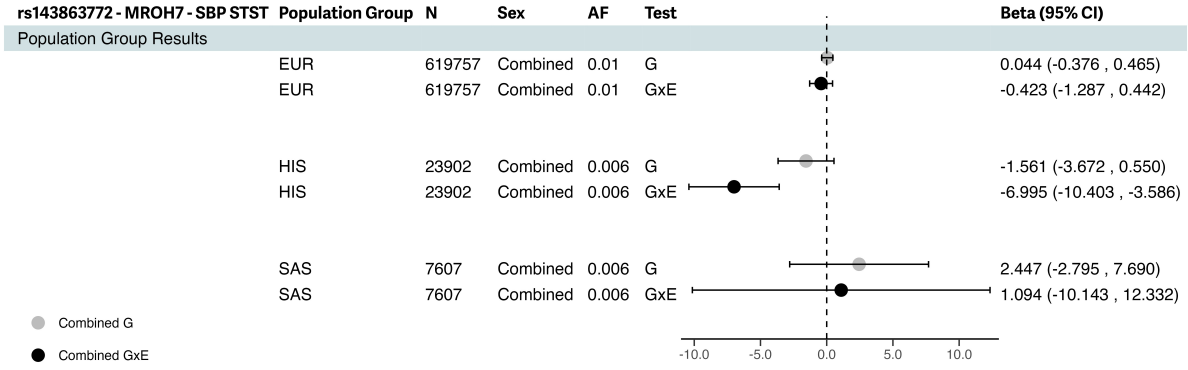


6. rs1035064 *(ZNF682*) was identified in male-specific meta-analysis for systolic blood pressure by the 1df interaction test for interaction with STST.

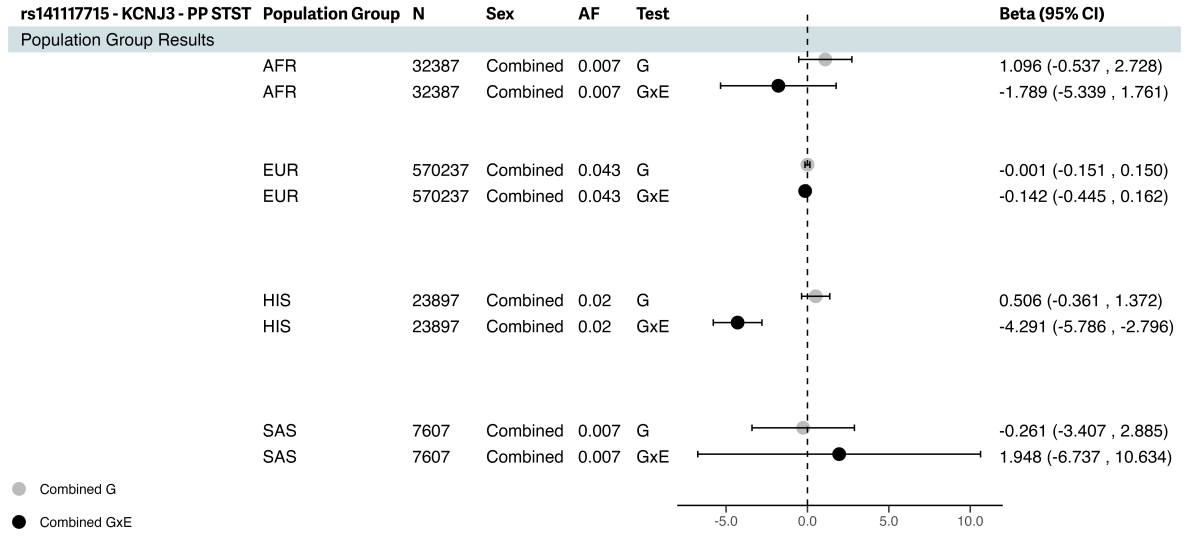


D. HIS-Specific Variants

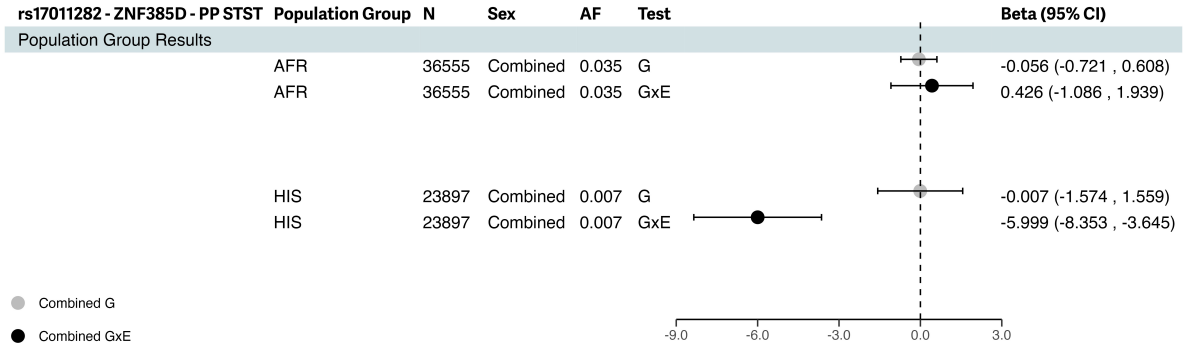
1. rs14383772 *(MROH7)*, was identified in combined sex meta-analysis for systolic blood pressure by the 2df joint test driven by interaction with STST.



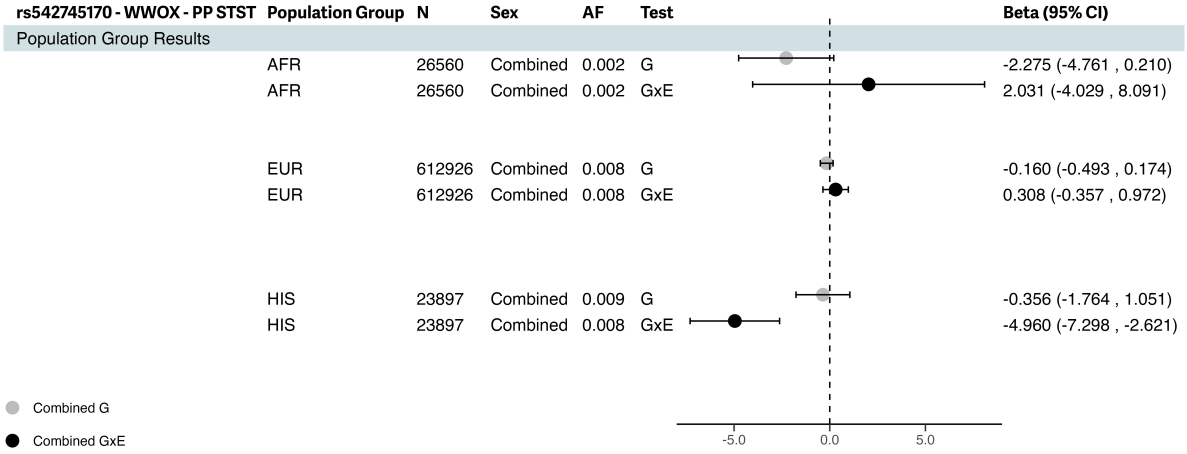
2. rs141117715 *(KCNJ3)*, was identified in combined sex meta-analysis for pulse pressure by the 2df joint test driven by interaction with STST.



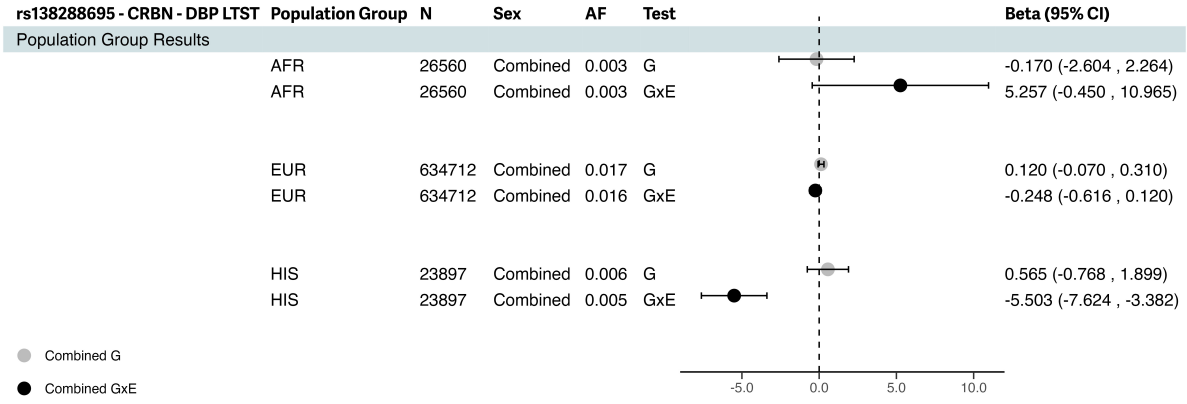
3. rs17011282 *(ZNF385D),* was identified in combined sex meta-analysis for pulse pressure by the 2df joint test driven by interaction with STST.



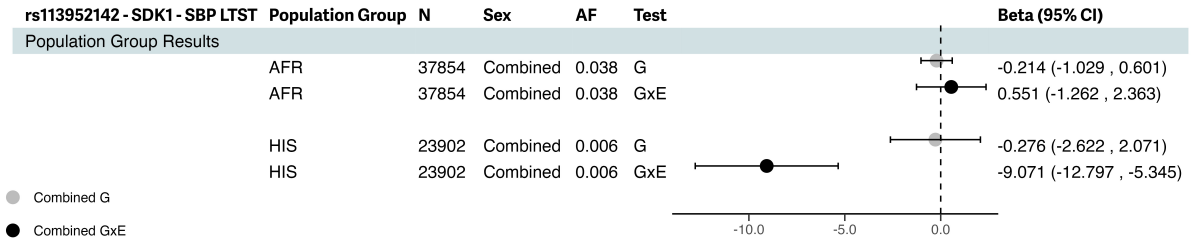
4. rs542745170 *(WWOX)* was identified in combined sex meta-analysis for pulse pressure by the 2df joint test driven by the interaction with STST.



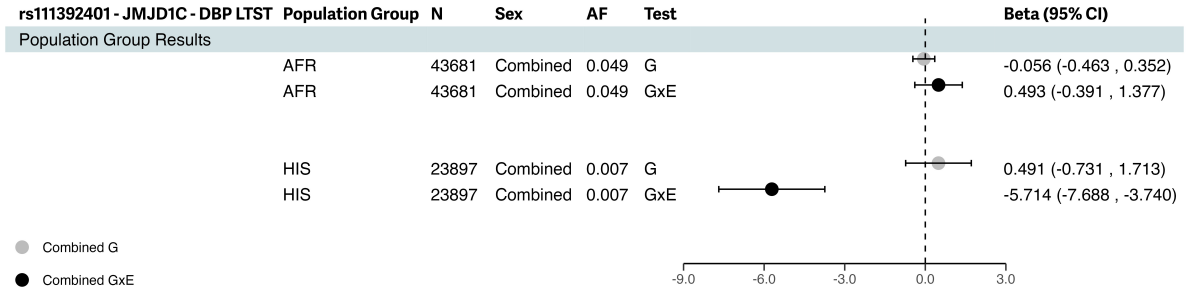
5. rs138288695 *(CRBN)* was identified in combined sex meta-analysis for diastolic blood pressure by the 2df joint test driven by interaction with LTST.



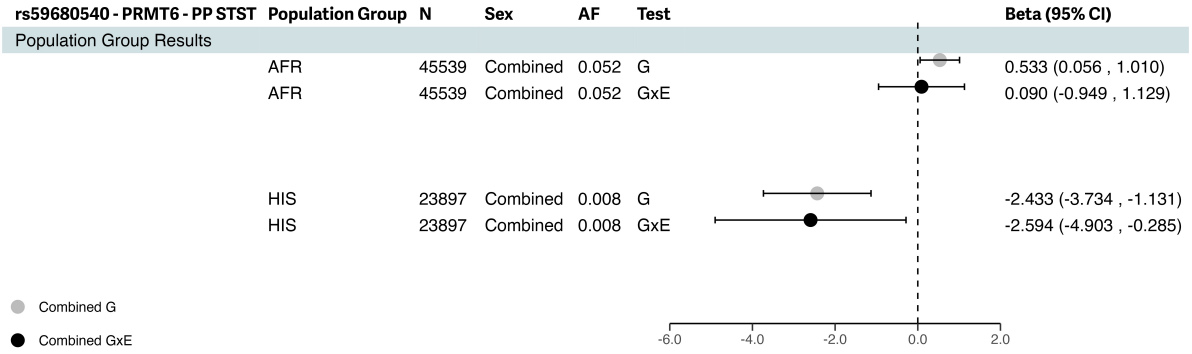
6. rs113952142 *(SDK1)* was identified in combined sex meta-analysis for systolic blood pressure by the 2df joint test driven by interaction with LTST.



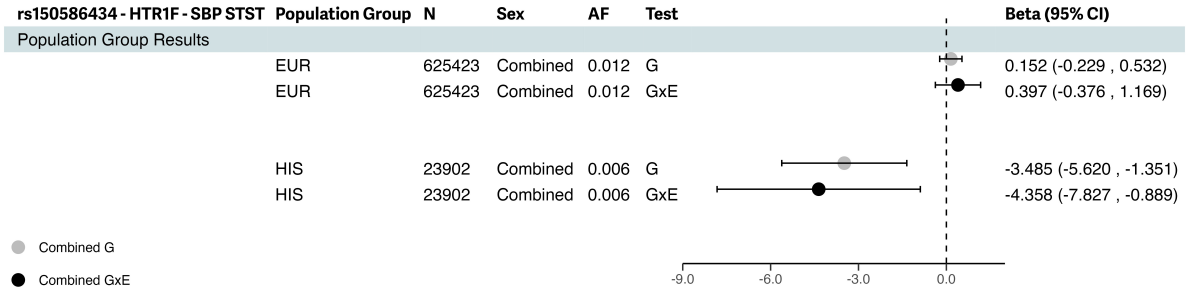
7. rs111392401 *(JMJD1C)* was identified in combined sex meta-analysis for diastolic blood pressure by the 2df joint test driven by interaction with LTST.



8. rs59680540 *(PRMT6)* was identified in combined sex meta-analysis for pulse pressure by the 2df joint test, not driven by interaction with STST.

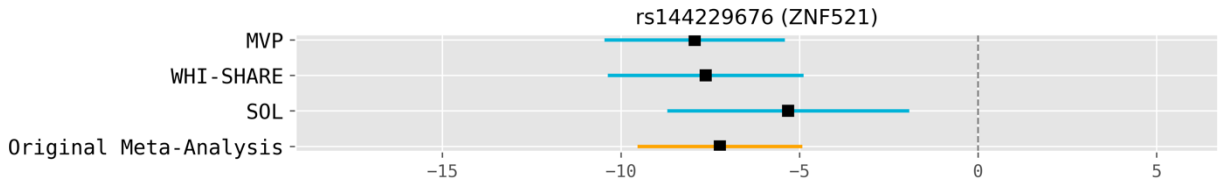


9. rs150586434 *(HTR1F)* was identified in combined sex meta-analysis for systolic blood pressure by the 2df joint test, not driven by interaction with STST.

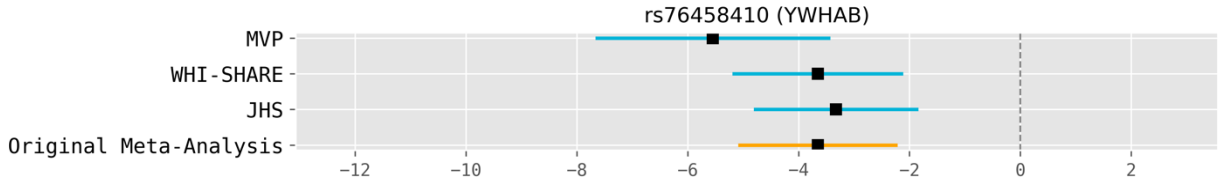


Supplementary Fig S4. Leave-One-Study-Out Sensitivity Meta-Analysis **Note:** Sensitivity meta-analyses for the 1df GxE interaction test was conducted on the novel gene-sleep duration loci identified in at least three cohorts. Loci identified by the 2df joint test not driven by the interaction effect (termed "supported by interaction" in Supplementary Table 4) are rs34761985 *(ST6GAL2)* and rs13032423 *(VRK2).* 95% confidence intervals are color-coded: yellow for original meta-analysis, and blue for the sensitivity analysis. Effect estimates are shown as black squares.

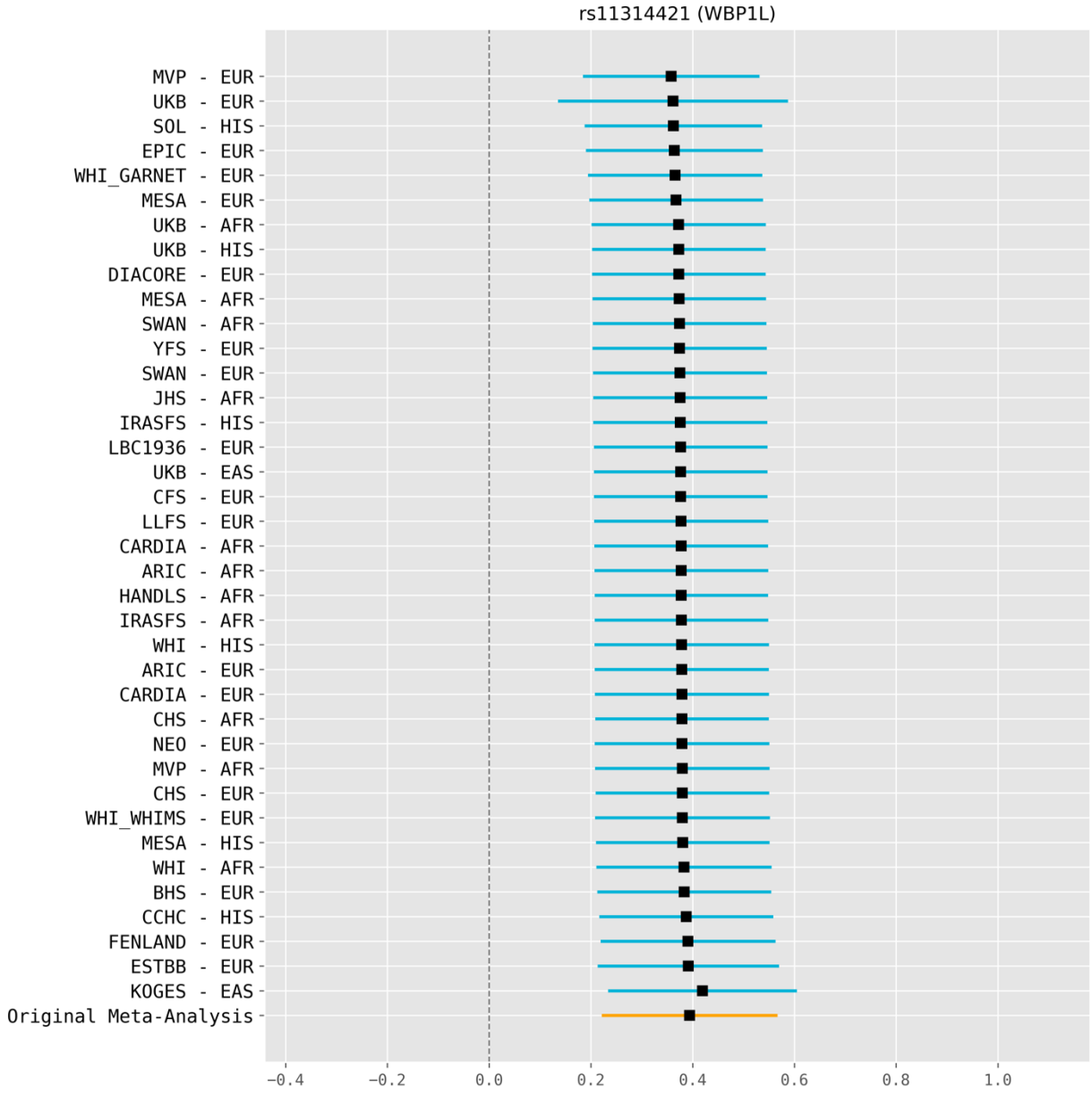
A. Rs144229676



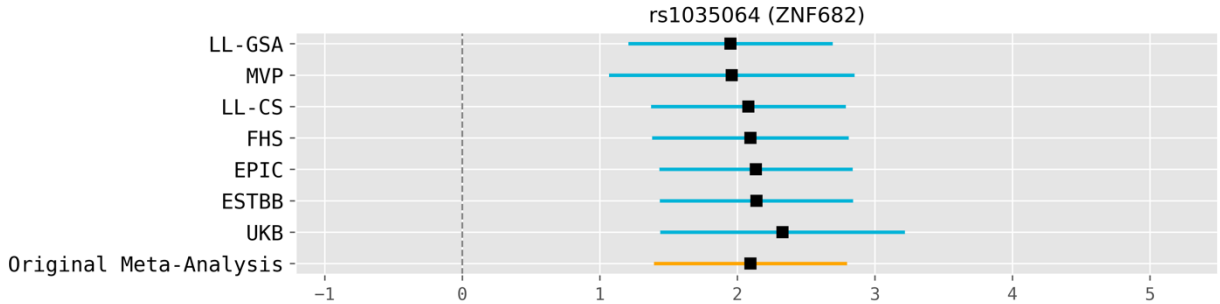
B. Rs76458410



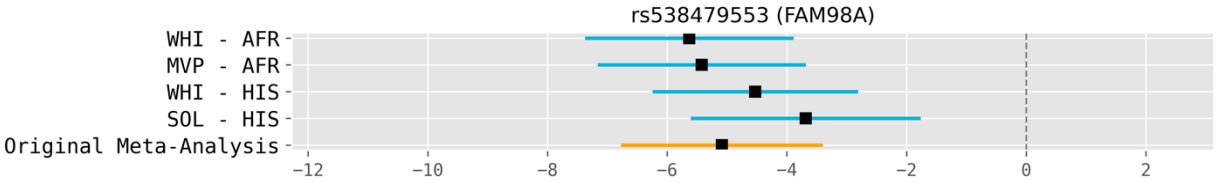
C. **Rs11314421**



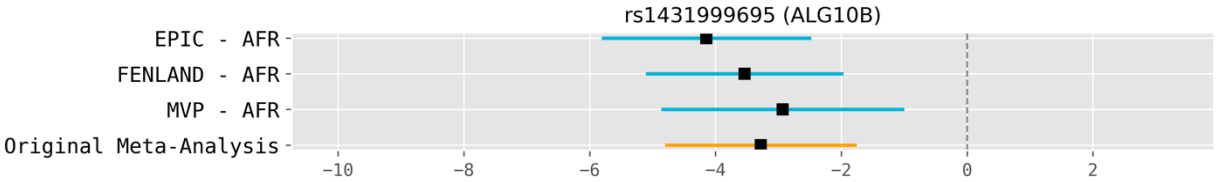
D. **Rs1035064**



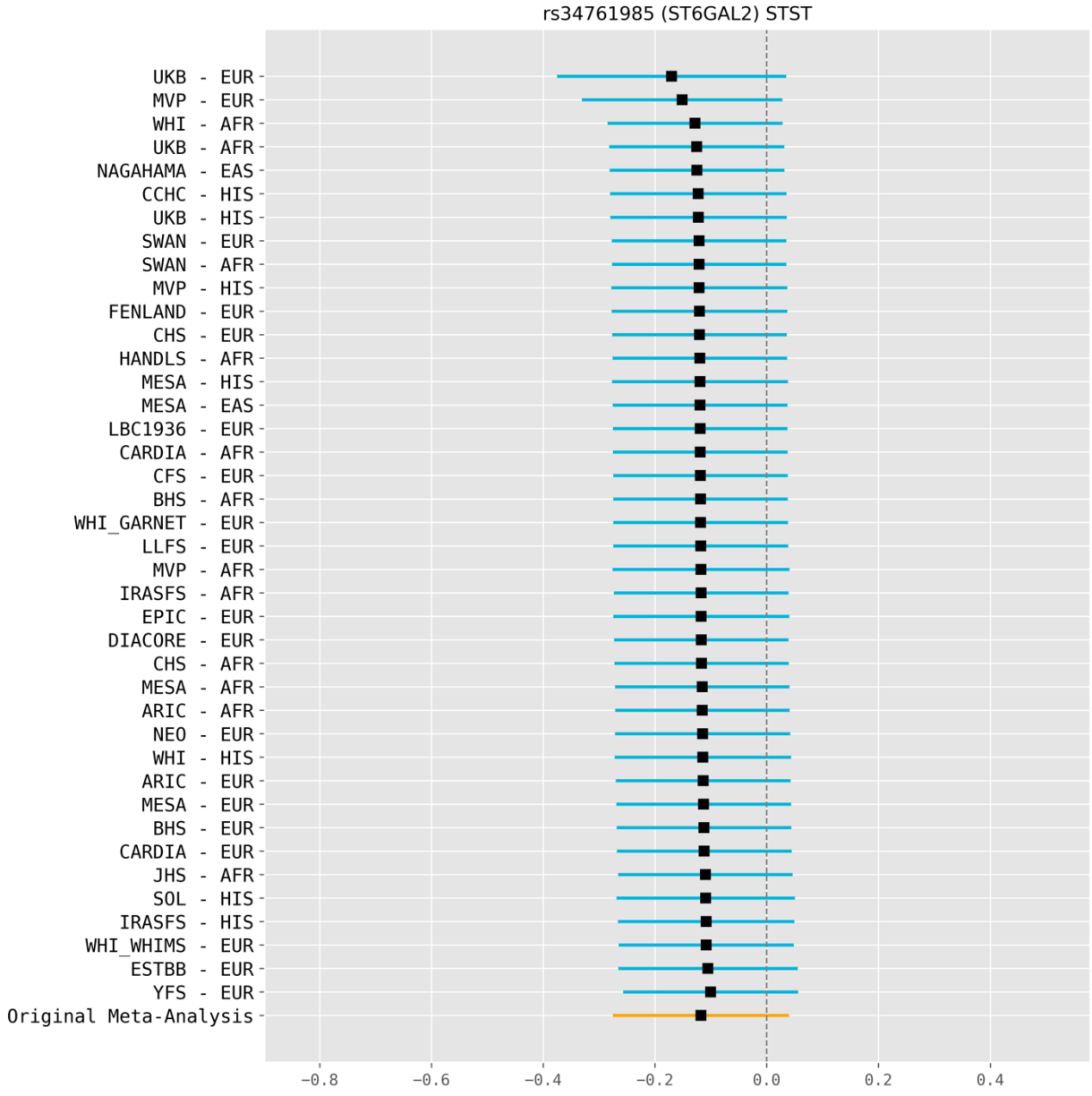
E. Rs538479553



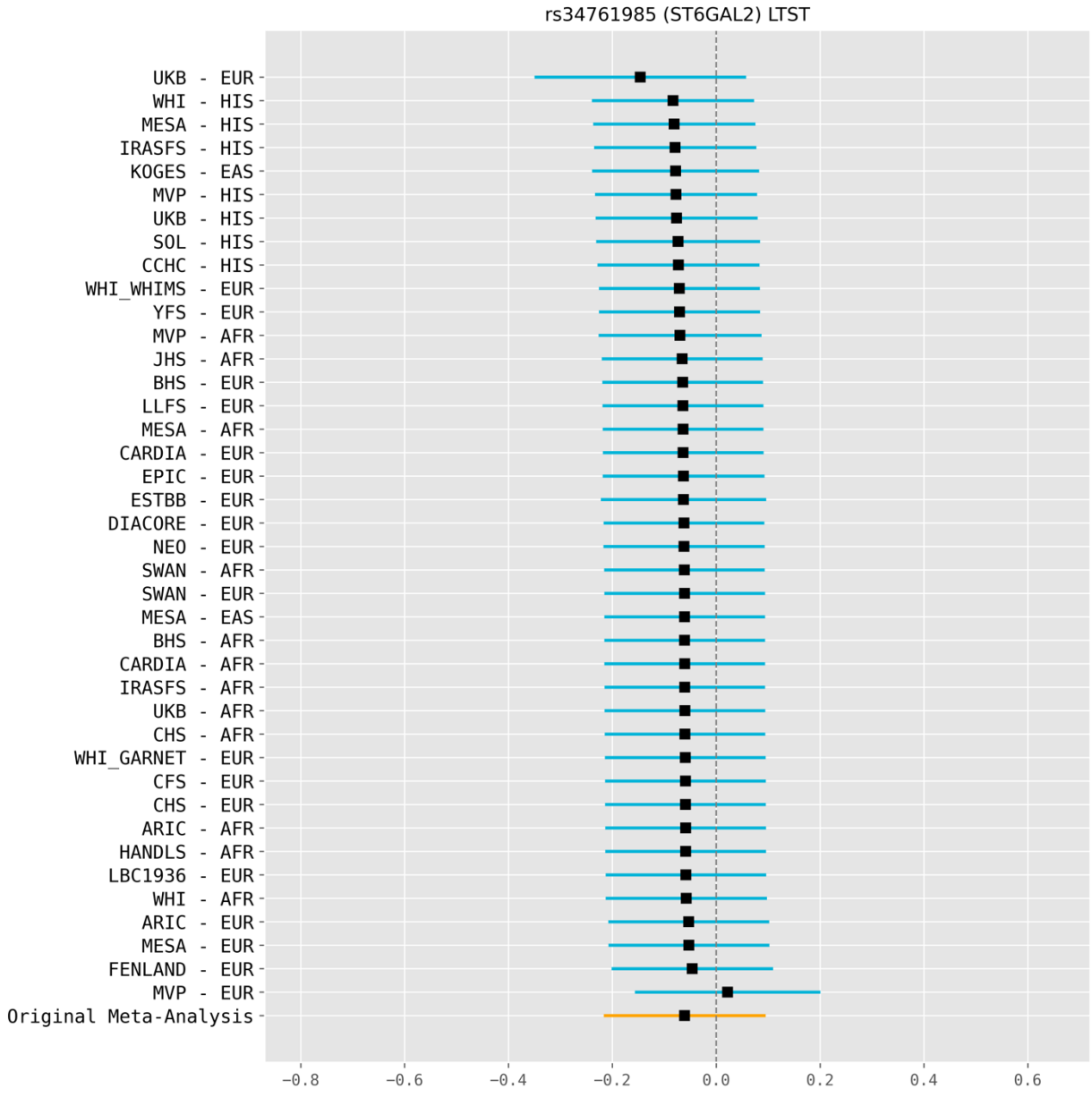
F. Rs1431999695



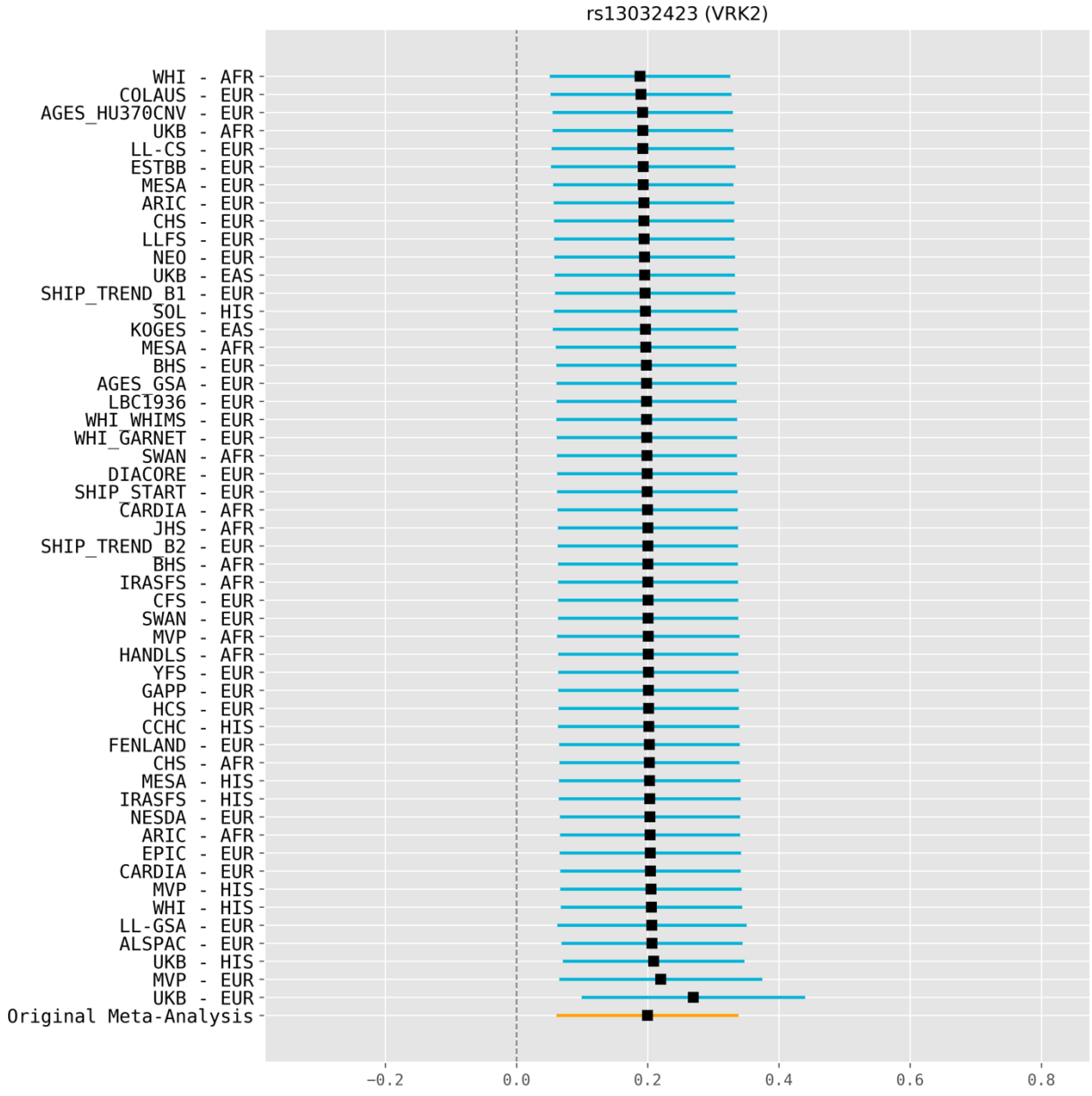
G. Rs34761985 (*STST Exposure)*



H. Rs34761985 (*LTST Exposure)*



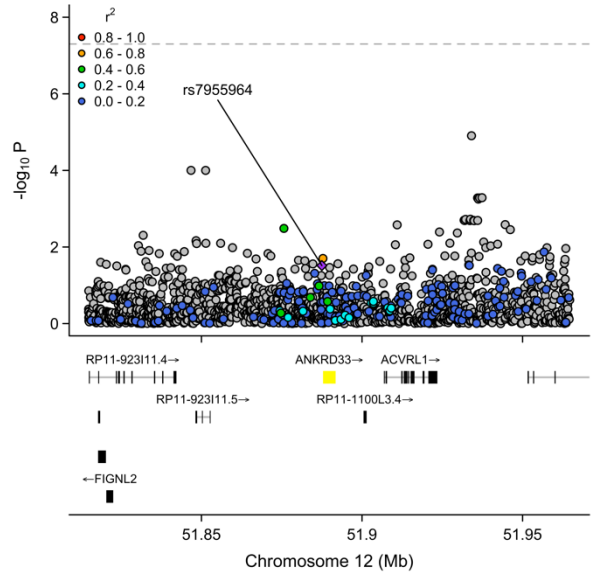
I. Rs13032423



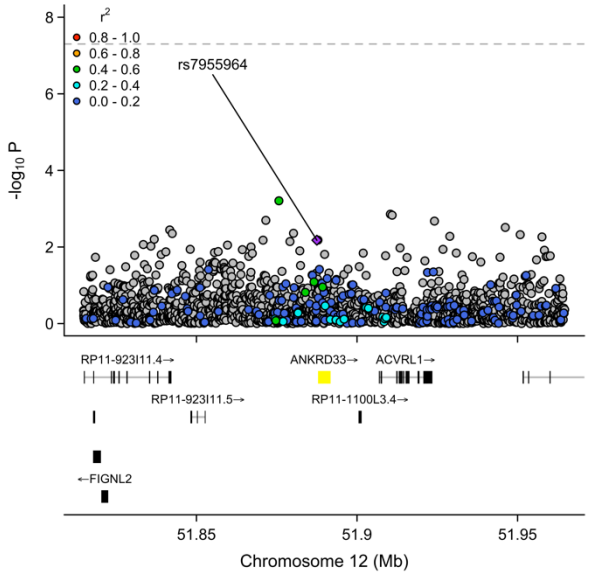
Supplementary Fig S5. Regional Association Plots Assessing Prior Gene-Sleep Duration Loci in Cross-Population Meta-Analysis in Combined Sex **Note:** In prior work (*Wang et al 2021*) three gene-sleep duration loci were reported for BP traits. rs7955964 was identified for mean arterial pressure (MAP), so we display results for the outcome measure (SBP, DBP, or PP) with the minimum p-value for this variant, as we did not use MAP as an outcome in this analysis. Below we show that these 3 loci show modest/weak signals in this current analysis plausibly due to improved sample size and multi-ethnic data incorporation. P-values and standard errors are reported additionally in Supplementary Table S5. Below, in each figure the plot displays coloring based on LD information from *LDLink* (1000G GRCh38 High Coverage, *ALL* populations) with prior reported index variant shown as a dark purple diamond.

A. rs7955964 - *SBP - LTST*

2df G,GxE Joint Test

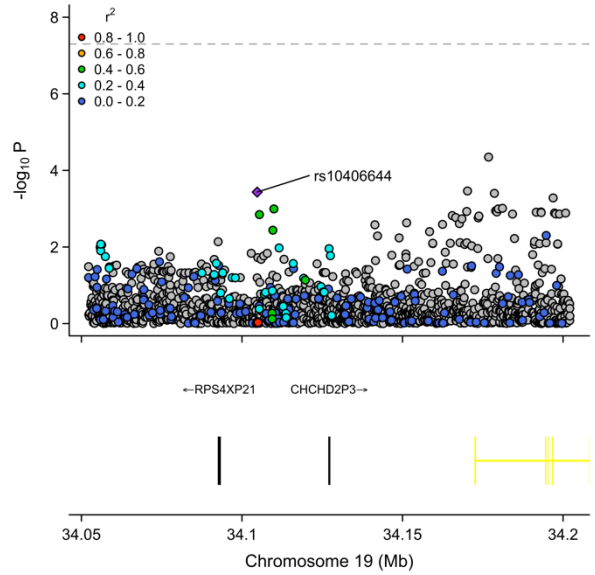


1df GxE Interaction Test

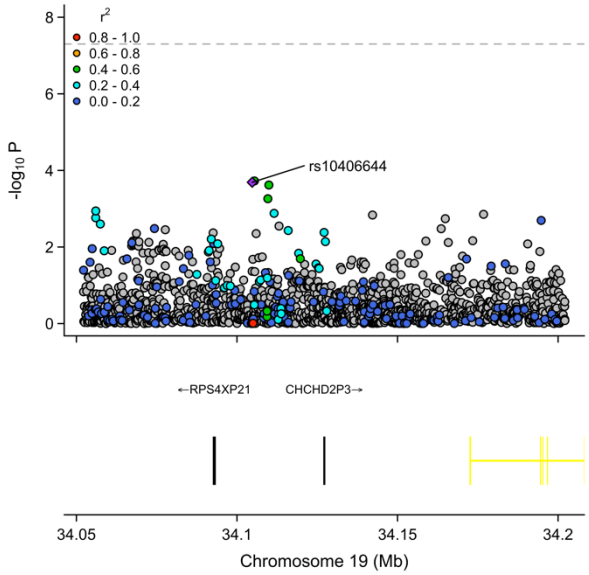


B. rs10406644 - *PP – STST*

2df G,GxE Joint Test

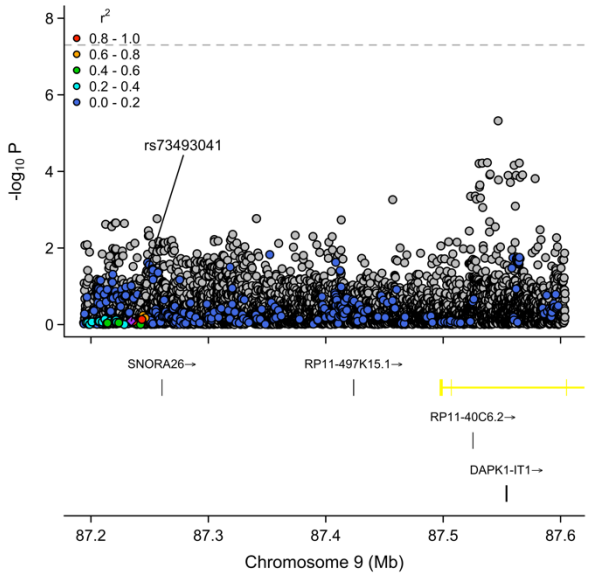


1df GxE Interaction Test

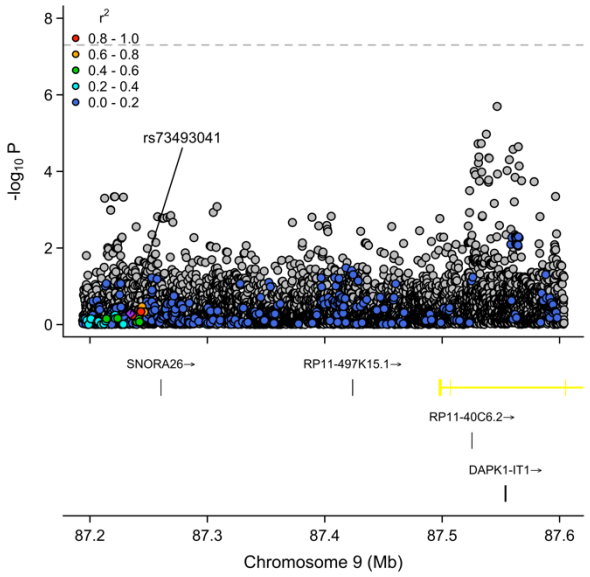


A. rs73493041 - *DBP – STST*

2df G,GxE Joint Test

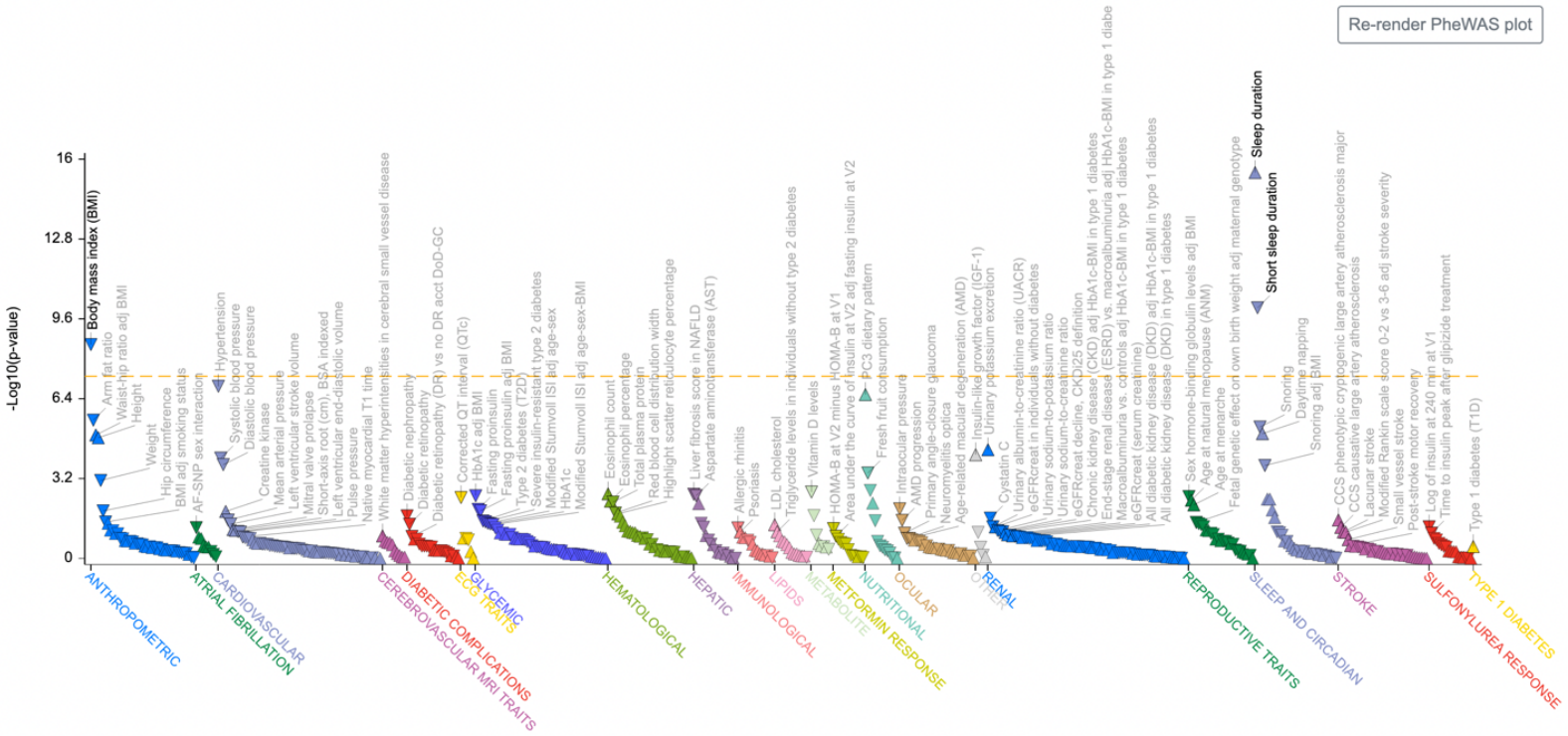


1df GxE Interaction Test



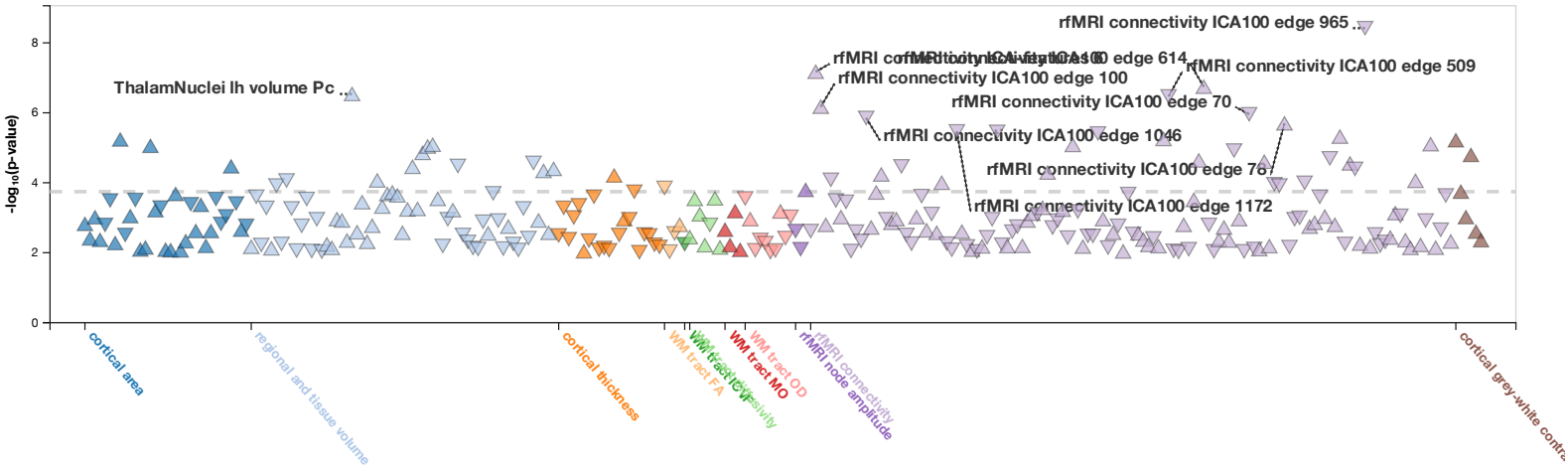
Supplementary Fig. S6. Phenome-wide Association Results From Common Metabolic Diseases Knowledge Portal for rs13032423 *(VRK2)*

Note: Below are p-values plotted and derived from (https://md.hugeamp.org/) from past GWAS studies.

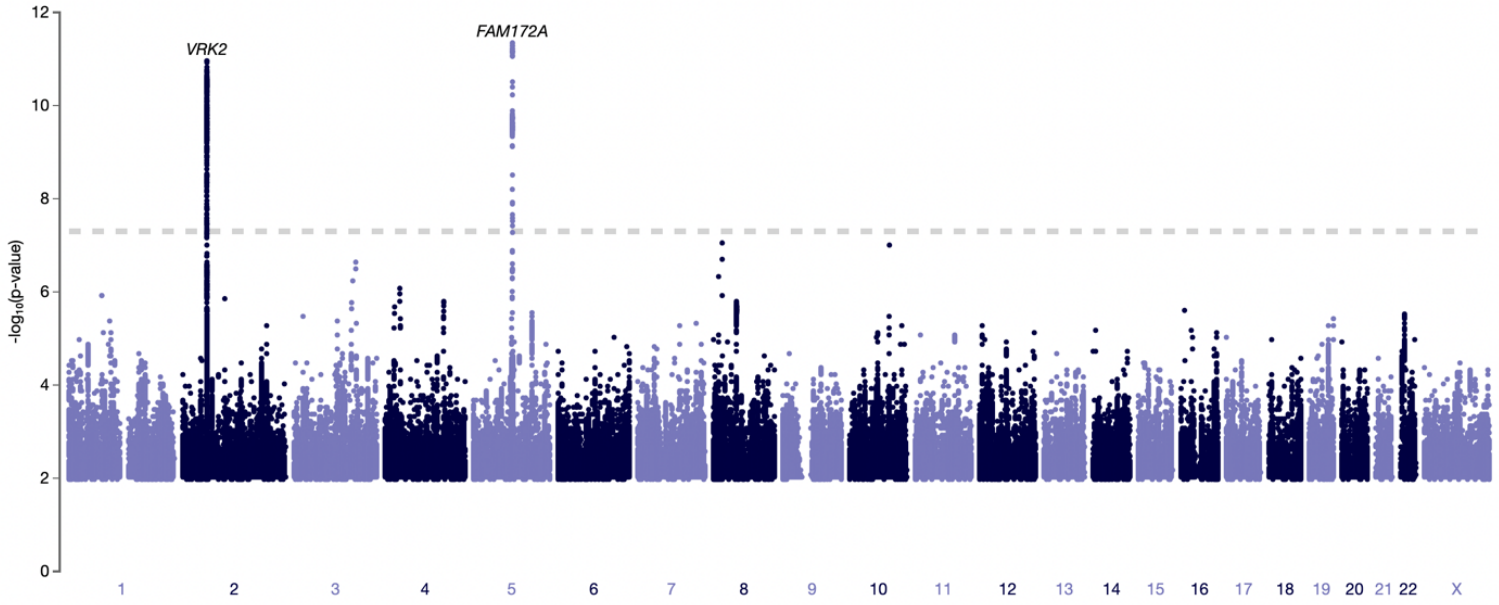


Supplementary Fig S7. Brain Imaging Association Results (p<5e-08) From Oxford Brain Imaging Genetics Server (BIG40)

A. Phenome-wide Association Results for *rs13032423 (VRK2)*



B. Genome-wide Association Results for *rfMRI connectivity ICA100 edge 965*



Supplementary Notes

A. Study Descriptions

Age Gene/Environment Susceptibility Reykjavik Study (AGES): 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.

ALSPAC: Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study (PMID 22507742, 22507743). The initial number of pregnancies enrolled is 14,541 (for these at least one questionnaire has been returned or a 'Children in Focus' clinic data had been attended by 19/07/99). Of these initial pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. Questionnaires were sent at regular intervals, and biological samples were taken from mothers and children including blood samples, from which DNA was extracted. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol (PMID 18929686). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendation of the ALSPAC Ethics and Law Committee at the time. Sleep duration was self-reported between July 2002 and May 2004 by ALSPAC mothers and during 25-year follow-up (November 2017 ~ July 2018) by ALSPAC children. Blood pressure traits were measured in the first focus on mothers clinic (December 2008 ~ July 2011) for ALSPAC mothers and in the focus clinic during follow-up (June 2015 ~ October 2017) for ALSPAC children when they were around 24-year-old. For eligible participants from the same family (i.e. ALSPAC mother-child pairs), we randomly selected one of them to be included in the analyses. Thus, our study relied on 3793 genetically unrelated participants of European descent.

Atherosclerosis Risk in Communities Study (ARIC): 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 additional triennial follow-up

examinations, a fifth exam in 2011-2013, a sixth exam in 2016-2017, and a seventh exam in 2018-2019, an eighth exam in 2020, a ninth exam in 2021-2022, and tenth exam in 2023. The eleventh exam is due to start in 2024. The ARIC study has been described in detail previously (PMC8667593; Wright JD, Folsom AR, Coresh J, et al. The ARIC (Atherosclerosis Risk In Communities) Study: JACC Focus Seminar 3/8. J Am Coll Cardiol. 2021 Jun 15;77(23):2939-2959).

Bogalusa Heart Study (BHS): The BHS study is population-based panel study to investigate the early natural history of cardiovascular disease and risk factors from childhood to adulthood among a biracial sample (65% white and 35% African American) of residents from Bogalusa, Louisiana. The study was established in 1973 by Dr. Gerald Berenson. To date, 9 surveys were conducted in children and adolescents aged 4 to 17 years, and 11 surveys were conducted among adults aged 18 to 51 years who were examined previously as children. At each survey, a standard questionnaire was used by trained research staffs to collect participants' information on family status, levels of education, income, medical history and health behaviors. Clinical measures were collected following stringent protocols. The current study included 630 participants who were born between 1959 and 1979, examined at least once in childhood, and surveyed during the follow-up visit between 2013 and 2016. Genome-wide genotypes were assayed using the Illumina Human610 BeadChip. The genotype data were further imputed to the TOPMed reference panel using the TOPMed Imputation Server following a stringent genotype imputation protocol developed by the University of Michigan.

The Coronary Artery Risk Development in Young Adults (CARDIA): CARDIA is a prospective multicenter study of the development and determinants of clinical and subclinical cardiovascular disease and their risk factors. It began in 1985-1986 with a group of 5,115 black and white men and women aged 18-30 years, recruited from four US centers. 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 participants were selected so that there would be approximately the same number of people in subgroups of race, gender, education (high school or less and more than high school) and age (18-24 and 25-30). These same participants were asked to participate in follow-up examinations during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), 2010-2011 (Year 25), 2015-2016 (Year 30), and 2020-2022 (Year 35).
Data collection protocols have been described previously (PMID: 3204420). Weight, height, systolic blood pressure and diastolic blood pressure were measured using standard protocols with participants wearing light clothing and no shoes. Morning venous blood samples were obtained after an overnight fast of at least 8 hours. Total cholesterol and triglycerides were measured enzymatically, HDL-C was determined by precipitation with dextran sulfate magnesium chloride, and LDL cholesterol was calculated using the Friedewald equation. Fasting plasma glucose and insulin were measured with the hexokinase–ultraviolet and radioimmunoassay methods, respectively (Linco Research, St Charles, MO, USA).
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.

Cameron County Hispanic Cohort (CCHC): The CCHC (Cameron County Hispanic Cohort) is an ongoing, longitudinal study that was initiated in 2004 to investigate the burden of metabolic-related conditions and disparities in a Mexican American community. The ongoing study has recruited over 5000 participants through community-based research assistants who through a randomization process contact families living at the US-Mexico border in Cameron County, TX to voluntarily enroll in the program. They are then invited to visit the Clinical Research Unit located in facilities provided by Valley Baptist Medical Center, Brownsville, TX. Comprehensive clinical examinations and collection of specimens have been conducted and archived for further analysis. A subset of 4076 individuals have been genotyped using the Illumina MEGA array and the results have been imputed to TOPMed phase 8 reference data.

The Cleveland Family Study (CFS): is the largest family-based study of sleep apnea worldwide, consisting of 2,284 individuals (46% African American) from 361 families studied on up to 4 occasions over a period of 16 years. The study was begun in 1990 with the initial aims of quantifying the familial aggregation of sleep apnea. NIH renewals provided expansion of the original cohort (including increased minority recruitment) and longitudinal follow-up, with the last exam occurring in February 2006. 632 African Americans were genotyped on the Affymetrix array 6.0 platform through the CARe Consortium with suitable genotying quality control. A further 122 African-Americans had genotyping based on the Illumina OmniExpress + Exome platform. Genomes were imputed by TOPMed imputation server separately.

Cardiovascular Health Study (CHS): 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 (1). 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. 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. Data for this analysis were from the study visit in 1996-1997. 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.

1. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991; 1:263-76.

CoLaus: The CoLaus study is a population-based cohort of 6733 participants from Lausanne (Switzerland) aged 35-75 at recruitment (2003-2006). This study collects detailed and standardized phenotypes to investigate biological, genetic and environmental determinants of cardiovascular disease and their association with mental disorders.
Initiated in 2003, the main aims of the CoLaus study were:

- To better understand the epidemiology of cardiovascular risk factors and diseases in the Swiss population.
- To discover new genetic determinants of these conditions.

- To determine the nature of the associations between cardiovascular disease and mental disorders

Since then, three follow-up surveys have been completed (2009-2012, 2014-2016, 2018-2020) and a forth one is ongoing since 2022. A detailed description of the participants' selection, inclusion criteria and methods used can be found in the following manuscript:
Firmann M, Mayor V, Marques Vidal P, Bochud M, Pécoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, et al. The CoLaus study: a population-based study to investigate the genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovascular Disorders. 2008; 8:6. PMID: 18366642; PMCID: PMC2311269; DOI: 10.1186/1471-2261-8-6.

DIAbetes COhoRtE (DIACORE): is a German prospective cohort study of 3,000 adult European diabetes mellitus type 2 outpatients, with a primary focus on renal events. Four follow-up examinations were conducted within 10 years after baseline inclusion. At each visit including, a core phenotyping protocol was performed that included a standardized interview, a physical examination, the determination of standard laboratory parameters from serum, urine and whole blood in a central laboratory and biobanking of biomaterials. The design of the DIACAORE study (Dorhofer L, Lammert A, Krane V, et al. Study design of DIACORE (DIAbetes COhoRtE)—a cohort study of patients with diabetes mellitus type 2. BMC Med Genet. 2013;14:25) and exemplary results (Rheinberger M, Jung B, Segiet T, et al. Poor risk factor control in outpatients with diabetes mellitus type 2 in Germany: The DIAbetes COhoRtE (DIACORE) study. PLoS ONE 2019;14(3): e0213157) were published previously.

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 health effects of regular physical exercise and a healthy diet in a population-based random sample of Finnish men and women aged 55-74 years living in the city of Kuopio in 2002. The 3000 men and women who were invited to participate in the study were obtained from the national population registry. Altogether 2062 men and women expressed their willingness to participate in the study, and 1479 of them attended the baseline measurements in 2005 - 2006. The prespecified exclusion criteria were medical or other conditions that prohibit engagement in exercise intervention or the assessments, as judged by a physician. After these exclusions, 1410 individuals aged 57-78 years at baseline in 2005-2006 were randomized into the resistance exercise, aerobic exercise, diet, combined resistance exercise and diet, combined aerobic exercise and diet, or control group.

European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk: The EPIC-Norfolk study (DOI 10.22025/2019.10.105.00004) is a prospective population-based cohort study which recruited 25,639 men and women aged 40-79 years at baseline between 1993 and 1997 from 35 participating general practices in Norfolk, UK [PMID:10466767]. Individuals attended for a baseline health check including the provision of blood samples for concurrent and future analysis. Further health check visits have been conducted since the baseline visit. Participants have contributed information about their diet, lifestyle and health through questionnaires and health checks over two decades. Sleep information was collected at the second heath check that was conducted in 1998-2000 (ages 42-82 years) with 15,786 participants. DNA has been extracted from all EPIC participants and stored blood has been analysed for an extensive range of classical and novel biomarkers. Sample quality control was performed including gender check, relatedness check, and ancestry check. The Norwich Local

Research Ethics Committee granted ethical approval for the study. All participants gave written informed consent.

EstBB: The population-based Estonian Biobank (EstBB) contains data for 213,000 inhabitants of Estonia (~20% of the adult population). For the participants, a comprehensive questionnaire (providing objective information, and information on, e.g., physical activity and diet) is filled out and DNA, plasma, and white blood cell samples are stored. The database is updated by regular linkage to the national health databases. The EstBB project is being conducted according to the Estonian Human Genes Research Act, and all participants have signed a broad informed consent form (PMID: 24518929).

The Fenland Study: The Fenland study (DOI 10.22025/2017.10.101.00001) is a population-based cohort study that uses objective measures of disease exposure to investigate the influence of diet, lifestyle and genetic factors on the development of diabetes and obesity. The first phase of the Fenland Study was conducted between 2005 and 2015, and the volunteers are recruited from general practice lists in and around Cambridgeshire (Cambridge, Ely, and Wisbech) in the United Kingdom from birth cohorts from 1950–1975. Participants who attended the first phase of the study were invited to phase 2 of the study between 2014 and 2020, and the sleep data is available at this phase.

Framingham Heart Study (FHS): 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.

Genetic and phenotypic determinants of blood pressure and other cardiovascular risk factors (GAPP): GAPP is a population-based prospective cohort study involving a representative sample of initially healthy adults aged 25-41 years at baseline and residing in the Principality of Liechtenstein. Exclusion criteria were the presence of cardiovascular disease, diabetes, obstructive sleep apnea and a body mass index >35kg/m2. A standardized 12-lead ECG was obtained in all participants. Baseline characteristics were obtained in all participants using standard methodology. The main goal of GAPP is to assess the mechanisms for the development of cardiovascular risk factors over time.

Genetic Epidemiology Network of Salt-Sensitivity (GenSalt): The GenSalt study is a unique NHLBI-sponsored family feeding-study designed to examine the interaction between genes and dietary sodium intake on BP. A detailed description of the GenSalt study design and participants has been reported previously[1]. Briefly, 3,142 participants from 633 Han families from rural, north China were ascertained through a proband with untreated pre-hypertension or stage-1 hypertension identified from a population-based BP screening. Individuals who had stage 2 hypertension, secondary hypertension, and a history of clinical cardiovascular disease or diabetes

or were pregnant, heavy alcohol drinkers, or currently on a low-sodium diet or BP lowering medication were excluded from the study, with a total of 1,906 GenSalt probands and their siblings, spouses, and offspring eligible for the 7-day low sodium and 7-day high sodium dietary interventions. At baseline, a standard questionnaire was administered by a trained staff member to collect information on family pedigree, demographic characteristics, personal and family medical history, and lifestyle risk factors. Body weight and height were measured twice in light indoor clothing without shoes. Body mass index was calculated as weight in kilograms per height in square meters. BP was measured three times at the same time each morning during the three-day baseline examination by trained and certified. The mean of the 9 BP measures was used in subsequent analyses. Blood specimens were collected by venipuncture to measure lipids, creatinine, and other laboratory values. Among the 1,906 intervention participants, 1,881 underwent genome-wide genotyping and whole genome sequencing.

1. The GenSalt Collaborative Research Group. GenSalt: rationale, design, methods and baseline characteristics of study participants. *J Hyperten.*2007;21:639-646.
2. Perloff D, Grim C, Flack J, Frohglich ED, Hill M, McDonald M, Morgenstern BZ. Human blood pressure determination by sphygmomanometer. *Circulation.* 1993;88:2460–2470.

Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS): 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 American and White residents of Baltimore, Maryland. This unique study entering its 20th year has longitudinally assessed 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, age-associated disease, and cognitive decline. The study recruited 3,720 participants from Baltimore, MD with a mean age of 47.7 years, 2,200 African Americans and 1,520 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 Project number AG000513.

Hispanic Community Health Study/Study of Latinos (HCHS/SOL): The HCHS/SOL is a multicenter prospective cohort of 16,000 Hispanic/Latino adults designed to investigate the role of acculturation in disease, and to identify other traits that impact Hispanic/Latino health. HCHS/SOL is the most diverse and comprehensive study of Hispanic/Latino health, with participants of Cuban, Puerto Rican, Dominican, Mexican or Central/South American origin. Participants were recruited through four sites affiliated with San Diego State University, Northwestern University in Chicago, Albert Einstein College of Medicine in Bronx, New York, and the University of Miami, using a census block and household sampling design. Study participants who were self-identified Hispanic/Latino and aged 18-74 years underwent extensive psycho-social, clinical assessments, and biospecimen collection during the baseline visit (2008-2011). A re-examination of the HCHS/SOL cohort was conducted during 2015-2017, and visit 3, which began in 2020, is ongoing. Annual telephone follow-up interviews have been conducted

since study inception to determine health outcomes of interest. (dbGaP study accession number: phs000555).

HCS (Hunter Community Study): The HCS is a community-based longitudinal investigation that was commenced in Australia in 2004-2005. The study aims to investigate retired and near-retired persons by sampling older Australians aged 55–85, randomly selected from electoral rolls in a regional area on the heavily populated east coast (New South Wales). There were 3253 participants who completed at least some baseline measures. Follow-up was obtained through health record linkage up to 2017, representing over 10 years of health outcomes and hospitalizations.

Insulin Resistance Atherosclerosis Study Family Study (IRASFS): The IRASFS was a family study designed to examine the genetic and epidemiologic basis of glucose homeostasis traits and abdominal adiposity. Briefly, self-reported Mexican American pedigrees were recruited in San Antonio, TX and San Luis Valley, CO. Probands with large families were recruited from the initial non-family-based IRAS, which was modestly enriched for impaired glucose tolerance and T2D. Inclusion of IRASFS data is limited to 1040 normoglycemic individuals in 88 pedigrees with genotype data from the Illumina OmniExpress and Omni 1S arrays and imputation to the 1000 Genome Integrated Reference Panel (phase I).

JHS (Jackson Heart Study): The JHS is a longitudinal, community-based observational cohort study of 5,306 adults investigating the role of environmental and genetic factors in the development of cardiovascular disease in African Americans. Between 2000 and 2004, 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 [1-3]. 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.

1. Wyatt SB, Diekelmann N, Henderson F, Andrew ME, Billingsley G, Felder SH, et al. A community-driven model of research participation: the Jackson Heart Study Participant Recruitment and Retention Study. *Ethn Dis*. 2003;13(4):438-55. PubMed PMID: 14632263.

2. Taylor HA, Jr., Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn Dis*. 2005;15(4 Suppl 6):S6-4-17. PubMed PMID: 16320381.

3. Fuqua SR, Wyatt SB, Andrew ME, Sarpong DF, Henderson FR, Cunningham MF, et al. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. *Ethn Dis*. 2005;15(4 Suppl 6):S6-18-29. PubMed PMID: 16317982.

Korean Genome and Epidemiology Study (KOGES): KoGES is a large-scale prospective cohort study with a comprehensive range of phenotypic measures and biological samples

collected on approximately 210,000 individuals. KoGES's long-term objective is to develop comprehensive and applicable healthcare guidelines for common complex diseases in Koreans, reduce the burden of chronic diseases and improve the quality of life. KoGES includes population-based cohorts, the community-based Ansan and Ansung study, the urban community-based health examinee study, and the rural community-based cardiovascular disease association study. The cohorts consist of community-dwellers and participants recruited from the national health examinee registry, men and women, aged ≥ 40 years at baseline. A total of 72,000 samples were genotyped with KoreanChip, a customized array optimized for the Korean population, and imputed using IMPUTE4 with 1000 Genomes Project Phase 3 data and the Korean reference genome as a reference panel. Measures of the baseline recruitment, and only genotyped samples that met the following exclusion criteria were used in the analyses: low call rate (<97%), excessive heterozygosity, excessive singletons, gender discrepancy, and cryptic first-degree relatives. SNPs with low HWE p value ($<10^{-6}$) or low call rate (<95%) were excluded. Variants with imputation quality score (IQS) < 0.8 and MAF <1% were excluded after imputation.

1. Kim, Yeonjung, Bok-Ghee Han, and KoGES Group. "Cohort profile: the Korean genome and epidemiology study (KoGES) consortium." International journal of epidemiology 46.2 (2017): e20-e20.
2. Moon, Sanghoon, et al. "The Korea Biobank Array: design and identification of coding variants associated with blood biochemical traits." Scientific reports 9.1 (2019): 1-11.
3. Nam, Kisung, Jangho Kim, and Seunggeun Lee. "Genome-wide study on 72,298 individuals in Korean biobank data for 76 traits." Cell Genomics 2.10 (2022): 100189.

Lothian Birth Cohort 1936 (LBC1936): LBC1936 consists of 1091 relatively healthy individuals, most of whom took part in the Scottish Mental Survey of 1947 at the age of ~11 years old. They were recruited to a study to determine influences on cognitive ageing at age ~70 years, when almost all lived independently in the Lothian region of Scotland. For this project, data was drawn from LBC1936 Wave 3 (when sleep data was obtained).They have taken part in six waves of testing in later life (at mean ages 70, 73, 76, 79, 82 and 85 years). At each wave they underwent a series of cognitive and physical tests.[1,2]

1. Deary IJ, Gow AJ, Pattie A, Starr JM. Cohort profile: the Lothian Birth Cohorts of 1921 and 1936. Int J Epidemiol 2012;41:1576-1584.
2. Taylor AM, Pattie A, Deary IJ. Cohort Profile Update: The Lothian Birth Cohorts of 1921 and 1936. Int J Epidemiol 2018;47:1042-1042r

Lifelines: (https://lifelines.nl/) Lifelines 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. (Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol. 2014 Dec 14.)
Lifelines was genotyped in 2 stages: the first stage consisted of ~15,000 participants and used the Illumina CytoSNP chip; the second stage included ~35,000 participants and used the Illumina GSA chip. Due to the differences in genotyping, these two groups are analysed separately. Samples that are present, or have close relatives in both groups, are excluded from the CytoSNP dataset prior to analysis.

The Long Life Family Study (LLFS): LLFS is a longitudinal, population-based multigenerational family cohort designed to study genetic, behavioral, and environmental factors in families exhibiting exceptional longevity. Families were sampled from four clinical centers: Boston University Medical Center in Boston, MA; Columbia College of Physicians and Surgeons in New York City, NY; the University of Pittsburgh in Pittsburgh, PA, USA; and the University of Southern Denmark, Denmark. The characteristics, recruitment, eligibility, and enrollment were previously described (PMID: 21258136, PMID: 34739053). The first clinical exam started in 2006 and recruited 4,953 individuals in 539 two-generational families that demonstrated clustering for exceptional survival in the upper generation. The second clinical exam (2014-2017) revisited 2,933 European descent individuals from 528 families. The third clinical exam (2021-) is recruiting the participants from second exam and a few new ones from the grandchild generation. The individuals were genotyped using ~2.3 million SNPs from the Illumina Omni chip, then imputed on Version R2 of the TOPMed reference panel using the Michigan Imputation Server (https://imputation.biodatacatalyst.nhlbi.nih.gov/#!), which used Eagle v2.4 for phasing and minimac4 v1.3.3 for imputation.

Multi-Ethnic Study of Atherosclerosis (MESA): 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, including the recently completed Exam 6 (2016-2018). MESA Exam 7 will be completed by early 2024. Participants have been contacted every 9 to 12 months throughout the study to assess clinical morbidity and mortality. Informed

consent was obtained for extensive data sharing (dbGaP) and genetic/omic studies, including candidate genes (NHLBI CARe), genome-wide scans (NHLBI SHARe), exome sequencing (NHBLI ESP) and, most recently, the NHLBI TOPMed program.

1. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002 Nov 1;156(9):871-81. PubMed PMID: 12397006.

Million Veteran Program (MVP): The MVP is a mega-biobank that was launched in 2011 and supported entirely by the Veterans Health Administration Office of Research and Development in the United States. The MVP received ethical and study protocol approval from the VA Central Institutional Review Board (IRB) in accordance with the principles outlined in the Declaration of Helsinki. The specific design, initial demographics and quality-control procedures of the MVP have been detailed previously (10.1016/j.jclinepi.2015.09.016).

The Nagahama Study (NAGAHAMA): Details on this cohort can be found in the profile paper for this study at https://link.springer.com/chapter/10.1007/978-981-16-5727-6_7. This is a large-scale genome cohort in Japan that commenced in 2007, as The Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience. At the frequency of every 5 years, lifestyle, clinical, and environmental measurements were collected along with data on disease trajectories, and blood and urine samples.

The Netherlands Epidemiology of Obesity study (NEO): 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.

Netherlands Study of Depression and Anxiety (NESDA): The NESDA is an ongoing longitudinal cohort study to examine the prevalence, long-term course and consequences of depressive and anxiety disorders in the adult population. A detailed description of the study can be found elsewhere[1]. Briefly, a total of 2981 participants, consisting of a healthy control group, people with a history of depressive or anxiety disorder and people with current depressive and/or anxiety disorder, were recruited from community (19%), primary care (54%), and outpatient psychiatric clinics (27%), and included at the baseline assessment in 2004-2007. Inclusion criteria were a lifetime diagnosis of major depressive disorder or anxiety disorder, age 18-65 years, and self-reported western European ancestry. Excluded were those who were not fluent in Dutch, and those with a primary diagnosis of psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe substance use or dependence. Biological sample collection and biobanking procedures (i.e. blood sampling and DNA isolation) took place during the baseline visit and has been previously described in detail [2].

NESDA samples were genotyped using either the Perlegen-Affymetrix 5.0, or Affymetrix 6.0 genotyping chip and called with BirdSeed. SNPs were excluded if unmapped or mapped to multiple locations, call rate<95%, MAF<0.01, HWE p-value<10^{-5}, unmapped to build 36, allele frequency difference with 1000Genomes reference >20%, or palindromic SNPs with allele frequency>35%. Samples were removed if call rate<90%, deviant heterozygosity, abs(PLINK F)>0.1, sex mismatch, unexpected relatedness, or non-Caucasian. Imputation was performed with Impute software using the 1000Genomes Phase 1 Integrated Release 3 ALL reference panel.

1. Penninx BW, Beekman AT, Smit JH, et al. The netherlands study of depression and anxiety (NESDA): Rationale, objectives and methods. *International journal of methods in psychiatric research*. 2008;17(3):121-140.

2. Boomsma DI, Willemsen G, Sullivan PF, et al. Genome-wide association of major depression: Description of samples for the GAIN major depressive disorder study: NTR and NESDA biobank projects. *European Journal of Human Genetics*. 2008;16(3):335.

Study of Health in Pomerania (SHIP): The Study of Health In Pomerania (SHIP) is a prospective longitudinal population-based cohort study in Mecklenburg-Western Pomerania assessing the prevalence and incidence of common diseases and their risk factors (PMID: 20167617 and 35348705). SHIP encompasses the two independent cohorts SHIP-START 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-START 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 consent was obtained from each of the study participants.
Genome-wide SNP-typing was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (SHIP-START samples), the Illumina Infinium HumanOmni2.5 BeadChip, or the

Illumina Infinium Global Screening Array (SHIP-TREND samples). Array processing was carried out in accordance with the manufacturer's standard recommendations. Genotypes were determined using the Birdseed2 clustering algorithm for SHIP-START, GenomeStudio Genotyping Module v1.0, and GenomeStudio 2.0 Genotyping Module (GenCall) for SHIP-TREND.

Study of Women's Health Across the Nation (SWAN): The **S**tudy of **W**omen's Health **A**cross the **N**ation (SWAN) is a multi-site, multiracial/ethnic longitudinal study of women's health designed to describe the biological, behavioral, and psychosocial characteristics that occur during midlife and the menopausal transition. In addition to characterizing reproductive aging, SWAN focuses on the impact of menopause on age-related chronic diseases, such as diabetes, cardiovascular disease, depression, bone loss and osteoporosis, as well as physical and cognitive functioning. The SWAN cohort was enrolled in 1996-97 and consists of 3302 community-based women from seven sites with data from five race/ethnic groups: Black (n=935), Chinese (n=250), Hispanic (n=286), Japanese (n=281), and White (n=1550). To be eligible for enrollment women had to be aged 42 to 52 years old, have an intact uterus and at least one ovary, have had a menstrual period in the previous three months, and not be taking hormones. SWAN participants have completed 15 approximately annual follow-up visits since enrollment. During follow-up visits 5 and 6 (2001-2003), 1757 women from six sites were consented to provide genetic materials for whom extracted DNA was successfully obtained for 1536 women: Black (n=410), Chinese (n=151), Hispanic (n=0), Japanese (n=168), and White (n=807). This analysis was done separately for Whites and Blacks.

Sowers MF, Crawford S, Sternfeld B, Morganstein DG, Gold EB, Greendale G, Evans D, Neer R, Matthews K, Sherman S, Lo A, Weiss G, Kelsey J. SWAN: A multi-center, multi-ethnic, community-based cohort study of women and the menopausal transition. In: Lobo RA, Kelsey JL, Marcus R, editors. Menopause: biology and pathobiology. San Diego, CA: Academic Press; 2000. p. 175-88

TwinsUK: The TwinsUK registry is a national register of adult twins recruited as volunteers without selecting for any particular disease or traits PMID: 31526404. It is among the most detailed omics and phenotypic BioResource worldwide, including over 14,000 twins comparable to the general population for lifestyle characteristics. Genome-wide genotypes were assayed using a combined Illumina Human310 + Illumina Human610 BeadChip. The genotype data were imputed to the TOPMed reference panel using the TOPMed Imputation Server following a stringent genotype imputation protocol developed by the University of Michigan. A subset of 2,827 of genotyped twins with overlapping sleep and BP data were included in the analysis. All twins provided informed written consent and the study was approved by St Thomas' Hospital Research Ethics Committee (REC Ref: EC04/015).

UK Biobank (UKB): UK Biobank (UKB, www.ukbiobank.ac.uk) is a large longitudinal biobank study in the United Kingdom which was established to improve understanding of the genetic and environmental causes of common diseases including cardiovascular diseases. In addition to self-reported disease outcomes and extensive health and life-style questionnaire data, UKB participants are being tracked through their NHS records and national registries (including

cause of death and Hospital Episode Statistics). In 2017, UKB released the genotypes of 488,377 participants profiled with a custom SNP array. Genotyping QC was performed centrally by UKB, and genotypes imputed to Haplotype Reference Consortium (HRC) panel were released for 488,377 participants. Sample selection for the Gene-Lifestyle Interaction projects was based on available datasets for traits and lifestyle measures.

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(1, 2). 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. Study recruitment and exclusion criteria have been described previously(1, 2). 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. 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.
Genome wide association study (GWAS) non-overlapping samples are composed of (a) 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), (b) 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 (c) the WHI SNP Health Association Resource (WHI SHARe), a randomly selected sample of 8,515 African American and 3,642 Hispanic women from WHI. Genotyping was performed using Affymetrix 6.0 (WHI-SHARe), HumanOmniExpressExome-8v1_B (WHIMS) and Illumina HumanOmni1-Quad v1-0 B (GARNET). Quality control of the GWAS data included variant and sample call rates >95%, and included identification of genetically related individuals. Principal components were computed using methods developed by Price et al(3). Imputation was performed using the TOPMed Imputation Server and freeze 8 reference multi-ethnic panel (build hg38). Due to some overlap of WHI participants with the TOPMed reference panel, we re-calculated the estimated imputation quality based on only the samples not on TOPMed reference panel, to account for the over-estimation of imputation quality given by the imputation software(4). Variants with an imputation quality (Rsq) <0.3 were filtering out. 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. Analyses were performed using LinGxEScanR software.

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The Cardiovascular Risk in Young Finns Study (YFS): 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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Lifelines Cohort Study:
Raul Aguirre-Gamboa (1), Patrick Deelen (1), Lude Franke (1), Jan A Kuivenhoven (2), Esteban A Lopera Maya (1), Ilja M Nolte (3), Serena Sanna (1), Harold Snieder (3), Morris A Swertz (1), Peter M. Visscher (3,4), Judith M Vonk (3), Cisca Wijmenga (1), Naomi Wray (4)

(1) Department of Genetics, University of Groningen, University Medical Center Groningen, The Netherlands
(2) Department of Pediatrics, University of Groningen, University Medical Center Groningen, The Netherlands
(3) Department of Epidemiology, University of Groningen, University Medical Center Groningen, The Netherlands
(4) Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia.

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MVP Program Office

- Sumitra Muralidhar, Ph.D., Program Director
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420
- Jennifer Moser, Ph.D., Associate Director, Scientific Programs
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420
- Jennifer E. Deen, B.S., Associate Director, Cohort & Public Relations
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420

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- J. Michael Gaziano, M.D., M.P.H.
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- Elizabeth Hauser, Ph.D.
  Durham VA Medical Center, 508 Fulton Street, Durham, NC 27705
- Amy Kilbourne, Ph.D., M.P.H.
  VA HSR&D, 2215 Fuller Road, Ann Arbor, MI 48105
- Michael Matheny, M.D., M.S., M.P.H.
  VA Tennessee Valley Healthcare System, 1310 24th Ave. South, Nashville, TN 37212
- Dave Oslin, M.D.
  Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104

MVP Co-Principal Investigators

- J. Michael Gaziano, M.D., M.P.H.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Philip S. Tsao, Ph.D.

VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304

MVP Core Operations

- Lori Churby, B.S., Director, MVP Regulatory Affairs
  VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
- Stacey B. Whitbourne, Ph.D., Director, MVP Cohort Management
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Jessica V. Brewer, M.P.H., Director, MVP Recruitment & Enrollment
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Shahpoor (Alex) Shayan, M.S., Director, MVP Recruitment and Enrollment Informatics
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Luis E. Selva, Ph.D., Executive Director, MVP Biorepositories
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Saiju Pyarajan Ph.D., Director, Data and Computational Sciences
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Kelly Cho, M.P.H, Ph.D., Director, MVP Phenomics Data Core
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Scott L. DuVall, Ph.D., Director, VA Informatics and Computing Infrastructure (VINCI)
  VA Salt Lake City Health Care System, 500 Foothill Drive, Salt Lake City, UT 84148
- Mary T. Brophy M.D., M.P.H., Director, VA Central Biorepository
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- MVP Coordinating Centers
    - MVP Coordinating Center, Boston - J. Michael Gaziano, M.D., M.P.H.
      VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
    - MVP Coordinating Center, Palo Alto – Philip S. Tsao, Ph.D.
      VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
    - MVP Information Center, Canandaigua – Brady Stephens, M.S.
      Canandaigua VA Medical Center, 400 Fort Hill Avenue, Canandaigua, NY 14424
    - Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque – Todd Connor, Pharm.D.; Dean P. Argyres, B.S., M.S.
      New Mexico VA Health Care System, 1501 San Pedro Drive SE, Albuquerque, NM 87108

MVP Publications and Presentations Committee

- Co-Chair: Themistocles L. Assimes, M.D., Ph. D
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- Co-Chair: Adriana Hung, M.D.; M.P.H
  VA Tennessee Valley Healthcare System, 1310 24th Ave. South, Nashville, TN 37212
- Co-Chair: Henry Kranzler, M.D.
  Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104

MVP Local Site Investigators

- Samuel Aguayo, M.D., Phoenix VA Health Care System

650 E. Indian School Road, Phoenix, AZ 85012
- Sunil Ahuja, M.D., South Texas Veterans Health Care System
  7400 Merton Minter Boulevard, San Antonio, TX 78229
- Kathrina Alexander, M.D., Veterans Health Care System of the Ozarks
  1100 North College Avenue, Fayetteville, AR 72703
- Xiao M. Androulakis, M.D., Columbia VA Health Care System
  6439 Garners Ferry Road, Columbia, SC 29209
- Prakash Balasubramanian, M.D., William S. Middleton Memorial Veterans Hospital
  2500 Overlook Terrace, Madison, WI 53705
- Zuhair Ballas, M.D., Iowa City VA Health Care System
  601 Highway 6 West, Iowa City, IA 52246-2208
- Elizabeth S. Bast, M.D., M.P.H., Miami VA Health Care System
  1201 NW 16th Street, 11 GRC, Miami FL 33125
- Jean Beckham, Ph.D., Durham VA Medical Center
  508 Fulton Street, Durham, NC 27705
- Sujata Bhushan, M.D., VA North Texas Health Care System
  4500 S. Lancaster Road, Dallas, TX 75216
- Edward Boyko, M.D., VA Puget Sound Health Care System
  1660 S. Columbian Way, Seattle, WA 98108-1597
- David Cohen, M.D., Portland VA Medical Center
  3710 SW U.S. Veterans Hospital Road, Portland, OR 97239
- Louis Dellitalia, M.D., Birmingham VA Medical Center
  700 S. 19th Street, Birmingham AL 35233
- Gerald Wayne Dryden, Jr., M.D., Ph.D., Louisville VA Medical Center
  800 Zorn Avenue, Louisville, KY 40206
- L. Christine Faulk, M.D., Robert J. Dole VA Medical Center
  5500 East Kellogg Drive, Wichita, KS 67218-1607
- Joseph Fayad, M.D., VA Southern Nevada Healthcare System
  6900 North Pecos Road, North Las Vegas, NV 89086
- Daryl Fujii, Ph.D., VA Pacific Islands Health Care System
  459 Patterson Rd, Honolulu, HI 96819
- Saib Gappy, M.D., John D. Dingell VA Medical Center
  4646 John R Street, Detroit, MI 48201
- Frank Gesek, Ph.D., White River Junction VA Medical Center
  163 Veterans Drive, White River Junction, VT 05009
- Jennifer Greco, M.D., Sioux Falls VA Health Care System
  2501 W 22nd Street, Sioux Falls, SD 57105
- Michael Godschalk, M.D., Richmond VA Medical Center
  1201 Broad Rock Blvd., Richmond, VA 23249
- Todd W. Gress, M.D., Ph.D., Hershel “Woody” Williams VA Medical Center
  1540 Spring Valley Drive, Huntington, WV 25704
- Samir Gupta, M.D., M.S.C.S., VA San Diego Healthcare System
  3350 La Jolla Village Drive, San Diego, CA 92161
- Salvador Gutierrez, M.D., Edward Hines, Jr. VA Medical Center
  5000 South 5th Avenue, Hines, IL 60141
- John Harley, M.D., Ph.D., Cincinnati VA Medical Center

3200 Vine Street, Cincinnati, OH 45220
- Mark Hamner, M.D., Ralph H. Johnson VA Medical Center
  109 Bee Street, Mental Health Research, Charleston, SC 29401
- Daniel J. Hogan, M.D., Bay Pines VA Healthcare System
  10,000 Bay Pines Blvd Bay Pines, FL 33744
- Adriana Hung, M.D., M.P.H., VA Tennessee Valley Healthcare System
  1310 24th Avenue, South Nashville, TN 37212
- Robin Hurley, M.D., W.G. (Bill) Hefner VA Medical Center
  1601 Brenner Ave, Salisbury, NC 28144
- Pran Iruvanti, D.O., Ph.D., Hampton VA Medical Center
  100 Emancipation Drive, Hampton, VA 23667
- Frank Jacono, M.D., VA Northeast Ohio Healthcare System
  10701 East Boulevard, Cleveland, OH 44106
- Darshana Jhala, M.D., Philadelphia VA Medical Center
  3900 Woodland Avenue, Philadelphia, PA 19104
- Scott Kinlay, M.B.B.S., Ph.D., VA Boston Healthcare System
  150 S. Huntington Avenue, Boston, MA 02130
- Michael Landry, Ph.D., Southeast Louisiana Veterans Health Care System
  2400 Canal Street, New Orleans, LA 70119
- Peter Liang, M.D., M.P.H., VA New York Harbor Healthcare System
  423 East 23rd Street, New York, NY 10010
- Suthat Liangpunsakul, M.D., M.P.H., Richard Roudebush VA Medical Center
  1481 West 10th Street, Indianapolis, IN 46202
- Jack Lichy, M.D., Ph.D., Washington DC VA Medical Center
  50 Irving St, Washington, D. C. 20422
- Tze Shien Lo, M.D., Fargo VA Health Care System
  2101 N. Elm, Fargo, ND 58102
- C. Scott Mahan, M.D., Charles George VA Medical Center
  1100 Tunnel Road, Asheville, NC 28805
- Ronnie Marrache, M.D., VA Maine Healthcare System Center, Augusta, ME 04330
- Stephen Mastorides, M.D., James A. Haley Veterans' Hospital
  13000 Bruce B. Downs Blvd, Tampa, FL 33612
- Kristin Mattocks, Ph.D., M.P.H., Central Western Massachusetts Healthcare System
  421 North Main Street, Leeds, MA 01053
- Paul Meyer, M.D., Ph.D., Southern Arizona VA Health Care System
  3601 S 6th Avenue, Tucson, AZ 85723
- Jonathan Moorman, M.D., Ph.D., James H. Quillen VA Medical Center
  Corner of Lamont & Veterans Way, Mountain Home, TN 37684
- Providencia Morales, R.N., Northern Arizona VA Health Care System
  500 Highway 89 North, Prescott, AZ 86313
- Timothy Morgan, M.D., VA Long Beach Healthcare System
  5901 East 7th Street Long Beach, CA 90822
- Maureen Murdoch, M.D., M.P.H., Minneapolis VA Health Care System
  One Veterans Drive, Minneapolis, MN 55417
- Eknath Naik, M.D., Ph.D., West Palm Beach VA Medical Center,
  7305 North Military Trail, West Palm Beach, FL 33410-6400

- James Norton, Ph.D., VA Health Care Upstate New York
  113 Holland Avenue, Albany, NY 12208
- Olaoluwa Okusaga, M.D., Michael E. DeBakey VA Medical Center
  2002 Holcombe Blvd, Houston, TX 77030
- Michael K. Ong, M.D., VA Greater Los Angeles Health Care System
  11301 Wilshire Blvd, Los Angeles, CA 90073
- Kris Ann Oursler, M.D., Salem VA Medical Center
  1970 Roanoke Blvd, Salem, VA 24153
- Ismene Petrakis, M.D., VA Connecticut Healthcare System
  950 Campbell Avenue, West Haven, CT 06516
- Samuel Poon, M.D., Manchester VA Medical Center
  718 Smyth Road, Manchester, NH 03104
- Emily Potter, Pharm.D., VA Eastern Kansas Health Care System
  4101 S 4th Street Trafficway, Leavenworth, KS 66048
- Michael Rauchman, M.D., St. Louis VA Health Care System
  915 North Grand Blvd, St. Louis, MO 63106
- Amneet S. Rai, Pharm.D., VA Sierra Nevada Health Care System
  975 Kirman Avenue, Reno, NV 89502
- Richard Servatius, Ph.D., Syracuse VA Medical Center
  800 Irving Avenue, Syracuse, NY 13210
- Satish Sharma, M.D., Providence VA Medical Center
  830 Chalkstone Avenue, Providence, RI 02908
- River Smith, Ph.D., Eastern Oklahoma VA Health Care System
  1011 Honor Heights Drive, Muskogee, OK 74401
- Peruvemba Sriram, M.D., N. FL/S. GA Veterans Health System
  1601 SW Archer Road, Gainesville, FL 32608
- Patrick Strollo, Jr., M.D., VA Pittsburgh Health Care System
  University Drive, Pittsburgh, PA 15240
- Neeraj Tandon, M.D., Overton Brooks VA Medical Center
  510 East Stoner Ave, Shreveport, LA 71101
- Philip Tsao, Ph.D., VA Palo Alto Health Care System
  3801 Miranda Avenue, Palo Alto, CA 94304-1290
- Gerardo Villareal, M.D., New Mexico VA Health Care System
  1501 San Pedro Drive, S.E. Albuquerque, NM 87108
- Jessica Walsh, M.D., VA Salt Lake City Health Care System
  500 Foothill Drive, Salt Lake City, UT 84148
- John Wells, Ph.D., Edith Nourse Rogers Memorial Veterans Hospital
  200 Springs Road, Bedford, MA 01730
- Jeffrey Whittle, M.D., M.P.H., Clement J. Zablocki VA Medical Center
  5000 West National Avenue, Milwaukee, WI 53295
- Mary Whooley, M.D., San Francisco VA Health Care System
  4150 Clement Street, San Francisco, CA 94121
- Peter Wilson, M.D., Atlanta VA Medical Center
  1670 Clairmont Road, Decatur, GA 30033
- Junzhe Xu, M.D., VA Western New York Healthcare System
  3495 Bailey Avenue, Buffalo, NY 14215-1199

- Shing Shing Yeh, Ph.D., M.D., Northport VA Medical Center
  79 Middleville Road, Northport, NY 11768
- Andrew W. Yen, M.D., VA Northern California Health Care System
  10535 Hospital Way, Mather, CA 95655

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Clinical Centers: University of Michigan, Ann Arbor – Carrie Karvonen-Gutierrez PI, 2021-present, Siobán Harlow, PI 2011 – 2021, MaryFran Sowers, PI 1994-2011; Massachusetts General Hospital, Boston, MA – Massachusetts General Hospital, Boston, MA – Sherri-Ann

Burnett-Bowie, PI 2020 – Present; Joel Finkelstein, PI 1999 – 2020; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Imke Janssen, PI 2020 – Present; Howard Kravitz, PI 2009 – 2020; Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Elaine Waetjen and Monique Hedderson, PIs 2020 – Present; Ellen Gold, PI 1994 - 2020; University of California, Los Angeles – Arun Karlamangla, PI 2020 – Present; Gail Greendale, PI 1994 - 2020; Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004; and the University of Pittsburgh, Pittsburgh, PA – Rebecca Thurston, PI 2020 – Present; Karen Matthews, PI 1994 - 2020.
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