Multi-ancestry genome-wide smoking interaction study of 387,272 individuals identifies novel lipid loci

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Abstract

The concentrations of high- and low-density lipoprotein cholesterol and triglycerides are influenced by smoking, but it is unknown whether genetic associations with lipids may be modified by smoking. We conducted a multi-ancestry genome-wide gene-smoking interaction study in 133,805 individuals with follow-up in an additional 253,467 individuals. Combined meta-analyses identified 13 novel loci, some of which were detected only because the association differed by smoking status. Additionally, we demonstrated the importance of including diverse populations, particularly in studies of interactions

with lifestyle factors, where genomic and lifestyle differences by ancestry may contribute to novel findings.

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Serum lipids, such as triglycerides (TG) and high- and low-density lipoprotein cholesterol (HDL and LDL), are influenced by both genetic and lifestyle factors. Over 250 lipid loci have been identified,[1-6] yet, it is unclear to what extent lifestyle factors modify the effects of these variants, or those yet to be identified. Smoking is associated with an unfavorable lipid profile,[7,8] warranting its investigation as a lifestyle factor that potentially modifies genetic associations with lipids. Identifying interactions using traditional 1 degree of freedom (1df) tests of SNP x smoking terms may have low power, except in very large sample sizes. To enhance the detection of loci, a 2 degree of freedom (2df) test that jointly evaluates the interaction and main effects was developed.[9]

The Gene-Lifestyle Interactions Working Group, under the aegis of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium[10], was formed to conduct analyses of lifestyle interactions in the genetic basis of cardiovascular traits. As both genetic and lifestyle factors differ across populations with different ancestry backgrounds, and to address the underrepresentation of non-European populations in genomic research, great effort went into creating a large, multi-ancestry resource for these investigations.[11] Here, we report a genome-wide interaction study that uses both the 1df test of interaction and the 2df joint test of main and interaction effects to test the hypothesis that genetic associations of serum lipids differ by smoking status.

Results

Novel Loci

We conducted genome-wide interaction meta-analyses for current and ever-smoking status in up to 133,805 individuals of European (EUR), African (AFR), Asian (ASN) and Hispanic (HISP) ancestries (**Supplementary Tables 1-3**), with follow-up of 17,921 variants with $p \leq 10^{-6}$ (not pruned for linkage disequilibrium [LD]) in an additional 253,467 individuals of EUR, AFR, ASN, HISP, and Brazilian (BR) ancestries (**Supplementary Tables 4-6**), as described in **Figure 1**. Of these, 16,389 variants, representing

487 loci, passed filters and were included in stage 2 analyses (loci defined by physical distance +/- 1 MB). Ninety percent of variants (14,733) and 22% of loci (109) replicated in stage 2 (for variants: $p < 0.05/16,389$, for loci: $p < 0.05/487$). We conducted meta-analyses of stage 1 and 2 results (Manhattan Plots **Supplementary Figure 1**; QQ Plots, **Supplementary Figure 2**) and identified 13 novel loci with $p < 5 \times 10^{-8}$ that were at least 1 MB away from previously reported lipid loci (**Table 1**; results by stage: **Supplementary Table 7**; forest plots: **Supplementary Figures 3** and **4**; regional association plots: **Supplementary Figure 5**). These loci had low false discovery rate (FDR) q-values (all $q < 3 \times 10^{-4}$; **Supplementary Table 8**). We report all novel loci with $p < 5 \times 10^{-8}$ as well as those significant using an even more stringent threshold ($p < 6.25 \times 10^{-9}$) adjusted for 2 smoking exposures, 2 interaction tests, and ancestry-specific and trans-ancestry tests. The patterns observed in these results are described below and illustrated using output from stage 1 meta-analyses, where results from a series of models were available, including a main effect model, a main effect model stratified by smoking exposure, and a smoking-adjusted main effect model (**Figure 1; Supplementary Table 9**).

Strikingly, many novel loci were statistically significant only in AFR meta-analyses. For 7 of the 13 novel loci, the minor allele frequencies (MAF) of the index variants were highest in AFR, such that inter-ancestry differences in MAF and/or LD may explain the failure to detect similar associations in other ancestries. However, some AFR only associations were unlikely to be due to diminished power in non-AFR meta-analyses. For instance, the effect of rs12740061 (*LOC105378783*) on HDL was significantly modified by current smoking status among AFR ($p_{1df}=7.4 \times 10^{-9}$; **Figure 2, Table 1**), such that the genetic effect was stronger among current smokers than non-smokers (**Supplementary Table 9**). In contrast, there was virtually no evidence for association in any other ancestry, despite higher MAF: AFR 0.05, EUR 0.24, ASN 0.11, HISP 0.17 (**Figure 2**). The potential influence of under-adjustment for PCs on these results was evaluated by excluding the 6 studies that adjusted for only 1 PC (the average number of PCs

used for AFR studies was 4.2); effect estimates were similar and p-values were reduced or similar, consistent with a ~20% reduction in sample size (**Supplementary Table 10**).

We observed interactions where notable associations were only found among current or ever-smokers, with effect sizes close to zero among non- or never-smokers. We observed a statistically significant association for the 2df joint test of main and interaction effects for rs7364132 (*DGCR8*) × ever-smoking on TG (p_{2df}=2.5 × 10^{-8}; **Table 1**). Main effect models stratified by smoking status showed a strong genetic association with TG among ever smokers (difference in mean lnTG per A allele β= -0.05 lnTG, p=7.9 × 10^{-8}), with a negligible association among never-smokers (β = 0.01 lnTG, p=0.19; **Figure 3A**). This association was not significant in a non-stratified main effect model (**Table 1; Supplementary Table 9**), and was only detectable when modeling permitted a different association across smoking strata (i.e. a stratified model or a model with an interaction term). Similar results were observed for rs79950627 (*MIR4686*) × current smoking on LDL (**Figure 3B**), and rs56167574 (*PRKAG2*) × ever smoking on LDL (**Figure 3C, Supplementary Table 9**).

While for some interactions the association among smokers is larger and more statistically significant, for others the evidence of association was observed in the unexposed group in the opposite direction. For instance, current smoking modified the association between rs73453125 (*CNTNAP2*) and LDL (**Table 1**). In stratified main effect models, the A allele was associated with lower LDL among current smokers (β = -8.1 mg/dL, p=2.2 × 10^{-7}), but higher LDL among non-smokers (β = 2.18 mg/dL, p=0.01; **Figure 4**, **Supplementary Table 9**). In a non-stratified smoking-adjusted main effects model, no association between this variant and LDL was detected (β = 0.3 mg/dL, p=0.98). Similar results were observed for rs12740061 (*LOC105378783*) (**Supplementary Table 9**).

Although many interactions manifested as associations significant only or more strongly in smokers, for rs10937241 (*ETV5*), rs34311866 (*TMEM175*), rs10101067 (*EYA1*)**,** and rs77810251 (*PTPRZ1*), the

associations observed among non- or never-smokers were more statistically significant. Notably, in stratified main effect models, rs77810251 was associated with increased HDL among never-smokers (β = 0.05 lnHDL, $p = 6.3 \times 10^{-11}$) with no significant association among ever-smokers (β = -0.005 lnHDL, p = 0.56; **Figure 5; Supplementary Table 9**). In a smoking-adjusted main effect model of never- and ever-smokers together, the association between this variant and HDL was markedly reduced (β = 0.02 lnHDL, $p = 1.6 \times 10^{-4}$).

The 2df joint test simultaneously evaluates both main and smoking interaction effects; some of our results appear to capture largely a main effect of the variant on the trait. For instance, the 2df test for rs12144063 (*EYA3*) detected an association ($p = 1.3 \times 10^{-10}$), while the 1df test of interaction does not (p= 0.75). The minor alleles for this and 3 other variants (rs10937241 [*ETV5*], rs34311866 [*TMEM175*], and rs10101067 [*EYA1*]) were common across populations and their effects were small in magnitude and yet reached genome-wide statistical significance (rs10101067 [*EYA1*]; **Figure 6**), consistent with expectations for novel main effect loci in well-studied populations. There are 2 findings, however, for which the relatively large sample size in the AFR meta-analyses appeared to facilitate detection. The MAF for rs73729083 (*CREB3L2*) was much greater among AFR than in HISP and ASN (this variant was not present among EUR), and the variant effect estimates were large and consistent across ancestries, while the interaction effect estimates were inconsistent, with wide confidence intervals (**Supplementary Figure 3F**). The minor allele for rs4758675 (*B3GNT4*) was only present in AFR (**Supplementary Figure 3L**), but variant effect estimates were consistent across AFR studies, with interaction effect estimates approaching the null (**Supplementary Figure 4E**). In total, 6 of the 13 novel loci that we identified appear to be driven by main effects of the variant while the remainder show some evidence of interaction.

There were 16 additional novel loci identified in stage 1 meta-analyses (p_{1df} or $p_{2df} < 5 \times 10^{-8}$) for which the variants were unavailable for analysis in stage 2 cohorts. These loci were identified only in AFR meta-

analyses (many were AFR-specific variants; **Table 2**). Due to the relatively small number and size of available AFR cohorts in stage 2 (total n = 7,217, n < 2,000 within each cohort), these relatively low frequency variants did not pass filters for minor allele count within exposure groups. Nevertheless, these associations had low FDR q-values (all $q < 2.4 \times 10^{-4}$) in stage 1, and some appear worthy of further investigation. One particularly interesting candidate is rs17150980 (*MAGI2*) × ever-smoking on TG ($p_{2df}=1.4 \times 10^{-9}$), for which consistent effects for both the variant and the interaction were observed across AFR studies, but not in other ancestries (**Supplementary Figure 6**).

As we ran analyses for both current and ever-smoking status, we evaluated novel associations across smoking exposures to further characterize those loci (**Supplementary Table 11**). For the 6 probable main effect loci (*EYA3*, *ETV5*, *TMEM175*, *CREB3L2*, *EYA1*, *B3GNT4*), an association of similar statistical significance was observed across smoking status definitions for the 2df joint test of the main and the interaction effects, with similar lack of effect for the 1df test of the interaction, consistent with the interpretation that the choice of smoking status exposure was of minimal importance, as the main effect was the key driver of the association. For our variant in which a stronger association was observed among non-smokers (*PTPRZ1*), the p value for the 1df interaction was dramatically reduced (from 9.5×10^{-7} for ever-smoking to 0.011 for current smoking), consistent with any smoke exposure altering the association between this variant and HDL, and including former smokers with the never smokers (as in the current smoking analysis) diluting the observed association among never smokers. For the statistically significant reported interactions with current smoking, all the effect estimates were greatly reduced in the ever-smoking analysis, consistent with active smoking being the relevant exposure. For the reported interactions with ever-smoking, the interactions with current smoking had markedly reduced statistical significance, consistent with a drop in power from excluding former smokers from the exposed group.

We conducted a secondary analysis of smoking dose in two of our AFR cohorts with measured cigarettes per day for 4 interaction loci (see methods for selection criteria): rs12740061 (*LOC105378783*), rs73453125 (*CNTNAP2*), rs79950627 (*MIR4686*), and rs7364132 (*DGCR8*). For each of these variants, a stronger association was observed with increasing smoking dose (**Supplementary Table 12**), and the interaction was statistically significant for all variants but one, which was just over our threshold for statistical significance (rs7364132, p=0.0035 vs. p < 0.0021).

To confirm the independence of novel loci, we conducted conditional analysis of our novel loci by conditioning on variants at known lipids loci (**Supplementary Table 13**). We found no evidence that the new associations were driven by variants at known lipids loci. Imputation quality for these variants was high (minimum 0.75), with sample-size weighted average imputation quality of 0.90, and minor allele frequencies that match what has been reported in publicly-available datasets (**Supplementary Table 14**).

Interactions at Known Loci

We also examined interactions at known lipid loci. Since associations for the 2df test of joint effects at known lipid loci are expected to predominantly reflect previously identified main effects, we exclusively evaluated the 1df test of interaction. There were no interactions within known loci that were statistically significant (p < 0.05/269 known loci in our data). To evaluate whether the proportion of known variants with $p_{1df} < 0.05$ was higher than would be expected by chance (5%), we conducted binomial tests for each trait-exposure combination (p-values Bonferroni-corrected for multiple tests). There was significant enrichment of known variants with 1df interaction p < 0.05: HDL-current smoking $p = 9.6 \times 10^{-12}$, HDL-ever smoking $p = 5.9 \times 10^{-7}$, LDL-current smoking $p = 8.4 \times 10^{-15}$, LDL-ever smoking $p = 3.1 \times 10^{-5}$, TG-current smoking $p = 4.0 \times 10^{-3}$, TG-ever smoking $p = 3.1 \times 10^{-4}$. We conducted power calculations under different interaction scenarios to determine the conditions under which an interaction analysis

and a main effect analysis would both be sufficiently powered to detect the same locus (i.e. when an interaction could be detected in a locus previously identified in a main effect analysis; **Supplementary Table 15**). At current trans-ancestry meta-analyses sample sizes and assuming a large effect size, there was limited power to detect either a main effect or an interaction when an association was larger or only present among smokers (main effect <1%; interaction 77%), or when associations differed in magnitude but not direction (main effect >99%; interaction <1%); thus, making it unlikely to detect an interaction at a known locus. We were well-powered for both interaction and main effect analyses to detect smoking interactions for which smoking eliminates or drastically reduces a large association among non- or never-smokers. We identified one such interaction in our data, for *PTPRZ1* in AFR only, which may not have been previously identified in a main effect analysis because of limited power of AFR main effect analyses thus far.

Proportion Variance Explained by Identified Loci

Ten studies from four ancestries were used to calculate the proportion of the variance in lipid traits explained by the genome-wide statistically significant novel loci: 13 loci from stage 1 and 2 combined meta-analyses (**Table 1**), and 16 loci from stage 1 that were not available in stage 2 analyses (**Table 2**). Two different methods were used (**Online Methods**), and the range of findings across these methods are presented (**Supplementary Table 16**). In AFR, novel variants and their interactions explained 1.0-2.7% of HDL, 0.7-2.6% of LDL, and 1.3-3.2% of TG. The proportion explained was smaller among EUR (0.06-0.14% of HDL, 0.01-0.07% of LDL, and 0.10-0.19% of TG), ASN (0.27-0.86% of HDL, 0.09-0.82% of LDL, and 0.8-1.5% of TG), and HISP (0.2-0.4% of HDL, 0.2-0.5% of LDL, and 0.2-0.4% of TG). These results should be considered in the context of the inter-ancestry MAF differences: the proportion of novel variants that could be evaluated varied dramatically by ancestry, with 94-97% among the AFR cohorts,

but only 32-39% among the EUR and ASN cohorts, and 55% in the HISP cohort. In contrast, each of the cohorts investigated had similar proportions of the requested known variants (83-96%).

Reproducing Known Lipids Associations

We evaluated the degree to which our data reproduce previously reported lipid loci (given that approximately 81% of cohorts in stage 1 were included both in this and in previous efforts, this analysis is not a formal replication). For comparability with traditional GWAS, we evaluated results from stage 1 main effect models. Of the 356 previously reported associations for 279 variants (compiled from[1-6,12]; some variants were associated with multiple lipid traits), there were 236 associations for 189 variants that were confirmed in our data (consistent direction and $p < 0.05/356$), for a 66.3% concordance rate (**Supplementary Table 17**).

Bioinformatics

To characterize the potential impact of our novel associations for chronic disease risk and to investigate biological mechanisms, we conducted a series of follow-up analyses and annotations. We performed extensive bioinformatics annotation on variants within the 13 novel loci from stage 1 and 2 meta-analysis (**Table 1**) and the 16 novel loci from stage 1 meta-analysis that could not be evaluated in stage 2 (**Table 2**). The 78 variants were within 29 loci and were in or near 33 unique genes (**Supplementary Table 18**). We conducted look-up of these variants in previously conducted GWAS for related traits (**Supplementary Tables 19-24**), the Genotype-Tissue Expression (GTEx v7.0) portal and Regulome DB (**Supplementary Table 25**), HaploReg v4.1 (**Supplementary Table 26**), and an analysis of *cis*- and *trans*-eQTL in whole blood from Framingham Heart Study participants (**Supplementary Table 27**). Additionally, for each trait we performed DEPICT gene prioritization (**Supplementary Tables 28-30**), gene set enrichment (**Supplementary Tables 31-33**), and tissue or cell type enrichment analyses[13]

(**Supplementary Tables 34-37**), using both novel and known loci. Notable findings from these follow-up analyses are summarized below by locus.

Consistent with our observations of an association of the C allele for rs10101067 (*EYA1*) with higher TG, this allele was associated with increased risk of coronary artery disease (β = 0.036, p= 0.03; **Supplementary Table 19**), ischemic stroke (β = 0.11, p= 0.04; **Supplementary Table 20**), and higher waist to hip ratio adjusted for BMI (β = 0.029 units, p= 6.5×10^{-4}, with similar results observed for waist circumference adjusted for BMI; **Supplementary Table 21**).

We found an association of the T allele of rs12144063 (*EYA3*) with lower HDL concentration. This allele and the minor alleles for other variants in this locus were associated with increased risk of all stroke types (β = 0.05, p = 0.04), as well as stroke subtypes (**Supplementary Table 20**). rs7529792, a variant in LD with rs12144063 (r^2 with rs12144063 = 0.97) regulates gene expression of *EYA3* and has a high Regulome DB score (1b; **Supplementary Table 25**). Haploreg also shows regulatory features for rs12144063, including being in a promoter location expressed in liver and brain, in enhancer histone marks, and at DNAse marks for *EYA3* (**Supplementary Table 26**). DEPICT predicted a role for these variants in regulating *EYA3* and *XKR8* (**Supplementary Table 28**), a phospholipid scramblase important in apoptotic signaling[14].

We report an interaction between smoking and rs77810251 (*PTPRZ1*) with the minor allele associated with higher HDL only among never-smokers. While this variant was not available in look-up data for GIANT, a variant in this locus with a similar association, rs740965, was associated with lower BMI among EUR (β = -0.01 kg/m^2, p= 0.01, similar results for trans-ancestry analysis). This variant was also associated with lower waist circumference adjusted for BMI among EUR women (β = -0.016, p= 0.04; **Supplementary Table 21**). *PTPRZ1* was shown to be downregulated in cells treated with an acute dose of nicotine[15], which supports our observation of a lack of an association of *PTPRZ1* variants among ever

smokers despite what was seen among never smokers. Other variants in this locus were found to be *trans*-eQTLs for *ARHGAP5-AS1*, *FIG4*, *HNMT*, and *IL11* (**Supplementary Table 27**).

We report a main effect of rs34311866 on HDL and TG. rs34311866 is a missense variant in *TMEM175,* which has been associated with Parkinson's disease[16] and type 2 diabetes[17]. This variant contributes to the regulation of *DGKQ* ($p = 5.3 \times 10^{-21}$) and is an eQTL of *DGKQ* in adipose, artery, lung, nerve and thyroid tissue (**Supplementary Table 25**). The expression of *DGKQ* is more strongly regulated by another significantly associated variant in this locus, rs4690220, which is located upstream of *IDUA* and in an intron of *SLC26A1*. This variant had a high score in the RegulomeDB (1f), supporting a potential functional effect (**Supplementary Table 25**). Importantly, *DGKQ* is involved in cholesterol metabolism[18], bile acid signaling, glucose homoeostasis in hepatocytes[19], primary biliary cirrhosis[20], and Parkinson's disease[21-24]. DGKQ interacts with the key lipid loci LPL, LIPG, and PNPLA3 (**Supplementary Figure 7**). These results suggest that the observed association of these variants with HDL and TG could act through regulation of *DGKQ* on cholesterol metabolism. Also, rs34311866 is a *trans*-eQTL for *GNPDA1* (**Supplementary Table 27**); expression of this gene has previously been associated with a set of traits, including hyperlipidemia[25].

In our data, there was a significant rs12740061 (*LOC105378783*) × smoking interaction, such that the minor allele was associated with decreased HDL only among current smokers. This variant is a *trans*-eQTL for *TAS1R1* (**Supplementary Table 27**). Variants in this gene have been found to influence taste receptors, notably affecting cigarette smoking habits[26].

DISCUSSION

In this study, we evaluated gene-smoking interactions in large, multi-ancestry, meta-analyses of serum lipids, using varying associations among smoking subgroups to improve the ability to detect novel lipid

loci. We report 13 novel loci for serum lipids from stage 1 and 2 meta-analyses. Sixteen additional statistically significant novel loci were found in stage 1 but were unavailable in stage 2. All 29 novel associations had a low q-value ($p < 3 \times 10^{-4}$). Using both the 1df test of interaction and the 2df joint test of main and interaction effects in this study allowed us to improve our inferences based on the results: the 2df test bolstered the power to detect interactions, while the 1df test could discriminate between associations that predominantly reflected main effects vs. interactions.

Our results provide support for future efforts to evaluate lifestyle interactions with complex traits. We identified loci for which an association with serum lipids was only observed in either current-/ever-smokers or non-/never-smokers. In traditional main effect models at these loci, the signal from one subgroup was not detected when all individuals were evaluated together (with or without adjustment for smoking). In such a scenario, these loci could only be observed by an analysis that was either smoking-stratified or contained an interaction term, highlighting the importance of considering potential effect modification by lifestyle factors in association studies. Additionally, through use of the joint 2df test of main and interaction, we identified 6 loci for which the association appeared to represent a main effect of the variant on lipids. Consistent with this characterization, 5 of these loci were within 500 KB of variants identified in recent large-scale association studies using main effect models: *ETV*[27-29], *TMEM175*[28], *EYA1*[28], *EYA3*[28], and *B3GNT4*[28].

With 23,753 AFR individuals in the Stage 1 analyses and 30,970 AFR individuals included overall, this work represents one of the largest studies of serum lipids conducted in AFR. It is therefore not surprising that two of our novel lipid loci (*CREB3L2* [LDL] and *B3GNT4* [TG]) appear to be driven primarily by genetic main effects, as evidence for an association for these loci comes only from the 2df joint test of interaction and main effects, with no support from the 1df test of interaction ($p > 0.5$). Importantly, these associations could not have been detected in EUR: the C allele for rs4758675 (*B3GNT4*) is present

only among AFR, and the C allele for rs73729083 (*CREB3L2*) is in much higher frequency among AFR than in other ancestries and is absent in EUR.

In addition to these probable main effect loci, the prominence of novel loci that were statistically significant only in the meta-analyses of African ancestry individuals deserves further discussion. Some findings could not be effectively evaluated in other ancestry groups as a result of inter-ancestry differences in minor allele frequencies: the minor alleles for half of the variants were much more frequent in AFR compared to other ancestries. More puzzling, however, is the discovery of loci with evidence of strong interactions in AFR but not in meta-analyses in other ancestries, despite comparable or higher allele frequencies, such as were observed with rs12740061 (*LOC105378783*; **Figure 2**) or rs17150980 (*MAGI2*; **Supplementary Figure 6**). This phenomenon suggests inter-ancestry differences in either genomic or environmental context. There are variants in LD ($r^2 > 0.2$) among AFR for rs12740061 (*LOC105378783*) and rs17150980 (*MAGI2*) that are not in LD with these variants in other ancestries[30]. However, these variants were directly tested in our study with no evidence of an association in non-AFR ancestries. Thus, it is unlikely that inter-ancestry LD differences explain these results, although unmeasured causal variants are a possibility. Inter-ancestry differences in smoking are also a potential explanation for differences observed in AFR compared to other ancestries. In addition to known inter-ancestry differences in smoking patterns[31], there are pronounced ancestry differences in preferred cigarette type, with over 85% of AFR smokers using menthol cigarettes compared to 29% of EUR smokers (in the US)[32]. Menthol cigarettes are thought to facilitate greater absorption of harmful chemicals because of deeper inhalation[31,33] through desensitization of nicotinic acetylcholine receptors that cause nicotine-induced irritation[34]. Evidence for an excess risk of cardiovascular disease associated with mentholated cigarettes, however, is equivocal[35-39]. Additionally, ancestry differences in smoking-related metabolites and carcinogens have been reported[40-43], and differential metabolism of key compounds may underlie observed differences by ancestry. Some behaviors/conditions that co-occur

with smoking may also differ by ancestry, and this additional factor may modify the observed genetic associations with serum lipids.

The biological mechanisms through which smoking influences the observed genetic associations will require further investigation, as the myriad components of cigarette smoke and their downstream consequences (including oxidative stress and inflammation) affect pathways throughout the body[44]. However, we do have evidence for differential expression of *PTPRZ1*[15], *LPL*[15] and *LDLR*[45] in cells exposed to an acute dose of nicotine. Also, concentrations of CETP[46], ApoB[47], and LPL[48] are associated with smoking status.

The sample size attained for diverse ancestries is a key strength of our study, particularly among AFR, in whom we were able to conduct the largest meta-analyses of lipids GWAS to date. As such, we identified loci that had not been previously detected in meta-analyses of ancestries that are better represented in genomic research. Additionally, our use of nested models in our stage 1 analyses allowed us to more fully characterize loci and directly compare our models to those without an interaction term, adjusted for smoking, or stratified by smoking status. Despite these strengths, however, a smaller number of AFR studies were available for stage 2, resulting in an inability to follow up on some of our stage 1 low frequency findings.

In conclusion, this large, multi-ancestry genome-wide study of gene-smoking interactions on serum lipids identified 13 novel loci based on combined analysis of stages 1 and 2, and an additional 16 novel loci based on stage 1 that were unavailable in stage 2. Some loci were detected only in analyses stratified by smoking status or with a smoking interaction term, thus motivating further study of gene × environment interactions with other lifestyle factors in order to identify new loci for lipids and other complex traits. We demonstrate the importance of including diverse populations, reaching a sufficient sample size in these analyses for discovery of novel lipid loci for AFR. Careful consideration of ancestry

may be of particular importance for gene × environment interactions, as ancestry may be a proxy for both genomic and environmental context.

Online Methods

Details regarding motivation and methodology of this and other projects of the CHARGE Gene-Lifestyle Interactions Working Group are available in our recently published methods paper[11].

Participants

Analyses included men and women between 18 and 80 years of age of European (EUR), African (AFR), Asian (ASN), Hispanic (HISP), and (in stage 2 only) Brazilian (BR) ancestry. Participating studies are described in **Supplementary Materials**, with further details of sample sizes, trait distribution, and data preparation available in **Supplementary Tables 1-6**. Considerable effort was expended to engage as many studies of diverse ancestry as possible. This work was approved by the Washington University in St. Louis Institutional Review Board and complies with all relevant ethical regulations. Each study obtained informed consent from participants and received approval from the appropriate institutional review boards.

Phenotypes

Analyses evaluated the concentrations of high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides (TG). LDL could be either directly assayed or derived using the Friedewald equation[49] (if TG ≤ 400 mg/dL and individuals were fasting for at least 8 hours). Lipid-lowering drug use was defined as any use of a statin drug or any unspecified lipid-lowering drug after 1994 (when statin use became common). If LDL was directly assayed, adjustment for lipid-lowering drug was performed by dividing the LDL value by 0.7. If LDL was derived using the Friedewald equation, total

cholesterol was first adjusted for lipid-lowering drug use (total cholesterol/0.8) before calculation of LDL by the Friedewald equation. No adjustments were made for any other lipid medication, nor were adjustments made to HDL or TG for medication use. If samples were from individuals who were non-fasting (fasting ≤ 8 hours), then neither TG nor calculated LDL were used. Both HDL and TG were natural log-transformed, while LDL remained untransformed. In the event that multiple measurements of lipids were available (i.e. in a longitudinal study), analysts selected the visit for which data were available for the largest number of participants, and the measurement from that visit was included in analyses.

Environmental Exposure Status

Smoking variables evaluated were current smoking status (yes/no) and ever smoking status (yes/no). Current smokers were included in the exposed group for both of these variables, and never smokers were included in the unexposed group for both of these variables. Former smokers were included in the unexposed group for the current smoking variable and the exposed group for the ever-smoking variable. Smoking variables were coded as 0/1 for unexposed/exposed groups.

Genotype Data

Genotyping was performed by each participating study using genotyping arrays from either Illumina (San Diego, CA, USA) or Affymetrix (Santa Clara, CA, USA). Each study conducted imputation using various software. The cosmopolitan reference panel from the 1000 Genomes Project Phase I Integrated Release Version 3 Haplotypes (2010-11 data freeze, 2012-03-14 haplotypes) was specified for imputation and used by most studies, with some using the HapMap Phase II reference panel instead. Only variants on the autosome and with MAF of at least 0.01 were considered. Specific details of each participating study's genotyping platform and imputation software are described (**Supplementary Tables 3** and **6).** Genotype was coded as the dosage of the imputed genetic variant, coded additively (0,1,2).

Stage 1 Analysis

Stage 1 genome-wide interaction analyses included 29 cohorts contributing data from 51 study/ancestry groups and up to 133,805 individuals of EUR, AFR, ASN, and HISP ancestry (**Supplementary Tables 1-3**). All cohorts ran three models in all individuals: a main effect model, a model adjusted for smoking, and an interaction model that included a multiplicative interaction term between the variant and smoking status (**Figure 1**). Additionally, the main effect model was run stratified by smoking exposure. All models were run for 3 lipids traits (HDL, LDL, and TG) and 2 smoking exposures (current smoking and ever smoking). Thus, each study/ancestry group completed 30 GWAS (using 5 models × 3 traits × 2 exposures).

All models were adjusted for age, sex, and field center (as appropriate). Principal components derived using genotyped SNPs were included based on the study analyst's discretion. All AFR cohorts were requested to include at least the first principal component, and 71% of AFR cohorts used multiple PCs (with 25% using 10 PCs). The average number of PCs used was 4.2. Additional cohort-specific covariates could be included if necessary to control for other potential confounding factors. Studies including participants from multiple ancestry groups conducted and reported analyses separately by ancestry. Participating studies provided the estimated genetic main effect and robust estimates of standard error for all requested models. In addition, for the models with an interaction term, studies also reported the interaction effects and robust estimates of their standard errors, and a robust estimate of the corresponding covariance matrix between the main and interaction effects. To obtain robust estimates of covariance matrices and robust standard errors, studies with only unrelated participants used R packages; either sandwich[50] or ProbABEL[51]. If the study included related individuals, either generalized estimating equations (R package geepack[52]) or linear mixed models (GenABEL[53], MMAP, or R) were used.

Sample code provided to studies to generate these data has been previously published (see Supplementary Materials [11]).

Extensive quality control (QC) was performed using EasyQC[54] (www.genepi-regensburg.de/easyqc) on study-level (examining the results of each study individually), and then on ancestry-level (examining all studies within each ancestry group together). Study-level QC consisted of exclusion of all variants with MAF < 0.01, extensive harmonization of alleles, and comparison of allele frequencies with ancestry-appropriate 1000 Genomes reference data. Ancestry-level QC included the compilation of summary statistics on all effect estimates, standard errors and p-values across studies to identify potential outliers, and production of SE-N and QQ plots to identify analytical problems (such as improper trait transformations)[55]. Variants were excluded from ancestry-specific meta-analyses for an imputation score < 0.5; the same threshold was implemented regardless of imputation software, as imputation quality measures are shown to be similar across software[56]. Additionally, variants were excluded if the minimum of the minor allele count in the exposed or unexposed groups × imputation score was less than 20. To be included in meta-analyses, each variant had to be available from at least 3 studies or 5,000 individuals contributing data.

Meta-analyses were conducted for all models using the inverse variance-weighted fixed effects method as implemented in METAL[57] (http://genome.sph.umich.edu/wiki/METAL). We evaluated both a 1 degree of freedom test of interaction effect (1df) and a 2 degree of freedom joint test of main and interaction effects (2df), following previously published methods[9]. A 1df Wald test was used to evaluate the 1df interaction, as well as the main effect and the smoking-adjusted main effect in models without an interaction term. A 2df Wald test was used to jointly test the effects of both the variant and the variant x smoking interaction[58]. Meta-analyses were conducted within each ancestry separately, and then trans-

ancestry meta-analyses were conducted on all ancestry-specific meta-analyses. Genomic control correction was applied before all meta-analyses.

Variants that were associated in any analysis at $p \leq 10^{-6}$ were carried forward for analysis in Stage 2. A total of 17,921 variants from 519 loci (defined by physical distance +/- 1 MB) were selected for Stage 2 analyses.

Stage 2 Analysis

Variants selected for Stage 2 were evaluated in 50 cohorts, with data from 75 separate ancestry/study groups totaling up to 253,467 individuals (**Supplementary Tables 4-6**). In addition to the 4 ancestry groups listed above, stage 2 analyses also included studies of Brazilian (BR) individuals. BR were considered only in the trans-ancestry meta-analyses, since there were no stage 1 BR results for meta-analysis. In stage 2, variants were evaluated only in a model with the interaction term (**Figure 1**).

Study- and ancestry-level QC was carried out as in stage 1. In contrast to stage 1, no additional filters were included for the number of studies or individuals contributing data to stage 2 meta-analyses, as these filters were implemented to reduce the probability of false positives, and were less relevant in stage 2. Stage 2 variants were evaluated in all ancestry groups and for all traits, no matter what specific meta-analysis met the p-value threshold in the stage 1 analysis. Genomic control was not applied to stage 2 meta-analyses, given the expectation of association. To ensure quality of analyses, all quality control and meta-analyses of replication data were completed independently by analysts at two different institutions (ARB and JLB [NIH], EL, XD, and CTL [Boston University]), with differences resolved through consultation.

Meta-Analyses of Stages 1 and 2

Given the increased power of combined meta-analysis of stage 1 and 2 results compared with a discovery and replication strategy[59], combined stage 1 and 2 meta-analyses were carried out for all the selected variants . We report variants significant at 5×10^{-8} as well as those significant at Bonferroni correction for 2 smoking traits, 2 interaction tests, and ancestry-specific and trans-ancestry testing, with p-value of 6.25×10^{-9} ($5 \times 10^{-8}/8$). Loci that are significant at the stricter p-value are identified in main tables. Loci were defined based on physical distance (+/- 1 MB) and are described by the index variant (*i.e.* the most statistically significant variant within each locus). Novelty was determined by physical distance (+/- 1 MB) from known lipids loci compiled from large meta-analyses[1-5,12]. False Discovery Rate q values were determined using EasyStrata (http://www.genepi-regensburg.de/easystrata) to implement the Benjamini-Hochberg method of calculation[60]. Results were visualized using R 3.1.0[61], including the package 'forestplot'[62] (**Supplementary Figures 3 and 4**), and LocusZoom v1.4 (http://locuszoom.sph.umich.edu/; **Supplementary Figure 5**) for regional association plots.

Smoking Dose Analysis

To further characterize these associations, we evaluated an interaction between smoking dose and a few of the observed novel loci. While smoking dose data was not available for many of the included studies, we conducted secondary analysis on smoking dose interaction in a subset of loci in our two largest AFR studies: WHI-SHARE and ARIC. We identified 4 loci from our main results (*LOC105378783*, *CNTNAP2*, *MIR4686*, *DGCR8*) for follow-up based on the following criteria: an interaction locus (as opposed to a probable main effect), stronger association observed among smokers compared to non-/never-smokers, the presence of contributing cohort(s) with smoking dose variables available and with $p < 0.05$ for reported result (to ensure sufficient power for analysis). We investigated these 4 loci using 3 methods of characterizing cigarettes per day: a quantitative variable, a categorical variable based on meaningful dose levels (less than a half a pack, between a half a pack and a pack, and more than a pack

per day), and binary variable defined by the median of cigarettes per day in that cohort. Dose variables were defined separately by smoking status, such that cigarettes per day for former smokers were set to 0 for variables defined for current smokers, while the cigarettes per day for both current and former smokers were quantified when defined for ever smokers. Statistical significance was set at $p < 0.0021$, Bonferroni correction for investigation of 4 loci, 3 smoking dose variables, and 2 smoking status exposures.

Conditional Analyses

To assess independence of novel loci from established lipids loci, we conducted conditional analyses using GCTA[63]. GCTA's conditional and joint analysis option (COJO) calculates approximate conditional and joint association analyses based on summary statistics from a GWAS meta-analysis and individual genotype data from an ancestry-appropriate reference sample (for LD estimation). For novel loci from predominantly AFR meta-analyses, the LD reference set included unrelated AFR from HUFS, CFS, JHS, ARIC, and MESA (total N = 8,425). For novel loci from predominantly EUR meta-analyses, the LD reference set included unrelated EUR from ARIC (total N = 9,770). Excluding HUFS, these data were accessed through dbGaP[64] (ARIC phs000280.v2.p1, phs000090.v2.p1; CFS phs000284.v1.p1; JHS phs000286.v4.p1, phs000499.v2.p1; and MESA phs000209.v13.p1, phs000420.v6.p3) and imputed to 1000 Genomes phase 1 v. 3 using the Michigan Imputation Server[65]. For loci with a $p < 5 \times 10^{-8}$ for the 1df test of interaction, results from stage 1 and 2 meta-analyses were adjusted for all known lipids loci. A method for running conditional analyses for 2df tests has not been implemented within GCTA, therefore we evaluated loci with a $p < 5 \times 10^{-8}$ for the 2df joint test of main and interaction effects by conditioning stage 1 stratified analyses on known lipids loci (stratified analyses were not conducted in stage 2 studies). The conditioned 2df joint test of main and interaction effects was then calculated using EasyStrata[55] on the conditioned stratified results.

Power Calculations for Detecting Interactions at Known Lipids Loci

To better contextualize our lack of detection of an interaction at a known locus, we conducted power calculations under a variety of scenarios. We explored the power to detect both an interaction and a main effect, making assumptions based on our data, as the sample sizes achieved in this project are comparable to the largest main effect GWAS for lipids[1,5]. Using previously developed analytical power formulas[66], we evaluated three interaction scenarios: a pure interaction effect (no effect in non-smokers and a positive effect in current smokers), a quantitative interaction (effects in the same direction across strata, but of different magnitude), and a qualitative interaction (effects in opposite directions and of different magnitude). We assumed stage 1 + 2 sample sizes and 19% prevalence of smoking (as in our data). For the purposes of illustration, we assumed relatively large effects which explain 0.06% of the variance in the lipid trait; the median variance explained from known lipid loci, as estimated from a previous publication (their Supplemental Table 1)[2], is 0.04%.

Proportion of Variance Explained

To evaluate the proportion of the variance explained by our novel associations, we conducted additional analyses of our variants of interest in cohorts of diverse ancestries (**Supplementary Table 16**). In each of 10 studies from 4 ancestries (EUR, AFR, ASN, and HISP), we ran a series of nested regression models to determine the relative contribution of each set of additional variables. The first model included only standard covariates (age, sex, center, principal components, etc.). The second model additionally included smoking status (both current and ever smoking). The third added known variants[1-5,12]. The fourth model added all novel variants, and the last model also included interaction terms for novel variants. For the purposes of this analysis, novel variants included the lead variant for each genome-wide significant locus in the meta-analyses of stages 1 and 2 (**Table 1**) and that were significant but only available in stage 1 meta-analyses (**Table 2**). By subtracting the r^2 values from each of these nested

regression models, the proportion of variance explained by the additional set of variables was determined. We conducted these analyses using two approaches. In Approach 1, all variants with MAF ≥ 0.01 and imputation quality ≥ 0.3 were included in regression models. While the imputation quality threshold used for the main analyses (≥ 0.5) was higher in order to reduce the risk of spurious associations, we selected a lower threshold for this secondary analysis to maximize the number of variants of interest included. In Approach 2, to avoid possible overfitting, stepwise regression was used for variant selection, such that only variants that were associated ($p < 0.05$) were retained in the model. All variants were considered in models for each trait and ancestry, regardless of the trait or ancestry in which the association was identified.

Reproducing Previously Reported Lipids Associations

To evaluate the degree to which our data confirmed previous associations, we evaluated statistically significant associations reported from recent large meta-analyses[1-5,12]. In the event of overlap between reports, the most statistically significant variant-trait association was considered, for a total of 346 unique associations for 269 variants. Output from our main effect models (stage 1) was extracted for all ancestries for each previously reported variant-trait combination. Reproducibility was determined by $p < 0.05$ in any ancestry and a consistent direction of effect (**Supplementary Table 17**).

Functional Inference

To evaluate the degree to which our novel variants might influence other cardiometabolic traits, we extracted our novel variants (**Tables 1** and **2**) from previous studies. **Supplementary Tables 19-24** present the association of these variants with coronary artery disease and myocardial infarction, using data from the CARDIoGRAM consortium[67]; neurological traits, using data from the Neurology Working Group of the CHARGE Consortium; anthropometry, using data from the GIANT consortium [68]; adiposity × smoking interaction, using data from the GIANT consortium[69]; diabetes and related traits, using data

from MAGIC[70], AAGILE[71], and DIAGRAM[72,73]; and kidney outcomes, using data from the COGENT-Kidney consortium[74].

To conduct functional annotation of our novel variants (**Supplementary Tables 18, 25-27**), we used NCBI Entrez gene (ncbi.nlm.nih.gov/gene/) for gene information, dbSNP (ncbi.nlm.nih.gov/snp/) to translate positions to human genome build 38, HaploReg (v4.1)[30] and RegulomeDB[75] for gene expression and regulation data from ENCODE and RoadMap projects, and GTEx v7.0 (gtextportal.org) for additional gene expression information. We also investigated our novel variants in *cis*- and *trans*-eQTL data based on analysis of the whole blood of Framingham Heart Study participants[76].

Pathway and Gene Set Enrichment Analyses

We conducted DEPICT analyses[13] based on genome-wide significant ($p < 5 \times 10^{-8}$) variants separately for the three traits HDL, LDL and TG (**Supplementary Tables 28-37**). To obtain input for the prioritization and enrichment analyses, DEPICT first created a list of non-overlapping loci by applying a combined distance and LD based threshold (500 KB flanking regions and LD $r^2 > 0.1$) between the associated variants and the 1000 Genomes reference data[77]. DEPICT then obtained lists of overlapping genes by applying an LD based threshold ($r^2 > 0.5$) between the non-overlapping variants and known functional coding or cis-acting regulatory variants for the respective genes. Finally, the major histocompatibility complex region on chromosome 6 (base position 25,000,000 - 35,000,000) was removed from further analyses. DEPICT prioritized genes at associated regions by comparing functional similarity of genes across associated loci using a gene score that was adjusted for several confounders, such as gene length. Utilizing lead variants from 500 pre-compiled null GWAS the scoring step was repeated 50 times to obtain an experiment-wide FDR for the gene prioritization. Second, DEPICT conducted gene-set enrichment analyses based on a total of 14,461 pre-compiled reconstituted gene sets. The reconstituted gene sets involve 737 Reactome database pathways[78], 2,473 phenotypic gene sets (derived from the

Mouse Genetics Initiative*)*[79], 184 Kyoto Encyclopedia of Genes and Genomes (KEGG) database pathways[80], 5,083 Gene Ontology database terms[81], and 5,984 protein molecular pathways (derived from protein-protein interactions[82]). Third, DEPICT conducted tissue and cell type enrichment analyses based on expression data in any of the 209 MeSH annotations for 37,427 microarrays of the Affymetrix U133 Plus 2.0 Array platform. In addition, we used STRING database (string-db.org) for identifying protein x protein interactions.

Data Availability

The summary results on which this manuscript is based will be used for pleiotropy and pathway analyses, which were outlined as part of the NIH grant that supports this work. Within 6 months of completing these planned analyses, all summary results will be made available in dbGaP (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000930.v5.p1).

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Author Contributions

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Yun J Sung					X	
Michael R Brown				X	X	
Aldi T Kraja			X		X	
Thomas W Winkler				X	X	X
Ioanna Ntalla				X	X	
Karen Schwander		X	X		X	
Elise Lim			X	X	X	
Xuan Deng			X	X	X	
Xiuqing Guo	X			X	X	
Jingmin Liu			X	X	X	
Yingchang Lu		X		X	X	
Ching-Yu Cheng	X			X	X	
Xueling Sim			X	X	X	
Dina Vojinovic				X	X	
Jennifer E Huffman			X	X	X	
Solomon K Musani	X		X	X	X	
Changwei Li		X	X	X	X	
Mary F Feitosa		X	X	X	X	
Melissa A Richard				X	X	
Raymond Noordam				X	X	
Jennifer Baker					X	
Hugues Aschard	X				X	
Traci M Bartz				X	X	
Daniel I. Chasman	X		X	X	X	X
Jingzhong Ding	X	X			X	
Rajkumar Dorajoo			X	X	X	
Alisa K Manning					X	
Tuomo Rankinen	X	X	X	X	X	

Author	PARTICIPATE IN STUDY CONCEPT AND DESIGN	PARTICIPATE IN PHENOTYPE DATA ACQUISITION AND/OR QC	PARTICIPATE IN GENOTYPE DATA ACQUISITION AND/OR QC	PARTICIPATE IN DATA ANALYSIS AND INTERPRETATION	REVIEWED AND APPROVED MANUSCRIPT	PERFORMED LOOK-UPS
Albert V Smith			X	X	X	
Salman M. Tajuddin				X	X	
Wei Zhao			X	X	X	
Maris Alver		X	X		X	
Mathilde Boissel		X	X		X	
Jin Fang Chai			X	X	X	
Xu Chen				X	X	
Jasmin Divers	X	X		X	X	
Evangelos Evangelou		X	X	X	X	
Chuan Gao			X	X	X	
Anuj Goel		X	X	X	X	
Yanick Hagemeijer			X	X	X	
Sarah E Harris		X	X	X	X	
Fernando P Hartwig			X	X	X	
Meian He	X	X			X	
Andrea R.V.R. Horimoto		X	X	X	X	
Fang-Chi Hsu		X	X	X	X	
Yi-Jen Hung		X			X	
Anne U Jackson				X	X	
Anuradhani Kasturiratne		X			X	
Pirjo Komulainen	X	X			X	
Brigitte Kühnel				X	X	
Karin Leander		X	X	X	X	
Keng-Hung Lin		X			X	
Jian'an Luan		X	X	X	X	
Leo-Pekka Lyytikäinen			X	X	X	
Nana Matoba				X	X	
Ilja M Nolte			X	X	X	
Maik Pietzner			X	X	X	
Bram Prins			X	X	X	

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Muhammad Riaz				X	X	
Antonietta Robino	X			X	X	
M. Abdullah Said				X	X	
Nicole Schupf	X	X	X		X	
Robert A Scott	X	X	X		X	
Tamar Sofer		V		V	X	
Alena Stančáková				X	X	
Fumihiko Takeuchi				X	X	
Bamidele O. Tayo		X	X	X	X	
Peter J Van der Most			X	X	X	
Tibor V. Varga				X	X	
Tzung-Dau Wang		X			X	
Yajuan Wang	X	X			X	
Erin B Ware			X	X	X	
Wanging Wen					X	
Yong-Bing Xiang					X	
Lisa R Yanek		X	X	X	X	
Weihua Zhang					X	
Jing Hua Zhao		X	X	X	X	
Adebowale Adeyemo					X	
Saima Afaq					X	
Najaf Amin			X		X	
Marzyeh Amini		X	X	X	X	
Dan E Arking			X		X	
Zorayr Arzumanyan			X		X	
Tin Aung	X				X	
Christie Ballantyne	X	X			X	
Graham R. Barr		X			X	
Lawrence F. Bielak		X		X	X	
Eric Boerwinkle	X		X		X	

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Erwin P Bottinger	X	X	X		X	
Ulrich Broeckel					X	
Morris Brown	X	X			X	
Brian E Cade		X	X		X	
Archie Campbell		X			X	
Mickaël Canouil		X	X		X	
Sabanayagam Charumathi	X				X	
Guanjie Chen				X	X	
Yii-Der Ida Chen			X		X	
Kaare Christensen	X	X	X		X	
COGENT-Kidney Consortium					X	X
Maria Pina Concas		X	X		X	
John M Connell	X	X	X		X	
Lisa de las Fuentes					X	
H. Janaka de Silva	X	X			X	
Paul S de Vries				X	X	
Ayo Doumatey					X	
Qing Duan					X	
Charles B Eaton					X	
Ruben N Eppinga			X	X	X	
Jessica D Faul	X	X			X	
James S. Floyd				X	X	
Nita G Forouhi	X	X			X	
Terrence Forrester	X	X			X	
Oscar H Franco		X			X	
Yechiel Friedlander			X		X	
Ilaria Gandin	X			X	X	
He Gao					X	
Sina A Gharib				X	X	
The GIANT Consortium					X	

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Bruna Gigante		X	X		X	
Franco Giulianini			X	X	X	
Hans J. Grabe		X			X	
Misa Graff					X	X
C Charles Gu					X	
Tamara B Harris	X				X	
Sami Heikkinen			X	X	X	
Chew-Kiat Heng			X		X	
Makoto Hirata		X			X	
James E. Hixson	X		X	X	X	
M Arfan Ikram	X				X	
InterAct Consortium					X	
David R Jacobs, Jr		X			X	
Yucheng Jia				X	X	
Roby Joehanes					X	
Craig Johnson		X			X	
Jost Bruno Jonas	X	X		X	X	
Anne E Justice					X	X
Tomohiro Katsuya		X			X	
Chiea Chuen Khor	X		X		X	
Tuomas O Kilpeläinen					X	
Woon-Puay Koh	X	X			X	
Ivana Kolcic	X	X	X		X	
Charles Kooperberg			X		X	
Jose E. Krieger	X	X	X		X	
Steve B Kritchevsky				X	X	
Michiaki Kubo	X	X	X	X	X	
Johanna Kuusisto	X				X	
Timo A Lakka	X	X			X	
Carl D. Langefeld	X	X		X	X	

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Claudia Langenberg	X	X	X		X	
Lenore J Launer	X				X	
Benjamin C Lehne					X	
Cora E Lewis		X			X	
Yize Li					X	
Jingjing Liang		X	X		X	
Shiow Lin				X	X	
Ching-Ti Liu	X		X	X	X	
Jianjun Liu	X		X		X	
Kiang Liu		X			X	
Marie Loh					X	
Kurt K Lohman	X	X	X		X	
Tin Louie				V	X	
Anna Luzzi			X		X	
Reedik Mägi		X	X		X	
Anubha Mahajan				X	X	X
Ani W. Manichaikul		X			X	
Colin A. McKenzie	X	X			X	
Thomas Meitinger		X			X	
Andres Metspalu		X	X		X	
Yuri Milaneschi		X			X	
Lili Milani		X	X		X	
Karen L Mohlke	X				X	
Yukihide Momozawa			X		X	
Andrew P Morris				X	X	X
Alison D Murray		X			X	
Mike A. Nalls			X	X	X	
Matthias Nauck		X			X	
Christopher P Nelson		X	X	X	X	
Kari North					X	

Author	PARTICIPATE IN STUDY CONCEPT AND DESIGN	PARTICIPATE IN PHENOTYPE DATA ACQUISITION AND/OR QC	PARTICIPATE IN GENOTYPE DATA ACQUISITION AND/OR QC	PARTICIPATE IN DATA ANALYSIS AND INTERPRETATION	REVIEWED AND APPROVED MANUSCRIPT	PERFORMED LOOK-UPS
Jeff R O'Connell					X	
Nicholette D. Palmer			X	X	X	
George J Papanicolau		X			X	
Nancy L. Pedersen	X	X	X		X	
Annette Peters		X			X	
Patricia A. Peyser		X		X	X	
Ozren Polasek	X	X	X		X	
Neil Poulter	X	X			X	
Olli T Raitakari	X	X			X	
Alex P Reiner		X		X	X	
Frida Renström		X	X		X	
Treva K. Rice	X	X	X	X	X	
Stephen S. Rich		X	X		X	
Jennifer G Robinson					X	
Lynda M. Rose		X	X	X	X	
Frits R Rosendaal	X	X	X		X	
Igor Rudan					X	
Carsten O. Schmidt		X			X	
Pamela J Schreiner		X			X	
William R Scott					X	
Peter Sever	X	X			X	
Yuan Shi		X			X	
Stephen Sidney		X			X	
Mario Sims	X	X		X	X	
Jennifer A. Smith		X	X	X	X	
Harold Snieder				X	X	
John M Starr	X	X	X		X	
Konstantin Strauch			X		X	
Heather M Stringham		X			X	
Nicholas YQ Tan		X			X	

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Hua Tang					X	
Kent D Taylor			X		X	
Yik Ying Teo	X		X		X	
Yih Chung Tham		X			X	
Henning Tiemeier		X			X	
Stephen T Turner	X	X	X		X	
André G Uitterlinden			X		X	
Understanding Society Scientific Group		X	X		X	
Diana van Heemst		X		X	X	
Melanie Waldenberger		X			X	
Heming Wang		X	X		X	
Lan Wang			X	X	X	
Lihua Wang				X	X	
Wen Bin Wei	X	X		X	X	
Christine A Williams				X	X	
Gregory Wilson Sr	X	X		X	X	
Mary K Wojczynski		X			X	
Jie Yao				X	X	
Kristin Young					X	X
Caizheng Yu	X	X			X	
Jian-Min Yuan	X	X			X	
Jie Zhou					X	
Alan B. Zonderman	X	X	X	X	X	
Diane M Becker	X	X	X	X	X	
Michael Boehnke	X				X	
Donald W. Bowden	X	X			X	
John C Chambers					X	
Richard S. Cooper	X	X		X	X	
Ulf de Faire	X	X	X		X	
Ian J Deary	X	X	X		X	

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Zeggini Eleftheria			X		X	
Paul Elliott					X	
Tõnu Esko		X	X		X	
Martin Farrall	X			X	X	
Paul W. Franks		X	X		X	
Barry I. Freedman	X	X	X	X	X	
Philippe Froguel	X				X	
Paolo Gasparini	X				X	
Christian Gieger		X		X	X	
Bernardo L Horta	X	X	X		X	
Jyh-Ming Jimmy Juang		X			X	
Yoichiro Kamatani	X			X	X	
Candace M Kammerer	X	X	X		X	
Norihiro Kato	X		X		X	
Jaspal S Kooner					X	
Markku Laakso	X				X	
Cathy C Laurie	X		X		X	
I-Te Lee		X			X	
Terho Lehtimäki	X	X	X		X	
Lifelines Cohort Study	X	X	X	X	X	
Patrik K.E. Magnusson	X	X	X		X	
Albertine J Oldehinkel	X	X			X	
Brenda Penninx		X			X	
Alexandre C. Pereira	X	X	X	X	X	
Rainer Rauramaa	X	X			X	
Susan Redline	X				X	
Nilesh J Samani	X	X	X	X	X	
James Scott					X	
Xiao-Ou Shu					X	
Pim van der Harst	X	X	X	X	X	

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Dabeeru C Rao	X	X	X	X	X	
Charles N Rotimi	X	X	X	X	X	
L. Adrienne Cupples	X	X	X	X	X	

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Figure Legends

Figure 1. Study Overview: Summary of data included in this study. [1]16,389 variants passed filtering criteria and were included in stage 2 analyses. [2]Trans-ancestry (TRANS) stage 1 and 2 combined meta-analyses were meta-analyses of stage 1 TRANS and stage 2 TRANS meta-analyses, and not meta-analyses of ancestry-specific stage 1 and stage 2 combined meta-analyses.

Figure 2. Interaction of rs12740061 (*LOC105378783*) and Current Smoking (1df): An interaction between rs12740061 and current smoking is observed among the AFR cohorts using the 1df test of interaction, but this association is not observed among the other ancestries. Interaction betas (95% confidence intervals) and p values are displayed.

Figure 3. Associations Observed Primarily Among Smokers: Comparison of the p values for stage 1 models, where a series of models were available, reveals genetic associations present primarily in the smoking subgroup for A.) rs7364132 (*DGCR8*) × ever-smoking on TG, B.) rs79950627 (*MIR4686*) × current smoking on LDL, and C.) rs56167574 (*PRKAG2*) × ever smoking on LDL.

Figure 4. rs73453125 × Current Smoking on LDL: For rs73453125, the direction of the genetic association differed by smoking status, such that the minor allele was associated with lower LDL among current smokers and higher LDL among non-smokers. The association was not detected in a model that was not stratified by smoking status. Variant betas (95% confidence intervals) and p values drawn from stage 1 models, where a series of models were available.

Figure 5. Association Observed Primarily Among Never-Smokers: In comparison of p values from stage 1 models for rs77810251 (*PTPRZ1*), a significant association with HDL was observed only among never-smokers.

Figure 6. rs10101067 *(EYA1)* × Current Smoking on TG (2df): Using the 2df joint test of the main and interaction effects, an association between rs10101067 and TG was identified. Given the lack of association using the 1df test of interaction (p = 0.069), it is probable that this observation represents a novel main effect TG locus. Variant main and interaction betas (95% confidence intervals) and p values are displayed.

Table 1: Statistically Significant ($p < 5\times10^{-8}$) Results in Stage 1 and 2 Meta-Analysis

						Stage 1 + 2				Stage 1
Index Variant (Nearest Gene)[1]	**Bld 37 Chr:Position**	**1000 Genomes Freq[2] AFR/AMR/ASN/EUR**	**Tested Allele – Freq**	**Ancestry**	**Trait/ Exposure[3]**	**Effect (SE)**	**Interaction Effect (SE)**	**1df Interaction P-value[4]**	**2df Joint P-value[4]**	**Adj. Main Effect P-value[5]**
					Loci with Evidence for Interaction					
rs12740061 (*LOC105378783*)	1:69407810	0.01/0.17/0.02/0.22	T – 0.05	AFR	lnHDL/CS	0.020 (0.0082)	-0.11 (0.019)	**7.4E-9**	**2.4E-8**	0.98
rs77810251 (*PTPRZ1*)	7:121504149	0.02/0.22/0.34/0.11	A – 0.04	AFR	lnHDL/ES	0.052 (0.0083)	-0.060 (0.012)	9.5E-7	**1.2E-9***	1.6E-4
rs73453125 (*CNTNAP2*)	7:146084573	0.09/0.02/0/0	A – 0.07	TRANS,AFR	LDL/CS	1.9 (0.69)	-8.3 (1.4)	1.7E-7	**2.0E-8**	0.76
rs56167574 (*PRKAG2*)	7:151245975	0.13/0.01/0/0	A – 0.12	AFR	LDL/ES	1.9 (0.80)	-6.1 (1.1)	**1.5E-8**	8.4E-8	0.08
rs79950627 (*MIR4686*)	11:2233790	0.06/0.01/0/0	A – 0.05	TRANS,AFR	LDL/CS	-0.10 (0.79)	-8.4 (1.6)	1.4E-6	**7.2E-9**	0.25
rs60029395 (*ZNF729*)	19:22446748	0.15/0.01/0.03/0	A – 0.13	AFR	lnTG/CS	0.041 (0.0092)	-0.097 (0.018)	**3.3E-8**	8.2E-8	0.17
rs7364132 (*DGCR8*)	22:20096172	0.19/0.02/0/0	A – 0.16	AFR,TRANS	lnTG/ES	0.012 (0.0091)	-0.066 (0.013)	8.8E-7	**2.5E-8**	0.0055
					Probable Main Effect Loci (No Evidence of Interaction)					
rs12144063 (*EYA3*)	1:28406047	0.35/0.28/0.53/0.30	T – 0.37	TRANS	lnHDL/CS,ES	-0.0042 (0.00069)	-0.00033 (0.0016)	0.75	**1.3E-10***	4.7E-7
rs10937241 (*ETV5*)	3:185822774	0.30/0.31/0.58/0.19	A – 0.17	EA,TRANS	lnHDL/CS,ES	-0.0079 (0.0012)	0.0021 (0.0026)	0.65	**4.2E-12***	4.5E-7
rs34311866 (*TMEM175*)	4:951947	0.01/0.07/0.12/0.20	C – 0.17	TRANS,EA	lnHDL,lnTG/CS	-0.0058 (0.00097)	0.0014 (0.0022)	0.61	**1.6E-9***	2.1E-6
rs73729083 (*CREB3L2*)	7:137559799	0.11/0.04/0.02/0	C – 0.05	TRANS,AFR	LDL/ES,CS	-3.7 (0.66)	-0.37 (0.95)	0.53	**1.3E-14***	**2.0E-10**
rs10101067 (*EYA1*)	8:72407374	0.04/0.07/0.13/0.06	C – 0.08	TRANS	lnTG/CS	0.014 (0.0025)	-0.0092 (0.0053)	0.069	**4.1E-8**	2.1E-6
rs4758675 (*B3GNT4*)	12:122691738	0.02/0/0/0	C – 0.02	AFR	lnTG/CS	-0.13 (0.025)	-0.029 (0.057)	0.85	**1.3E-8**	**3.6E-8**

*Abbreviations: African ancestry (AFR), Current Smoking (CS), European ancestry (EUR), Ever-Smoking (ES), Trans-ancestry (TRANS). [1]Listed variants represent the lead associations within 1 MB region for the 2 and 1 degree of freedom tests of the variant × smoking interaction after excluding variants within 1 MB of known lipids loci. If variant is in/within 2 KB of a gene, that gene name is listed; [2]Frequency of the tested allele in 1000 Genomes data by ancestry: Asian (ASN), Americas (AMR), African (AFR), and European (EUR);[3]If the region was associated with the trait in more than one meta-analysis, the most statistically significant result is listed first and described in table; [4]Bolding indicates genome-wide statistical significance; [5]P-values in this column come from a smoking-adjusted main effect model (available in Stage 1 cohorts only, see Figure 1); *Findings with an asterisk are statistically significant using a stricter p-value threshold, after Bonferroni correction for 2 smoking traits, 2 interaction tests, and ethnic and trans-ethnic testing ($p < 5 \times 10^{-8}/8 = 6.25 \times 10^{-9}$).*

Table 2: Statistically Significant ($p < 5\times10^{-8}$) Results in Stage 1 Meta-Analysis Unavailable in Stage 2[1]

Index Variant (Nearest Gene)[2]	Bld 37 Chr:Position	1000 Genomes Freq[3] AFR/AMR/ASN/EUR	Tested Allele – Freq	Ancestry	Trait/ Exposure	Effect (SE)	Interaction Effect (SE)	1df Interaction P-value[3]	2df Joint P-value[4]	Adj. Main Effect P-value[5]
rs140602625 (*EXOC6B*)	2:72849325	0.01/0/0/0	C – 0.02	AFR	LDL/CS	-3.4 (3.1)	-35 (7.1)	1.0E-6	**1.5E-8**	0.018
rs114138886 (*LOC107985905*)	2:84428024	0.02/0/0/0	T – 0.02	AFR	LDL/CS	2.4 (2.9)	-29 (5.4)	9.3E-8	**4.4E-8**	0.47
rs149776574 (*REEP1*)	2:86472455	0.01/0.08/0/0.06	G – 0.02	AFR	lnTG/CS	-0.048 (0.033)	0.40 (0.069)	**4.2E-10***	**5.1E-10***	0.88
rs143396479 (*LOC105374426/TMEM33*)	4:41911366	0.02/0/0/0	A – 0.01	AFR	LDL/ES	-16.0 (2.6)	15 (4.5)	0.022	**6.8E-9**	0.0094
rs148187465 (*MARCH1*)	4:164639694	0.01/0/0/0	C – 0.01	AFR	LDL/CS	-2.1 (3.0)	-32 (6.2)	3.7E-7	**4.9E-9***	0.032
rs76687692 (*G3BP1*)	5:151189283	0.03/0/0/0	A – 0.01	AFR	LDL/CS	2.7 (3.2)	25 (5.5)	0.0013	**4.8E-9***	0.0016
rs73339842 *(LOC105377701)*	5:164967406	0.02/0.01/0/0	G – 0.02	AFR	lnTG/CS	0.046 (0.033)	-0.41 (0.071)	**8.5E-9**	**3.3E-8**	0.96
rs115580718 (*BMP6*)	6:7880037	0.02/0/0/0	G – 0.01	AFR	lnTG/CS	-0.12 (0.036)	-0.29 (0.082)	0.00045	**1.2E-9***	1.6E-6
rs17150980 (*MAGI2*)	7:78173734	0/0.12/0.45/0.01	C – 0.03	AFR	lnTG/ES	-0.17 (0.028)	0.24 (0.044)	7.5E-8	**1.4E-9***	0.085
rs116592443 (*LYZL2*)	10:30884890	0.02/0/0/0	A – 0.01	AFR	lnTG/CS	0.073 (0.038)	-0.46 (0.081)	**1.8E-8**	1.2E-7	0.76
rs115628664 (*UNC5B*)	10:72899880	0.03/0/0/0	G – 0.01	AFR	lnTG/CS	0.027 (0.040)	-0.39 (0.071)	**4.7E-8**	**6.7E-9***	0.44
rs183911507 (*TP53I11*)	11:44978366	0.01/0/0/0	G – 0.02	AFR	lnTG/CS	-0.043 (0.029)	0.33 (0.059)	**1.7E-8**	6.5E-8	0.82
rs199771018 (*STOML3*)	13:39507838	0.02/0/0/0	T – 0.02	AFR	lnHDL/CS	-0.019 (0.019)	0.23 (0.037)	**1.2E-9***	**6.3E-10***	0.55
rs190976513 (*LOC105370255*)	13:71114207	0.02/0.01/0/0	A – 0.02	AFR	LDL/CS	-5.1 (2.6)	-20 (5.2)	9.3E-5	**3.2E-8**	1.1E-4
rs182600360 (*LOC105370531*)	14:63607120	0.02/0/0/0	A – 0.02	AFR	LDL/CS	6.6 (3.3)	-39 (7.1)	**4.4E-8**	3.3E-7	0.56
rs62064821 (*CCT6B*)	17:33280904	0.01/0.04/0/0.06	T – 0.01	AFR	LDL/CS	8.5 (3.3)	-30 (5.5)	**3.1E-8**	6.0E-7	0.17

Abbreviations: African ancestry (AFR), Current Smoking (CS), Ever-Smoking (ES). [1]All loci have some evidence for interaction ($p<0.05$ for 1df test of interaction); thus, results not categorized into "Loci with Evidence for Interaction" or "Probable Main Effects (without evidence for interaction)"; [2]Listed variants represent the lead associations within 1 MB region for the 2 and 1 degree of freedom tests of the variant × smoking interaction after excluding variants within 1 MB of known lipids loci. If variant is in/within 2 KB of a gene, that gene name is listed; [3]Frequency of the tested allele in 1000 Genomes data by ancestry: Asian (ASN), Americas (AMR), African (AFR), and European (EUR); [4]Bolding indicates genome-wide statistical significance; [5]P-values in this column come from a smoking-adjusted main effect model (available in Stage 1 cohorts only, see Figure 1).
**Findings with an asterisk indicate statistical significance using a stricter p-value threshold, after Bonferroni correction for 2 smoking traits, 2 interaction tests, and ethnic and trans-ethnic testing ($5 \times 10^{-8}/8 = 6.25 \times 10^{-9}$).*