Sugar-Sweetened Beverage Consumption May Modify Associations Between Genetic Variants in the CHREBP (Carbohydrate Responsive Element Binding Protein) Locus and HDL-C (High-Density Lipoprotein Cholesterol) and Triglyceride Concentrations

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Abstract

Background ---Carbohydrate responsive element binding protein (ChREBP) is a transcription factor that responds to sugar consumption. Sugar-sweetened beverage (SSB) consumption and genetic variants in the *CHREBP* locus have separately been linked to high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) concentrations. We hypothesized that SSB consumption would modify the association between genetic variants in the *CHREBP* locus and dyslipidemia.

Methods ---Data from 11 cohorts from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (N=63,599) and the UK Biobank (UKB) (N=59,220) were used to quantify associations of SSB consumption, genetic variants, and their interaction on HDL-C and TG concentrations using linear regression models. A total of 1,606 single-nucleotide polymorphisms (SNPs) within or near *CHREBP* were considered. SSB consumption was estimated from validated questionnaires and participants were grouped by their estimated intake.

Results ---In a meta-analysis, rs71556729 was significantly associated with higher HDL-C concentrations only among the highest SSB consumers (β, 2.12 [95% CI, 1.16–3.07] mg/dL per allele; *P*<0.0001), but not significantly among the lowest SSB consumers (*p*=0.81; *p*$_{\text{Diff}}$<0.0001). Similar results were observed for two additional variants (rs35709627 and rs71556736). For TG, rs55673514 was positively associated with TG concentrations only among the highest SSB consumers (β, 0.06 [95% CI, 0.02–0.09] ln-mg/dL per allele, *P*=0.001), but not the lowest SSB consumers (*p*=0.84; *p*$_{\text{Diff}}$=0.0005).

Conclusions ---Our results identified genetic variants in the *CHREBP* locus that may protect against SSB-associated reductions in HDL-C and other variants that may exacerbate SSB-associated increases in TG concentrations.

Clinical Trial Registration ---Some participating cohorts were registered at URL: https://www.clinicaltrials.gov/ with unique identifiers: NCT00005131 (Atherosclerosis Risk in

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Communities), NCT00005133 (Cardiovascular Health Study), NCT00005121 (Framingham Offspring Study), NCT00005487 (Multi-Ethnic Study of Atherosclerosis), and NCT00000479 (Women's Health Study: parent study of the Women's Genome Health Study).

Keywords

sugars; genetics; carbohydrates; dyslipidemia; triglyceride; epidemiology; nutrition

Introduction

Low circulating high-density lipoprotein cholesterol (HDL-C) and elevated fasting triglyceride (TG) concentrations are positively associated with risk of type 2 diabetes (T2D) and cardiovascular disease (CVD).[1–5] Both genetic and environmental factors, including diet, are important determinants of HDL-C and TG concentrations.[5–7] Genetic determinants of HDL-C and TG concentrations have been identified in genome-wide association studies (GWAS),[8–12] but the extent to which genetic variants interact with environmental exposures is unknown. It is plausible that unrecognized genetic variants or genetic effects may be suppressed or exacerbated by environmental factors, such as diet.

Carbohydrate Responsive Element Binding Protein (ChREBP) is a transcription factor that regulates glucose and lipid metabolism in response to sugar consumption, including sugar from sugar sweetened beverages (SSB).[13,14] GWAS have consistently observed an association between single nucleotide polymorphisms (SNPs) in the *CHREBP* locus (also known as *MLXIPL*), and HDL-C and TG concentrations.[8,9,15,16] In animal studies, hepatic ChREBP is robustly activated by dietary fructose, a major constituent of SSB, and potentiates hepatic lipogenesis and TG secretion.[14,17–20] These findings are consistent with large population-based studies in which high SSB consumption has been associated with elevated fasting plasma TG and reduced HDL-C concentrations,[21–24] and increased T2D[25–27] and CVD[21] risk. Thus, SNPs within the *CHREBP* locus present promising candidates for gene-SSB interactions on circulating HDL-C and TG concentrations.

These pieces of biological, epidemiological and genetic evidence suggest that SSB consumption may modify how genetic variants within the *CHREBP* locus influence plasma lipid concentrations in some individuals. Although reduction of SSB consumption is increasingly being encouraged globally,[28] public health efforts to reduce SSB consumption have achieved limited success and SSB consumption remains a modifiable dietary exposure that contributes substantially to the burden of T2D and CVD worldwide.[29,30] A better understanding of the mechanisms underlying the SSB-ChREBP-lipid relationship may reveal novel mechanisms that contribute to the pathogenesis of T2D and CVD risk. Understanding these mechanisms may provide alternative strategies and approaches to reduce metabolic disease that may complement or facilitate dietary interventions.

The present study aimed to examine whether SSB consumption may modify the association of genetic variants within the *CHREBP* locus on HDL-C and TG concentrations in aggregated data from cohorts who are part of the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) consortium.[31] Descriptions of the CHARGE cohorts are

included in the supplemental material, Table I. We further used data from the UK Biobank (UKB) to assess the reproducibility of these findings in an independent cohort.[32]

Methods

Methods are available in the Supplemental Material. The data that support the findings of this study are available from the corresponding author upon reasonable request. All study participants provided written informed consent, and approval for all study protocols was granted by local institutional review boards and/or oversight committees.

Results

General characteristics and mean dietary intakes for the eleven CHARGE cohorts are shown in Table 1. Replication of previous findings on associations of SSB consumption and SNPs with lipid traits in the CHARGE cohorts are presented in the Supplemental Results in the Supplemental Material.

Difference Test Interactions between SSB Consumption and SNPs on HDL-C and TG in CHARGE Cohorts

We identified 55 SNPs that displayed a significant (p_{Diff} <0.0001) or suggestive (p_{Diff} <0.005) difference in estimated effect by category of SSB consumption on HDL-C concentrations in either of the two covariate models in the meta-analysis of the CHARGE cohorts. Among these 55 top SNPs, four distinct signals for HDL-C concentrations were observed when applying the difference test interaction. Two distinct SNPs in moderate LD (linkage disequilibrium) with one another [rs35709627 and rs71556729; R^2 = 0.55 (Figure II in the Supplemental Material)] and in low LD with the top SNP identified in the overall analysis for HDL-C concentrations (R^2<0.3) displayed a statistically significant difference in effect by category of SSB intake on HDL-C concentrations in fully adjusted models (Model 2; p_{Diff}<0.0001) (Table 2 and Figures III and IV in the Supplemental Material). In model 2, each additional minor allele at rs35709627 [β (SE): 2.72 (0.72), p=0.0002] and rs71556729 [β (SE): 3.89 (1.04), p=0.0002] was associated with higher mean concentrations of HDL-C concentrations among the highest SSB consumers (> 1 serving/day), but was not associated with mean HDL-C concentrations among the lowest SSB consumers (<1 serving/ month; p>0.05). The effect sizes of these SNPs among the highest SSB consumers were consistent across all the cohorts. There was no heterogeneity (I^2=0%) observed for the top 4 distinct signals (statistically significant and suggestive) among the highest SSB consumers (>1 serving/day), which could be due to low power to detect heterogeneity given the smaller sample size available among the highest SSB consumers (maximum n=4,033).

No statistically significant differences in effect by category of SSB intake on TG concentrations were observed when applying the difference test (p_{Diff} >0.0001 for all SNPs). One SNP (rs799157) in moderate LD with a top SNP identified in the overall analysis for TG concentrations (Table X in the Supplemental Material; R^2 with rs42124=0.44) displayed a suggestive difference in effect by category of SSB intake on TG concentrations in minimally adjusted models (Model 1; p_{Diff} =0.005) (Table 2). Each additional minor allele at rs799157 was associated with higher mean TG concentrations among the highest SSB

consumers (> 1 serving/day) [β (SE): 0.11 (0.03) ln-mg/dl, p=0.002], but this association was attenuated among the lowest SSB consumers [β (SE): 0.01 (0.01) ln-mg/dl, p=0.11] (Figure V in the Supplemental Material). The direction of the effect size of this SNP among the highest SSB consumers was consistent across all the cohorts in which these SNPs were available, and heterogeneity was low among the highest SSB consumers ($I^2 = 0\%$).

Cross-Product Interactions between SSB Consumption and SNPs on HDL-C and TG in CHARGE Cohorts

No statistically significant cross-product interactions between SNPs and SSB consumption on HDL-C or TG concentrations were observed ($p_{\text{interaction}}$>0.0001), while some tests were suggestive ($p_{\text{interaction}}$<0.005) (Table 2). Three SNPs displayed a suggestive interaction with SSB consumption on HDL-C concentrations in either covariate model, and the clumping identified two distinct signals (rs71556729 and rs79578725). One SNP (rs55673514) displayed a suggestive interaction with SSB on TG concentrations in Model 2. Forest plots for top distinct signals in SSBxSNP interaction analyses on lipid traits are presented in Figures VI and VII in the Supplemental Material.

Interactions between SSB Consumption and SNPs on Lipid Traits in the UKB and Meta-Analysis with CHARGE Cohort Results

General characteristics and mean dietary intakes for the 59,220 UKB participants are shown in Table VI in the Supplemental Material. Two out of five top signals for HDL-C (rs35709627 and rs71556729) and one out of two top signals for TG in the CHARGE consortium were replicated among the UKB participants (Table VII in the Supplemental Material). In a meta-analysis of the top results from the CHARGE consortium and data from the UKB, three out of the five top SNPs for HDL-C and one out of the two top SNPs for TG concentrations displayed statistically significant interactions (Table 3). The top SNP for HDL-C concentrations was located at rs71556729 (Figure 1A). In fully adjusted models, the association between the minor allele at rs71556729 with HDL-C concentrations was observed only among the highest SSB consumers [β (95% CI): 2.12 (1.16, 3.07) mg/dl, p<0.0001], and not the lowest SSB consumers (p=0.81; p_{Diff} <0.0001). Similarly, two SNPs in low to moderate LD with rs71556729 (*TBL2*-rs35709627: R^2 with rs71556729=0.55; rs71556736: R^2 with rs71556729=0.19) displayed similar statistically significant differences in effect by category of SSB intake (p_{Diff} <0.0001). The SNP at rs55673514 displayed a suggestive interaction with TG concentrations in the CHARGE meta-analysis and was statistically significant after including data from the UKB (Figure 1B, p_{Diff} <0.0005). The association of the minor allele at rs55673514 with TG concentrations was observed only among the highest SSB consumers [β (95% CI): 0.06 (0.02, 0.09) ln-mg/dl, p=0.001], and not the lowest SSB consumers (p=0.84). The SNP at rs55673514 is not in appreciable LD with any of the top SNPs in the overall analysis for TG concentrations (R^2<0.1). A heatmap of LD among top SNPs in overall and interaction analyses is provided in Figure II in the Supplemental Material. Sensitivity analyses examining the influence of adjustment for other dietary factors and fasting hours among UKB participants yielded similar results for the top SNPs identified in the meta-analysis (Supplemental Results in the Supplemental Material).

Discussion

In this study, including up to 86,241 participants for whom genetic and SSB consumption data were available, we identified novel interactions between genetic variants at the *CHREBP* locus and SSB consumption on HDL-C and TG concentrations. Our data suggest that the magnitude of the inverse association between SSB consumption and HDL-C concentrations is lower among individuals harboring genetic variants at rs71556729, rs35709627, and/or rs71556736 and the positive association between SSB consumption and TG concentrations is exacerbated among individuals harboring genetic variants at rs55673514. In the CHARGE cohorts, we also observed a consistent inverse association between SSB consumption on fasting HDL-C and positive association on TG concentrations. We also replicated previously observed main associations between SNPs in the *CHREBP* locus and HDL-C and TG concentrations.

Our study provides evidence that SSB consumption may modify the association of genetic variants in the *CHREBP* locus with HDL-C and TG concentrations. Participants with the minor allele at rs71556729, rs35709627, and/or rs71556736 and high SSB consumption had higher mean HDL-C concentrations than those with the major allele who also had high SSB consumption. This suggests that participants with the minor allele at rs71556729 (MAF [minor allele frequency] = 0.05), rs35709627 (MAF = 0.05), and/or rs71556736 (MAF = 0.13) may be protected against SSB-induced reductions in HDL-C concentrations. The region containing these SNPs is enriched for enhancer histone marks and these SNPs lie within putative regulatory motifs for transcription factors that could potentially regulate ChREBP expression and function in an SSB dependent manner.[33] Similarly, rs55673514, which associates with TG only among the highest SSB consumers, lies within a region enriched for enhancer histone marks in several tissues, including liver.[33] Given the strong inverse relationship between HDL-C and TG concentrations, additional investigation into how these SNPs may independently influence HDL-C or TG concentrations could provide new insights into the distinct mechanisms contributing to plasma HDL-C and TG concentrations. Additional discussion of main associations between SNPs and SSB on TG and HDL-C in the CHARGE cohorts is provided in the Supplemental Discussion in the Supplemental Material.

The rs71556729 interaction was a top signal when testing for interactions using the difference test and the cross-product interaction test on HDL-C concentrations in the CHARGE cohorts. However, when applying the cross-product interaction test, the interaction appeared less significant than the result from the difference test. This may be due to heterogeneity in the association between rs71556729 and HDL-C concentrations resulting from increased misclassification of SSB consumption among those reporting low (1-4 servings/month) to moderate (1-2 and 3-7 servings/week) SSB consumption (Figure IV in the Supplemental Material). These results suggest that the difference test may be a useful method for identifying gene-diet interactions in observational studies, and this could be due to a reduction in misclassification of SSB intake and the potential to detect non-linear interaction effects. However, we do not comprehensively compare the difference test to the cross-product interaction test. Future methodological studies comparing the usefulness of

these two methods with varying degrees of misclassification and types of exposures may be useful to inform future gene-diet interaction studies.

There is a limited body of evidence describing how genes implicated in various diseases may interact with SSB consumption to modify cardiometabolic health and noncommunicable disease risk.[34] One large prospective cohort study among Swedish adults examined whether genetic risk for dyslipidemia (using a weighted genetic risk score) interacted with SSB consumption to influence plasma lipid concentrations, but no significant interactions were observed.[35] Although genetic risk scores can be useful for translation, as previously shown for the interaction between SSB consumption and genetic risk for obesity,[36] a weakness of genetic risk scores is that aggregation of multiple SNPs from across the genome does not allow inclusion of potential interacting SNPs that may not be associated with the outcome in overall analyses. In addition, interaction effects of SNPs may be mitigated by the null interaction effects of other SNPs included in the genetic risk score. The candidate gene approach in the current study allows for the potential to generate hypotheses of the mechanisms underlying the interaction that could be tested using animal and human models in future studies.

No previous studies have examined the interaction between SNPs in the *CHREBP* region and SSB consumption on lipid concentrations. We previously investigated how selected SNPs in the ChREBP-FGF21 pathway interacted with SSB consumption to influence fasting insulin and glucose measures among 34,748 adults from CHARGE cohorts, but we did not identify a significant cross-product interaction that was consistent among the discovery and replication phases of that study.[37] In the current study, we applied a comprehensive approach that tested a wide range of SNPs in the *CHREBP* region that were not necessarily identified in GWAS. Given that our suggestive interaction results do not include any SNPs that were statistically significant in the overall SNP analyses, our data indicate that there may be additional SNPs not identified in GWAS contributing to the heritability of HDL-C and TG concentrations, but their contribution is influenced by SSB consumption. Similar to previous GWAS for body mass index that have identified new loci when adjusting for environmental factors[38,39], we provide an additional example of how missing genetic heritability may be revealed when accounting for environmental factors, such as SSB consumption in the current study.

The strengths of our study include the large sample size attained through meta-analysis of multiple independent cohorts, the ability to standardize the analyses conducted in all cohorts through a collaborative approach, the use of an external cohort to validate findings, and the use of multiple methods to screen for potential interactions between SSB consumption and over 1,606 SNPs in the *CHREBP* region on HDL-C and TG concentrations. The analytic approach revealed novel SNPs that may contribute to unexplained heritability of HDL-C and TG concentrations. Limitations of this study include its observational design that constrain our ability to infer causality, the sample of European-descent adults that limits generalizability, the use of self-reported dietary data from food frequency questionnaires and 24-hour recall that may lead to misclassification of food and nutrient intakes, and the possibility of residual confounding, even after controlling for potential dietary and lifestyle factors that co-vary with SSB intake. Our focus on the comparison of the highest SSB

consumers to the lowest SSB consumers helps minimize this potential misclassification by focusing on extreme consumption patterns. Misclassification in the UKB is likely given that a snapshot of intake on a single day cannot provide a reliable estimate of usual SSB consumption. However, this misclassification is likely non-differential by genotype, which would only result in attenuation of our results. Additionally, while our definition of SSB did consider a range of SSB, it was not comprehensive. For example, it did not include commonly consumed beverages, such as sweetened tea or coffee, and we included several types of SSB in the same exposure definition (colas and fruit drinks). The blood collection among UKB participants was conducted after less than the recommended 8 hours of fasting prior to measurement of lipids. We adjusted for fasting hours to help account for this variability and conducted a sensitivity analysis to examine the top interactions observed by fasting hours. The LD-based method used to estimate the number of independent tests in the region may be overly conservative, which could potentially lead to inflation of type II error rate. Thus, we additionally present suggestive results that did not reach statistical significance. Given these weaknesses, results from this study should be used to inform future studies with larger samples sizes or detailed experimental studies. Minority populations are disproportionality burdened by dyslipidemia and have higher SSB intake,[40,41] and thus more studies in these populations may help reduce health inequality and disparity.

In conclusion, our findings suggest that the minor alleles of three SNPs in the *CHREBP* region (rs71556729, rs35709627, and rs71556736) may be protective against SSB-induced low HDL-C concentrations and the minor allele at rs55673514 may exacerbate positive associations between SSB consumption and TG concentrations. Several of the top SNPs identified in the interaction analyses were not top SNPs identified in the overall analyses, providing evidence that some genetic associations may be revealed only when conditioned on environmental factors, such as the range of SSB consumption in the current study. As larger datasets with genetics, diet, and lipids data become available, additional suggestive interactions between SSB consumption and SNPs within the *CHREBP* region on HDL-C and TG concentrations observed here may warrant further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

HDL-C	high-density lipoprotein cholesterol
TG	triglyceride
T2D	type 2 diabetes
CVD	cardiovascular disease
GWAS	genome-wide association studies

ChREBP	Carbohydrate Responsive Element Binding Protein
SSB	sugar-sweetened beverages
SNPs	single nucleotide polymorphisms
CHARGE	Cohorts for Heart and Aging Research in Genetic Epidemiology
UKB	UK Biobank

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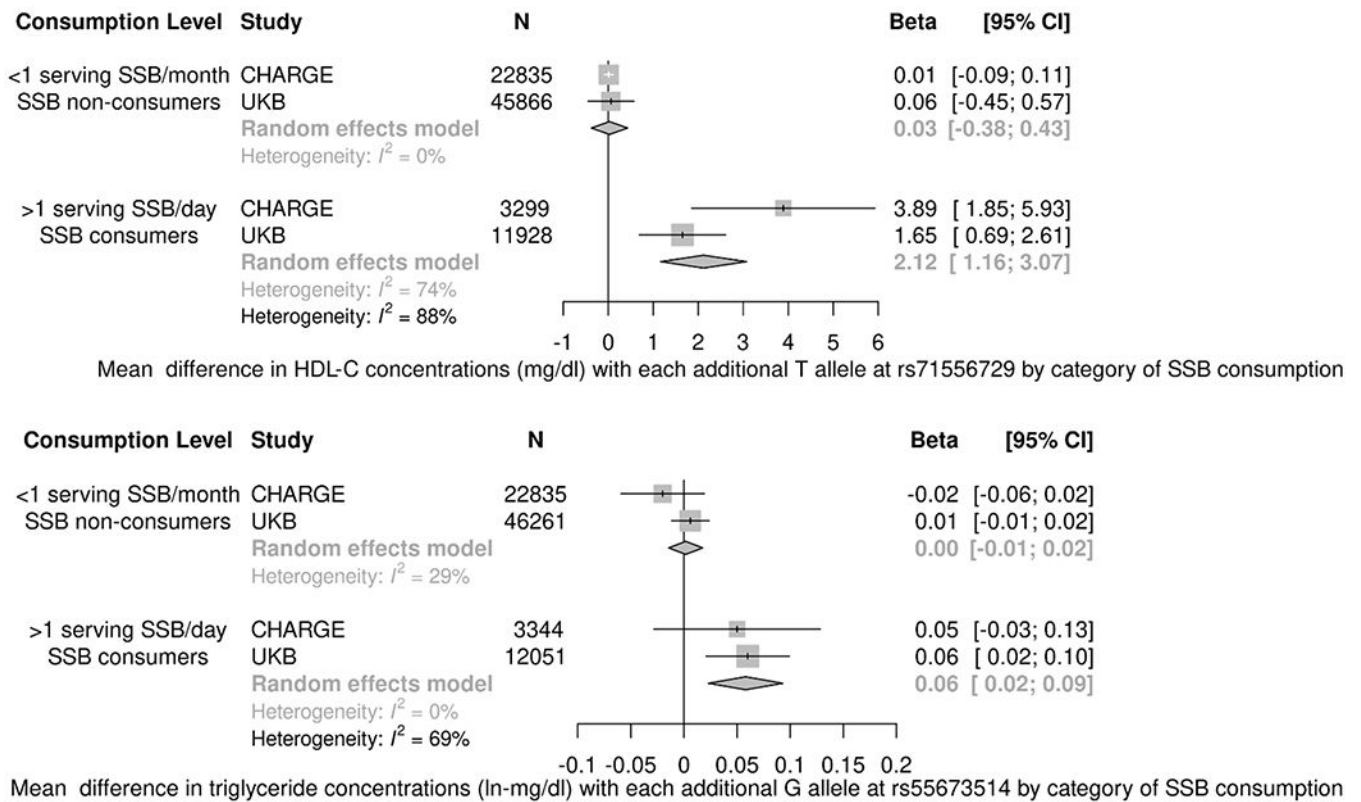
Figure 1.
Associations between top candidate SNPs and HDL-C and TG concentrations stratified by category of SSB intake in a meta-analysis of the CHARGE cohorts and the UKB. **A)** In a random effects meta-analysis of the CHARGE cohorts and the UKB, the association of the minor allele at rs71556729 with HDL-C concentrations was observed only among the highest SSB consumers [β (95% CI): 2.12 (1.16, 3.07) mg/dl, $p<0.0001$], and not the lowest SSB consumers ($p=0.81$; $p_{Diff}<0.0001$); **B)** In a random effects meta-analysis of the CHARGE cohorts and the UKB, the association of the minor allele at rs55673514 with TG concentrations was observed only among the highest SSB consumers [β (95% CI): 0.06 (0.02, 0.09) ln-mg/dl, $p=0.001$], and not the lowest SSB consumers ($p=0.84$; $p_{Diff}<0.0005$); Linear regression models represent associations between each additional effect allele and HDL-C (mg/dl) or TG (ln-mg/dl) concentrations among SSB consumption categories accounting for family, population structure, and/or field center (where applicable) and adjusting for age, sex, total energy intake, education, smoking, physical activity, alcohol intake, and body mass index. Intake categories are different for the highest SSB consumers (CHARGE: >1 serving/day; UKB: SSB consumers) and lowest SSB consumers (CHARGE: <1 serving/month; UKB: SSB non-consumers) in the two samples. CI, confidence interval; CHARGE, Cohorts for Heart and Aging Research in Genetic Epidemiology; HDL-C, high-density lipoprotein cholesterol concentrations; I^2, percentage of variance in a meta-analysis that is attributable to study heterogeneity; SSB, sugar-sweetened beverage consumption; TG, triglyceride concentrations; UKB, UK Biobank.

Table 1.

General characteristics of participating CHARGE consortium cohorts[*]

Characteristics	Raine Study	ARIC	FHS	NEO	Fenland	YFS	WGHS	WHI	MESA	CHS	RS
Country	Australia	USA	USA	Netherlands	UK	Finland	USA	USA	USA	USA	Netherlands
n	617	10,924	6,382	5,694	10,022	1,782	16,284	1,109	1,805	3,196	5,784
Age (years)	20 (1)	55 (6)	49 (14)	56 (6)	49 (7)	38 (5)	55 (7)	65 (7)	70 (10)	72 (5)	66 (8)
Sex (% women)	52.4	52.7	54.3	52.0	53.3	55.9	100	100	51.2	61.0	57.8
Body Mass Index (kg/m^2)	24.5 (5.2)	27.0 (4.8)	27.4 (5.5)	30.0 (4.8)	26.9 (4.8)	25.9 (4.6)	25.9 (4.9)	28.6 (5.7)	28.0 (5.3)	26.3 (4.4)	26.5 (3.7)
Current Smoker (%)	13.5	24.2	13.4	16.0	12.0	27.6	11.7	10.1	7.0	11.4	23.4
Completed High School (%)	81.5	84.9	98.0	93.0	81.8	75.4	100	94.7	96.5	75.1	60.8
Fasting HDL–C (mg/dl)	51 (13)	51 (17)	54 (17)	55 (16)	59 (16)	52 (13)	54 (15)	58 (15)	57 (18)	55 (16)	53 (14)
Fasting TG (mg/dl)	85 (2)	137 (90)	117 (87)	130 (85)	106 (81)	122 (82)	119 (89)	156 (92)	107 (59)	140 (76)	137 (71.0)
Dietary Intakes											
SSB intake (servings/d)	0.7 (1.0)	0.5 (0.9)	0.4 (0.8)	0.4 (0.8)	0.3 (0.6)	0.3 (0.5)	0.3 (0.6)	0.2 (0.6)	0.1 (0.5)	0.1 (0.3)	0.1 (0.2)
<1 serving/month (%)	13.6	35.7	33.9	49.4	35.8	23.6	44.8	58.0	70.0	63.4	71.9
1-4 serving/month (%)	14.4	16.3	24.3	13.8	24.6	31.9	22.0	19.3	12.4	16.9	13.5
1-2 serving/week (%)	23.8	12.1	9.76	14.1	14.0	17.1	13.1	3.5	2.2	0.06	6.4
3-7 serving/week (%)	29.2	25.7	21.3	11.7	15.2	21.0	15.1	15.3	8.6	18.7	7.5
>1 serving/day (%)	19.0	10.3	10.8	11.0	10.4	6.3	5.0	3.9	2.3	0.9	0.8
Energy Intake (kcal/d)	1,857 (850)	1,644 (599)	1,956 (645)	2,291 (763)	1,935 (578)	2,381 (762)	1,732 (524)	1,698 (670)	1708 (734)	2,024 (654)	2,046 (1,409)
Saturated Fat Intake (% total energy)	16.1 (3.1)	12.2 (3.1)	11.1 (2.9)	12.4 (2.9)	12.5 (3.0)	11.8 (2.4)	10.2 (2.5)	11.6 (3.3)	11.3 (3.3)	10.4 (2.2)	14.4 (3.1)
Fruit intake (servings/d)	1.9 (1.3)	1.5 (1.3)	1.1 (1.0)	1.1 (0.9)	2.7 (2.2)	3.4 (3.1)	1.9 (1.2)	1.8 (1.2)	2.1 (1.7)	2.7 (1.5)	1.2 (1.0)
Vegetable Intake (servings/d)	1.7 (0.9)	1.7 (1.2)	2.0 (1.1)	2.8 (1.5)	5.0 (2.5)	1.4 (1.8)	3.9 (2.3)	2.2 (1.3)	2.4 (1.5)	2.8 (1.5)	2.8 (2.1)
Whole Grain Intake (servings/d)	0.8 (1.0)	1.1 (1.1)	1.2 (1.2)	NA	1.8 (1.4)	3.2 (1.9)	1.5 (1.2)	1.2 (0.8)	1.0 (0.8)	1.0 (0.7)	3.4 (2.9)
Fish Intake (servings/d)	0.4 (0.6)	0.3 (0.3)	0.4 (0.4)	0.2 (0.2)	0.4 (0.3)	1.3 (0.9)	0.3 (0.2)	0.2 (0.2)	0.3 (0.3)	0.3 (0.3)	0.1 (0.2)
Nuts/Seeds Intake (servings/d)	0.1 (0.2)	0.4 (0.6)	0.6 (0.9)	0.8 (1.0)	0.2 (0.3)	0.1 (0.1)	0.3 (0.4)	0.2 (0.3)	0.5 (0.6)	0.2 (0.3)	0.2 (2.1)
Alcohol Intake (g/d)	7.8 (8.9)	6.7 (13.5)	10.5 (14.8)	15.5 (17.4)	9.5 (12.7)	8.6 (13.4)	4.3 (8.5)	5.0 (10.2)	8.8 (15.5)	5.5 (12.9)	11.1 (15.5)

Epidemiology in Obesity Study (NEO), The Fenland Study (Fenland), Young Finns Study (YFS), Women's Genome Health Study (WGHS), Women's Health Initiative (WHI), Multi-Ethnic Study of Atherosclerosis (MESA), Cardiovascular Health Study (CHS), and the Rotterdam Study (RS).

CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; HDL-C, high-density lipoprotein cholesterol concentrations; n, total sample size; SSB, sugar-sweetened beverages; TG, triglyceride concentrations.

Table 2.

Top SNPs in meta-analysis of difference test ($p_{Diff}<0.005$) and cross-product ($p_{interact}<0.005$) interactions between SSB consumption and SNPs on HDL-C and TG concentrations in CHARGE consortium cohorts[*]

SNP	Location (Hg19)	Alleles (E/A)[†]	Minor Allele Frequency	Model[‡]	SSB Intake Category	n	Effect Size (SE)[§]	P-value	Direction[‖]	I²	p[#]
HDL-C (mg/dl)											
Difference Test											p Diff
rs35709627[††]	72999171	A/G	0.05	Model 1	<1 serving/month	24,389	-0.01 (0.04)	0.86	+++—+++??	23%	1.98E-05**
					>1 serving/day	4,033	3.23 (0.77)	2.94E-05	+?+?+?+??	0%	
				Model 2	<1 serving/month	23,801	0.006 (0.04)	0.86	+++—+++??	30%	0.0001
					>1 serving/day	3,955	2.72 (0.72)	0.0002	+?+?+?+??	0%	
rs71556729[††]	72989516	T/C	0.05	Model 1	<1 serving/month	23,974	0.02 (0.06)	0.77	+?++++—??	0%	4.78E-05**
					>1 serving/day	3,359	4.47 (1.10)	5.02E-05	??+?+?+??	0%	
				Model 2	<1 serving/month	22,835	0.01 (0.05)	0.83	+?++—?-??	0%	0.0001
					>1 serving/day	3,299	3.89 (1.04)	0.0002	??+?+?+??	0%	
rs71556736	73034929	T/C	0.13	Model 1	<1 serving/month	24,389	-0.0005 (0.02)	0.98	++++++—++?-	60%	0.0003
					>1 serving/day	4,033	1.65 (0.47)	0.0004	+?+?+?+??	0%	
				Model 2	<1 serving/month	23,801	0.007 (0.02)	0.69	++++++—++??	67%	0.002
					>1 serving/day	3,955	1.34 (0.43)	0.002	+?+?+?+??	0%	
rs73137017	72974413	G/A	0.04	Model 1	<1 serving/month	24,020	-0.05 (0.06)	0.46	—+++++??	0%	0.002
					>1 serving/day	3,933	-3.13 (0.99)	0.002	-?-?-?-??	0%	
				Model 2	<1 serving/month	23,437	-0.008 (0.05)	0.88	++—++—??	0%	0.003
					>1 serving/day	3,855	-2.64 (0.91)	0.004	-?-?-?-??	0%	
Cross-Product Interaction Test											p interact
rs71556729	72989516	T/C	0.03	Model 1	-	55,418	0.66 (0.21)	-	+++++?+——	0%	0.001
				Model 2	-	53,394	0.68 (0.20)	-	+++?+?+++?-	26%	0.0007

SNP	Location (Hg19)	Alleles (E/A)[†]	Minor Allele Frequency	Model[‡]	SSB Intake Category	n	Effect Size (SE)[§]	P-value	Direction[||]	I²	p[#]
HDL-C (mg/dl)											
Difference Test											P Diff
rs79578725	73002455	A/G	0.05	Model 1	-	53,662	−0.51 (0.18)	-	+?−+−?−−−−−	0%	0.005
				Model 2	-	52,328	−0.18 (0.17)	-	+?++−?−−−−−	0%	0.28
TG (ln-mg/dl)											
Difference Test											P Diff
rs799157	73020301	T/C	0.05	Model 1	<1 serving/month	23,974	0.02 (0.01)	0.11	+?++++−++??	59%	0.005
					>1 serving/day	4,033	0.11 (0.03)	0.002	+?+?+?+?+??	0%	
				Model 2	<1 serving/month	23,403	0.02 (0.01)	0.17	+?++−−?+?	68%	0.008
					>1 serving/day	3,955	0.09 (0.03)	0.004	+?+?+?+?	0%	
Cross-Product Interaction Test											P interact
rs55673514	73021456	G/A	0.04	Model 1	-	57,977	0.02 (0.01)	-	−+++++++?++	17%	0.04
				Model 2	-	56,578	0.02 (0.01)	-	−+++++++++?	0%	0.005

*Top signals represent suggestive interactions pDiff<0.005 or pinteract<0.005[c]

[†]Alleles presented as effect (E)/alternative (A) alleles

[‡]Model 1 adjusted for age (years), sex (male/female), total energy intake (kcal/day) field center (CHS, FHS, YFS, Fenland, RS, MESA), and accounted for family or population structure where applicable (FHS, YFS, Fenland, NEO, MESA, WGHS, Raine Study, MESA); Model 2 adjusted for Model 1 covariates plus cohort-specific definition of education, smoking, physical activity, alcohol intake, and body mass index (kg/m²).

[§]For the difference test, β (SE) represents the direction and magnitude of the difference in the outcome trait with each additional effect allele among categories of SSB consumption. For the cross-product interaction test, β (SE) represents the direction and magnitude of the difference in the outcome trait with each additional effect allele, per each increase in category of SSB intake (<1 serving/month, 1-4 servings/month, 1-2 servings/week, 3-7 servings/week, >1 serving/day).

[||]Order of cohorts for regression coefficient directions: Framingham Heart Study, Young Finns Study, Fenland Study, Cardiovascular Health Study, Netherlands Epidemiology in Obesity Study, Rotterdam Study, Women's Genome Health Study, Women's Health Initiative, Atherosclerosis Risk in Communities Sutyd, The Raine Study, Multi-Ethnic Study of Atherosclerosis (+, positive effect size; -, negative effect size; ?, SNP not available in cohort).

[#]P represents pDiff for the difference test for the highest and lowest category of SSB intake (<1 serving/month vs. >1 serving/day). P represents pinteract for the cross-product interaction regression coefficient of additive SSBxSNP categories.

††Linkage disequilibrium (R^2) between rs13240662 and rs71556729=0.55 in European ancestry groups of Phase 3 (Version 5) of the 1000 Genomes Project.

**Indicates a statistically significant interaction based on Bonferonni-corrected pDiff or $p$interact<0.0001

CHARGE, Cohorts for Heart and Aging Research in Genetic Epidemiology; HDL-C, high-density lipoprotein cholesterol concentrations; SE, standard error; SNP, single nucleotide polymorphism; SSB, sugar-sweetened beverages; TG, triglyceride concentrations.

Table 3.

Fixed-effects meta-analysis of top candidate SNPs for difference test interactions between SSB consumption and SNPs on HDL-C and TG concentrations in CHARGE consortium cohorts and UKB[*]

SNP	Location (Hg19)	Alleles (E/A)[†]	MAF	SSB Intake Category	n	Effect Size (SE)	P-value	Direction[‡]	I^2	P Diff
HDL-C (mg/dl)										
rs71556729[§]	72989516	T/C	0.05	Low	68,701	0.01 (0.05)	0.81	++	0 %	1.5E-06[//]
				High	15,227	2.06 (0.44)	3.48E-06	++	74 %	
rs35709627[§]	72999171	A/G	0.05	Low	69,667	0.01 (0.04)	0.74	++	0 %	1.0E-05[//]
				High	15,883	1.37 (0.32)	2.15E-05	++	87 %	
rs71556736	73034929	T/C	0.13	Low	69,667	0.02 (0.02)	0.33	++	93 %	2.5E-05[//]
				High	15,882	0.84 (0.20)	3.27E-05	++	42 %	
rs73137017	72974413	G/A	0.04	Low	69,303	0.01 (0.05)	0.82	++	0 %	0.04
				High	15,783	0.73 (0.37)	0.05	++	81 %	
rs79578725	73002455	A/G	0.05	Low	68,929	-0.02 (0.04)	0.64	--	21 %	0.55
				High	15,783	-0.22 (0.36)	0.53	--	0 %	
TG (ln-mg/dl)										
rs55673514	73021456	G/A	0.04	Low	69,096	-0.002 (0.01)	0.84	+-	29 %	0.0005[//]
				High	15,395	-0.06 (0.02)	0.001	--	0 %	
rs799157	73020301	T/C	0.05	Low	70,235	0.03 (0.01)	2.55E-07	++	59 %	0.05
				High	16,006	0.06 (0.02)	0.0002	++	19 %	

[*]
Top candidates represent statistically significant or suggestive interactions (pDiff<0.005 or pInteract<0.005) in CHARGE cohort meta-analysis. Models adjusted for age, sex, total energy intake, field center and accounted for family or population structure where applicable plus education, smoking, physical activity, alcohol intake, and body mass index (kg/m^2). For the difference test, interaction coefficients are shown as β (SE), where β represents the direction and magnitude of change in the outcome trait with each additional effect allele among participants with low (CHARGE:<1 serving/month; UKB: non-consumers) or high (CHARGE: >1 serving/day; UKB: consumers) SSB consumption.

[†]
Alleles presented as effect (E)/alternative (A) alleles

[‡]
Order of cohorts for regression coefficient directions: CHARGE cohorts, UKB (+, positive effect size; −, negative effect size).

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§Linkage disequilibrium (R^2) between rs13240662 and rs71556729=0.55 in European ancestry groups of Phase 3 (Version 5) of the 1000 Genomes Project.

‖Indicates a statistically significant interaction based on Bonferroni-corrected pDiff<0.01 (0.05/5 top signals) for HDL–C and pDiff<0.025 (0.05/2 top signals) for TG concentrations

CHARGE, Cohorts for Heart and Aging Research in Genetic Epidemiology; HDL–C, high-density lipoprotein cholesterol; MAF, minor allele frequency; SNP, single nucleotide polymorphism; SSB, sugar-sweetened beverages; TG, triglyceride; and UKB, UK Biobank.