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Relation of Lipid Gene Scores to Longitudinal Trends in Lipid Levels and Incidence of Abnormal Lipid Levels Among Individuals of European Ancestry: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Multiple genetic loci have been associated with blood lipid levels. We tested the hypothesis that people with an unfavorable lipid gene profile would experience a greater increase in lipid levels and a higher incidence of abnormal lipid levels, relative to those with more favorable lipid gene profiles.

Methods and Results—9,328 European-descent individuals in ARIC (ages 45–64 y) were followed for 9 years. Separate gene scores were created for each lipid phenotype based on 95 loci identified in a published GWAS of >100,000 European-descent individuals. Adjusted linear and survival models were used to estimate associations with lipid levels and incidence of lipid-lowering medication or abnormal lipid levels. Age and sex interactions were also explored. The cross-sectional difference (mg/dL) per one standard deviation (SD) was −1.89 for HDL-C, 9.5 for LDL-C, and 22.8 for triglycerides ($p<5 \times 10^{-34}$ for all). Longitudinally, overall triglyceride levels rose over time, and each SD greater triglyceride gene score was associated with an average increase in triglyceride levels of 0.3 mg/dL (p=0.003) over 3-years. The HDL-C, LDL-C and total cholesterol gene scores were not related to change. All lipid gene scores were positively related to incidence of abnormal lipid levels over follow-up (HRs per SD ranged from 1.15–1.36).

Conclusions—Associations of genetic variants with lipid levels over time are complex, with the triglyceride gene score positively related to change in triglycerides levels. Similar longitudinal results were not observed for LDL-C or HDL-C levels. Unfavorable gene scores were nevertheless related to higher incidence of abnormal levels.

Keywords

lipids; longitudinal trends; gene score; Atherosclerosis Risk in Communities (ARIC)

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Background

Several recent genome-wide association studies (GWAS) in Caucasians have successfully localized common DNA sequence variants that are cross-sectionally associated with blood lipoprotein levels[1–14]. Most recently, Teslovich *et al* published a meta-analysis of 46 GWASs, together comprising >100,000 individuals of European ancestry. In total, 95 loci were significantly associated with lipid phenotypes (i.e. total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides)[12]. Given that individual loci only have modest effects, in several GWAS authors have computed summary lipid gene scores, to assess whether the cumulative allelic dosage of risk alleles at these loci contributed to quantitative variation in lipoprotein levels in their study populations[1–3, 12].

Virtually all prior work evaluating the relation of lipid gene scores to lipid levels has been cross-sectional. However, lipid levels often change with age or over time. Etiologically, it is of interest to know whether the genotypic effects are stable, or if they vary with time, across the lifespan. Though largely unexplored, there is some evidence suggesting that the effects of some SNPs may vary across the life-course[3, 15–18]. It has been hypothesized that the differential effects may be due to age-dependent gene expression, changes in the penetrance of underlying genes, and/or gene-environment interactions related to the effect of cumulative exposure to certain environmental factors[16]. Further, it is unknown whether sex interactions exist in the effect of lipid genotype scores on circulating lipid levels. Lipid levels are known to vary by sex[19], and sex-differences in the effects of some alleles have been noted[2, 3, 20, 21].

In order to better understand the effects of GWAS-identified SNPs on lipid levels we created phenotype-specific lipid gene scores in order to test the hypothesis that, over 9 years of follow-up, there would be interactions between lipid gene scores and time, such that people with less favorable lipid gene scores would experience a greater increase in lipid levels and a higher incidence of abnormal lipid levels than people with more favorable lipid gene scores. We also evaluated whether sex-interactions were present in the cross-sectional relations of lipid gene scores to lipid levels.

Methods

Study Design, Population, and Data Collection

The ARIC study is a multi-center population-based prospective cohort study designed to investigate the etiology and natural history of atherosclerosis in middle-aged adults[22]. Participants were recruited from four US communities: Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD. The study cohort included 15,792 white and black men and women aged 45–64 years at baseline, in 1987–1989 (visit 1). Cohort reexaminations took place at 3-year intervals; response rates were 93%, 86%, and 81% at visit 2 (1990–1992), 3 (1993–1995), and 4 (1996–1998), respectively.

At each visit ARIC participants underwent interviews, venipuncture, and measurement of blood pressure and anthropometrics. Trained interviewers ascertained basic demographic data, medical history, information about personal habits, and medication use. Study participants were asked to bring all medications, vitamins, and supplements taken in the 2 weeks prior to the examination. All medication names were transcribed and coded.

This analysis includes only ARIC Caucasians who consented for genetic analyses and had successful GWAS genotyping. Further, for LDL-C and triglyceride analyses datapoints were excluded in instances when the participant did not fast for 8 hours prior to venipuncture.

Local institutional review boards approved the ARIC protocol, and all participants gave informed consent.

Lipid Measurement

Fasting (minimum 8 hr) blood samples were drawn from an antecubital vein into tubes containing EDTA, and were sent to the ARIC Central Lipid Laboratory (Baylor College of Medicine, Houston) for processing. Total plasma cholesterol[23] and triglycerides[24] were determined by enzymatic methods. HDL-C was measured after dextran-magnesium precipitation[25], and the Friedewald equation[26] was used to calculate LDL-C in those with triglyceride levels under 400 mg/dL.

Lipid Medication Use

Because many participants took antihyperlipidemic medications, it was necessary to account for these medications when analyzing lipid levels. As recommended by Tobin *et al*[27], in order to estimate, among medication users, what values might have been had the participants not been taking medication, medication use was taken into account by adding a constant. This approach has been shown to be preferable to other approaches, such as including medication use as an indicator variable in multivariate models or excluding antihyperlipidemic medication users, which may introduce bias, and similar to more complex methods such as censored normal regression models[27].

The constant used was dependent on the specific type of medication(s) used. For HMG-CoA reductase inhibitors (statins) and fibric acid derivatives we used the estimates recommended by Wu[28] (Statins: LDL-C = +49.9 mg/dL, HDL-C = −2.3, TG = +18.4, TC = +52.1; Fibrates: LDL-C=+40.1, HDL-C = −5.9, TG = +57.1, TC = +46.1). For bile acid sequestrants and niacin we used the mid-point of the range provided in the Adult Treatment Panel (ATP) III Final Report[29], applied to ARIC mean values: for bile acid sequestrants LDL-C = +40.5, HDL-C = −1.9, TG = 0.0 and for niacin LDL-C = +24.7, HDL-C = −9.9, TG = +89.4. ATP III did not report estimates for the effects of bile acid sequestrants and niacin on total cholesterol, and we were unable to find stable estimates elsewhere. As an approximation, based on the effects of statins and fibrates on total cholesterol, we estimated the effects of bile acid sequestrants and niacin on total cholesterol by adding the absolute values for change in LDL-C and HDL-C. Thus, for bile acid sequestrant users we added 42.4 to total cholesterol values, and for niacin users we added 34.6 to total cholesterol values. Sensitivity analyses were explored to evaluate the robustness of our approach and assumptions.

Genotyping

In the ARIC Study, genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0. Genotyping and quality control methods are described in detail elsewhere[30]. Briefly, excluded were subjects who disallowed DNA use, those with unintentional duplicates with higher missing genotype rates, suspected mixed/contaminated samples, scans from one problem plate, samples with a mismatch between called and phenotypic sex, samples with genotype mismatch with 39 previously genotyped SNPs, suspected first-degree relative of an included individual, and genetic outliers based on average IBS statistics and principal components analysis using EIGENSTRAT. SNPs were excluded due to no chromosome location, being monomorphic, having call rate <95%, MAF <1% or HWE-P $<10^{-5}$. After the filtering, 669,450 SNPs were used in the imputation to 2,543,887 autosomal SNPs from HapMap Phase II CEU samples using MACH v1.0.16.[30]

Gene Score Creation

We used SNPs identified in the Teslovich GWAS[12] to create the lipid gene scores. The Teslovich GWAS is much larger than any previous lipid GWAS, and conglomerated the majority of populations included in prior GWASs.

Separate effect size-based gene scores were created for each lipid phenotype. Gene score creation involved several steps:

1. We first determined the number of unfavorable alleles for each individual. For genotyped SNPs, each unfavorable allele was counted as +1. For imputed SNPs we utilized the predicted number of unfavorable alleles, as estimated by the MACH imputation.[30] MACH provides an approximation of the expected number of copies of a selected allele, ranging from 0 (no chance the person had the selected allele) to 2 (both alleles were the selected allele).
2. To account for the differing effect sizes of the SNPs, the number of unfavorable alleles from each SNP was multiplied by the absolute value of the additive effect size published in the Teslovich GWAS[12].
3. Then, for each person, we summed the estimates (number of unfavorable alleles*effect size) across all individual SNPs included in the gene score for each phenotype. This sum was then rescaled by dividing by the phenotype-specific average effect size (the average effect of all SNPs included in the gene score)
4. Lastly, we divided each phenotype-specific gene score by 1 SD.

Please note that the dual rescaling of steps 3 and 4 are mathematically unnecessary, as a single rescaling would yield the identical results. We chose to rescale twice in order to maximize the transparency and interpretability of our gene scores. The rescaling in step 3 permits, in Table 2, reporting of the mean number of unfavorable alleles for each score. The rescaling by 1 SD, in step 4, enhances interpretability and comparisons across phenotypes.

As based on the Teslovich manuscript, a total of 47 SNPs were included in the HDL-C gene score (ARIC: 13 directly genotyped, 34 imputed), 37 in the LDL-C gene score (ARIC: 12 directly genotyped, 25 imputed), 32 in the triglyceride gene score (ARIC: 6 directly genotyped, 26 imputed) and 52 in the total cholesterol gene score (ARIC: 14 directly genotyped, 38 imputed). SNPs included in the lipid gene score, along with their imputation status, are shown in the Supplemental Table 1.

Notably, ARIC was a primary discovery cohort in the Teslovich paper[12], contributing 7.8% (7,841 of 100,184) of individuals of European descent. As such, the initial SNP identification in Teslovich and subsequent testing of relations of the gene scores to baseline lipid levels in this study are not entirely independent.

Statistical Analysis

Means (standard deviations) and frequencies (percents) were used to describe characteristics of participants at each of the four ARIC visits. General linear regression (PROC GLM) was used to evaluate the main effects of phenotype-specific lipid gene scores on baseline lipid levels, adjusted for age, sex, and center. The percent variance of lipid levels explained by the phenotype-specific gene scores, after adjustment for age, sex, and center, was determined using the “effectsize” command in the SAS Proc GLM model statement, which is the sum of squared deviations around the gene score mean (Type III sum of squares for the gene score effect) divided by the sum of squared deviations around the grand mean plus the sum of squared deviations around the gene score mean (total sum of squares + gene score sum of squares) (SAS Institute Inc., 2007). Interactions between sex and lipid gene scores on lipid

levels were explored by using cross-product terms in the models. Sex stratified results were also reported regardless of whether an interaction was present, given inherent interest.

Associations between lipid gene scores and changes in lipid levels over time were assessed using linear mixed models, implemented in PROC MIXED. These models allow for estimation of both a fixed effect (population average) of the gene score over time as well as model the individual-level variability in the intercept and slope. Participants who provide outcome data on at least one time point are retained in the model. Given the balanced longitudinal design, the four time points of the study were used as an ordinal variable with time 1 coded as zero. Age, sex, and study center were included in all models as covariates for estimation of the intercept and slope parameters. An unstructured variance structure was specified. Product terms of time and each covariate were used to account for covariate effects on the estimated slope parameter. Prior to examining the effect of the gene score on each outcome, we first modeled the outcome with a random intercept and with both a random intercept and a random slope. We compared the fit of these models using standard indices (i.e., AIC, deviance). We then incorporated the gene score and its product term with time to examine the association with the baseline outcome value and the rate of change over time. Examination of the distribution of the random effects and the model residuals were consistent with the assumptions of linear mixed effects regression. As a final consideration, we incorporated an interaction between age and gene score on the intercept and slope parameters. In the case of a significant interaction, we explored the effect of the interaction by estimating separate models within categories of age.

Note that we did not model gene score-by-age interactions, but instead, as has been done in similar analyses[17], we analyzed the associations of longitudinal change with gene scores as well as gene score-by-time interactions. This approach was selected in order to maximize statistical power; participants entered into the study at different ages and they were not followed-up annually, therefore, each participant only contributed data to certain age groups, and the sample size for each individual age group is much more limited than that for each follow-up time point[17]. From the standpoint of interpreting our results, however, the most uniform and evident change in participants' characteristics during follow-up was age; therefore the most plausible interpretation is that longitudinal effects would mostly reflect age effects[17]. In secondary analyses, we conducted the linear mixed models regression analyses stratified by 10-yr age category (i.e. baseline age of 45–54 or 55–64).

Cox proportional hazards regression was used to evaluate the relation of gene scores with incidence of abnormal lipid levels. Incidence was defined by medication use or levels beyond ATP III[29] cut-points (mg/dL): HDL-C ≤ 40, LDL-C ≥ 160, triglycerides ≥ 200, total cholesterol ≥ 240. Participants who had abnormal lipid levels or were on lipid-lowering medications at baseline were excluded from this analysis. Person-years, which were calculated separately for each phenotype, accrued from the participant's baseline examination until incidence of abnormal lipid levels, loss-to-follow-up, death, disenrollment, or the participant's fourth ARIC visit. Models were adjusted for age, sex, and center.

Results

Cohort Description

The cohort of 9,328 Caucasian ARIC participants had a mean age of 54 years at baseline, and 53% were female (Table 1). At baseline in 1987–89, mean (SD) levels of HDL-C, LDL-C, triglycerides and total cholesterol were 50.3 (16.8) mg/dL, 139 (39) mg/dL, 139 (94) mg/dL, and 216 (42) mg/dL respectively. 3.4% were taking pharmacologic agents to improve their lipid levels.

Over 9 years of follow-up, overall HDL-C levels remained fairly stable, while LDL-C levels decreased and triglyceride levels increased (Table 1). The prevalence of hypercholesterolemia and use of medications to lower lipid levels increased greatly over the course of follow-up.

Cross-sectional relation of lipid gene scores to lipid levels

In cross-sectional analyses all four lipid gene scores were significantly related to their corresponding phenotypes ($p<5 \times 10^{-34}$ for all) (Table 2). After adjusting for age, sex, and center, the HDL-C gene score explained 1.6% of the variance in baseline HDL-C levels, and each standard deviation increase in the HDL-C gene score was associated with 1.89 mg/dL lower HDL-C levels. Sex modified the relation of the HDL-C gene score to HDL-C levels ($p = 0.05$). In stratified analyses, the association per 1 standard deviation higher HDL-C gene score was stronger among women (−2.16 mg/dL) than men (−1.56 mg/dL). For LDL, the LDL-C gene score explained 6.0% of the variation in LDL-C levels, and each standard deviation higher LDL-C gene score was associated with 9.5 mg/dL higher LDL-C levels. There was no evidence of sex-interactions in the relation of the LDL-C gene score to LDL-C levels. Similarly, the triglyceride gene score explained 6.0% of the variation in triglyceride levels, and levels were 22.8 mg/dL higher for each standard deviation higher triglyceride gene score. There was an interaction by sex ($p < 0.0001$), with each standard deviation higher triglyceride gene score having a greater association among men (26.5 mg/dL) then women (19.2 mg/dL). For total cholesterol, the gene score explained 6.8% of the variation, and each standard deviation higher total cholesterol gene score was associated with 10.7 mg/dL higher levels. No significant sex-interactions were present in the relation of the total cholesterol gene scores to levels of total cholesterol.

Longitudinal relation of lipid gene scores to lipid levels

Using linear mixed models regression (Table 3 and Supplemental Tables 2–5), each standard deviation higher triglyceride gene score was associated with an increase in triglyceride levels of 0.3 mg/dL ($p = 0.003$) for each 3-year time-period. This result remained significant even after adjusting for BMI ($p = 0.002$). There was a three-way interaction ($p=0.01$; age*gene score*time) in that the greater increase in triglyceride levels at higher triglyceride gene scores was stronger among younger participants (age: 45–54; time*gene score interaction beta: 0.52; p-value: 0.0003) than older participants (age: 55–64; beta: 0.07; p-value: 0.62). The HDL-C gene score, LDL-C gene score and total cholesterol gene score were not significantly related to change in levels of their respective phenotypes.

In sensitivity analyses, we explored omitting people upon starting use of lipid lowering medications, and including only people in the analysis with lipid levels for all 4 visits. Results of these sensitivity analyses were similar to those of the primary analyses (data not shown).

Incidence of abnormal lipid levels

Lipid gene scores were positively related to incidence of abnormal lipid levels (Table 4). The HR (95% CI) for developing abnormal HDL-C levels per each standard deviation higher HDL-C gene score was 1.15 (1.10, 1.20). For LDL-C the comparable HR was 1.41 (1.32, 1.50), while for triglycerides it was 1.49 (1.41, 1.56), and for total cholesterol 1.36 (1.29, 1.45). Lipid gene scores for LDL-C, triglycerides, and total cholesterol also predicted incidence of lipid-lowering medication use, regardless of actual lipid levels. There was no evidence to suggest that sex or age significantly modified the relations of lipid gene scores to incidence of abnormal lipid levels or use of lipid lowering medications.

Notably, for all traits, participants with higher gene scores had mean baseline lipid values closer to "abnormal" thresholds used to define incidence than did participants with lower lipid gene scores. For example, the cut-point for HDL-C was 40 mg/dL; the mean (SD) of HDL-C for those in the highest quartile of HDL-C gene score was 48.3 (16.0) mg/dL versus 53.4 (17.4) mg/dL for those in the lowest quintile. Similarly, those in the top quartile of LDL-C gene scores had mean LDL-C values closer to the abnormal cut-point (160 mg/dL) than those in the lowest quartile [149.3 (38.0) vs. 125.7 (36.8)]. The same held true for triglycerides [cutpoint: 200 mg/dL, mean among upper gene score quartile = 166.7 (117.0) mg/dL, mean among lower gene score quartile = 112.0 (63.8) mg/dL] and total cholesterol [cutpoint: 240 mg/dL, mean among upper gene score quartile = 227.7 (40.8) mg/dL, mean among lower gene score quartile = 201.8 (39.1) mg/dL].

Discussion

Using SNPs identified in a recently published lipid GWAS which included over 100,000 Caucasians[12], we created phenotype-specific effect size-based lipid gene scores, then related these scores to lipid levels in nearly 10,000 Caucasian participants of the ARIC cohort. For all four phenotypes, the lipid gene scores were cross-sectionally related to lipid levels, and longitudinally related to incidence of abnormal lipid levels and use of antihyperlipidemic medications. Further, across time, participants with higher triglyceride gene scores experienced greater rise in their triglyceride levels than participants with lower triglyceride gene scores. HDL-C, LDL-C, and total cholesterol gene-scores were not related to change in levels of their respective phenotypes.

Cross-sectional findings

As expected, lipid gene scores were cross-sectionally related to lipid levels. For all phenotypes, however the gene scores explained relatively little variation (<7%) in lipid levels. Teslovich et al reported that, applied to Framingham Heart Study data, lipid gene scores explained more variation (9.6% to 12.4%) in lipid phenotype levels. Previous studies which have created lipid GWAS gene scores have found the scores to explain 3% to 6% of lipid level variation[2, 3].

We also evaluated whether the association of the lipid gene scores with cross-sectional lipid levels varied by sex. Modest sex interactions were observed, with the HDL-C gene score being more strongly related to HDL-C levels among women, and the triglyceride gene score being more strongly related to triglyceride levels among men. Lipid levels are known to vary by sex[19], and sex-differences in the associations for some alleles have been noted[2, 3, 20, 21]. Gonadal hormones are believed to modify both SNP penetrance and expressivity[21].

Prospective associations

The primary aim of the manuscript was to evaluate whether phenotype-specific lipid gene scores were associated with change in levels of corresponding lipid phenotypes. Different lipid phenotypes change at dissimilar rates at different points in the life course. By middle-age, in the U.S., HDL-C levels have reached fairly stable values, and LDL-C levels are stable or given recent secular trends decrease, while triglyceride levels continue to rise[31–33]. This may explain, in part, why we observed a positive association between the triglyceride gene score and change in triglyceride levels in these initially 45–64 year olds, while for other phenotypes the results were null. Notably, the modest triglyceride findings persisted even after adjusting for BMI, which is positively related to triglyceride levels. The HDL-C, LDL-C and total cholesterol gene scores were not related to changes in their respective phenotypes in this middle-aged population. In a previous study of younger population (mean

age 40.8 years) higher levels of a total cholesterol gene score were associated with greater increases in total cholesterol across time[18]

For all lipid phenotypes, lipid gene scores predicted incidence of abnormal levels or medication use. People with greater gene scores were closer to lipid cut-points at baseline, and consequently were more likely to exceed abnormal cut-points over follow-up. The cross-sectional relations of lipid gene scores to lipid levels, along with the incidence of abnormal lipid level findings suggest that as additional SNPs or rare variants are identified and a greater proportion of variance explained, it may be possible that lipid genotype scores could assist in primordial prevention by helping, along with other factors, to identify individuals who would be at greatest risk of developing abnormal lipid levels across their lifecourse.

Our results must be interpreted within the context of typical changes in lipid levels, as a consequence of both aging and secular trends. In the ARIC sample, between baseline (1987–1989) and visit 4 (1996–1998), HDL-C levels fluctuated but remained fairly stable, while LDL-C levels decreased, and triglyceride levels increased. This mirrors national trends, based on National Health and Nutrition Examination Survey (NHANES) data, which show that during a similar timeframe (between 1988–1994 and 1999–2002) LDL-C cholesterol levels decreased, there was no change in HDL-C levels, and there was a nonsignificant increase in triglyceride levels[32]. Regardless of secular trends in lipid levels, individual-level linear mixed models analysis of lipid levels among ARIC participants enabled exploration of contrasts between individuals with different lipid gene scores.

Strengths and Limitations

Strengths of this study are the large-population-based sample and the multiple lipid measurements across time. Limitations include some SNPs being imputed, potential lipid measurement error, and the fact that we had to estimate the effect medication use had on lipid levels. In sensitivity analyses, however, results were similar when medication users were excluded, suggesting that improperly accounting for medication use did not substantially bias our results. Further, as our sample consisted of middle-aged Caucasians, our results may not be generalizable to populations of different age-ranges and non-whites. Given that LDL-C and HDL-C levels are fairly stable by middle-age[31–33], it would be interesting to evaluate the relation of HDL-C and LDL-C gene scores to change in HDL-C and LDL-C levels in a younger population. Lastly, though there are many advantages to using gene scores, use of gene scores prohibits identification of the individual SNPs most strongly related to lipid levels or change in lipid levels.

Conclusions

In this sample of nearly 10,000 Caucasians, lipid gene scores were related to cross-sectional lipid levels, and prospectively associated with incidence of abnormal lipid levels and use of antihyperlipidemic medications. Additionally, the triglyceride gene score was associated with increases in triglyceride levels over time. As additional relevant genes are identified and a greater proportion of the variance of lipid levels are explained, it is possible that gene scores might be better reflective of lifetime exposure to serum lipids than a measurement taken at a single point in time. Understanding the relation between gene scores and the evolution of blood lipids over time has potential to enhance information used in CVD risk prediction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics, lipid levels, and pharmacologic use of lipid-lowering treatments across study visits: ARIC Caucasians, 1987–1998

	Visit 1 (1987–1989)	Visit 2 (1990–1992)	Visit 3 (1993–1995)	Visit 4 (1996–1998)
N	9345	9016	8286	7556
Demographics				
Age, years ± SD	54.3 ± 5.7	57.2 ± 5.7	60.3 ± 5.6	63.1 ± 5.6
Female, n (%)	4932 (52.9)	4739 (52.7)	4385 (53.0)	4030 (53.4)
Physiologic Characteristics				
BMI, kg/m^2 ± SD	27.0 ± 4.8	27.0 ± 4.8	27.0 ± 4.8	28.3 ± 5.3
Waist, cm ± SD	96 ± 13	96 ± 13	96 ± 13	101 ± 14
Prevalent diabetes, n (%)	812 (8.7)	1029 (11.4)	1026 (12.4)	1025 (13.6)
Mean Lipid Values*, mg/dL ± SD				
HDL-C Range	50.3 ± 16.8 [2.6 to 134.8]	48.1 ± 16.5 [11.0 to 130.0]	50.7 ± 18.0 [8.2 to 149.0]	48.4 ± 16.4 [8.2 to 175.0]
LDL-C Range	139 ± 39 [14 to 505]	136 ± 38 [10 to 467]	132 ± 37 [10 to 367]	130 ± 36 [18 to 434]
Triglycerides Range	139 ± 94 [24 to 1894]	145 ± 93 [28 to 2376]	154 ± 93 [22 to 1368]	157 ± 90 [20 to 991]
Total Cholesterol Range	216 ± 42 [68 to 594]	212 ± 41 [80 to 558]	212 ± 40 [77 to 510]	209 ± 40 [77 to 611]
Lipid Medication Usage, n (%)				
Statins	57 (0.6)	256 (2.7)	529 (5.7)	959 (10.3)
Fibrates	94 (1.0)	203 (2.2)	207 (2.2)	163 (1.7)
Bile acid sequestrants	54 (0.6)	90 (1.0)	63 (0.7)	52 (0.6)
Niacin	95 (1.0)	139 (1.5)	153 (1.6)	99 (1.1)
Any lipid medication use	319 (3.4)	662 (7.1)	906 (9.7)	1213 (13.0)
Abnormal Lipid Values*, n (%)				
HDL-C, < 40 mg/dL	2744 (29.4)	3180 (35.4)	2502 (30.3)	2572 (34.1)
LDL-C, ≥ 160 mg/dL	2340 (25.5)	1825 (20.7)	1245 (15.3)	881 (11.9)
Triglycerides, ≥ 200 mg/dL	1419 (15.2)	1527 (17.0)	1568 (19.0)	1554 (20.6)
Total Cholesterol, ≥ 240 mg/dL	2281 (24.5)	1770 (19.6)	1487 (18.0)	1024 (13.6)

*Constants were applied to account for use of pharmacologic lipid-lowering treatments.

Table 2

Relation of HDL-C, LDL-C, triglyceride, and total cholesterol lipid gene scores with cross-sectional lipid levels, and interactions with sex*: ARIC Caucasians, 1987–1989

	HDL-C	LDL-C	Triglycerides	Total cholesterol
Lipid gene scores				
Unfavorable alleles†, Mean (SD)	40.2 (4.3)	37.2 (3.9)	34.2 (3.6)	56.0 (4.4)
Variance in lipid levels explained by score	1.6%	6.0%	6.0%	6.8%
Difference in lipid levels per 1 SD in gene scores				
Overall, mg/dL	−1.89 (−2.19, −1.59)	9.5 (8.7, 10.2)	22.8 (21.0, 24.6)	10.7 (9.9, 11.5)
p-value	4.74×10^{-34}	6.07×10^{-126}	1.79×10^{-127}	1.07×10^{-145}
Sex interaction				
Men, mg/dL	−1.56 (−1.93, −1.20)	9.6 (8.5, 10.6)	26.5 (23.6, 29.4)	10.6 (9.4, 11.7)
Women, mg/dL	−2.16 (−2.63, −1.69)	9.5 (8.5, 10.6)	19.2 (16.9, 21.5)	10.9 (9.8, 12.0)
Interaction p-value	0.05	0.86	<0.0001	0.77

*Baseline lipid levels used. Models adjusted for age, sex, and center.

†Gene scores were created for each lipid phenotype, as the sum of unfavorable alleles multiplied by their respective effect sizes, then divided by the average effect size.

Table 3

Time trends in lipid levels according to phenotype-specific lipid gene scores: ARIC Caucasians, 1987–1998

		Change (mg/dL) per 1 standard deviation in gene scores over 3 year period*					
		Model 1			Model 2		
		Change	SE	p-value	Change	SE	p-value
HDL-C							
Initial status	Intercept	37.62	[1.50]	<.0001	35.92	[1.43]	<.0001
	HDLscore	−1.90	[0.15]	<.0001	−1.89	[0.14]	<.0001
Rate of change	Intercept (time)	0.30	[0.13]	0.02	0.68	[0.13]	<.0001
	HDLscore* time	0.01	[0.01]	0.71	0.00	[0.01]	0.72
LDL-C							
Initial status	Intercept	95.5	[3.7]	<.0001	98.2	[3.7]	<.0001
	LDLscore	9.4	[0.4]	<.0001	9.5	[0.4]	<.0001
Rate of change	Intercept (time)	2.8	[0.4]	<.0001	2.2	[0.4]	<.0001
	LDLscore* time	−0.1	[0.0]	0.06	−0.1	[0.0]	0.06
Triglycerides							
Initial status	Intercept	98.4	[8.8]	<.0001	110.8	[8.4]	<.0001
	TGscore	22.6	[0.9]	<.0001	22.4	[0.9]	<.0001
Rate of change	Intercept (time)	7.2	[1.0]	<.0001	4.4	[1.0]	<.0001
	Tgscore* time	0.3	[0.1]	0.003	0.3	[0.1]	0.002
Total Cholesterol							
Initial status	Intercept	151.8	[3.9]	<.0001	155.0	[3.9]	<.0001
	Tcscore	10.7	[0.4]	<.0001	10.8	[0.4]	<.0001
Rate of change	Intercept (time)	4.5	[0.4]	<.0001	3.8	[0.4]	<.0001
	Tcscore* Time	0.0	[0.0]	0.37	0.0	[0.0]	0.37

Model 1: Adjusted for age, sex, center, age*time, center*time.

Model 2: Adjusted for Model 1 + waist circumference, waist circumference*time.

* The gene scores and waist circumference were centered at grand means in order to enhance interpretability of the intercepts.

Table 4

Hazard ratio (95% CI) of abnormal lipid levels and use of lipid-lowering medications per 1 standard deviation in lipid gene scores*: ARIC Caucasians, 1987–1998

Incident abnormal serum lipid levels†¥		
Lipid gene score	**N events**	**HR (95% CI)**
HDL-C	1752	1.15 (1.10, 1.20)
LDL-C	1067	1.41 (1.32, 1.50)
Triglycerides	1629	1.49 (1.41, 1.56)
Total Cholesterol	1179	1.36 (1.29, 1.45)
Incident abnormal serum lipid levels† or use of lipid-lowering medications‡¥		
Lipid gene score	N events	HR (95% CI)
HDL-C	2232	1.10 (1.06, 1.15)
LDL-C	1469	1.35 (1.28, 1.42)
Triglycerides	2182	1.36 (1.30, 1.42)
Total Cholesterol	1570	1.32 (1.26, 1.39)
Incident use of lipid lowering medications‡§		
Lipid gene score	N events	HR (95% CI)
HDL-C	1378	1.03 (0.98, 1.09)
LDL-C	1378	1.39 (1.32, 1.46)
Triglycerides	1378	1.25 (1.19, 1.32)
Total Cholesterol	1378	1.44 (1.37, 1.52)

*Adjusted for age, sex, and center.

†Cut-points (mg/dL): HDL-C ≤ 40, LDL-C ≥ 160, triglycerides ≥ 200, total cholesterol ≥ 240

‡Use of HMG-CoA reductase inhibitors (statins), fibric acid derivatives, bile acid sequestrants and/or niacin

¥Among participants with normal lipid levels and not on medications at baseline

§Among participants not on lipid-lowering medication at baseline, regardless of baseline lipid levels