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Sugar-Sweetened Beverage Consumption and Plasma Lipoprotein Cholesterol, Apolipoprotein, and Lipoprotein Particle Size Concentrations in US Adults

Danielle E Haslam,[1,2,3] Daniel I Chasman,[4] Gina M Peloso,[5] Mark A Herman,[6] Josée Dupuis,[5,7] Alice H Lichtenstein,[8] Caren E Smith,[9] Paul M Ridker,[4,10] Paul F Jacques,[1] Samia Mora,[4,10] and Nicola M McKeown[11]

[1]Nutritional Epidemiology Program, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA; [2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [3]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [4]Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [5]Department of Biostatistics, School of Public Health, Boston University, Boston, MA, USA; [6]Division of Endocrinology, Metabolism, and Nutrition, Department of Medicine, School of Medicine, Duke University, Durham, NC, USA; [7]National Heart, Lung, and Blood Institute's Framingham Heart Study and Population Sciences Branch, Framingham, MA, USA; [8]Cardiovascular Nutrition Laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA; [9]Nutrition and Genomics Laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA; [10]Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; and [11]Programs of Nutrition, Department of Health Sciences, Sargent College of Health and Rehabilitation Sciences, Boston University, Boston, MA, USA

ABSTRACT

Background: Prospective cohort studies have found a relation between sugar-sweetened beverage (SSB) consumption (sodas and fruit drinks) and dyslipidemia. There is limited evidence linking SSB consumption to emerging features of dyslipidemia, which can be characterized by variation in lipoprotein particle size, remnant-like particle (RLP), and apolipoprotein concentrations.

Objectives: To examine the association between SSB consumption and plasma lipoprotein cholesterol, apolipoprotein, and lipoprotein particle size concentrations among US adults.

Methods: We examined participants from the Framingham Offspring Study (FOS; 1987–1995, $n = 3047$) and the Women's Health Study (1992, $n = 26{,}218$). Concentrations of plasma LDL cholesterol, apolipoprotein B (apoB), HDL cholesterol, apolipoprotein A1 (apoA1), triglyceride (TG), and non–HDL cholesterol, as well as total cholesterol:HDL cholesterol ratio and apoB:apoA1 ratio, were quantified in both cohorts; concentrations of apolipoprotein E, apolipoprotein C3, RLP-TG, and RLP cholesterol (RLP-C) were measured in the FOS only. Lipoprotein particle sizes were calculated from nuclear magnetic resonance signals for lipoprotein particle subclass concentrations (TG-rich lipoprotein particles [TRL-Ps]: very large, large, medium, small, and very small; LDL particles [LDL-Ps]: large, medium, and small; HDL particles [HDL-Ps]: large, medium, and small). SSB consumption was estimated from food frequency questionnaire data. We examined the associations between SSB consumption and all lipoprotein and apoprotein measures in linear regression models, adjusting for confounding factors such as lifestyle, diet, and traditional lipoprotein risk factors.

Results: SSB consumption was positively associated with LDL cholesterol, apoB, TG, RLP-TG, RLP-C, and non–HDL cholesterol concentrations and total cholesterol:HDL cholesterol and apoB:apoA1 ratios; and negatively associated with HDL cholesterol and apoA1 concentrations (P-trend range: <0.0001 to 0.008). After adjustment for traditional lipoprotein risk factors, SSB consumers had smaller LDL-P and HDL-P sizes; lower concentrations of large LDL-Ps and medium HDL-Ps; and higher concentrations of small LDL-Ps, small HDL-Ps, and large TRL-Ps (P-trend range: <0.0001 to 0.001).

Conclusions: Higher SSB consumption was associated with multiple emerging features of dyslipidemia that have been linked to higher cardiometabolic risk in US adults. *J Nutr* 2022;152:2534–2545.

Keywords: carbohydrates, sugar-sweetened beverages, observational study, nutrition, lipoprotein particle size, diabetes, dyslipidemia, lipoproteins

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Introduction

Sugar-sweetened beverages (SSBs) are the largest single source of added dietary sugars in the United States (US) (1), contributing 24% of added sugars (2). Consumption of SSBs has been associated with increased risk for a variety of cardiometabolic disorders, including cardiovascular disease (CVD) (3–6), obesity (7), type 2 diabetes (T2D) (8), and metabolic syndrome (MetSyn) (9). A common risk factor shared by these conditions is dyslipidemia, a condition characterized by one or more of the following: elevated triglyceride (TG), elevated LDL cholesterol, elevated non–HDL cholesterol, and/or low HDL cholesterol concentrations. Although dyslipidemia encompasses a variety of lipoprotein-associated risk factors, lowering LDL cholesterol concentrations is currently the primary target for CVD risk reduction due to available and efficacious pharmacotherapy (10). The role that HDL cholesterol and TG concentrations play in the development of cardiometabolic disorders is less clear (11, 12). Although evidence from observational studies is mixed, the majority have observed adverse associations between SSB consumption and traditional dyslipidemia patterns in adults (5, 13–19).

In addition to the traditional criteria of dyslipidemia, novel lipoprotein biomarkers may reveal "distinct" dyslipidemia patterns independently associated with cardiometabolic diseases (20–22). Plasma TG and cholesterol are carried in lipoprotein particles that vary in size from small to very large, including TG-rich lipoprotein particles (TRL-Ps), LDL particles (LDL-Ps), and HDL particles (HDL-Ps) (23). Remnant-like particles (RLPs) are formed from chylomicrons and TRL-Ps during delipidation by lipoprotein lipase (24, 25). Apolipoprotein B (apoB) is associated with chylomicrons, LDL-Ps, and TRL-Ps, and apolipoprotein E (apoE) is associated with TRL-Ps, where they both can serve as a ligands for LDL receptor–mediated lipoprotein clearance. Apolipoprotein A1 (apoA1), the primary apoprotein of HDL-Ps, is a cofactor for lecithin cholesterol acyltransferase, an enzyme that catalyzes the esterification of cholesterol on HDL-Ps. Apolipoprotein C3 (apoC3), a protein present in chylomicrons and TRL-Ps, inhibits lipoprotein lipase activity, hence slowing TG clearance from plasma (10, 26, 27).

Emerging examples of distinct dyslipidemias include diabetic and atherogenic dyslipidemias. Common characteristics include high TG, small LDL-P and RLP, along with low HDL cholesterol concentrations. This pattern is commonly observed among individuals with T2D and MetSyn (20, 21, 28, 29). The utility of measuring additional lipoprotein components may be to better define individualized risk to enhance personalized clinical therapy (30–37). Animal studies suggest that consumption of fructose, a major component of SSBs, activates hepatic and enterocyte de novo lipogenesis and upregulates expression of related enzymes (38–40). Human intervention studies suggest that consumption of SSBs may promote diabetic dyslipidemia (18, 41, 42) and high carbohydrate diets may shift lipoprotein particle size profiles to atherogenic patterns (43–48). To date, no observational studies have examined the association between SSB consumption and concentrations of apolipoproteins, RLPs, and lipoprotein sizes.

The objective of the present study was to examine the association between SSB consumption and plasma lipoprotein cholesterol, apolipoprotein, and lipoprotein particle size concentrations among participants from the Framingham Offspring Study (FOS) and Women's Health Study (WHS) to generate hypotheses by which SSBs may influence distinct dyslipidemia patterns and cardiometabolic disease risk.

Methods

Subjects

The study population consisted of participants from the FOS and WHS. The Framingham Heart Study is a long-standing prospective cohort study in Framingham, Massachusetts, that began in 1948. Data from the FOS cohort (49), which includes the offspring of the original Framingham Heart Study participants, at examination 4 (1987–1991; n = 4019) and examination 5 (1991–1995; n = 3799) were used in the current study. FOS participants underwent a detailed medical history, physical examination, and standard laboratory tests during both examination periods. The WHS is a prospective cohort of North American female health care professionals aged ≥45 y (50, 51), where approximately 72% of the participants provided a voluntary blood sample (n = 28,346). The WHS began as a randomized placebo-controlled trial of low-dose aspirin, β-carotene, and vitamin E for the primary prevention of CVD and cancer and ran from 1993 to 2004 (clinicaltrials.gov: NCT00000479). The WHS continues to follow participants annually on an observational basis. Participants provided demographic, diet, lifestyle, and medical history data via standard questionnaires for both cohorts. All participants provided written informed consent before study participation. The institutional review board approved all study protocols and procedures for the current study for human research at Boston University Medical Campus, Tufts University Health Sciences, and Brigham and Women's Hospital.

A total of 3306 FOS participants provided dietary data (examination 5) and fasting plasma samples for lipoprotein measures (examinations 4 and 5). FOS participants were excluded if they provided invalid dietary data (n = 9), lipoprotein measurements were not available (examination 4: n = 182; examination 5: n = 9), or they were using lipid-lowering therapy at the time of the fasting blood draw

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Supplemental Material and Supplemental Tables 1–5 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.

Address correspondence to DH (e-mail: nhdah@channing.harvard.edu).

Abbreviations used: apoA1, apolipoprotein A1; apoB, apolipoprotein B; apoC3, apolipoprotein C3; apoE, apolipoprotein E; CVD, cardiovascular disease; FOS, Framingham Offspring Study; HDL-C, HDL cholesterol; HDL-P, HDL particle; LDL-C, LDL cholesterol; LDL-P, LDL particle; MetSyn, metabolic syndrome; NMR, nuclear magnetic resonance; RLP, remnant-like particle; RLP-C, remnant-like particle cholesterol; RLP-TG, remnant-like particle triglyceride; SSB, sugar-sweetened beverage; TC, total cholesterol; TG, triglyceride; TRL-P, triglyceride-rich lipoprotein particle; T2D, type 2 diabetes; WHS, Women's Health Study.

(examination 4: $n = 116$; examination 5: $n = 241$), reducing the sample size to 2999 at examination 4 and 3047 at examination 5. A total of 28,346 participants provided baseline data in the WHS. Participants were excluded if they provided invalid dietary data or none ($n = 842$), lipoprotein measurements were not available ($n = 395$), or they were using lipid-lowering therapy ($n = 891$), reducing the sample size to 26,218 for this analysis. In some WHS participants, baseline blood samples were collected <8 h after a meal. Thus, results excluding these participants are presented in the **Supplemental Material** for the 18,805 (66%) participants who provided a baseline blood sample ≥8 h after a meal (fasting subsample).

Assessment of lipoprotein outcomes

Plasma samples from study participants in the FOS at examination 5 and the WHS at baseline were used to measure traditional lipoprotein cholesterol measures. In the FOS, HDL cholesterol, TG, and total cholesterol (TC) were measured with an Abbott Diagnostics ABA-200 analyzer (52), and LDL cholesterol was calculated according to the Friedewald equation (53) (LDL cholesterol = TC − HDL cholesterol − TG/5) and reported as not available if TG ≥ 400 mg/dL. Among WHS participants, HDL cholesterol, TG, and TC were measured using a Hitachi autoanalyzer from Roche Diagnostics, and LDL cholesterol was determined directly using a Roche homogenous assay (50). Non–HDL cholesterol concentrations were calculated as TC minus HDL cholesterol concentrations, and the TC:HDL cholesterol ratio was calculated by dividing TC by HDL cholesterol concentrations.

Plasma samples from study participants in the FOS at examination 4 (unless otherwise noted) and the WHS at baseline were used to measure emerging lipoprotein and apolipoprotein measures. Using proton nuclear magnetic resonance (NMR) spectroscopy (54), the following lipoprotein particle size concentrations were measured: TRL-P (very large, large, medium, small, and very small), LDL-P (large, medium, and small), and HDL-P (large, medium, and small). From these data, the NMR analysis software calculates TRL-P, LDL-P, and HDL-P mean size (nm diameter), which can be used to provide an assessment of lipoprotein particle size profiles. Lipoprotein particle size profiles for FOS participants at examination 4 were measured with the LPI assay version (LipoScience Inc.). This provides slightly different size groupings (**Supplemental Table 1**) and different units [cholesterol concentrations within each subclass (mg/dL)] than the LP4 assay version, which was used to measure lipoprotein particle size profiles for WHS participants (particle concentrations within each subclass [nmol/L for TRL-P and LDL-P; μmol/L for HDL-P]) (LP4 NMR MetaboProfile Analysis; LipoScience/LabCorp Global Research Services). The newer LP4 NMR assay provided NMR-derived concentrations of apoB and apoA1 among WHS participants, a method that is highly correlated with standard assays ($r \approx 0.95$). In the FOS, apoA1 and apoB were measured using noncompetitive ELISA (Tufts University) (55, 56); apoC3 and apoE were measured at examination 5 using corresponding Wako Autokits; and RLP cholesterol (RLP-C) and RLP triglyceride (RLP-TG) concentrations were measured at examination 4 using previously described assays (57–59). In both cohorts, the apoB:apoA1 ratio was calculated by dividing apoB by apoA1.

Assessment of dietary intakes

Usual dietary intakes in the past year were estimated using the Harvard 126-item (FOS examination 5) and 131-item (WHS) semiquantitative food frequency questionnaire (FFQ) (60, 61). The FFQ consisted of a list of foods with standard serving sizes and a selection of nine frequency categories ranging from none or <1 serving per month to ≥6 servings per day. Participants with implausible energy intake were excluded from the analysis based on cohort-specific cutoffs (FOS: <600 kcal/d for men and women, ≥4000 kcal/d for women, ≥4200 kcal/d for men, and if >13 food items were left blank on the FFQ; WHS: <600 and ≥3500 kcal/d). Both FFQs have been examined for reproducibility and validity for nutrients and foods in women and men in various cohorts (60–63). Measures of apoA1, apoB, RLP, and lipoprotein particle size profiles were measured in the FOS at examination 4; however, dietary intake data were not measured at this examination period. Based on other examination periods, SSB intake does not substantially change between consecutive examinations (e.g., for SSB intake at examination 5 and 6, $r^2 = 0.52$), and estimates reflect approximate habitual SSB consumption patterns. Thus, for these lipoprotein measures measured only at examination 4, examination 5 dietary intakes were used to approximate dietary intakes at examination 4 in FOS participants.

Estimates of SSB consumption in both cohorts included the following categories *1*) Coke, Pepsi, or other cola beverages with sugar; *2*) caffeine-free Coke, Pepsi, or other cola beverages with sugar; *3*) other carbonated beverages with sugar (e.g., 7-Up, ginger ale); and *4*) Hawaiian Punch, lemonade, or other noncarbonated fruit drinks. One serving of an SSB is equivalent to 360 mL (12 fl oz). Food groupings were based on the 2020 *Dietary Guidelines for Americans* (2), and nutrient intakes were calculated from FFQ data by multiplying the frequency of consumption of a food item by the nutrient contents per standard serving size for the given food item.

Covariate assessment

In each cohort, participants provided general demographic, lifestyle, and medical history data via standard questionnaires. Education was assessed by asking about the highest degree or level of education that the participant had completed. Participants were grouped into categories (FOS: less than high school, graduated high school, some college, or graduated college; WHS: less than bachelor degree, bachelor degree, graduate degree). In the FOS, participants were classified as diabetic if their fasting blood glucose was ≥126 mg/dL or their nonfasting blood glucose was ≥200 mg/dL. In the WHS, participants self-reported whether they were diagnosed with diabetes. FOS participants completed a standardized physical examination, which included height and weight measurements. WHS participants provided self-reported height and weight; high correlations between self-reported and measured weights ($r = 0.97$) have been demonstrated in US women of similar age (64). BMI was calculated as weight divided by height (kg/m^2). Alcohol intake was assessed by asking the number of alcoholic beverages consumed in a typical week in the previous year and expressed as g/d. Current smokers were defined as participants who reported currently smoking (WHS) or smoking regularly in the past year (FOS). Physical activity was evaluated through standard questionnaires in the FOS (examination 5 only) (65) and WHS (66). Potential confounding through other dietary components was explored through adjustment of individual dietary factors (percentage energy from saturated fat and servings per day of fruit, vegetables, whole grains, fish, and nuts/seeds).

Statistical analyses

Participants were grouped by categories of SSB consumption (servings: <1/mo, 1–4/mo, 1–2/wk, 3–7/wk, >1/d), similar to previous studies (18, 19, 67, 68). Linear (WHS) and linear mixed effects (FOS) regression models were used to examine the association between SSB consumption and LDL cholesterol, HDL cholesterol, TG, non–HDL cholesterol, TC:HDL cholesterol ratio, apoB, apoA1, apoB:apoA1, TRL-P (very large, large, medium, small, and very small), LDL-P (large, medium, and small), and HDL-P (large, medium, and small). In the FOS cohort, familial correlation was accounted for by adding a random effect in the model with a covariance structure proportional to the kinship matrix as implemented in the *lmekin* function of the *coxme* R package (https://cran.r-project.org). Similar models were used to explore the RLP-TG, RLP-C, apoE, and apoC3 outcomes that were available only in the FOS cohort. A natural logarithmic transformation was applied to TG concentrations, and quantile normalization was applied to RLP concentrations to approximate normal distributions. Due to differences in unit measures between FOS and WHS participants and skewed distributions, lipoprotein particle size concentrations (TRL-P, LDL-P, and HDL-P measures) were harmonized through quantile normalization. Four models were performed. Model 1 adjusted for age (continuous), sex (FOS only: male, female), fasting status (WHS only: ≥8 h, <8 h, or missing hours since last meal), and total energy intake (continuous). Model 2 adjusted for model 1 covariates plus education (FOS: less than high school, graduated high school, some college,

graduated college; WHS: less than bachelor degree, bachelor degree, graduate degree), income (WHS only: <50,000/y, ≥$50,000/y) (69), current smoking status (yes, no), race (WHS only: non-Hispanic white, black, Asian, other), physical activity (FOS: continuous index; WHS: continuous metabolic equivalents), alcohol (g/d), current diabetes (yes, no), servings per day (vegetables, whole fruits, whole grains, nuts/seeds, and seafood), and percentage energy from saturated fat (continuous). Model 3 adjusted for model 2 covariates plus BMI (continuous), which is a marker of adiposity and could be a mediator in the association between SSB consumption and lipoprotein measures. Model 4 adjusted for model 3 covariates plus total lipoprotein concentration [TG (ln), HDL cholesterol, or LDL cholesterol for TRL-P, HDL-P, and LDL-P measures, respectively] and was applied only for lipoprotein particle size measures. Model 4 allowed us to examine the association of SSB consumption with the lipoprotein particle size measures independent of the association between SSBs and traditional lipoprotein measures. Models were run separately for the WHS and FOS cohorts, and regression coefficients and standard errors were combined through fixed effects multivariate meta-analyses (70) using the *mvmeta* R package. To assess for a linear trend across categories, SSB category was treated as a continuous variable, and regression coefficients and standard errors were combined through fixed effects univariate meta-analysis using the *meta* R package. The Cochrane Q statistic and the I^2 statistic were used to examine the heterogeneity of the associations between the cohorts.

Likelihood ratio testing comparing models with and without multiplicative interaction terms was used to assess effect modification by sex (male, female; FOS only) and BMI (<25, 25–29.9, ≥30). Among WHS participants, sensitivity analyses were conducted among the fasting subsample. All statistical analyses were performed using SAS (version 9.4 or higher; SAS Institute) and R (version 3.1 or higher) statistical software. All reported P values are two-sided, and results were considered statistically significant at a global $P < 0.05$, corrected for multiple end points using the Tukey method (71).

Results

Table 1 presents the characteristics of participants within each cohort among the highest and lowest categories of SSB consumption. Full descriptive statistics stratified by all five categories of SSB intake are displayed in **Supplemental Table 2** (FOS) and **Supplemental Table 3** (WHS). Among FOS participants, the highest SSB consumers were less likely to be women. In both cohorts, the highest SSB consumers were younger, more likely to smoke, and less likely to have diabetes. Additionally, WHS participants consuming more SSBs had achieved lower levels of education, were less physically active and had a higher BMI, whereas FOS participants consuming more SSBs had achieved higher levels of education and were more physically active. Lipoprotein profiles were less favorable among the highest SSB consumers. Total energy intake was higher with increasing SSB consumption, although fruit, vegetable, whole grain, seafood, and alcohol consumption was lower with increasing SSB consumption.

Associations between SSB intake and lipoprotein and apolipoprotein concentrations

Table 2 presents the associations of SSB intake with lipoprotein and apolipoprotein concentrations among categories of SSB intake (reference: <1 serving per month) in FOS, WHS, and combined analyses. In the combined analyses using the fully adjusted models (model 3), participants in the highest category of SSB intake (>1 serving per day) had higher mean concentrations of LDL cholesterol ($\beta \pm$ SE: 2.1 ± 1.0 mg/dL), TG (0.11 ± 0.01 ln-mg/dL), non–HDL cholesterol (5.0 ± 1.2 mg/dL), TC:HDL cholesterol ratio (0.36 ± 0.04), apoB (4.6 ± 0.8), and apoB:apoA1 ratio (0.05 ± 0.007), and lower HDL cholesterol (–3.5 ± 0.4 mg/dL) and apoA1 (−4.1 ± 0.7 mg/dL) concentrations, compared with those in the lowest category of SSB intake (<1 serving per month). Trend analyses indicated a statistically significant linear trend across the five categories of SSB intake for all lipoprotein and apolipoprotein measures (P-trend <0.001). In analyses restricted to the FOS cohort, participants in the highest category of SSB intake (>1 serving per day) had higher mean concentrations of RLP-TG ($\beta \pm$ SE: 0.22 ± 0.08 mg/dL; P-trend = 0.001) and RLP-C (0.13 ± 0.08 mg/dL; P-trend = 0.008). No significant associations were observed for apoE or apoC3 concentrations in the FOS cohort. No significant interactions ($P < 0.05$) between SSB consumption and sex or BMI were observed in fully adjusted models. We observed similar results when analyses were limited to the fasting subsample of WHS participants (**Supplemental Table 4**).

Associations between SSB intake and lipoprotein particle size measures

Table 3 and Figure 1 present the mean differences in lipoprotein particle size concentrations between the highest SSB consumers (>1 serving per day) and the lowest (<1 serving per month), with the P-trend across five categories of SSB intake in FOS, WHS, and combined analyses. After adjustment for traditional lipoprotein measures and potential confounding factors (model 4), the highest SSB consumers compared with the lowest had a smaller mean LDL-P size ($\beta \pm$ SE: −0.10 ± 0.01 nm; P-trend <0.0001) and HDL-P size (−0.02 ± 0.01 nm; P-trend = 0.001), with lower concentrations of large LDL-Ps (−0.18 ± 0.03; P-trend <0.0001) and medium HDL-Ps (−0.10 ± 0.03; P-trend <0.0001) and higher concentrations of small LDL-Ps (0.14 ± 0.03; P-trend <0.0001) and small HDL-Ps (0.16 ± 0.03; P-trend <0.0001). Among TRL-P measures, SSB was significantly associated only with higher concentrations of large TRL-Ps ($\beta \pm$ SE: 0.06 ± 0.02; P-trend = 0.0009). There was no evidence of heterogeneity between the cohorts for these significant associations ($P > 0.05$). However, significant heterogeneity was observed for medium LDL-Ps ($P = 0.0002$), where higher SSB consumption was associated with higher concentrations of medium LDL-Ps only among FOS participants (P-trend = 0.001). A similar trend was not observed among WHS participants (P-trend = 0.16), which is likely due to differences in the way that small/medium particles were grouped in the two versions of the LipoProfile assay (Supplemental Table 1).

Associations between all categories of SSB consumption and lipoprotein particle sizes from the multivariate meta-analysis in all four covariate models are presented in Figure 1 and **Supplemental Table 5**. Before adjusting for total TG concentrations (model 3), higher SSB consumption (trend across categories: <1 serving per month to >1 serving per day) was significantly associated with larger TRL-P particle size [$\beta \pm$ SE (serving: >1/d compared with <1/mo): 1.21 ± 0.22 nm; P-trend <0.0001), higher concentrations of all TRL-P particle fractions (very large: 0.10 ± 0.03; P-trend = 0.0009; large: 0.20 ± 0.03; P-trend <0.0001; medium: 0.14 ± 0.03; P-trend <0.0001; small: 0.01 ± 0.03; P-trend = 0.05: very small: 0.09 ± 0.03; P-trend <0.0001), and lower concentrations of large HDL-Ps (–0.20 ± 0.03; P-trend <0.0001). All other associations were similar across all covariate models. Similar associations between SSB consumption and lipoprotein particle sizes were observed when analyses were limited to the fasting subsample of WHS participants (Supplemental Table 4), and no significant interactions ($P < 0.05$) were observed by sex or BMI.

TABLE 1 Characteristics of the FOS and WHS participants by cohort and category of SSB intake[1]

	FOS				WHS			
	Overall	<1 SSB serving/mo	>1 SSB serving/d	*P*-trend	Overall	<1 SSB serving/mo	>1 SSB serving/d	*P*-trend
n	3047	1100	312		26,218	11,751	1400	
SSB servings/wk, median		0	14.0			0	14.0	
Sex: women, %	54.1	64.5	34.3	<0.0001	100	100	100	
Age, y	54.3 (9.8)	55.9 (9.7)	51.1 (10.2)	<0.0001	54.6 (7.0)	54.8 (7.0)	52.6 (6.0)	<0.0001
Current smoker, %	19.4	15.7	30.1	<0.0001	11.6	10.2	20.4	<0.0001
Diabetic, %	6.5	8.9	5.8	<0.0001	2.5	3.6	2.0	<0.0001
Education: bachelor degree, %	33.6	31.2	33.7	<0.0001	43.6	46.8	32.3	<0.0001
BMI, kg/m^2	27.3 (5.0)	27.6 (5.3)	27.5 (4.9)	0.35	25.9 (4.9)	25.9 (4.9)	26.4 (5.7)	0.03
Physical activity index[2,3]	34.8 (6.1)	34.1 (5.5)	36.1 (7.3)	<0.0001	—	—	—	
Physical activity,[3] MET h/wk	—	—	—		5.9 (17.6)	6.9 (18.3)	3.4 (14.0)	<0.0001
Traditional plasma lipoprotein measures								
LDL-C, mg/dL	126 (32)	125 (33)	124 (31)	0.44	124 (34)	123 (34)	126 (36)	<0.0001
HDL-C, mg/dL	51 (15)	53 (16)	45 (13)	<0.0001	54 (15)	55 (16)	49 (14)	<0.0001
TG,[3] mg/dL	122 (88)	119 (86)	134 (106)	<0.0001	121 (90)	119 (89)	135 (111)	<0.0001
Non–HDL-C, mg/dL	153 (38)	152 (38)	154 (37)	0.01	157 (41)	156 (41)	162 (43)	<0.0001
Ratio total: HDL-C	4.4 (1.5)	4.2 (1.5)	4.8 (1.5)	<0.0001	4.2 (1.3)	4.1 (1.3)	4.6 (1.5)	<0.0001
Plasma apolipoprotein measures								
apoB, mg/dL	97 (25)	97 (26)	99 (27)	0.03	94 (23)	94 (22)	96 (24)	<0.0001
apoA1, mg/dL	144 (30)	149 (33)	136 (24)	<0.0001	154 (30)	156 (30)	146 (29)	<0.0001
apoB:apoA1	0.70 (0.23)	0.67 (0.23)	0.75 (0.24)	<0.0001	0.71 (0.24)	0.69 (0.23)	0.77 (0.26)	<0.0001
apoE, mg/dL	10.1 (4.8)	10.4 (4.9)	9.9 (4.2)	0.08	—	—	—	
apoC3, mg/dL	16.3 (4.5)	16.5 (4.3)	16.2 (4.7)	0.27	—	—	—	
Other plasma lipoprotein measures								
RLP-TG, mg/dL	18.0 (13.2)	17.6 (11.5)	21.3 (16.7)	<0.0001	—	—	—	
RLP-C, mg/dL	7.1 (2.2)	7.0 (2.0)	7.6 (2.8)	0.0005	—	—	—	
TRL-P[4]								
Mean size, nm	46.2 (9.3)	45.9 (9.2)	47.9 (10.1)	<0.0001	44.1 (7.5)	44.0 (7.6)	45.2 (8)	0.0004
Very large[3]	3.7 (6.5)	3.5 (5.5)	4.7 (9.9)	0.0001	0.10 (0.10)	0.10 (0.10)	0.12 (0.20)	0.02
Large[3]	2.7 (25)	2.2 (21)	4.3 (33.9)	<0.0001	0.9 (3.9)	0.8 (3.8)	1.2 (4.7)	<0.0001
Medium[3]	30.6 (37)	28.4 (34.3)	34.5 (39.9)	<0.0001	12.6 (16.7)	12.0 (16.6)	14.6 (17.9)	<0.0001
Small[3]	14.1 (18.6)	13.6 (18.7)	14.0 (18.9)	0.79	47.1 (47.7)	45.7 (48.2)	46.6 (49.2)	<0.0001
Very small[3]	1.1 (6.6)	1.1 (6.8)	1.4 (5.9)	0.23	77.9 (55.1)	77.3 (54.7)	81.9 (56.8)	<0.0001
LDL-P[4]								
Mean size, nm	20.9 (0.6)	20.9 (0.5)	20.8 (0.6)	<0.0001	20.9 (0.5)	20.9 (0.4)	20.8 (0.5)	<0.0001
Large[3]	53.2 (48.5)	55 (47.1)	43.5 (47.3)	<0.0001	183 (306)	196 (306)	123 (311)	<0.0001
Medium[3]	20.6 (32.8)	19.9 (30.4)	25.3 (29.4)	0.0005	17 (348)	17 (343)	10 (334)	0.008
Small[3]	13.7 (23.5)	12.5 (22.7)	17 (28.4)	<0.0001	926 (638)	913 (602)	1012 (746)	<0.0001

(*Continued*)

TABLE 1 (*Continued*)

	FOS				WHS			
	Overall	<1 SSB serving/mo	>1 SSB serving/d	*P*-trend	Overall	<1 SSB serving/mo	>1 SSB serving/d	*P*-trend
HDL-P[4]								
Mean size, nm	9.2 (0.5)	9.2 (0.5)	9.0 (0.4)	<0.0001	9.0 (0.4)	9.0 (0.4)	8.9 (0.4)	<0.0001
Large	10.5 (7.1)	11.6 (7.9)	8.1 (5.6)	<0.0001	2.5 (1.5)	2.6 (1.6)	2.1 (1.4)	<0.0001
Medium	22.9 (10.2)	24.6 (10.9)	19.8 (9.1)	<0.0001	5.7 (2.8)	5.9 (2.9)	5.1 (2.6)	<0.0001
Small	17.8 (4.9)	17.3 (5.0)	18.1 (4.7)	0.003	16.4 (3.4)	16.3 (3.5)	16.8 (3.4)	<0.0001
Dietary intakes								
Total energy, kcal/d	1869 (612)	1661 (541)	2368 (595)	<0.0001	1733 (529)	1612 (490)	2148 (548)	<0.0001
Saturated fat, % total energy	10.6 (2.8)	10.4 (3.0)	10.0 (2.5)	0.98	10.2 (2.5)	10.1 (2.6)	9.8 (2.4)	0.06
Servings/d								
Fruits[3]	0.6 (1.1)	0.7 (1.1)	0.5 (1.0)	<0.0001	1.5 (1.5)	1.5 (1.4)	1.2 (1.5)	<0.0001
Vegetables[3]	1.7 (1.2)	1.8 (1.2)	1.6 (1.0)	0.0005	3.3 (2.7)	3.3 (2.7)	3.0 (2.7)	<0.0001
Whole grain[3]	0.6 (1.3)	0.7 (1.4)	0.4 (1.1)	<0.0001	1.0 (1.3)	1.0 (1.4)	0.7 (1.1)	<0.0001
Nuts/seeds[3]	0.2 (0.4)	0.1 (0.4)	0.2 (0.5)	<0.0001	0.1 (0.3)	0.1 (0.2)	0.1 (0.3)	0.04
Seafood[3]	0.3 (0.4)	0.3 (0.4)	0.2 (0.3)	0.05	0.2 (0.2)	0.2 (0.2)	0.2 (0.1)	<0.0001
Alcohol,[3] g/d	1.2 (13.5)	1.1 (12.7)	0.6 (14.0)	0.14	0.3 (4.6)	0.4 (5.9)	0.1 (2.1)	<0.0001

[1] Values are means (SD) unless otherwise noted. Dashes in cells indicate no data. Maximum available observations (*n*) for analyses. All FOS values are derived from examination 5 data except apoB, apoA1, apoB:apoA1 ratio, and all "other lipoprotein measures," which were derived from examination 4 data. *P*-trend represents the *P* value for regression coefficients where five categories of SSB intake (serving: <1/mo, 1–4/mo, 1–2/wk, 3–7/wk, >1/d) are treated as a continuous variable in unadjusted models. Descriptive statistics for all five categories of SSB intake are displayed in Supplemental Table 2 (FOS) and Supplemental Table 3 (WHS). One serving was equivalent to the following: 360 mL, SSB; 0.5 cup, fruit; 1 cup, vegetables; 1 oz, whole grains; 1 oz, nuts/seeds; and 3.5 oz, seafood. apoA1, apolipoprotein A1; apoB, apolipoprotein B; apoC3, apolipoprotein C3; apoE, apolipoprotein E; FOS, Framingham Offspring Study; HDL-C, HDL cholesterol; HDL-P, HDL particle; LDL-C, LDL cholesterol; LDL-P, LDL particle; MET, metabolic equivalent; RLP-C, remnant-like particle cholesterol; RLP-TG, remnant-like particle triglyceride; SSB, sugar-sweetened beverage; TG, triglyceride; TRL-P, triglyceride-rich lipoprotein particle; WHS, Women's Health Study.

[2] Physical activity index calculated in FOS participants was previously defined (65).

[3] Geometric mean (IQR).

[4] In the FOS, the LPI assay measured cholesterol concentrations (mg/dL) within each lipoprotein subclass, whereas the LP4 assay used in the WHS measured particle concentrations (nmol/L for TRL-P and LDL-P; μmol/L for HDL-P) within each lipoprotein subclass.

TABLE 2 Associations between SSB intake and plasma lipoprotein and apolipoprotein concentrations in the FOS and WHS

	SSB serving,[1] β (SE)						Adjusted	
	<1/mo	1–4/mo	1–2/wk	3–7/wk	>1/d	*P*-trend	*P*-trend[2]	*P*-heterogeneity
FOS[3]								
n	1100	710	289	635	312			
SSB servings/wk,[1] median	0	0.5	1.5	4.0	14.0			
LDL-C, mg/dL	Ref	1.4 (1.6)	3.0 (2.2)	3.0 (1.7)	0.9 (2.5)	0.18	0.48	
HDL-C, mg/dL	Ref	−0.6 (0.6)	−1.3 (0.8)	−2.3 (0.7)	−1.6 (0.9)	0.0009	0.002	
TG, ln-mg/dL	Ref	0.04 (0.02)	0.04 (0.03)	0.09 (0.03)	0.13 (0.04)	0.0001	0.0001	
Non–HDL-C, mg/dL	Ref	2.5 (1.7)	3.8 (2.4)	5.5 (1.9)	4.2 (2.7)	0.008	0.02	
TC:HDL-C	Ref	0.02 (0.01)	0.05 (0.01)	0.04 (0.01)	0.04 (0.02)	0.0001	0.0001	
RLP-TG, mg/dL	Ref	−0.01 (0.05)	0.15 (0.07)	0.15 (0.06)	0.22 (0.08)	0.001	0.001	
RLP-C, mg/dL	Ref	−0.001 (0.05)	0.2 (0.07)	0.14 (0.05)	0.13 (0.08)	0.003	0.008	
apoB, mg/dL	Ref	1.1 (1.1)	6.3 (1.6)	2.6 (1.2)	4.1 (1.8)	0.003	0.008	
apoA1, mg/dL	Ref	−2.3 (1.3)	−1.7 (1.8)	−4.1 (1.4)	−2.4 (2.1)	0.02	0.06	
apoB:apoA1	Ref	0.07 (0.06)	0.14 (0.09)	0.26 (0.07)	0.23 (0.10)	0.0003	0.0005	
apoE, mg/dL	Ref	−0.4 (0.3)	−0.2 (0.4)	0.1 (0.3)	0.2 (0.4)	0.54	0.93	
apoC3, mg/dL	Ref	0.2 (0.2)	0.3 (0.3)	0.4 (0.2)	0.5 (0.3)	0.07	0.20	
WHS[3]								
n	11,751	5724	3384	3959	1400			
SSB servings/wk,[1] median	0	0.5	1.4	4.0	14.0			
LDL-C, mg/dL	Ref	0.4 (0.6)	1.8 (0.7)	1.9 (0.7)	2.3 (1.1)	0.0005	0.001	
HDL-C, mg/dL	Ref	−1.0 (0.2)	−2.1 (0.3)	−2.4 (0.3)	−3.9 (0.4)	<0.0001	<0.0001	
TG, ln-mg/dL	Ref	0.02 (0.01)	0.05 (0.01)	0.07 (0.01)	0.10 (0.02)	<0.0001	<0.0001	
Non–HDL-C, mg/dL	Ref	0.6 (0.7)	2.6 (0.8)	3.6 (0.8)	5.2 (1.3)	<0.0001	<0.0001	
TC:HDL-C	Ref	0.07 (0.02)	0.17 (0.02)	0.21 (0.02)	0.37 (0.04)	<0.0001	<0.0001	
apoB, mg/dL	Ref	0.8 (0.4)	2.3 (0.5)	3.2 (0.5)	4.7 (0.8)	<0.0001	<0.0001	
apoA1, mg/dL	Ref	−1.6 (0.4)	−3.0 (0.5)	−2.3 (0.5)	−4.3 (0.8)	<0.0001	<0.0001	
apoB:apoA1	Ref	0.01 (0.004)	0.03 (0.005)	0.04 (0.004)	0.06 (0.01)	<0.0001	<0.0001	
Combined results[4]								
LDL-C, mg/dL	Ref	0.5 (0.5)	1.9 (0.7)	2.0 (0.6)	2.1 (1.0)	0.0002	0.0006	0.94
HDL-C, mg/dL	Ref	−1.0 (0.2)	−2.0. (0.3)	−2.4 (0.3)	−3.5 (0.4)	<0.0001	<0.0001	0.19
TG, ln-mg/dL	Ref	0.02 (0.01)	0.05 (0.01)	0.07 (0.01)	0.11 (0.01)	<0.0001	<0.0001	0.83
Non–HDL-C, mg/dL	Ref	0.8 (0.6)	2.7 (0.8)	3.8 (0.7)	5.0 (1.2)	<0.0001	<0.0001	0.86
TC:HDL-C	Ref	0.07 (0.02)	0.17 (0.02)	0.22 (0.02)	0.36 (0.04)	<0.0001	<0.0001	0.55
apoB, mg/dL	Ref	0.8 (0.4)	2.8 (0.5)	3.1 (0.5)	4.6 (0.8)	<0.0001	<0.0001	0.07
apoA1, mg/dL	Ref	−1.6 (0.39)	−2.9 (0.5)	−2.6 (0.5)	−4.1 (0.7)	<0.0001	<0.0001	0.41
apoB:apoA1	Ref	0.01 (0.004)	0.03 (0.004)	0.04 (0.004)	0.05 (0.007)	<0.0001	<0.0001	0.36

[1]One serving of SSB is equivalent to 360 mL. apoA1, apolipoprotein A1; apoB, apolipoprotein B; apoC3, apolipoprotein C3; apoE, apolipoprotein E; FOS, Framingham Offspring Study; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Ref, reference; RLP-C, remnant-like particle cholesterol; RLP-TG, remnant-like particle triglyceride; SSB, sugar-sweetened beverage; TC, total cholesterol; TG, triglyceride; WHS, Women's Health Study.
[2]Adjusted for multiple end points using the Tukey method (94).
[3]Values are regression coefficients for SSB intake in mixed effects models accounting for family structure (FOS) and generalized linear models (WHS) adjusted for the following: age, sex (FOS only), fasting status (WHS only), total energy intake, smoking status, education status, income (WHS only), current diabetes status, physical activity, alcohol intake, body mass index, whole fruit intake, vegetable intake, whole grains intake, seafood intake, nuts/seeds intake, and saturated fatty acid intake (percentage of total energy).
[4]Study estimates from the two cohorts were combined through fixed effects meta-analyses.

Discussion

In this study of two large US cohorts, SSB consumption was significantly associated with concentrations of lipoprotein cholesterol, apolipoproteins, and lipoprotein particle size concentrations that have been linked to adverse cardiometabolic outcomes. We identified novel associations between SSB intake and higher apoB:apoA1 ratio and concentrations of non–HDL cholesterol, apoB, RLP-TG and RLP-C; lower concentrations of apoA1; and smaller LDL-P and HDL-P size. We also replicated previously observed associations of SSB consumption with TC:HDL cholesterol ratio and HDL cholesterol, LDL cholesterol, and TG concentrations.

Our analysis is the largest to date that examines the associations between SSB intake and a wide range of lipoprotein concentrations. These results are consistent with several other studies observing that higher SSB consumption associates with lower concentrations of HDL cholesterol and higher concentrations of LDL cholesterol, TG, and TC:HDL cholesterol ratio (5, 14, 17–19, 68, 72). In addition to previously observed associations, our results indicate that SSB intake is associated with non–HDL cholesterol, apoB, apoA1, RLP-C, and RLP-TG concentrations and apoB:apoA1 ratio, all in the direction that has been associated with increased cardiometabolic risk in previous studies (10, 24, 30–36). Although measurement of apoB and apoA1 concentrations are not currently recommended over lipoprotein measures in clinical settings (36, 73), emerging data suggest that these measures can improve risk assessment and their elevation may confer greater risk over traditionally measured clinical risk factors (10, 26, 74). RLP concentrations are another emerging CVD risk factor (25, 75–77), and to date, few interventions have considered whether dietary sugars or

TABLE 3 Associations between SSB intake and plasma lipoprotein particle size concentrations in the FOS and WHS[1]

	FOS ($n = 3047$)		WHS ($n = 26,218$)		Combined results[2]			
	β (SE)[3]	*P*-trend	β (SE)[3]	*P*-trend	β (SE)[3]	*P*-trend	Adjusted *P*-trend[4]	*P*-heterogeneity
TRL-P								
Mean size, nm	0.57 (0.56)	0.39	0.33 (0.19)	0.51	0.36 (0.18)	0.38	0.80	0.41
Very Large	0.06 (0.06)	0.28	0.02 (0.03)	0.58	0.03 (0.03)	0.90	0.99	0.75
Large	0.06 (0.05)	0.21	0.06 (0.02)	0.0008	0.06 (0.02)	0.0003	0.0009	0.99
Medium	−0.03 (0.05)	0.55	0.001 (0.02)	0.70	−0.004 (0.02)	0.89	0.99	0.76
Small	0.04 (0.08)	0.35	−0.02 (0.03)	0.23	−0.02 (0.03)	0.15	0.37	0.46
Very small	0.01 (0.08)	0.62	0.01 (0.03)	0.38	0.01 (0.03)	0.32	0.71	0.85
LDL-P								
Mean size, nm	−0.08 (0.04)	0.02	−0.10 (0.01)	<0.0001	−0.10 (0.01)	<0.0001	<0.0001	0.86
Large	0.08 (0.07)	0.23	−0.23 (0.03)	<0.0001	−0.18 (0.03)	<0.0001	<0.0001	0.72
Medium	0.22 (0.07)	0.001	−0.06 (0.03)	0.16	−0.02 (0.03)	0.86	0.99	0.0002
Small	−0.17 (0.08)	0.01	0.19 (0.03)	<0.0001	0.14 (0.03)	<0.0001	<0.0001	0.57
HDL-P								
Mean size, nm	−0.06 (0.02)	0.05	−0.01 (0.01)	0.002	−0.02 (0.01)	0.0004	0.001	0.45
Large	−0.10 (0.04)	0.31	−0.02 (0.02)	0.28	−0.04 (0.02)	0.16	0.41	0.53
Medium	−0.03 (0.05)	0.61	−0.12 (0.03)	<0.0001	−0.10 (0.03)	<0.0001	<0.0001	0.11
Small	0.14 (0.08)	0.11	0.16 (0.03)	<0.0001	0.16 (0.03)	<0.0001	<0.0001	0.08

[1] Values are regression coefficients for the highest category of SSB intake [serving: >1/d; $n = 1400$ (WHS: median = 14.0/wk), $n = 312$ (FHS: median = 14.0/wk)] compared with the lowest category of SSB intake [serving: <1/mo; $n = 11,751$ (WHS: median = 0.0/d), $n = 1100$ (FHS: median = 0.0/d)] on quantile-normalized particle concentrations using mixed effects models accounting for family structure in FHS and generalized linear models in WHS. Models were adjusted for the following: age, sex (FHS only), fasting status (WHS only), total energy intake, smoking status, education status, income (WHS only), current diabetes status, physical activity, alcohol intake, body mass index, whole fruit intake, vegetable intake, whole grains intake, seafood intake, nuts/seeds intake, saturated fatty acid intake (percentage of total energy), and total lipid measure (triglyceride, LDL cholesterol, and HDL cholesterol concentrations for TRL-P, LDL-P, and HDL-P concentrations, respectively). *P*-trend represents the *P* value for regression coefficients where the category of SSB intake (servings: <1/mo, 1–4/mo, 1–2/wk, 3–7/wk, >1/d) is treated as a continuous variable. One serving of SSB is equivalent to 360 mL. FOS, Framingham Offspring Study; HDL-P, HDL particle; LDL-P, LDL particle; SSB, sugar-sweetened beverage; TRL-P, triglyceride-rich lipoprotein particle; WHS, Women's Health Study.
[2] Study estimates from the two cohorts were combined through fixed effects meta-analyses.
[3] SSB servings: >1/d vs. <1/mo.
[4] Adjusted for multiple end points using the Tukey method (94).

SSBs influence RLP concentrations. One randomized controlled trial with 48 participants observed that consumption of SSBs at 25% of total energy intake over 2 weeks resulted in significant increases in RLP-C and RLP-TG concentrations (41). Thus, the findings suggest that reducing SSB consumption may result in concomitant RLP reduction.

The results of our study indicate that SSB consumption is significantly associated with smaller HDL-P and LDL-P size, independent of total HDL cholesterol and LDL cholesterol concentrations. Observations included a significant negative association between SSB consumption and large LDL-P and medium HDL-P concentrations and a positive association between SSB consumption and small LDL-P, small HDL-P, and large TRL-P concentrations. Despite the controversy around the clinical utility of these measures of lipoprotein particle size (78), in observational studies, smaller HDL-P and LDL-P size and larger TRL-P size have been associated with higher risk for T2D (34, 37, 79, 80), hypertension (22), MetSyn (52), peripheral artery disease (74), and CVD (74, 81–83), independent of traditional lipoprotein measures. Thus, continued investigation of the function and determinants of lipoprotein particle size is warranted to understand its unique contribution in the atherosclerotic process (78, 84). For example, in vitro studies have demonstrated that smaller LDL-Ps have an increased affinity for LDL binding sites, which may increase cellular uptake rates in arterial tissue (85, 86). Further investigation of the mechanisms by which lipoprotein particle size and type may influence cardiometabolic risk is required (i.e., through differences in cholesterol and TG content by particle size, particle concentration, or functional properties related to particle size). These investigations may lead to novel biomarker discovery that could improve cardiometabolic disease risk prediction and extend insights gained from the current study related to high SSB consumption and dyslipidemia patterns.

The findings in this study are novel as no previous observational studies have investigated the association between SSB consumption and lipoprotein particle size concentrations among adults. One cross-sectional study among 74 Swiss children observed that high total fructose intake was the only significant dietary predictor of LDL-P size out of 11 categories of macronutrient intake (87). Two small intervention studies (<50 participants) comparing consumption of glucose-, fructose-, and sugar-sweetened beverages within ranges of normal intake over 2- to 3-wk periods also observed that consumption of either fructose- or sugar-sweetened beverages led to lower LDL-P size (41, 42). Several randomized controlled trials have examined the effect of low-carbohydrate diets on LDL-P size; a meta-analysis of 16 studies indicated that carbohydrate restriction reduces the number of small LDL-Ps (48). Our findings are consistent with these prior studies, where we observed higher concentrations of small LDL-Ps among the highest SSB consumers.

Investigators have also observed significant associations between poor overall diet quality and lower plasma concentrations of large HDL-Ps (88) and higher concentrations of small HDL-Ps and medium and large TRL-Ps (89). These associations are in the same direction as the associations of SSB consumption with smaller HDL-P and larger TRL-P size that we observed in our study, despite the attenuation of the association with TRL-P size after adjustment for TG concentrations. Large prospective studies have observed that greater concentrations of large TRL-Ps are associated with a

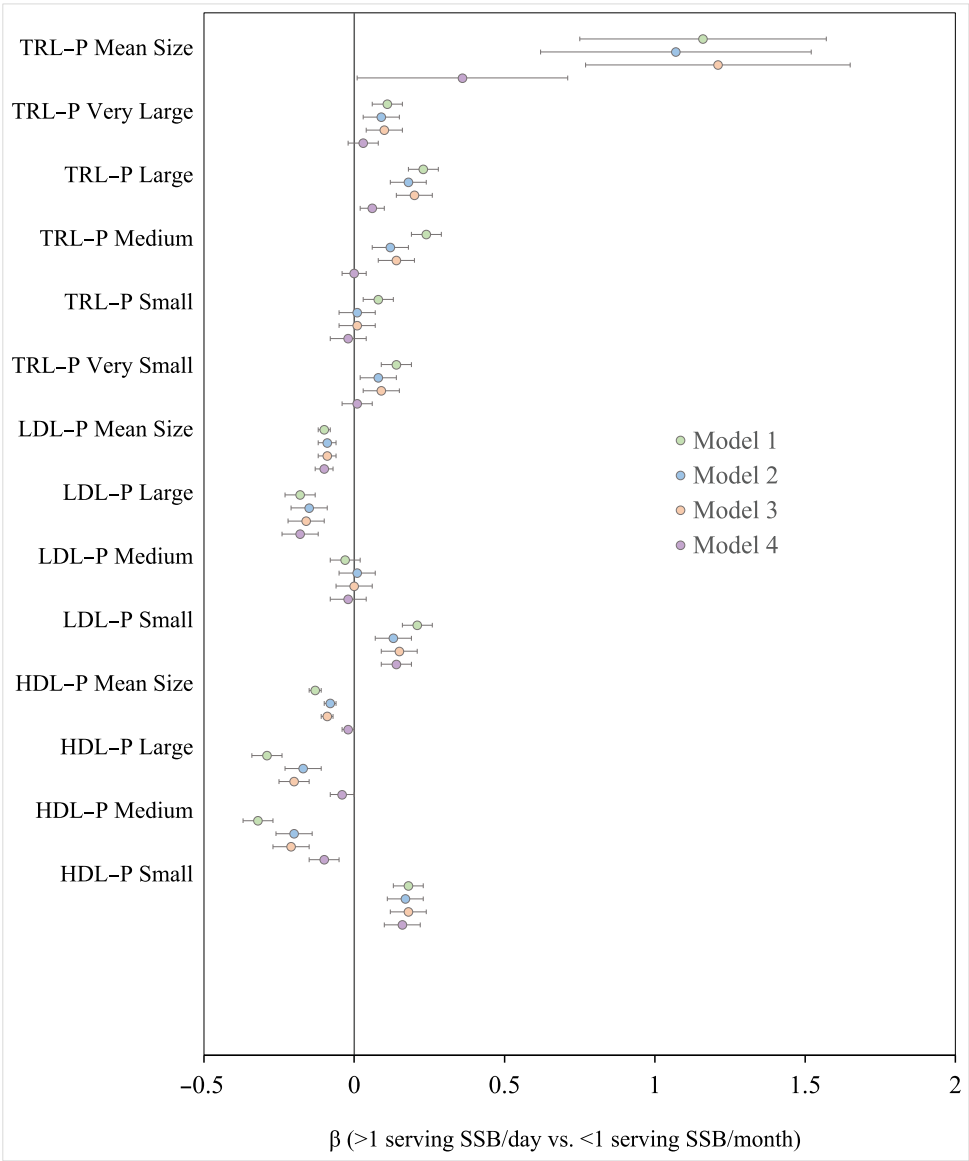

FIGURE 1 Mean difference in plasma lipoprotein particle size concentrations among individuals consuming >1 SSB serving per day compared with <1 SSB serving per month in a fixed effect meta-analysis of the Framingham Offspring Study (FOS; $n = 3047$) and Women's Health Study (WHS; $n = 26{,}218$). Values are regression coefficients (β) comparing the highest SSB consumers (>1 SSB serving per day) with the lowest (<1 SSB serving per month) in fixed effect meta-analyses on quantile-normalized particle concentrations. Meta-analyses are based on mixed effects models accounting for family structure in FOS and generalized linear models in WHS, adjusted for the following. Model 1: age, sex (FOS only), fasting status (WHS only), and total energy intake. Model 2: model 1 covariates plus smoking status, education status, income (WHS only), current diabetes status, physical activity, alcohol intake, whole fruit intake, vegetable intake, whole grains intake, seafood intake, nuts/seeds intake, and saturated fatty acid intake (percentage of total energy). Model 3: model 2 covariates plus body mass index. Model 4: model 3 covariates plus total lipid measure (triglyceride, LDL cholesterol, and HDL cholesterol concentrations for TRL-P, LDL-P, and HDL-P concentrations, respectively). One SSB serving is equivalent to 360 mL. Horizontal bars indicate 95% CIs. HDL-P, HDL particle; LDL-P, LDL particle; SSB, sugar-sweetened beverage; TRL-P, triglyceride-rich particle.

higher risk for T2D compared with small TRL-Ps (34, 79) and that concentrations of large TRL-Ps were elevated among adults with nonalcoholic fatty liver disease (90). Interestingly, two small intervention studies that compared low-carbohydrate diets and low-fat weight loss diets for 3–6 mo observed larger decreases in concentrations of large TRL-Ps compared with small TRL-Ps (91, 92) for the low-carbohydrate diet, suggesting a potential role of diets low in carbohydrates on TRL-P size. Thus, the combination of data from these previous studies and this current study suggests that further research into differences in lipoprotein metabolism could reveal new mechanisms by which SSB consumption may increase risk for cardiometabolic diseases, particularly diabetic dyslipidemia. Overall, the effect sizes of the observed associations are relatively small, and larger studies with longitudinal follow-up are needed to determine the potential clinical relevance of these findings.

The strengths of our study include a large sample size, the ability to adjust for multiple confounding factors, and the ability to examine a wide range of lipoprotein concentrations in two independent cohorts. However, the research design also has some limitations. The design of this study limits our ability to infer causality between SSB consumption and the outcomes

of interest, and the use of self-reported dietary data can lead to misclassification of food and nutrient intakes. These FFQs did not include an exhaustive list of all potential sources of SSBs, such as consumption of sweetened coffee/tea. However, estimates of beverage consumption during the time of data collection (1987–1995) suggest that consumption of coffee/tea (sweetening not captured) was low compared with consumption of SSBs (93). Among FOS participants, measurements of apoA1, apoB, RLP, and lipoprotein particle size concentrations were derived from blood draws at examination 4, whereas dietary intakes were estimated at examination 5. Thus, a limitation in the FOS analysis is that estimated dietary intakes may not reflect dietary intakes at the time of the blood draw. However, the consistency of the associations between SSB consumption and lipoprotein particle size concentrations in the FOS and WHS adds confidence that our estimates of dietary intakes are informative. Generalizability of our study is also limited by our sample of predominantly European-descent adults and by the inclusion of only women and health professionals in the WHS; hence, these participants likely have a higher socioeconomic status than the general population.

In conclusion, our findings suggest that higher consumption of SSBs is associated with multiple measures of plasma lipoprotein concentrations that have been linked to adverse cardiometabolic outcomes, including traditional and emerging measures of lipoprotein cholesterol, apolipoprotein, and lipoprotein particle concentrations. These data suggest that differences in lipoprotein particle sizes are a potential pathway by which SSB intake may increase risk for cardiometabolic diseases.

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Data Availability

The Framingham Heart Study data sets used for the described analyses were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap through accession phs000007.v29.p10.

References

1. Rosinger A, Herrick K, Gahche J, Park S. Sugar-sweetened beverage consumption among US adults, 2011–2014. Hyattsville (MD): National Center for Health Statistics; 2017. NCHS data brief 270.
2. US Department of Agriculture, US Department of Health and Human Services. Dietary guidelines for Americans, 2020–2025. 9th ed. Washington (DC): US Department of Agriculture; 2020.
3. Malik VS. Sugar sweetened beverages and cardiometabolic health. Curr Opin Cardiol 32(5):572–9.
4. Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr 2009;89(4):1037–42.
5. de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC, Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. Circulation 2012;125(14):1735–41.
6. Yin J, Zhu Y, Malik V, Li X, Peng X, Zhang FF, Shan Z, Liu L. Intake of sugar-sweetened and low-calorie sweetened beverages and risk of cardiovascular disease: a meta-analysis and systematic review. Adv Nutr 2021;12(1):89–101.
7. Malik VS, Hu FB. The role of sugar-sweetened beverages in the global epidemics of obesity and chronic diseases. Nat Rev Endocrinol 2022;18:205–18.
8. Wang M, Yu M, Fang L, Hu R-Y. Association between sugar-sweetened beverages and type 2 diabetes: a meta-analysis. J Diabetes Investig 2015;6(3):360–6.
9. Narain A, Kwok CS, Mamas MA. Soft drink intake and the risk of metabolic syndrome: a systematic review and meta-analysis. Int J Clin Pract 2017;71(2):e12927.
10. Grundy Scott M, Stone Neil J, Bailey Alison L, Beam C, Birtcher Kim K, Blumenthal Roger S, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. Circulation 2018;139(25):e1082–143.
11. Rader DJ, Hovingh GK. HDL and cardiovascular disease. Lancet North Am Ed 2014;384(9943):618–25.
12. Navar AM. The evolving story of triglycerides and coronary heart disease risk. JAMA 2019;321(4):347–9.
13. Velasquez-Melendez G, Molina M, Benseñor IM, Cardoso LO, Fonseca M de JM, Moreira AD, Pereira TSS, Barreto SM. Sweetened soft drinks consumption is associated with metabolic syndrome: cross-sectional analysis from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). J Am Coll Nutr 2017;36(2):99–107.
14. Hert KA, Fisk PS, II, Rhee YS, Brunt AR. Decreased consumption of sugar-sweetened beverages improved selected biomarkers of chronic disease risk among US adults: 1999 to 2010. Nutr Res 2014;34(1):58–65.
15. Høstmark AT, Tomten SE. Cola intake and serum lipids in the Oslo Health Study. Appl Physiol Nutr Metab 2009;34(5):901–6.
16. Khosravi-Boroujeni H, Sarrafzadegan N, Mohammadifard N, Alikhasi H, Sajjadi F, Asgari S, Esmaillzadeh A. Consumption of sugar-sweetened beverages in relation to the metabolic syndrome among Iranian adults. Obes Facts 2012;5(4):527–37.
17. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D'Agostino RB, Gaziano JM, Ramachandran VS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation 2007;116(5):480–8.
18. Haslam Danielle E, Peloso Gina M, Herman Mark A, Dupuis J, Lichtenstein Alice H, Smith Caren E. McKeown NM. Beverage consumption and longitudinal changes in lipoprotein concentrations and incident dyslipidemia in US adults: the Framingham Heart Study. J Am Heart Assoc 2020;9(5):e014083.
19. Yu Z, Ley SH, Sun Q, Hu FB, Malik VS. Cross-sectional association between sugar-sweetened beverage intake and cardiometabolic biomarkers in US women. Br J Nutr 2018;119(5):570–80.
20. Dake AW, Sora ND. Diabetic dyslipidemia review: an update on current concepts and management guidelines of diabetic dyslipidemia. Am J Med Sci 2016;351(4):361–5.
21. Xiao C, Dash S, Morgantini C, Hegele RA, Lewis GF. Pharmacological targeting of the atherogenic dyslipidemia complex: the next frontier in CVD prevention beyond lowering LDL cholesterol. Diabetes 2016;65(7):1767–78.
22. Paynter NP, Sesso HD, Conen D, Otvos JD, Mora S. Lipoprotein subclass abnormalities and incident hypertension in initially healthy women. Clin Chem 2011;57(8):1178–87.
23. Otvos JD. Measurement of lipoprotein subclass profiles by nuclear magnetic resonance spectroscopy. Clin Lab 2002;48:171–80.
24. Twickler TB, Dallinga-Thie GM, Cohn JS, Chapman MJ. Elevated remnant-like particle cholesterol concentration. Circulation 2004;109(16):1918–25.
25. Cao Y-X, Zhang H-W, Jin J-L, Liu H-H, Zhang Y, Xu R-X, et al. Prognostic utility of triglyceride-rich lipoprotein-related markers in patients with coronary artery disease. J Lipid Res 2020;61(9):1254–62.
26. Andrikoula M, McDowell IFW. The contribution of ApoB and Apoa1 measurements to cardiovascular risk assessment. Diabetes Obes Metab 2008;10(4):271–8.

27. Semenkovich CF, Goldberg AC, Goldberg IJ. Disorders of lipid metabolism. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM , editors. Williams textbook of endocrinology. 13th ed. Philadelphia (PA): Elsevier; 2016. p. 1660–700.
28. Wu L, Parhofer KG. Diabetic dyslipidemia. Metabolism 2014;63(12):1469–79.
29. Aday Aaron W, Lawler Patrick R, Cook Nancy R, Ridker Paul M, Mora S, Pradhan Aruna D. Lipoprotein particle profiles, standard lipids, and peripheral artery disease incidence. Circulation 2018;138(21):2330–41.
30. Vakkilainen J, Steiner G, Ansquer J-C, Aubin F, Rattier S, Foucher C, et al. Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: the diabetes atherosclerosis intervention study (DAIS). Circulation 2003;107(13):1733–7.
31. van der Steeg WA, Holme I, Boekholdt SM, Larsen ML, Lindahl C, Stroes ESG, et al. High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk. The IDEAL and EPIC-Norfolk studies. J Am Coll Cardiol 2008;51(6):634–42.
32. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Low-density lipoprotein subclass patterns and risk of myocardial infarction. JAMA 1988;260(13):1917–21.
33. Stampfer MJ, Krauss RM, Ma J, Blanche PJ, Holl LG, Sacks FM, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. JAMA 1996;276(11):882–8.
34. Mackey RH, Mora S, Bertoni AG, Wassel CL, Carnethon MR, Sibley CT, et al. Lipoprotein particles and incident type 2 diabetes in the multi-ethnic study of atherosclerosis. Diabetes Care 2015;38(4):628–36.
35. Koskinen J, Magnussen CG, Würtz P, Soininen P, Kangas AJ, Viikari JS, et al. Apolipoprotein B, oxidized low-density lipoprotein, and LDL particle size in predicting the incidence of metabolic syndrome: the Cardiovascular Risk in Young Finns Study. Eur J Prev Cardiol 2012;19(6):1296–303.
36. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation 2009;119(7):931–9.
37. Bragg F, Kartsonaki C, Guo Y, Holmes M, Du H, Yu C, et al. Circulating metabolites and the development of type 2 diabetes in Chinese adults. Diabetes Care 2022;45(2):477–80.
38. Hannou SA, Haslam DE, McKeown NM, Herman MA. Fructose metabolism and metabolic disease. J Clin Invest 2018;128(2):545–55.
39. Herman MA, Birnbaum MJ. Molecular aspects of fructose metabolism and metabolic disease. Cell Metab 2021;33(12):2329–54.
40. Steenson S, Umpleby AM, Lovegrove JA, Jackson KG, Fielding BA. Role of the enterocyte in fructose-induced hypertriglyceridaemia. Nutrients 2017;9(4):349.
41. Stanhope KL, Bremer AA, Medici V, Nakajima K, Ito Y, Nakano T, et al. Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-Cholesterol, and apolipoprotein-B in young men and women. J Clin Endocrinol Metab 2011;96(10): E1596–605.
42. Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I, Berthold HK, Spinas GA, Berneis K. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. Am J Clin Nutr 2011;94(2):479–85.
43. Guay V, Lamarche B, Charest A, Tremblay AJ, Couture P. Effect of short-term low- and high-fat diets on low-density lipoprotein particle size in normolipidemic subjects. Metabolism 2012;61(1): 76–83.
44. Faghihnia N, Tsimikas S, Miller ER, Witztum JL, Krauss RM. Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. J Lipid Res 2010;51(11): 3324–30.
45. LeCheminant JD, Smith BK, Westman EC, Vernon MC, Donnelly JE. Comparison of a reduced carbohydrate and reduced fat diet for LDL, HDL, and VLDL subclasses during 9-months of weight maintenance subsequent to weight loss. Lipids Health Dis 2010;9(1):54.
46. Jones JL, Comperatore M, Barona J, Calle MC, Andersen C, McIntosh M, Najm W, Lerman RH, Fernandez ML. A Mediterranean-style, low–glycemic-load diet decreases atherogenic lipoproteins and reduces lipoprotein(a) and oxidized low-density lipoprotein in women with metabolic syndrome. Metabolism 2012;61(3):366–72.
47. Gerber PA, Berneis K. Regulation of low-density lipoprotein subfractions by carbohydrates. Curr Opin Clin Nutr Metab Care 2012;15(4):381–5.
48. Falkenhain K, Roach LA, McCreary S, McArthur E, Weiss EJ, Francois ME, Little JP. Effect of carbohydrate-restricted dietary interventions on LDL particle size and number in adults in the context of weight loss or weight maintenance: a systematic review and meta-analysis. Am J Clin Nutr 2021;114(4):1455–66.
49. Kannel WB, Feinleib M, McNAMARA PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. Am J Epidemiol 1979;110(3):281–90.
50. Ridker PM, Chasman DI, Zee RYL, Parker A, Rose L, Cook NR, Buring JE. Rationale, design, and methodology of the Women's Genome Health Study: a genome-wide association study of more than 25 000 initially healthy American women. Clin Chem 2008;54(2): 249–55.
51. Lee I-M, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study. A randomized controlled trial. JAMA 2005;294(1):56–65.
52. Kathiresan S, Otvos JD, Sullivan LM, Keyes MJ, Schaefer EJ, Wilson PWF, et al. Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study. Circulation 2006;113(1):20–29.
53. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18(6):499–502.
54. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. Clin Lab Med 2006;26(4):847–70.
55. Ordovas JM, Peterson JP, Santaniello P, Cohn JS, Wilson PW, Schaefer EJ. Enzyme-linked immunosorbent assay for human plasma apolipoprotein B. J Lipid Res 1987;28(10):1216–24.
56. Schaefer EJ, Ordovas JM. Metabolism of apolipoproteins A-I, A-II, and A-IV. Methods Enzymol 1986;129:420–43.
57. Campos E, Nakajima K, Tanaka A, Havel RJ. Properties of an apolipoprotein E-enriched fraction of triglyceride-rich lipoproteins isolated from human blood plasma with a monoclonal antibody to apolipoprotein B-100. J Lipid Res 1992;33(3):369–80.
58. Nakajima K, Saito T, Tamura A, Suzuki M, Nakano T, Adachi M, Tanaka A, Tada N, Nakamura H, Campos E. Cholesterol in remnant-like lipoproteins in human serum using monoclonal anti apo B-100 and anti apo A-I immunoaffinity mixed gels. Clin Chim Acta 1993;223(1-2):53–71.
59. McNamara JR, Shah PK, Nakajima K, Cupples LA, Wilson PWF, Ordovas JM, Schaefer EJ. Remnant lipoprotein cholesterol and triglyceride reference ranges from the Framingham Heart Study. Clin Chem 1998;44(6):1224–32.
60. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135(10):1114–26.
61. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH,Speizer FE.Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122(1):51–65.
62. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18(4):858–67.
63. Feskanich D, Rimm EB,Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, Willett WC. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93(7):790–6.
64. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1(6):466–73.
65. Kannel WB, Sorlie P. Some health benefits of physical activity: the Framingham study. Arch Intern Med 1979;139(8):857–61.
66. Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Corsano KA, Rosner B, Kriska A, Willett WC. Reproducibility and validity

of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23(5):991–9.

67. Qi Q, Chu AY, Kang JH, Jensen MK, Curhan GC, Pasquale LR, Ridker PM, Hunter DJ, Willett WC, Rimm EB, et al. Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med 2012;367(15):1387–96.
68. Haslam DE, Peloso GM, Guirette M, Imamura F, Bartz TM, Pitsillides AN, Wang CA, Li-Gao R, Westra JM, Pitkänen N, et al. 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. Circ Genom Precis Med 2021;14(4):e003288.
69. Albert MA, Durazo EM, Slopen N, Zaslavsky AM, Buring JE, Silva T, Chasman DI, Williams DR. Study design: cumulative psychological stress and cardiovascular disease risk in middle aged and older women: rationale, design and baseline characteristics. Am Heart J 2017;192: 1–12.
70. Becker BJ, Wu M-J. The synthesis of regression slopes in meta-analysis. Statistical Science 2007;22(3):414–29.
71. Sankoh AJ, Huque MF, Dubey SD. Some comments on frequently used multiple endpoint adjustment methods in clinical trials. Stat Med 1997;16(22):2529–42.
72. Duffey KJ, Gordon-Larsen P, Steffen LM, Jacobs DR, Popkin BM. Drinking caloric beverages increases the risk of adverse cardiometabolic outcomes in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Clin Nutr 2010;92(4):954–9.
73. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non–HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA 2005;294(3):326–33.
74. Levin MG, Zuber V, Walker VM, Klarin D, Lynch J, Malik R, Aday AW, Bottolo L, Pradhan AD, Dichgans M, et al. Prioritizing the role of major lipoproteins and subfractions as risk factors for peripheral artery disease. Circulation 2021;144(5):353–64.
75. McNamara JR, Shah PK, Nakajima K, Cupples LA, Wilson PWF, Ordovas JM Schaefer EJ Remnant-like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study. Atherosclerosis 2001;154(1):229–36.
76. Joshi PH, Khokhar AA, Massaro JM, Lirette ST, Griswold ME, Martin SS, et al. Remnant lipoprotein cholesterol and incident coronary heart disease: the Jackson Heart and Framingham Offspring Cohort studies. J Am Heart Assoc Cardiovasc Cerebrovasc Dis 2016;5:e002765.
77. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol 2013;61(4):427–36.
78. Mora S. Advanced lipoprotein testing and subfractionation is not (yet) ready for routine clinical use. Circulation 2009;119(17):2396–404.
79. Mora S, Otvos JD, Rosenson RS, Pradhan A, Buring JE, Ridker PM. Lipoprotein particle size and concentration by nuclear magnetic resonance and incident type 2 diabetes in women. Diabetes 2010;59(5):1153–60.
80. Sokooti S, Flores-Guerrero JL, Heerspink HJL, Connelly MA, Bakker SJL, Dullaart RPF. Triglyceride-rich lipoprotein and LDL particle subfractions and their association with incident type 2 diabetes: the PREVEND study. Cardiovasc Diabetol 2021;20:(1):156.
81. Prats-Uribe A, Sayols-Baixeras S, Fernández-Sanlés A, Subirana I, Carreras-Torres R, Vilahur G, et al. High-density lipoprotein characteristics and coronary artery disease: a Mendelian randomization study. Metabolism 2020;112:154351.
82. Teis A, Cediel G, Amigó N, Julve J, Aranyó J, Andrés-Cordón J, et al. Particle size and cholesterol content of circulating HDL correlate with cardiovascular death in chronic heart failure. Sci Rep 2021;11(1):3141.
83. Liou L, Kaptoge S. Association of small, dense LDL-cholesterol concentration and lipoprotein particle characteristics with coronary heart disease: a systematic review and meta-analysis. PLoS One 2020;15(11):e0241993.
84. Superko HR. Advanced lipoprotein testing and subfractionation are clinically useful. Circulation 2009;119(17):2383–95.
85. Galeano NF, Al-Haideri M, Keyserman F, Rumsey SC, Deckelbaum RJ. Small dense low density lipoprotein has increased affinity for LDL receptor-independent cell surface binding sites: a potential mechanism for increased atherogenicity1. J Lipid Res 1998;39(6):1263–73.
86. Björnheden T, Babyi A, Bondjers G, Wiklund O. Accumulation of lipoprotein fractions and subfractions in the arterial wall, determined in an in vitro perfusion system. Atherosclerosis 1996;123(1-2):43–56.
87. Aeberli I, Zimmermann MB, Molinari L, Lehmann R, l'Allemand D, Spinas GA, Berneis K. Fructose intake is a predictor of LDL particle size in overweight schoolchildren. Am J Clin Nutr 2007;86(4):1174–8.
88. Hernáez Á, Castañer O, Elosua R, Pintó X, Estruch R, Salas-Salvadó J, Corella D, Arós F, Serra-Majem L, Fiol M, et al. Mediterranean diet improves high-density lipoprotein function in high-cardiovascular-risk individuals: a randomized controlled trial. Circulation 2017;135:633–43.
89. Millar SR, Navarro P, Harrington JM, Shivappa N, Hébert JR, Perry IJ, Phillips CM. Comparing dietary score associations with lipoprotein particle subclass profiles: a cross-sectional analysis of a middle-to older-aged population. Clin Nutr 2021;40(7):4720–9.
90. Kaikkonen JE, Würtz P, Suomela E, Lehtovirta M, Kangas AJ, Jula A, Mikkilä V, Viikari JSA, Juonala M, Rönnemaa T, et al. Metabolic profiling of fatty liver in young and middle-aged adults: cross-sectional and prospective analyses of the Young Finns Study. Hepatology 2017;65(2):491–500.
91. Seshadri P, Iqbal N, Stern L, Williams M, Chicano KL, Daily DA, McGrory J, Gracely EJ, Rader DJ, Samaha FF. A randomized study comparing the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and C-reactive protein levels in patients with severe obesity. Am J Med 2004;117(6):398–405.
92. Wood RJ, Volek JS, Liu Y, Shachter NS, Contois JH, Fernandez ML. Carbohydrate restriction alters lipoprotein metabolism by modifying VLDL, LDL, and HDL subfraction distribution and size in overweight men. J Nutr 2006;136(2):384–9.
93. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. Am J Prev Med 2004;27(3):205–10.
94. Tukey JW, Ciminera JL, Heyse JF. Testing the statistical certainty of a response to increasing doses of a drug. Biometrics 1985;41(1): 295–301.