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Gene-educational attainment interactions in a multi-ancestry genome-wide meta-analysis identify novel blood pressure loci

A full list of authors and affiliations appears at the end of the article.

Abstract

Educational attainment is widely used as a surrogate for socioeconomic status (SES). Low SES is a risk factor for hypertension and high blood pressure (BP). To identify novel BP loci, we performed multi-ancestry meta-analyses accounting for gene-educational attainment interactions using two variables, “Some College” (yes/no) and “Graduated College” (yes/no). Interactions were evaluated using both a 1 degree of freedom (DF) interaction term and a 2DF joint test of genetic and interaction effects. Analyses were performed for systolic BP, diastolic BP, mean arterial pressure, and pulse pressure. We pursued genome-wide interrogation in Stage 1 studies (N=117 438) and follow-up on promising variants in Stage 2 studies (N=293 787) in five ancestry groups. Through combined meta-analyses of Stages 1 and 2, we identified 84 known and 18 novel BP loci at genome-wide significance level ($P<5\times10^{-8}$). Two novel loci were identified based on the 1DF test of interaction with educational attainment, while the remaining 16 loci were identified through the 2DF joint test of genetic and interaction effects. Ten novel loci were identified in individuals of African ancestry. Several novel loci show strong biological plausibility since they involve physiologic systems implicated in BP regulation. They include genes involved in the central nervous system-adrenal signaling axis (*ZDHHC17*, *CADPS*, *PIK3C2G*), vascular structure and function (*GNB3, CDON*), and renal function (*HAS2* and *HAS2-AS1, SLIT3*). Collectively, these findings suggest a role of educational attainment or SES in further dissection of the genetic architecture of BP.

Introduction

Educational attainment is among the most widely used indices of socioeconomic status (SES) in epidemiologic studies.[1, 2] Multiple studies have demonstrated a step-wise decline in all-cause mortality with increasing levels of education.[1] Compared with other measures of SES, such as income and occupation, the use of educational attainment has several advantages: it is stable after young adulthood, simple to capture, has a low non-response

Address Correspondence to: Lisa de las Fuentes, MD, MS, Cardiovascular Division, Dept of Medicine, Division of Biostatistics, Washington University School of Medicine, 660 S. Euclid Avenue, Campus Box 8086, St. Louis, MO 63110-1093, Phone: (314) 747-8163, lfuentes@wustl.edu, Yun Ju Sung, PhD, Division of Biostatistics, Washington University School of Medicine, 660 S. Euclid Avenue, Campus Box 8067, St. Louis, MO 63110-1093, Phone: (314) 362-0053, yunju@wustl.edu.

Supplementary Data

Supplementary Data include Supplementary Study Descriptions, Supplementary Acknowledgments, three figures, and nine tables.

Conflict of Interest

The authors declare no conflict of interests.

rate, and is not affected by poor health in adulthood.[1, 3] Furthermore, the relationship between educational attainment and cardiovascular disease traits tend to be more consistent and stronger.[4] Higher educational attainment is related to improved health efficacy (such as preventive health behaviors and problem-solving capacity), improved access to health care, and more favorable socio-psychological conditions (such as personal control and social support).[2, 3]

Several variables of educational attainment investigated in epidemiologic studies in relation to cardiovascular risk traits include continuous variables (such as years of education) and various partitions (such as completing high school or completing college degree).[5–11] Low educational attainment is related to high blood pressure (BP) and increased hypertension (HTN) risk as evidenced in a meta-analysis of 51 studies across 20 countries.[3] Educational attainment is also related to coronary artery disease,[12] coronary calcification,[13] and other cardiovascular risk traits including metabolic syndrome,[10] lipid levels,[9, 10, 14] smoking behavior,[12, 15] salt intake,[16, 17] and leisure-time physical activity.[18] Furthermore, the genetic effects on HTN may vary as a function of educational attainment. For example, a heritability study of European-ancestry male twins showed higher heritability of HTN at higher education levels ($h^2 = 0.63$ with >14 years of education compared to $h^2 = 0.46$ with ≤ 14 years of education),[19] suggesting interactions between genes and educational attainment.

While genome-wide association studies have investigated the genetic contributions to educational attainment,[6] there has been no comprehensive effort to examine the role played by gene-environment interactions in BP using educational attainment as the environmental exposure. Within the CHARGE Gene-Lifestyle Interactions Working Group,[20] we performed genome-wide meta-analysis of systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and pulse pressure (PP), accounting for gene-educational attainment interactions. Based on the availability of data across participating studies, we considered two educational attainment variables, “Some College” (yes/no, for any education beyond high school) and “Graduated College” (yes/no, for completing a 4-year college degree). Herein we report our findings based on up to 411 225 individuals from five ancestry groups.

Subjects and Methods

Participating studies

We performed our analysis in two stages (Figure 1). A total of 42 cohorts including 117 438 men and women (aged 18–80 years) from European (EUR), African (AFR), Asian (ASN), Hispanic (HIS), and Brazilian (BRZ) ancestries contributed to Stage 1 genome-wide interaction analyses (Table S1). An additional 49 cohorts including 293 787 individuals contributed to Stage 2 analyses of top single nucleotide variants (SNVs, also including a small number of insertion and deletion [indels] variants) selected from Stage 1 (Table S2). Participating studies are described in the Supplementary Material. Since discoveries to date are largely from EUR populations, considerable effort was made to recruit most of the available non-EUR cohorts into Stage 1. Each study obtained informed consent from participants and approval from the appropriate institutional review boards.

Phenotype and lifestyle variables

We performed our analysis for SBP, DBP, MAP, and PP. After computing SBP and DBP when multiple measurements were available, we adjusted for antihypertensive medication use by adding 15 mmHg and 10 mmHg to SBP and DBP, respectively.[21] After medication adjustment, MAP was computed as (SBP + 2DBP)/3, and PP was computed as SBP minus DBP (SBP - DBP). To reduce the influence of possible outliers, Winsorizing was performed for each BP value that was more than 6 standard deviations away from the mean. Descriptive statistics for these 4 BP traits are presented in Tables S3 and S4. For educational attainment, two dichotomous variables were created. The first variable, 'Some College' (SomeCol), was coded as 1 if the subject received any education beyond high school, including vocational school (and as 0 if no education beyond high school). The second variable, 'Graduated College' (GradCol), was coded as 1 if the subject completed at least a 4-year college degree (and as 0 for any education less than a 4-year degree). Subjects with missing data for BP, education attainment, or any covariates were excluded from analysis.

Genotype data

Genotyping was performed by each participating study using Illumina (San Diego, CA, USA) or Affymetrix (Santa Clara, CA, USA) genotyping arrays. Imputation was performed using the 1000 Genomes Project[22] Phase I Integrated Release Version 3 Haplotypes (2010–11 data freeze, 2012–03–14 haplotypes) as a reference panel, in most cohorts. Information on genotype and imputation for each study is presented in Tables S5 and S6.

Analysis methods

Each study performed association analyses using the following model:

$$E(Y) = \beta_0 + \beta_G G + \beta_E Educ + \beta_{GE} G * Educ + \beta_C C$$

where Y is the BP variable (SBP, DBP, MAP, or PP value), Educ is the educational variable (SomeCol or GradCol), and G is the dosage of the imputed genetic variant coded additively from 0 to 2. C is the vector of covariates, including age, sex, field center (for multi-center studies), and principal components. In addition, studies in Stage 1 performed association analysis using the following genetic main effect model with education attainment:

$$E(Y) = \beta_0 + \beta_G G + \beta_E Educ + \beta_C C .$$

Each study provided the estimated SNV effect (β_G), estimated SNV-educational attainment interaction effect (β_{GE}), their robust standard errors, and a robust estimate of the covariance between β_G and β_{GE}. We performed meta-analysis using the 1 degree of freedom (DF) test of the interaction effect (β_{GE}) and 2DF test of both SNV (β_G) and interaction effects (β_{GE}). Inverse-variance weighted meta-analysis was performed for the 1DF test and the joint meta-analysis of Manning et al[23] for the 2DF test, both using METAL.[24] In Stage 1 EUR, AFR, ASN meta-analyses, variants were included if they were available in more than 5 000 samples or at least 3 cohorts (these filters were not applied to BRZ or HIS because of the fewness of cohorts included in these meta-analyses). We applied genomic

control correction[25] twice in Stage 1, first for study-specific GWAS results and again for meta-analysis results. Genome-wide significant ($P < 5\times10^{-8}$) and suggestive ($P < 1\times10^{-6}$) variants in Stage 1 were taken forward into Stage 2 analysis. Genomic control correction was not applied to the Stage 2 results as association test was performed for select variants. Results presented reflect meta-analyses combining Stages 1 and 2. Loci were defined by physical distance (± 1Mb around the index SNV of the respective locus).

Quality control (QC)

Each participating cohort in Stage 1 excluded variants with minor allele frequency (MAF) < 1%. We performed extensive QC using the R package EasyQC[26] for all cohort-specific and meta-analysis results. For Stages 1 and 2, we excluded all variants with imputation quality measure < 0.5. In addition, to remove unstable study-specific results that reflected small sample size, low minor allele count (MAC), or low imputation quality, we excluded variants for which the minimum of (MAC0, MAC1) x imputation quality < 20, where MAC0 and MAC1 are the MAC in the two education strata (Educ = 0 and Educ = 1). The allele frequencies provided by each cohort were compared against those from the relevant ancestry-specific 1000 Genomes reference panel. Marker names were harmonized to ensure consistency across cohorts. In addition, we visually compared summary statistics (e.g., mean, median, standard deviation, inter-quartile range) of all effect estimates, standard errors (SEs), and p-values. We examined SE-N plots[26] and quantile-quantile (QQ) plots to reveal issues with trait transformation or other analytical problems. Any problems encountered during QC steps were resolved through communication with the analysts from the participating studies. More detailed information about the QC steps, including major QC problems encountered and how they were resolved, are described elsewhere.[20, 27]

Characterization of functional roles

A suite of tools implemented in FUMA GWAS[28] were used to identify functional roles for the index variants and nearby variants in linkage disequilibrium (LD; $r^2 \geq 0.2$) in each of the novel BP loci. LD information was obtained from the 1000 Genomes Project reference genome for the ancestry with the most significant ancestry-specific association. If the most significant association was in trans-ancestry analyses, the reference genome for the ancestry with the next most significant association was used instead.[29] One index insertion/deletion locus was not identified in any of the reference genomes by FUMA and therefore not detailed. Nearest gene annotations were limited to protein coding, long non-coding RNAs (lncRNAs), and non-coding RNAs (ncRNAs) within 10kb of index variants and variants in LD ($r^2 \geq 0.2$) with the index variant.[30]

For the index and LD variants, we used the RegulomeDB score,[31] which reflects a summary of annotations with known and predicted regulatory elements such as DNAase hypersensitivity, binding sites of transcription factors, and promoter regions, and Combined Annotation Dependent Depletion (CADD)[32] scores, which predict deleteriousness of variants. The 15-core chromatin state (ChromHMM)[33, 34] was assessed for 129 epigenomes (labeled E001-E129) to identify histone modifications consistent with epigenetic regulation of gene expression. Expression quantitative trait loci (eQTLs) were determined using the GTEx_v7 database[35] for index and LD variants. Using nearest-gene annotations, FUMA

GWAS was used to generate tissue-specific gene expression data (GTEx V7 dataset, 53 tissue types); significance was determined as a Benjamini-Hochberg false discovery rate (FDR) < 0.05.

Results

Overview

We performed a meta-analysis of gene-education interactions on SBP, DBP, MAP, and PP in two stages (Figure 1). In Stage 1, we pursued genome-wide interrogation in 117 438 individuals of European (EUR), African (AFR), Asian (ASN), Hispanic (HIS), and Brazilian (BRZ) ancestries (summary information, Table 1). After extensive quality control (QC), we performed genome-wide meta-analyses at approximately 18.8 million single nucleotide variants (SNVs) and a small number of insertion and deletion (indels) variants imputed using the 1000 Genomes Project reference panel (QQ plots, Figure S1). Through the 1DF test of the interaction effect and the 2DF joint test of the SNV and interaction effects, we identified 1 481 genome-wide significant ($P < 5\times10^{-8}$) and 3 309 suggestive ($P < 1\times10^{-6}$) variants associated with any BP trait in any ancestry and/or in trans-ancestry analysis. All significant and suggestive variants were tested for association in 293 787 additional individuals of EUR, AFR, ASN, and HISP ancestries in Stage 2.

We performed meta-analyses combining Stages 1 and 2 (Manhattan Plots, Figure S2). We identified 84 known BP loci. This includes 82 loci identified through main-effect only analyses,[36–41] including 18 recently reported by Hoffmann *et al*,[42] Evangelou *et al*,[43] and Giri *et al*;[44] and two loci (*TFAP2A* and *PCDH9*) recently reported by our consortium through gene-smoking and gene-alcohol interaction analyses,[27, 45] which suggest the inter-correlated nature of the various lifestyle traits.

We identified 18 novel genome-wide significant loci ($P < 5\times10^{-8}$) located at least 1Mb away from any known BP loci (Table 2). Nine loci were identified through the combined analyses of Stage 1 and 2; the remaining nine loci were identified in Stage 1 but not available in Stage 2 for combined analyses (Table S7). The LocusZoom plots of these novel loci are presented in Figure S3. Two loci (*SLIT3* and *HRH4*) were identified through the 1DF test of interaction effects. At both loci, the genetic effect on DBP was stronger and beneficial in higher education and weaker and detrimental in lower education. For example, at *SLIT3*, the minor allele A was associated with a 4.82 mmHg lower DBP in higher education (GradCol=1), whereas it was associated with a 2.25 mmHg higher DBP in GradCol=0. The remaining 16 loci were identified through the 2DF joint test of the SNV and interaction effects; twelve loci were identified considering ‘Some College’ (SomeCol) and four loci were identified considering ‘Graduated College’ (GradCol).

Ancestry-specific and trans-ancestry analyses

Novel loci were identified through separate analyses of AFR (12 loci), EUR (1 locus), trans-ancestry (4 loci), and in both AFR and trans-ancestry (1 locus). This highlights the importance of including non-EUR populations to identify novel BP loci. By nature, AFR populations carry more rare and low-frequency variants that may be very rare or

monomorphic in other ancestral groups;[22] the MAF for the novel index SNVs range from 0.02–0.04 in AFR. The enhanced discovery of novel loci in AFR ancestry may be attributable to the relatively higher MAF in this population versus in EUR. For example, rs141962517 (*CAPDS*) with a MAF = 0.02 in AFR was significantly associated with SBP (2DF $P = 3.07\times10^{-10}$; 1DF Interaction $P = 1.99\times10^{-7}$); this variant was not present in other ancestries after filtering.

Among the 18 novel loci, three loci were identified only through trans-ancestry analyses, as none of the ancestry-specific analyses reached genome-wide significance. For example, the index SNV (rs189555401) representing the four-variant locus within *PIK3C2G* was suggestively associated with DBP ($P = 1.31\times10^{-7}$) in AFR and not even nominally associated in HIS ($P = 9.67\times10^{-2}$). However, in trans-ancestry analysis combining these two ancestral groups, the association reached genome-wide significance ($P = 4.10\times10^{-8}$).

Functional annotation and eQTL evidence

To obtain functional annotations for the index variants and nearby variants in LD ($r^2 \geq 0.2$), we used FUMA GWAS.[28] Among the 18 index variants representing our novel loci, two variants were intronic to a non-coding RNA (ncRNA), six variants were intronic, nine variants were intergenic, and the remaining variant (rs66907226) was an indel without available annotation. Among the 499 variants that include both the index variants and nearby variants in LD, there were four exonic, four exonic-ncRNA, 119 intronic, 67 intronic-ncRNA, two 3' untranslated region (UTR), seven up/downstream flanking, and 296 intergenic variants (Table S8). Of the 499 variants, 13 had RegulomeDB[31] scores better than or equal to 3a, suggesting at least moderate evidence for involvement in transcription regulation (Table S9). Thirty-two SNVs have CADD[32] scores ≥10, representing the top 10% of predicted deleteriousness for SNVs genome-wide. A single SNV (rs112332671) ~20kb upstream of *HAS2* and 16 kb downstream of the ncRNA *HAS2-AS1* had a CADD score of 20.1, placing it in the top 1% of predicted deleteriousness.

The 15-core chromatin state (ChromHMM)[33] was assessed for 127 epigenomes in the 17 index variants (Table S9). Two had histone chromatin markers in regions flanking the transcription start site and one in a region associated with strong transcription in relevant tissues including brain. Among all 499 LD variants, 45 had histone chromatin markers characteristic of a transcription start site, 64 had markers consistent with strong transcription, and 25 were in enhancer regions. One LD variant (rs555713705) was identified as *cis*-acting expression trait loci (eQTLs)[46, 47] for heart tissue in the GTEx_v7 database (FDR p-value ranging from 3.90×10^{-3}).

Biologic plausibility of the new BP loci

Three novel BP loci are related to the central nervous system (CNS)-adrenal signaling axis that is critical for BP regulation. A locus (Figure 2A) adjacent to *ZDHHC17*, identified in AFR and in trans-ancestry analyses, encodes a membrane protein that mediates fusion of synaptic vesicles to the plasma membrane. *CADPS* (Figure 2B), identified in AFR, is expressed in CNS tissue. Three variants in LD have CADD scores >10, and four SNVs have ChromHMM state signals consistent with strong evidence of transcription regulation.

PIK3C2G, identified in trans-ancestry analyses, also shows roles in CNS-adrenal signaling. Three variants in LD in this locus have CADD scores >10, including one with a CADD score of 18 that is predicted to reside in an enhancer region in fetal adrenal cells.

Two novel BP loci are related to renal fibrosis and cation exchange. A locus, which includes a variant intragenic to *SLIT3*, showed interaction evidence with educational attainment in AFR (rs142385399, $P = 2.79\times10^{-8}$). A locus also identified in AFR includes *HAS2* and *HAS2-AS1*, which play roles in renal fibrosis. In addition, we identified two novel BP loci related to pathways involved in vascular smooth muscle cell structure and function. A locus identified by trans-ancestry analyses included a variant intragenic to *CDON*, which is expressed in vascular smooth muscle cells. A locus identified in AFR includes *GNB3*, which encodes a subunit critical for signal transduction of several vasoactive peptide G protein-coupled receptors involved in BP regulation. A SNV in this locus shows ChromHMM chromatin states consistent with strong transcription regulation in multiple tissues, and three SNVs have strong *cis*-eQTL association with *GNB3* expression in nerve, artery and skeletal muscle tissue (minimum FDR p-value 1.20×10^{-43}).

Discussion

A relationship between educational attainment and BP has been well demonstrated.[48–51] Furthermore, African-ancestry individuals have been shown to have a higher burden of HTN than European-ancestry.[52] However, higher-educated African-ancestry individuals bear approximately twice the burden of HTN as compared to their European-ancestry counterparts,[48, 51] demonstrating that educational differences did not fully account for this observed racial disparity. Herein, we reported genome-wide meta-analyses for SBP, DBP, MAP, and PP accounting for gene-educational attainment interactions across five ancestry groups. We pursued a genome-wide interrogation in 117 438 individuals (in Stage 1) and follow-up analysis at selected variants in 293 787 additional individuals (in Stage 2). Through the combined meta-analysis of stages 1 and 2, we identified 84 known and 18 novel loci at genome-wide significance. As known loci have been discussed elsewhere, this report highlights several novel loci show biologic plausibility by involving physiologic systems implicated in BP regulation.

The central nervous system (CNS)-adrenal signaling axis is critical for BP regulation. Three novel BP loci (*ZDHHC17, CADPS*, and *PIK3C2G*) are related to these pathways. In neurons, *ZDHHC17* encodes a membrane protein that mediates fusion of synaptic vesicles to the plasma membrane, enabling the release of neurotransmitters.[53] Murine *zdhhc17* knockout models show impaired hippocampal memory and reduced synaptic plasticity, providing potential biological links to working memory and subsequent educational attainment.[54] Although a biological connection between *ZDHHC17* and BP traits is not well established, *zdhhc17* expression induces neurite outgrowth in a rodent adrenal-derived cell line.[55] *Cadps* plays a role in regulating the fusion of neuroendocrine vesicles and release of vasoactive catecholamines in calf adrenal and neural tissue.[56] *Pik3c2g* encodes a phosphoinositide kinases that is expressed in a sexually dimorphic pattern specifically in a zone of the mouse adrenal cortex believed to play a role in steroid sex hormone production.[57] Furthermore, *PIK3C2G* is under-expressed in human hypertensive kidneys,

providing a potential biological link between the expression of adrenal mineralocorticoid hormones and their target organ.[58] Among alcohol-preferring rats, *pik3c2g* expression is also increased in the cerebral periaqueductal gray, a region involved in pain, fear, and anxiety responses,[59] possibly providing a link to drivers of socioeconomic status in humans.[60] Notably, the loci including *ZDHHC17* and *CADPS* demonstrated some evidence of interaction with educational attainment ($P = 1.72\times10^{-5}$ and 1.99×10^{-7}, respectively).

Two new BP loci (*HAS2* and *HAS2-AS1, SLIT3*) show potential roles in renal function. A locus which includes a variant intragenic to *SLIT3* had a significant interaction term with educational attainment. *SLIT3* encodes a cell-cell adhesion molecule that binds its receptor, ROBO4, in human-derived endothelial stem cells directing the formation of vascular networks.[61] *SLIT3* also plays a role in directing neuronal growth in the brain,[62, 63] and in renal and cardiac development.[64] A locus including *HAS2* and *HAS2-AS1* is also of interest for roles played in renal fibrosis. *HAS2-AS1* is an antisense ncRNA simultaneously expressed and thought to stabilize the *HAS2* transcript.[65]

Two new BP loci (*GNB3, CDON*) have been shown to regulate pathways involved in vascular smooth muscle cell structure and function. We identified a locus in *GNB3*, which encodes a G protein-coupled receptor subunit involved in BP regulation. Several candidate gene association studies have identified the synonymous *GNB3* variant C825T (rs5443), resulting in a splice variant of the β3 subunit, as significantly associated with essential HTN,[66, 67] with BP response to diuretic[68] and β-adrenergic receptor blockade,[69] and other cardiovascular traits.[70] Another locus identified by trans-ancestry analyses included a variant intragenic to *CDON*; this gene is expressed in vascular smooth muscle cells,[71] and encodes a cell-surface receptor complex that regulates myocyte differentiation in rodents.[72]

This large-scale multi-ancestry study has several limitations. First, the practice of adjusting SBP and DBP by adding 15 and 10 mm Hg for antihypertensive use is based on a method derived from a European-ancestry cohort.[21] While this approach is common among GWAS of BP traits,[36] we acknowledge that this practice may not be equally appropriate and/or justified in all ancestry groups. Second, while the sample sizes in diverse ancestries are a strength, resulting in the identification of several novel BP loci particularly in African ancestry, several identified loci included low-frequency variants that require further validation. Third, main effect only analysis without educational attainment was not performed, and this limits our ability to resolve if novel loci identified through the 2DF joint test could be found without considering educational attainment. Fourth, the use of educational attainment as a proxy for SES can present some challenges. The socioeconomic impact of education has changed over time and may differ according to birth cohort, as well as in other subgroups defined by gender, ancestry, region, and/or country.[1, 49] Even with similar levels of educational attainment, social and environmental experiences were different between AFR and EUR individuals in United States, especially those educated in the 1960s and 1970s, resulting in residual confounding inequities between the ancestral groups.[9, 73] This additional source of heterogeneity may have reduced power for trans-ancestry analyses.

In summary, this multi-ancestry study that used gene-education interactions on BP traits identified 18 novel loci and validated 84 known BP loci. Ten novel loci were identified

in individuals of African ancestry, demonstrating the need for pursuing genetic studies in diverse populations. Several novel loci involve physiologic systems implicated in BP regulation including genes involved in CNS-adrenal signaling, vascular structure and function, and renal function. Two loci showed interaction evidence with educational attainment. These findings may identify a role for educational attainment and SES in further dissection of the genetic architecture of BP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Lisa de las Fuentes[1,2], Yun Ju Sung[2], Raymond Noordam[3], Thomas Winkler[4], Mary F. Feitosa[5], Karen Schwander[2], Amy R. Bentley[6], Michael R. Brown[7], Xiuqing Guo[8], Alisa Manning[9,10], Daniel I. Chasman[11,12], Hugues Aschard[13,14], Traci M. Bartz[15], Lawrence F. Bielak[16], Archie Campbell[17], Ching-Yu Cheng[18,19], Rajkumar Dorajoo[20], Fernando P. Hartwig[21,22], A.R.V.R. Horimoto[23], Changwei Li[24], Ruifang Li-Gao[25], Yongmei Liu[26], Jonathan Marten[27], Solomon K. Musani[28], Ioanna Ntalla[29], Tuomo Rankinen[30], Melissa Richard[31], Xueling Sim[32], Albert V. Smith[33,34], Salman M. Tajuddin[35], Bamidele O. Tayo[36], Dina Vojinovic[37], Helen R. Warren[29,38], Deng Xuan[39], Maris Alver[40,41], Mathilde Boissel[42], Jin-Fang Chai[32], Xu Chen[43], Kaare Christensen[44], Jasmin Divers[45], Evangelos Evangelou[46,47], Chuan Gao[48], Giorgia Girotto[49,50], Sarah E. Harris[51], Meian He[52], Fang-Chi Hsu[45], Brigitte Kühnel[53,54], Federica Laguzzi[55], Xiaoyin Li[56,57], Leo-Pekka Lyytikäinen[58,59], Ilja M. Nolte[60], Alaitz Poveda[61], Rainer Rauramaa[62], Muhammad Riaz[63], Rico Rueedi[64,65], Xiao-ou Shu[66], Harold Snieder[60], Tamar Sofer[67], Fumihiko Takeuchi[68], Niek Verweij[69], Erin B. Ware[70], Stefan Weiss[71,72], Lisa R. Yanek[73], Najaf Amin[37], Dan E. Arking[74], Donna K. Arnett[75], Sven Bergmann[64,65], Eric Boerwinkle[7,76], Jennifer A. Brody[77], Ulrich Broeckel[78], Marco Brumat[49], Gregory Burke[79], Claudia P. Cabrera[29,38], Mickaël Canouil[42], Miao Li Chee[80], Yii-Der Ida Chen[8], Massimiliano Cocca[50], John Connell[81], H. Janaka de Silva[82], Paul S. de Vries[7], Gudny Eiriksdottir[34], Jessica D. Faul[70], Virginia Fisher[39], Terrence Forrester[83], Ervin F. Fox[84], Yechiel Friedlander[85], He Gao[46,86], Bruna Gigante[87,88], Franco Giulianini[89], Chi Charles Gu[2], Dongfeng Gu[90], Tamara B. Harris[91], Jiang He[92,93], Sami Heikkinen[94,95], Chew-Kiat Heng[96,97], Steven Hunt[98,99], M. Arfan Ikram[37,100], Marguerite R. Irvin[101], Mika Kähönen[102,103], Maryam Kavousi[37], Chiea Chuen Khor[20,104], Tuomas O. Kilpeläinen[105,106], Woon-Puay Koh[32,107], Pirjo Komulainen[62], Aldi T. Kraja[5], J.E. Krieger[23], Carl D. Langefeld[45], Yize Li[2], Jingjing Liang[56], David C.M. Liewald[51], Ching-Ti Liu[39], Jianjun Liu[20,32], Kurt K. Lohman[108], Reedik Mägi[40], Colin A. McKenzie[83], Thomas Meitinger[109,110], Andres Metspalu[40,41], Yuri Milaneschi[111], Lili Milani[40], Dennis O. Mook-Kanamori[25,112], Mike A. Nalls[113,114], Christopher P. Nelson[115,116], Jill M. Norris[117], Jeff O'Connell[118,119], Adesola Ogunniyi[120], Sandosh Padmanabhan[121], Nicholette D. Palmer[122], Nancy L. Pedersen[43], Thomas Perls[123], Annette Peters[54,124], Astrid Petersmann[125], Patricia A. Peyser[16], Ozren Polasek[126,127,128],

David J. Porteous[17,51], Leslie J. Raffel[129], Treva K. Rice[2], Jerome I. Rotter[8], Igor Rudan[130], Oscar-Leonel Rueda-Ochoa[37], Charumathi Sabanayagam[18,19], Babatunde L. Salako[120], Pamela J. Schreiner[131], James M. Shikany[132], Stephen S. Sidney[133], Mario Sims[28], Colleen M. Sitlani[77], Jennifer A. Smith[16,70], John M. Starr[134,135], Konstantin Strauch[136,137], Morris A. Swertz[138], Alexander Teumer[72,139], Yih Chung Tham[18], André G. Uitterlinden[37,140], Dhananjay Vaidya[73], M. Yldau van der Ende[69], Melanie Waldenberger[53,54,124], Lihua Wang[5], Ya-Xing Wang[141], Wen-Bin Wei[142], David R. Weir[70], Wanqing Wen[66], Jie Yao[8], Bing Yu[7], Caizheng Yu[52], Jian-Min Yuan[143,144], Wei Zhao[16], Alan B. Zonderman[145], Diane M. Becker[73], Donald W. Bowden[122], Ian J. Deary[51], Marcus Dörr[72,146], Tõnu Esko[40,147], Barry I Freedman[148], Philippe Froguel[42,149], Paolo Gasparini[49,50], Christian Gieger[53,150], Jost Bruno Jonas[151,152], Candace M. Kammerer[153], Norihiro Kato[68], Timo A. Lakka[62,94,154], Karin Leander[55], Terho Lehtimäki[58,59], Lifelines Cohort Study[155], Patrik K.E. Magnusson[43], Pedro Marques-Vidal[156], Brenda W.J.H. Penninx[111], Nilesh J. Samani[115,116], Pim van der Harst[69,157], Lynne E. Wagenknecht[79], Tangchun Wu[52], Wei Zheng[66], Xiaofeng Zhu[56], Claude Bouchard[30], Richard S. Cooper[36], Adolfo Correa[28], Michele K. Evans[35], Vilmundur Gudnason[34,158], Caroline Hayward[27], Bernardo L. Horta[21], Tanika N. Kelly[92], Stephen B. Kritchevsky[159], Daniel Levy[160,161], Walter R. Palmas[162], A.C. Pereira[23], Michael M. Province[5], Bruce M. Psaty[163,164], Paul M. Ridker[12,89], Charles N. Rotimi[6], E. Shyong Tai[32,107,165], Rob M. van Dam[32,165], Cornelia M. van Duijn[37,166], Tien Yin Wong[18,19], Kenneth Rice[167], W. James Gauderman[168], Alanna C. Morrison[7], Kari E. North[169], Sharon L.R. Kardia[16], Mark J. Caulfield[29,38], Paul Elliott[46,86], Patricia B. Munroe[29,38], Paul W. Franks[61,170], Dabeeru C. Rao[2], Myriam Fornage[31]

Affiliations

[1.]Cardiovascular Division, Department of Medicine, Washington University, St. Louis, MO 63110, USA.

[2.]Division of Biostatistics, Washington University School of Medicine, St. Louis, MO 63110, USA.

[3.]Section of Gerontology and Geriatrics, Department of Internal Medicine, Leiden University Medical Center, Leiden 2333ZA, The Netherlands.

[4.]Department of Genetic Epidemiology, University of Regensburg, Regensburg 93051, Germany.

[5.]Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St. Louis, MO 63108, USA.

[6.]Center for Research on Genomics and Global Health, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA.

[7.]Human Genetics Center, Department of Epidemiology, Human Genetics, and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX 77030, USA.

[8].The Institute for Translational Genomics and Population Sciences, Division of Genomic Outcomes, Department of Pediatrics, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA 90502, USA.

[9].Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA 02114, USA.

[10].Department of Medicine, Harvard Medical School, Boston, MA 02115, USA.

[11].Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA 02215, USA.

[12].Harvard Medical School, Boston, MA 02115, USA.

[13].Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA.

[14].Centre de Bioinformatique, Biostatistique et Biologie Intégrative (C3BI), Institut Pasteur, Paris 75724, France.

[15].Cardiovascular Health Research Unit, Biostatistics and Medicine, University of Washington, Seattle, WA 98101, USA.

[16].Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA.

[17].Centre for Genomic & Experimental Medicine, Institute of Genetics & Molecular Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK.

[18].Ocular Epidemiology, Singapore Eye Research Institute, Singapore National Ecy Centre, Singapore 169856, Singapore.

[19].Ophthalmology & Visual Sciences Academic Clinical Program (Eye ACP), Duke-NUS Medical School, Singapore 169857, Singapore.

[20].Genome Institute of Singapore, Agency for Science Technology and Research, Singapore 138672, Singapore.

[21].Postgraduate Programme in Epidemiology, Federal University of Pelotas, Pelotas, RS 96020-220, Brazil.

[22].Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol BS8 2BN, UK.

[23].Laboratory of Genetics and Molecular Cardiology, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, SP 5403000, Brazil.

[24].Epidemiology and Biostatistics, University of Georgia at Athens College of Public Health, Athens, GA 30602, USA.

[25].Department of Clinical Epidemiology, Leiden University Medical Center, Leiden 2333ZA, Netherlands.

[26].Public Health Sciences, Epidemiology and Prevention, Wake Forest University Health Sciences, Winston-Salem, NC 27157, USA.

[27]Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK.

[28]Jackson Heart Study, Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39213, USA.

[29]Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK.

[30]Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA, USA.

[31]Institute of Molecular Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX 70808, USA.

[32]Saw Swee Hock School of Public Health, National University Health System and National University of Singapore, Singapore 117549, Singapore.

[33]Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109, USA.

[34]Icelandic Heart Association, Kopavogur 201, Iceland.

[35]Health Disparities Research Section, Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA.

[36]Department of Public Health Sciences, Loyola University Chicago, Maywood, IL 60153, USA.

[37]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands.

[38]NIHR Barts Cardiovascular Biomedical Research Unit, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, London EC1M 6BQ, UK.

[39]Biostatistics, Boston University School of Public Health, Boston, MA 02118, USA.

[40]Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu 51010, Estonia.

[41]Department of Biotechnology, Institute of Molecular and Cell Biology, University of Tartu, Tartu 51010, Estonia.

[42]CNRS UMR 8199, European Genomic Institute for Diabetes (EGID), Institut Pasteur de Lille, University of Lille, Lille 59000, France.

[43]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Stockholm 17177, Sweden.

[44]Unit of Epidemiology, Biostatistics and Biodemography, Department of Public Health, Southern Denmark University, Odense 5000, Denmark.

[45]Biostatistical Sciences, Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA.

[46]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London W2 1PG, UK.

[47]Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina 45110, Greece.

[48]Molecular Genetics and Genomics Program, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA.

[49]Medical Genetics, Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste 34100, Italy.

[50]Institute for Maternal and Child Health - IRCCS “Burlo Garofolo”, Trieste 34100, Italy.

[51]Department of Psychology, Centre for Cognitive Ageing and Cognitive Epidemiology, The University of Edinburgh, Edinburgh EH8 9JZ, UK.

[52]Department of Occupational and Environmental Health and State Key Laboratory of Environmental Health for Incubating, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.

[53]Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg 85764, Germany.

[54]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg 85764, Germany.

[55]Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm 17177, Sweden.

[56]Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH 44106, USA.

[57]Department of Mathematics and Statistics, University of Minnesota, Duluth, MN 55812, USA.

[58]Department of Clinical Chemistry, Fimlab Laboratories, Tampere 33520, Finland.

[59]Department of Clinical Chemistry, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, University of Tampere, Tampere 33014, Finland.

[60]University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen 9700RB, The Netherlands.

[61]Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University Diabetes Centre, Skåne University Hospital, Malmö, Skåne 205 02, Sweden.

[62]Foundation for Research in Health Exercise and Nutrition, Kuopio Research Institute of Exercise Medicine, Kuopio 70100, Finland.

[63]College of Medicine, Biological Sciences and Psychology, Health Sciences, The Infant Mortality and Morbidity Studies (TIMMS), Leicester LE1 7RH, UK.

[64]Department of Computational Biology, University of Lausanne, Lausanne 1011, Switzerland.

[65]Swiss Institute of Bioinformatics, Lausanne 1015, Switzerland.

[66]Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN 37203, USA.

[67]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, MA 02115, USA.

[68]Department of Gene Diagnostics and Therapeutics, Research Institute, National Center for Global Health and Medicine, Tokyo 1628655, Japan.

[69]University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen 9700, The Netherlands.

[70]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI 48104, USA.

[71]Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald 9713GZ, Germany.

[72]DZHK (German Centre for Cardiovascular Health), Partner Site Greifswald, Greifswald 17475, Germany.

[73]Division of General Internal Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.

[74]McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

[75]Dean's Office, University of Kentucky College of Public Health, Lexington, KY 40536, USA.

[76]Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX 77030, USA.

[77]Cardiovascular Health Research Unit, Medicine, University of Washington, Seattle, WA 98101, USA.

[78]Section of Genomic Pediatrics, Department of Pediatrics, Medicine and Physiology, Medical College of Wisconsin, Milwaukee, WI 53226, USA.

[79]Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC 27109, USA.

[80]Statistics Unit, Singapore Eye Research Institute, Singapore National Eye Centre, Singapore 169856, Singapore.

[81]Ninewells Hospital & Medical School, University of Dundee, Dundee, Scotland DD1 9SY, UK.

[82]Department of Medicine, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka.

[83]Tropical Metabolism Research Unit, Tropical Medicine Research Institute, University of the West Indies, Mona JMAAW15, Jamaica.

[84]Cardiology, Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA.

[85]Braun School of Public Health, Hebrew University-Hadassah Medical Center, Jerusalem 91120, Israel.

[86]MRC-PHE Centre for Environment and Health, Imperial College London, London W2 1PG, UK.

[87]Cardiovascular Unit, Bioclinicum, Department of Medicine, Karolinska Hospital, Stockholm 17164, Sweden.

[88]Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd University Hospital, Stockholm 18288, Sweden.

[89]Brigham and Women's Hospital, Boston, MA 02215, USA.

[90]Department of Epidemiology, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

[91]Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA.

[92]Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA 70112, USA.

[93]Medicine, Tulane University School of Medicine, New Orleans, LA 70112, USA.

[94]Institute of Biomedicine, School of Medicine, University of Eastern Finland, Kuopio Campus, Kuopio 70211, Finland.

[95]Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland, Kuopio 70211, Finland.

[96]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119228, Singapore.

[97]Khoo Teck Puat – National University Children's Medical Institute, National University Health System, Singapore 119228, Singapore.

[98]Cardiovascular Genetics, Department of Internal Medicine, University of Utah, Salt Lake City, UT 84108, USA.

[99]Weill Cornell Medicine in Qatar, Doha, Qatar.

[100]Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands.

[101]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL 35294, USA.

[102]Department of Clinical Physiology, Tampere University Hospital, Tampere 33521, Finland.

[103]Department of Clinical Physiology, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, University of Tampere, Tampere 33014, Finland.

[104]Department of Biochemistry, National University of Singapore, Singapore 117596, Singapore.

[105]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen DK-2200, Denmark.

[106]Department of Environmental Medicine and Public Health, The Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

[107]Health Services and Systems Research, Duke-NUS Medical School, Singapore 169857, Singapore.

[108]Public Health Sciences, Biostatistics and Data Science, Wake Forest University Health Sciences, Winston-Salem, NC 27157, USA.

[109]Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg 85764, Germany.

[110]Institute of Human Genetics, Technische Universität München, Munich 80333, Germany.

[111]Department of Psychiatry, Amsterdam Neuroscience and Amsterdam Public Health Research Institute, VU University Medical Center, Amsterdam 1081 BT, The Netherlands.

[112]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden 2333ZA, Leiden.

[113]Molecular Genetics Section, Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD 20895, USA.

[114]Data Tecnica International, Glen Echo, MD 20812, USA.

[115]Department of Cardiovascular Sciences, University of Leicester, Leicester LE3 9QP, UK.

[116]NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester LE3 9QP, UK.

[117]Department of Epidemiology, University of Colorado Denver, Aurora, CO 80045, USA.

[118]Division of Endocrinology, Diabetes, and Nutrition, University of Maryland School of Medicine, Baltimore, MD, USA.

[119]Program for Personalized and Genomic Medicine, University of Maryland School of Medicine, Baltimore, MD, USA.

[120]Department of Medicine, University of Ibadan, Ibadan, Oyo, Nigeria.

[121]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8TA, UK.

[122]Biochemistry, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA.

[123]Department of Medicine, Geriatrics Section, Boston Medical Center, Boston University School of Medicine, Boston, MA 02118, USA.

[124]DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Neuherberg 85764, Germany.

[125]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald 17475, Germany.

[126]University of Split School of Medicine, Split, Croatia.

[127]University Hospital Split, Split, Croatia.

[128]Psychiatric Hospital “Sveti Ivan”, Zagreb, Croatia.

[129]Division of Genetic and Genomic Medicine, Department of Pediatrics, University of California, Irvine, CA 92868, USA.

[130]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh EH8 9AG, UK.

[131]Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, Minneapolis, MN 55454, USA.

[132]Division of Preventive Medicine, School of Medicine, University of Alabama at Birmingham, Birmingham, AL 25249, USA.

[133]Division of Research, Kaiser Permanente of Northern California, Oakland, CA, USA.

[134]Alzheimer Scotland Dementia Research Centre, The University of Edinburgh, Edinburgh EH8 9AZ, UK.

[135]Centre for Cognitive Ageing and Cognitive Epidemiology, The University of Edinburgh, Edinburgh, UK.

[136]Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg 85764, Germany.

[137]Institute of Medical Informatics Biometry and Epidemiology, Ludwig-Maximilians-Universitat Munchen, Munich 80539, Germany.

[138]University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen 9700RB, The Netherlands.

[139]Institute for Community Medicine, University Medicine Greifswald, Greifswald 17475, Germany.

[140]Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands.

[141]Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Ophthalmology and Visual Science Key Lab, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China.

[142]Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China.

[143]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261, USA.

[144]Division of Cancer Control and Population Sciences, UPMC Hillman Cancer, University of Pittsburgh, Pittsburgh, PA 15232, USA.

[145]Behavioral Epidemiology Section, Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA.

[146]Department of Internal Medicine B, University Medicine Greifswald, Greifswald 17475, Germany.

[147]Broad Institute of the Massachusetts Institute of Technology and Harvard University, Boston, MA 02142, USA.

[148]Section on Nephrology, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA.

[149]Department of Genomics of Common Disease, Imperial College London, London W12 0NN, UK.

[150]German Center for Diabetes Research (DZD e.V.), Neuherberg 85764, Germany.

[151]Department of Ophthalmology, Medical Faculty Mannheim, University Heidelberg, Mannheim, Germany 68167, Germany.

[152]Beijing Institute of Ophthalmology, Beijing Ophthalmology and Visual Science Key Lab, Beijing Tongren Eye Center, Capital Medical University, Beijing 100730, China.

[153]Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261, USA.

[154]Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio 70211, Finland.

[155]Lifelines Cohort, Groningen 9700RB, The Netherlands.

[156]Department of Medicine, Internal Medicine, Lausanne University Hospital and University of Lausanne, Lausanne 1011, Switzerland.

[157]Durrer Center for Cardiogenetic Research, ICIN-Netherlands Heart Institute, Ultrecht, The Netherlands.

[158]Faculty of Medicine, University of Iceland, Reykjavik 101, Iceland.

[159]Sticht Center for Health Aging and Alzheimer's Prevention, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA.

[160]NHLBI Framingham Heart Study, Framingham, MA 01702, USA.

[161]Population Sciences Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, NIH, Bethesda, MD 20892, USA.

[162]Division of General Medicine, Department of Medicine, Columbia University Medical Center, New York, NY 10032, USA.

[163]Cardiovascular Health Research Unit, Epidemiology, Medicine and Health Services, University of Washington, Seattle, WA 98101, USA.

[164]Kaiser Permanente Washington Health Research Institute, Seattle, WA 98101, USA.

[165]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119228, Singapore.

[166]Nuffield Department of Population Health, University of Oxford, Oxford, UK.

[167]Department of Biostatistics, University of Washington, Seattle, WA 98195, USA.

[168]Biostatistics, Preventive Medicine, University of Southern California, Los Angeles, CA 90032, USA.

[169]Epidemiology, University of North Carolina Gilling School of Global Public Health, Chapel Hill, NC 27514, USA.

[170]Department of Public Health & Clinical Medicine, Umeå University, Umeå, Västerbotten 901 85, Sweden.

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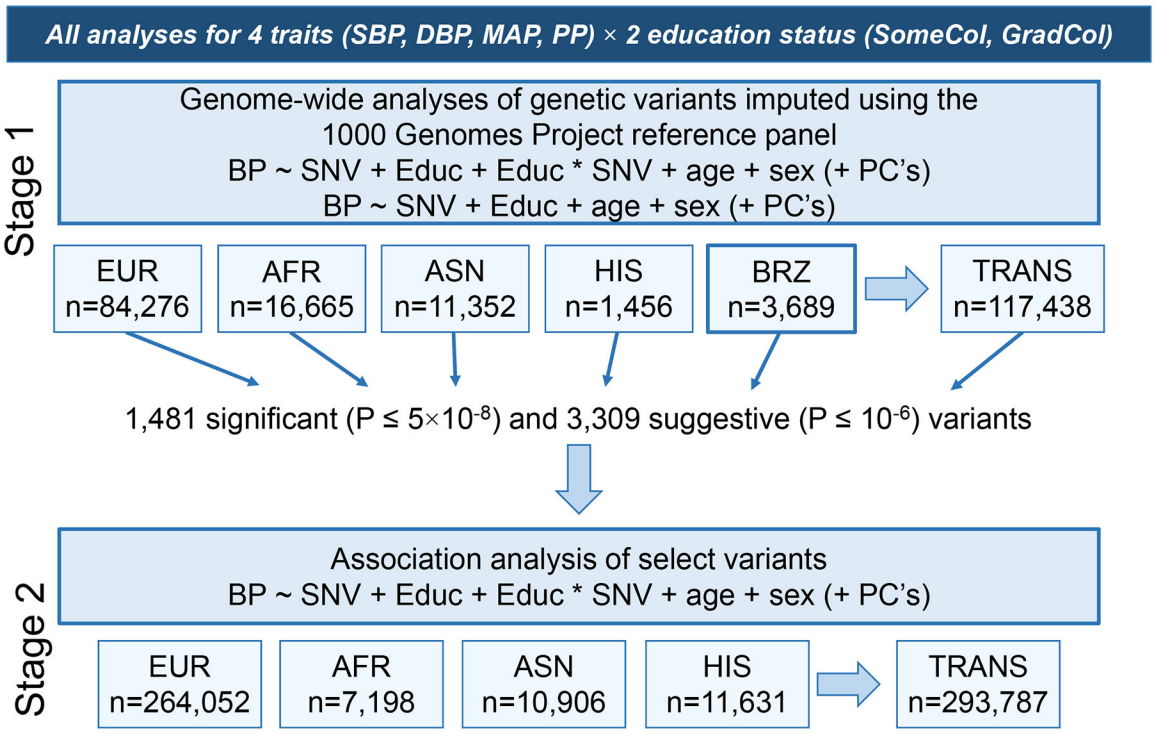

Figure 1.

Study design with summary of data included in this study. Educ: education status (considering either SomeCol or GradCol status separately); PC: principal component; EUR: European; AFR: African; ASN: Asian; HIS: Hispanic; BRZ: Brazilian; SNV: single nucleotide variant; TRANS; trans-ancestry (i.e., combining all ancestry groups through meta-analysis).

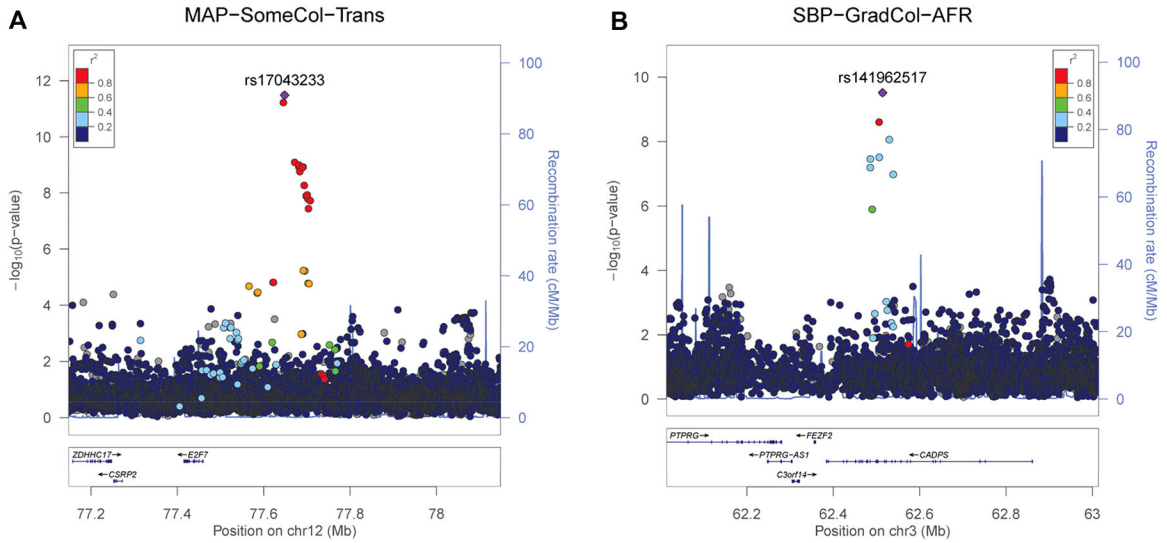

Figure 2: LocusZoom plots for 2 BP loci related to CNS-adrenal signaling

(A) MAP-associated locus adjacent to *ZDHHC17*, identified in AFR and in trans-ancestry, shows roles in CNS-adrenal signaling. In neurons, *ZDHHC17* encodes a membrane protein that mediates fusion of synaptic vesicles to the plasma membrane, enabling the release of neurotransmitters. Murine *zdhhc17* knockout models show impaired hippocampal memory and reduced synaptic plasticity, providing potential biological links to working memory and subsequent educational attainment.

(B)A locus intragenic to *CADPS*, identified in AFR, is of potential biologic relevance given this gene's expression in CNS tissue and role in regulating the fusion of neuroendocrine vesicles and release of vasoactive catecholamines from both adrenal and neural tissue. Three LD SNVs have CADD scores >10, and four LD SNVs have ChromHMM state signals consistent with strong evidence of transcription regulation.

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. The plots were created using LocusZoom (http://locuszoom.sph.umich.edu/).

Table 1.

Basic characteristics of cohorts in Stages 1 and 2 in each ancestry

	Max. N	Some College? (Yes/No)		Grad. College? (Yes/No)		% Male	% HT	% HT Meds	Age		SBP		DBP		MAP		PP	
Stage 1		**N**	**% Yes**	**N**	**% Yes**				**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
EUR	84 276	47 870	57.7	79 040	34.6	32.9	28.7	17.0	54.7	7.8	130.3	19.1	78.3	11.2	95.6	12.6	52.0	13.1
AFR	16 665	16 665	48.8	16 665	21.6	40.6	52.4	40.3	51.5	9.2	134.4	23.2	81.2	13.4	98.9	15.5	53.2	16.1
ASN	11 352	11 352	10.0	748	38.9	53.0	49.6	29.5	56.8	9.4	139.3	16.1	80.2	11.1	99.9	13.5	59.1	16.2
BRZ	3 689	3 689	36.8	3 689	17.5	45.6	29.0	7.6	34.5	3.8	123.4	15.3	76.6	10.0	92.2	11.1	46.8	10.2
HIS	1 456	1 456	35.2	1 456	9.8	48.4	41.4	33.3	60.8	9.73	131.2	24.8	74.9	11.7	93.6	14.9	56.4	18.5
Stage 1 Total	*117 438*	*81 032*	*47.8*	*101 598*	*31.5*	*36.5*	*34.2*	*21.4*	*53.9*	*8.1*	*131.6*	*19.4*	*78.8*	*11.5*	*96.4*	*13.1*	*52.8*	*13.8*
Stage 2																		
EUR	264 052	242 524	54.3	257 037	26.3	47.6	48.5	21.7	54.9	8.9	138.5	20.2	83.3	11.4	101.7	13.4	55.2	13.6
AFR	7 198	7 198	20.8	7 198	10.9	40.4	56.8	44.1	54.7	9.5	137.6	21.8	83.8	12.9	101.7	14.8	53.8	14.9
ASN	10 906	10 906	21.4	5 947	10.9	40.1	37.4	24.9	55.8	9.0	134.2	23.1	80.7	12.8	98.6	15.4	53.5	14.8
HIS	11 631	11 631	35.5	11 631	14.6	41.1	25.4	15.0	45.3	13.6	123.6	19.7	75.0	11.8	91.2	13.6	48.6	13.1
Stage 2 Total	*293 787*	*272 259*	*51.3*	*281 813*	*25.1*	*46.6*	*47.4*	*22.1*	*54.6*	*9.1*	*137.7*	*20.3*	*82.9*	*11.5*	*101.2*	*13.6*	*54.8*	*13.7*
TOTAL	*411 225*	*353 291*	*50.5*	*383 411*	*26.8*	*43.7*	*43.6*	*21.9*	*54.4*	*8.8*	*136.0*	*20.1*	*81.7*	*11.5*	*99.8*	*13.4*	*54.2*	*13.7*

The cell entries for the covariates and BP traits corresponds to sample-size weighted averages across all cohorts in each category.

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Table 2.

Eighteen new loci associated with BP traits that are at least 1Mb away from any known BP locus.

Locus	Nearest Gene	rsID	Chr:Pos	EA	EAF (AFR/ASN/EUR/HIS)	Genetic Effect		GxE Interaction		P-value		Trait	Educ.	Anc.
						Effect	SE	Effect	SE	Interaction	2DF Joint			
1	*CDC14A*	rs114558965	1:100829685	a	0.97/. /. /1.00	−0.23	1.02	5.02	1.27	2.54E-03	2.86E-09	SBP	SC	AFR
2	*LIN01249*	rs9308788	2:4711095	a	0.02/0.22/0.06/0.06	2.97	2.13	−11.93	2.64	5.04E-05	4.47E-08	SBP	GC	AFR
3	*ARL4C*	rs145586115	2:235604646	t	0.97/. /. /0.99	4.80	0.87	−2.57	1.29	1.16E-01	1.92E-08	SBP	SC	AFR
4	*CADPS*	rs141962517	3:62514061	t	0.98/. /. /.	−2.46	1.54	12.85	2.23	1.99E-07	3.07E-10	SBP	GC	AFR
5	*PCDH7*	rs74458816	4:31363388	a	0.03/. /. /0.00	−0.18	0.70	−3.46	0.91	2.26E-03	4.90E-09	MAP	SC	AFR
6	*EIF4E*	rs2141284	4:99704167	a	. /. /0.01/0.01	−1.35	0.22	1.01	0.38	2.16E-02	6.73E-09	MAP	GC	TRANS
7	*SPEF2*	rs115523707	5:35756623	t	0.03/. /0.00/0.00	−0.83	0.64	−2.73	0.88	5.91E-02	7.22E-09	PP	SC	AFR
8	*ANKRD34B*	rs66907226	5:79863455	d	0.46/0.81/0.58/0.69	0.48	0.14	0.04	0.18	9.86E-01	4.43E-08	SBP	SC	EUR
9	*SLCO4C1*	rs114175587	5:100994204	t	0.02/. /. /0.00	−4.84	0.83	3.84	1.29	3.55E-03	2.40E-08	PP	SC	TRANS
10	*SLIT3*	rs142385399	5:168166731	a	0.04/. /0.00/0.01	2.25	0.74	−7.07	1.22	2.79E-08	4.76E-08	DBP	GC	AFR
11	*THSD7A*	rs200612978	7:11493906	d	0.03/0.03/. /0.01	−0.40	1.27	−4.94	1.57	5.71E-02	4.81E-08	SBP	SC	AFR
12	*HAS2-AS1*	rs112332671	8:122673983	a	0.02/. /. /0.00	−1.37	1.18	−4.55	1.52	6.03E-02	1.89E-09	PP	SC	AFR
13	*CDON*	rs12295584	11:125841078	a	0.95/. /0.99/0.99	2.87	0.57	−1.07	0.84	2.20E-01	4.71E-08	SBP	SC	TRANS
14	*DSTNP2*	rs75535814	12:6996683	t	0.02/. /. /0.00	−8.78	1.45	7.24	1.95	3.17E-04	5.79E-09	SBP	SC	AFR
15	*PIK3C2G*	rs189555401	12:18443065	t	0.03/. /. /0.01	−3.23	0.57	1.82	1.15	8.92E-02	4.10E-08	DBP	GC	TRANS
16	*E2F7; ZDHHC17*	rs17043233	12:77648216	t	0.02/. /. /0.00	−4.07	0.58	4.26	0.90	1.72E-05	1.39E-11	MAP	SC	TRANS
17	*HRH4*	rs8099516	18:22108763	t	0.04/. /. /0.01	1.71	0.61	−5.39	0.95	7.83E-09	5.04E-08	DBP	GC	AFR
18	*LOC100289473*	rs113809930	20:1711768	a	0.98/0.88/0.97/0.94	−0.69	0.79	3.67	0.94	1.70E-03	3.48E-08	DBP	SC	AFR

Positions are based on build 37. Effect is in mmHg unit. BP: blood pressure; DBP: diastolic BP; EA: effect allele; EAF: effect allele frequency observed in our cohorts; MAP: mean arterial pressure; P: P-value of the joint test with 2 degrees of freedom of genetic main and interaction effects; PP: pulse pressure; SBP: systolic BP; SE: standard error; 2DF Joint 1DF Interaction P: P-value of the interaction test with 1 degree of freedom. The smallest P-values between 1DF interaction test and the joint 2DF test are in boldface

SC: SomeCol; GC: GradCol; EUR: European; AFR: African; TRANS; trans-ancestry (i.e., combining all ancestry groups through meta-analysis).