ARTICLE OPEN

Check for updates

Multi-ancestry genome-wide association analyses incorporating SNP-by-psychosocial interactions identify novel loci for serum lipids

Amy R. Bentley[1,109]✉, Michael R. Brown[2,109], Solomon K. Musani[3], Karen L. Schwander[4], Thomas W. Winkler[5], Mario Sims[6], Tuomas O. Kilpeläinen[7,8], Hugues Aschard[9,10], Traci M. Bartz[11], Lawrence F. Bielak[12], Jin-Fang Chai[13], Kumaraswamy Naidu Chitrala[14], Nora Franceschini[15], Mariaelisa Graff[15], Xiuqing Guo[16], Fernando P. Hartwig[17], Andrea R.V.R. Horimoto[11,18], Elise Lim[19], Yongmei Liu[20], Alisa K. Manning[21,22], Ilja M. Nolte[23], Raymond Noordam[24], Melissa A. Richard[25,26], Albert V. Smith[27], Yun Ju Sung[28], Dina Vojinovic[29,30,31], Rujia Wang[32], Yujie Wang[15], Mary F. Feitosa[4], Sarah E. Harris[33], Leo-Pekka Lyytikäinen[34,35], Giorgio Pistis[36], Rainer Rauramaa[37], Peter J. van der Most[23], Erin Ware[38], Stefan Weiss[39,40], Wanqing Wen[41], Lisa R. Yanek[42], Dan E. Arking[43], Donna K. Arnett[44], Christie Ballantyne[45,46], Eric Boerwinkle[2,47], Yii-Der Ida Chen[16], Martha L. Daviglus[48], Lisa de las Fuentes[49,50], Paul S. de Vries[2], Joseph A. C. Delaney[51,52,53,54], Amanda M. Fretts[51,53], Lynette Ekunwe[55], Jessica D. Faul[38], Linda C. Gallo[56], Sami Heikkinen[57], Georg Homuth[39], M. Arfan Ikram[29], Carmen R. Isasi[58], Jost Bruno Jonas[59,60], Liisa Keltikangas-Järvinen[61], Pirjo Komulainen[37], Aldi T. Kraja[62], Jose E. Krieger[18], Lenore Launer[63], Lifelines Cohort Study*, Jianjun Liu[64], Kurt Lohman[65], Annemarie I. Luik[29], Ani W. Manichaikul[66,67,68], Pedro Marques-Vidal[69], Yuri Milaneschi[70], Stanford E. Mwasongwe[71], Jeffrey R. O'Connell[72], Kenneth Rice[11], Stephen S. Rich[66,67,68], Pamela J. Schreiner[73], Lars Schwettmann[74,75], James M. Shikany[76], Xiao-ou Shu[41], Jennifer A. Smith[12,38], Harold Snieder[23], Nona Sotoodehnia[77], E. Shyong Tai[78], Kent D. Taylor[79], Lesley Tinker[80], Michael Y. Tsai[81], André G. Uitterlinden[82], Cornelia M. van Duijn[29,83], Diana van Heemst[24], Melanie Waldenberger[84], Robert B. Wallace[85], Hwee-Lin Wee[13], David R. Weir[38], Wen-Bin Wei[86], Ko Willems van Dijk[87,88], Gregory Wilson[89], Jie Yao[16], Kristin L. Young[15], Xiaoyu Zhang[19], Wei Zhao[12,38], Xiaofeng Zhu[90], Alan B. Zonderman[63], Ian J. Deary[33], Christian Gieger[84,91,92], Hans Jörgen Grabe[93,94], Timo A. Lakka[37,57,95], Terho Lehtimäki[34,35], Albertine J. Oldehinkel[96], Martin Preisig[36], Ya-Xing Wang[60], Wei Zheng[41], Michele K. Evans[63], Michael Province[4], James Gauderman[97], Vilmundur Gudnason[98,99], Catharina A. Hartman[96], Bernardo L. Horta[100], Sharon L. R. Kardia[12], Charles Kooperberg[80], Ching-Ti Liu[19], Dennis O. Mook-Kanamori[101,102], Brenda WJH Penninx[70], Alexandre C. Pereira[18], Patricia A. Peyser[12], Bruce M. Psaty[103], Jerome I. Rotter[16], Xueling Sim[13], Kari E. North[15], Dabeeru C. Rao[49], Laura Bierut[104], Clint L. Miller[66,67,68], Alanna C. Morrison[2], Charles N. Rotimi[1,109], Myriam Fornage[25,109] and Ervin R. Fox[55,109]

This is a U.S. Government work and not under copyright protection in the US; foreign copyright protection may apply 2025

Serum lipid levels, which are influenced by both genetic and environmental factors, are key determinants of cardiometabolic health and are influenced by both genetic and environmental factors. Improving our understanding of their underlying biological mechanisms can have important public health and therapeutic implications. Although psychosocial factors, including depression, anxiety, and perceived social support, are associated with serum lipid levels, it is unknown if they modify the effect of genetic loci that influence lipids. We conducted a genome-wide gene-by-psychosocial factor interaction (G×Psy) study in up to 133,157 individuals to evaluate if G×Psy influences serum lipid levels. We conducted a two-stage meta-analysis of G×Psy using both a one-degree of freedom (1df) interaction test and a joint 2df test of the main and interaction effects. In Stage 1, we performed G×Psy analyses on up to 77,413 individuals and promising associations ($P < 10^{-5}$) were evaluated in up to 55,744 independent samples in Stage 2. Significant findings ($P < 5 \times 10^{-8}$) were identified based on meta-analyses of the two stages. There were 10,230 variants from 120 loci significantly associated with serum lipids. We identified novel associations for variants in four loci using the 1df test of interaction, and five additional loci using the 2df joint test that were independent of known lipid loci. Of these 9 loci, 7 could not have been detected without modeling the interaction as there was no evidence of association in a standard GWAS model. The genetic diversity of included samples was key in identifying these novel loci: four of the lead variants displayed very low frequency in European ancestry populations. Functional annotation highlighted promising loci for further experimental follow-up, particularly rs73597733 (*MACROD2*), rs59808825 (*GRAMD1B*), and rs11702544 (*RRP1B*). Notably, one of the genes in identified loci (*RRP1B*) was found to be a target of the approved drug Atenolol suggesting potential for drug repurposing. Overall, our findings suggest that taking interaction between genetic variants and psychosocial factors into account and including genetically diverse populations can lead to novel discoveries for serum lipids.

Translational Psychiatry (2025)15:207 ; https://doi.org/10.1038/s41398-025-03418-z

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

Received: 20 June 2024 Revised: 14 May 2025 Accepted: 2 June 2025
Published online: 20 June 2025

INTRODUCTION

The concentrations of key serum lipids, such as high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), and triglycerides (TG) are routinely assessed to determine an individual's cardiometabolic clinical risk profile, and to guide drug therapy (e.g., statins) aiming to reduce the morbidity and mortality associated with diseases such as coronary artery disease, stroke, and type 2 diabetes. Serum lipid levels are known to be influenced both by lifestyle, including diet, physical activity, smoking, and alcohol consumption, as well as genetic factors, with over 700 lipids loci identified using genome-wide association studies (GWAS) [1–3]. Although the importance of both genetic and lifestyle factors is well-established, the interplay between these two factors on serum lipid levels is less well understood. The Gene-Lifestyle Interactions Working Group, under the aegis of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium [4], has developed a framework for studying gene-lifestyle interactions for cardiometabolic traits in large, multi-ancestry meta-analyses [5]. This strategy has facilitated the discovery of novel lipids loci in studies accounting for interactions with smoking [6], physical activity [7], alcohol consumption [8], educational attainment [9], and sleep duration [10], suggesting that these lifestyle factors may indeed modulate genetic effects on serum lipids. The loci identified in these efforts could potentially explain how lifestyle exposures can contribute to disturbances in lipid levels.

Psychosocial factors, especially depression, contribute to the pathogenesis of cardiovascular diseases (e.g., myocardial infarction) and increased mortality in patients with coronary heart disease [11–13], and Mendelian Randomization (MR) analysis suggests that this association is causal [14]. Depression and depressive symptoms are associated with serum lipid concentrations [13, 15], the plasma lipidome [16, 17], and lipid metabolism, with distinct metabolic signatures associated with various symptom dimensions [18]. *APOE* alleles associated with serum lipids have also been associated with anxiety and depression [19, 20]. Some evidence from MR analyses suggests that depression increases TG and decreases HDLC [21]. Serum lipids may also mediate the association between depression and cardiovascular disease. The association between depression and coronary artery disease was attenuated when an MR analysis was adjusted for serum lipids [14]. Similarly, in one study, nearly a third of the association of depression with arterial stiffness, a key intermediary of major cardiovascular events, was found to be mediated by metabolic syndrome, particularly hypertriglyceridemia among men [22]. Low social support has been associated with high cholesterol in a nationally representative US nonelderly population [23] and with high cholesterol, LDL, and non-HDL cholesterol among type 2 diabetics and their families [24]. Both anxiety and depression have been associated with elevated triglycerides [25]. Proposed mechanisms through which psychosocial factors and serum lipids may influence each other include high dietary intake of saturated fat and cholesterol, gut dysbiosis, the hypothalamic-pituitary-adrenal axis, and neuroinflammation [26–28]. Both direct and indirect mechanisms, such as psychosocial factor-associated changes in lifestyle or medication use, are plausible. This may confound interaction effects. Importantly, there is evidence for a genetic contribution to some of these psychosocial factors, particularly depression [29–33].

In this study, we assess how incorporating interaction between genetic variants and psychosocial factors (depressive symptoms, anxiety symptoms, and low social support) helps identify lipid loci missed by standard marginal genetic effect GWAS. To maximize the transferability of our results and to address known gaps in the field, we prioritized the inclusion of diverse population groups, as ancestry can influence both genetic (e.g. frequency of variants, linkage disequilibrium around associated signals) and psychosocial factors (e.g. presence of stigma, availability of healthcare access). We conducted multi-ancestry meta-analyses of genome-wide variant × psychosocial factor interaction (G×Psy) studies on serum lipids in up to 133,157 individuals.

RESULTS

In this study of psychosocial factors and serum lipids, we meta-analyzed data on up to 133,157 individuals from 50 genome-wide interaction studies using a two-stage study design (Fig. 1; Study Details Supplementary Tables S1-2; Supplementary Note). Sample sizes and descriptive statistics of the studies participating in Stages 1 and 2 analyses are summarized in Supplementary Table 2. Study participants included European ancestry (EUR; 67.5%; $n = 89{,}939$), African ancestry (AFR; 14.4%; $n = 19{,}133$), Hispanic/Latino (HISP; 12.0%; $n = 15{,}949$), Asian ancestry (ASN; 3.5%; $n = 4672$), and Brazilian individuals (BRZ; 2.6%; $n = 3464$; see Methods for further details regarding selection of groups and population descriptors). All psychosocial factors were coded as binary variables. On average, 17.5% of Stage 1 participants were reported to have elevated depressive symptoms (DEPR) and 24.2% had elevated anxiety symptoms [ANXT], based on standard cutpoints, with a similar distribution among Stage 2 participants (15.8% [DEPR] and 24.3% [ANXT]). Low social support (SOCS) was defined as the lowest quartile of the distribution (Methods). Fewer studies had data on SOCS ($n = 23$) and ANXT ($n = 21$) than DEPR ($n = 50$; harmonization of psychosocial factors is described in Supplementary Table 3).

In Stage 1 population-specific and cross-population meta-analyses (CPMA), we identified 15,774 variants that met our selection criteria of $P < 10^{-5}$ for either the 1 degree of freedom interaction test (1df) or the 2df joint test of the main and interaction effects (2df; Fig. 1). These variants were carried forward for further analysis in Stage 2 samples. In the meta-analysis of stages 1 and 2, there were 10,230 variants from 120 loci that were significantly associated in at least one model using either statistical test (P_{1df} or $P_{2df} < 5 \times 10^{-8}$; Supplementary Table 4). We found seven variants in four loci that were associated with serum lipids with a genome-wide significant p-value for the 1df test of interaction (Table 1). For instance, among those reporting low social support, the A allele of rs11949029 was associated with a much lower LDLC concentration than among those who did not ($\beta_{Interaction}n = -19.2$, SE 3.5 mg/dL, $P_{1df} = 4.1 \times 10^{-8}$; Fig. 2A). Thus, among those with low social support, this allele was associated with 12.6 mg/dL lower LDLC, but 6.6 mg/dL higher LDLC among those not reporting low social support. In meta-analyses that did not include a multiplicative term (i.e. a standard GWAS model; available only for stage 1 studies), no association of the variant with LDLC was observed ($P = 0.69$), even after adjustment for SOCS ($P = 0.75$).

A significant association using the 2df joint test of the main effect and interaction can represent the main effect of a variant, its interaction with the exposure, or both. To exclude associations driven primarily by the main effect, we considered as previously unidentified only those variants with $P_{2df} < 5 \times 10^{-8}$ that were independent of known loci (defined as ± 500 kb from the 95% credible sets reported in Graham *et al* [1] or variants reported in other major publications [34–39]). There were 14 variants and 8 loci that were significantly associated with serum lipids using the 2df test and independent from known loci (Table 2). Six of these loci displayed nominal significance for an interaction effect ($P_{1df} < 0.05$). This includes three of the four loci that were genome-wide significant using the 1df test, with the remaining two near this threshold. Among these is rs59808825 (*GRAMD1B* [nearest gene]), for which the main effect of the C allele on LDLC was positive ($\beta = 5.0$, SE = 2.1 mg/dL) but an inverse interaction effect with ANXT ($\beta_{Interaction} = -22.9$, SE = 4.2 mg/dL), so that the total effect of the C allele among those reporting anxiety symptoms was negative ($P_{2df} = 8.8 \times 10^{-9}$; Fig. 2B). In the main

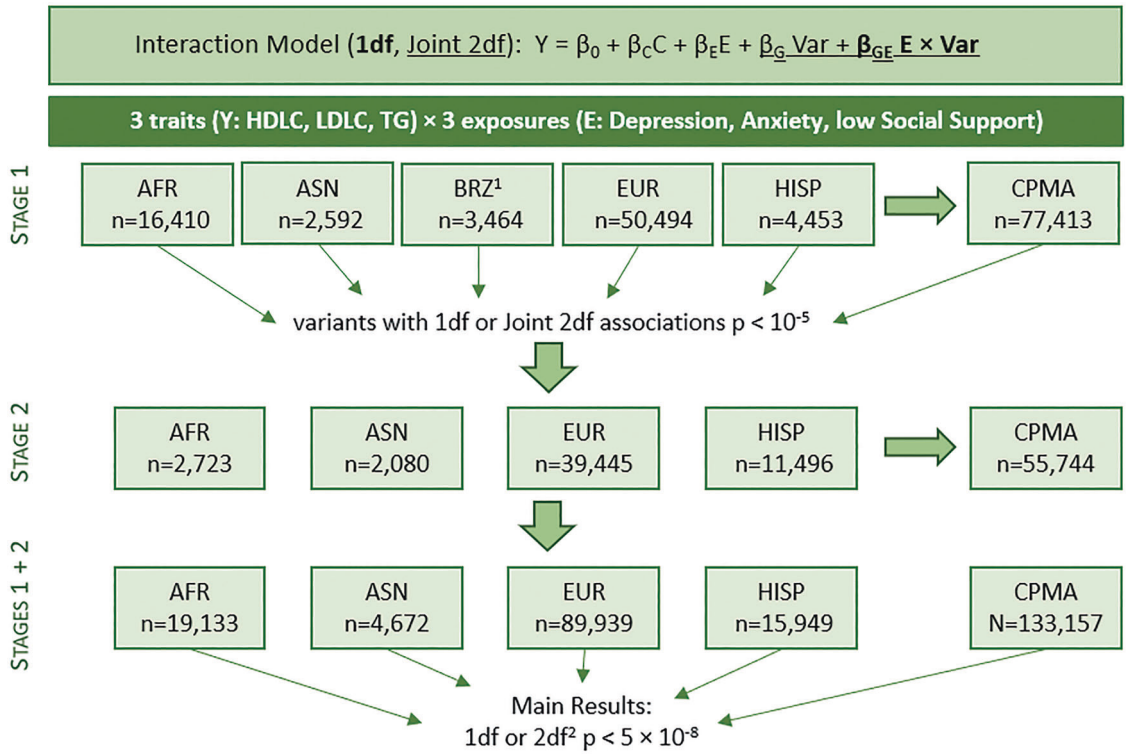


Fig. 1 Study design. *African ancestry (AFR), Asian ancestry (ASN), Brazilian (BRZ), European ancestry (EUR), Hispanic (HISP), cross-population meta-analysis (CPMA)1 Brazilian samples were only available in Stage 1, so a Stage 1 + 2 meta-analysis of BRZ was not possible. These samples are include in the cross-population Stage 1 + 2 meta-analysis; 2 As the 2df results joinly measure the variant's main and interaction effects, our main results only include those 2df findings that are also more than 500 kb from known lipids loci.*

effect only meta-analysis, no association between rs59808825 and LDLC was observed ($P = 0.13$). Of the 8 loci identified through the 2df test, two associations had $P_{1df} \geq 0.1$, suggesting that the 2df test may reflect novel main effect associations (though we cannot exclude that G×Psy interactions may contribute to these findings but are undetectable at the current sample sizes). For instance, the joint 2df test was significant for rs34636484 (*CD96*) × SOCS on LDLC ($P_{2df} = 3.1E\text{-}8$), while the 1df test was not ($P_{1df} = 0.27$; Supplementary Figure 4C). rs11702544 (*RRP1B*) × DEPR on HDLC was also plausibly driven by a main effect (Supplementary Figure 4H). Importantly, both of these potential main effect associations were identified in the CPMA results, highlighting the importance of including diverse populations for novel discoveries.

The inclusion of underrepresented population groups in this study also provided an advantage in identifying novel interaction associations, with associations observed at four lead loci at which no data from EUR studies were available because of a minor allele frequency < 0.01. For instance, an interaction of rs11949029 (*CTC-207P7.1*) and SOCS on LDLC was statistically significant for both the 1df test of interaction (Fig. 2A) and the 2df test of interaction and main effect (Supplementary Figure 4D) and was driven by data from the AFR and HISP populations. In this case, there was consistency of both the main and interaction associations across backgrounds. Such consistency was common among these lead findings; however, there were a few associations that were driven predominantly by one population, despite the availability of data for other groups. In the interaction between rs61248562 (*UNC13 C*) and DEPR on HDLC, the observed association among EUR reached statistical significance ($\beta = 0.14$; $SE = 0.025$; $P_{1df} = 5.2 \times 10^{-9}$; Supplementary Figure 3C), yet this association was not seen in other populations despite a comparable number of samples with available data (EUR 15,052 vs. AFR 13,069 and HISP 15,977) and larger effect allele frequencies (EUR 0.02 vs. AFR 0.16 and HISP 0.07). As expected, the CPMA for this association was greatly reduced in statistical significance ($P_{1df} = 1.5 \times 10^{-3}$). Similarly, the rs73597733 (*MACROD2*) × DEPR interaction on HDLC in AFR ($P_{1df} = 8.4 \times 10^{-9}$) was not seen in HISP ($P_{1df} = 0.43$; Supplementary Figure 3D).

Of the 10 lead associations in 9 loci that reached genome-wide statistical significance in the meta-analyses of Stages 1 and 2 (for one locus there were significant associations in two population groups), 4 were significant in both stages ($P < 0.05$) while 6 were only significant in stage 1 (Supplementary Table 5). There were 16 variants in 9 loci that were considered as the novel associated variant set for annotation and follow-up: those associated with either $P_{1df} < 5 \times 10^{-8}$ (seven variants in four loci) or $P_{2df} < 5 \times 10^{-8}$ and independent of known lipids loci (14 variants in 8 loci; five variants in three loci overlapping in 1df and 2df findings). The novel associated variants were characterized using FUMA. As expected, most of the variants were annotated to be intronic ($n = 10$) or intergenic ($n = 3$; Supplementary Table 6). While a single signal was detected for most of the described loci in Tables 1 and 2, the associated region on chromosome 21 (CPMA-HDL-DEPR) had three independent genomic signals at variants rs11702544, rs6518309, and rs9977076. Each of these variants is an eQTL for three genes in a variety of tissues, including whole blood: *PDXK*, *RRP1B*, and *HSF2BP* [40] (Supplementary Table 7).

We also evaluated 257 variants in LD with our lead variants ($R^2 \geq 0.6$ in 1000 Genomes, Phase 3 ALL; Supplementary Table 8). Evaluation of these variants in RegulomeDB identified 75 variants (29.2%) with functional prediction scores ≤ 3, indicating moderate to high potential for regulatory effects. Variants within the locus on chromosome 21 characterized by rs11702544, rs6518309, and rs9977076 (*RRP1B*) had the lowest RegulomeDB scores in this set: 1a ($n = 1$) and 1b ($n = 6$), which indicates that they are likely to affect transcription factor binding to the gene targets, in this case *HSF2BP*, *RRP1B*, or *LINC00313*. These variants were also tested in our data and nearly reached statistical significance for the 2df

Table 1. Genome-wide variants significantly associated with serum lipids using a 1 df test of interaction in Meta-Analysis of Stages 1 & 2.

rsid Index Variant *Nearest Gene*[a]	Chr:BP (GRCh37	Tested Allele: Freq	Main Effect	SE	Interaction Effect	SE	P_{1df}[b]	P_{2df}[b]	Population, Sample Size	Lipid[c]	Psychosocial Factor
rs11949029 *RNU4-73P*	5:163470425	A:0.02	6.6	2.2	-19.2	3.5	**4.1E-08**	**2.4E-08**	CPMA, $n = 16,927$	LDLC	SOCS
rs59808825 *GRAMD1B*	11:123152496	C:0.03	5.0	2.1	-22.9	4.2	**4.3E-08**	**8.8E-09**	CPMA, $n = 5,973$	LDLC	ANXT
rs61248562 *RP11-643A5.2*	15:54249794	I[d]:0.02	−0.024	0.015	0.14	0.025	**5.2E-09**	6.9E-08	EUR, $n = 15,052$	HDLC	DEPR
rs73597733 *MACROD2*	20:15941137	A:0.04	−0.015	0.010	0.14	0.025	**8.4E-09**	**1.0E-08**	AFR, $n = 11,234$	HDLC	DEPR

[a]Nearest gene determined based on ANNOVAR annotations implemented in FUMA. While the "Nearest Gene" is listed for simplicity, we acknowledge that the nearest gene may not be of functional relevance for the given variant.
[b]Bolded values indicate $P < 5 \times 10^{-8}$.
[c]Analyses were conducted on natural log-transformed HDLC and TG values, while LDLC was untransformed (all original values in mg/dL).
[d]Insertion.

interaction with DEPR on HDLC (P_{2df} range 2.4×10^{-6} to 4.2×10^{-7}), with similar effect sizes in all.

Next, we assessed the predicted chromatin state around our 16 novel associated variants using the minimum 15-core chromatin state models calculated across 127 tissue/cell types [41]. We identified histone chromatin markers in regions associated with strong transcription ($n = 6$; Supplementary Table 6). In the 257 variants in LD with our lead variants, there were histone chromatin markers consistent with active ($n = 13$) or flanking active ($n = 21$) transcription start sites, transcription at the 3′ or 5′ end ($n = 7$), or in regions associated with strong transcription ($n = 50$) (Supplementary Table 8). For most of our loci, significant chromatin interactions were detected between regions containing our variants and regions overlapping gene promoters (Supplementary Table 9); for instance, between the locus on chromosome 21 (lead variant rs11702544) and regions overlapping the promoter of multiple genes, including *PDXK*, *RR1BP*, and *HSF2BP*.

Finally, to explore the potential clinical relevance of our findings, we performed an integrated druggability analysis of identified genes, as previously described [42]. We queried high and medium priority candidate gene targets (identified by FUMA and OpenTargets) using the Drug-Gene Interaction database (DGIdb), which revealed 2 genes annotated as clinically actionable or members of the druggable genome (Supplementary Table 10). Several of these gene targets are implicated in ion transport (*NKAIN3*), vitamin metabolism (*PDXK*), and immune or viral response (*CD96*, *RRP1B*) pathways. We identified 1 gene, *RRP1B*, with a reported drug interaction. *RRP1B* was shown to interact with an FDA-approved drug, Atenolol, that has been evaluated in late-stage clinical trials using DrugBank and ClinicalTrials.gov databases (Supplementary Table 10). Atenolol is a well-established anti-hypertensive drug used to treat high blood pressure, heart failure, or angina in some patients. Together these results suggest a potential drug repurposing opportunity to intervene in a common pathway implicated in cardiometabolic disorders.

DISCUSSION

In this study, we investigated genome-wide variant-by-psychosocial factor interactions (G×Psy) in large, multi-ancestry meta-analyses of serum lipids. We identified nine novel lipid loci using this strategy, including four loci based on the 1df test of interaction and eight loci based on the 2df joint test of interaction and main effects (with three loci significantly associated using both strategies). Importantly, most of these associations could not have been identified in a standard GWAS that does not take interaction into account. Our inclusion of relatively large sample sizes representing diverse ancestries facilitated novel findings. Functional annotation highlights the promise of some of these identified loci for understanding the potential influence of psychosocial factors on serum lipids.

Both the 1df test of interaction and the 2df test of main effect and interaction identified statistically significant results for rs73597733 (intronic to *MACROD2*) × DEPR on HDLC, in which the main effect of the variant was near zero, with a large positive association among those with depressive symptoms. Intriguingly, an interaction between an intronic variant in *MACROD2* (not in LD with rs73597733) was previously found between thiazide diuretic use and HDLC [43]. Other intronic variants in *MACROD2* have been associated with the ceramides and sphingomyelins, suggesting a potential role in lipids pathways [44]. There is a large body of evidence for associations of intronic variants in *MACROD2* with complex psychosocial, neurological, and psychiatric traits, including: attention deficit hyperactivity disorder [45, 46], morningness (being a morning person) [47], risk-taking behavior [48], eating disorders [49], autism [50–52], and bipolar disorder [52, 53]. Infants with atypical neonatal neurobehavioral scores had differentially methylated CpG sites within the *MACROD2* gene [54]. *Macrod2*

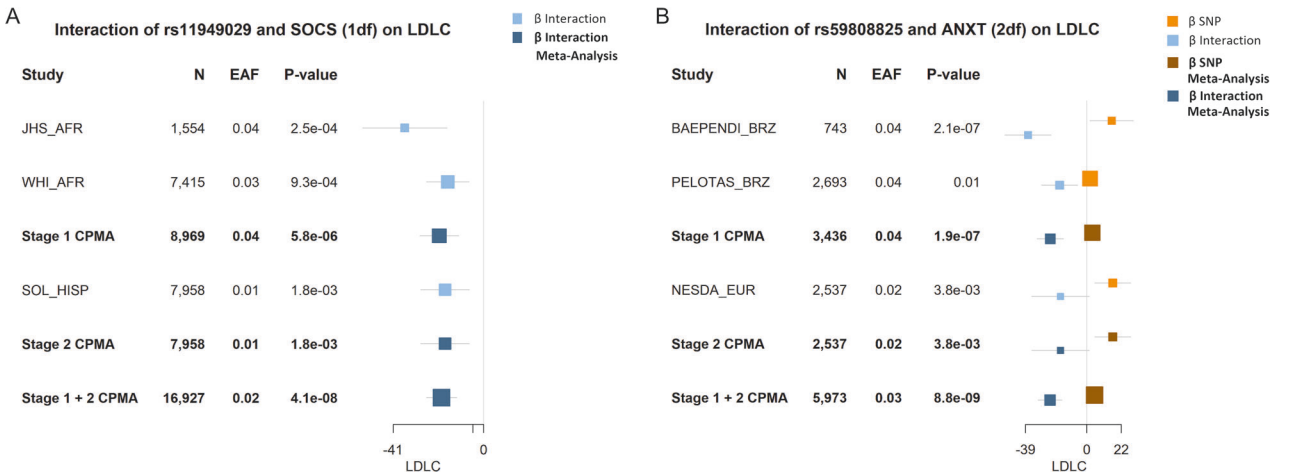


Fig. 2 Forest Plots of Key Findings. Forest plot showing all studies contributing data on an interaction of **A**. rs11949029 × social support (SOCS) on LDLC using a 1df test of the interaction term (this interaction was also statistically significant using the 2df joint test of the main effect and interaction, shown in Supplementary Figure 4D); and **B**. rs59808825 × anxiety symptoms (ANXT) on LDLC. Box size represents the precision of the estimate, with larger boxes shown for results with lower variance. *Abbreviations: African ancestry (AFR), Brazilian (BRZ), Effect Allele Frequency (EAF), European Ancestry (EUR), Hispanic (HISP), cross-population meta-analysis (CPMA).*

knockout mouse models displayed hyperactivity that became more pronounced with age [55]. Intronic variants in *MACROD2* have also been associated with measures of cognitive ability [56–58] and a variety of brain measurements [59–63]. Given the significant evidence for the involvement of this gene in a range of complex psychological and psychiatric phenotypes and a previous finding for an interactive effect on HDLC, our reported finding of an interaction between an intronic variant in *MACROD2* and DEPR on HDLC seems of particular interest and worthy of further investigation.

An association between rs59808825 (110 kb upstream of *GRAMD1B*) and ANXT on LDLC was $P < 5 \times 10^{-8}$ for both the 2df joint test of main effect and interaction and the 1df test of interaction, and no association was observed for this variant in an analysis without interaction modeled. *GRAMD1B* was identified as a locus for schizophrenia in multiple studies [64–69], a condition that has been linked with anxiety [70, 71]. The protein encoded by *GRAMD1B*, Gramd1b or Aster-B, has a role in cholesterol homeostasis, transporting accessible cholesterol from the plasma membrane to the endoplasmic reticulum [72, 73]. It was recently discovered that Aster proteins including Aster-B are key players in dietary lipid absorption in mice: the systemic absorption of dietary cholesterol was reduced by treatment with a small-molecule Aster inhibitor and mice without intestinal Aster proteins were protected from diet-induced hypercholesterolemia [74]. While further investigation is needed to propose a biological mechanism that might underlie the observed interaction between this variant and ANXT on LDLC, the known associations between nearby *GRAMD1B* with both complex psychiatric and psychological phenotypes and absorption of dietary lipid are intriguing.

We identified a 2df interaction of DEPR with variants on chromosome 21 (lead variant rs11702544 [*RRP1B*]) that appeared to represent a novel main effect of a common variant on HDLC. Interestingly, there was some evidence for an association of rs11702544 with HDLC using a standard GWAS model in the recent Global Lipids Genetics Consortium results ($P = 2.2E\text{-}6$) [1], consistent with the contribution of a main effect of this variant contributing to the 2df joint test of main effect and interaction. FUMA annotation identified 3 independent genomic loci in this region, each of which is an eQTL for *PDXK*, *RRP1B*, and *HSF2BP*. Each of the genes has been previously associated with risk of diseases for which serum lipids concentration is a key risk factor: *PDXK* and *RRP1B* with coronary artery disease [75] and *HSF2BP* with cardiovascular disease [76]. *PDXK* encodes a protein essential for the generation of the active form of Vitamin B_6. *PDXK* mRNA levels in adipose tissue were strongly associated with adipogenic, lipid-droplet-related, and lipogenic genes, and administration of the active form of Vitamin B_6 led to increased adipogenic markers in adipocyte precursor cells [77]. While the role for variants in this locus in HDLC concentration is not clear, they have been shown to affect *PDXK* expression, which could affect HDLC concentration through the expression of genes involved in lipogenesis. Our druggability analysis also identified *PDXK* as part of the druggable genome. *RRP1B* is a target gene that interacts with the beta-blocker drug Atenolol, which is sometimes used to treat hypertension and chronic angina.

We also identified an association using the 2df test rs34636484 (*CD96*) × SOCS on LDLC. The main effect appeared to contribute more to the association than the interaction at this locus, as the association was also apparent in a standard GWAS model in our data and the 1df test of interaction was not significant ($P = 0.27$). Based on these results, the association at rs34636484 appears to represent a novel main effect locus; however, this result should be interpreted with caution. The association of rs34636484 and LDLC was recently evaluated in the Global Lipids Genetics Consortium with a much larger sample size ($n = 1{,}393{,}230$ at this locus) and was not statistically significant ($P = 0.029$) [1].

Some of our significant associations were fairly consistent across studies within the same population group, but with no compelling evidence of association in other population groups, despite the availability of data. For instance, rs61248562 (*UNC13C*) × DEPR on HDLC was significant only among EUR, and not AFR or HISP in whom allele frequencies were higher and sample sizes were comparable. Similarly, an interaction of rs73597733 (*MACROD2*) × DEPR on HDLC in AFR was not seen in HISP at similar sample sizes (with a slightly lower allele frequency). It is unclear why these associations may differ by population group, but this phenomenon has been reported in previous gene-lifestyle interaction publications [6, 78, 79]. Differences in gene-lifestyle interactions across populations may arise from genomic factors, such as variations in linkage disequilibrium that lead to the tagging of different variants, as well as from lifestyle factors, such as differences in the measurement of or the experience of the psychosocial factor or in the behaviors or conditions associated with that psychosocial factor.

Psychosocial factors are complex traits that are associated with a variety of other factors, including some lifestyle exposures that we have previously evaluated using the same genome-wide

Table 2. Genome-wide variants significantly associated with serum lipids using a 2df joint test of main effect and interaction in Meta-Analysis of Stages 1 & 2 and were independent of known lipids loci[a].

rsid Index Variant *Nearest Gene*[b]	Chr:BP (GRCh37)	Tested Allele: Freq	Main Effect	SE	Interaction Effect	SE	P_{1df}[c]	P_{2df}[c]	Population, Sample Size	Lipid[d]	Psychosocial Factor
rs6730082 *RNU4-73P*	2:9877621	C:0.26	−0.0038	0.0040	−0.045	0.0096	3.1E-06	**2.5E-08**	AFR, $n = 16{,}886$	HDLC	DEPR
rs142378953 *AC090043.1*	3:1695235	G:0.01	0.039	0.032	0.24	0.060	6.0E-05	**4.9E-08**	CPMA, $n = 18{,}911$	TG	DEPR
rs34636484 *CD96*	3:111356092	G:0.03	-4.5	0.80	1.8	1.6	0.27	**3.1E-08**	CPMA, $n = 42{,}162$	LDLC	SOCS
rs11949029 *CTC-207P7.1*	5:163470425	A:0.02	6.6	2.2	−19.0	3.5	**4.1E-08**	**2.4E-08**	CPMA, $n = 16{,}927$	LDLC	SOCS
rs4562311 *NKAIN3*	8:63589187	G:0.22	0.013	0.014	−0.13	0.032	3.5E-05	**8.5E-09**	CPMA, $n = 6{,}667$	TG	ANXT
rs59808825 *GRAMD1B*	11:123152496	C:0.03	5.0	2.1	−22.9	4.2	**4.3E-08**	**8.8E-09**	CPMA, $n = 5{,}973$	LDLC	ANXT
rs73597733 *MACROD2*	20:15941137	A:0.04	-0.015	0.010	0.14	0.025	**8.4E-09**	**1.0E-08**	AFR, $n = 11{,}234$	HDLC	DEPR
rs11702544 *RRP1B*	21:45091861	C:0.39	0.0049	0.0010	0.0043	0.0027	0.1	**2.3E-08**	CPMA[e]/EUR, $n = 100{,}182$	HDLC	DEPR

[a]Listed variants were more than 500 KB from 95% Credible Sets reported in Graham et al. (https://doi.org/10.1038/s41586-021-04064-3).
[b]Index variant is for the most statistically significant association in the region and Nearest Gene is determined based on ANNOVAR annotations implemented in FUMA. While the "Nearest Gene" is listed for simplicity, we acknowledge that the nearest gene may not be of functional relevance for the given variant.
[c]Bolded values indicate $P < 5 \times 10^{-8}$.
[d]Analyses were conducted on natural log-transformed HDLC and TG values, while LDLC was untransformed (all original values in mg/dL).
[e]The most statistically significant analysis (indicated) is displayed in table. Full results for all genome-wide significant associations given in Supplementary Table S4.

interaction study approach. Overlap in the interaction results for this study and previous analyses for one of these associated lifestyle factors could be very informative for disentangling the mechanism underlying these statistical interactions. We compared our statistically significant findings with those that we have previously reported for genome-wide interactions of smoking [6], alcohol intake [8], physical activity [7], educational attainment [9], and sleep duration [10] on serum lipids; no overlap among the results was identified. If one of our loci were found to be associated with a psychosocial factor, that could provide additional context into the relationship between psychosocial factors and serum lipids. To explore this possibility, we evaluated recent GWAS for these traits [29, 33, 80–84], but did not identify any overlap with our loci of interest.

Some of the strengths of this study include the relatively large sample sizes for a study of psychosocial factors, with analyses including up to 133,157 individuals. Also notable was the particular attention to the inclusion of non-European ancestry individuals (reaching over 19,000 AFR and nearly 16,000 HISP, although the number of ASN and BRZ was smaller, <5000 per population). The sample sizes for the non-European ancestry groups, however, were relatively small in size, particularly in terms of the statiscial power needed for a gene-environment interaction study. We used a two-stage design with both a 1df test of interaction and a 2df joint test of main effect and interaction, an approach that is well-established for the study of gene-lifestyle interactions [6–10, 78, 79, 85, 86]. Our study also has some limitations. First, we had a smaller sample size for Stage 2, particularly for certain populations; as a result, the power for our two-stage approach was reduced. Second, despite our best efforts to harmonize psychosocial factors, the use of different instruments to measure these outcomes may have resulted in heterogeneity among studies, which would have reduced the power to identify lipids loci. In addition, these phenotypes themselves are quite complex and heterogeneous, and that complexity is not reflected in our categorization. Moreover, although our sample size is large for a study of lipids and psychosocial factors, it is not large enough to enable correction for multiple testing with adequate statistical power, and so its results need further validation. We did not have enough statistical power to usefully evaluate differences in these interactions by sex, which may prove to be of interest, as there are differences in the pathophysiology of cardiovascular disease by sex, and women experience a greater burden of depression [87]. Additionally, the association between TG and depressive symptoms has been shown to differ by sex, with men showing a stronger association [88], and low social support had a greater adverse effect on cardiovascular disease prevention among men than women [89]. Evaluating these interactions would require much greater sample sizes than were available in the current study. Although we have organized our contributing studies into population groups, there is likely to be meaningful heterogeneity within those groups in terms of relevant environmental background. For instance, the East Asian population group included individuals living in China as well as individuals with ancestry in China living in the United States. Information regarding neuropsychiatric medication use was not collected, though it is possible that use of these medications might directly or indirectly influence serum lipid levels [90]. In silico functional annotation and druggability analyses identified loci and candidate drug-gene interactions that are of interest for further follow-up; future experimental studies are needed to validate these findings.

In summary, we identified novel lipids loci in this large, multi-ancestry meta-analyses of genome-wide interaction studies of variants and psychosocial factors. Understanding these loci may help to disentangle the complex interplay between factors such as anxiety, depression, and low social support on serum lipids, a key biomarker of cardiometabolic risk.

MATERIALS AND METHODS

Study design

We adopted a two-stage study design (Fig. 1) that was implemented according to the Gene-Lifestyle Interactions Working Group of the CHARGE consortium [5]. We included men and women aged between 18 to 80 years of age with available data on lipids and psychosocial factors, and with genotype data imputed to the 1000 Genomes reference panel.

Stage 1 included 77,413 individuals in 31 study/population groups. Each study conducted genome-wide analyses (GWAS) incorporating a variant-by-psychosocial factor multiplicative interaction term. Centralized quality control was carried out, which was followed by a meta-analysis within and across five population groups: African ancestry (AFR), Asian ancestry (ASN), Brazilian (BRZ), European ancestry (EUR), and Hispanic (HISP). Variants that showed suggestive ($P < 10^{-5}$) associations for either a 1df test of interaction or a 2df joint test of interaction and main effect were carried forward for evaluation in Stage 2. Stage 2 analyses included data on 55,744 individuals from 19 studies distributed in 4 population groups. As no BRZ samples were included in Stage 2, no population-specific Stage 1 + 2 meta-analysis was undertaken, though the BRZ samples were included in cross-population meta-analyses (CPMA). Analytical details (Supplementary Table S1) and descriptive statistics (Supplementary Table S2) of each participating study for Stages 1 and 2 are provided.

Phenotypes and lifestyle variables studied

Analyses were conducted separately for three lipid parameters: HDLC, LDLC, and TG. HDLC and TG were directly assayed and natural log-transformed prior to analysis. LDLC was either directly assayed or derived using the Friedewald equation: LDLC = TG − HDLC − (TG / 5), if TG ≤ 400 mg/dL [91]. If a sample was drawn from an individual who had not been fasting for at least 8 h, then neither TG nor derived LDLC values were used. LDLC values were adjusted for lipid-lowering medication use (defined as the use of a statin or of any unspecified lipid-lowering medication after 1994, when statin usage became common). If LDLC was directly assayed, adjustment for lipid-lowering drugs was performed by dividing the LDLC value by 0.7. If LDLC was derived using the Friedewald equation, total cholesterol was first adjusted for lipid-lowering drug use (total cholesterol/0.8) before calculation of LDLC. No adjustments were made for any other lipid medication, nor were adjustments made to HDLC or triglycerides for medication use. For longitudinal studies where multiple lipid measurements were available, analysts selected the measurement with the largest sample size for analysis.

The three psychosocial variables (elevated depressive symptoms [DEPR], low social support [SOCS], and elevated anxiety symptoms [ANXT]) were measured within each cohort using validated screening questionnaires and coded as binary (yes/no) variables. A standard cut point was used for DEPR and ANXT, and SOCS was defined based on the lowest quartile of perceived social support. Further details regarding the instruments used within each study are given (Supplementary Table 3). Where multiple measurements of psychosocial factors were available, we used the questionnaire administered concomitantly with the measurement of serum lipids.

Genotyping and imputation

To harmonize data across studies, all studies imputed to 1000 Genomes data. Details on genotyping and imputation for each of the included studies are given in Supplementary Table 1. Most studies used Affymetrix (Santa Clara, CA, USA) or Illumina (San Diego, CA, USA) arrays and imputed to the cosmopolitan reference panel of the 1000 Genomes Project Phase I Integrated Release Version 3 Haplotypes. Prior to analysis, studies excluded all variants with minor allele frequency <0.01 or those that mapped to the X and Y chromosomes or the mitochondria.

Study-level genome-wide analysis

Each cohort participating in Stage 1 analysis regressed serum lipids (Y) on the variant (G), psychosocial factor (E), and their interaction (G×E), with adjustment for covariates (C) including age, sex, principal components, and study-specific variables (listed for each study in Supplementary Table 1):

$$Y = \beta_0 + \beta_G G + \beta_E E + \beta_{G\times E} G\times E + \beta_C C$$

The 1df test was based on the null hypothesis H_0: $\beta_{G\times E} = 0$, while the 2df test was based on H_0: $\beta_G = \beta_{G\times E} = 0$. [92] To ensure robust estimates of covariance matrices and robust standard errors, studies of unrelated subjects used either the sandwich R package or ProbABEL genetic software [93]. Family studies used Mixed Model Analysis for Pedigrees and populations (MMAP), a comprehensive mixed model program that provides an optimized and flexible platform incorporating a wide range of covariance structures. Stage 2 studies carried out the same regressions, but only on the variants that reached suggestive significance ($P < 10^{-5}$) in Stage 1 for any trait in population-specific or cross-population meta-analysis. For comparison, stage 1 studies also ran a main effect model (serum lipids as a function of the variant with adjustment for covariates and study-specific variables) and a main effect model additionally adjusted for the psychosocial factor.

Population groups

Appropriate selection of population descriptors is a matter of considerable discussion in the field and consensus regarding optimal terms has not yet emerged. In this work, contributing studies were subdivided into population groups based on where individuals included in those studies were expected to cluster genetically to reduce the potential for spurious findings due to population structure and to maximize the potential for discovery within a population. Inclusion of samples within a particular cluster of genetic similarity was based on consultation with study teams given their expertise and understanding of the study population. Our approach includes African ancestry (AFR), Asian ancestry (ASN), Brazilian (BRZ), European ancestry (EUR), and admixed Hispanic/Latino and Native American participants (HISP). The AFR population group includes sub-Saharan Africans as well as participants with predominantly African ancestry living in the United States. The ASN population group includes participants of predominantly Asian ancestry living in East Asia, Singapore, or the United States. The EUR population group includes participants with predominantly European ancestry living in Europe or the United States. The HISP population group includes admixed Hispanic/Latino and Native American participants living in the United States. Brazilian individuals (BRZ) were analyzed separately after consultation with local researchers regarding the genetic clustering of these participants.

Quality control and cross-population meta-analysis

We performed extensive study- and population-level quality control (QC) using the R package EasyQC for all GWAS results [94]. In study-level QC, allele frequencies for each study were compared visually to an ancestry-matched 1000 genomes reference panel to identify systematic errors in data preparation (no variants were excluded), and marker names were harmonized to ensure consistency across studies. Any resulting concerns were resolved in consultation with the contributing study. Variants were excluded if the imputation quality score was less than 0.5 or if $2\times MAF\times N_{exposed}\times$imputation quality score was less than 20. Population-level QC was also conducted prior to meta-analysis to check for any outliers among included studies, which might suggest improper trait transformation or model specification, among other things.

We then conducted population-specific and cross-population meta-analysis in Stage 1 using the approach developed by Manning et al. [95] and implemented in METAL [95, 96]. This method performs a joint meta-analysis of the variant and the G×Psy exposure regression coefficients and then uses a 2df test to identify genetic variants driven jointly by main and interaction effects. Additionally, we used the inverse-variance weighted meta-analysis implemented in METAL to meta-analyze G×Psy interaction coefficients alone using a 1df test. Variants in the Stage 1 meta-analysis had to be present in at least 2 cohorts or at least 3000 individuals for AFR and EUR, with a lower threshold ($n = 2000$) set for ASN, BRZ, and HISP because of the smaller number of individuals available in these ancestries. In Stage 2, we used the same approach as in Stage 1 to perform population-specific and cross-population meta-analyses. After combining results from Stages 1 and 2, variants with $P < 5.0\times10^{-8}$ for either the 2df joint test of the main effect and the interaction or the 1df test of the interaction were considered significant. Results with a heterozygosity p-value < 0.05 were evaluated further and excluded if results were driven by a single cohort.

The novelty of associated loci was determined by comparison to the recent Global Lipids Genetic Consortium results for GWAS meta-analyses including approximately 1.65 million individuals with notable inclusion of those of diverse ancestral backgrounds [1]. The 95% credible sets from the meta-analyses of all lipids traits (available at http://csg.sph.umich.edu/willer/public/glgc-lipids2021/results/credible_sets/) were compiled. Variants were considered novel if they were 500 kb from all variants listed in this list, as well as those reported in other major publications [34–39].

Identification of independent genomic loci and functional annotation

Identification of genetic loci related to each of the three serum lipids and functional annotation was accomplished using Functional Mapping and Annotation of GWAS (FUMA) v1.5.6 (http://fuma.ctglab.nl/) [97]. Variants were grouped into genomic loci using an $R^2 < 0.6$ (1000 Genomes, Phase 3 ALL as the reference population) and a merge distance of 250 kb. Functional annotation was conducted using output from the set of tools incorporated within FUMA, including RegulomeDB score, Combined Annotation Dependent Deletion (CADD) score [98], 15-core chromatin state (ChromHMM) [41, 99, 100], and expression Quantitative Trait Loci (eQTL) on the variants from lead associations as well as those in LD with those variants ($R^2 > 0.1$), using all tissues and all included databases (including GTex, BloodeQTL, BIOS, and BRAINEAC).

Druggability analysis

We first used the Drug-Gene Interaction database (DGIdb; v4.2.0) to query psychosocial factors-lipid interacting genes to determine the potential druggability of the candidate gene targets. We annotated genes for implicated pathways and functions using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. We annotated the druggability target categories and queried all interacting drugs reported in 41 databases (BaderLabGenes, CarisMolecularIntelligence, dGene, FoundationOneGenes, GO, HingoraniCasas, HopkinsGroom, HumanProteinAtlas, IDG, MskImpact, Oncomine, Pharos, RussLampel, Tempus, CGI, CIViC, COSMIC, CancerCommons, ChEMBL, ChemblDrugs, ChemblInteractions, ClearityFoundationBiomarkers, ClearityFoundationClinicalTrial, DTC, DoCM, DrugBank, Ensembl, Entrez, FDA, GuideToPharmacology, JAX-CKB, MyCancerGenome, MyCancerGenomeClinicalTrial, NCI, OncoKB, PharmGKB, TALC, TEND, TTD, TdgClinicalTrial, Wikidata). We queried protein targets for available active ligands in ChEMBL. We queried gene targets in the druggable genome using the most recent druggable genome list established by the NIH Illuminating the Druggable Genome Project (https://github.com/druggablegenome/IDGTargets) available through the Pharos web platform. We also queried FDA-approved drugs, late-stage clinical trials, and disease indications in the DrugBank, ChEMBL, ClinicalTrials.gov databases and provided results for the top MESH and DrugBank indications and clinical trials.

DATA AVAILABILITY

All summary results are available in the GWAS Catalog with the following Accession IDs: AFR.HDLC.ANXT.2df (GCST90570645); AFR.HDLC.ANXT.1df (GCST90570646); AFR.HDLC.DEPR.2df (GCST90570647); AFR.HDLC.DEPR.1df (GCST90570648); AFR.HDLC.SOCS.2df (GCST90570649); AFR.HDLC.SOCS.1df (GCST90570650); AFR.LDLC.ANXT.2df (GCST90570651); AFR.LDLC.ANXT.1df (GCST90570652); AFR.LDLC.DEPR.2df (GCST90570653); AFR.LDLC.DEPR.1df (GCST90570654); AFR.TG.ANXT.2df (GCST90570655); AFR.TG.ANXT.1df (GCST90570656); AFR.TG.DEPR.2df (GCST90570657); AFR.TG.DEPR.1df (GCST90570658); ASN.HDLC.DEPR.2df (GCST90570659); ASN.HDLC.DEPR.1df (GCST90570660); ASN.LDLC.DEPR.2df (GCST90570661); ASN.LDLC.DEPR.1df (GCST90570662); ASN.TG.DEPR.2df (GCST90570663); ASN.TG.DEPR.1df (GCST90570664); EUR.HDLC.ANXT.2df (GCST90570665); EUR.HDLC.ANXT.1df (GCST90570666); EUR.HDLC.DEPR.2df (GCST90570667); EUR.HDLC.DEPR.1df (GCST90570668); EUR.HDLC.SOCS.2df (GCST90570669); EUR.HDLC.SOCS.1df (GCST90570670); EUR.LDLC.ANXT.2df (GCST90570671); EUR.LDLC.ANXT.1df (GCST90570672); EUR.LDLC.DEPR.2df (GCST90570673); EUR.LDLC.DEPR.1df (GCST90570674); EUR.LDLC.SOCS.2df (GCST90570675); EUR.LDLC.SOCS.1df (GCST90570676); EUR.TG.ANXT.2df (GCST90570677); EUR.TG.ANXT.1df (GCST90570678); EUR.TG.DEPR.2df (GCST90570679); EUR.TG.DEPR.1df (GCST90570680); EUR.TG.SOCS.2df (GCST90570681); EUR.TG.SOCS.1df (GCST90570682); HISP.HDLC.DEPR.2df (GCST90570683); HISP.HDLC.DEPR.1df (GCST90570684); HISP.HDLC.SOCS.2df (GCST90570685); HISP.HDLC.SOCS.1df (GCST90570686); HISP.LDLC.DEPR.2df (GCST90570687); HISP.LDLC.DEPR.1df (GCST90570688); HISP.LDLC.SOCS.2df (GCST90570689); HISP.LDLC.SOCS.1df (GCST90570690); HISP.TG.DEPR.2df (GCST90570691); HISP.TG.DEPR.1df (GCST90570692); HISP.TG.SOCS.2df (GCST90570693); HISP.TG.SOCS.1df (GCST90570694); CPMA.HDLC.ANXT.2df (GCST90570695); CPMA.HDLC.ANXT.1df (GCST90570696); CPMA.HDLC.DEPR.2df (GCST90570697); CPMA.HDLC.DEPR.1df (GCST90570698); CPMA.HDLC.SOCS.2df (GCST90570699); CPMA.HDLC.SOCS.1df (GCST90570700); CPMA.LDLC.ANXT.2df (GCST90570701); CPMA.LDLC.ANXT.1df (GCST90570702); CPMA.LDLC.DEPR.2df (GCST90570703); CPMA.LDLC.DEPR.1df (GCST90570704); CPMA.LDLC.SOCS.2df (GCST90570705); CPMA.LDLC.SOCS.1df (GCST90570706); CPMA.TG.ANXT.2df (GCST90570707); CPMA.TG.ANXT.1df (GCST90570708); CPMA.TG.DEPR.2df (GCST90570709); CPMA.TG.DEPR.1df (GCST90570710); CPMA.TG.SOCS.2df (GCST90570711); CPMA.TG.SOCS.1df (GCST90570712)

REFERENCES

1. Graham SE, Clarke SL, Wu K-HH, Kanoni S, Zajac GJM, Ramdas S, et al. The power of genetic diversity in genome-wide association studies of lipids. Nature. 2021;600:675–9. https://doi.org/10.1038/s41586-021-04064-3.
2. Hoffmann TJ, Theusch E, Haldar T, Ranatunga DK, Jorgenson E, Medina MW, et al. A large electronic-health-record-based genome-wide study of serum lipids. Nat Genet. 2018;50:401–13. https://doi.org/10.1038/s41588-018-0064-5.
3. Klarin D, Damrauer SM, Cho K, Sun YV, Teslovich TM, Honerlaw J, et al. Genetics of blood lipids among ~300,000 multi-ethnic participants of the Million Veteran Program. Nat Genet. 2018;50:1514–23. https://doi.org/10.1038/s41588-018-0222-9.
4. Psaty BM, O'Donnell CJ, Gudnason V, Lunetta KL, Folsom AR, Rotter JI, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: design of prospective meta-analyses of genome-wide association studies from 5 cohorts. Circ Cardiovasc Genet. 2009;2:73–80. https://doi.org/10.1161/CIRCGENETICS.108.829747.
5. Rao DC, Sung YJ, Winkler TW, Schwander K, Borecki I, Cupples LA, et al. Multi-ancestry study of gene-lifestyle interactions for cardiovascular traits in 610 475 individuals from 124 cohorts: design and rationale. Circ Cardiovasc Genet. 2017;10:e001649 https://doi.org/10.1161/CIRCGENETICS.116.001649.
6. Bentley AR, Sung YJ, Brown MR, Winkler TW, Kraja AT, Ntalla I, et al. Multi-ancestry genome-wide gene-smoking interaction study of 387,272 individuals identifies new loci associated with serum lipids. Nat Genet. 2019;51:636–48. https://doi.org/10.1038/s41588-019-0378-y.
7. Kilpelainen TO, Bentley AR, Noordam R, Sung YJ, Schwander K, Winkler TW, et al. Multi-ancestry study of blood lipid levels identifies four loci interacting with physical activity. Nat Commun. 2019;10:376 https://doi.org/10.1038/s41467-018-08008-w.
8. de Vries PS, Brown MR, Bentley AR, Sung YJ, Winkler TW, Ntalla I, et al. Multi-ancestry genome-wide association study of lipid levels incorporating gene-alcohol interactions. Am J Epidemiol. 2019;188:1033–54. https://doi.org/10.1093/aje/kwz005.
9. de Las Fuentes L, Schwander KL, Brown MR, Bentley AR, Winkler TW, Sung YJ, et al. Gene-educational attainment interactions in a multi-population genome-wide meta-analysis identify novel lipid loci. Front Genet. 2023;14:1235337 https://doi.org/10.3389/fgene.2023.1235337.
10. Noordam R, Bos MM, Wang H, Winkler TW, Bentley AR, Kilpeläinen TO, et al. Multi-ancestry sleep-by-SNP interaction analysis in 126,926 individuals reveals lipid loci stratified by sleep duration. Nat Commun. 2019;10:5121 https://doi.org/10.1038/s41467-019-12958-0.
11. Carney RM, Freedland KE. Depression and coronary heart disease. Nat Rev Cardiol. 2017;14:145–55. https://doi.org/10.1038/nrcardio.2016.181.
12. Juonala M, Pulkki-Råback L, Elovainio M, Hakulinen C, Magnussen CG, Sabin MA, et al. Childhood psychosocial factors and coronary artery calcification in adulthood: the cardiovascular risk in young finns study. JAMA Pediatrics. 2016;170:466–72. https://doi.org/10.1001/jamapediatrics.2015.4121.
13. Harshfield EL, Pennells L, Schwartz JE, Willeit P, Kaptoge S, Bell S, et al. Association between depressive symptoms and incident cardiovascular diseases. JAMA. 2020;324:2396–405. https://doi.org/10.1001/jama.2020.23068.
14. Li GH, Cheung CL, Chung AK, Cheung BM, Wong IC, Fok MLY, et al. Evaluation of bi-directional causal association between depression and cardiovascular diseases: a Mendelian randomization study. Psychol Med. 2022;52:1765–76. https://doi.org/10.1017/s0033291720003566.
15. Wei YG, Cai DB, Liu J, Liu RX, Wang SB, Tang YQ, et al. Cholesterol and triglyceride levels in first-episode patients with major depressive disorder: a meta-analysis of case-control studies. J Affect Disord. 2020;266:465–72. https://doi.org/10.1016/j.jad.2020.01.114.
16. Tkachev A, Stekolshchikova E, Vanyushkina A, Zhang H, Morozova A, Zozulya S, et al. Lipid alteration signature in the blood plasma of individuals with schizophrenia, depression, and bipolar disorder. JAMA Psychiatry. 2023;80:250–9. https://doi.org/10.1001/jamapsychiatry.2022.4350.
17. Bot M, Milaneschi Y, Al-Shehri T, Amin N, Garmaeva S, Onderwater GLJ, et al. Metabolomics profile in depression: a pooled analysis of 230 metabolic markers in 5283 cases with depression and 10,145 controls. Biol Psychiatry. 2020;87:409–18. https://doi.org/10.1016/j.biopsych.2019.08.016.
18. Brydges CR, Bhattacharyya S, Dehkordi SM, Milaneschi Y, Penninx B, Jansen R, et al. Metabolomic and inflammatory signatures of symptom dimensions in major depression. Brain, Behavior, Immun. 2022;102:42–52. https://doi.org/10.1016/j.bbi.2022.02.003.
19. Xu C, Padilla V, Lozano S, Gamez D, Su BB, Wang X, et al. APOE gene associated with dementia-related traits, depression, and anxiety in the hispanic population. Genes. 2023;14:1405.
20. Wang WW, Liu XL, Ruan Y, Wang L, Bao TH. Depression was associated with apolipoprotein E ε4 allele polymorphism: A meta-analysis. Iran J Basic Med Sci. 2019;22:112–7. https://doi.org/10.22038/ijbms.2018.30825.7436.

21. Zhang M, Chen J, Yin Z, Wang L, Peng L. The association between depression and metabolic syndrome and its components: a bidirectional two-sample Mendelian randomization study. Transl Psychiatry. 2021;11:633 https://doi.org/10.1038/s41398-021-01759-z.
22. Dregan A, Rayner L, Davis KAS, Bakolis I, Arias de la Torre J, Das-Munshi J, et al. Associations between depression, arterial stiffness, and metabolic syndrome among adults in the UK Biobank Population Study: a mediation analysis. JAMA Psychiatry. 2020;77:598–606. https://doi.org/10.1001/jamapsychiatry.2019.4712.
23. Datta BK, Coughlin SS, Gummadi A, Mehrabian D, Ansa BE. Perceived social support and cardiovascular risk among nonelderly adults in the United States. Am J Cardiol. 2023;209:146–53. https://doi.org/10.1016/j.amjcard.2023.09.106.
24. García-Ulloa AC, Miranda-Gil V, Díaz-Pineda M, Garnica-Carrillo MF, Serrano-Pérez NH, Tron-Gomez MS, et al. Comparison of metabolic, lifestyle and mental health parameters in people with diabetes and relatives with and without family support. Diabetes Metab Syndr Obes: Targets Ther. 2024;17:239–45. https://doi.org/10.2147/dmso.S445890.
25. Skogberg N, Castaneda AE, Agyemang C, Koponen P, Lilja E, Laatikainen T. The association of depressive and anxiety symptoms with the metabolic syndrome and its components among Russian, Somali, and Kurdish origin adults in Finland: a population-based study. J Psychosom Res. 2022;159:110944 https://doi.org/10.1016/j.jpsychores.2022.110944.
26. Milaneschi Y, Simmons WK, van Rossum EFC, Penninx BWJH. Depression and obesity: evidence of shared biological mechanisms. Mol Psychiatry. 2019;24:18–33. https://doi.org/10.1038/s41380-018-0017-5.
27. Zou L, Tian Y, Wang Y, Chen D, Lu X, Zeng Z, et al. High-cholesterol diet promotes depression- and anxiety-like behaviors in mice by impact gut microbe and neuroinflammation. J Affect Disord. 2023;327:425–38. https://doi.org/10.1016/j.jad.2023.01.122.
28. Yu H, Qin X, Yu Z, Chen Y, Tang L, Shan W. Effects of high-fat diet on the formation of depressive-like behavior in mice. Food Funct. 2021;12:6416–31. https://doi.org/10.1039/D1FO00044F.
29. Cheng B, Cheng S, Jia Y, Liu L, Meng P, Qi X, et al. Genome-wide association studies in non-anxiety individuals identified novel risk loci for depression. Eur Psychiatry. 2022;65:e38 https://doi.org/10.1192/j.eurpsy.2022.32.
30. Meng P, Ye J, Chu X, Cheng B, Cheng S, Liu L, et al. Associations between genetic loci, environment factors and mental disorders: a genome-wide survival analysis using the UK Biobank data. Transl Psychiatry. 2022;12:17 https://doi.org/10.1038/s41398-022-01782-8.
31. Pinakhina D, Yermakovich D, Vergasova E, Kasyanov E, Rukavishnikov G, Rezapova V, et al. GWAS of depression in 4520 individuals from the Russian population highlights the role of MAGI2 (S-SCAM) in the gut-brain axis. Front Genet. 2023;13:972196 https://doi.org/10.3389/fgene.2022.972196.
32. Schoeler T, Speed D, Porcu E, Pirastu N, Pingault J-B, Kutalik Z. Participation bias in the UK Biobank distorts genetic associations and downstream analyses. Nat Hum Behav. 2023;7:1216–27. https://doi.org/10.1038/s41562-023-01579-9.
33. Silveira PP, Pokhvisneva I, Howard DM, Meaney MJ. A sex-specific genome-wide association study of depression phenotypes in UK Biobank. Mol Psychiatry. 2023;28:2469–79. https://doi.org/10.1038/s41380-023-01960-0.
34. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat Genet. 2013;45:1345–52. https://doi.org/10.1038/ng.2795.
35. Lanktree MB, Elbers CC, Li Y, Zhang G, Duan Q, Karczewski KJ, et al. Genetic meta-analysis of 15,901 African Americans identifies variation in EXOC3L1 is associated with HDL concentration[S]. J Lipid Res. 2015;56:1781–6. https://doi.org/10.1194/jlr.P059477.
36. Peloso GM, Auer PL, Bis JC, Voorman A, Morrison AC, Stitziel NO, et al. Association of low-frequency and rare coding-sequence variants with blood lipids and coronary heart disease in 56,000 whites and blacks. Am J Hum Genet. 2014;94:223–32. https://doi.org/10.1016/j.ajhg.2014.01.009.
37. Spracklen CN, Chen P, Kim YJ, Wang X, Cai H, Li S, et al. Association analyses of East Asian individuals and trans-ancestry analyses with European individuals reveal new loci associated with cholesterol and triglyceride levels. Hum Mol Genet. 2017;26:1770–84. https://doi.org/10.1093/hmg/ddx062.
38. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010;466:707–13. https://doi.org/10.1038/nature09270.
39. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, et al. Discovery and refinement of loci associated with lipid levels. Nat Genet. 2013;45:1274–83. https://doi.org/10.1038/ng.2797.
40. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science. 2015;348:648–60. https://doi.org/10.1126/science.1262110.
41. GTEx Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science. 2015;348:648–60. https://doi.org/10.1126/science.1262110.
42. Kavousi M, Bos MM, Barnes HJ, Lino Cardenas CL, Wong D, Lu H, et al. Multi-ancestry genome-wide study identifies effector genes and druggable pathways for coronary artery calcification. Nat Genet. 2023;55:1651–64. https://doi.org/10.1038/s41588-023-01518-4.
43. de Las Fuentes L, Sung YJ, Sitlani CM, Avery CL, Bartz TM, Keyser C, et al. Genome-wide meta-analysis of variant-by-diuretic interactions as modulators of lipid traits in persons of European and African ancestry. Pharmacogenomics J. 2020;20:482–93. https://doi.org/10.1038/s41397-019-0132-y.
44. Montasser ME, Aslibekyan S, Srinivasasainagendra V, Tiwari HK, Patki A, Bagheri M, et al. An Amish founder population reveals rare-population genetic determinants of the human lipidome. Commun Biol. 2022;5:334 https://doi.org/10.1038/s42003-022-03291-2.
45. Rao S, Baranova A, Yao Y, Wang J, Zhang F. Genetic relationships between attention-deficit/hyperactivity disorder, autism spectrum disorder, and intelligence. Neuropsychobiology. 2022;81:484–96. https://doi.org/10.1159/000525411.
46. Karlsson Linnér R, Mallard TT, Barr PB, Sanchez-Roige S, Madole JW, Driver MN, et al. Multivariate analysis of 1.5 million people identifies genetic associations with traits related to self-regulation and addiction. Nat Neurosci. 2021;24:1367–76. https://doi.org/10.1038/s41593-021-00908-3.
47. Jansen PR, Watanabe K, Stringer S, Skene N, Bryois J, Hammerschlag AR, et al. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. Nat Genet. 2019;51:394–403. https://doi.org/10.1038/s41588-018-0333-3.
48. Karlsson Linnér R, Biroli P, Kong E, Meddens SFW, Wedow R, Fontana MA, et al. Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nat Genet. 2019;51:245–57. https://doi.org/10.1038/s41588-018-0309-3.
49. Kushima I, Imaeda M, Tanaka S, Kato H, Oya-Ito T, Nakatochi M, et al. Contribution of copy number variations to the risk of severe eating disorders. Psychiatry Clin Neurosci. 2022;76:423–8. https://doi.org/10.1111/pcn.13430.
50. Anney RJL, Ripke S, Anttila V, Grove J, Holmans P, Huang H, et al. Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. Mol Autism. 2017;8:21 https://doi.org/10.1186/s13229-017-0137-9.
51. Bacchelli E, Cameli C, Viggiano M, Igliozzi R, Mancini A, Tancredi R, et al. An integrated analysis of rare CNV and exome variation in Autism Spectrum Disorder using the Infinium PsychArray. Sci Rep. 2020;10:3198 https://doi.org/10.1038/s41598-020-59922-3.
52. Wu Y, Cao H, Baranova A, Huang H, Li S, Cai L, et al. Multi-trait analysis for genome-wide association study of five psychiatric disorders. Transl Psychiatry. 2020;10:209 https://doi.org/10.1038/s41398-020-00902-6.
53. Bigdeli TB, Fanous AH, Li Y, Rajeevan N, Sayward F, Genovese G, et al. Genome-wide association studies of schizophrenia and bipolar disorder in a diverse cohort of US veterans. Schizophrenia Bull. 2021;47:517–29. https://doi.org/10.1093/schbul/sbaa133.
54. Everson TM, Marsit CJ, Michael O'Shea T, Burt A, Hermetz K, Carter BS, et al. Epigenome-wide analysis identifies genes and pathways linked to neurobehavioral variation in preterm infants. Sci Rep. 2019;9:6322 https://doi.org/10.1038/s41598-019-42654-4.
55. Crawford K, Oliver PL, Agnew T, Hunn BHM, Ahel I. Behavioural characterisation of Macrod1 and Macrod2 knockout mice. Cells. 2021;10:368.
56. Hill WD, Marioni RE, Maghzian O, Ritchie SJ, Hagenaars SP, McIntosh AM, et al. A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence. Mol Psychiatry. 2019;24:169–81. https://doi.org/10.1038/s41380-017-0001-5.
57. Davies G, Lam M, Harris SE, Trampush JW, Luciano M, Hill WD, et al. Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. Nat Commun. 2018;9:2098 https://doi.org/10.1038/s41467-018-04362-x.
58. Lee JJ, Wedow R, Okbay A, Kong E, Maghzian O, Zacher M, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat Genet. 2018;50:1112–21. https://doi.org/10.1038/s41588-018-0147-3.
59. Fan CC, Loughnan R, Makowski C, Pecheva D, Chen C-H, Hagler DJ, et al. Multivariate genome-wide association study on tissue-sensitive diffusion metrics highlights pathways that shape the human brain. Nat Commun. 2022;13:2423 https://doi.org/10.1038/s41467-022-30110-3.
60. van der Meer D, Kaufmann T, Shadrin AA, Makowski C, Frei O, Roelfs D, et al. The genetic architecture of human cortical folding. Sci Adv. 2021;7:eabj9446 https://doi.org/10.1126/sciadv.abj9446.
61. Sha Z, Schijven D, Carrion-Castillo A, Joliot M, Mazoyer B, Fisher SE, et al. The genetic architecture of structural left–right asymmetry of the human brain. Nat Hum Behav. 2021;5:1226–39. https://doi.org/10.1038/s41562-021-01069-w.

62. Smith SM, Douaud G, Chen W, Hanayik T, Alfaro-Almagro F, Sharp K, et al. An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank. Nat Neurosci. 2021;24:737–45. https://doi.org/10.1038/s41593-021-00826-4.
63. Shadrin AA, Kaufmann T, van der Meer D, Palmer CE, Makowski C, Loughnan R, et al. Vertex-wise multivariate genome-wide association study identifies 780 unique genetic loci associated with cortical morphology. Neuroimage. 2021;244:118603 https://doi.org/10.1016/j.neuroimage.2021.118603.
64. Lam M, Chen C-Y, Li Z, Martin AR, Bryois J, Ma X, et al. Comparative genetic architectures of schizophrenia in East Asian and European populations. Nat Genet. 2019;51:1670–8. https://doi.org/10.1038/s41588-019-0512-x.
65. Periyasamy S, John S, Padmavati R, Rajendren P, Thirunavukkarasu P, Gratten J, et al. Association of schizophrenia risk with disordered niacin metabolism in an indian genome-wide association study. JAMA Psychiatry. 2019;76:1026–34. https://doi.org/10.1001/jamapsychiatry.2019.1335.
66. Pardiñas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat Genet. 2018;50:381–9. https://doi.org/10.1038/s41588-018-0059-2.
67. Ikeda M, Takahashi A, Kamatani Y, Momozawa Y, Saito T, Kondo K, et al. Genome-wide association study detected novel susceptibility genes for schizophrenia and shared trans-populations/diseases genetic effect. Schizophrenia Bull. 2019;45:824–34. https://doi.org/10.1093/schbul/sby140.
68. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. 2022;604:502–8. https://doi.org/10.1038/s41586-022-04434-5.
69. Li Z, Chen J, Yu H, He L, Xu Y, Zhang D, et al. Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. Nat Genet. 2017;49:1576–83. https://doi.org/10.1038/ng.3973.
70. Hall J. Schizophrenia — an anxiety disorder? Br J Psychiatry. 2017;211:262–3. https://doi.org/10.1192/bjp.bp.116.195370.
71. Bulbena A, Bulbena-Cabre A. Schizophrenia and anxiety: yes, they are relatives not just neighbours. Br J Psychiatry. 2018;213:498–498. https://doi.org/10.1192/bjp.2018.126.
72. Naito T, Saheki Y. GRAMD1-mediated accessible cholesterol sensing and transport. Biochimica et Biophysica Acta - Mol Cell Biol Lipids. 2021;1866:158957 https://doi.org/10.1016/j.bbalip.2021.158957.
73. Ercan B, Naito T, Koh DHZ, Dharmawan D, Saheki Y. Molecular basis of accessible plasma membrane cholesterol recognition by the GRAM domain of GRAMD1b. EMBO J. 2021;40:e106524 https://doi.org/10.15252/embj.2020106524.
74. Ferrari A, Whang E, Xiao X, Kennelly JP, Romartinez-Alonso B, Mack JJ, et al. Aster-dependent nonvesicular transport facilitates dietary cholesterol uptake. Science. 2023;382:eadf0966 https://doi.org/10.1126/science.adf0966.
75. Aragam KG, Jiang T, Goel A, Kanoni S, Wolford BN, Atri DS, et al. Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. Nat Genet. 2022;54:1803–15. https://doi.org/10.1038/s41588-022-01233-6.
76. Kichaev G, Bhatia G, Loh PR, Gazal S, Burch K, Freund MK, et al. Leveraging polygenic functional enrichment to improve GWAS power. Am J Hum Genet. 2019;104:65–75. https://doi.org/10.1016/j.ajhg.2018.11.008.
77. Moreno-Navarrete JM, Jove M, Ortega F, Xifra G, Ricart W, Obis È, et al. Metabolomics uncovers the role of adipose tissue PDXK in adipogenesis and systemic insulin sensitivity. Diabetologia. 2016;59:822–32. https://doi.org/10.1007/s00125-016-3863-1.
78. Sung YJ, de las Fuentes L, Winkler TW, Chasman DI, Bentley AR, Kraja AT, et al. A multi-ancestry genome-wide study incorporating gene–smoking interactions identifies multiple new loci for pulse pressure and mean arterial pressure. Hum Mol Genet. 2019;28:2615–33. https://doi.org/10.1093/hmg/ddz070.
79. Sung YJ, Winkler TW, de las Fuentes L, Bentley AR, Brown MR, Kraja AT, et al. A large-scale multi-ancestry genome-wide study accounting for smoking behavior identifies multiple significant loci for blood pressure. Am J Hum Genet. 2018;102:375–400. https://doi.org/10.1016/j.ajhg.2018.01.015.
80. Amare AT, Vaez A, Hsu YH, Direk N, Kamali Z, Howard DM, et al. Bivariate genome-wide association analyses of the broad depression phenotype combined with major depressive disorder, bipolar disorder or schizophrenia reveal eight novel genetic loci for depression. Mol Psychiatry. 2020;25:1420–9. https://doi.org/10.1038/s41380-018-0336-6.
81. Backman JD, Li AH, Marcketta A, Sun D, Mbatchou J, Kessler MD, et al. Exome sequencing and analysis of 454,787 UK Biobank participants. Nature. 2021;599:628–34. https://doi.org/10.1038/s41586-021-04103-z.
82. Li QS, Tian C, Hinds D. Genome-wide association studies of antidepressant class response and treatment-resistant depression. Transl Psychiatry. 2020;10:360 https://doi.org/10.1038/s41398-020-01035-6.
83. Mitchell BL, Campos AI, Whiteman DC, Olsen CM, Gordon SD, Walker AJ, et al. The Australian genetics of depression study: new risk loci and dissecting heterogeneity between subtypes. Biol Psychiatry. 2022;92:227–35. https://doi.org/10.1016/j.biopsych.2021.10.021.
84. Yakovchik AY, Tolynyova DV, Kashtanova DA, Sutulova ER, Ivanov MV, Mamchur AA, et al. Genetics of psycho-emotional well-being: genome-wide association study and polygenic risk score analysis. Front Psychiatry. 2023;14:1188427 https://doi.org/10.3389/fpsyt.2023.1188427.
85. Wang H, Noordam R, Cade BE, Schwander K, Winkler TW, Lee J, et al. Multi-ancestry genome-wide gene–sleep interactions identify novel loci for blood pressure. Mol Psychiatry. 2021;26:6293–304. https://doi.org/10.1038/s41380-021-01087-0.
86. Feitosa MF, Kraja AT, Chasman DI, Sung YJ, Winkler TW, Ntalla I, et al. Novel genetic associations for blood pressure identified via gene-alcohol interaction in up to 570K individuals across multiple ancestries. PLoS ONE. 2018;13:e0198166 https://doi.org/10.1371/journal.pone.0198166.
87. Bucciarelli V, Caterino AL, Bianco F, Caputi CG, Salerni S, Sciomer S, et al. Depression and cardiovascular disease: The deep blue sea of women's heart. Trends Cardiovasc Med. 2020;30:170–6. https://doi.org/10.1016/j.tcm.2019.05.001.
88. Xu L, Wang K, Wang S, Liu L, Lv X, Song Y. Sex differences in the association between serum lipids and depressive symptoms: a longitudinal population-based study. J Affect Disord. 2021;291:154–62. https://doi.org/10.1016/j.jad.2021.05.011.
89. Blakoe M, Petrova D, Garcia-Retamero R, Gonçalves K, Catena A, Ramírez Hernández JA, et al. Sex moderates the relationship between social support and cardiovascular prevention behaviors in middle-aged and older adults. Ann Behav Med. 2023;57:877–87. https://doi.org/10.1093/abm/kaad030.
90. Olfson M, Marcus SC, Corey-Lisle P, Tuomari AV, Hines P, L'Italien GJ. Hyperlipidemia following treatment with antipsychotic medications. Am J Psychiatry. 2006;163:1821–5. https://doi.org/10.1176/ajp.2006.163.10.1821.
91. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.
92. Kraft P, Yen YC, Stram DO, Morrison J, Gauderman WJ. Exploiting gene-environment interaction to detect genetic associations. Hum Heredity. 2007;63:111–9. https://doi.org/10.1159/000099183.
93. Aulchenko YS, Struchalin MV, van Duijn CM. ProbABEL package for genome-wide association analysis of imputed data. BMC Bioinforma. 2010;11:134 https://doi.org/10.1186/1471-2105-11-134.
94. Winkler TW, Day FR, Croteau-Chonka DC, Wood AR, Locke AE, Magi R, et al. Quality control and conduct of genome-wide association meta-analyses. Nat Protoc. 2014;9:1192–212. https://doi.org/10.1038/nprot.2014.071.
95. Manning AK, LaValley M, Liu CT, Rice K, An P, Liu Y, et al. Meta-analysis of gene-environment interaction: joint estimation of SNP and SNP x environment regression coefficients. Genet Epidemiol. 2011;35:11–18. https://doi.org/10.1002/gepi.20546.
96. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;26:2190–1. https://doi.org/10.1093/bioinformatics/btq340.
97. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun. 2017;8:1826 https://doi.org/10.1038/s41467-017-01261-5.
98. Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet. 2014;46:310–5. https://doi.org/10.1038/ng.2892.
99. Ernst J, Kellis M. ChromHMM: automating chromatin-state discovery and characterization. Nat Methods. 2012;9:215–6. https://doi.org/10.1038/nmeth.1906.
100. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet. 2016;48:481–7. https://doi.org/10.1038/ng.3538.

ACKNOWLEDGEMENTS

This project was largely supported by two grants from the U.S. National Heart, Lung, and Blood Institute (NHLBI), the National Institutes of Health, R01HL118305 and R01HL156991. This research was supported in part by the Intramural Research Program of the National Human Genome Research Institute (NHGRI) in the Center for Research on Genomics and Global Health (CRGGH—Z01HG200362). CRGGH is also supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Center for Information Technology, and the Office of the Director at the National Institutes of Health. Tuomas O. Kilpeläinen was supported by grants from the Novo Nordisk Foundation (NNF18CC0034900, NNF21SA0072102,

NNF22OC0074128, NNF23SA0084103). W. Jim Gauderman was supported by the National Cancer Institute (NCI; P01 CA196569). The views expressed in this manuscript are those of the authors and do not necessarily represent the views of NHLBI, NHGRI, the NCI; the National Institutes of Health; or the U.S. Department of Health and Human Services. Study-specific acknowledgments are included in the Supplementary Note. The authors gratefully acknowledge the invaluable contributions of Adolfo Correa, Lisa W. Martin, Annette Peters, and Astrid Petersmann. The authors would also like to recognize L. Adrienne Cupples, Diane M. Becker, and John M. Starr, who participated in this effort, but passed away prior to the completion of the manuscript.

AUTHOR CONTRIBUTIONS

ARB and SKM drafted the manuscript with substantial contributions from MRB, KLS, TWW, CLM, DCR, CNR, MF, and ERF. HA, ARB, MRB, LFB, MF, MFF, ERF, LdlF, JG, ATK, TOK, C-TL, CLM, AKM, SKM, RN, JRO'C, MProvince, BMP, PAP, DCR, KR, SSR, CNR, YJS, KLS, PSdV, TWW, XZhu contributed to the conception and design of the work. HA, NA, DEA, DKA, ARB, MRB, LB, TMB, CB, EB, Y-DIC, J-FC, KNC, MLD, KWvD, JACD, IJD, CMvD, LE, MKE, JDF, AMF, NF, MF, ERF, MFF, VG, LCG, MG, XG, CG, HJG, CAH, DvH, FPH, GH, ARVRH, SEH, SH, MAI, CRI, JBJ, LK-J, PK, SLRK, CK, JEK, C-TL, JL, KL, TAL, TL, LL, L-PL, EL, YL, D-OMK, CLM, ACM, AKM, AWM, SKM, PJvdM, PM-V, SEM, YM, IMN, RN, KEN, AJO, BWJHP, ACP, PAP, MPreisig, GP, CNR, MAR, JIR, RR, DCR, XS, PJS, LS, JMS, X-oS, JAS, HS, NS, KLS, MS, AVS, KDT, LT, MYT, AGU, DV, EW, MW, GW, SW, Y-XW, RBW, H-LW, DRW, W-BW, RW, WW, YW, JY, LRY, XZhang, XZhu, WZheng, WZhao, ABZ contributed in the acquisition, analysis, or interpretation of the data. MRB conducted centralized data cleaning and meta-analyses. TWW designed the software pipeline used for harmonization, visualization, and quality control of study data. DEA, HA, TMB, LFB, EB, KNC, JACD, LE, MKE, MFF, NF, AMF, LdlF, MG, JG, LG, HJG, ARVRH, DvH, SEH, CRI, MAI, ATK, C-TL, AIL, L-PL, PM-V, YM, SEM, RN, JRO'C, AJO, PAP, GP, MPreisig, MProvince, BP, KR, SSR, JIR, JAS, JMS, PJS, X-oS, EST, LT, PSdV, RBW, SW, H-LW, KLY, LRY, WZheng, WZhao, XZhu made substantial revisions to the manuscript. All authors approved the manuscript.

FUNDING

Open access funding provided by the National Institutes of Health.

COMPETING INTERESTS

The authors declare the following competing interests: BMP serves on the Data and Safety Monitoring Board of a clinical trial funded by the manufacturer (Zoll LifeCor) and on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson; CMvD was sponsored by GlaxoSmithKline; HJG received travel grants and speakers honoraria from Fresenius Medical Care, Neuraxpharm and Janssen Cilag as well as research funding from Fresenius Medical Care; JBJ serves in the Advisory Board Novartis; Patent holder with Biocompatibles UK Ltd. (Franham, Surrey, UK) (Title: Treatment of eye diseases using encapsulated cells encoding and secreting neuroprotective factor and / or anti-angiogenic factor; Patent number: 20120263794), and Europäische Patentanmeldung 16 720 043.5 and Patent application US 2019 0085065 A1 (Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

For all participating cohorts, the appropriate institutional review boards approved research activities and informed consent was obtained from each participant. Further details on all participating cohorts is given in the Supplementary Note.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41398-025-03418-z.

Correspondence and requests for materials should be addressed to Amy R. Bentley.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

This is a U.S. Government work and not under copyright protection in the US; foreign copyright protection may apply 2025

[1]Center for Research on Genomics and Global Health, National Human Genome Research Institute, Bethesda, MD 20892, USA. [2]Department of Epidemiology, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX 77030, USA. [3]MerexAgRight Farm, Ltd., Kitale, Kenya. [4]Division of Statistical Genomics, Washington University, St. Louis, MO, USA. [5]Department of Epidemiology, University of Regensburg, Regensburg 93051, Germany. [6]Department of Social Medicine, Population and Public Health, University of California, Riverside School of Medicine, Riverside, CA 92521, USA. [7]Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen DK-2200, Denmark. [8]The Novo Nordisk Foundation Center for Genomic Mechanisms of Disease, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA. [9]Institut Pasteur, Université Paris Cité, Department of Computational Biology, F-75015 Paris, France. [10]Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA. [11]Department of Biostatistics, University of Washington, Seattle, WA 98101, USA. [12]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA. [13]Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore 117549, Singapore. [14]Department of Engineering Technology, University of Houston, Sugar Land, TX 77479, USA. [15]Department of Epidemiology, University of North Carolina, Chapel Hill, NC 27516, USA. [16]Department of Pediatrics, The Institute for Translational Genomics and Population Sciences, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA 90502, USA. [17]Department of Epidemiology, Federal University of Pelotas, Pelotas, RS 96020-220, Brazil. [18]Heart Institute (InCor), University of São Paulo Medical School, São Paulo, SP 05403-900, Brazil. [19]Department of Biostatistics, Boston University, Boston, MA 02118, USA. [20]Department of Medicine, Division of Cardiology, Duke University School of Medicine, Durham, NC 27701-2047, USA. [21]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA 02114, USA. [22]Department of Medicine, Harvard Medical School, Boston, MA 02115, USA. [23]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen 9713 GZ, The Netherlands. [24]Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, Leiden 2333ZA, the Netherlands. [25]McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX 77030, USA. [26]Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA. [27]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA. [28]Division of Biostatistics, Washington University, St. Louis, MO 63110, USA. [29]Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands. [30]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden 2300 RC, The Netherlands. [31]IQVIA, 1101 CT Amsterdam, the Netherlands. [32]Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [33]Lothian Birth Cohorts, Department of Psychology, The University of Edinburgh, Edinburgh EH8 9JZ, UK. [34]Department of Clinical Chemistry, Fimlab Laboratories, Tampere 33520, Finland. [35]Department of Clinical Chemistry, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere 33014, Finland. [36]Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Prilly, Vaud 1008, Switzerland. [37]Foundation for Research in Health Exercise and Nutrition, Kuopio Research Institute of Exercise Medicine, Kuopio 70100, Finland. [38]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI 48104, USA. [39]Interfaculty Institute of Genetics and Functional Genomics, University Medicine Greifswald, Greifswald 17489, Germany. [40]German Center for Cardiovascular Research (DZHK), partner site Greifswald, Greifswald 17475, Germany. [41]Division of Epidemiology, Vanderbilt University Medical Center, Nashville, TN 37203, USA. [42]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA. [43]McKusick-Nathans Institute, Department of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA. [44]Department of Epidemiology

and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29169, USA. [45]Section of Cardiovascular Research, Baylor College of Medicine, Houston, TX 77030, USA. [46]Houston Methodist Debakey Heart and Vascular Center, Houston, TX 77030, USA. [47]Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX 77030, USA. [48]Institute for Minority Health Research, University of Illinois Chicago, Chicago, IL 60612, USA. [49]Center for Biostatistics and Data Science, Institute for Informatics, Data Science, and Biostatistics (I2BD), Washington University School of Medicine, St. Louis, MO 63110, USA. [50]Division of Cardiology, Washington University, St. Louis, MO 63110, USA. [51]Department of Epidemiology, University of Washington, Seattle, WA, USA. [52]Department of Medicine, University of Washington, Seattle, WA, USA. [53]Cardiovascular Health Research Unit, University of Washington, Seattle, WA, USA. [54]College of Pharmacy, University of Manitoba, Winnipeg, MB R3E 0T5, Canada. [55]Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39213, USA. [56]Department of Psychology, San Diego State University, San Diego, CA, USA. [57]Institute of Biomedicine, School of Medicine, University of Eastern Finland, Kuopio Campus, Kuopio 70100, Finland. [58]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA. [59]Institute of Molecular and Clinical Ophthalmology Basel IOB, Basel, Switzerland. [60]Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Ophthalmology and Visual Science Key Lab, Beijing Tongren Hospital, Capital Medical University, Beijing, China. [61]Department of Psychology and Logopedics, University of Helsinki, Helsinki 00014, Finland. [62]University of Mississippi Medical Center, Jackson, MS 39213, USA. [63]Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA. [64]Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore, Singapore 138672, Singapore. [65]Department of Medicine, Duke Molecular Physiology Institute Duke University School of Medicine, Durham, NC 27701-2047, USA. [66]Center for Public Health Genomics, University of Virginia, Charlottesville, VA 22908, USA. [67]Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA. [68]Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA, USA. [69]Department of Medicine, Internal Medicine, Lausanne University Hospital and University of Lausanne, Rue du Bugnon 46, CH- 1011 Lausanne, Switzerland. [70]Department of Psychiatry, Amsterdam Neuroscience and Amsterdam Public Health Research Institute, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam 1081 HJ, the Netherlands. [71]Veritas Management Group, Inc., Alpharetta, GA 30072, USA. [72]Division of Endocrinology, Diabetes, and Nutrition, University of Maryland School of Medicine, Baltimore, MD, USA. [73]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA. [74]Department of Health Services Research, School of Medicine and Health Services, Carl von Ossietzky Universität Oldenburg, Oldenburg 26111, Germany. [75]Institute for Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg 85764, Germany. [76]Division of Preventive Medicine, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL 35205, USA. [77]Cardiovascular Health Research Unit, Division of Cardiology, University of Washington, Seattle, Washington 98195, USA. [78]Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore, Singapore 119228, Singapore. [79]Department of Pediatrics, LA Biomed at Harbor-UCLA Medical Center, Torrance, CA 90502, USA. [80]Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, WA 98109, USA. [81]Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455, USA. [82]Department of Internal Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands. [83]Nuffield Department of Population Health, University of Oxford, Oxford, UK. [84]Research Unit Molecular Epidemiology, Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg 85764, Germany. [85]Department of Epidemiology, University of Iowa College of Public Health, Iowa City, IA, USA. [86]Beijing Tongren Eye Center, Beijing Key Laboratory of Intraocular Tumor Diagnosis and Treatment, Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing Tongren Hospital, Capital Medical University, Beijing, China. [87]Department of Human Genetics, Leiden University Medical Center, Leiden 2333ZA, The Netherlands. [88]Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, Leiden 2333ZA, The Netherlands. [89]School of Public Health, Jackson State University, Jackson, MS 39213, USA. [90]Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH 44106, USA. [91]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg 85764, Germany. [92]German Center for Diabetes Research (DZD), Partner München-Neuherberg, Neuherberg, Germany. [93]German Centre for Neurodegenerative Diseases (DZNE), Site Rostock/Greifswald, Greifswald 17475, Germany. [94]Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald 17489, Germany. [95]Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland. [96]Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen 9713 GZ, the Netherlands. [97]Division of Biostatistics, Department of Population and Public Health Sciences, University of Southern California, Los Angeles, CA 90032, USA. [98]Icelandic Heart Association, Icelandic Heart Association, Kópavogur 201, Iceland. [99]Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [100]Postgraduate Program in Epidemiology, Federal University of Pelotas, Pelotas, RS 96020-220, Brazil. [101]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden 2333ZA, the Netherlands. [102]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden 2333ZA, the Netherlands. [103]Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Systems and Population Health, University of Washington, Seattle, USA. [104]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA. [109]These authors contributed equally: Amy R. Bentley, Michael R. Brown, Charles N. Rotimi, Myriam Fornage, Ervin R. Fox. *A list of authors and their affiliations appears at the end of the paper. ✉email: amy.bentley@nih.gov

LIFELINES COHORT STUDY

Raul Aguirre-Gamboa[105], Patrick Deelen[105], Lude Franke[105], Jan A. Kuivenhoven[106], Esteban A. Lopera Maya[105], Ilja M. Nolte[107], Serena Sanna[105], Harold Snieder[107], Morris A. Swertz[105], Peter M. Visscher[107,108], Judith M. Vonk[107], Cisca Wijmenga[105] and Naomi Wray[108]

[105]Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [106]Department of Pediatrics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [107]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [108]Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia.

Supplementary Material

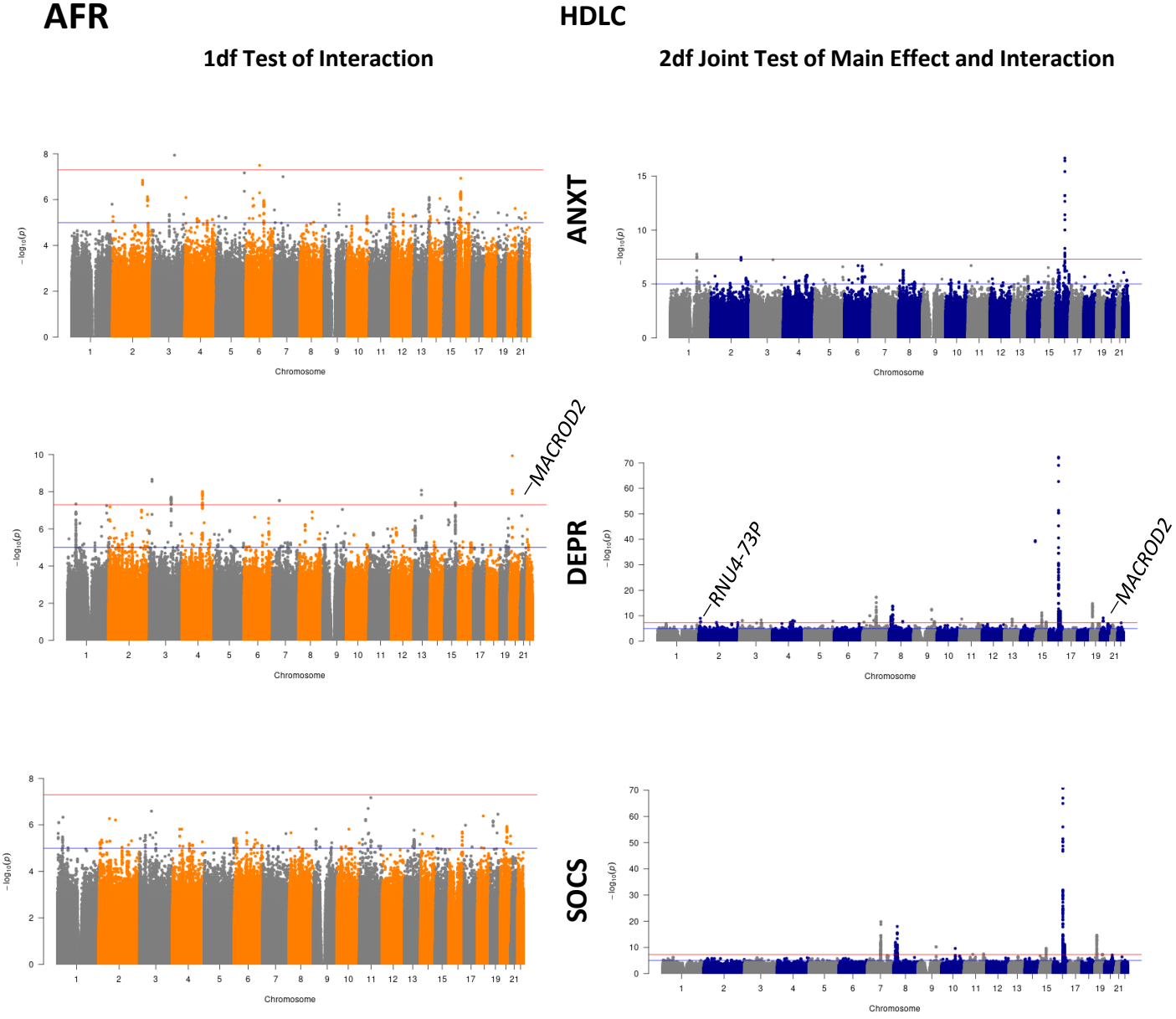
Multi-Ancestry Genome-Wide Association Analyses Incorporating SNP-by-Psychosocial Interactions Identify Novel Loci for Serum Lipids

Amy R. Bentley, Michael R. Brown, Solomon K. Musani, Karen L. Schwander, Thomas W. Winkler, *et al.*

Contents

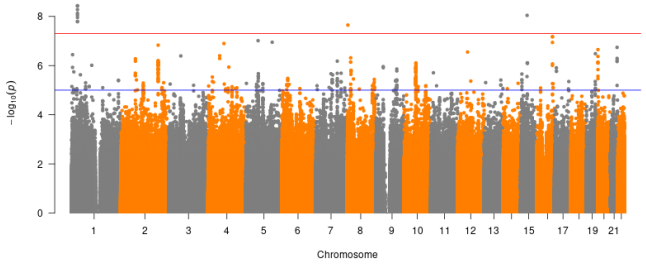
Supplemental Figures

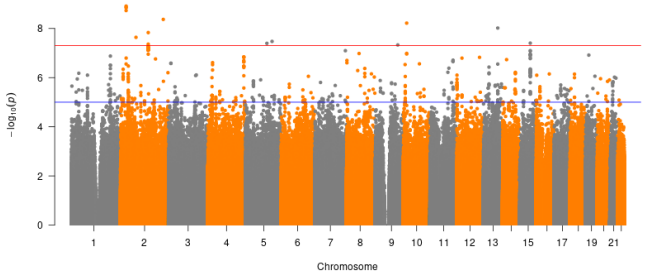
Supplemental Figure 1: Manhattan Plots. Shown are Manhattan plots for all meta-analyses conducted for both the 1df test of interaction (orange/gray) and the 2df test of main effect and interaction (blue/gray). Stage 1 + 2 results are given where available, with Stage 1 only results included for all variants for which follow-up in Stage 2 was not sought. Lead novel associations from either the 1df test of interaction (**Table 1**) or the 2df test of main effect and interaction (**Table 2**) are annotated with the name of the nearest gene.



AFR

1df Test of Interaction



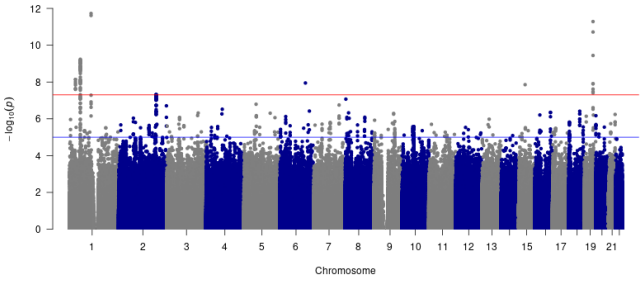


None

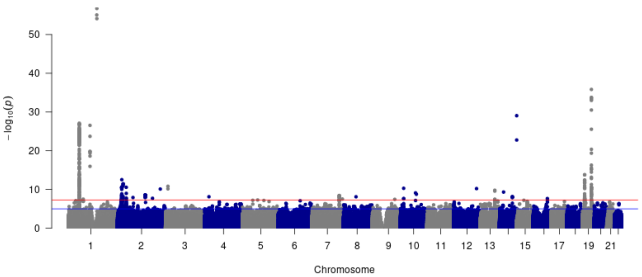
LDLC

2df Joint Test of Main Effect and Interaction

ANXT



DEPR

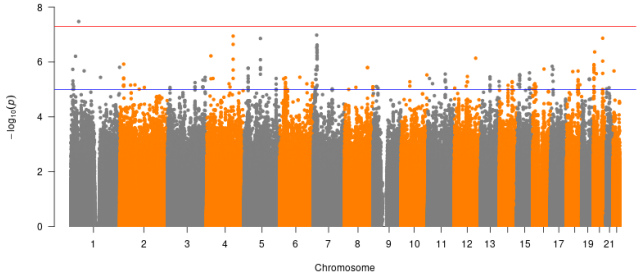


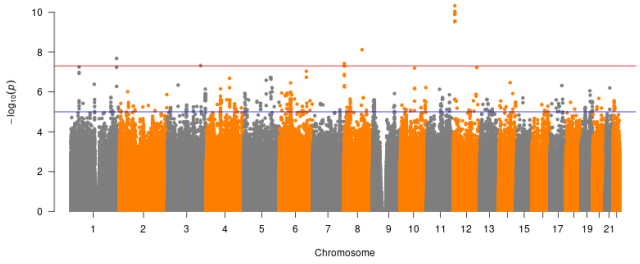
SOCS

None

AFR

1df Test of Interaction



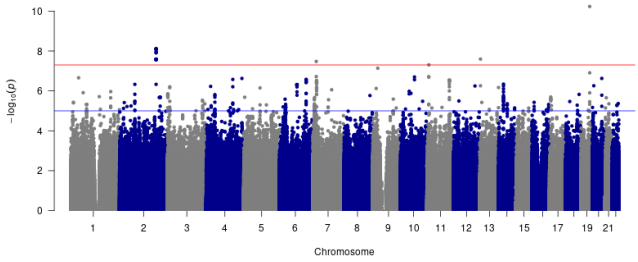


None

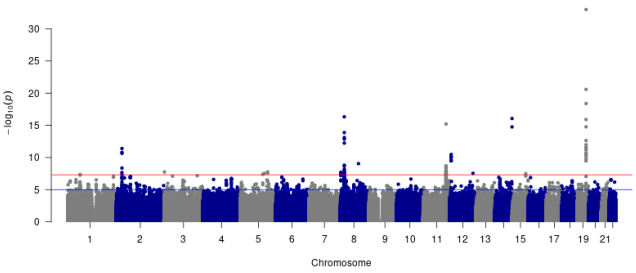
TG

2df Joint Test of Main Effect and Interaction

ANXT



DEPR



SOCS

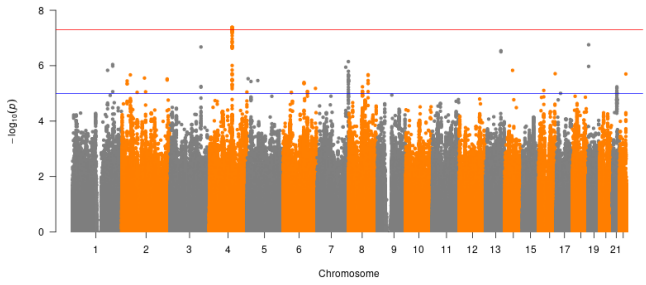
None

ASN

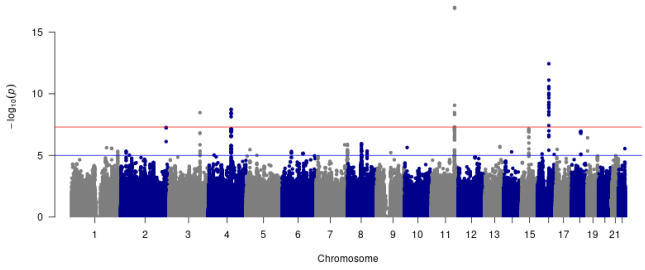
Note: ASN cohorts only had DEPR results.

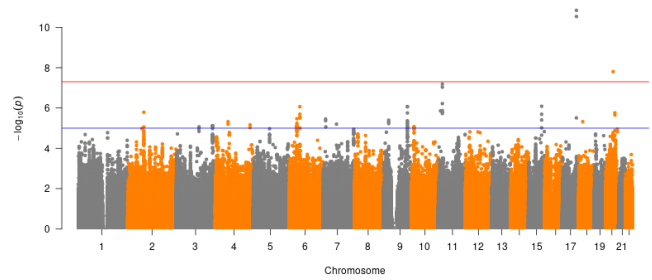
1df Test of Interaction

2df Joint Test of Main Effect and Interaction

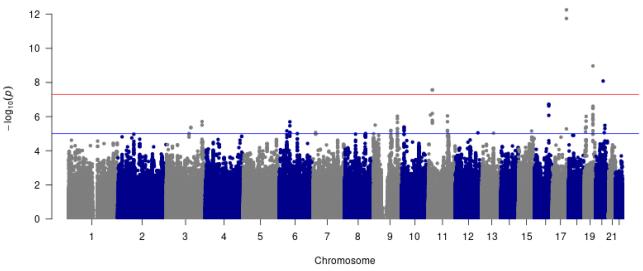


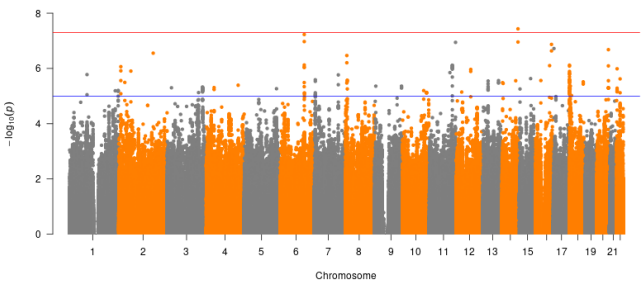
HDLC-DEPR



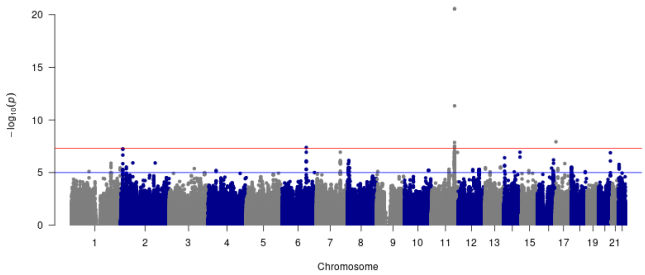


LDLC-DEPR



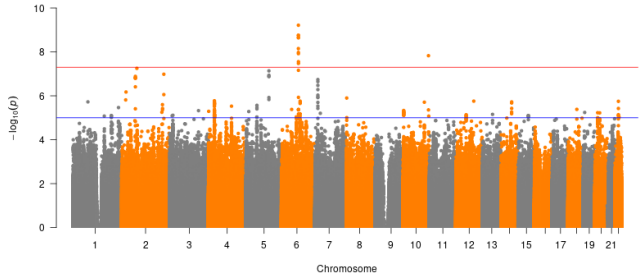


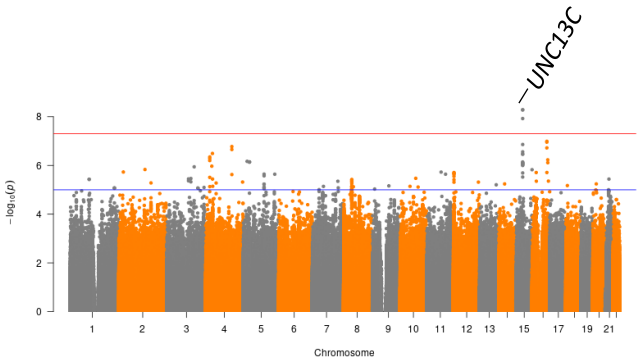
TG-DEPR

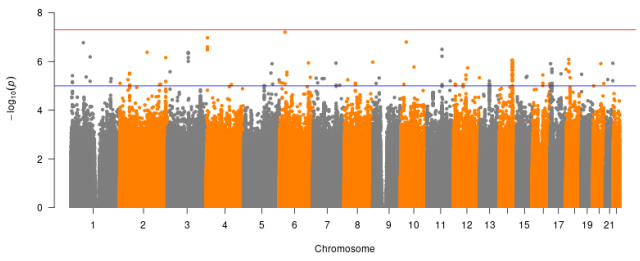


EUR

1df Test of Interaction



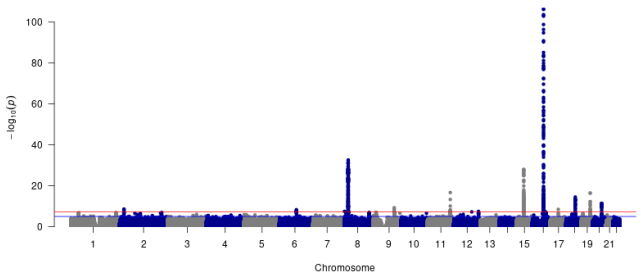




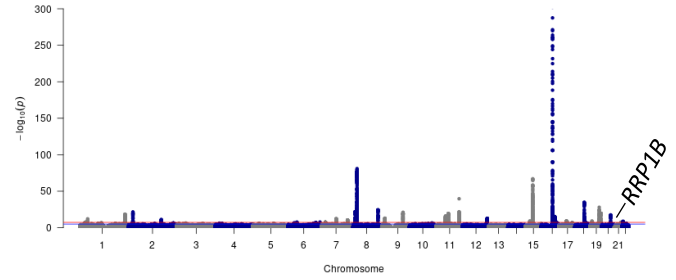
HDLC

2df Joint Test of Main Effect and Interaction

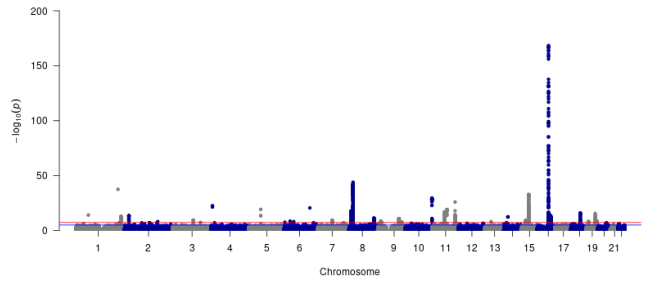
ANXT



DEPR

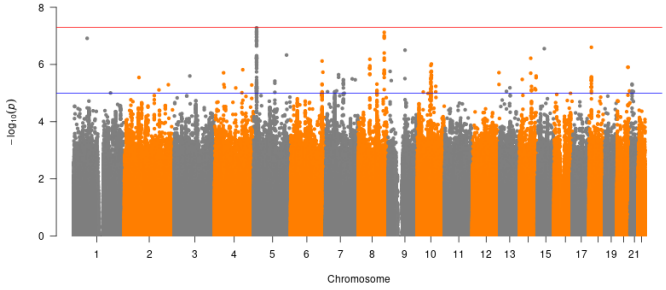


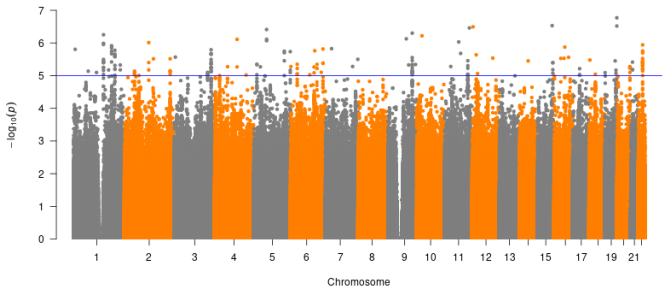
SOCS

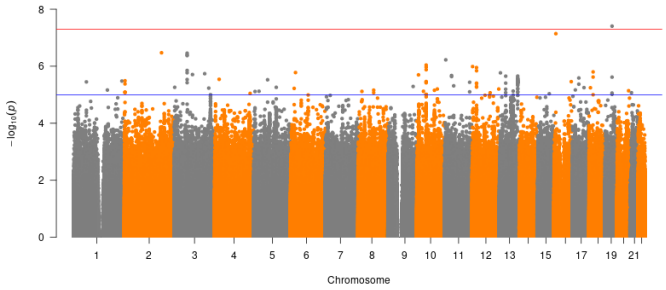


EUR

1df Test of Interaction



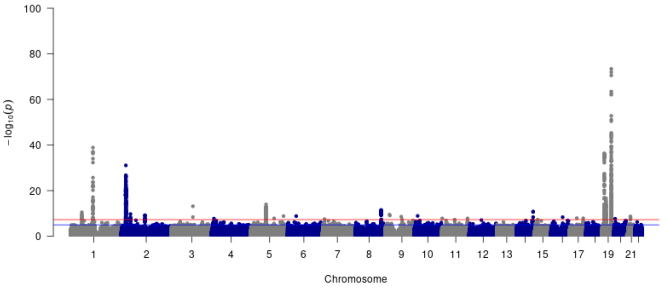




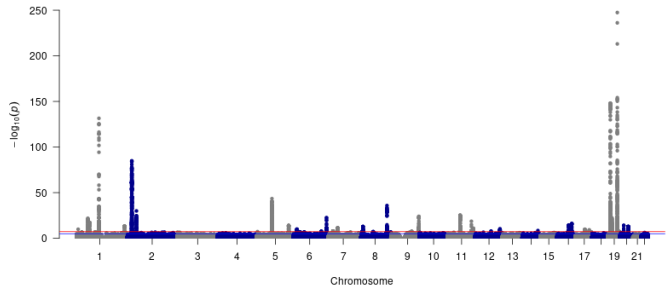
LDLC

2df Joint Test of Main Effect and Interaction

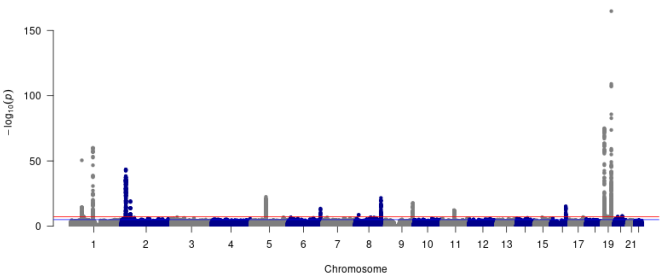
ANXT



DEPR



SOCS

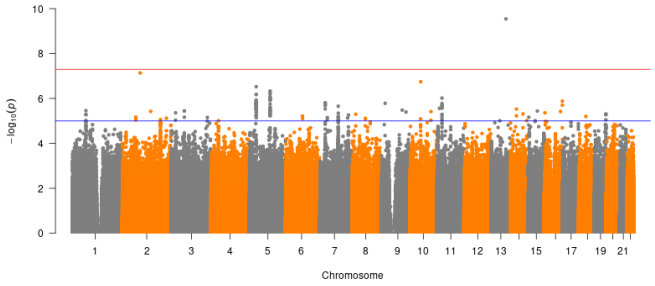


EUR

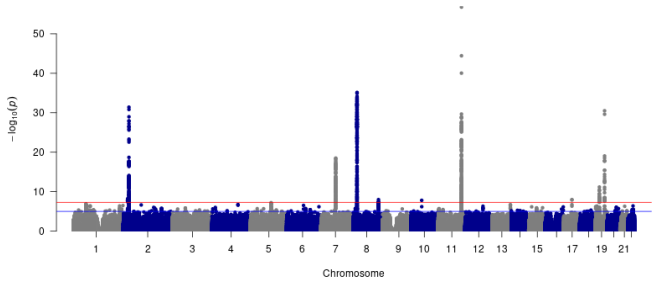
TG

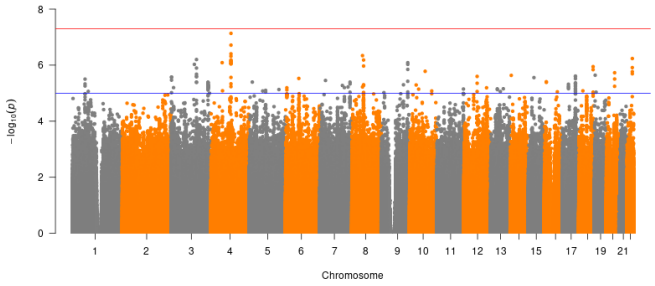
1df Test of Interaction

2df Joint Test of Main Effect and Interaction

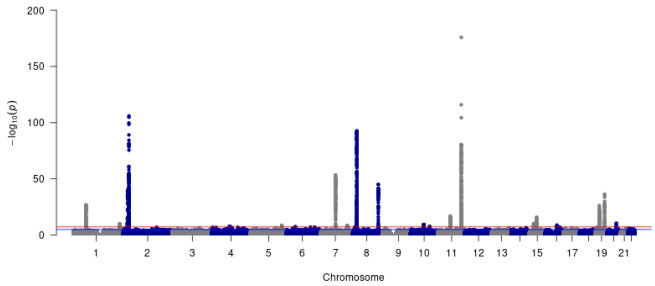


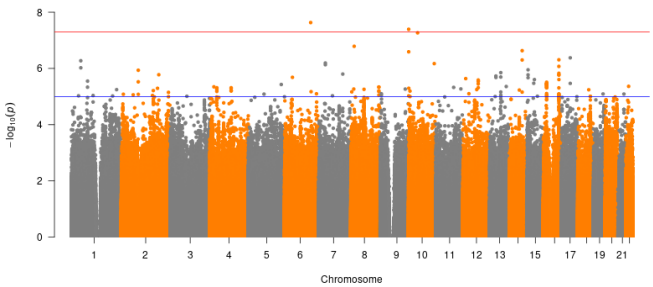
ANXT



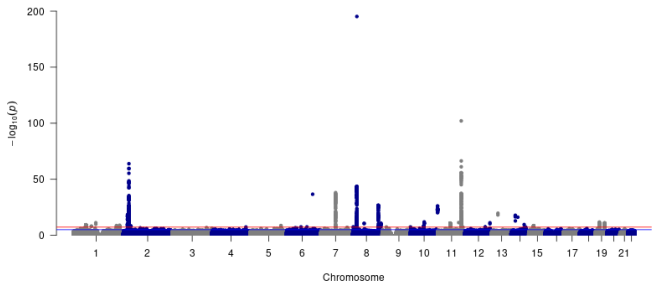


DEPR





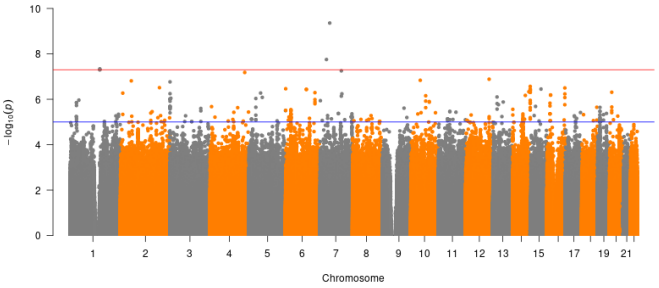
SOCS

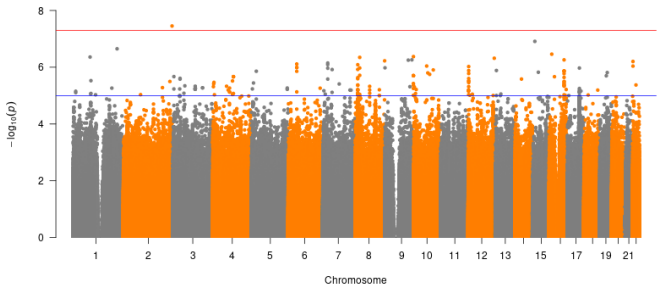


HISP

1df Test of Interaction

None





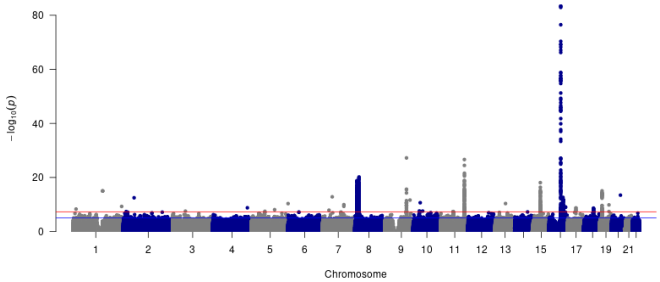
HDLC

2df Joint Test of Main Effect and Interaction

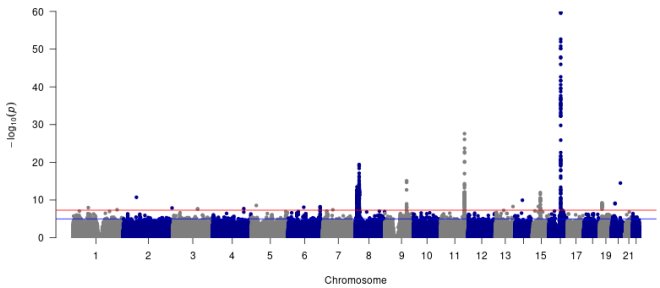
ANXT

None

DEPR



SOCS



HISP

1df Test of Interaction

None

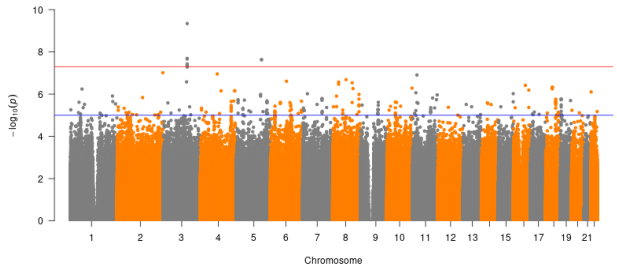
LDLC

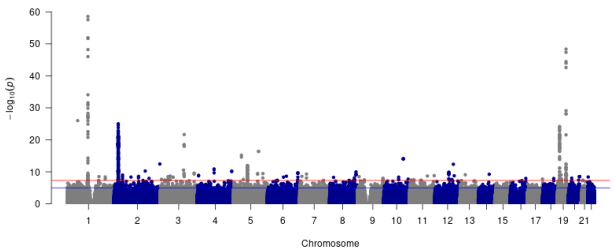
2df Joint Test of Main Effect and Interaction

None

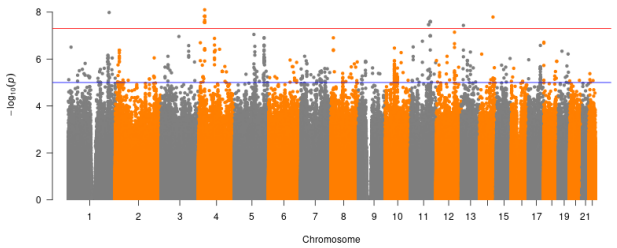
ANXT

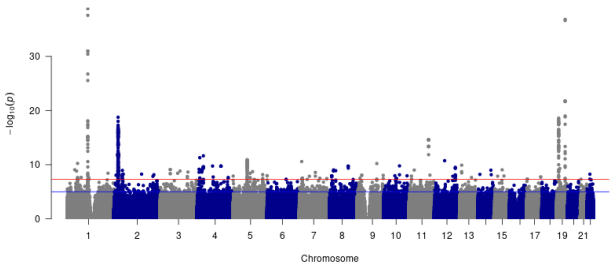
DEPR





SOCS





HISP

TG

1df Test of Interaction

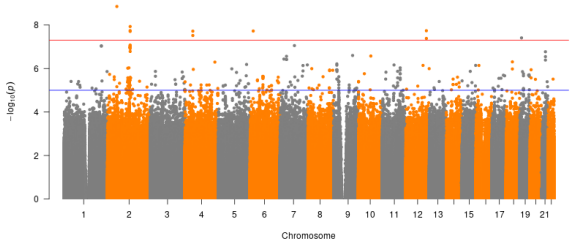
2df Joint Test of Main Effect and Interaction

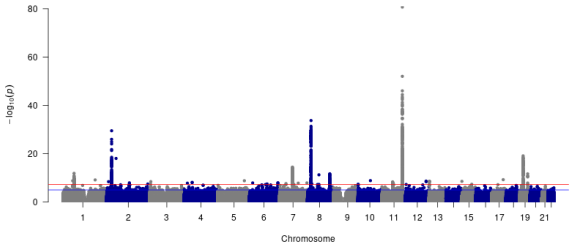
ANXT

None

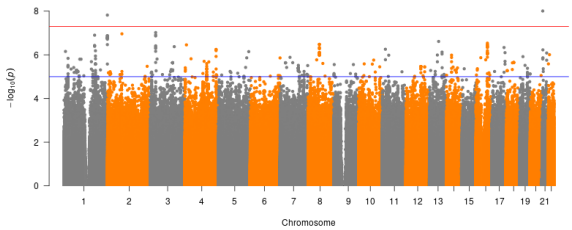
None

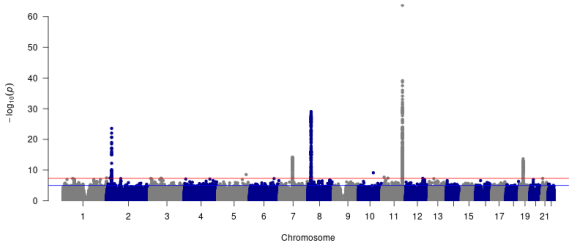
DEPR





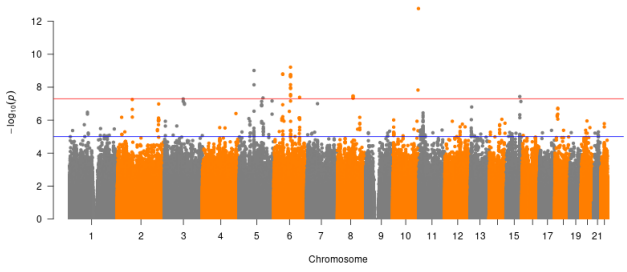
SOCS

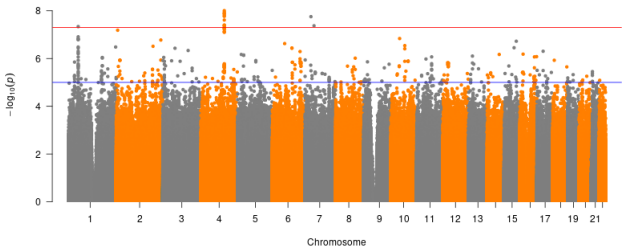


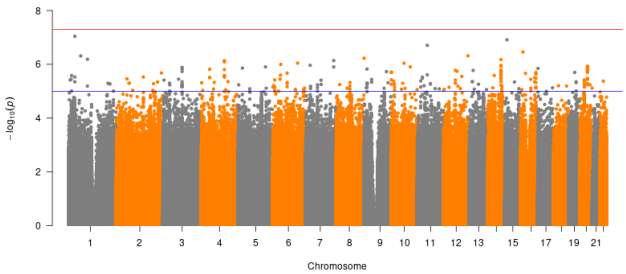


CPMA

1df Test of Interaction



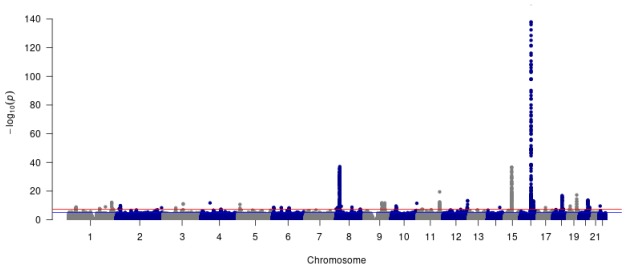




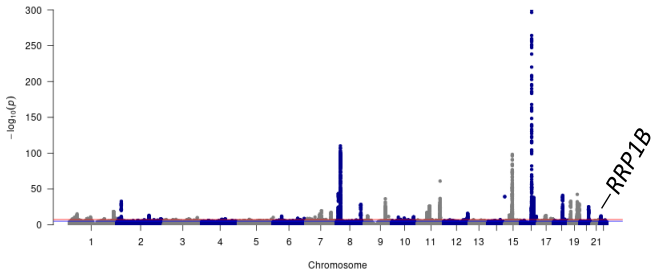
HDLC

2df Joint Test of Main Effect and Interaction

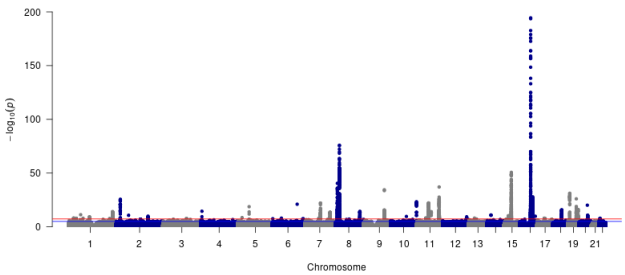
ANXT



DEPR

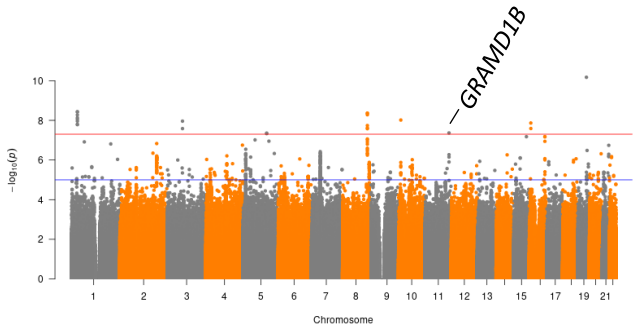


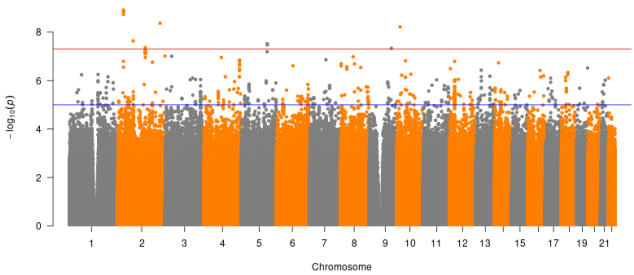
SOCS

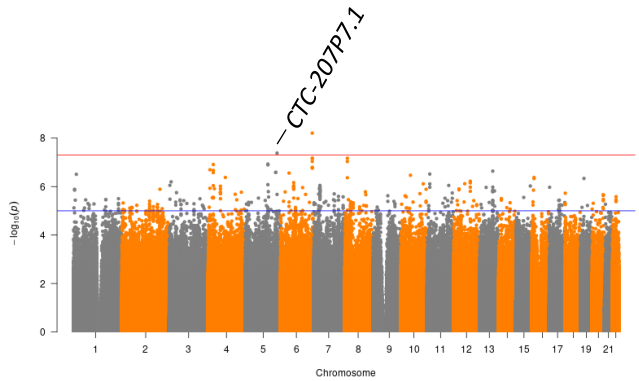


CPMA

1df Test of Interaction



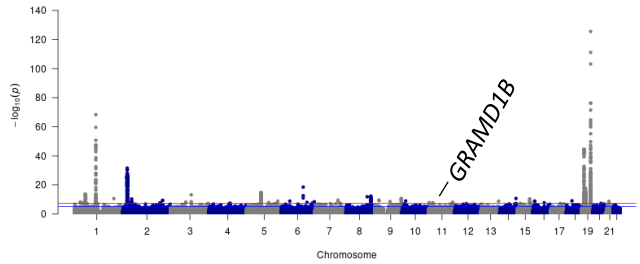




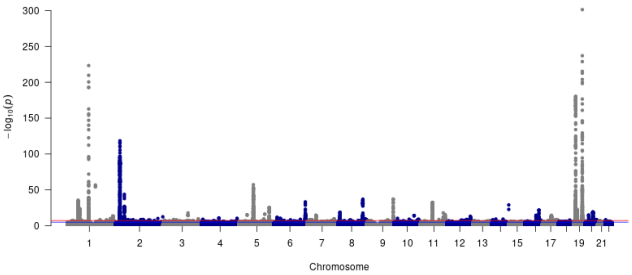
LDLC

2df Joint Test of Main Effect and Interaction

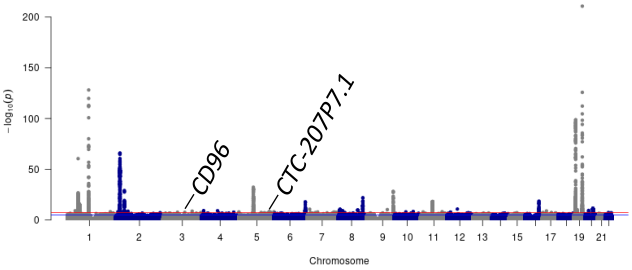
ANXT



DEPR



SOCS

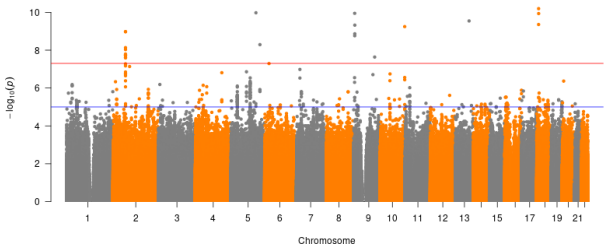


CPMA

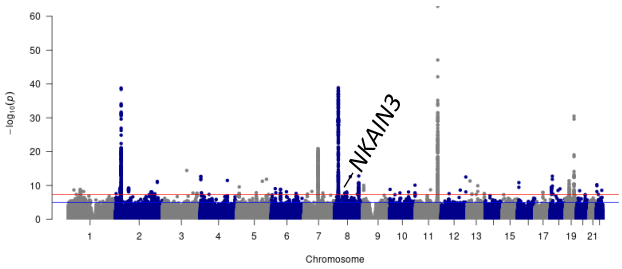
TG

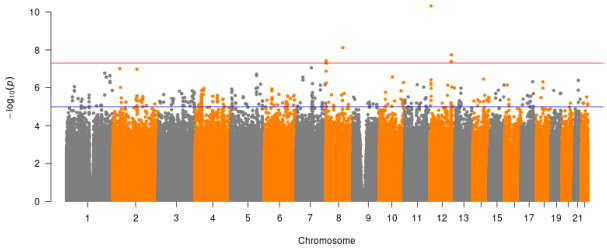
1df Test of Interaction

2df Joint Test of Main Effect and Interaction

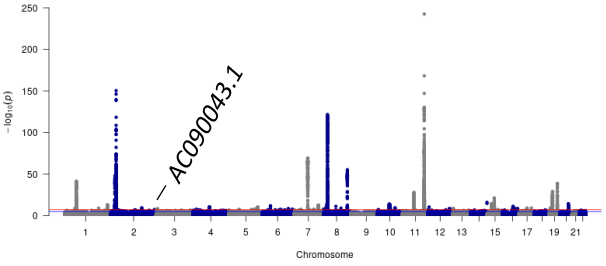


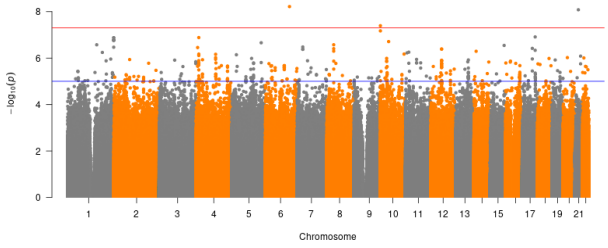
ANXT



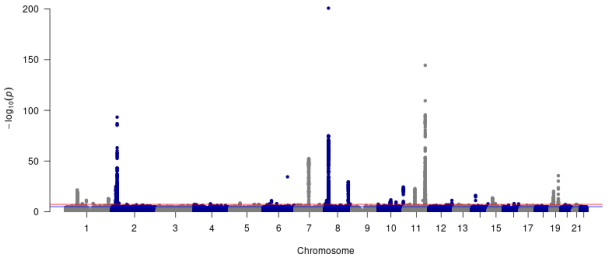


DEPR



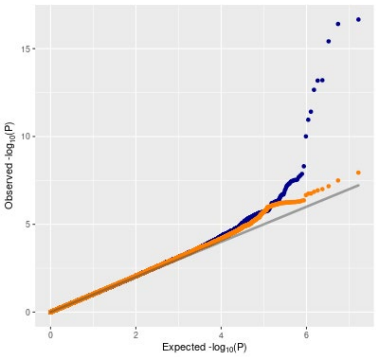
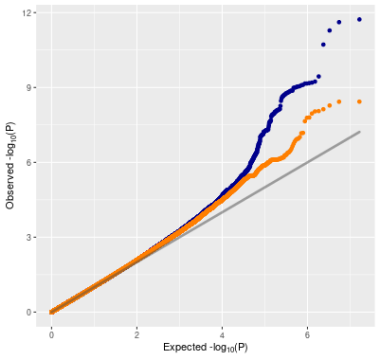
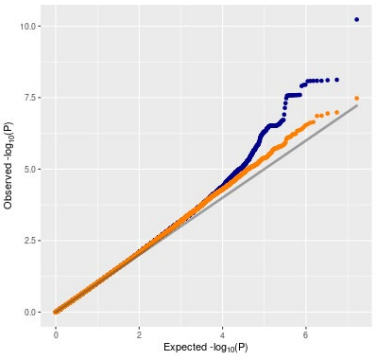
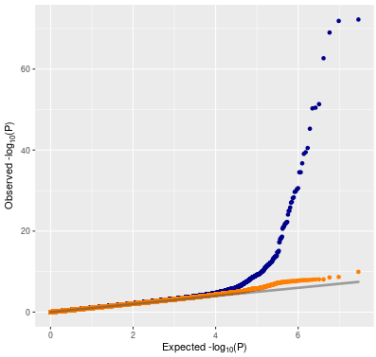
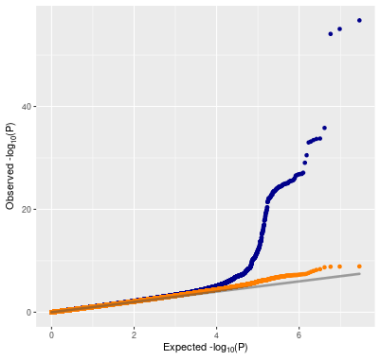
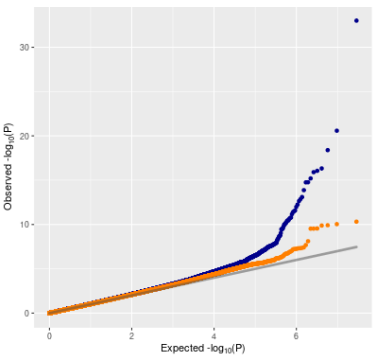
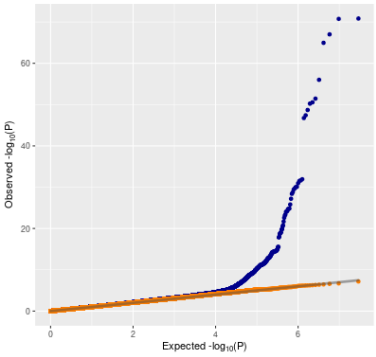


SOCS



Supplemental Figure 2: QQ Plots. Shown are QQ plots for all meta-analyses conducted for both the 1df test of interaction (orange) and the 2df test of main effect and interaction (blue). Stage 1 + 2 results are given where available, with Stage 1 only results included for all variants for which follow-up in Stage 2 was not sought.

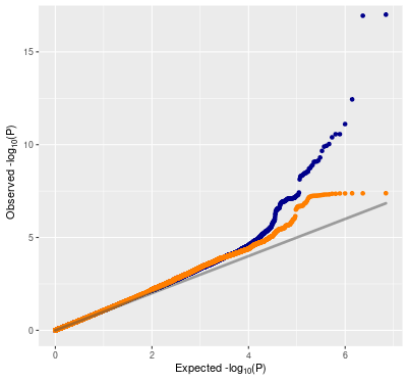
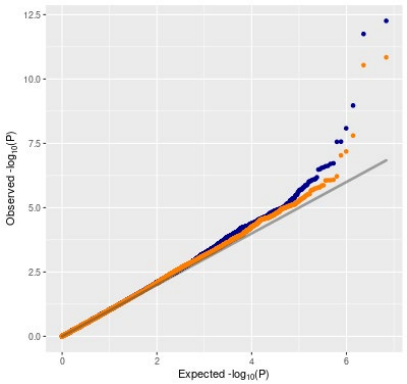
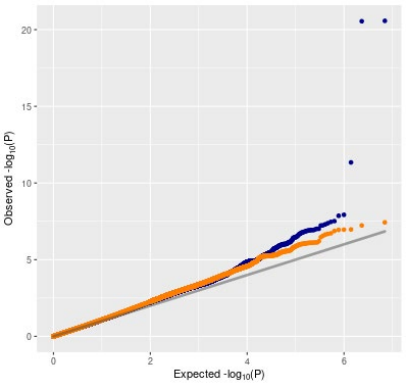
AFR

	HDLC	LDLC	TG
ANXT			
DEPR			
SOCS		*None*	*None*

1df Test of Interaction

2df Joint Test of Main Effect and Interaction

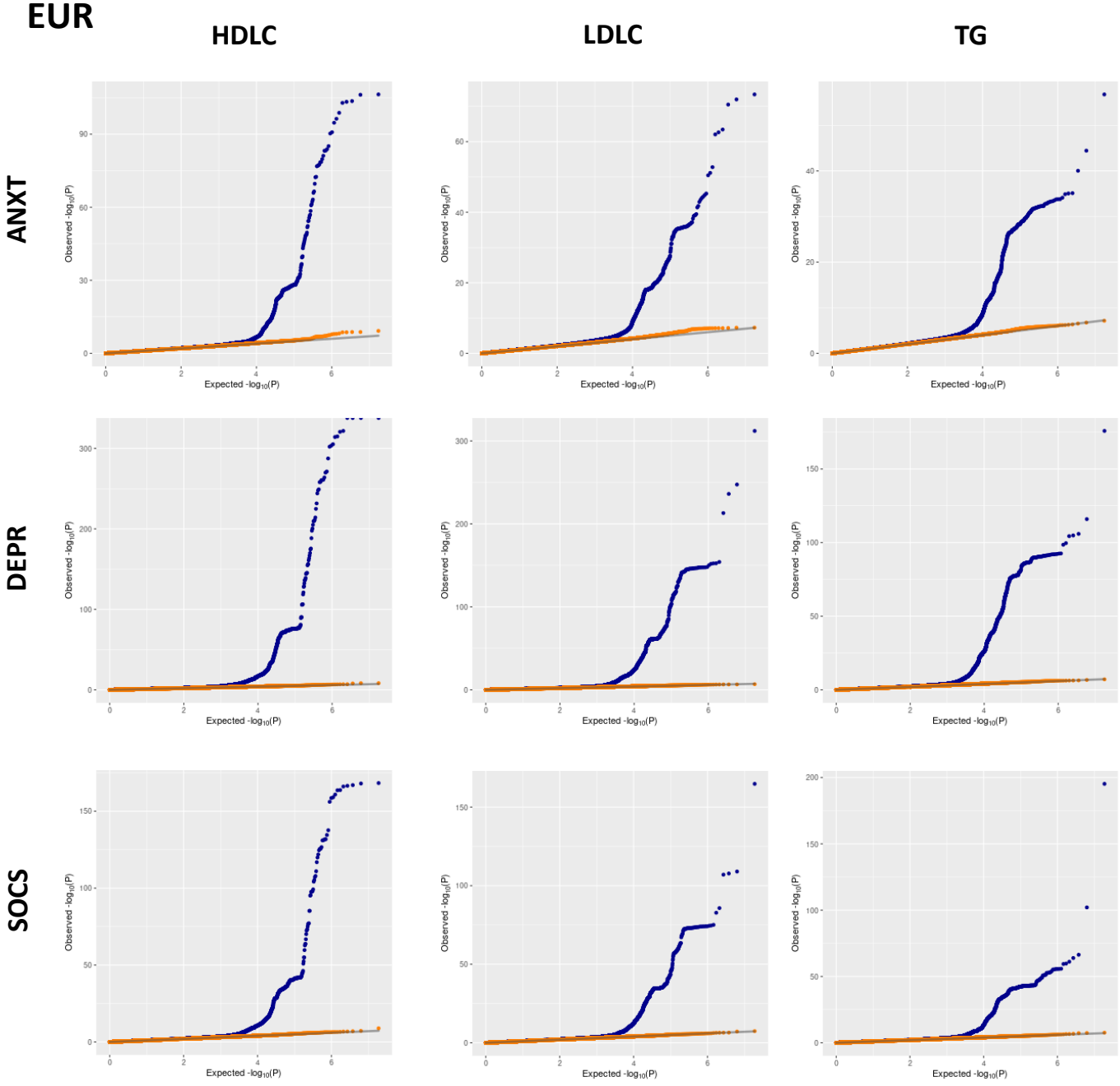
ASN

	HDLC	LDLC	TG
ANXT	*None*	*None*	*None*
DEPR			
SOCS	*None*	*None*	*None*

1df Test of Interaction

2df Joint Test of Main Effect and Interaction

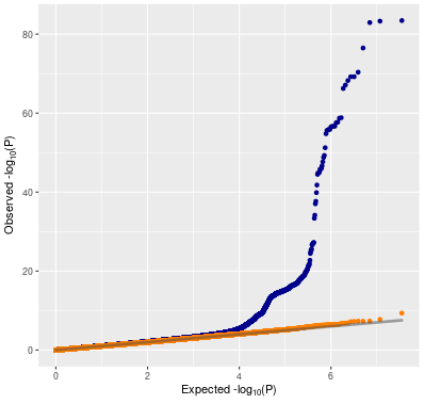
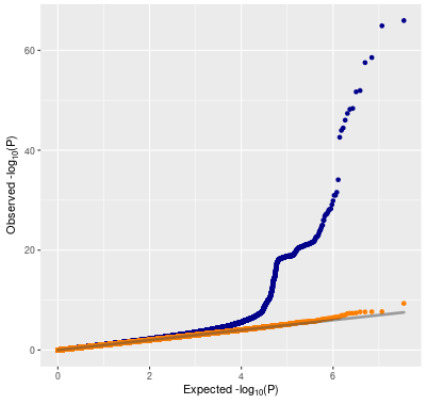
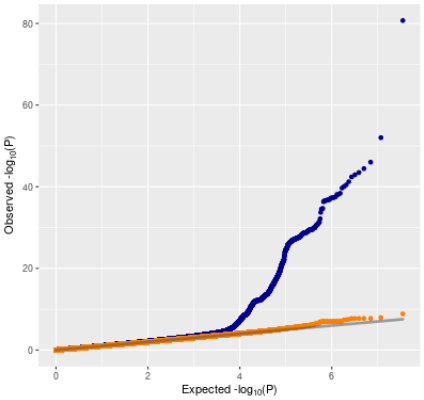
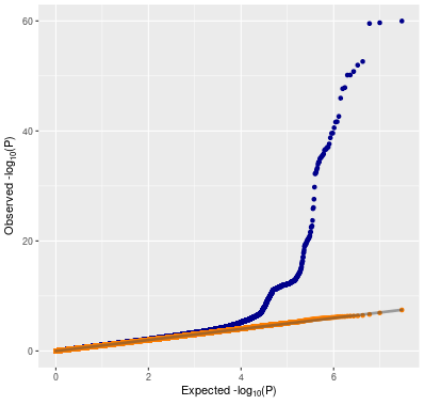
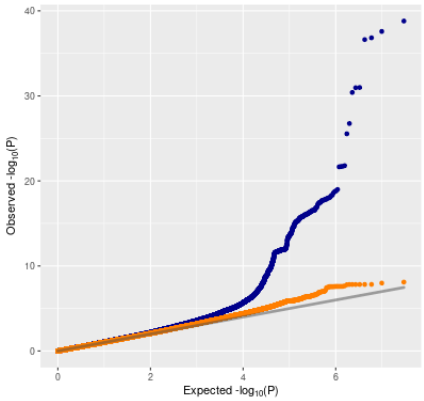
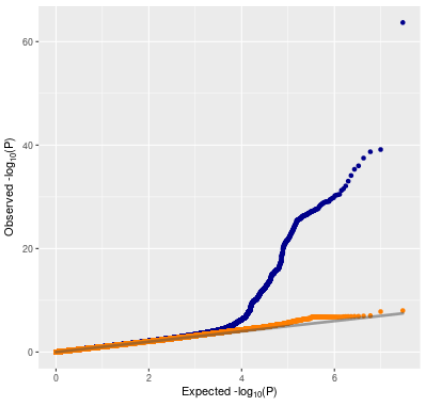
EUR



1df Test of Interaction

2df Joint Test of Main Effect and Interaction

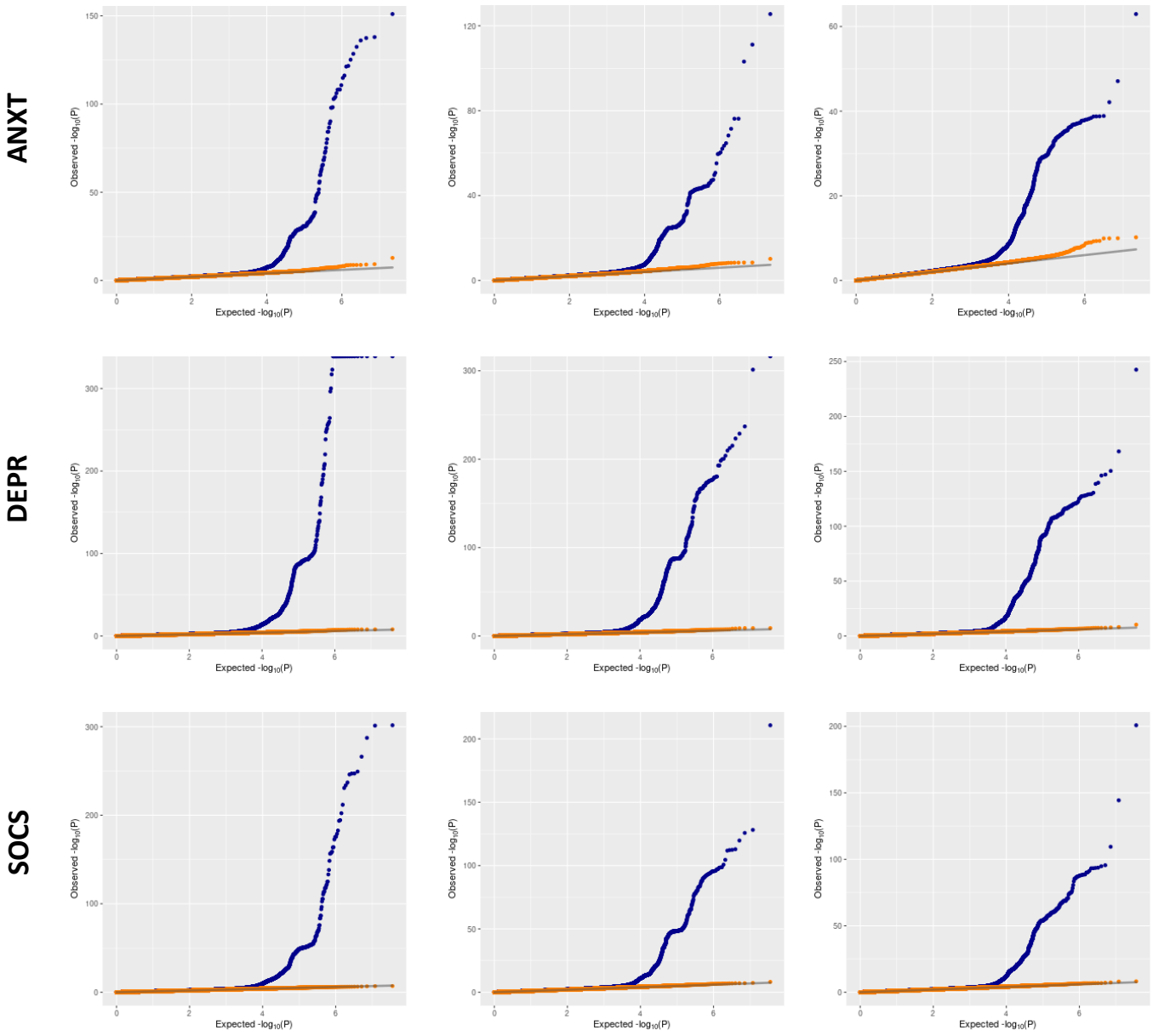
HISP

	HDLC	LDLC	TG
ANXT	*None*	*None*	*None*
DEPR			
SOCS			

1df Test of Interaction

2df Joint Test of Main Effect and Interaction

CPMA

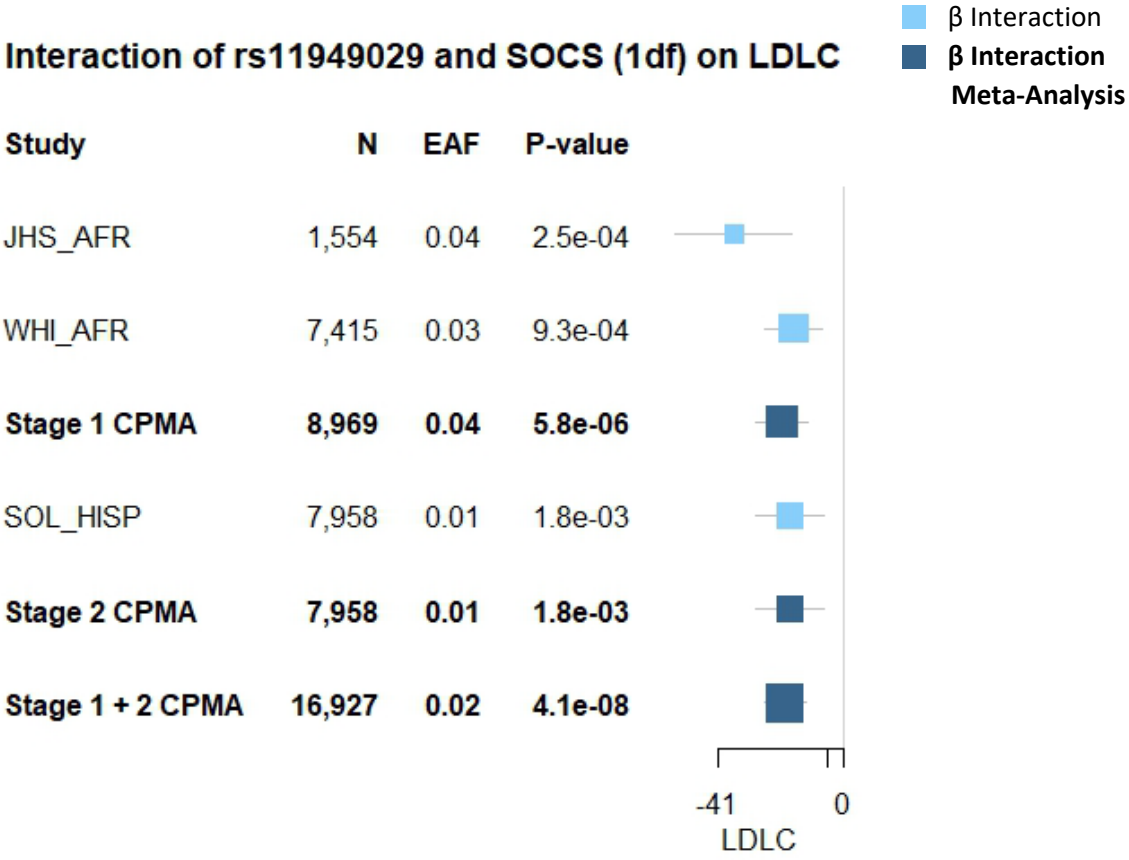


1df Test of Interaction

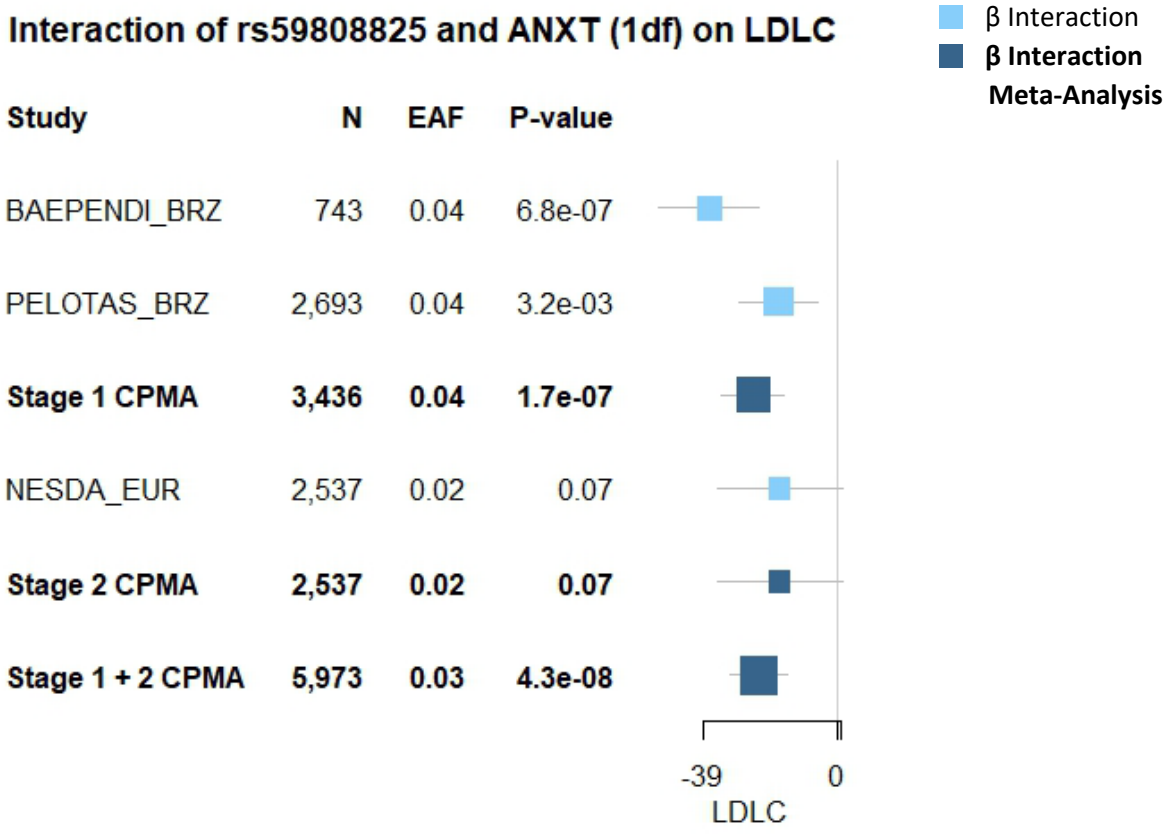
2df Joint Test of Main Effect and Interaction

Supplemental Figure 3: Forest Plot of Statistically Significant 1df Interaction Results. Shown are all individual study results with data for the given locus (when the number of contributing studies is large, only meta-analysis results are shown for readability). If only a population-specific result is shown, then that locus was not present or did not pass filters in contributing studies in any other population. Shown in blue is the beta-coefficient for the multiplicative interaction term between the variant and the listed psychosocial factor on lipid concentration. Box size represents the precision of the estimate, with larger boxes shown for results with lower variance.

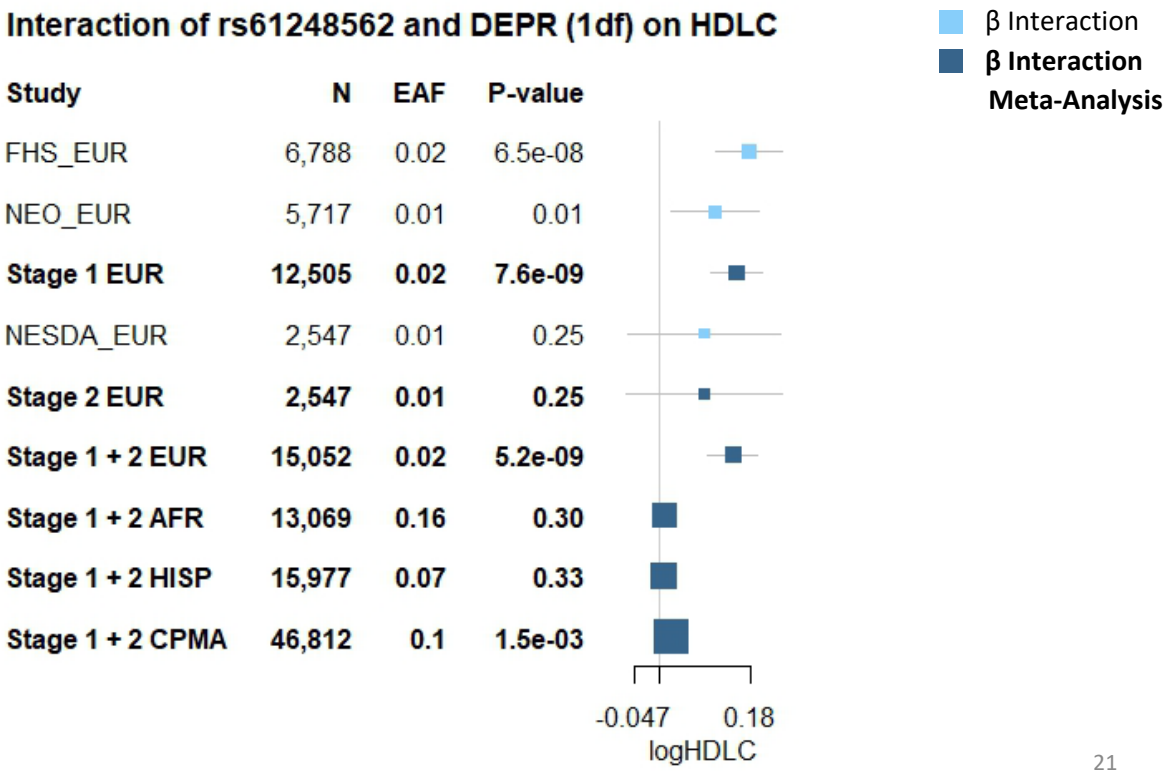
A.



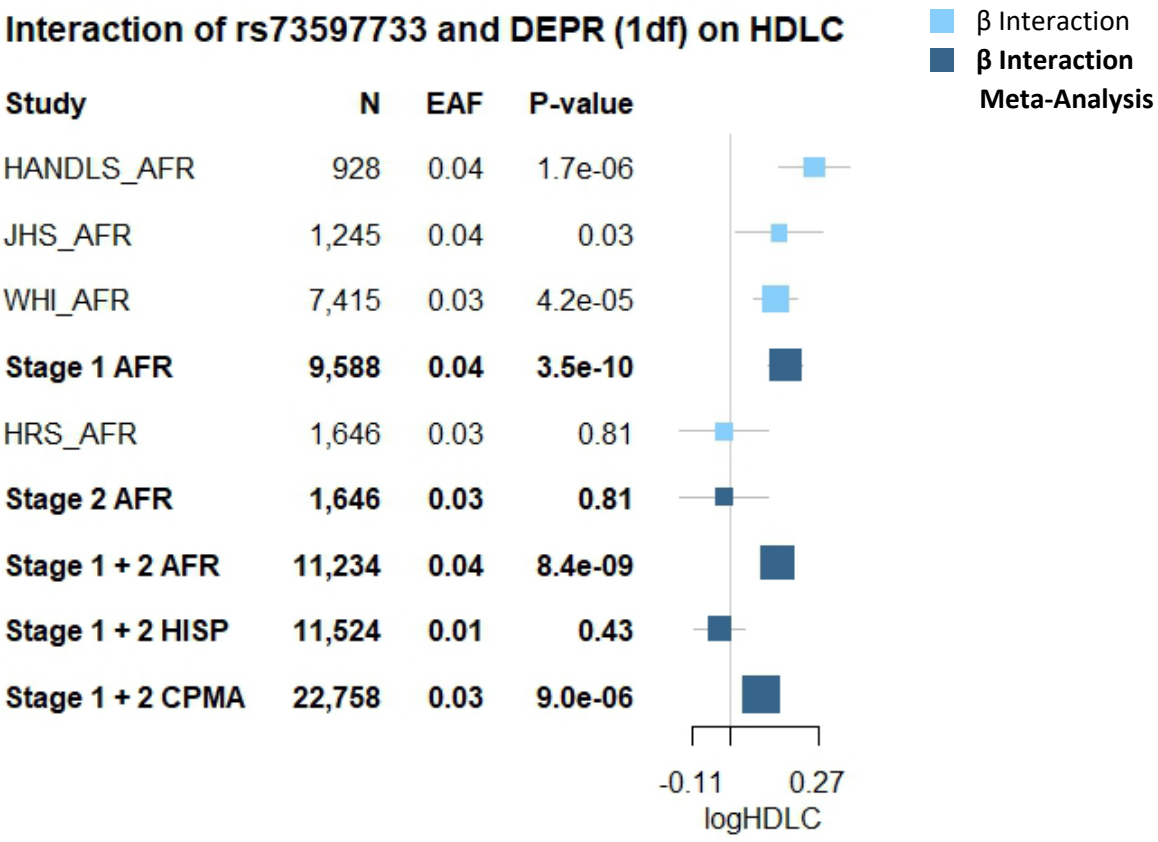
B.


Interaction of rs59808825 and ANXT (1df) on LDLC
β Interaction
β Interaction Meta-Analysis
Study N EAF P-value
BAEPENDI_BRZ 743 0.04 6.8e-07
PELOTAS_BRZ 2,693 0.04 3.2e-03
Stage 1 CPMA 3,436 0.04 1.7e-07
NESDA_EUR 2,537 0.02 0.07
Stage 2 CPMA 2,537 0.02 0.07
Stage 1 + 2 CPMA 5,973 0.03 4.3e-08
-39
0
LDLC

C.

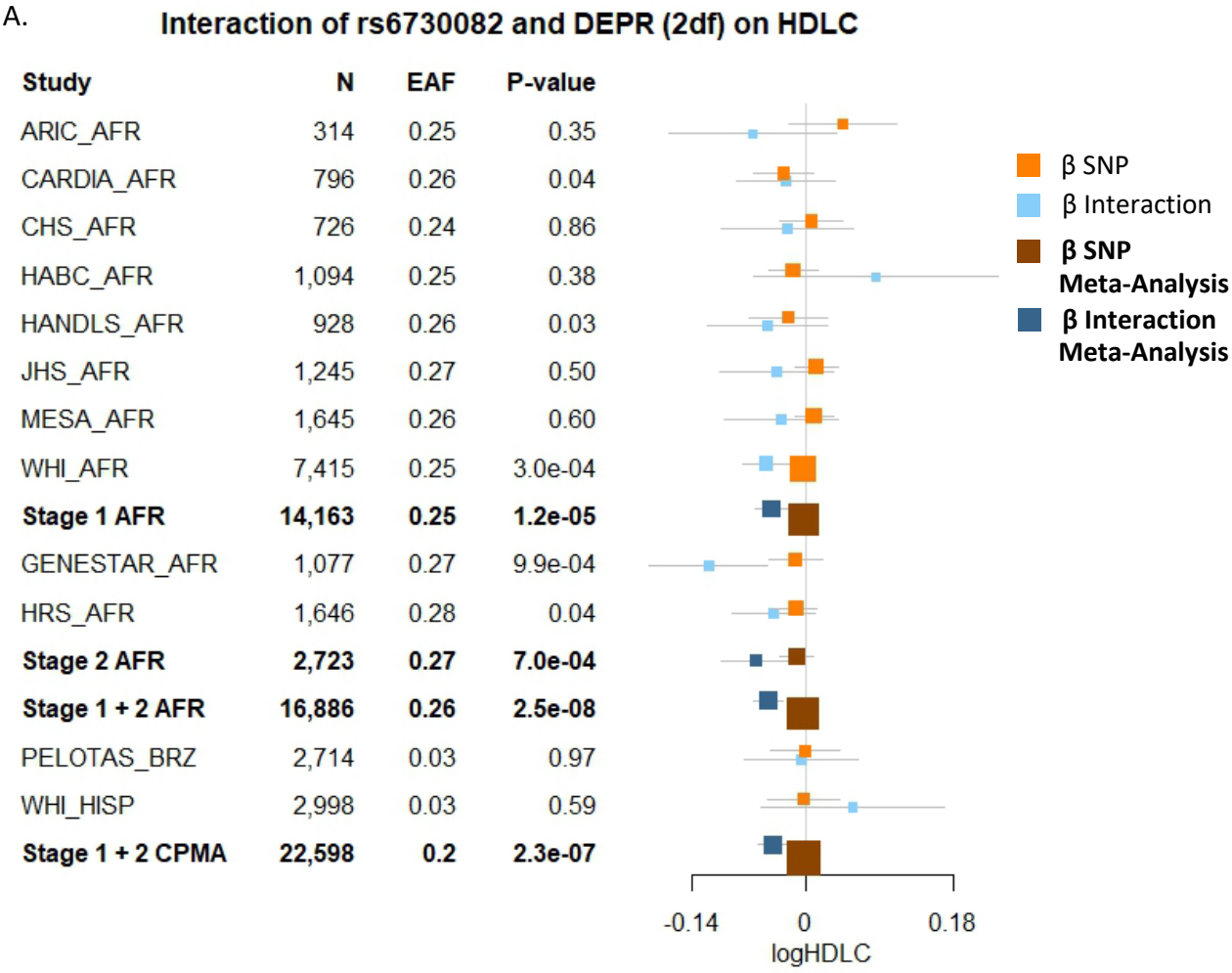

Interaction of rs61248562 and DEPR (1df) on HDLC
β Interaction
β Interaction Meta-Analysis
Study N EAF P-value
FHS_EUR 6,788 0.02 6.5e-08
NEO_EUR 5,717 0.01 0.01
Stage 1 EUR 12,505 0.02 7.6e-09
NESDA_EUR 2,547 0.01 0.25
Stage 2 EUR 2,547 0.01 0.25
Stage 1 + 2 EUR 15,052 0.02 5.2e-09
Stage 1 + 2 AFR 13,069 0.16 0.30
Stage 1 + 2 HISP 15,977 0.07 0.33
Stage 1 + 2 CPMA 46,812 0.1 1.5e-03
-0.047
0.18
logHDLC

D.


Interaction of rs73597733 and DEPR (1df) on HDLC
β Interaction
β Interaction
Meta-Analysis
Study N EAF P-value
HANDLS_AFR 928 0.04 1.7e-06
JHS_AFR 1,245 0.04 0.03
WHI_AFR 7,415 0.03 4.2e-05
Stage 1 AFR 9,588 0.04 3.5e-10
HRS_AFR 1,646 0.03 0.81
Stage 2 AFR 1,646 0.03 0.81
Stage 1 + 2 AFR 11,234 0.04 8.4e-09
Stage 1 + 2 HISP 11,524 0.01 0.43
Stage 1 + 2 CPMA 22,758 0.03 9.0e-06
-0.11
0.27
logHDLC

Supplemental Figure 4: Forest Plot of Statistically Significant 2df Main Effect and Interaction Results. Shown are all individual study results with data for the given locus (when the number of contributing studies is large, only meta-analysis results are shown for readability). If only a population-specific result is shown, then that locus was not present or did not pass filters in contributing studies in any other population. Shown in blue is the beta-coefficient for the multiplicative interaction term between the variant and the listed psychosocial factor on lipid concentration, while the orange is the beta-coefficient for the main effect term in the same model. Box size represents the precision of the estimate, with larger boxes shown for results with lower variance.

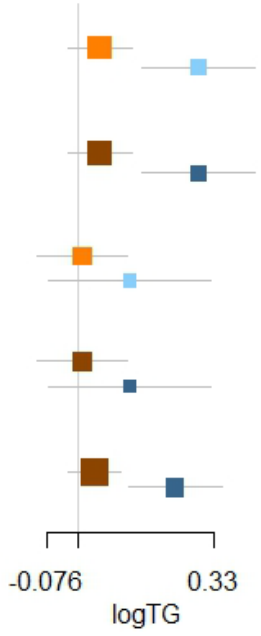
A.



B.

Interaction of rs142378953 and DEPR (2df) on TG

Study	N	EAF	P-value
WHI_AFR	7,415	0.01	1.8e-08
Stage 1 CPMA	**7,415**	**0.01**	**1.8e-08**
SOL_HISP	11,496	0.002	0.26
Stage 2 CPMA	**11,496**	**0.002**	**0.26**
Stage 1+2 CPMA	**18,911**	**0.01**	**4.9e-08**

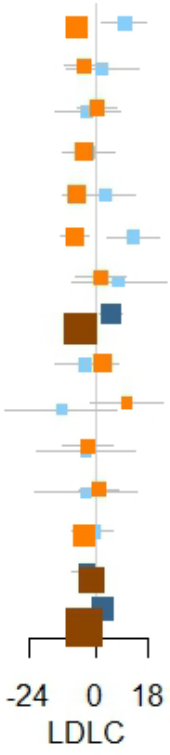


β SNP
β Interaction
β SNP Meta-Analysis
β Interaction Meta-Analysis

C.

Interaction of rs34636484 and SOCS (2df) on LDLC

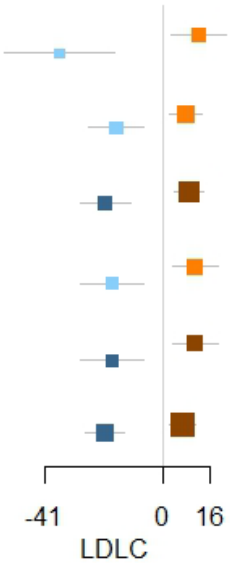
Study	N	EAF	P-value
ARIC_EUR	7,366	0.04	5.7e-05
CARDIA_EUR	1,617	0.04	0.46
CHS_EUR	2,939	0.03	0.77
MESA_EUR	2,541	0.04	0.03
WHI-GARNET_EUR	3,635	0.03	5.7e-03
WHI-WHIMS_EUR	4,955	0.03	3.1e-03
WHI_HISP	2,998	0.02	0.45
Stage 1 CPMA	**26,051**	**0.03**	**2.5e-08**
KORA_F3_EUR	2,639	0.04	0.70
NESDA_EUR	2,332	0.04	0.13
PSYCOLAUS_EUR	1,631	0.03	0.51
YFS_EUR	1,551	0.03	0.92
SOL_HISP	7,958	0.08	6.7e-03
Stage 2 CPMA	**16,111**	**0.03**	**0.02**
Stage 1 + 2 CPMA	**42,162**	**0.03**	**3.1e-08**



D.

Interaction of rs11949029 and SOCS (2df) on LDLC

Study	N	EAF	P-value
JHS_AFR	1,554	0.0404	8.0e-04
WHI_AFR	7,415	0.0344	3.0e-03
Stage 1 CPMA	**8,969**	**0.0354**	**2.1e-05**
SOL_HISP	7,958	0.0059	1.6e-04
Stage 2 CPMA	**7,958**	**0.0059**	**1.6e-04**
Stage 1 + 2 CPMA	**16,927**	**0.0215**	**2.3e-08**

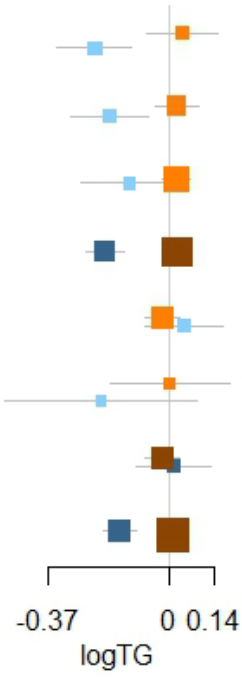


β SNP
β Interaction
β SNP Meta-Analysis
β Interaction Meta-Analysis

E.

Interaction of rs4562311 and ANXT (2df) on TG

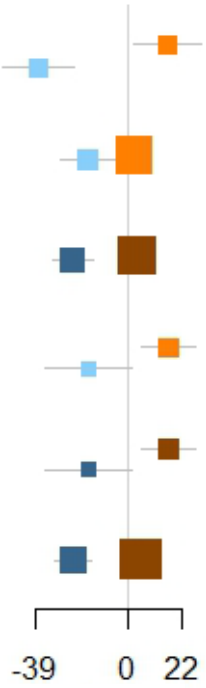
Study	N	EAF	P-value
BAEPENDI_BRZ	750	0.06	1.8e-08
CARDIA_AFR	807	0.31	5.6e-03
MESA_AFR	1,607	0.32	0.21
Stage 1 CPMA	**3,164**	**0.25**	**5.5e-11**
GENESTAR_AFR	1,069	0.29	0.67
KORA_F4_EUR	2,434	0.01	0.18
Stage 2 CPMA	**3,503**	**0.1**	**0.75**
Stage 1 + 2 CPMA	**6,667**	**0.17**	**8.5e-09**

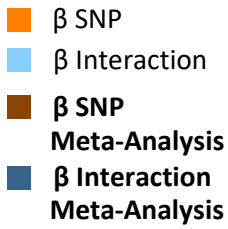


F.

Interaction of rs59808825 and ANXT (2df) on LDLC

Study	N	EAF	P-value
BAEPENDI_BRZ	743	0.04	2.1e-07
PELOTAS_BRZ	2,693	0.04	0.01
Stage 1 CPMA	**3,436**	**0.04**	**1.9e-07**
NESDA_EUR	2,537	0.02	3.8e-03
Stage 2 CPMA	**2,537**	**0.02**	**3.8e-03**
Stage 1 + 2 CPMA	**5,973**	**0.03**	**8.8e-09**

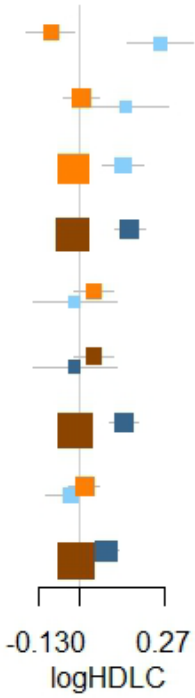




G.

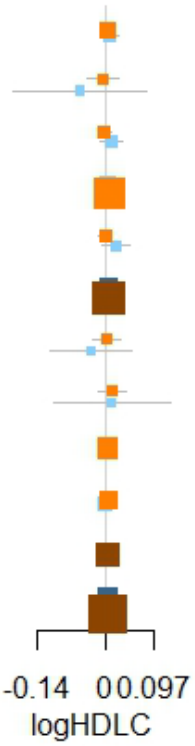
Interaction of rs73597733 and DEPR (2df) on HDLC

Study	N	EAF	P-value
HANDLS_AFR	928	0.04	2.6e-06
JHS_AFR	1,245	0.04	0.04
WHI_AFR	7,415	0.03	2.2e-04
Stage 1 AFR	**9,588**	**0.04**	**9.6e-10**
HRS_AFR	1,646	0.03	0.35
Stage 2 AFR	**1,646**	**0.03**	**0.35**
Stage 1 + 2 AFR	**11,234**	**0.04**	**1.0e-08**
SOL_HISP	11,524	0.01	0.71
Stage 1 + 2 CPMA	**22,758**	**0.02**	**2.7e-05**



H. **Interaction of rs11702544 and DEPR (2df) on HDLC**

Study	N	EAF	P-value
Stage 1 AFR	14,499	0.45	0.16
Stage 1 ASN	748	0.21	0.64
Stage 1 BRZ	3,464	0.41	0.61
Stage 1 EUR	34,079	0.42	3.3e-07
Stage 1 HISP	4,453	0.29	0.33
Stage 1 CPMA	**57,243**	**0.41**	**1.1e-07**
Stage 2 AFR	1,077	0.47	0.77
Stage 2 ASN	982	0.23	0.65
Stage 2 EUR	30,338	0.4	0.10
Stage 2 HISP	11,524	0.3	0.42
Stage 2 CPMA	**42,939**	**0.38**	**0.08**
Stage 1 + 2 CPMA	**100,182**	**0.4**	**2.3e-08**



β SNP
β Interaction
β SNP Meta-Analysis
β Interaction Meta-Analysis

Study Descriptions

AGES (Age Gene/Environment Susceptibility Reykjavik Study): The AGES Reykjavik study originally comprised a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967. A total of 19,381 people attended, resulting in a 71% recruitment rate. The study sample was divided into six groups by birth year and birth date within month. One group was designated for longitudinal follow up and was examined in all stages; another was designated as a control group and was not included in examinations until 1991. Other groups were invited to participate in specific stages of the study. Between 2002 and 2006, the AGESReykjavik study re-examined 5,764 survivors of the original cohort who had participated before in the Reykjavik Study.

ARIC (Atherosclerosis Risk in Communities): The ARIC study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792 individuals, predominantly European American and African American, aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed three additional triennial follow-up examinations, a fifth exam in 2011-2013, a sixth exam in 2016-2017, a seventh exam in 2018-2019, an eighth exam in 2020, and a ninth exam in 2022. The ARIC study has been described in detail previously:

1. 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

Baependi Heart Study (Brazil): The Baependi Heart Study, is an ongoing family-based cohort conducted in a rural town of the state of Minas Gerais. The study has enrolled approximate 2,200 individuals (over 10% of the town's adult population) and 10-year follow up period of longitudinal data. Briefly, probands were selected at random across 11 out of the 12 census districts in Baependi. After enrolment, the proband's first-degree (parents, siblings, and offspring), second-degree (half-siblings, grandparents/grandchildren, uncles/aunts, nephews/nieces, and double cousins), and third-degree (first cousins, great uncles/aunts, and great nephews/nieces) relatives, and his/her respective spouse's relatives resident both within Baependi (municipal and rural area) and surrounding towns were invited to participate. Only individuals age 18 and older were eligible to participate in the study. The study is conducted from a clinic/office in an easily accessible sector of the town, where the questionnaires were completed. A broad range of phenotypes ranging from cardiovascular, neurocognitive, psychiatric, imaging, physiologic and several layers of endophenotypes like metabolomics and lipidomics have been collected throughout the years Details about follow-up visits and available data can be found in the cohort profile paper (PMID: 18430212). DNA samples were genotyped using the Affymetrix 6.0 genechip. After quality control, the data were prephased using SHAPEIT and imputed using IMPUTE2 based on 1000 Genomes haplotypes.

BES (Beijing Eye Study): The Beijing Eye Study is a population-based study that assesses the associated and risk factors of ocular and general diseases in a Chinese population. The study was initialized in 2001 and collected data from 4439 subjects aged ≥ 40 years and living in seven communities in the Beijing area. Three of these communities were located in a rural district and four were located in an urban district. The BES was followed-up in 2006, with 3251 of the original subjects participating, and in 2011, with 2695 subjects returning for the follow-up examination.

At the examinations in 2006 and 2011, trained research staffs asked the subjects questions from a standard questionnaire providing information on the family status, level of education, income, quality of life, psychic depression, physical activity, and known major systemic diseases. Fasting blood samples were taken for measurement of concentrations of substances such as blood lipids, glucose, and glycosylated hemoglobin. Individuals were classified as self-reported non-smokers or self-reported current smokers. Alcohol consumption habits based on number of drinks per day were collected. Physical activity was assessed in questions on the number of hours per day and number of days per week spent on intensively or moderately performed sport activities, spent on walking, on riding a bicycle, and spent on sitting. All variables used in analyses were taken from examinations in 2006 or in 2011. The BES subjects were genotyped on two arrays, Illumina Human610-Quad (N = 832) and Illumina OmniExpress (N = 814).

CARDIA (Coronary Artery Risk Development in Young Adults): CARDIA is a longitudinal multicenter study with 5,115 Black and White participants 18-30 years of age at baseline, recruited from four centers in 1985-1986. The recruitment was done from the total community in Birmingham, AL; from selected census tracts in Chicago, IL and Minneapolis, MN; and from the Kaiser Permanente health plan membership in Oakland, CA. The details of the study design for the CARDIA study have been previously published.[1] Ten examinations have been completed since initiation of the study, respectively in the years 0, 2, 5, 7, 10, 15, 20, 25, 30, and 35. 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.

Age and race were self-reported at baseline using standardized questionnaires, as were use of cholesterol-lowering medication, and smoking status (current, former, or never). All participants were asked to fast for 12 hours before each clinic visit. Lipid measures were performed on plasma blood samples drawn from the antecubital vein and stored at −70° C until analyzed. Plasma total cholesterol, HDL-cholesterol, and triglyceride concentrations were measured using enzymatic methods;[2] HDL-cholesterol concentrations were measured after dextran-sulfate-magnesium precipitation of other lipoproteins.[3] LDL-cholesterol concentrations were estimated with the Friedewald equation for individuals with fasting triglyceride values less than 400 mg/dL.[4] The test-retest correlations for total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were 0.98 to 0.99.[5]

1. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hully SB, Jacobs DR Jr., Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988;41:1105–1116.

2. Warnick GR. Enzymatic methods for quantification of lipoprotein lipids. Methods Enzymol. 1986;129:101–123.

3. Warnick GR, Benderson J, Albers JJ. Dextran sulfate-Mg2+ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. Clin Chem. 1982;28:1379–1388.

4. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.

5. Gross M, Steffes M, Jacobs DR Jr., Yu X, Lewis L, Lewis CE, Loria CM. Plasma F2-isoprostanes and coronary artery calcification: the CARDIA Study. Clin Chem. 2005;51:125–131.

CHS (Cardiovascular Health Study): CHS is a population-based cohort study of risk factors for cardiovascular disease in adults 65 years of age or older conducted across four field centers (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. 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|PsyCoLaus: The CoLaus|PsyCoLaus study is a population-based cohort of 6734 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. The main aims of the study were: 1) to better understand the epidemiology of cardiovascular risk factors and diseases in the Swiss population; 2) to discover new genetic determinants of these conditions; and 3) 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 fourth one is ongoing since 2022. A detailed description of the participants' selection, inclusion criteria and methods used can be found in the following manuscripts:

1. 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.

2. Preisig M, Waeber G, Vollenweider P, Bovet P, Rothen S, Vandeleur C, et al. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. BMC psychiatry. 2009;9:9. PMID: 19292899 PMCID: PMC2667506 DOI: 10.1186/1471-244X-9-9.

DR's EXTRA (Dose-Responses to Exercise Training): The Dose-Responses to Exercise Training (DR's EXTRA) Study is a 4-year RCT on the effects of regular physical exercise and

healthy diet on endothelial function, atherosclerosis and cognition in a randomly selected population sample (n=3000) of Eastern Finnish men and women, identified from the national population register, aged 55-74 years. Of the eligible sample, 1410 individuals were randomized into one of the 6 groups: aerobic exercise, resistance exercise, diet, combined aerobic exercise and diet, combined resistance exercise and diet, or reference group following baseline assessments. During the four year intervention the drop-out rate was 15%.

ERF (Erasmus Rucphen Family study): Erasmus Rucphen Family is a family based study that includes inhabitants of a genetically isolated community in the South-West of the Netherlands, studied as part of the Genetic Research in Isolated Population (GRIP) program.[1,2] The goal of the study is to identify the risk factors in the development of complex disorders. Study population includes approximately 3,000 individuals who are living descendants of 22 couples who lived in the isolate between 1850 and 1900 and had at least six children baptized in the community church. All data were collected between 2002 and 2005. All participants gave informed consent, and the Medical Ethics Committee of the Erasmus University Medical Centre approved the study.

1. Pardo, Luba M., et al. "The effect of genetic drift in a young genetically isolated population." Annals of human genetics 69.3 (2005): 288-295.

2. Aulchenko, Yurii S., et al. "Linkage disequilibrium in young genetically isolated Dutch population." European Journal of Human Genetics 12.7 (2004): 527.

FHS (Framingham Heart Study): FHS began in 1948 with the recruitment of an original cohort of 5,209 men and women (mean age 44 years; 55 percent women). In 1971 a second generation of study participants was enrolled; this cohort (mean age 37 years; 52% women) consisted of 5,124 children and spouses of children of the original cohort. A third generation cohort of 4,095 children of offspring cohort participants (mean age 40 years; 53 percent women) was enrolled in 2002-2005 and are seen every 4 to 8 years. Details of study designs for the three cohorts are summarized elsewhere. At each clinic visit, a medical history was obtained with a focus on cardiovascular content, and participants underwent a physical examination including measurement of height and weight from which BMI was calculated. For this study, lipid measurements were used from the first exam of the 2nd generation (1971-1975) and the 3rd generation (2002-2005) cohorts. Fasting levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using standard enzymatic methods in accordance with LRC protocols. LDL cholesterol was calculated using the Friedewald formula.

GeneSTAR (Genetic Studies of Atherosclerosis Risk): GeneSTAR is a family-based prospective study of more than 4000 participants begun in 1983 to determine phenotypic and genetic causes of premature cardiovascular disease. Families were identified from 1983-2006 from probands with a premature coronary disease event prior to 60 years of age who were identified at the time of hospitalization in any of 10 hospitals in the Baltimore, Maryland area. Their apparently healthy 30-59 year old siblings without known coronary disease were recruited and screened between 1983 and 2006. From 2003-2006, adult offspring over 21 years of age of all participating siblings and probands, as well as the coparents of the offspring were recruited and screened. Genotyping was performed in 3,232 participants on the Illumina 1Mv1_c platform. Demographic information including education level was self-reported by participants. Medical history including medication use was assessed by the study nurse or physician.

GENOA (Genetic Epidemiology Network of Arteriopathy): GENOA is one of four networks in the NHLBI Family-Blood Pressure Program (FBPP). [The FBPP Investigators, 2002; Daniels et al., 2004] GENOA's long-term objective is to elucidate the genetics of target organ complications of hypertension, including both atherosclerotic and arteriosclerotic complications involving the heart, brain, kidneys, and peripheral arteries. The longitudinal GENOA Study recruited European-American and African-American sibships with at least 2 individuals with clinically diagnosed essential hypertension before age 60 years. All other members of the sibship were invited to participate regardless of their hypertension status. Participants were diagnosed with hypertension if they had either 1) a previous clinical diagnosis of hypertension by a physician with current anti-hypertensive treatment, or 2) an average systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg based on the second and third readings at the time of their clinic visit. Exclusion criteria were secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes mellitus, or active malignancy. During the first exam (1995-2000), 1,583 European Americans from Rochester, MN and 1,854 African Americans from Jackson, MS were examined. Between 2000 and 2005, 1,241 of the European Americans and 1,482 of the African Americans returned for a second examination. In a GENOA follow-up study (2009-2011), 752 African American participated in a third examination. Depression was only evaluated in the third examination; thus, the analysis for this project includes African American participants who participated in this examination. Because African-American probands for GENOA were recruited through the Atherosclerosis Risk in Communities (ARIC) Jackson field center participants, we excluded ARIC participants from GENOA analysis.

1. The FBPP Investigators. Multi-center genetic study of hypertension: The Family Blood Pressure Program (FBPP). Hypertension 2002;39:3-9. PubMed PMID: 11799070.

2. Daniels PR, Kardia SL, Hanis CL, Brown CA, Hutchinson R, Boerwinkle E, Turner ST; Genetic Epidemiology Network of Arteriopathy study. Familial aggregation of hypertension treatment and control in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. Am J Med. 2004;116:676-81. PubMed PMID: 15121494.

HANDLS (Healthy Aging in Neighborhoods of Diversity across the Life Span): HANDLS is a community-based, longitudinal epidemiologic study examining the influences of race and socioeconomic status (SES) on the development of age-related health disparities among a sample of socioeconomically diverse African Americans and whites. This unique study will assess over a 20-year period physical parameters and also evaluate genetic, biologic, demographic, and psychosocial, parameters of African American and white participants in higher and lower SES to understand the driving factors behind persistent black-white health disparities in overall longevity, cardiovascular disease, and cognitive decline. The study recruited 3,722 participants from Baltimore, MD with a mean age of 47.7 years, 2,200 African Americans and 1,522 whites, with 41% reporting household incomes below the 125% poverty delimiter.

Genotyping was done on a subset of self-reporting African American participants by the Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health (NIH). A larger genotyping effort included a small subset of self-reporting European ancestry samples. This research was supported by the Intramural Research Program of the NIH, NIA and the National Center on Minority Health and Health Disparities.

HCHS/SOL (Hispanic Community Health Study/ Study of Latinos): The HCHS/SOL is a community-based cohort study of 16,415 self-identified Hispanic/Latino persons aged 18–74

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

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

Genotyping: Genotyping was performed by the Center for Inherited Disease Research (CIDR) using the Illumina Human1M-Duo BeadChip system. Samples were excluded from the dataset for the reasons of sample failure, genotypic sex mismatch, and first-degree relative of an included individual based on genotype data. Genotyping was successful in 1663 Caucasians. Analysis was restricted to SNPs with minor allele frequency ≥ 1%, call rate ≥97% and HWE p≥10-6. Genotypes were available on 914,263 high quality SNPs for imputation based on the HapMap CEU (release 22, build 36) using the MACH software (version 1.0.16). A total of 2,543,888 imputed SNPs were analyzed for association with vitamin D levels.

Association analysis: Linear regression models were used to generate cohort-specific residuals of naturally log transformed vitamin D levels adjusted for age, sex, BMI and season defined as summer (June-August), fall (September-November), winter (December to February) and spring (March to May) standardized to have mean 0 and variance of 1. Association between the additively coded SNP genotypes and the vitamin D residuals standardized was assessed using linear regression models. For imputed SNPs, expected number of minor alleles (i.e. dosage) was used in assessing association with the vitamin D residuals.

HRS (Health & Retirement Study): The Health and Retirement Study (HRS) is a longitudinal survey of a representative sample of Americans over the age of 50. The current sample is over 26,000 persons in 17,000 households. Respondents are interviewed every two years about

income and wealth, health and use of health services, work and retirement, and family connections. DNA was extracted from saliva collected during a face-to-face interview in the respondents' homes. These data represent respondents who provided DNA samples and signed consent forms in 2006, 2008, and 2010. Respondents were removed if they had missing genotype or phenotype data.

1. Juster, F. T., Suzman, R. (1995). An Overview of the Health and Retirement Study, Journal of Human Resources 30:Suppl: S7-S56.

2. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort Profile: the Health and Retirement Study (HRS). Int. J. Epidemiol. 2014; 43 (2): 576-585. PMID: 24671021.

3. Crimmins, E.M., Guyer H., Langa K.M., Ofstedal M.B., Wallace R.B., and Weir D.R. (2008). Documentation of Physical Measures, Anthropometrics and Blood Pressure in the Health and Retirement Study. HRS Documentation Report DR-011. http://hrsonline.isr.umich.edu/sitedocs/userg/dr-011.pdf

JHS (Jackson Heart Study): The Jackson Heart Study is a longitudinal, community-based observational cohort study investigating the role of environmental and genetic factors in the development of cardiovascular disease in African Americans. Between 2000 and 2004, a total of 5,306 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):438-455.

2. Taylor HA, Jr., Wilson JG, Jones DW, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. Ethn Dis 2005; 15:S6-17.

3. Fuqua SR, Wyatt SB, Andrew ME, et al. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. Ethn Dis 2005; 15:S6-29.

KORA (Cooperative Health Research in the Augsburg Region): The KORA study is a series of independent population-based epidemiological surveys of participants living in the region of Augsburg, Southern Germany. All survey participants are residents of German nationality identified through the registration office and were examined in 1994/95 (KORA S3) and 1999/2001 (KORA S4). In the KORA S3 and S4 studies 4,856 and 4,261 subjects have been examined implying response rates of 75% and 67%, respectively. 3,006 subjects participated in a 10-year follow-up examination of S3 in 2004/05 (KORA F3), and 3080 of S4 in 2006/2008

(KORA F4). The age range of the participants was 25 to 74 years at recruitment. Informed consent has been given by all participants. The study has been approved by the local ethics committee. Individuals for genotyping in KORA F3 and KORA F4 were randomly selected and these genotypes are taken for the analysis of the phenotypes in KORA S3 and KORA S4.

LBC1936 (Lothian Birth Cohort 1936): LBC1936 consists of 1091 (548 male) relatively healthy individuals who underwent cognitive and medical testing at a mean age of 69.6 years (SD = 0.8). They were born in 1936, most took part in the Scottish Mental Survey of 1947, and almost all lived independently in the Lothian region of Scotland.[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 (Netherlands Biobank): Lifelines (https://lifelines.nl/) is a multi-disciplinary prospective population-based cohort study using a unique three-generation design to examine the health and health-related behaviors of 167,729 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 and complex genetics. 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. 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-biobank.com. (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 group authors (genetics): Behrooz Z Alizadeh,[1] H Marike Boezen,[1] Lude Franke,[2] Pim van der Harst,[3] Gerjan Navis,[4] Marianne Rots,[5] Harold Snieder,[1] Morris Swertz,[2] Bruce HR Wolffenbuttel,[6] Cisca Wijmenga.[2]

[1] Department of Epidemiology, University of Groningen, University Medical Center Groningen, The Netherlands; [2] Department of Genetics, University of Groningen, University Medical Center Groningen, The Netherlands; [3] Department of Cardiology, University of Groningen, University Medical Center Groningen, The Netherlands; [4] Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Center Groningen, The Netherlands; [5] Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, The Netherlands; [6] Department of Endocrinology, University of Groningen, University Medical Center Groningen, The Netherlands

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

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.

NEO (The Netherlands Epidemiology of Obesity study): The NEO was designed for extensive phenotyping to investigate pathways that lead to obesity-related diseases. The NEO study is a population-based, prospective cohort study that includes 6,671 individuals aged 45–65 years, with an oversampling of individuals with overweight or obesity. At baseline, information on demography, lifestyle, and medical history have been collected by questionnaires. In addition, samples of 24-h urine, fasting and postprandial blood plasma and serum, and DNA were collected. Genotyping was performed using the Illumina HumanCoreExome chip, which was subsequently imputed to the 1000 genome reference panel. Participants underwent an extensive physical examination, including anthropometry, electrocardiography, spirometry, and measurement of the carotid artery intima-media thickness by ultrasonography. In random subsamples of participants, magnetic resonance imaging of abdominal fat, pulse wave velocity of the aorta, heart, and brain, magnetic resonance spectroscopy of the liver, indirect calorimetry, dual energy X-ray absorptiometry, or accelerometry measurements were performed. The collection of data started in September 2008 and completed at the end of September 2012. Participants are currently being followed for the incidence of obesity-related diseases and mortality.

NESDA (Netherlands Study of Depression and Anxiety): NESDA is a multi-center study designed to examine the long-term course and consequences of depressive and anxiety disorders (http://www.nesda.nl)[1]. NESDA included both individuals with depressive and/or anxiety disorders and controls without psychiatric conditions. Inclusion criteria were age 18-65 years and self-reported western European ancestry while exclusion criteria were not being fluent in Dutch and having a primary diagnosis of another psychiatric condition (psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe substance use disorder).

1. Penninx, B.W. et al. Cohort profile of the longitudinal Netherlands Study of Depression and Anxiety (NESDA) on etiology, course and consequences of depressive and anxiety disorders. J Affect Disord. 2021 May 15;287:69-77.

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

RS (Rotterdam Study): The Rotterdam Study is a prospective, population-based cohort study among individuals living in the well-defined Ommoord district in the city of Rotterdam in The Netherlands.[1] The aim of the study is to determine the occurrence of cardiovascular, neurological, ophthalmic, endocrine, hepatic, respiratory, and psychiatric diseases in elderly people. The cohort was initially defined in 1990 among 7,983 persons, aged 55 years and older, who underwent a home interview and extensive physical examination at the baseline and during follow-up rounds every 3-4 years (RS-I). Cohort was extended in 2000/2001 (RS-II, 3,011 individuals aged 55 years and older) and 2006/2008 (RS-III, 3,932 subjects, aged 45 and older; since 2016, the cohort was expanded to include persons aged 40 years and older).[1] The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

1. Ikram, M.A., Kieboom, B.C., Brouwer, W.P. et al. The Rotterdam Study. Design update and major findings between 2020 and 2024. Eur J Epidemiol (2024). https://doi.org/10.1007/s10654-023-01094

SP2-1M / SP2-610 (Singapore Prospective Study Program): The SP2 (Singapore Prospective Study Program) is a population-based study of diabetes and cardiovascular disease in Singapore. It first surveyed subjects (Chinese, Malay and Indian) from four cross-sectional studies that were conducted in Singapore between 1982 and 1998. Subjects were between the ages of 24-95 years and represented a random sample of the Singapore population. Subjects

were re-visited between 2003 and 2007. Among the 10,747 individuals who were eligible, 5,157 subjects completed a questionnaire and the subsequent clinical examinations. Of the 5,517 subjects, 2,434 Chinese were genotyped on a combination of Illumina 610, 1M and 550 arrays. Fasting HDL-C, TC and TG were measured by an automated analyzer autoanalyzer (ADVIA 2400, Bayer Diagnostics). LDL-C was calculated from Friedewald formula. Data from this revisit were utilized for this study.

1. Nang EE, Khoo CM, Tai ES, Lim SC, Tavintharan S, Wong TY, Heng D, Lee J. Is there a clear threshold for fasting plasma glucose that differentiates between those with and without neuropathy and chronic kidney disease?: the Singapore Prospective Study Program. Am J Epidemiol. 2009 Jun 15;169(12):1454-62. doi: 10.1093/aje/kwp076. Epub 2009 Apr 30. PMID: 19406920.

2. Tan KHX, Tan LWL, Sim X, Tai ES, Lee JJ, Chia KS, van Dam RM. Cohort Profile: The Singapore Multi-Ethnic Cohort (MEC) study. Int J Epidemiol. 2018 Jun 1;47(3):699-699j. doi: 10.1093/ije/dyy014. PMID: 29452397.

SHIP (Study of Health in Pomerania): The Study of Health In Pomerania (SHIP) is a prospective longitudinal population-based cohort study in Mecklenburg-West Pomerania assessing the prevalence and incidence of common diseases and their risk factors (PMID: 20167617). SHIP encompasses the two independent cohorts SHIP-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 centre for a computer-assisted personal interviews and extensive physical examinations. The study protocol was approved by the medical ethics committee of the University of Greifswald. Oral and written informed consents was obtained from each of the study participants.

Genome-wide SNP-typing was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 or the Illumina Human Omni 2.5 array (SHIP-TREND samples). Array processing was carried out in accordance with the manufacturer's standard recommendations. Genotypes were determined using GenomeStudio Genotyping Module v1.0 (GenCall) for SHIP-TREND and the Birdseed2 clustering algorithm for SHIP-START. Imputation of genotypes in SHIP-START and SHIP-TREND was performed with the software IMPUTE v2.2.2 based on 1000 Genomes release March 2012.

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

The Shanghai Men's Health Study (SMHS) is an ongoing population-based cohort study of 61,480 Chinese men who were aged between 40 and 74 years, were free of cancer at enrollment, and lived in urban Shanghai, China; 45,766 (74.4%) provided a blood samples. Recruitment for the SMHS was initiated in 2002 and completed in 2006. The self-administered questionnaire includes information on demographic characteristics, disease and surgery histories, personal habits (such as cigarette smoking, alcohol consumption, tea drinking, and ginseng use), residential history, occupational history, and family history of cancer.

Genotyping and imputation: Genomic DNA was extracted from buffy coats by using a Qiagen DNA purification kit (Valencia, CA) or Puregene DNA purification kit (Minneapolis, MN) according to the manufacturers' instructions and then used for genotyping assays. The GWAS genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affy6.0) platform or Illumina 660, following manufacturers' protocols. After sample quality control, we exclude SNPs with 1) MAF <0.01; 2) call rate <95%; 2) bad genotyping cluster; and 3) concordance rate <95% among duplicated QC samples. Genotypes were imputed using the program MACH (http://www.sph.umich.edu/csg/abecasis/MACH/download/), which determines the probable distribution of missing genotypes conditional on a set of known haplotypes, while simultaneously estimating the fine-scale recombination map. Phased autosome SNP data from HapMap Phase II Asians (release 22) were used as the reference. To test for associations between the imputed SNP data with BMI, linear regression (additive model) was used, in which SNPs were represented by the expected allele count, an approach that takes into account the degree of uncertainty of genotype imputation (http://www.sph.umich.edu/csg/abecasis/MACH/download/).

The lipid profiles were measured at Vanderbilt Lipid Laboratory. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured using an ACE Clinical Chemistry System (Alfa Wassermann, Inc, West Caldwell, NJ). Low-density lipoprotein (LDL) cholesterol levels were calculated by using the Friedwald equation. The levels of LDL cholesterol were directly measured using an ACE Clinical Chemistry System for subjects with TG levels ≥ 400 mg/dL. Fasting status was defined as an interval between the last meal and blood draw of 8 hours or longer.

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

WHI (Women's Health Initiative): WHI is a long-term national health study that focuses on strategies for preventing common diseases such as heart disease, cancer and fracture in postmenopausal women. A total of 161,838 women aged 50–79 years old were recruited from 40 clinical centers in the US between 1993 and 1998. WHI consists of an observational study, two clinical trials of postmenopausal hormone therapy (HT, estrogen alone or estrogen plus progestin), a calcium and vitamin D supplement trial, and a dietary modification trial. Study recruitment and exclusion criteria have been described previously. 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 lists, 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.

The genome wide association study (GWAS) non-overlapping samples are composed of a case-control study (WHI Genomics and Randomized Trials Network – GARNET, which included all coronary heart disease, stroke, venous thromboembolic events and selected diabetes cases that happened during the active intervention phase in the WHI HT clinical trials and aged matched controls), women selected to be "representative" of the HT trial (mostly younger white HT subjects that were also enrolled in the WHI memory study - WHIMS) and the WHI SNP Health Association Resource (WHI SHARe), a randomly selected sample of 8,515 African American and 3,642 Hispanic women from WHI. GWAS was performed using Affymetrix 6.0 (WHI-SHARe), HumanOmniExpressExome-8v1_B (WHIMS), Illumina HumanOmni1-Quad v1-0 B (GARNET). Extensive quality control (QC) of the GWAS data included alignment (“flipping”) to the same reference panel, imputation to the 1000G data (using the recent reference panel - v3.20101123), identification of genetically related individuals, and computations of principal components (PCs) using methods developed by Price et al. (using EIGENSOFT software 53), and finally the comparison with self-reported ethnicity. After QC and exclusions from analysis protocol, the number of women included in analysis is 4,423 whites for GARNET, 5,202 white for WHIMS, 7,919 for SHARe African American and 3,377 for SHARe Hispanics.

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

Study Acknowledgments

Infrastructure for the CHARGE Consortium is supported in part by the National Heart, Lung, and Blood Institute grant R01HL105756. Infrastructure for the Gene-Lifestyle Working Group in Phase I was supported by the National Heart, Lung, and Blood Institute grant R01HL118305.

AGES (Age Gene/Environment Susceptibility Reykjavik Study): This study has been funded by NIH contract N01-AG012100, HSSN271201200022C, the NIA Intramural Research Program, an Intramural Research Program Award (ZIAEY000401) from the National Eye Institute, an award from the National Institute on Deafness and Other Communication Disorders (NIDCD) Division of Scientific Programs (IAA Y2-DC_1004-02), Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study.

ARIC (Atherosclerosis Risk in Communities) Study: The ARIC study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (75N92022D00001, 75N92022D00002, 75N92022D00003, 75N92022D00004, 75N92022D00005). The authors thank the staff and participants of the ARIC study for their important contributions. Funding was also supported by R01HL087641 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

Baependi Heart Study (Brazil): The Baependi Heart Study was supported by Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) (Grant 2013/17368-0), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Hospital Samaritano Society (Grant 25000.180.664/2011-35), through Ministry of Health to Support Program Institutional Development of the Unified Health System (SUS-PROADI).

BES (Beijing Eye Study): The Beijing Eye Study has been funded by the National Natural Science Foundation of China (grant 81170890, 81570835) and the Beijing Municipal of Health Reform and Development Project (grant 2019-4).

CARDIA (Coronary Artery Risk Development in Young Adults): The Coronary Artery Risk Development in Young Adults Study (CARDIA) is supported by contracts 75N92023D00002, 75N92023D00003, 75N92023D00004, 75N92023D00005, and 75N92023D00006 from the National Heart, Lung, and Blood Institute (NHLBI). Genotyping was funded as part of the NHLBI Candidate-gene Association Resource (N01-HC-65226) and the NHGRI Gene Environment Association Studies (GENEVA) (U01-HG004729, U01-HG04424, and U01-HG004446). This manuscript has been reviewed by CARDIA for scientific content.

CHS (Cardiovascular Health Study): This Cardiovascular Health Study (CHS) research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, HHSN268200960009C, HHSN268201800001C N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, 75N92021D00006; and NHLBI grants U01HL080295, U01HL130114, R01HL087652, R01HL105756, R01HL103612, R01HL085251,

and R01HL120393 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CoLaus|PsyCoLaus: The CoLaus|PsyCoLaus study was supported by unrestricted research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (grants 3200B0–105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468, 33CS30-148401, 33CS30_177535, 3247730_204523 and 320030_220190) and the Swiss Personalized Health Network (grant 2018DRI01).

The above first six SNF grants were attributed to Martin Preisig, the seventh to Julien Vaucher and the eight to Carole Clair. One grant from GlaxoSmithKline (no number) was attributed to Martin Preisig for PsyCoLaus, a second grant from GlaxoSmithKline (no number) was attributed to Gérard Waeber and Peter Vollenweider for CoLaus. The grant from the Faculty of Biology and Medicine of Lausanne (no number) was attributed to Peter Vollenweider and the grant from the Swiss Personalized Health Network was attributed to a consortium. The authors would like to express their gratitude to the participants in the Lausanne CoLaus|PsyCoLaus study.

DR's EXTRA (Dose-Responses to Exercise Training): The study was supported by grants from Ministry of Education and Culture of Finland (722 and 627; 2004-2010); Academy of Finland (102318, 104943, 123885, 211119); European Commission FP6 Integrated Project (EXGENESIS), LSHM-CT-2004-005272; City of Kuopio; Juho Vainio Foundation; Finnish Diabetes Association; Finnish Foundation for Cardiovascular Research; Kuopio University Hospital; Päivikki and Sakari Sohlberg Foundation; Social Insurance Institution of Finland 4/26/2010.

ERF (Erasmus Rucphen Family study): The ERF study as a part of EUROSPAN (European Special Populations Research Network) was supported by European Commission FP6 STRP grant number 018947 (LSHG-CT-2006-01947) and also received funding from the European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F4-2007-201413 by the European Commission under the programme "Quality of Life and Management of the Living Resources" of 5th Framework Programme (no. QLG2-CT-2002-01254). High-throughput analysis of the ERF data was supported by joint grant from Netherlands Organisation for Scientific Research and the Russian Foundation for Basic Research (NWO-RFBR 047.017.043). We are grateful to all study participants and their relatives, general practitioners and neurologists for their contributions and to P. Veraart for her help in genealogy, J. Vergeer for the supervision of the laboratory work, P. Snijders for his help in data collection and E.M. van Leeuwen for genetic imputation.

FHS (Framingham Heart Study): This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual

input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract Nos. N01-HC-25195 and HHSN268201500001I) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. This research was partially supported by grant R01-DK089256 from the National Institute of Diabetes and Digestive and Kidney Diseases (MPIs: Ingrid B. Borecki, L. Adrienne Cupples, Kari North).

GeneSTAR (Genetic Studies of Atherosclerosis Risk): GeneSTAR was supported by National Institutes of Health grants from the National Heart, Lung, and Blood Institute (HL49762, HL58625, HL071025, U01 HL72518, HL087698, HL092165, HL099747, and K23HL105897), National Institute of Nursing Research (NR0224103), National Institute of Neurological Disorders and Stroke (NS062059), and by grants from the National Center for Research Resources to the Johns Hopkins General Clinical Research Center (M01-RR000052) and the Johns Hopkins Institute for Clinical & Translational Research (UL1 RR 025005).

GENOA (Genetic Epidemiology Network of Arteriopathy): Support for GENOA was provided by the National Heart, Lung and Blood Institute (HL119443, HL118305, HL054464, HL054457, HL054481, HL071917, HL085571, and HL087660) of the National Institutes of Health. Genotyping was performed at the Mayo Clinic (Stephen T. Turner, MD, Mariza de Andrade PhD, Julie Cunningham, PhD). We thank Eric Boerwinkle, PhD and Megan L. Grove from the Human Genetics Center and Institute of Molecular Medicine and Division of Epidemiology, University of Texas Health Science Center, Houston, Texas, USA for their help with genotyping. We would also like to thank the families that participated in the GENOA study.

HANDLS (Healthy Aging in Neighborhoods of Diversity across the Life Span): The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study was supported by the Intramural Research Program of the NIH, National Institute on Aging and the National Center on Minority Health and Health Disparities (project # Z01-AG000513 and human subjects protocol number 09-AG-N248). Data analyses for the HANDLS study utilized the high-performance computational resources of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, MD. (http://biowulf.nih.gov; http://hpc.nih.gov)).

HCHS/SOL (Hispanic Community Health Study/ Study of Latinos): The baseline examination of HCHS/SOL was supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (N01-HC65233), University of Miami (N01-HC65234), Albert Einstein College of Medicine (N01-HC65235), Northwestern University (N01-HC65236), and San Diego State University (N01-HC65237). The National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Neurological Disorders and Stroke, and NIH Office of Dietary Supplements additionally contributed funding to HCHS/SOL. The Genetic Analysis Center at the University of Washington was supported by NHLBI and NIDCR contracts (HHSN268201300005C AM03 and MOD03). Additional analysis support was provided by 1R01DK101855-01 and 13GRNT16490017. Genotyping was also supported by National Center for Advancing Translational Sciences UL1TR000124 and NIDDK DK063491 to the

Southern California Diabetes Endocrinology Research Center. This research was also supported in part by the Intramural Research Program of the NIDDK, contract no. HHSB268201200054C, and Illumina.

Health ABC (Health, Aging, and Body Composition): Health ABC was funded by the National Institutes of Aging. This research was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106. The GWAS was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

HRS (Health & Retirement Study): HRS is supported by the National Institute on Aging (NIA U01AG009740 and R03 AG046389). Genotyping was funded separately by NIA (RC2 AG036495, RC4 AG039029). Our genotyping was conducted by the NIH Center for Inherited Disease Research (CIDR) at Johns Hopkins University. Genotyping quality control and final preparation of the data were performed by the Genetics Coordinating Center at the University of Washington.

JHS (Jackson Heart Study): The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staffs and participants of the JHS.

KORA (Cooperative Health Research in the Augsburg Region): The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Furthermore, KORA is funded by the Bavarian State Ministry of Health and Care through the research project DigiMed Bayern (www.digimed-bayern.de).**LBC1936 (Lothian Birth Cohort 1936):** We thank the LBC1936 cohort participants and team members who contributed to these studies. Phenotype collection was supported by Age UK (The Disconnected Mind project). Genotyping was funded by the BBSRC (BB/F019394/1). The work was undertaken by The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1). Funding from the BBSRC and Medical Research Council (MRC) is gratefully acknowledged. We gratefully acknowledge the contribution of Lothian Birth Cohort co-author Professor John M. Starr, who died prior to the publication of this manuscript.

Lifelines (Netherlands Biobank): The Lifelines initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Center Groningen (UMCG), Groningen University and the Provinces in the North of the Netherlands (Drenthe, Friesland, Groningen). The generation and management of GWAS genotype data for the Lifelines Cohort Study is supported by the Netherlands Organization of Scientific Research NWO (grant 175.010.2007.006), the Economic Structure Enhancing Fund (FES) of the Dutch government, the Ministry of Economic Affairs, the Ministry of Education,

Culture and Science, the Ministry for Health, Welfare and Sports, the Northern Netherlands Collaboration of Provinces (SNN), the Province of Groningen, University Medical Center Groningen, the University of Groningen, Dutch Kidney Foundation and Dutch Diabetes Research Foundation.

The authors wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants.

MESA (Multi-Ethic Study of Atherosclerosis) and the **MESA SHARe** are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420, UL1TR001881, DK063491, and R01HL105756. Funding for SHARe genotyping was provided by NHLBI Contract N02-HL-64278. Genotyping was performed at Affymetrix (Santa Clara, California, USA) and the Broad Institute of Harvard and MIT (Boston, Massachusetts, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutes can be found at http://www.mesa-nhlbi.org.

NEO (The Netherlands Epidemiology of Obesity study): The authors of the NEO study thank all individuals who participated in the Netherlands Epidemiology in Obesity study, all participating general practitioners for inviting eligible participants and all research nurses for collection of the data. We thank the NEO study group, Petra Noordijk, Pat van Beelen and Ingeborg de Jonge for the coordination, lab and data management of the NEO study. The genotyping in the NEO study was supported by the Centre National de Génotypage (Paris, France), headed by Jean-Francois Deleuze. The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Center, and by the Leiden University, Research Profile Area Vascular and Regenerative Medicine. Dennis Mook-Kanamori is supported by Dutch Science Organization (ZonMW-VENI Grant 916.14.023).

NESDA (Netherlands Study of Depression and Anxiety): Funding was obtained from the Netherlands Organization for Scientific Research (Geestkracht program grant 10-000-1002); the Center for Medical Systems Biology (CSMB, NWO Genomics), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL), VU University's Institutes for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam, University Medical Center Groningen, Leiden University Medical Center, National Institutes of Health (NIH, R01D0042157-01A, MH081802, Grand Opportunity grants 1RC2 MH089951 and 1RC2 MH089995). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health.Computing was supported by BiG Grid, the Dutch e-Science Grid, which is financially supported by NWO.

Pelotas Birth Cohort Study (The 1982 Pelotas Birth Cohort Study, Brazil): The 1982 Pelotas Birth Cohort Study is conducted by the Postgraduate Program in Epidemiology at Universidade Federal de Pelotas with the collaboration of the Brazilian Public Health Association (ABRASCO). From 2004 to 2013, the Wellcome Trust supported the study. The International Development

Research Center, World Health Organization, Overseas Development Administration, European Union, National Support Program for Centers of Excellence (PRONEX), the Brazilian National Research Council (CNPq), and the Brazilian Ministry of Health supported previous phases of the study.

Genotyping of 1982 Pelotas Birth Cohort Study participants was supported by the Department of Science and Technology (DECIT, Ministry of Health) and National Fund for Scientific and Technological Development (FNDCT, Ministry of Science and Technology), Funding of Studies and Projects (FINEP, Ministry of Science and Technology, Brazil), Coordination of Improvement of Higher Education Personnel (CAPES, Ministry of Education, Brazil).

RS (Rotterdam Study): The Rotterdam Study is supported by the Erasmus MC University Medical Center and Erasmus University Rotterdam; The Netherlands Organisation for Scientific Research (NWO); The Netherlands Organisation for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); The Netherlands Genomics Initiative (NGI); the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. The contribution of inhabitants, general practitioners and pharmacists of the Ommoord district to the Rotterdam Study is gratefully acknowledged. The contributions to the Management Team specifically and the Rotterdam Study at large of the following persons are pivotal to the daily operations of the study and highly appreciated: Jacobus Lubbe, Gabriëlle Bakker, Eric Neeleman, Jeannette Vergeer, Anneke Korving, Pauline van Wijngaarden, Jolande Verkroost – van Heemst, Silvan Licher, and Isabel van der Velpen.

The generation and management of GWAS genotype data for the Rotterdam Study was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. The GWAS datasets are supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA), project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera, Marjolein Peters and Carolina Medina-Gomez for their help in creating the GWAS database, and Karol Estrada, Yurii Aulchenko and Carolina Medina-Gomez for the creation and analysis of imputed data.

SP2 (Singapore Prospective Study Program): The SP2 study is supported by individual research and clinical scientist award schemes from the National Medical Research Council (NMRC) and the Biomedical Research Council (BMRC) of Singapore, the Singapore Ministry of Health, National University of Singapore and National University Health System, Singapore. The Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore provided services for genotyping.

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

Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg- West Pomerania. The University of Greifswald is a member of the 'Center of Knowledge Interchange' program of the Siemens AG.

SWHS/SMHS (Shanghai Women's Health Study/ Shanghai Men's Health Study): We thank all the individuals who took part in these studies and all the researchers who have enabled this work to be carried out. The Shanghai Women's Health Study and the Shanghai Men's Health Study are supported by research grants UM1CA182910 and UM1CA173640 from the U.S. National Cancer Institute, respectively.

TRAILS (TRacking Adolescents' Individual Lives Survey): TRAILS is a collaborative project involving various departments of the University Medical Center and University of Groningen, the University of Utrecht, the Radboud University Medical Center, and the Parnassia Psychiatric Institute, all in the Netherlands. TRAILS has been financially supported by grants from the Netherlands Organization for Scientific Research NWO (Medical Research Council program grant GB-MW 940-38-011; ZonMW Brainpower grant 100-001-004; ZonMw Risk Behavior and Dependence grant 60-60600-97-118; ZonMw Culture and Health grant 261-98-710; Social Sciences Council medium-sized investment grants GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council project grants GB-MaGW 452-04-314 and GB-MaGW 452-06-004; ZonMw Longitudinal Cohort Research on Early Detection and Treatment in Mental Health Care grant 636340002; NWO large-sized investment grant 175.010.2003.005; NWO Longitudinal Survey and Panel Funding 481-08-013 and 481-11-001; NWO Vici 016.130.002, 453-16-007/2735, and Vi.C.191.021; NWO Gravitation 024.001.003), the Dutch Ministry of Justice (WODC), the European Science Foundation (EuroSTRESS project FP-006), the European Research Council (ERC-2017-STG-757364 and ERC-CoG-2015-681466), Biobanking and Biomolecular Resources Research Infrastructure BBMRI-NL (CP 32), the participating universities, and Accare Centre for Child and Adolescent Psychiatry. Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003) along with a supplement from the Dutch Brain Foundation.

We are grateful to everyone who participated in this research or who worked on this project to make it possible.

WHI (Women's Health Initiative): The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C." The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: https://www-whi-org.s3.us-west-2.amazonaws.com/wp-content/uploads/WHI-Investigator-Long-List.pdf

YFS (The Cardiovascular Risk in Young Finns Study): The Young Finns Study has been financially supported by the Academy of Finland: grants 356405, 322098, 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117797 (Gendi), and 141071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research ;

Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Diabetes Research Foundation of Finnish Diabetes Association; EU Horizon 2020 (grant 755320 for TAXINOMISIS and grant 848146 for To Aition); European Research Council (grant 742927 for MULTIEPIGEN project); Tampere University Hospital Supporting Foundation, Finnish Society of Clinical Chemistry, the Cancer Foundation Finland, and pBETTER4U_EU (Preventing obesity through Biologically and bEhaviorally Tailored inTERventions for you; project number: 101080117).

We thank the teams that collected data at all measurement time points; the persons who participated as both children and adults in these longitudinal studies; and biostatisticians Irina Lisinen, Johanna Ikonen, Noora Kartiosuo, Ville Aalto, and Jarno Kankaanranta for data management and statistical advice.