Multi-ancestry genome-wide gene-smoking interaction study of 387,272 individuals identifies new loci associated with serum lipids

Supplementary Material

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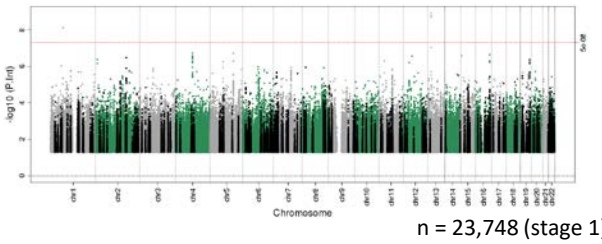
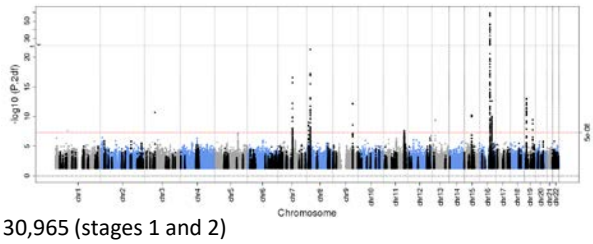
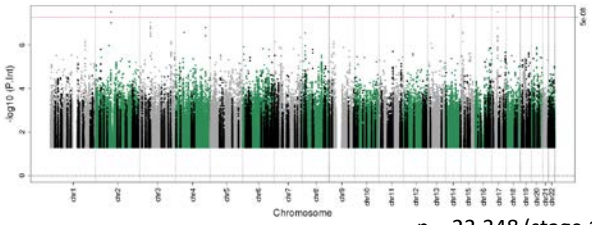
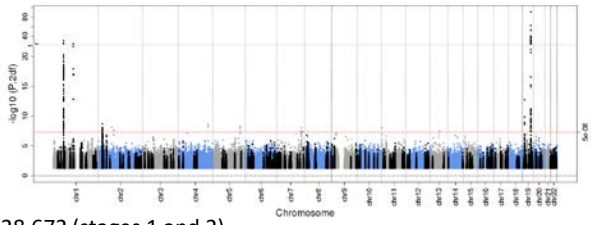
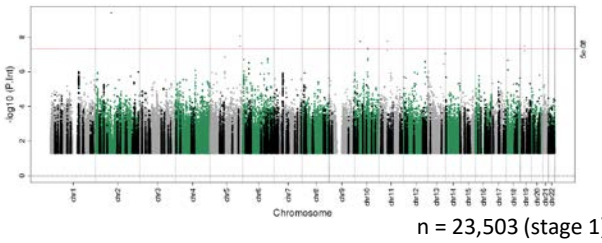
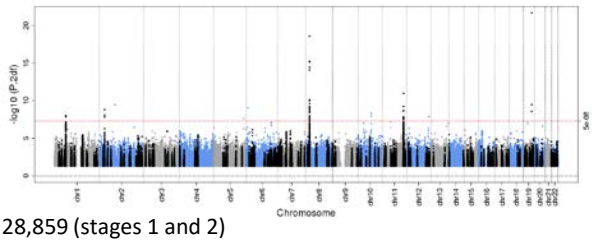
Supplementary Figure 1

Manhattan Plots. Shown are the genome-wide results for linear regression models of lipids traits that include both the variant and a variant × smoking status interaction term, adjusted for age, sex, PCs, study-specific covariates (as necessary) and smoking status. Shown are the p values for the 1df interaction test and the 2df joint test of interaction and main effect. Points shaded in black are within 1 MB of known lipids loci. Plots are drawn from genome-wide stage 1 results with stage 1 and 2 results added where available (i.e. for those variants that were included in follow-up).

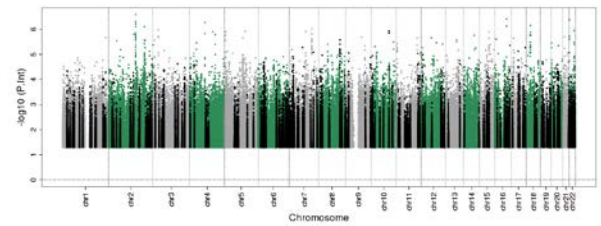
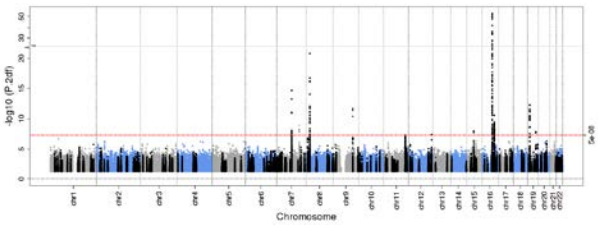
Supplementary Figure 1

African Ancestry

Current Smoking

	1df Test of Interaction	2df Joint Test of Main Effect and Interaction
HDL		
	n = 23,748 (stage 1) and 30,965 (stages 1 and 2)	
LDL		
	n = 23,348 (stage 1) and 28,672 (stages 1 and 2)	
Triglycerides		
	n = 23,503 (stage 1) and 28,859 (stages 1 and 2)	

Ever Smoking

HDL		
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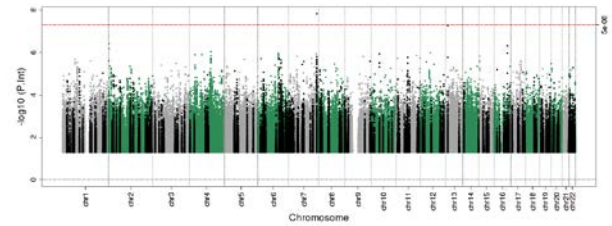
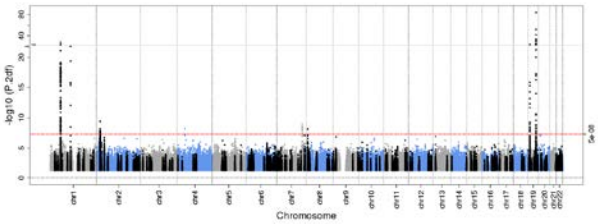
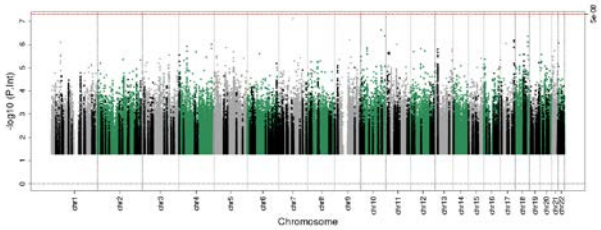
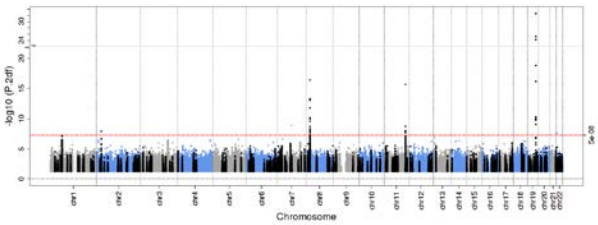
LDL		
	n = 23,353 (stage 1) and 27,071 (stages 1 and 2)	
Triglycerides		
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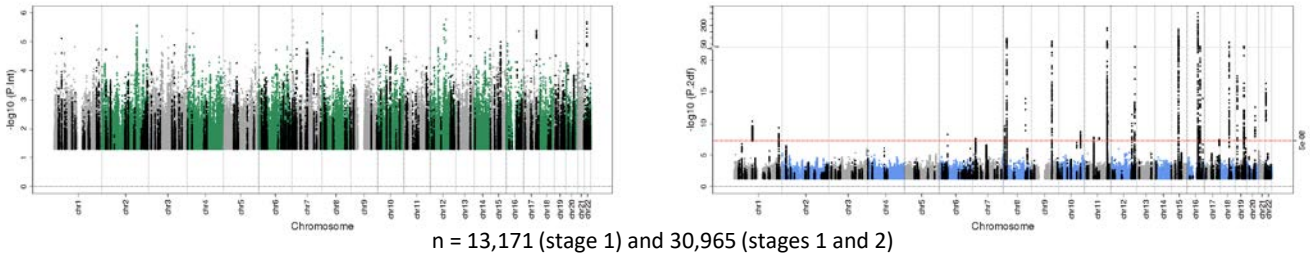
Asian Ancestry

Current Smoking

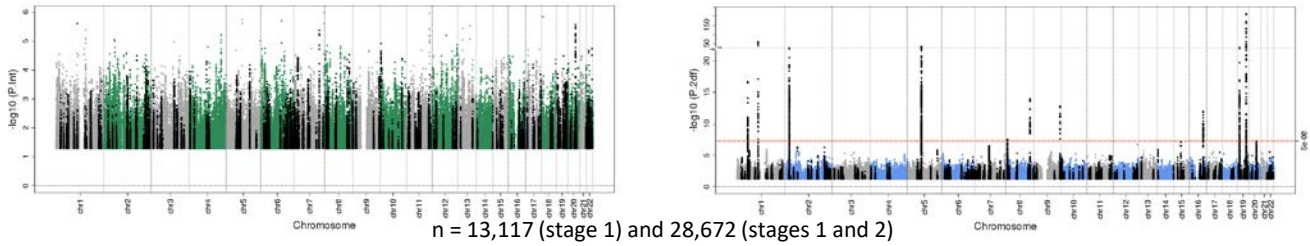
1df Test of Interaction | 2df Joint Test of Main Effect and Interaction

HDL



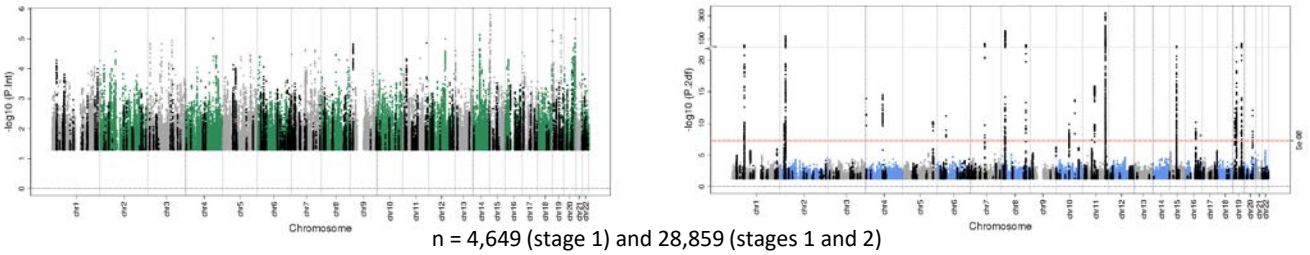
n = 13,171 (stage 1) and 30,965 (stages 1 and 2)

LDL



n = 13,117 (stage 1) and 28,672 (stages 1 and 2)

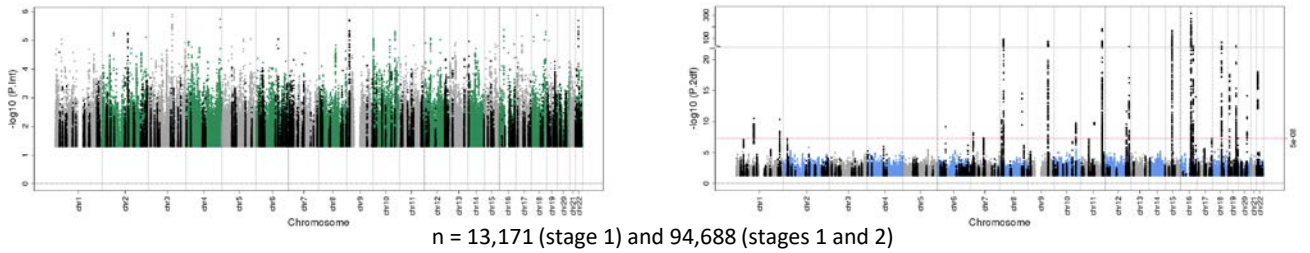
Triglycerides



n = 4,649 (stage 1) and 28,859 (stages 1 and 2)

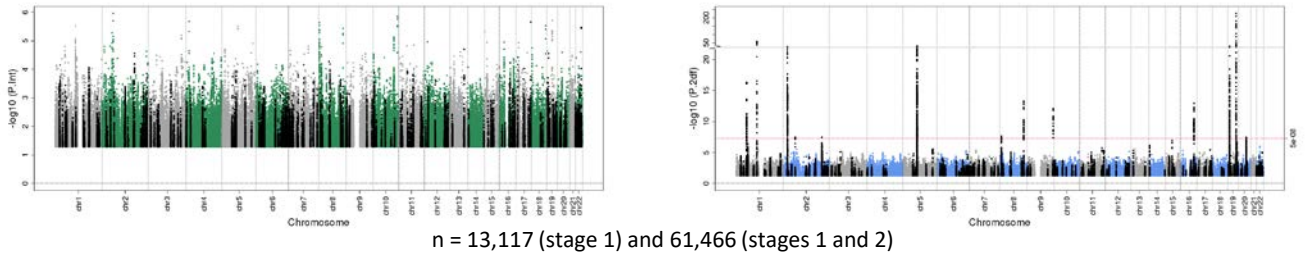
Ever Smoking

HDL



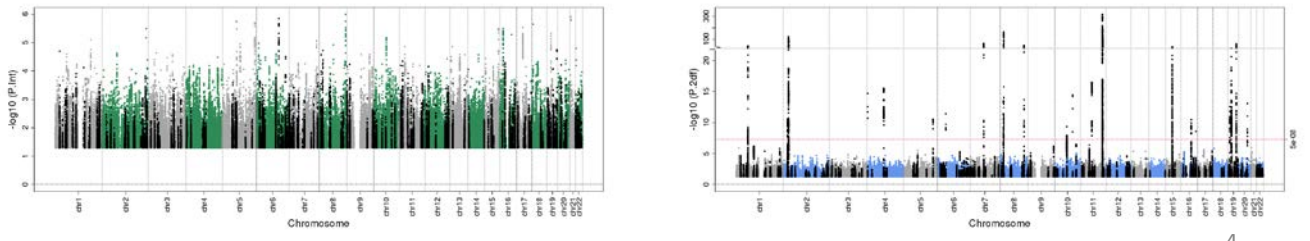
n = 13,171 (stage 1) and 94,688 (stages 1 and 2)

LDL



n = 13,117 (stage 1) and 61,466 (stages 1 and 2)

Triglycerides



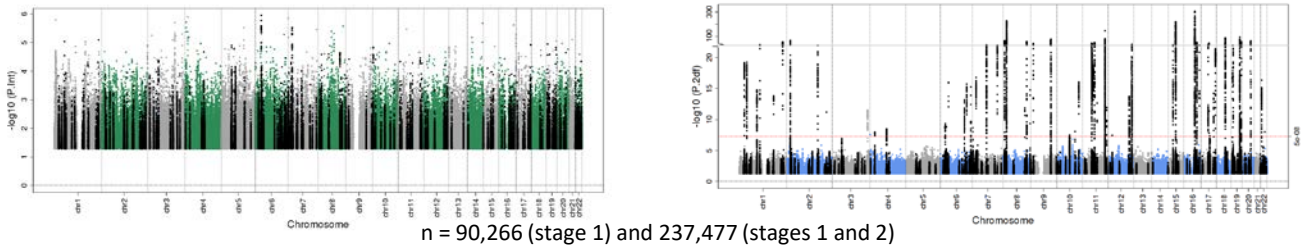
n = 4,649 (stage 1) and 116,570 (stages 1 and 2)

European Ancestry

Current Smoking

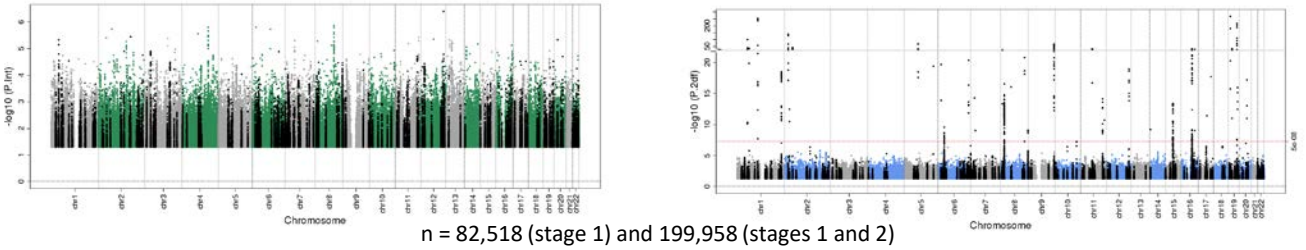
1df Test of Interaction | 2df Joint Test of Main Effect and Interaction

HDL



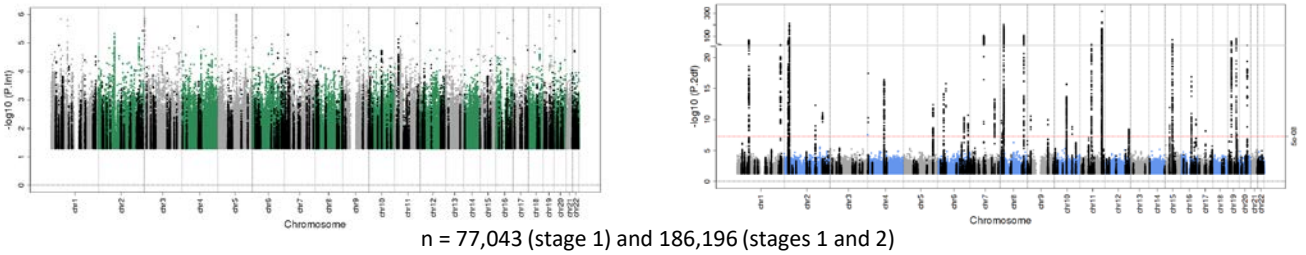
n = 90,266 (stage 1) and 237,477 (stages 1 and 2)

LDL



n = 82,518 (stage 1) and 199,958 (stages 1 and 2)

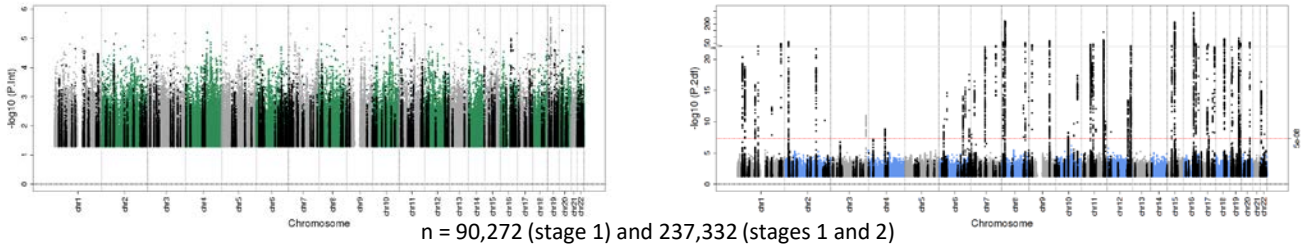
Triglycerides



n = 77,043 (stage 1) and 186,196 (stages 1 and 2)

Ever Smoking

HDL



n = 90,272 (stage 1) and 237,332 (stages 1 and 2)

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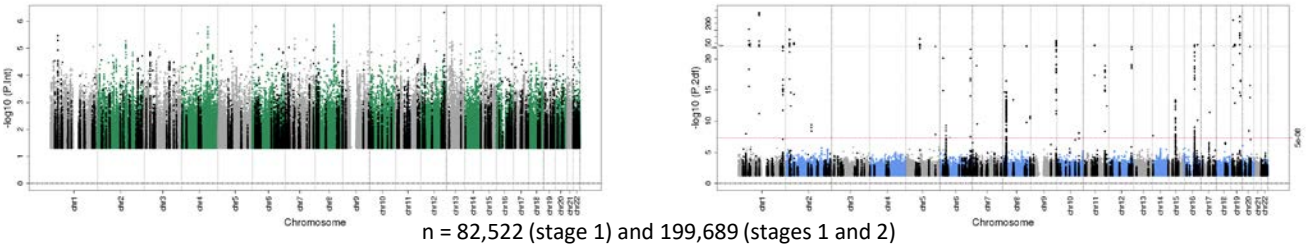

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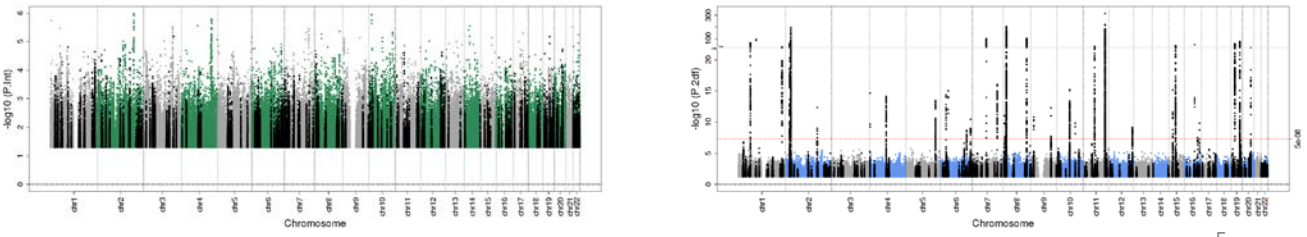
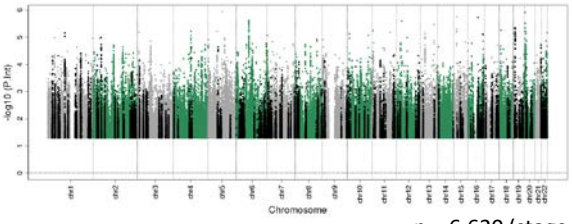
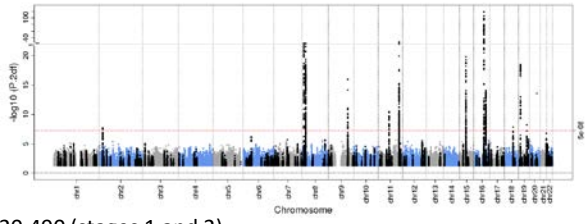
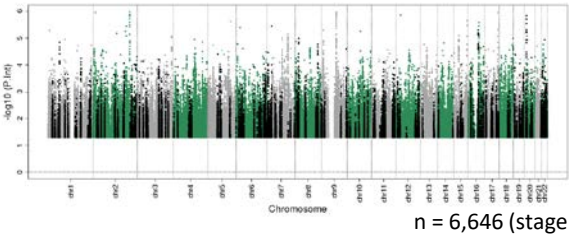
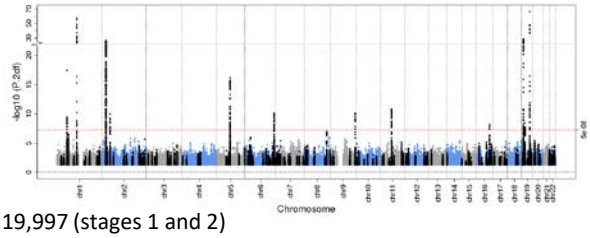
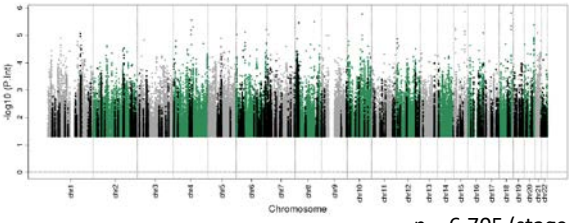
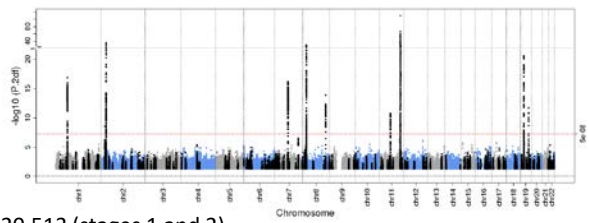


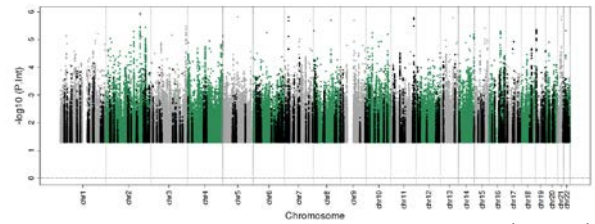
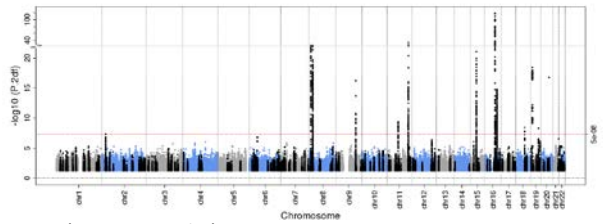
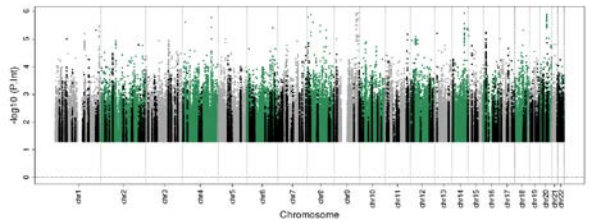
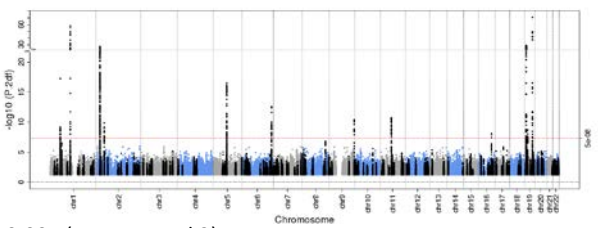
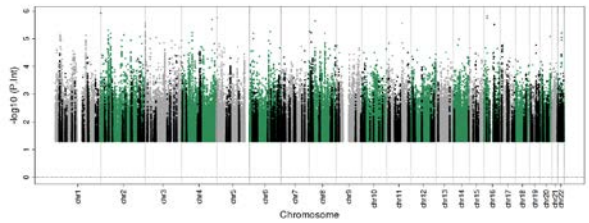
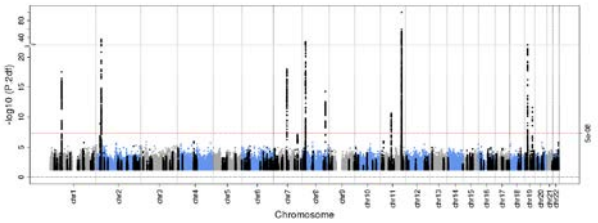
n = 77,047 (stage 1) and 185,638 (stages 1 and 2)

Hispanic Ancestry

Current Smoking

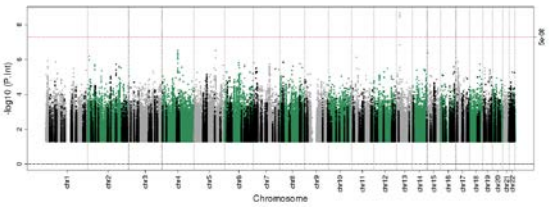
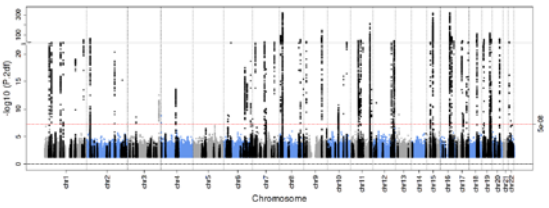
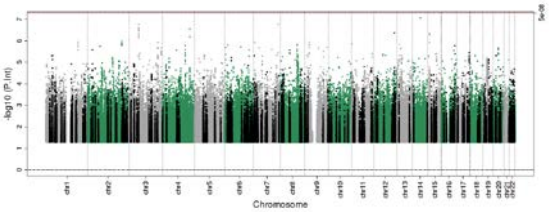
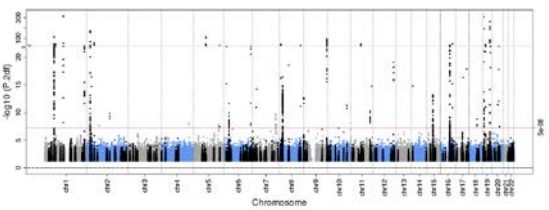
	1df Test of Interaction	2df Joint Test of Main Effect and Interaction
HDL		
	n = 6,620 (stage 1) and 20,490 (stages 1 and 2)	
LDL		
	n = 6,646 (stage 1) and 19,997 (stages 1 and 2)	
Triglycerides		
	n = 6,705 (stage 1) and 20,513 (stages 1 and 2)	

Ever Smokina

HDL		
	n = 6,620 (stage 1) and 20,490 (stages 1 and 2)	
LDL		
	n = 6,646 (stage 1) and 19,997 (stages 1 and 2)	
Triglycerides		
	n = 6,705 (stage 1) and 20,513 (stages 1 and 2)	

Trans-Ancestry

Current Smoking

	1df Test of Interaction	2df Joint Test of Main Effect and Interaction
HDL		
	n = 133,805 (stage 1) and 387,272 (stages 1 and 2)	
LDL		
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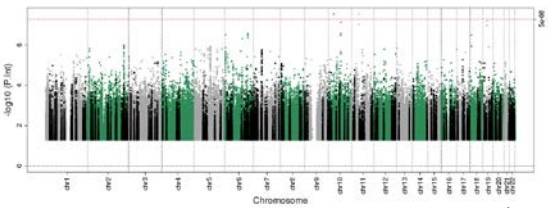
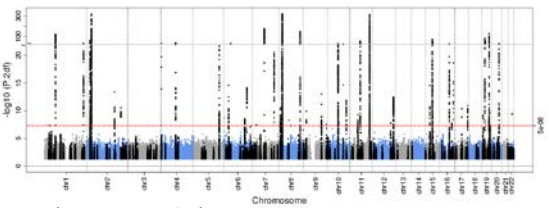
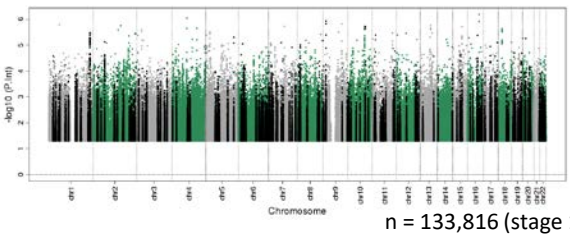
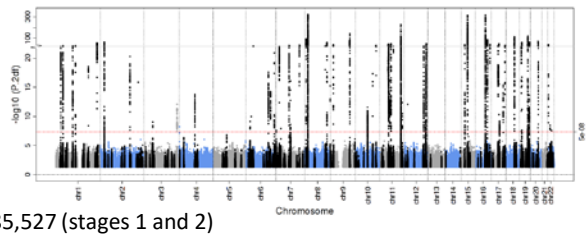
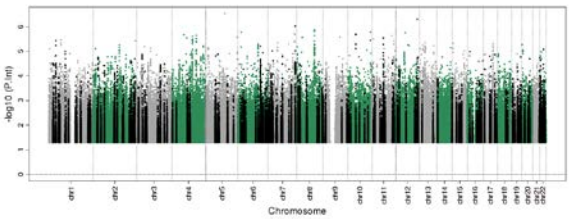
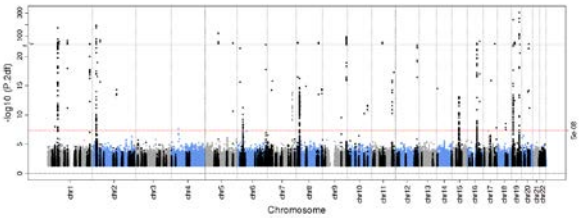
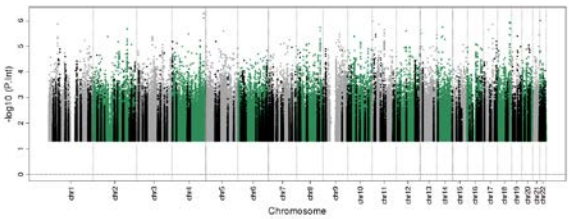
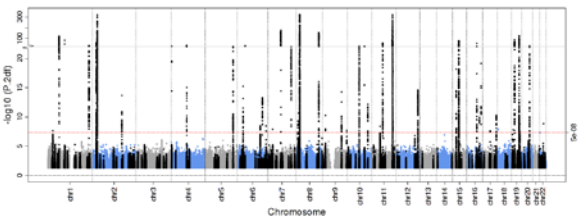
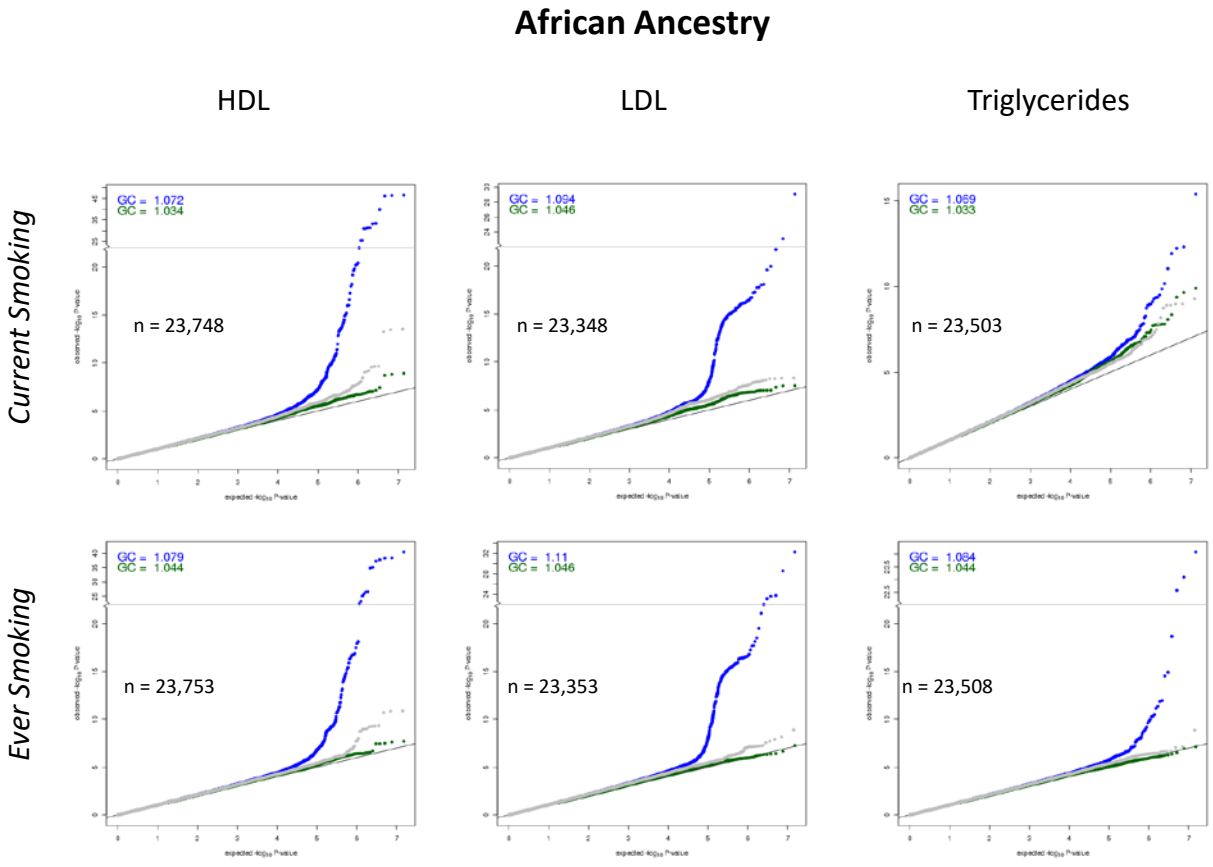
Triglycerides		
	n = 111,900 (stage 1) and 353,040 (stages 1 and 2)	

Ever Smoking

HDL		
	n = 133,816 (stage 1) and 385,527 (stages 1 and 2)	
LDL		
	n = 125,638 (stage 1) and 311,868 (stages 1 and 2)	
Triglycerides		
	n = 111,909 (stage 1) and 350,881 (stages 1 and 2)	

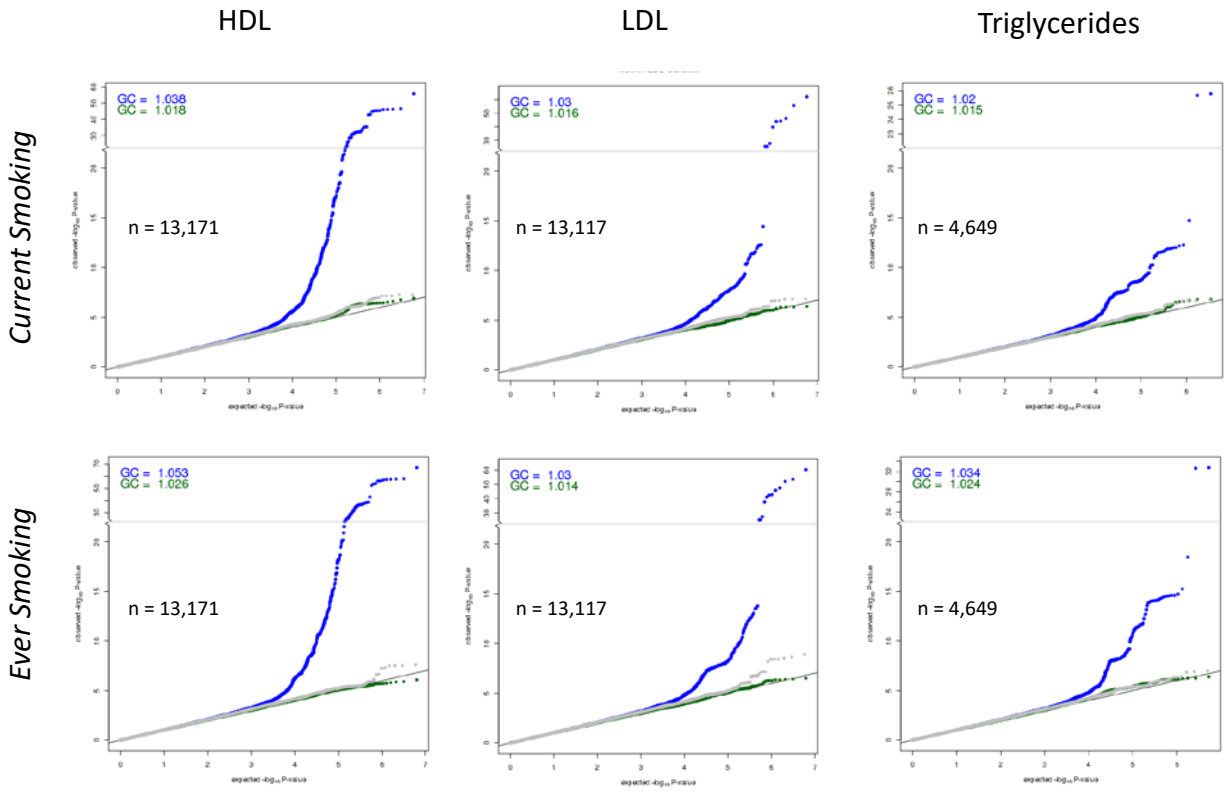
Supplementary Figure 2

QQ Plots. Shown are the p values for the genome-wide stage 1 results for linear regression models of lipids traits that include both the variant and a variant × smoking status interaction term, adjusted for age, sex, PCs, study-specific covariates (as necessary) and smoking status. Shown are the p values for the 2df joint test of interaction and main effect, the 2df joint test after excluding known lipids loci, and the 1df test of interaction. Points shaded in black are within 1 MB of known lipids loci.

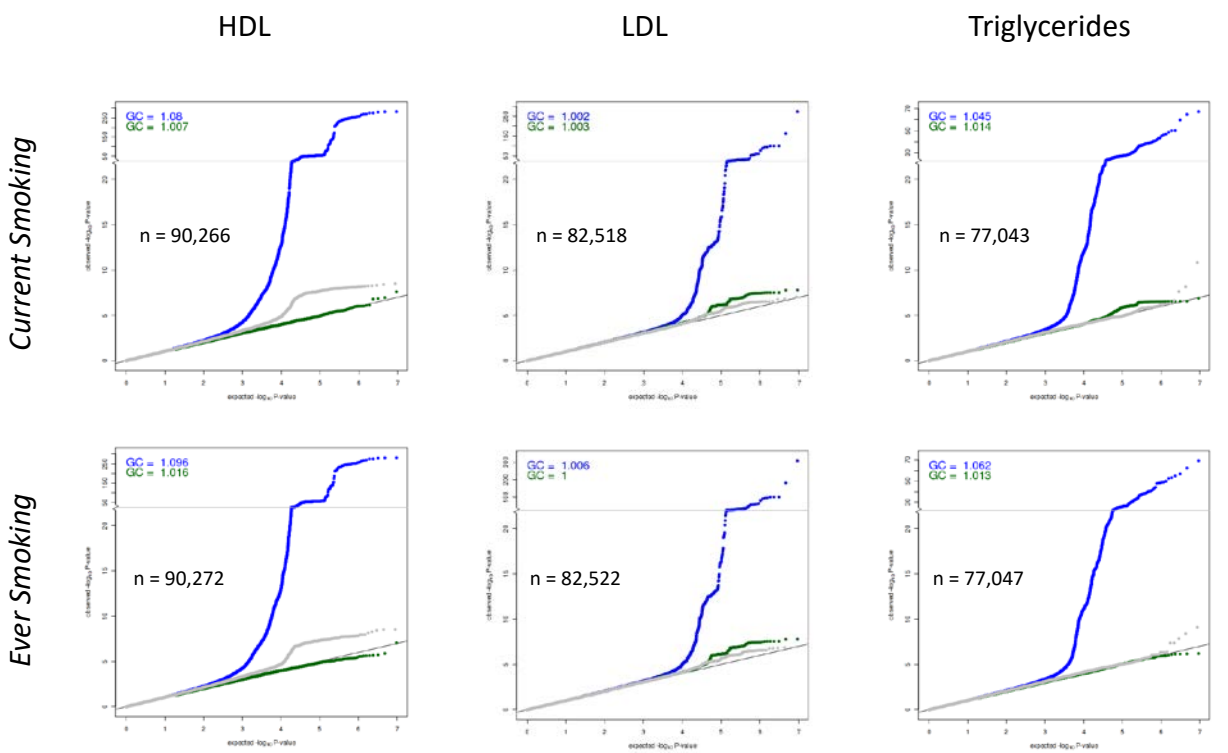


BLUE: 2df test, GRAY: 2df test excluding known loci, GREEN: 1df test

Asian Ancestry

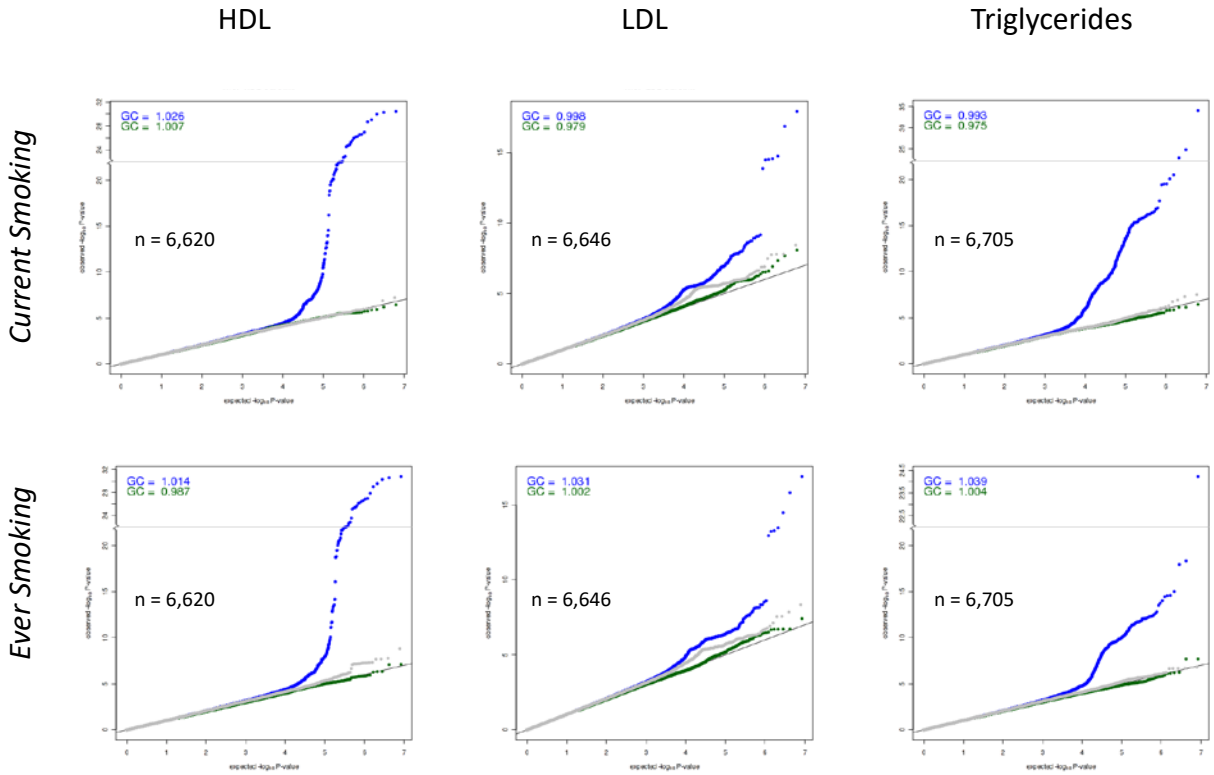


European Ancestry

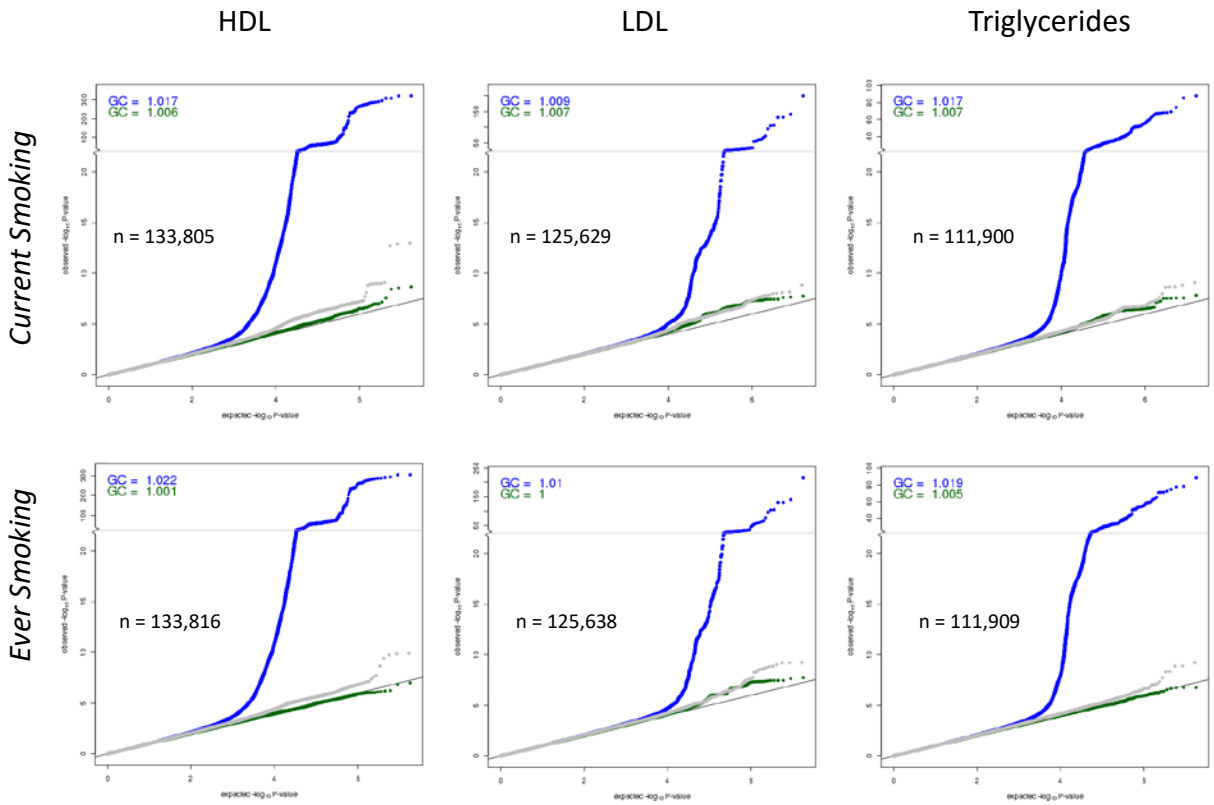


BLUE: 2df test, GRAY: 2df test excluding known loci, GREEN: 1df test

Hispanic Ancestry



Trans-Ancestry

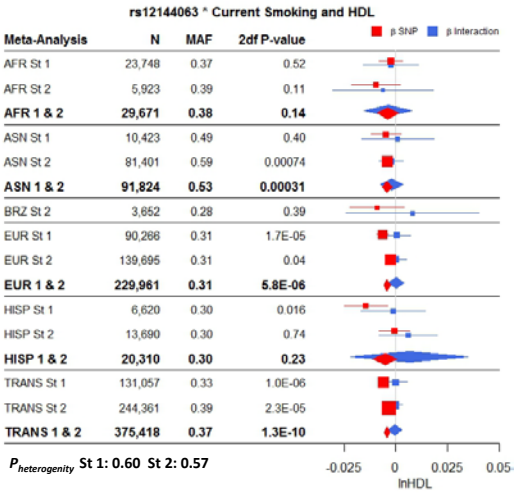


BLUE: 2df test, GRAY: 2df test excluding known loci, GREEN: 1df test

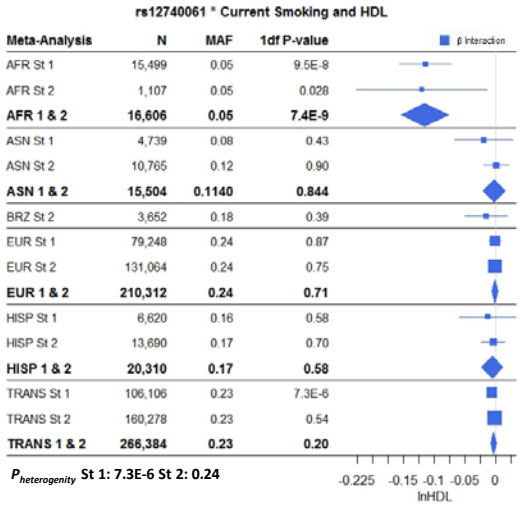
Supplementary Figure 3

Forest Plots of Novel Loci: The results of either the 2df test (β for Interaction and Main Effect shown) or 1df test (only β for Interaction shown), whichever was more statistically significant. 95% confidence intervals included.

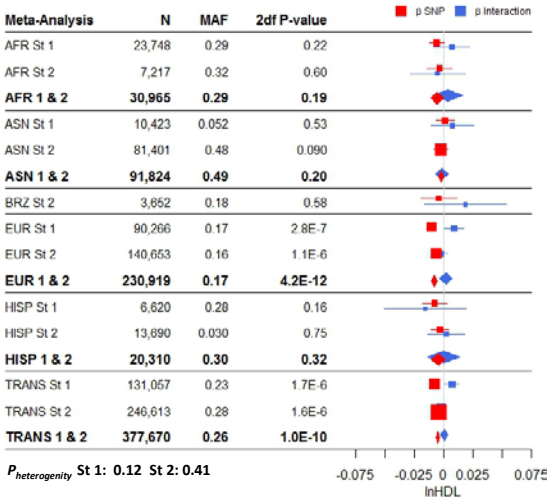
a



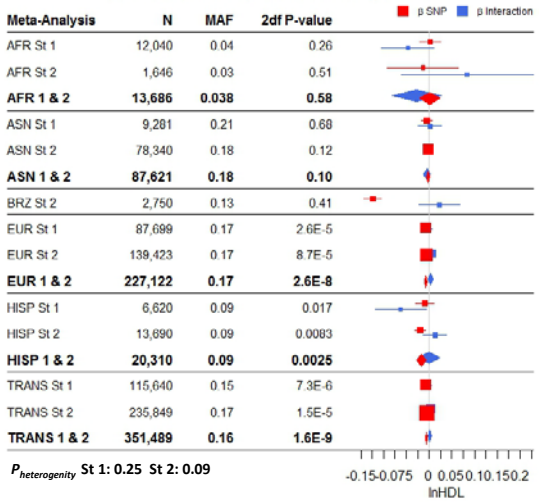
b



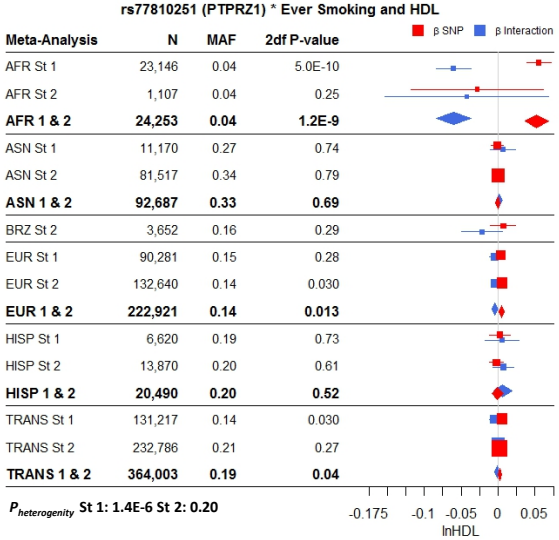
c



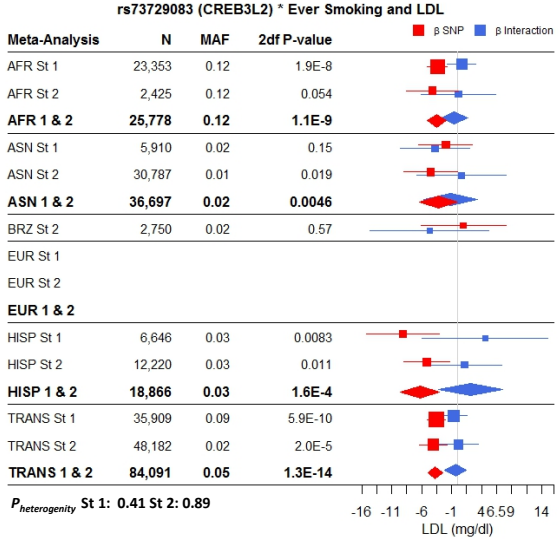
d



e



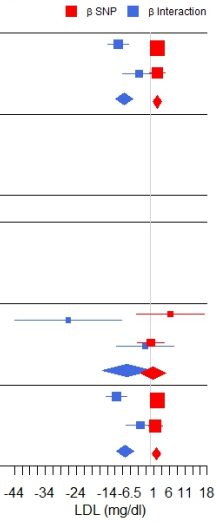
f



g

rs73453125 (CNTNAP2) * Current Smoking and LDL

Meta-Analysis	N	MAF	2df P-value
AFR St 1	22,645	0.09	1.4E-8
AFR St 2	3,675	0.09	0.22
AFR 1 & 2	**26,323**	**0.09**	**4.4E-08**
ASN St 1			
ASN St 2			
ASN 1 & 2			
BRZ St 2			
EUR St 1			
EUR St 2			
EUR 1 & 2			
HISP St 1	2,023	0.03	0.0065
HISP St 2	12,220	0.02	0.91
HISP 1 & 2	**14,243**	**0.02**	**0.15**
TRANS St 1	24,668	0.09	1.4E-9
TRANS St 2	15,595	0.03	0.27
TRANS 1 & 2	**40,566**	**0.07**	**2.0E-08**

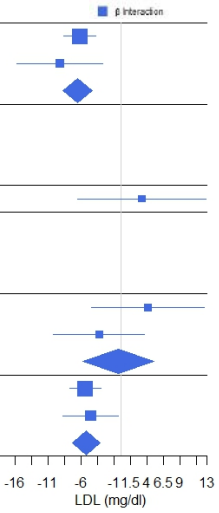


$P_{heterogenity}$ St 1: 0.18 St 2: 0.71

h

rs56167574 * Ever Smoking and LDL

Meta-Analysis	N	MAF	1df P-value
AFR St 1	23,353	0.12	5.3E-7
AFR St 2	2,425	0.11	0.0056
AFR 1 & 2	**25,778**	**0.12**	**1.5E-8**
ASN St 1			
ASN St 2			
ASN 1 & 2			
BRZ St 2	2,750	0.03	0.51
EUR St 1			
EUR St 2			
EUR 1 & 2			
HISP St 1	6,646	0.03	0.34
HISP St 2	12,220	0.02	0.36
HISP 1 & 2	**18,866**	**0.02**	**0.92**
TRANS St 1	29,999	0.11	8.5E-6
TRANS St 2	17,395	0.06	0.037
TRANS 1 & 2	**47,394**	**0.10**	**9.3E-7**

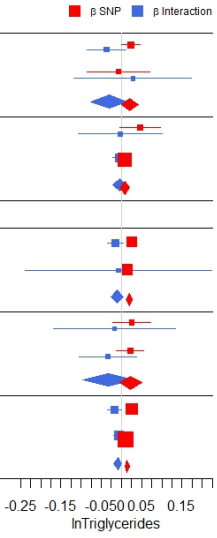


$P_{heterogenity}$ St 1: 0.02 St 2: 0.10

i

rs10101067 * Current Smoking and Triglycerides

Meta-Analysis	N	MAF	2df P-value
AFR St 1	22,188	0.05	0.10
AFR St 2	2,713	0.04	0.93
AFR 1 & 2	**24,901**	**0.05**	**0.14**
ASN St 1	2,761	0.11	0.13
ASN St 2	110,007	0.12	0.11
ASN 1 & 2	**112,768**	**0.12**	**0.062**
BRZ St 2			
EUR St 1	72,064	0.07	1.6E-05
EUR St 2	89,198	0.07	0.012
EUR 1 & 2	**161,262**	**0.07**	**4.9E-07**
HISP St 1	5,250	0.05	0.57
HISP St 2	13,625	0.05	0.44
HISP 1 & 2	**18,878**	**0.05**	**0.26**
TRANS St 1	102,263	0.07	5.7E-7
TRANS St 2	215,546	0.09	0.0018
TRANS 1 & 2	**317,809**	**0.08**	**4.1E-08**

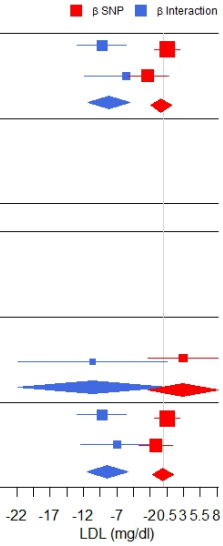


$P_{heterogenity}$ St 1: 0.89 St 2: 0.88

j

rs79950627 * Current Smoking and LDL

Meta-Analysis	N	MAF	2df P-value
AFR St 1	23,348	0.07	4.3E-7
AFR St 2	2,704	0.08	0.0056
AFR 1 & 2	**26,052**	**0.07**	**9.6E-9**
ASN St 1			
ASN St 2			
ASN 1 & 2			
BRZ St 2			
EUR St 1			
EUR St 2			
EUR 1 & 2			
HISP St 1			
HISP St 2	12,220	0.01	0.17
HISP 1 & 2	**12,220**	**0.01**	**0.17**
TRANS St 1	23,348	0.07	4.3E-7
TRANS St 2	14,924	0.02	0.0044
TRANS 1 & 2	**38,272**	**0.05**	**7.2E-9**

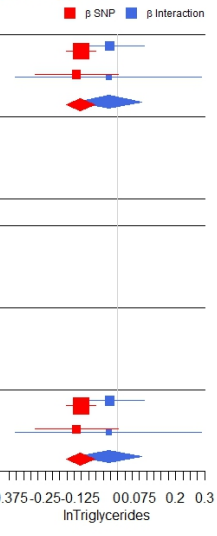


$P_{heterogenity}$ St 1: -- St 2: 0.22

k

rs4758675 (B3GNT4) * Current Smoking and Triglycerides

Meta-Analysis	N	MAF	2df P-value
AFR St 1	11,875	0.02	2.4E-7
AFR St 2	1,107	0.03	0.053
AFR 1 & 2	**12,982**	**0.02**	**1.3E-8**
ASN St 1			
ASN St 2			
ASN 1 & 2			
BRZ St 2			
EUR St 1			
EUR St 2			
EUR 1 & 2			
HISP St 1			
HISP St 2			
HISP 1 & 2			
TRANS St 1	21,875	0.02	2.4E-7
TRANS St 2	1,107	0.03	0.053
TRANS 1 & 2	**12,982**	**0.02**	**1.3E-8**

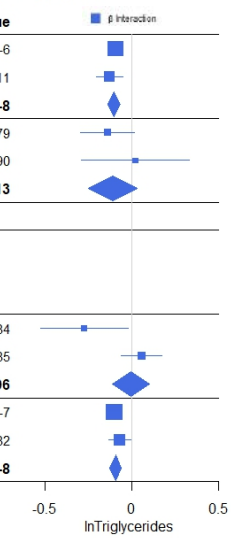


$P_{heterogenity}$ St 1: -- St 2: --

l

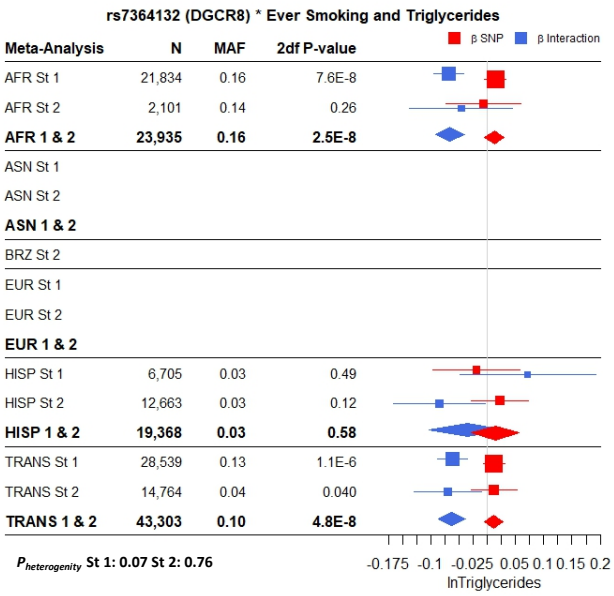
rs60029395 * Current Smoking and Triglycerides

Meta-Analysis	N	MAF	1df P-value
AFR St 1	15,747	0.12	5.4E-6
AFR St 2	3,301	0.16	0.0011
AFR 1 & 2	**19,048**	**0.13**	**3.3E-8**
ASN St 1	1,813	0.03	0.079
ASN St 2	1,417	ASN St 2	0.90
ASN 1 & 2	**3,230**	**0.03**	**0.13**
BRZ St 2			
EUR St 1			
EUR St 2			
EUR 1 & 2			
HISP St 1	2,046	0.04	0.034
HISP St 2	12,663	0.02	0.35
HISP 1 & 2	**14,709**	**0.02**	**0.96**
TRANS St 1	19,606	0.12	4.8E-7
TRANS St 2	17,381	0.12	0.032
TRANS 1 & 2	**36,987**	**0.12**	**6.6E-8**



$P_{heterogenity}$ St 1: 0.34 St 2: 0.03

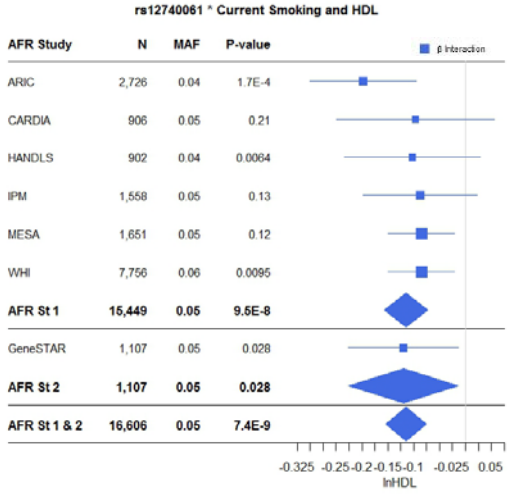
m


rs7364132 (DGCR8) * Ever Smoking and Triglycerides
β SNP
β Interaction
Meta-Analysis N MAF 2df P-value
AFR St 1 21,834 0.16 7.6E-8
AFR St 2 2,101 0.14 0.26
AFR 1 & 2 23,935 0.16 2.5E-8
ASN St 1
ASN St 2
ASN 1 & 2
BRZ St 2
EUR St 1
EUR St 2
EUR 1 & 2
HISP St 1 6,705 0.03 0.49
HISP St 2 12,663 0.03 0.12
HISP 1 & 2 19,368 0.03 0.58
TRANS St 1 28,539 0.13 1.1E-6
TRANS St 2 14,764 0.04 0.040
TRANS 1 & 2 43,303 0.10 4.8E-8
$P_{heterogenity}$ St 1: 0.07 St 2: 0.76
-0.175 -0.1 -0.025 0.05 0.1 0.15 0.2
lnTriglycerides

Supplementary Figure 4

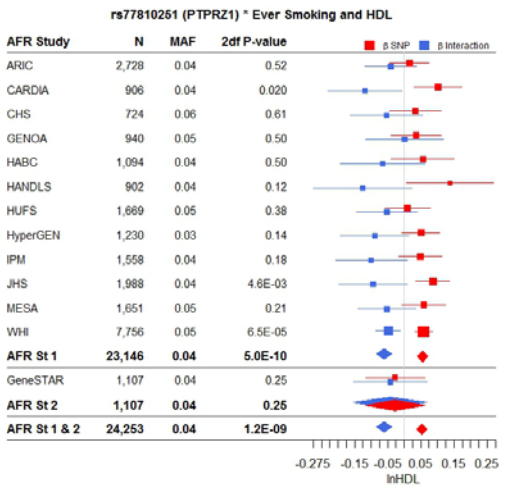
Within Ancestry Forest Plots of Novel Loci: For those associations that were only observed within one ancestry, results for all cohorts in the ancestry in which the association was observed. The results of either the 2df test (β for Interaction and Main Effect shown) or 1df test (only β for Interaction shown), whichever was more statistically significant. 95% confidence intervals included.

a



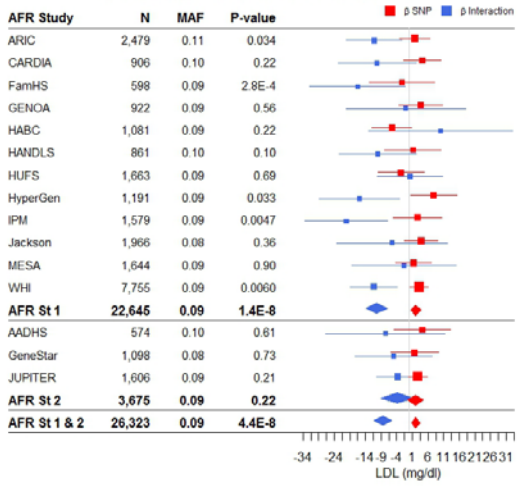
AFR Study	N	MAF	P-value
ARIC	2,726	0.04	1.7E-4
CARDIA	906	0.05	0.21
HANDLS	902	0.04	0.0064
IPM	1,558	0.05	0.13
MESA	1,651	0.05	0.12
WHI	7,756	0.06	0.0095
AFR St 1	**15,449**	**0.05**	**9.5E-8**
GeneSTAR	1,107	0.05	0.028
AFR St 2	**1,107**	**0.05**	**0.028**
AFR St 1 & 2	**16,606**	**0.05**	**7.4E-9**

b



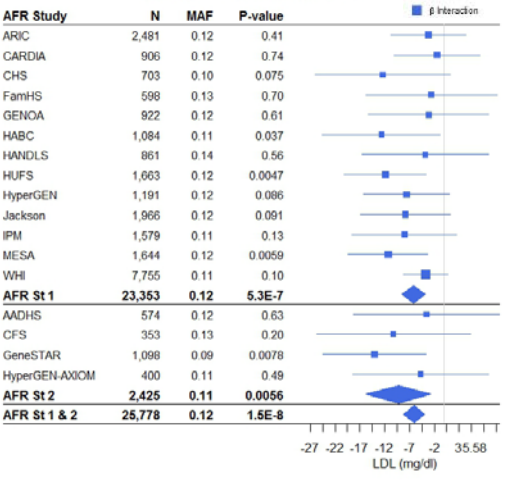
AFR Study	N	MAF	2df P-value
ARIC	2,728	0.04	0.52
CARDIA	906	0.04	0.020
CHS	724	0.06	0.61
GENOA	940	0.05	0.50
HABC	1,094	0.04	0.50
HANDLS	902	0.04	0.12
HUFS	1,669	0.05	0.38
HyperGEN	1,230	0.03	0.14
IPM	1,558	0.04	0.18
JHS	1,988	0.04	4.6E-03
MESA	1,651	0.05	0.21
WHI	7,756	0.05	6.5E-05
AFR St 1	**23,146**	**0.04**	**5.0E-10**
GeneSTAR	1,107	0.04	0.25
AFR St 2	**1,107**	**0.04**	**0.25**
AFR St 1 & 2	**24,253**	**0.04**	**1.2E-09**

c



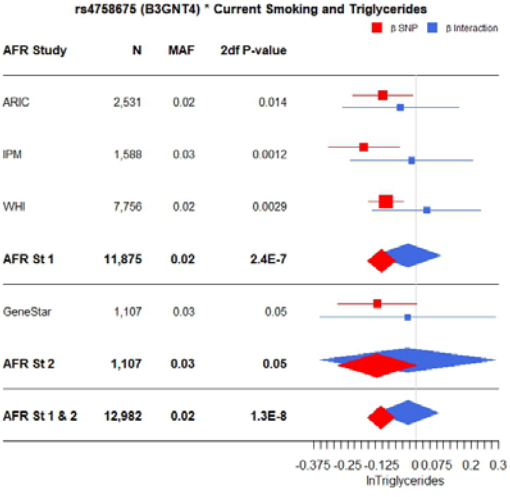
AFR Study	N	MAF	P-value
ARIC	2,479	0.11	0.034
CARDIA	906	0.10	0.22
FamHS	598	0.09	2.8E-4
GENOA	922	0.09	0.56
HABC	1,081	0.09	0.22
HANDLS	861	0.10	0.10
HUFS	1,663	0.09	0.69
HyperGen	1,191	0.09	0.033
IPM	1,579	0.09	0.0047
Jackson	1,966	0.08	0.36
MESA	1,644	0.09	0.90
WHI	7,755	0.09	0.0060
AFR St 1	**22,645**	**0.09**	**1.4E-8**
AADHS	574	0.10	0.61
GeneStar	1,098	0.08	0.73
JUPITER	1,606	0.09	0.21
AFR St 2	**3,675**	**0.09**	**0.22**
AFR St 1 & 2	**26,323**	**0.09**	**4.4E-8**

d



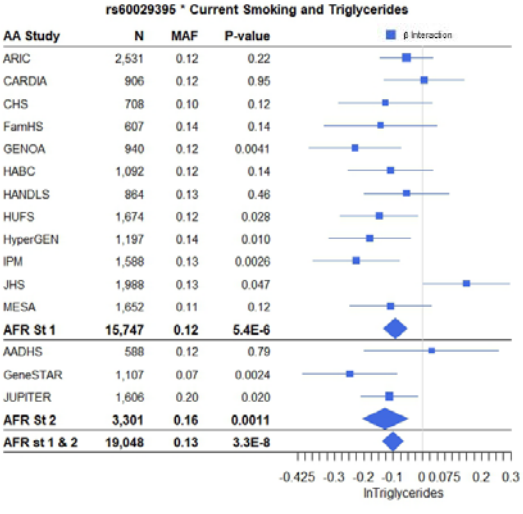
AFR Study	N	MAF	P-value
ARIC	2,481	0.12	0.41
CARDIA	906	0.12	0.74
CHS	703	0.10	0.075
FamHS	598	0.13	0.70
GENOA	922	0.12	0.61
HABC	1,084	0.11	0.037
HANDLS	861	0.14	0.56
HUFS	1,663	0.12	0.0047
HyperGEN	1,191	0.12	0.086
Jackson	1,966	0.12	0.091
IPM	1,579	0.11	0.13
MESA	1,644	0.12	0.0059
WHI	7,755	0.11	0.10
AFR St 1	**23,353**	**0.12**	**5.3E-7**
AADHS	574	0.12	0.63
CFS	353	0.13	0.20
GeneSTAR	1,098	0.09	0.0078
HyperGEN-AXIOM	400	0.11	0.49
AFR St 2	**2,425**	**0.11**	**0.0056**
AFR St 1 & 2	**25,778**	**0.12**	**1.5E-8**

e



AFR Study	N	MAF	2df P-value
ARIC	2,531	0.02	0.014
IPM	1,588	0.03	0.0012
WHI	7,756	0.02	0.0029
AFR St 1	**11,875**	**0.02**	**2.4E-7**
GeneStar	1,107	0.03	0.05
AFR St 2	**1,107**	**0.03**	**0.05**
AFR St 1 & 2	**12,982**	**0.02**	**1.3E-8**

f

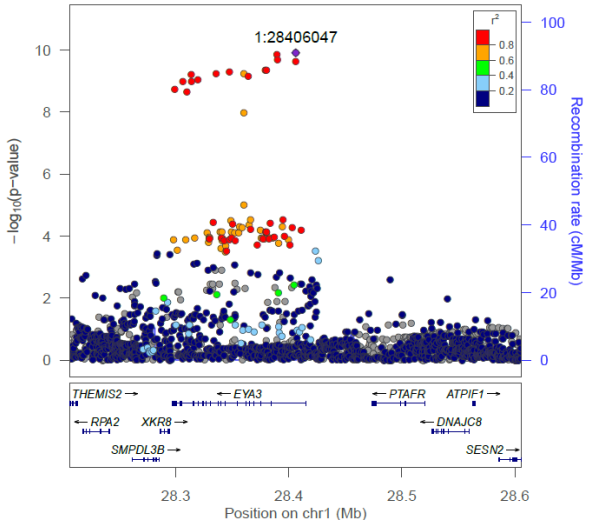


AA Study	N	MAF	P-value
ARIC	2,531	0.12	0.22
CARDIA	906	0.12	0.95
CHS	708	0.10	0.12
FamHS	607	0.14	0.14
GENOA	940	0.12	0.0041
HABC	1,092	0.12	0.14
HANDLS	864	0.13	0.46
HUFS	1,674	0.12	0.028
HyperGEN	1,197	0.14	0.010
IPM	1,588	0.13	0.0026
JHS	1,988	0.13	0.047
MESA	1,652	0.11	0.12
AFR St 1	**15,747**	**0.12**	**5.4E-6**
AADHS	588	0.12	0.79
GeneSTAR	1,107	0.07	0.0024
JUPITER	1,606	0.20	0.020
AFR St 2	**3,301**	**0.16**	**0.0011**
AFR st 1 & 2	**19,048**	**0.13**	**3.3E-8**

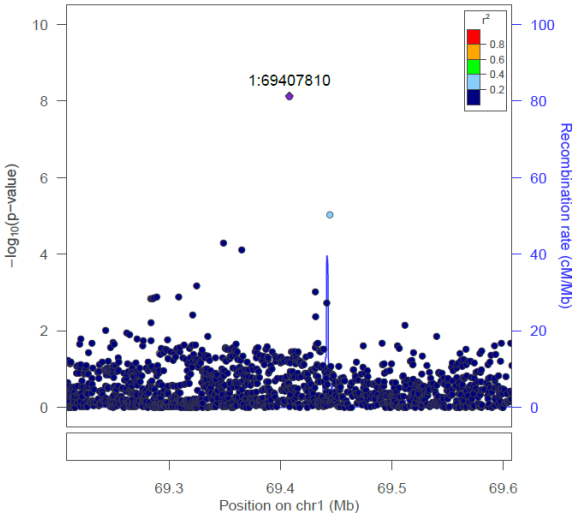
Supplementary Figure 5

Regional Association Plots for Novel Loci: LocusZoom plots showing p-values for stage 1 and 2 combined meta-analyses or stage 1 meta-analyses (if variant not carried forward to stage 2).

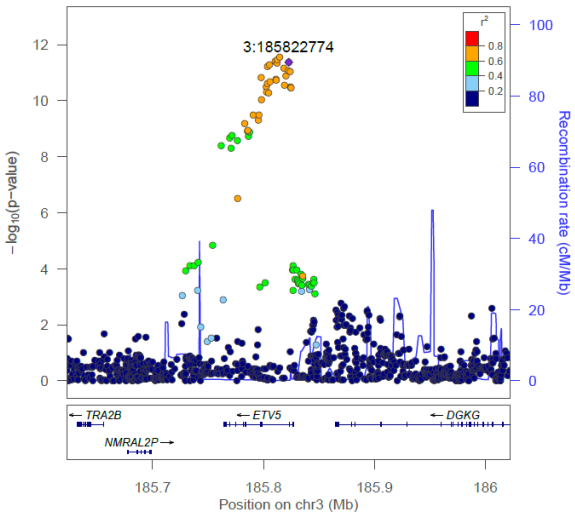
rs12144063 (*EYA3*) × Current Smoking and HDL
TRANS ancestry, 2df tests (n = 375,418)



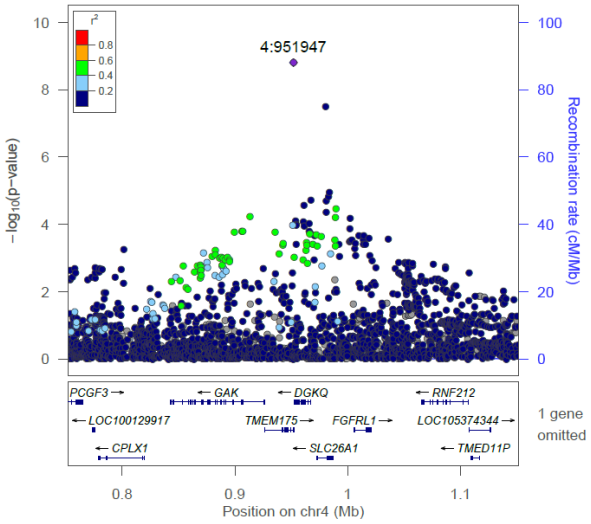
rs12740061 (*LOC105378783*) × Current Smoking and HDL
AFR ancestry, 1df tests (n = 16,606)



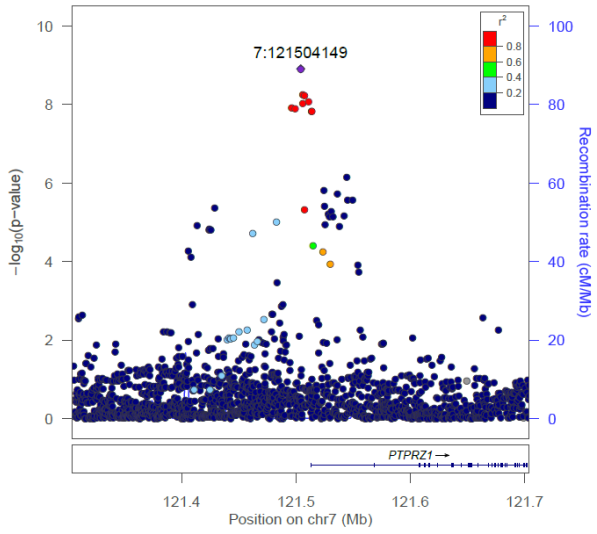
rs10937241 (*ETV5*) × Current Smoking and HDL
EUR ancestry, 2df tests (n = 230,919)



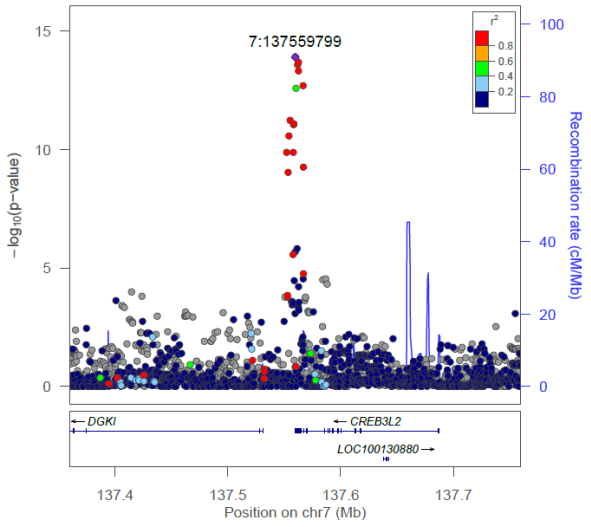
rs34311866 (*TMEM175*) × Current Smoking and HDL
TRANS ancestry, 2df tests (n = 351,489)



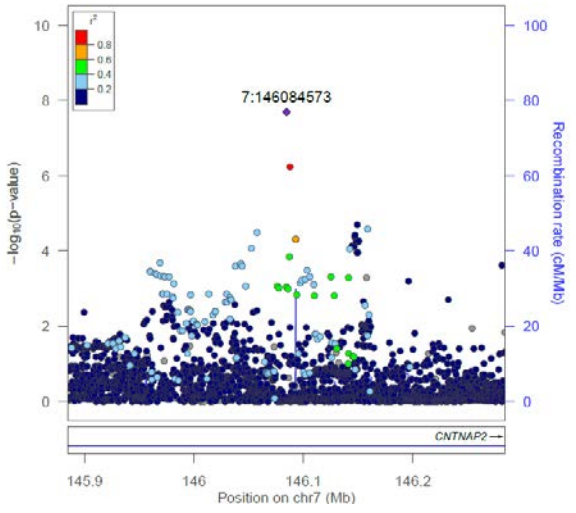
rs77810251 (*PTPRZ1*) × Ever Smoking and HDL
AFR ancestry, 2df tests (n = 24,253)



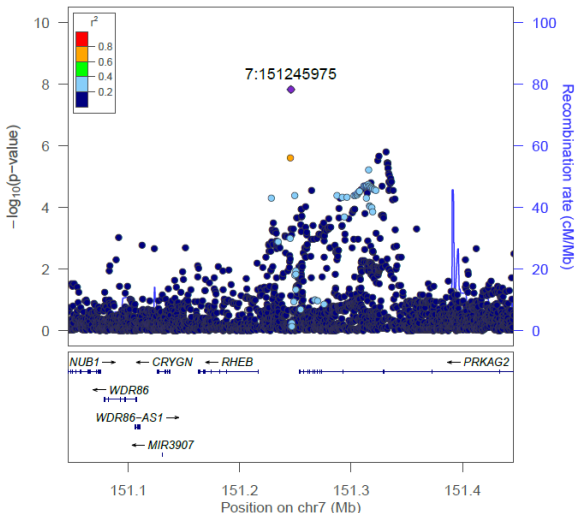
rs73729083 (*CREB3L2*) × Ever Smoking and LDL
TRANS ancestry, 2df tests (n = 84,091)



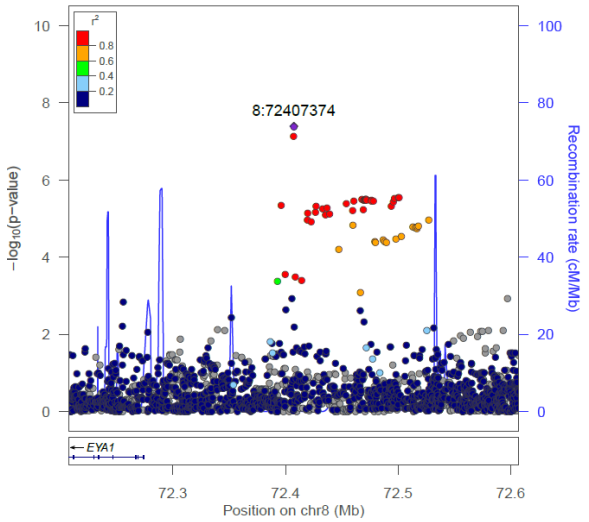
rs73453125 (*CNTNAP2*) × Current Smoking and LDL
TRANS ancestry, 2df tests (n = 40,566)



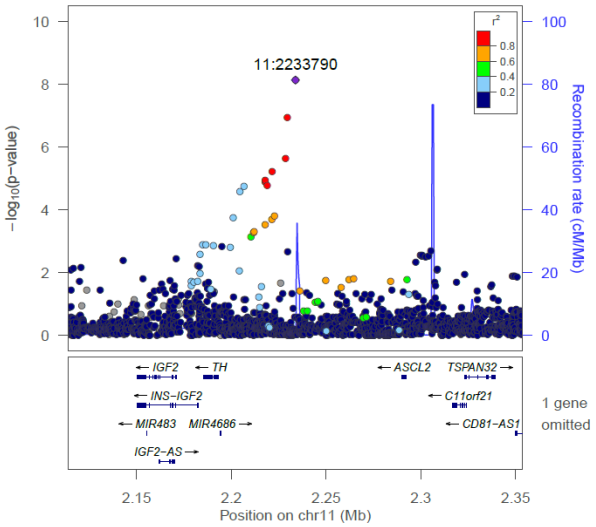
rs56167574 (*PRKAG2*) × Ever Smoking and LDL
AFR ancestry, 1df tests (n = 25,778)



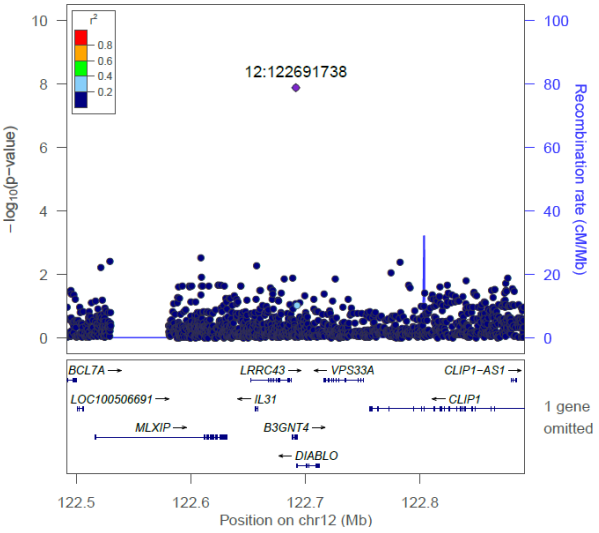
rs10101067 (*EYA1*) × Current Smoking and Triglycerides
TRANS ancestry, 2df tests (n = 317,809)



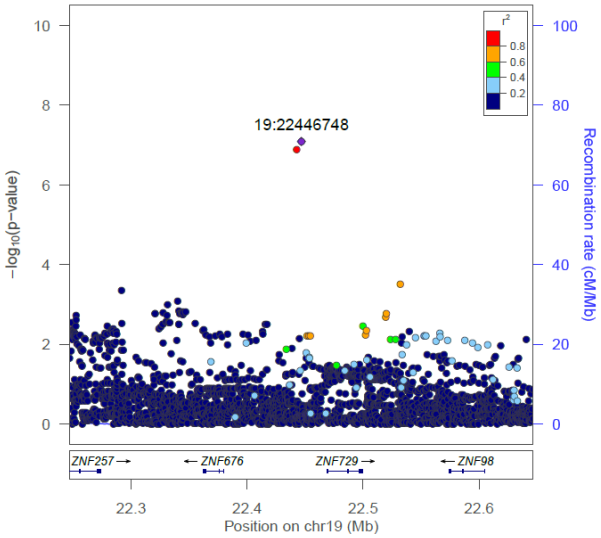
rs79950627 (*MIR4686*) × Current Smoking and LDL
TRANS ancestry, 2df tests (n = 38,272)



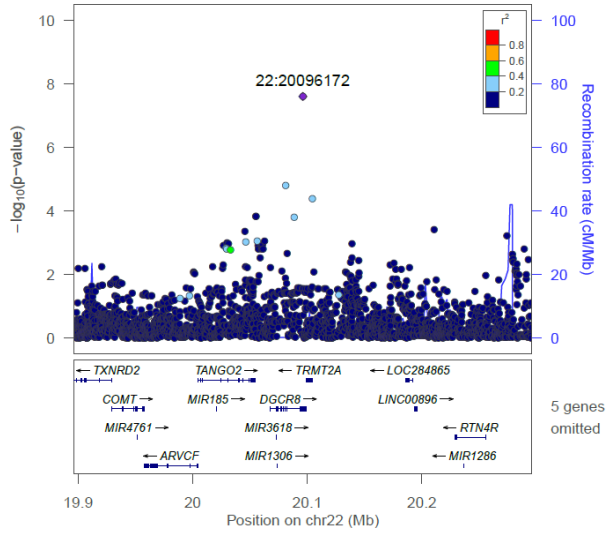
rs4758675 (*B3GNT4*) × Current Smoking and Triglycerides
AFR ancestry, 2df tests (n = 12,982)



rs60029395 (*ZNF729*) × Current Smoking and Triglycerides
AFR ancestry, 1df tests (n = 19,048)

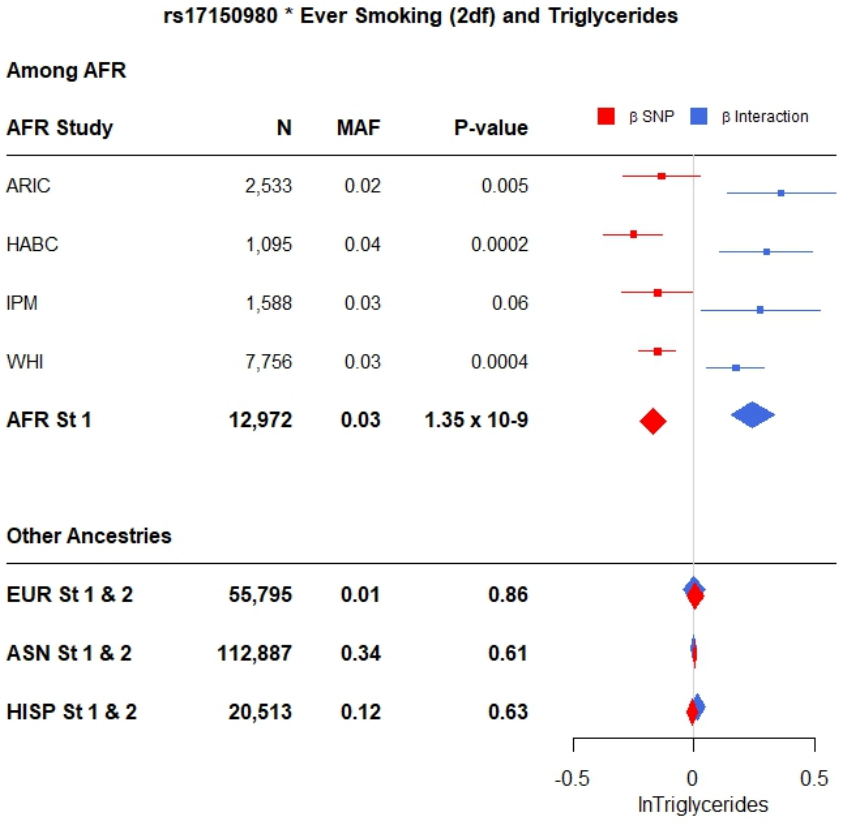


rs7364132 (*DGCR8*) × Ever Smoking and Triglycerides
AFR ancestry, 2df tests (n = 23,935)

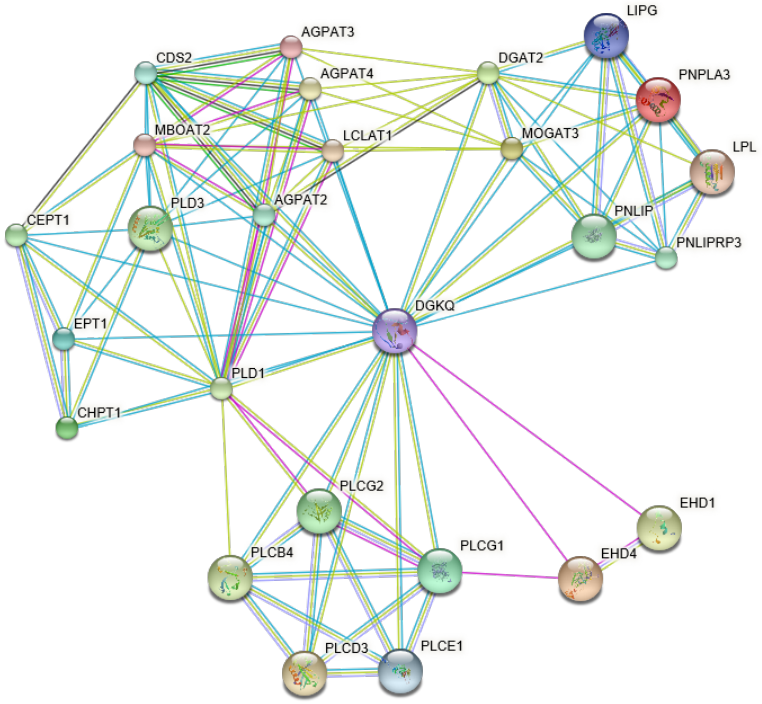


Supplementary Figure 6

rs17150980 × Ever-Smoking on Triglycerides, Stage 1 Meta-Analysis: The results for the 2df test (β for Interaction and Main Effect shown, with 95% confidence intervals) for Stage 1 meta-analyses. This variant was not available in any Stage 2 AFR studies, so follow-up was not possible.



Supplementary Figure 7



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Lifelines Cohort Study

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STAGE 1 STUDY DESCRIPTIONS: Brief descriptions are provided below for each of the discovery studies. Unless otherwise noted, the blood draw for serum lipids and the determination of smoking status occurred concurrently (either at the same study visit or within a few months of each other).

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, and a sixth exam in 2016-2017. The ARIC study has been described in detail previously (The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: Design and objectives. Am J Epidemiol. 1989;129:687-702).

Bio*Me* Biobank (Bio*Me* Biobank of Institute for Personalized Medicine at Mount Sinai): The Bio*Me* Biobank, founded in September 2007, is an ongoing, consented electronic medical record (EMR)-linked bio- and data repository that enrolls participants non-selectively from the Mount Sinai Medical Center patient population. The Bio*Me* Biobank currently (Winter 2015) comprises over 31,000 participants from diverse ancestries characterized by a broad spectrum of (longitudinal) biomedical traits. On average 400 new participants are consented each month. Bio*Me* participants represent the broad ancestral, ethnic and socioeconomic diversity with a distinct and population-specific disease burden, characteristic of Northern Manhattan communities served by Mount Sinai Hospital. Enrolled participants consent to be followed throughout their clinical care (past, present, and future) at Mount Sinai in real-time, integrating their genomic information with their electronic health record for discovery research and clinical care implementation. Bio*Me* participants are predominantly of African, Hispanic/Latino, and European ancestry. Participants who self-identify as Hispanic/Latino further report to be of Puerto Rican (39%), Dominican (23%), Central/South American (17%), Mexican (5%) or other Hispanic (16%) ancestry. More than 40% of European ancestry participants are genetically determined to be of Ashkenazi Jewish ancestry.

The IRB-approved Bio*Me* Biobank consent permits use of samples and de-identified linkable past, present and future clinical information from EMRs; re-contacting participants for enrollment in future research; unlimited duration of storage, and access to clinical information from the entire medical records, as well as local and external sharing of specimens and data.

The Bio*Me* Biobank has a longitudinal design as participants consent to make any EMR data from past (dating back as far as 2003), present and future inpatient or outpatient encounters available for research. The median number of clinical encounters per participant is 21, reflecting predominant enrollment of participants with common chronic conditions from primary care facilities. Mount Sinai's system-wide Epic EMR implementation captures a full spectrum of biomedical phenotypes, including clinical outcomes, covariate and exposure data. This clinical information is complemented by detailed information on ancestry, residence history, familial medical history, education, socio-economic status, physical activity, smoking, alcohol use, and weight history being collected in a systematic manner by interview-based questionnaire at time of enrollment. Phenotype harmonization and validation is critical to facilitate consortium-wide analyses. By applying advanced medical

informatics and data mining tools, high-quality and validated phenotype data can be culled from Mount Sinai's Epic EMR. Fully-implemented phenotype algorithms include; T2D, CKD, CAD, lipid disorders, peripheral artery disease, resistant hypertension, blood cell traits, abdominal aortic aneurism, venous thromboembolism among others (see also Phenotype KnowledgeBase (PheKB) of the eMERGE Network (http://emerge.mc.vanderbilt.edu/emerge-network).

A total of 14,017 participants have been genotyped for both GWAS (11,150 Illumina OmniExpress BeadChip, 2,867 Affymetrix Human SNP Array 6.0) *and* ExomeChip (Illumina HumanExome v1.0 BeadChip) arrays funded by institutional sources. An additional 16,000 Bio*Me* participants are scheduled for genotyping using the Illumina MEGA Chip (by April 2015), funded by NHGRI through our PAGEII grant (U01HG007417) (n=12,500) and through institutional funds (n=3,500).

CARDIA (Coronary Artery Risk Development in Young Adults): CARDIA is a prospective multicenter study with 5,115 adults Caucasian and African American participants of the age group 18-30 years, recruited from four centers at the baseline examination in 1985-1986. The recruitment was done from the total community in Birmingham, AL, from selected census tracts in Chicago, IL and Minneapolis, MN; and from the Kaiser Permanente health plan membership in Oakland, CA. The details of the study design for the CARDIA study have been previously published.(1) Eight examinations have been completed since initiation of the study, respectively in the years 0, 2, 5, 7, 10, 15, 20, 25, and 30. Written informed consent was obtained from participants at each examination and all study protocols were approved by the institutional review boards of the participating institutions. Age and race were self-reported 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, and triglyceride levels were measured using enzymatic methods (2); HDL levels were measured after dextran-sulfate-magnesium precipitation of other lipoproteins.(3) LDL levels 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, LDL, 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-Mg+2 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 (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.

CROATIA-Korcula: The CROATIA-Korcula study is a family-based, cross-sectional study in the isolated island of Korcula that included 965 examinees aged 18-95. Blood samples were collected in 2007 along with many clinical and biochemical measures and lifestyle and health questionnaires.

CROATIA-Vis: The CROATIA-Vis study is a family-based, cross-sectional study in the isolated island of Vis that included 1,056 examinees aged 8-93. Blood samples were collected in 2003 and 2004 along with many clinical and biochemical measures and lifestyle and health questionnaires.

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[1-2], studied as part of the Genetic Research in Isolated Population (GRIP) program. 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. Aulchenko YS, Heutink P, Mackay I et al: Linkage disequilibrium in young genetically isolated Dutch population. Eur J Hum Genet 2004; 12: 527–534.

2. Pardo LM, MacKay I, Oostra B, van Duijn CM, Aulchenko YS: The effect of genetic drift in a young genetically isolated population. Ann Hum Genet 2005; 69:288–295.

FamHS (Family Heart Study): The NHLBI FamHS study design, collection of phenotypes and covariates as well as clinical examination have been previously described (https://dsgweb.wustl.edu/fhscc/; PMID: 8651220). In brief, the FamHS recruited 1,200 families (approximately 6,000 individuals), half randomly sampled, and half selected because of an excess of coronary heart disease (CHD) or risk factor abnormalities as compared with age- and sex-specific population rates. The participants were sampled from four population-based parent studies: the Framingham Heart Study, the Utah Family Tree Study, and two centers for the Atherosclerosis Risk in Communities study (ARIC: Minneapolis, and Forsyth County, NC). These individuals attended a clinic exam (1994-1996) and a broad range of phenotypes were assessed in the general domains of CHD, atherosclerosis, cardiac and vascular function, inflammation and hemostasis, lipids and lipoproteins, blood pressure, diabetes and insulin resistance, pulmonary function, diet, education, socioeconomic status, habitual behavior, physical activity, anthropometry, medical history and medication use. Approximately 8 years later, study participants belonging to the largest pedigrees were invited for a second clinical exam (2002-04). The most important CHD risk factors were measured again, including lipids, parameters of glucose metabolism, blood pressure, anthropometry, and several biochemical and hematologic markers. In addition, a computed tomography examination provided measures of coronary and aortic calcification, and abdominal and liver fat burden. Medical history and medication use was updated. A total of 2,756 European ancestry subjects in 510 extended random and high CHD risk families

were studied. Also, 633 African ancestry subjects were recruited at ARIC field center at the University of Alabama in Birmingham. Informed consent was obtained from all participants.

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 2^{nd} generation (1971-1975) and the 3^{rd} 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. Current smoking and ever smoking data were also recorded at the first exam of each cohort and used in analyses.

GENOA (Genetic Epidemiology Network of Arteriopathy): GENOA is one of four networks in the NHLBI Family-Blood Pressure Program (FBPP; PubMed PMIDs 11799070, 15121494). GENOA's long-term objective is to elucidate the genetics of target organ complications of hypertension, including both atherosclerotic and arteriolosclerotic 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 $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg based on the second and third readings at the time of their clinic visit. Exclusion criteria were secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes mellitus, or active malignancy. During the first exam (1995-2000), 1,583 European Americans from Rochester, MN and 1,854 African Americans from Jackson, MS were examined. Between 2000 and 2005, 1,241 of the European Americans and 1,482 of the African Americans returned for a second examination. Because African-American probands for GENOA were recruited through the Atherosclerosis Risk in Communities (ARIC) Jackson field center participants, we excluded ARIC participants from analyses.

GenSalt (Genetic Epidemiology Network of Salt Sensitivity): GenSalt is a multi-center, family based study designed to identify, through dietary sodium and potassium intervention, salt-sensitivity susceptibility genes which may underlie essential hypertension in rural Han Chinese families. Approximately 629 families with at least one 'proband' with high blood pressure were recruited and tested for a wide variety of physiological, metabolic and biochemical measures at baseline and at multiple times during the 3-week intervention. The intervention consisted of one week on a low sodium diet, followed by one week on a high sodium diet, and finally one week on a high sodium diet with a potassium supplement.

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

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

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

Genotyping: Genotyping was performed by the Center for Inherited Disease Research (CIDR) using the Illumina Human1M-Duo BeadChip system. Samples were excluded from the dataset for the reasons of sample failure, genotypic sex mismatch, and first-degree relative of an included individual based on genotype data. Genotyping was successful in 1663 Caucasians. Analysis was restricted to SNPs with minor allele frequency $\geq$ 1%, call rate $\geq$97% and HWE p$\geq$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.

HERITAGE (Health, Risk Factors, Exercise Training and Genetics): The HERITAGE is the only known family-based study of exercise intervention to evaluate the role of genes and sequence variants involved in the response to a physically active lifestyle. The current study is based on the data collected at baseline of the study from 99 White families (244 males, 255 females). All subjects were required to be sedentary and free of chronic diseases at baseline. There are over 18 trait domains (e.g. dietary, lipids and lipoproteins, glucose and insulin metabolism [fasting and IVGTT], steroids, body composition and body fat distribution, cardiorespiratory fitness), for a grand total of over one thousand variables. Moreover, most of the outcome traits were measured twice on two separate days both at baseline and after exercise training was completed. Marker data include a genome-wide linkage scan and GWAS, in addition to a large number of candidate genes.

HUFS (Howard University Family Study): HUFS followed a population-based selection strategy designed to be representative of African American families living in the Washington, DC metropolitan area. The major objectives of the HUFS were to study the genetic and environmental basis of common complex diseases including hypertension, obesity and associated phenotypes. Participants were sought through door-to-door canvassing, advertisements in local print media and at health fairs and other community gatherings. In order to maximize the utility of this cohort for the study of multiple common traits, families were not ascertained based on any phenotype. During a clinical examination, demographic information was collected by interview.

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

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

GS:SFHS (Generation Scotland: Scottish Family Health Study): The Generation Scotland (www.generationscotland.org) Scottish Family Health Study (GS:SFHS) is a family-based genetic epidemiology cohort with DNA, other biological samples (serum, urine and cryopreserved whole blood) and socio-demographic and clinical data from approximately 24,000 volunteers, aged 18-98 years, in ~7,000 family groups. An important feature of GS:SFHS is the breadth of phenotype information, including detailed data on cognitive function, personality traits and mental health. Although data collection was cross-sectional, GS:SFHS becomes a longitudinal cohort as a result of the ability to link to routine NHS data, using the community health index (CHI) number.

JHS (Jackson Heart Study): The Jackson Heart Study is a longitudinal, community-based observational cohort study investigating the role of environmental and genetic factors in the development of cardiovascular disease in African Americans. Between 2000 and 2004, a total of 5301 participants were recruited from a tri-county area (Hinds, Madison, and Rankin Counties) that encompasses Jackson, MS. Details of the design and recruitment for the Jackson Heart Study cohort has been previously published.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.

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.

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.

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 approximately 7,900 persons, aged 55 years and older, who underwent a home interview and extensive physical examination at the baseline and during follow-up rounds every 3-4 years (RS-I). Cohort was extended in 2000/2001 (RS-II, 3,011 individuals aged 55 years and older) and 2006/2008 (RS-III, 3,932 subjects, aged 45 and older). Written informed consent was obtained from all participants and the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the study. For RS-II and RS-III, smoking determination and lipids measurements occurred concurrently; for RS-I, however, smoking status was determined during the initial study visit, while the blood draw for lipids measurements was conducted during a third follow-up visit to the study center.

1. Ikram, M.A., Brusselle, G.G.O., Murad, S.D., Duijn, C.M. van, Franco, O.H., Goedegebure, A., Klaver, C.C.W., Nijsten, T.E.C., Peeters, R.P., Stricker, B.H., Tiemeier, H., Uitterlinden, A.G., Vernooij, M.W., Hofman, A. The Rotterdam Study: 2018 update on objectives, design and main results. Eur J Epidemiol 2017 doi:10.1007/s10654-017-0321-4

SCHS-CHD (Singapore Chinese Health Study - Coronary Heart Disease): SCHS-CHD is a case-control study of coronary heart disease that was nested within the Singapore Chinese Health Study (SCHS), a prospective cohort study of 63,257 Singaporean Chinese men and women aged 45-74 years living in Singapore. We selected cases and controls from participants that provided blood samples and were free of coronary heart disease and stroke at the time of blood collection (N=24,454). Cases (N=760) had acute myocardial infarction (AMI) or died of coronary heart disease. AMI was identified through the Singapore Myocardial Infarction Registry or through the nationwide hospital discharge database followed by confirmation of AMI by cardiologists' review of medical records using the Multi-Ethnic Study of Atherosclerosis criteria (available at: http://www.mesa-nhlbi.org/manuals.aspx). Coronary heart disease deaths were identified through the Singapore Registry of Births and Deaths (ICD9 410-414 as first stated cause of death). Matched controls (N=1,491) were selected using a risk-set sampling strategy. Controls were participants who were alive and free of coronary heart disease at the time of the diagnosis or death of the index cases and were matched for age, sex, dialect group, year of recruitment and date of blood collection. In-person interviews and phlebotomy were conducted before the onset of disease and non-fasting venous blood was stored at -80^0C for extraction of DNA and blood biochemistry.

SEED (Singapore Epidemiology of Eye Diseases): SiMES (Singapore Malay Eye Study): SiMES is a population-based cross-sectional epidemiological study of 3,280 individuals from one of the three major ethnic groups residing in Singapore. In summary, 5,600 individuals have been selected by an age-stratified sampling strategy. Among these 4,168 individuals are eligible for this study. 3,280 individuals finally participated in the

study (78.7% response rate). All subjects were Malay and aged 40-80 years [PMID: 17365815; 25953847]. Non-fasting lipid levels were measured by an automated autoanalyzer (ADVIA 2400, Bayer Diagnostics). **SINDI (Singapore Indian Eye Study)**: SINDI is a population-based, cross-sectional study of Asian Indian adults aged 40–80 years residing in the Southwestern part of Singapore. Age stratified random sampling was used to select 6,350 eligible participants, of which 3,400 participated in the study (75.6% response rate). Detailed methodology has been published [PMID: 19995197; 25953847]. Non-fasting lipid levels were measured by an automated autoanalyzer (Beckman Coulter Unicel DxC 800). **SCES (Singapore Chinese Eye Study):** SCES is a population-based, cross-sectional study of Chinese adults aged 40–80 years residing in the Southwestern part of Singapore. Age stratified random sampling was used to select 6,350 eligible participants, of which 3,353 participated in the study (72.8% response rate). Detailed methodology has been published [PMID: 19995197; 25953847]. Non-fasting lipid levels were measured by an automated autoanalyzer (Beckman Coulter Unicel DxC 800).

SP2 (Singapore Prospective Study Program): SP2 is a population-based study of diabetes and cardiovascular disease in Singapore. It first surveyed subjects (Chinese, Malay and Indian) from four cross-sectional studies that were conducted in Singapore between 1982 and 1998. Subjects were between the ages of 24-95 years and represented a random sample of the Singapore population. Subjects were re-visited between 2003 and 2007. Among the 10,747 individuals who were eligible, 5,157 subjects completed a questionnaire and the subsequent clinical examinations [PMID: 19406920]. Data from this re-visit were utilized for this study. Fasting HDL-C, TC and TG were measured by an automated analyzer autoanalyzer (ADVIA 2400, Bayer Diagnostics). LDL-C was calculated from Friedewald formula [PMID: 4337382].

WGHS (Women's Genome Health Study): WGHS is a prospective cohort of female North American health care professionals representing participants in the Women's Health Study (WHS) trial who provided a blood sample at baseline and consent for blood-based analyses (PMID: 18070814). Participants in the WHS were 45 years or older at enrollment and free of cardiovascular disease, cancer or other major chronic illness. The current data are derived from 23,294 WGHS participants for whom whole genome genotype information was available at the time of analysis and for whom self-reported European ancestry could be confirmed by multidimensional scaling analysis of 1,443 ancestry informative markers in PLINK v. 1.06. At baseline, BP and lifestyle habits related to smoking, consumption of alcohol, and physical activity as well as other general clinical information were ascertained by a self-reported questionnaire, an approach which has been validated in the WGHS demographic, namely female health care professionals.

WHI (Women's Health Initiative): WHI is a long-term national health study that focuses on strategies for preventing common diseases such as heart disease, cancer and fracture in postmenopausal women. A total of 161,838 women aged 50–79 years old were recruited from 40 clinical centers in the US between 1993 and 1998. WHI consists of an observational study, two clinical trials of postmenopausal hormone therapy (HT, estrogen alone or estrogen plus progestin), a calcium and vitamin D supplement trial, and a dietary modification trial [1]. Study recruitment and exclusion criteria have been described previously [1]. Recruitment was done through mass mailing to age-eligible women obtained from voter registration, driver's license and Health Care Financing Administration or other insurance list, with emphasis on recruitment of minorities and older women [2]. Exclusions included participation in other randomized trials, predicted survival < 3 years, alcoholism, drug dependency, mental illness and dementia. For the CT, women were ineligible if they had a systolic BP > 200 mm Hg or diastolic BP > 105 mm Hg, a history of hypertriglyceridemia or breast cancer. Study protocols and consent forms were approved by the IRB at all participating institutions. Socio-demographic characteristics, lifestyle, medical history and self-reported medications were collected using standardized questionnaires at the screening visit. Physical measures of height, weight and blood pressure were measured at a baseline clinical visit [2]. 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.

1. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, Rossouw JE. The women's health initiative recruitment methods and results. Ann Epidemiol. 2003;13:S18-77

2. Design of the women's health initiative clinical trial and observational study. The women's health initiative study group. Control Clin Trials. 1998;19:61-109

STAGE 2 STUDY DESCRIPTIONS: Brief descriptions are provided below for each of the replication studies/cohorts. Unless otherwise noted, the blood draw for serum lipids and the determination of smoking status occurred concurrently (either at the same study visit or within a few months of each other).

AA-DHS (African American Diabetes Heart Study): AA-DHS objectives are to improve understanding of ethnic differences in CAC and CP in populations of African and European ancestry. The AA-DHS consists of self-reported African Americans with T2D recruited from two Wake Forest School of Medicine (WFSM) studies: the family-based Diabetes Heart Study (DHS) and unrelated individuals in the AA-DHS. DHS is a cross-sectional study of European American and African American families with siblings concordant for T2D. AA-DHS started after DHS and enrolled unrelated African Americans. The AA-DHS GWAS utilized the Illumina 5M chip with imputation to 1,000 Genomes.

Airwave (The Airwave Health Monitoring Study): The Airwave Health Monitoring Study (22) was established to evaluate possible health risks associated with use of TETRA, a digital communication system used by police forces and other emergency services in Great Britain since 2001. The study has been broadened to investigate more generally the health of the work force. From 2004, participants from each force who agreed to participate were enrolled either with an enrolment questionnaire or a comprehensive health screening performed locally. This includes questionnaire, 7-day food diaries, anthropometry, measurements of cardiovascular and cognitive function, blood chemistry, coagulation and hematology. By March 2015, the study had recruited 53,606 participants, of whom 45,433 had attended the health screening, and 14,002 have genotype data (1000G imputed).

Ref: Elliott, P. et al. The Airwave Health Monitoring Study of police officers and staff in Great Britain: rationale, design and methods. Environ Res 134, 280-5 (2014).

ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial): ASCOT is a randomised control clinical trial investigating the cardiac outcomes of blood pressure lowering and lipid lowering treatments. Of 19,342 hypertensive patients (40–79 years of age with at least three other cardiovascular risk factors) who were randomized to one of two antihypertensive regimens in ASCOT (atenolol, Beta-Blocker vs amlodipine, Calcium-Channel-Blocker), 10,305 patients with non-fasting total cholesterol concentrations of 6.5 mmol/l or less (measured at the non-fasting screening visit) had been randomly assigned additional atorvastatin 10 mg or placebo. Only a proportion of United Kingdom, Irish, Sweden, Norway, Finland and Denmark consented to contribute DNA and participate in genetic studies. PMID 11685901

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.

BBJ (Biobank Japan Project): The Biobank Japan (BBJ) Project was established in 2003 with the aim of the implementation of personalized medicine as a leading project of Ministry of Education, Culture, Sports, Science and Technology (MEXT). In collaboration with twelve cooperating institutes, the BBJ has recruited a total of 200,000 people, suffering from at least one of the 47 target common diseases, in the first phase (5-year period). BBJ has collected biospecimens including DNA and serum as well as various clinical and lifestyle information through interview or medical records by using standardized questionnaire. All participants gave written informed consent to this project and this study was approved by ethical committees of RIKEN and participating institutes.

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

BRIGHT (British Genetics of Hypertension): Participants of the BRIGHT Study are recruited from the Medical Research Council General Practice Framework and other primary care practices in the UK. Each case had a history of hypertension diagnosed prior to 60 years of age with confirmed blood pressure recordings corresponding to seated levels >150/100mmHg (1 reading) or mean of 3 readings >145/95 mmHg. BRIGHT is focused on recruitment of hypertensive individuals with BMI<30. Sample selection for GWAS was based on DNA availability and quantity. PMID 12826435

CAGE-Amagasaki (Cardio-metabolic Genome Epidemiology Network, Amagasaki Study): The Amagasaki Study (CAGE-Amagasaki) is an ongoing population-based cohort study of 5,743 individuals (3,435 males and 2,310 females), aged >18 years and recruited for a baseline examination between September 2002 to August 2003. Participants were interviewed by trained personnel to obtain information on medical and lifestyle variables, and consented to provide DNA for genotyping of molecular variants to investigate genetic susceptibility for so-called lifestyle-related diseases such as hypertension and cardiovascular disorder.

CFS (Cleveland Family Study): The Cleveland Family Study (CFS) is a family-based, longitudinal study designed to characterize the genetic and non-genetic risk factors for sleep apnea. In total, 2534 individuals (46% African American) from 352 families were studied on up to 4 occasions over a period of 16 years (1990-2006). The initial aim of the study was to quantify the familial aggregation of sleep apnea. 632 African Americans were genotyped on the Affymetrix array 6.0 platform through the CARe Consortium with suitable genotying quality control. A further 122 African-Americans had genotyping based on the Illumina OmniExpress + Exome platform. Genomes were imputed separately for each chip based on a 1000 Genomes Project Phase 3 Version 5 cosmopolitan template using SHAPEIT and IMPUTE2..

DESIR (Data from an Epidemiological Study on the Insulin Resistance): The DESIR cohort study aims to: describe and understand the relations between the abnormalities of the syndrome, their evolution, according to age and sex; search for risk factors of insulin resistance, in particular factors associated with the environment, lifestyle and genetic markers; quantify the links between the syndrome and both cardiovascular disease and diabetes; evaluate the frequency of the syndrome in terms of its consequences on public health.

DFTJ (Dongfeng-Tongji Cohort Study): The DFTJ-cohort study includes 27,009 retired employees from a state-owned automobile enterprise in China. This study was launched in 2008 and will be followed up every 5 years. In 2013 we conducted the first follow-up. By using semi-structural questionnaire and health examination, those having cancer or severe diseases were excluded. Fasting blood samples and detailed epidemiology data were collected. The main goal of the cohort was to identify the environmental and genetic risk factors and the gene-environment interactions on chronic diseases, and to find novel biomarkers for chronic disease and mortality prediction. Finally, 1,461 included in the present study with GWAS data. All of the participants wrote informed consent and the ethical committees in the Tongji Medical College approved this research project. Detailed information has been described in elsewhere(1).

QC criteria and imputation methods:

We did the GWAS scan on the DFTJ-cohort with Affymetrix Genome-Wide Human SNP Array 6.0 chips. In total, we genotyped 906,703 SNPs among 1,461 subjects. After stringent QC filtering, SNPs with MAF < 0.01, Hardy-Weinberg Equilibrium (HWE) < 0.0001, and SNP call rate < 95% were excluded. Individuals with call rates < 95% were also not included for further analysis. In total, we retained 1,452 subjects with 658,288 autosomal SNPs for statistical analyses, with an overall call rate of 99.68%. We used MACH 1.0 software to impute untyped SNPs using the LD information from the HapMap phase II database (CHB+JPT as a reference set (2007-08_rel22, released 2007-03-02). Imputed SNPs with high genotype information content (Rsq > 0.3 for MACH) were kept for the further association analysis.

Reference

1) Wang, F., Zhu, J., Yao, P., Li, X., He, M., Liu, Y., Yuan, J., Chen, W., Zhou, L., Min, X. et al. (2012) Cohort profile: The Dongfeng-Tongji cohort study of retired workers. International journal of epidemiology.

DHS (Diabetes Heart Study): The Diabetes Heart Study (DHS) is an ongoing family-based cohort study investigating the epidemiology and genetics of cardiovascular disease (CVD) in a population-based sample. The DHS recruited T2D-affected siblings without advanced renal insufficiency from 1998 through 2005 in western North Carolina. DHS has collected genetic data on 1,220 self-described European American (EA) individuals from 475 families. Genotyping was completed using an Affymetrix Genome-Wide Human SNP Array 5.0 with imputation of 1,000 Genomes project SNPs from this array using IMPUTE2 and the Phase I v2, cosmopolitan (integrated) reference panel, build 37.

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%.

EGCUT (Estonian Genome Center - University of Tartu (Estonian Biobank)): The Estonian Biobank is the population-based biobank of the Estonian Genome Center at the University of Tartu (www.biobank.ee; EGCUT). The entire project is conducted according to the Estonian Gene Research Act and all of the participants have signed the broad informed consent. The cohort size is up to 51535 individuals from 18 years of age and up, which closely reflects the age, sex and geographical distribution of the Estonian population. All of the subjects are recruited randomly by general practitioners and physicians in hospitals. A Computer Assisted Personal interview is filled within 1-2 hours at a doctor's office, which includes personal, genealogical, educational, occupational history and lifestyle data. Anthropometric measurements, blood pressure and resting heart rate are measured and venous blood taken during the visit. Medical history and current health status is recorded according to ICD-10 codes.

EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk: The European Prospective Investigation of Cancer (EPIC)-Norfolk study is a population-based cohort study established to study the links diet, lifestyle factors and cancer and other health outcomes. Participants are men and women who were aged between 40 and 79 when they joined the study and who lived in Norwich, UK and the surrounding towns and rural areas. They have been contributing information about their diet, lifestyle and health through questionnaires and health checks over two decades. The Norwich Local Research Ethics Committee granted ethical approval for the study. All participants gave written informed consent.

The EPIC-InterAct Case-Cohort Study: EPIC- InterAct is a type 2 diabetes case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study. EPIC was initiated in the late 1980s and involves collaboration between 23 research institutions across Europe in 10 countries. The majority of EPIC cohorts were recruited from the general population, with some exceptions. French cohorts included women who were members of a health insurance scheme for school and university employees; Turin and Ragusa (Italy) and the Spanish centres included some blood donors. Participants from Utrecht (Netherlands) and Florence (Italy) were recruited via a breast cancer screening program. The majority of participants recruited by the EPIC Oxford (UK) centre consisted of vegetarian and "health conscious" volunteers from England, Wales, Scotland, and Northern Ireland. EPIC-InterAct sampled a random sub-cohort and all individuals who subsequently developed incident T2DM over follow up from the full cohort of participants in EPIC who provided blood samples at baseline in Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden and the UK. Smoking status was determined at baseline and lipid measurements at baseline were undertaken in a centralized laboratory on all participants in the case-cohort study.

FENLAND (The Fenland Study): The Fenland study is a population-based cohort study that uses objective measures of disease expoure to investigate the influence of diet, lifestyle and genetic factors on the development of diabetes and obesity. The volunteers are recruited from general practice lists in and around Cambridgeshire (Cambridge, Ely, and Wisbech) in the United Kingdom from birth cohorts from 1950–1975.

FUSION (Finland-United States Investigation of NIDDM Genetics): The Finland-United States Investigation of NIDDM Genetics (FUSON) study is a long-term effort to identify genetic variants that predispose to type 2 diabetes (T2D) or that impact the variability of T2D-related quantitative traits. The FUSION GWAS sample consists of 1,161 Finnish T2D cases and 1,174 Finnish normal glucose-tolerant (NGT) controls (Scott et al. Science 2007). Cases are defined by fasting plasma glucose ≥ 7.0 mmol/l or 2-h plasma glucose ≥ 11.1 mmol/l, by report of diabetes medication use, or based on medical record review. 789 FUSION cases each reported at least one T2D sibling; 372 Finrisk 2002 T2D cases came from a Finnish population-based risk factor survey. NGT controls are defined by fasting glucose < 6.1 mmol/l and 2-h glucose < 7.8 mmol/l. FUSION controls include 119 subjects from Vantaa, Finland who were NGT at ages 65 and 70 years, 304 NGT spouses from FUSION families, and 651 Finrisk 2002 subjects. The controls were approximately frequency matched to the cases by age, sex, and birth province. Smoking and alcohol data are only available in the FUSION subset of our GWAS samples.

Scott, L.J. et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 316, 1341–1345, 2007.

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.

GLACIER (Gene x Lifestyle Interactions and Complex Traits Involved in Elevated Disease Risk): The Gene-Lifestyle interactions And Complex traits Involved in Elevated disease Risk (GLACIER) Study is nested within the Västerbotten Health Survey, which is part of the Northern Sweden Health and Disease Study, a population-based prospective cohort study from northern Sweden. Participants were genotyped with Illumina CardioMetaboChip array. This array contains ~200,000 variants, the majority being common variants. Systolic and diastolic blood pressures were measured once following a period of five minutes rest with the participant in the supine position using a mercury-gauge sphygmomanometer. Analysis of serum lipids (HDL-C, triglycerides and total cholesterol) were undertaken at the Department of Clinical Chemistry at Umeå University Hospital using routine methods. LDL-C was determined using the Friedewald formula. All participants completed a detailed, optically readable, health and lifestyle questionnaire including questions about smoking status and alcohol intake (FFQ). Cohort description - PMID: 25396097

GRAPHIC (Genetic Regulation of Arterial Pressure of Humans in the Community): The GRAPHIC Study comprises 2024 individuals from 520 nuclear families recruited from the general population in Leicestershire, UK between 2003-2005 for the purpose of investigating the genetic determinants of blood pressure and related cardiovascular traits. A detailed medical history was obtained from study subjects by standardized questionnaires and clinical examination was performed by research nurses following standard procedures. Measurements obtained included height, weight, waist-hip ratio, clinic and ambulatory blood pressure and a 12-lead ECG.

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

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

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

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

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

HyperGEN-AXIOM (Hypertension Genetic Epidemiology Network): HyperGEN is a family-based study that investigates the genetic causes of hypertension and related conditions in EA and AA subjects. HyperGEN recruited hypertensive sibships, along with their normotensive adult offspring, and an age-matched random sample. HyperGEN has collected data on 2,471 Caucasian-American subjects and 2,300 African-American subjects, from five field centers in Alabama, Massachusetts, Minnesota, North Carolina, and Utah. HyperGEN participates as a discovery study using GWAS available in a large subset of the samples. The remaining AA subjects without GWAS data were genotyped on the Affymetrix Axiom chip as part of a HyperGEN admixture mapping ancillary study. After excluding subjects already included in the original HyperGEN (or with family members included), this subset of approximately 450 AA subjects are included in the HyperGEN-AXIOM study which participates in replications.

Shetty PB, Tang H, Tayo BO, Morrison AC, Hanis CL, Rao DC, Young JH, Fox ER, Boerwinkle E, Cooper RS, Risch NJ, Zhu X; Candidate Gene Association Resource (CARe) Consortium. Variants in CXADR and F2RL1 are associated with blood pressure and obesity in African-Americans in regions identified through admixture mapping. J Hypertens. 2012 Oct;30(10):1970-6. PMID:22914544

INGI-CARL & INGI-FVG (Italian Network Genetic Isolates): INGI-FVG and INGI-CARL studies include samples coming from isolated populations and belong to the Italian Network of Genetic Isolates (INGI). The Carlantino cohort (INGI-CARL) is a population-based study including approximately 1000 samples from an isolated village of Southern Italy. INGI-CARL examined about 1000 subjects between 1998 and 2005 coming from a small village of the South of Italy situated in the extreme northern part of Puglia Region, while INGI-FVG involved about 1700 subjects between 2008 and 2011 coming from six different villages located in the North-East of Italy in Friuli Venezia Giulia region. A questionnaire was administered to each participant to obtain socio-demographic information, as well as data on professional activity, family history, eating habits and lifestyle, such as smoking, coffee and alcohol consumption, physical activity. Furthermore, a medical screening, including anamnesis, blood pressure, drugs and clinical chemistry evaluation (blood count and different biochemical parameters, such as lipids) were made. All participants gave their written informed consent.

IRAS (Insulin Resistance Atherosclerosis Study): The Insulin Resistance Atherosclerosis Study (IRAS) was an epidemiologic cohort study designed to examine the relationship between insulin resistance and carotid atherosclerosis across a range of glucose tolerance. Individuals of self-reported Mexican-American ethnicity were recruited in San Antonio, TX and San Luis Valley, CO. Recruitment was balanced across age and glucose tolerance status. Inclusion of IRAS data is limited to 194 normoglycemic individuals with genotype data from the Illumina OmniExpress and Omni 1S arrays and imputation to the 1000 Genome Integrated Reference Panel (phase I).

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

JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin): Genetic analysis was performed in a sub-population from JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), an international, randomized, placebo-controlled trial of rosuvastatin (20mg/day) in the primary prevention of cardiovascular disease conducted among apparently healthy men and women with LDL-C < 130 mg/dL and hsCRP ≥ 2 mg/L (PMIDs: 18997196, 22331829). Individuals with diabetes or triglyceride concentration >500mg/dL were excluded. The present analysis includes only individuals who provided consent for genetic analysis, had successfully collected genotype information, and who had either verified European or verified South African black ancestry.

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]

(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.

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

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.

LLFS (The Long Life Family Study): LLFS is a family-based cohort study, including four clinical centers: Boston University Medical Center in Boston, MA, USA, Columbia University College of Physicians and Surgeons in New York City, NY, USA, the University of Pittsburgh in Pittsburgh PA, USA, and University of

Southern Denmark, Denmark. The study characteristics, recruitment, eligibility and enrollment have been previously described (Pedersen et al., 2006, PMID: 17150149; Sebastiani et al., 2009, PMID: 19910380; Newman et al., 2011, PMID: 21258136). In brief, the LLFS was designed to determine genetic, behavioral, and environmental factors related to families of exceptionally healthy, elderly individuals. Phase 1 was conducted between 2006 and 2009 recruiting 4,953 individuals from 539 families. The probands were at least 79 years old in the USA centers, and 90 years old or above in Denmark. The families were selected to participate in the study based on The Family Longevity Selection Score (FLoSS) (Sebastiani et al., 2009, PMID: 19910380), a score generated according to birth-year cohort survival probabilities of the proband and siblings; probands and their families with FLoSS score of 7 or higher, at least one living sibling, and at least one living offspring (minimum family size of 3), who were able to give informed consent and willing to participate were recruited. The individuals were genotyped using ~2.3 million SNPs from the Illumina Omni chip, and then imputed on phased 1000 Genomes with Cosmopolitan data as a reference using MACH and MINIMAC. After excluding participants with 80 years and older, ~3,200 individuals have been included in the analyses for replication.

LOLIPOP (London Life Sciences Prospective Population Study): LOLIPOP is a population based prospective study of about 28K Indian Asian and European men and women, recruited from the lists of 58 General Practitioners in West London, United Kingdom between 2003 and 2008 [1]. Indian Asians had all four grandparents born on the Indian subcontinent. Europeans were of self-reported white ancestry. At enrolment all participants completed an interviewer-administered questionnaire for demographic data, medical history, and smoking and alcohol drinking habits. Anthropometric data were collected and blood pressure measured using an Omron 705CP with the mean of three measurements recorded. Blood samples were collected for the measurement of lipid profile after an overnight fasting of at least 8 hours. Aliquots of whole blood were stored at -80C for extraction of genomic DNA. The LOLIPOP study is approved by the local Research Ethics Committees and all participants provided written informed consent.

Loyola GxE (Kingston Gene-by-environment; subset of International Collaborative Study of Hypertension in Blacks (ICSHIB)): The Kingston GxE cohort was obtained from a survey conducted in Kingston, Jamaica as part of a larger project to examine gene by environment interactions in the determination of blood pressure among adults 25-74 years [PMID: 9103091]. The principal criterion for eligibility was a body mass index in either the top or bottom third of BMI for the Jamaican population. Participants were identified principally from the records of the Heart Foundation of Jamaica, a non-governmental organization based in Kingston, which provides low-cost screening services (height and weight, blood pressure, glucose, cholesterol) to the general public. Other participants were identified from among participants in family studies of blood pressure at the Tropical Metabolism Research Unit (TMRU) and from among staff members at the University of the West Indies, Mona.

Loyola SPT (Spanish Town; subset of International Collaborative Study of Hypertension in Blacks (ICSHIB)): Participants were recruited from Spanish Town, a stable, residential urban area neighboring the capital city of Kingston, Jamaica as part of the ICSHIB [PMID: 9103091]. A stratified random sampling scheme was used to recruit adult males and females aged 25–74 years from the general population. Spanish Town was chosen because its demographic make-up was broadly representative of Jamaica as a whole.

METSIM (Metabolic Syndrome In Men): The METSIM Study includes 10,197 men, aged from 45 to 73 years at recruitment, randomly selected from the population register of the Kuopio town, Eastern Finland, and examined in 2005-2010 (Stancakova A, et al. Diabetes 2009). The aim of the study is to investigate genetic and non-genetic factors associated with type 2 diabetes and cardiovascular disease and its risk factors.

Stancakova A, Javorsky M, Kuulasmaa T, Haffner SM, Kuusisto J, Laakso M: Changes in insulin sensitivity and insulin release in relation to glycemia and glucose tolerance in 6416 Finnish men. Diabetes 58:1212-1221, 2009.

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

OBA (French obese cases): Study of the genetics of obesity in adults.

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.

PREVEND (The Prevention of REnal and Vascular ENd stage Disease study): The PREVEND study is an ongoing prospective study investigating the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease. Inhabitants 28 to 75 years of age (n=85,421) in the city of Groningen, The Netherlands, were asked to complete a short questionnaire, 47% responded, and individuals were then selected with a urinary albumin concentration of at least 10 mg/L (n = 7,768) and a randomly selected control group with a urinary albumin concentration less than 10 mg/L (n = 3,395). Details of the protocol have been described elsewhere (Hillege HL et al. Circulation 2002;106:1777-82).

PROCARDIS (Precocious Coronary Artery Disease): The PROCARDIS (European collaborative study of the genetics of precocious coronary artery disease) study is a multi-centre case-control study in which CAD cases and controls were recruited from the United Kingdom, Italy, Sweden and Germany. Cases were defined as symptomatic CAD before age 66 years and 80% of cases also had a sibling in whom CAD had been diagnosed before age 66 years. CAD was defined as clinically documented evidence of myocardial infarction (MI) (80%), coronary artery bypass graft (CABG) (10%), acute coronary syndrome (ACS) (6%), coronary angioplasty (CA) (1%) or stable angina (hospitalization for angina or documented obstructive coronary disease) (3%). The cases included 2,136 cases who were half or full siblings. PROCARDIS controls had no personal or sibling history of CAD before age 66 years.

RHS (Ragama Health Study): The Ragama Health Study (RHS) is a population-based study of South Asian men and women aged 35-64yrs living in the Ragama Medical Officer of Health (MOH) area, near Colombo, Sri Lanka.* Consenting adults attended a clinic after a 12-h fast with available health records, and were interviewed by trained personnel to obtain information on medical, sociodemographic, and lifestyle variables. A 10-mL sample of venous blood was obtained from each subject. The concurrent study was performed in two tea plantation estates in the Lindula MOH area, near Nuwara Eliya (180 km from Colombo), to investigate the gene-environment interaction in a community with differing lifestyles (e.g., physical activity and diet).. The RHS is a collaborative effort between the Faculty of Medicine, University of Kelaniya and the National Center for Global Health and Medicine, Japan.

*Reference: Dassanayake, A.S. et al. Prevalence and risk factors for non-alcoholic fatty liver disease among adults in an urban Sri Lankan population. J Gastroenterol Hepatol 24, 1284-8 (2009).

SHEEP (Stockholm Heart Epidemiology Project): The SHEEP is a population based case-control study of risk factors for first episode of acute myocardial infarction. The study base comprised all Swedish citizens resident in the Stockholm county 1992-1994 who were 45-70 years of age and were free of previous clinically diagnosed myocardial infarction.

Cases were identified using three different sources: 1) coronary units and internal medicine wards for acute care in all Stockholm hospitals; 2) the National Patient Register; and 3) death certificates. For the present study, only cases who survived at least 28 days were considered (n=1213).

First time incident myocardial infarction cases (n=1213) were identified during a 2-year period (1992-1993) for men and during a 3-year period (1992-1994) for women. Controls (n=1561) were randomly recruited from the study population continuously over time within 2 days of the case occurrence and matched to cases on age (5-years interval), sex and hospital catchment area using computerized registers of the population of Stockholm. Five control candidates were sampled simultaneously to be able to replace potential non-respondent controls. Occasionally, because of late response of the initial control, both the first and alternative controls were considered resulting in the inclusion of more controls than cases. Postal questionnaires covering a wide range of exposure areas including occupational exposures, life style factors, social factors and health related factors were distributed to the participants. Clinical investigations were performed at least three months after myocardial infarction of cases and their matched controls. The investigations included blood samplings under fasting conditions with collection of whole blood for DNA extraction, serum and plasma. A biobank was established containing DNA, serum and plasma.

Exposure information based on both the questionnaire and biological data from the health examination was available for 78% of the male and 67% of the female non-fatal cases; the corresponding figures for their controls were 68% and 64%.

SHIP (Study of Health in Pomerania): The Study of Health In Pomerania (SHIP) is a prospective longitudinal population-based cohort study in Mecklenburg-West Pomerania assessing the prevalence and incidence of common diseases and their risk factors (PMID: 20167617). SHIP encompasses the two independent cohorts SHIP and SHIP-TREND. Participants aged 20 to 79 with German citizenship and principal residency in the study area were recruited from a random sample of residents living in the three local cities, 12 towns as well as 17 randomly selected smaller towns. Individuals were randomly selected stratified by age and sex in proportion to population size of the city, town or small towns, respectively. A total of 4,308 participants were recruited between 1997 and 2001 in the SHIP cohort. Between 2008 and 2012 a total of 4,420 participants were recruited in the SHIP-TREND cohort. Individuals were invited to the SHIP study 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. Imputation of genotypes in SHIP 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. Included in the current project were 892 women who had GWAS data and lipids data.

The Shanghai Men's Health Study (SMHS) is an ongoing population-based cohort study of 61,480 Chinese men who were aged between 40 and 74 years, were free of cancer at enrollment, and lived in urban Shanghai, China; 45,766 (74.4%) provided a blood samples. Recruitment for the SMHS was initiated in 2002 and completed in 2006. The self-administered questionnaire includes information on demographic characteristics, disease and surgery histories, personal habits (such as cigarette smoking, alcohol consumption, tea drinking, and ginseng use), residential history, occupational history, and family history of cancer. Included in the current project were 298 men who had GWAS data and lipids data.

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.

TAICHI-G: The TaiChi consortium consists of 7 studies that collaborated initially in a large scale metabochip study, and became an ongoing consortium for studies of cardiometabolic disease in the Chinese population in Taiwan. The seven studies included the following: 1) HALST (Healthy Aging Longitudinal Study in Taiwan), a population based epidemiologic study of older adults living in all major geographic regions of Taiwan established by the Taiwan National Health Research Institutes (NHRI); 2) SAPPHIRe (Stanford-Asian Pacific Program in Hypertension and Insulin Resistance), a family based study established in 1995 with an initial goal of identifying major genetic loci underlying hypertension and insulin resistance in East Asian populations, with Taiwan subjects participating in the TaiChi consortium; 3) TCAGEN (Taiwan Coronary Artery Disease GENetic), a cohort study that that enrolled patients undergoing coronary angiography or percutaneous intervention at the National Taiwan University Hospital (NTUH) in the setting of either stable angina pectoris or prior myocardial infarction; 4) TACT (TAiwan Coronary and Transcatheter intervention), a cohort study enrolled patients with angina pectoris and objective documentation of myocardial ischemia who underwent diagnostic coronary angiography and/or revascularization any time after October 2000 at the National Taiwan University Hospital (NTUH) (similar to TCAGEN but recruitment was independent of TCAGEN); 5) Taiwan DRAGON (Taiwan Diabetes and RelAted Genetic COmplicatioN), acohort study of Type 2 diabetes at Taichung Veterans General Hospital (Taichung VGH) in Taiwan, with participants including individuals with either newly diagnosed or established diabetes

(subjects with hyperglycemia who did not meet diagnostic criteria for Type 2 DM were not included); 6) TCAD (Taichung CAD study), includes patients with a variety of cardiovascular diseases who received care at the Taichung Veterans General Hospital (Taichung VGH), i.e. specifically individuals who were hospitalized for diagnostic and interventional coronary angiography examinations and treatment; 7) TUDR (Taiwan US Diabetic Retinopathy) enrolled subjects with Type 2 diabetes who received care at Taichung Veteran General Hospital (Taichung VGH), and a small number of subjects from Taipei Tri-Service General Hospital (TSGH); TUDR subjects underwent a complete ophthalmic and fundus examination to carefully document the presence and extent of retinopathy. From these 7 studies, samples for over 1,800 subjects were selected based on completeness of standard metabolic phenotyping and knowledge of cardiac disease status, to undergo GWAS genotyping with an Illumina human-omni 'chip' specific for Asian population (Illumina, San Diego, CA; cat. No. 20004337), hence TAICHI-G.

THRV (Taiwan study of Hypertensives Rare Variants): THRV proposed to identify rare and low frequency genetic variants for blood pressure and hypertension through whole exome sequencing of a subset of highly enriched Taiwan Chinese hypertensive families and as many matched controls. The Taiwan Chinese families (approximately N=1,200 subjects) were previously recruited as part of the NHLBI-sponsored SAPPHIRe Network which is part of the Family Blood Pressure Program (FBPP). The SAPPHIRe families were recruited to have multiple hypertensive sibs and some of them also included one normotensive/hypotensive sib. The matched controls (N=1,200) were selected from the large population-based HALST Study and a Hospital-based population, both in Taipei, Taiwan.

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

TUDR (Taiwan-US Diabetic Retinopathy): 2009 to present, is a cohort that enrolled subjects with Type 2 diabetes receiving care at Taichung Veteran General Hospital (Taichung VGH), and a small number of subjects from Taipei Tri-Service General Hospital. All TUDR subjects underwent a complete ophthalmic and fundus examination to carefully document the presence and extent of retinopathy.

TWINGENE (TwinGene of the Swedish Twin Registry): The aim of the TwinGene project has been to systematically transform the oldest cohorts of the Swedish Twin Registry (STR) into a molecular-genetic resource. Beginning in 2004, about 200 twins were contacted each month until the data collection was completed in 2008. A total of 21 500 twins were contacted where of 12 600 participated. Invitations to the study contained information of the study and its purpose. Along with the invitations consent forms and health questionnaire were sent to the subjects. When the signed consent forms where returned, the subjects were sent blood sampling equipment and asked to contact a local health facility for blood sampling. The study population was recruited among twins participating in the Screening Across the Lifespan Twin Study (SALT) which was a telephone interview study conducted in 1998-2002. Other inclusion criteria were that both twins in the pair had to be alive and living in Sweden. Subjects were excluded from the study if they preciously declined participation in future studies or if they had been enrolled in other STR DNA sampling projects. The subjects were asked to make an appointment for a health check-up at their local health-care facility on the morning Monday to Thursday and not the day before a national holiday, this to ensure that the sample would reach the KI biobank the following morning by overnight mail. The subjects were instructed to fast from 20.00 the previous night. By venipuncture a total of 50 ml of blood was drawn from each subject. Tubes with serum and blood for biobanking as well as for clinical chemistry tests were sent to KI by overnight mail. One 7ml EDTA tube of whole blood is stored in -80°C while

a second 7ml EDTA tube of blood is used for DNA extraction using Puregene extraction kit (Gentra systems, Minneapolis, USA). After excluding subjects in which the DNA concentration in the stock-solution was below 20ng/µl as well as subset of 302 female monozygous twin pairs participating in a previous genome wide effort DNA from 9896 individual subjects was sent to SNP&SEQ Technology Platform Uppsala, Sweden for genome wide genotyping with Illumina OmniExpress bead chip (all available dizygous twins + one twin from each available MZ twin pair). For this project, smoking status was determined during SALT (1998-2002), while blood draw for lipids measurement was conducted between 2004 and 2008.

UKHLS (Understanding Society / The UK Household Longitudinal Study): The United Kingdom Household Longitudinal Study, also known as Understanding Society (https://www.understandingsociety.ac.uk) is a longitudinal panel survey of 40.000 UK households (England, Scotland, Wales and Northern Ireland) representative of the UK population. Participants are surveyed annually since 2009 and contribute information relating to their socioeconomic circumstances, attitudes, and behaviours via a computer assisted interview. The study includes phenotypical data for a representative sample of participants for a wide range of social and economic indicators as well as a biological sample collection encompassing biometric, physiological, biochemical, and haematological measurements and self-reported medical history and medication use. The United Kingdom Household Longitudinal Study has been approved by the University of Essex Ethics Committee and informed consent was obtained from every participant. For this project, smoking status was determined at wave 2, while blood draws were conducted 5 months after wave 2 and 3 interviews; thus smoking status and lipid measurements were between 5 and 17 months apart.

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

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