ORIGINAL RESEARCH

Beverage Consumption and Longitudinal Changes in Lipoprotein Concentrations and Incident Dyslipidemia in US Adults: The Framingham Heart Study

Danielle E. Haslam, PhD; Gina M. Peloso, PhD; Mark A. Herman, MD; Josée Dupuis, PhD; Alice H. Lichtenstein, DSc; Caren E. Smith, MS, DVM; Nicola M. McKeown, PhD

***Background*—**Limited data are available on the prospective relationship between beverage consumption and plasma lipid and lipoprotein concentrations. Two major sources of sugar in the US diet are sugar-sweetened beverages (SSBs) and 100% fruit juices. Low-calorie sweetened beverages are common replacements.

***Methods and Results*—**Fasting plasma lipoprotein concentrations were measured in the FOS (Framingham Offspring Study) (1991–2014; N=3146) and Generation Three (2002–2001; N=3584) cohorts. Beverage intakes were estimated from food frequency questionnaires and grouped into 5 intake categories. Mixed-effect linear regression models were used to examine 4-year changes in lipoprotein measures, and Cox proportional hazard models were used to estimate hazard ratios for incident dyslipidemia, adjusting for potential confounding factors. We found that regular (>1 serving per day) versus low (<1 serving per month) SSB consumption was associated with a greater mean decrease in high-density lipoprotein cholesterol (β±standard error −1.6±0.4 mg/dL; P_{trend}<0.0001) and increase in triglyceride (β±standard error: 4.4±2.2 mg/dL; P_{trend}=0.003) concentrations. Long-term regular SSB consumers also had a higher incidence of high triglyceride (hazard ratio, 1.52; 95% CI, 1.03–2.25) compared with low consumers. Although recent regular low-calorie sweetened beverage consumers had a higher incidence of high non–high-density lipoprotein cholesterol (hazard ratio, 1.40; 95% CI, 1.17–1.69) and low-density lipoprotein cholesterol (hazard ratio, 1.27; 95% CI, 1.05–1.53) concentrations compared with low consumers, cumulative average intakes of low-calorie sweetened beverages were not associated with changes in non–high-density lipoprotein cholesterol, low-density lipoprotein cholesterol concentrations, or incident dyslipidemias.

***Conclusions*—**SSB intake was associated with adverse changes in high-density lipoprotein cholesterol and triglyceride concentrations, along with a higher risk of incident dyslipidemia, suggesting that increased SSB consumption may contribute to the development of dyslipidemia. **(*J Am Heart Assoc*. 2020;9:e014083. DOI: 10.1161/JAHA.119.014083.)**

Key Words: carbohydrates • dyslipidemia • fruit juice • low-calorie sweetened beverages • nutrition • observational study • sugar-sweetened beverages

An estimated 40% to 50% of adults in the United States can be classified as having dyslipidemia,[1] characterized by high triglyceride, high low-density lipoprotein cholesterol (LDL-C), and/or low high-density lipoprotein cholesterol (HDL-C) concentrations, predisposing them to increased risk for cardiovascular disease (CVD).[2] Thus, managing patients' blood lipid concentrations is a major focus for health professionals.[3] Dietary modification offers a promising strategy to both prevent and treat dyslipidemia.[4]

From the Nutritional Epidemiology Program, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA (D.E.H., N.M.M.); Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA (G.M.P., J.D.); Division of Endocrinology, Metabolism, and Nutrition, Department of Medicine, Duke University School of Medicine, Durham, NC, USA (M.A.H.); National Heart, Lung, and Blood Institute's Framingham Heart Study and Population Sciences Branch, Framingham, MA, USA (J.D.); Cardiovascular Nutrition Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA (A.H.L.); Nutrition and Genomics Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA (C.E.S.).

Accompanying Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014083

This study was presented as an abstract at Nutrition 2019, June 8-11, 2019, in Baltimore, MD.

Correspondence to: Nicola M McKeown, PhD, Nutrition Epidemiology Program, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston MA 02111. Email: nicola.mckeown@tufts.edu

Received July 25, 2019; accepted September 24, 2019.

Clinical Perspective

What Is New?

- In this cohort of US adults followed for a mean of 12.5 years, regular consumption of sugar-sweetened beverages, which includes sodas and fruit drinks, was associated with adverse changes in lipoprotein concentrations and increased incidence of dyslipidemias related to triglyceride and high-density lipoprotein cholesterol.
- While we observed some adverse changes in lipoprotein concentrations and incidence of dyslipidemia with recent consumption of low-calorie sweetened beverages, which includes naturally and artificially sweetened "diet" drinks, we observed no significant relationship between long-term low-calorie sweetened beverage consumption and incidence of dyslipidemias.
- Our study suggests that regular consumption of 100% fruit juice up to 1.5 servings per day was not associated with adverse changes in lipoprotein concentrations or incident dyslipidemias, but further research is warranted.

What Are the Clinical Implications?

- Our results support the recommendations to limit sugar-sweetened beverage intake and suggest that dyslipidemia may be one mechanistic pathway whereby sugar-sweetened beverage intake may increase cardiovascular disease risk.
- Dietary patterns low in sugar-sweetened beverages may contribute to maintenance of favorable plasma lipoprotein profiles.
- Consumption of low-calorie sweetened beverages and limited amounts of 100% fruit juice (up to 1.5 servings per day) do not appear to adversely influence lipoprotein concentrations.

Evidence from observational studies suggests that there is a positive association between added sugar intake and CVD risk,[5,6] particularly in the form of sugar-sweetened beverages (SSBs).[7] SSBs, such as sodas, fruit-flavored drinks, sports drinks, and presweetened coffees and teas, are a significant source of added sugars in the diets of US adults and a major contributor to excess energy intake.[8] One potential mechanism by which SSBs may increase the risk for CVD is through the development of dyslipidemia. Animal and human intervention trials suggest that consumption of large amounts of sugar, particularly those high in fructose, can rapidly induce dyslipidemia.[9–11] Several cross-sectional studies have observed that higher SSB consumption is adversely associated with lipid concentrations.[12–16] In the FHS (Framingham Heart Study), a higher incidence of hypertriglyceridemia and low HDL-C concentrations were observed among men with higher soft drink consumption.[17] In that report, soft drinks included both SSBs and low-calorie sweetened beverages (LCSBs).

One hundred percent fruit juices (FJs) and LCSBs are commonly used as alternative "healthier" beverages to SSBs.[18,19] Evidence from randomized controlled trials and observational studies is mixed for the association between LCSB[16,20,21] and FJ consumption[22,23] and CVD. These potential differences in physiological effects of SSBs, LCSBs, and FJs underscore the necessity to examine these beverage consumption exposures separately, which is in contrast to the aforementioned study among FHS participants[17] that combined both SSBs and LCSBs into one "soft drink" exposure.

The objective of the present study was to examine the association of SSB, LCSB, and FJ consumption with longitudinal changes in concentrations of triglyceride, LDL-C, HDL-C, and non–HDL-C in the FOS (Framingham Offspring Study) and GEN3 (Generation Three) cohorts. We hypothesized that greater SSB consumption would associate with unfavorable longitudinal changes in lipoprotein concentrations and incident dyslipidemia, and to a greater extent than LCSBs and FJs.

Methods

Study Participants

The FHS is a long-standing, prospective cohort study in Framingham, Massachusetts, that began in 1948. Data from FOS[24] at examination 5 (1991–1995; n=3799), examination 6 (1995–1998; n=3532), examination 7 (1998–2001; n=3539), examination 8 (2005–2008; n=3021), and examination 9 (2011–2014; n=2430), and GEN3[25] at examination 1 (2002–2005; n=4095) and examination 2 (2008–2011; n=3411), were used in the current study for up to 23 years of follow-up (mean follow-up, 12.5 years). In each cohort and at each examination cycle within FHS, participants underwent a detailed medical history, physical examination, and standard laboratory tests. Participants also provided demographic, diet, lifestyle, and medical history data via standard questionnaires. All participants provided written informed consent before study participation. All study protocols and procedures were approved by the institutional review boards for human research at Boston University Medical Campus and Tufts University Health Sciences. Requests by researchers on how to access the data for the purposes of reproducing the results can be made to the corresponding author.

Assessment of Lipid Outcomes

Fasting blood samples from FHS participants were used to measure plasma HDL-C (mg/dL), triglyceride (mg/dL), and total cholesterol (TC) (mg/dL) concentrations using standard assays at each examination. LDL-C concentrations were calculated according to the Friedewald equation (LDL-C=TC−HDL-C− triglyceride/5), and set to missing if

triglyceride concentrations were ≥400 mg/dL.[26] Non–HDL-C concentrations were calculated as TC minus HDL-C concentrations. Non–HDL-C concentrations were explored because observational studies have shown them to be more predictive of cardiovascular events than individual lipid concentrations alone.[27,28] Changes in each of these lipid measurements were calculated as the difference between 2 consecutive examinations. To correct for unequal time intervals between examinations, changes in lipoprotein concentrations were normalized to 4-year changes.

Four dyslipidemia outcomes were defined as: LDL-C concentrations ≥160 mg/dL or use of LDL-C–lowering medications; HDL-C concentrations <40 mg/dL in men or <50 mg/dL in women; triglyceride concentrations ≥175 mg/dL; and non–HDL-C concentrations ≥190 mg/dL or use of LDL-C–lowering medications. The cut points for LDL-C, HDL-C, triglyceride, and non–HDL-C concentrations are established cutoffs for CVD risk-enhancing factors in the 2018 Guideline on the Management of Blood Cholesterol.[4]

A total of 3146 FOS and 3584 GEN3 participants provided diet and lipid measures at baseline (examination 5 in FOS and examination 1 in GEN3 in this study). A total of 3182 FOS and 2805 GEN3 participants provided diet and lipid measures for at least 2 consecutive examination periods from examinations 5 to 9 in FOS and 1 to 2 in GEN3. FOS participants contributed multiple observations if diet and lipid measures were provided at >2 consecutive examination periods. Participants were excluded from each cohort if the change in lipoprotein concentrations was not within 4 SDs of the mean 4-year change within the respective cohort. A total of 58 FOS and 5 GEN3 participants were excluded because they were missing change in all lipoprotein concentration data, reducing the sample size to 3124 in the FOS cohort and 2800 in the GEN3 cohort for analysis of change in lipoprotein concentrations (a maximum of 11 659 observations in the pooled analysis). These criteria resulted in different sample sizes for each lipoprotein outcome: LDL-C (8598 observations among 3082 FOS participants and 2744 GEN3 participants), triglyceride (8818 observations among 3118 FOS participants and 2776 GEN3 participants), HDL-C (8787 observations among 3115 FOS participants and 2784 GEN3 participants), and non–HDL-C (8734 observations among 3111 FOS participants and 2777 GEN3 participants).

The analysis of the development of dyslipidemia was conducted in a smaller sample as participants were excluded from the analysis for the following reasons: prevalent dyslipidemia at baseline, use of LDL-C–lowering medications (for lipid outcomes that include LDL-C concentrations), or lack of follow-up data. Missing data for covariates were carried forward from the previous examination. After these exclusions, the sample sizes were as follows for the development of dyslipidemia: FOS cohort based on LDL-C (n=2161), HDL-C (n=1703), triglyceride (n=2116), and non–HDL-C (n=2205); and GEN3 cohort based on LDL-C (n=2377), HDL-C (n=2084), triglyceride (n=2426), and non–HDL-C (n=2400).

Beverage Consumption

Usual dietary intakes in the past year were estimated at each examination using the Harvard 126-item semi-quantitative food-frequency questionnaire (FFQ).[29] The FFQ was mailed to participants to be completed at home and returned at the study appointment. The FFQ consisted of a list of foods with standard serving sizes and a selection of 9 frequency categories ranging from none or <1 serving per month to ≥6 servings per day. Dietary information was considered valid only if reported energy intake was as follows: ≥600 kcal/d for both men and women; <4000 kcal/d for women; <4200 kcal/d for men; and if ≤13 food items were left blank on the FFQ. The relative validity of the FFQ in FHS has been examined for both nutrients and foods in men and women in other cohorts.[29,30]

Estimates of SSB consumption included the following categories: (1) Coke, Pepsi, or other cola with sugar; (2) caffeine-free Coke, Pepsi, or other cola with sugar; (3) other carbonated beverage with sugar (eg, 7Up, ginger ale); and (4) Hawaiian Punch, lemonade, or other noncarbonated fruit drinks. Estimates of FJ consumption included the following categories: (1) orange juice; (2) grapefruit juice; (3) apple juice or cider; and (4) other 100% FJs. Estimates of LCSB consumption included the following categories: (1) low-calorie cola, eg, Tab with caffeine; (2) low-calorie caffeine-free cola, eg, Pepsi Free; and (3) other low-calorie carbonated beverage, eg, Fresca, Diet 7Up, and diet ginger ale. The low-calorie sweeteners found in these beverages could include either naturally or artificially derived sweeteners that provide either no or few (<40 per serving) calories (kcal). One serving of SSB or LCSB is equivalent to 12 fluid ounces, and one serving FJ is equivalent to 8 fluid ounces.

Covariate Assessment

Education was assessed by asking the highest degree or level of school the participant had completed (obtained in FOS at examination 8 and GEN3 at examination 1), and participants were grouped into 4 categories (less than high school, high school, some college, graduated college). Participants self-reported whether they had taken medication for high blood cholesterol since their last examination, and participants were classified as having diabetes mellitus if their fasting blood glucose was ≥126 mg/dL or they were under current treatment for diabetes mellitus. In the GEN3 cohort, an additional criterion was applied where participants were classified as having diabetes mellitus if their nonfasting blood glucose was ≥200 mg/dL. Participants also completed a

standardized physical examination, which included measurements of height, weight, and waist circumference (measured at the level of the umbilicus in a standing position). Body mass index (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 grams per day. Current smokers were defined as participants who reported smoking regularly in the past year. Physical activity was evaluated through a standard exercise questionnaire.[31] Physical activity was not assessed at examination 6, so the physical activity estimates from examination 5 and examination 7 were used to estimate physical activity during the intervals of examination 5 to 6 and examination 6 to 7, respectively.

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. Potential confounding through other dietary components was explored through adjustment of individual dietary factors (percent energy from saturated fat and servings per day of fruit, vegetables, whole grains, fish, and nuts/seeds), as well as through a composite diet quality score: the 2015 Dietary Guidelines Adherence Index (2015 DGAI),[32] which reflects adherence to key recommendations based on the 2015 Dietary Guidelines for Americans.

Statistical Analyses

Linear mixed effects regression models were used to examine the association between beverage consumption patterns and 4-year changes in fasting LDL-C, HDL-C, triglyceride, and non–HDL-C concentrations using the *pedigreemm* R package (https://cran.r-project.org). Familial correlation and multiple observations per person were accounted for by adding a random effects term in the model with a covariance structure proportional to the kinship matrix and a random effects term for individual, respectively. To estimate usual dietary intakes and covariate data within each examination interval, the average of the two measurements within the examination intervals was computed. Beverage consumption was explored using 5 categories of intake (<1 serving per month, 1–4 servings per month, 1–2 servings per week, 3–7 servings per week, >1 serving per day), similar to previous studies.[16,33] Three models were performed. Model 1 adjusted for age (continuous), sex (male/female), total energy intake (continuous), baseline lipoprotein concentrations during each interval (continuous), education (less than high school, graduated high school, some college, or graduated college), current smoking status (yes/no), current diabetes mellitus (yes/no), physical activity index (continuous), alcohol (grams per day), use of LDL-C–lowering medication (yes/no; where applicable); model 2 adjusted for model 1 covariates plus servings per day of vegetables, whole fruits, whole grains, nuts/seeds, and seafood, as well as percent energy from saturated fat (continuous) and mutual adjustment for SSBs, LCSBs, and FJs (categorical as continuous). Model 3 adjusted for model 2 covariates plus the change in waist circumference (WC) (continuous), which is a marker of abdominal adiposity and could be in the causal pathway between beverage consumption and development of dyslipidemia. Covariate adjustment did not drastically change the results, so fully adjusted models are presented (model 3). Models were run separately for FOS and GEN3 cohorts, and then data were combined in a pooled analysis (adjusting for cohort). For the presentation of the cross-stratified association of SSBs and LCSBs on lipid concentrations in Figure 1, intakes were grouped as follows: low intake (<1 serving per month), medium intake (1–10 servings per month), and high intake (>3 servings per week). The joint association of SSBs and LCSBs was modeled as the interaction of the low/medium/high categories of intake among participants, and the models were compared using likelihood ratio testing with and without multiplicative interaction terms.

For analysis of the development of dyslipidemia, we applied Cox proportional hazards models with time-varying covariates and follow-up time as the underlying time scale to estimate hazard ratios (HRs) and 95% CIs of dyslipidemia for beverage consumption using the *survival* R package (https://cran.r-project.org). Given that the GEN3 participants were younger and followed for only 1 examination, the main analyses were performed in the FOS cohort and validation was performed in the GEN3 cohort. Family structure and multiple observations were accounted for using a robust standard error and clustering on family and individual, respectively. We tested the proportional hazard assumption by examining the scaled Schoenfeld residuals over time, and the assumption was unlikely violated. Beverage exposure was estimated as "recent" intake (ie, intake at the examination before developing dyslipidemia) and as "cumulative" average intake. In the FOS, cumulative mean intake was calculated as the mean intake reported at examinations up to and including the examination of dyslipidemia diagnosis (eg, fifth and sixth examinations for those who developed dyslipidemia by the sixth examination; the fifth, sixth, and seventh examinations for those who developed dyslipidemia by the seventh examination). For those who did not develop dyslipidemia during follow-up, the cumulative mean was calculated across all available examination data (examination 5 to examination 8). Beverage intakes were grouped in 5 categories in the same manner as the analysis of changes in lipoprotein concentrations, and we examined the linear trend by modeling beverage consumption categories as a continuous variable.

Multivariable Cox proportional hazards models were adjusted for potential confounders, which were updated at each examination cycle. Models were adjusted for age

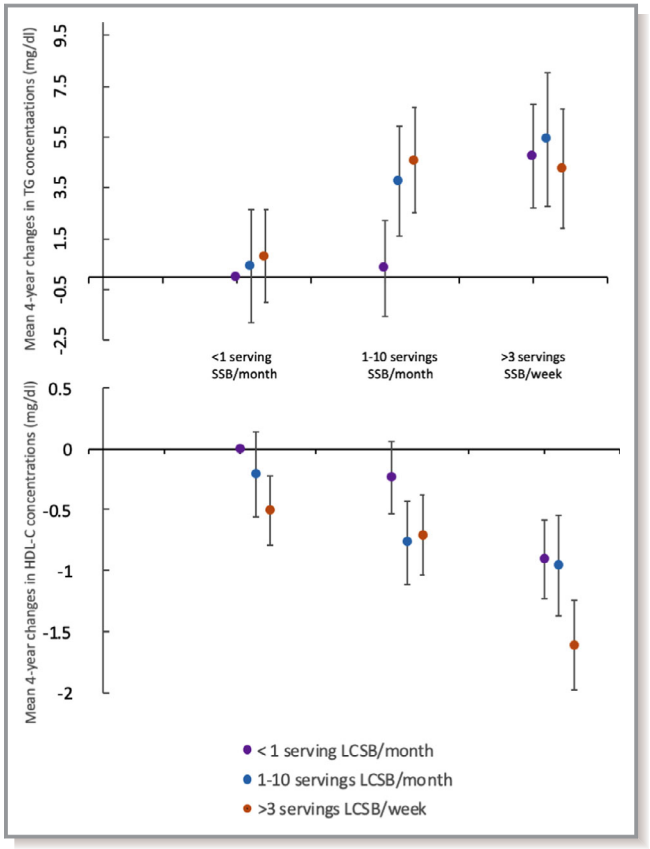

Figure 1. Relationship between cross-stratified sugar-sweetened beverage (SSB) and low-calorie sweetened beverage (LCSB) intakes for mean 4-year changes in high-density lipoprotein cholesterol (HDL-C) and triglyceride concentrations among Framingham cohorts (pooled data). Participants in the highest categories of both SSB and LCSB intakes had mean 4-year increases in triglyceride concentrations 4.3 mg/dL greater (β±standard error: 4.3±2.4 mg/dL; P=0.07) and mean 4-year decreases in HDL-C concentrations 1.6 mg/dL greater (β±SE: −1.6±0.4 mg/dL; P<0.0001) compared with those in the lowest categories of both SSB and LCSB intakes. There was little evidence of a significant interaction between SSB and LCSB intake (P>0.01 for the interaction). All changes in lipoprotein concentrations were adjusted for age, cohort, sex, total energy, baseline lipoprotein concentration, education, current smoking status, current diabetes mellitus status, physical activity index, alcohol intake, percent energy from saturated fat, change in waist circumference, and servings per day of vegetables, whole fruits, 100% fruit juice, whole grains, nuts/seeds, and seafood. Multivariable-adjusted β estimates for additional comparisons are presented in Table S2. Vertical error bars indicate standard errors for regression coefficients.

(continuous), sex (male/female), total energy (continuous), education (less than high school, graduated high school, some college, or graduated college), current smoking status (yes/no), current diabetes mellitus status (yes/no), physical activity index (continuous), alcohol (grams per day), WC (continuous), servings per day of vegetables, whole fruits, whole grains, nuts/seeds, and seafood, as well as percent energy from saturated fat (continuous) and mutual adjustment for SSBs, LCSBs, and FJs (categorical as continuous).

Secondary Analyses

For both analyses, likelihood ratio testing comparing models with and without multiplicative interaction terms were used to assess effect modification by sex (male/female) and BMI (<25 kg/m^2; 25–29.9 kg/m^2; ≥30 kg/m^2). No significant interactions were observed; thus, data are not stratified in the main analysis. Several sensitivity analyses were conducted to examine the consistency of the associations. To minimize reverse causation, analyses were performed eliminating those who developed diabetes mellitus or began taking lipid-lowering medications. To evaluate whether overall diet quality was adequately controlled for in our models, the dietary covariates (vegetables, whole fruits, whole grains, nuts/seeds, seafood, and saturated fat) were replaced with 2015 DGAI (calculated without the added sugar component).[32] Furthermore, we substituted adjustment for WC with BMI (continuous) and adjusted for both WC and BMI to consider whether overall adiposity, compared with abdominal adiposity, changed the reported associations.

All statistical analyses were performed using either SAS (version 9.4 or higher; SAS Institute) or R (version 3.1 or higher; https://cran.r-project.org) statistical software. All reported P values are 2-sided, and results were considered statistically significant at a Bonferroni-corrected P<0.01 (0.05/4 outcomes).

Results

Table 1 shows the characteristics of participants for each cohort and examination cycle. Mean age (±SD) at baseline was 54.8 years (±9.8 years) among FOS participants and 40.3 years (±8.8 years) among GEN3 participants. Participants smoked less, achieved more education, had increased BMI and WC, and a higher percent was classified as having diabetes mellitus and took LDL-C–lowering medications with each subsequent examination cycle. Lipoprotein concentrations (LDL-C, HDL-C, triglyceride, and non–HDL-C) improved across examination cycles. Differences in dietary intakes across examinations were not substantial (<0.5 servings per day), but statistically significant P for trends were observed. We observed a slight decrease in consumption of SSBs, FJs, and LCSBs among both FOS (1991–2008) and GEN3 (2002–2011) participants across examination cycles. Among FOS participants, mean intakes of total energy, vegetables, and seafood remained similar through the examination cycles, whereas increases were observed for energy from saturated

Table 1. Characteristics of Participants by Cohort and Examination Cycle.

	Framingham Offspring Study Cohort						Generation 3 Cohort		
	Examination 5: 1991–1995	Examination 6: 1995–1998	Examination 7: 1998–2001	Examination 8: 2005–2008	Examination 9: 2011–2014	*P* Trend*	Examination 1: 2002–2005	Examination 2: 2008–2011	*P* Value*
No.	3146	3008	2697	2529	2204		3584	3132	
Age, y	54.8 (9.8)	58.7 (9.6)	61 (9.4)	66.3 (8.9)	71.2 (8.7)	<0.0001	40.3 (8.8)	46.6 (8.7)	<0.0001
Women, %	53.1	53.6	54.3	55.2	54.9	0.09	54.3	54.1	0.88
Current smoker, %	19.1	15.1	12.0	8.4	5.8	0.002	14.5	9.9	<0.0001
Education (% some college)	60.5	62.3	64.6	66.3	68.9	<0.0001	85.3	84.5	0.75
BMI, kg/m^2	27.4 (5.0)	27.9 (5.1)	28.2 (5.3)	28.2 (5.4)	28.4 (5.4)	<0.0001	26.8 (5.5)	28.0 (5.8)	<0.0001
WC, in	36.5 (5.6)	38.4 (5.3)	39.3 (5.5)	39.9 (5.7)	40.1 (5.5)	<0.0001	36.5 (5.9)	38.1 (6.0)	<0.0001
Physical activity index	34.7 (6.1)	NA	37.9 (6.3)	35.3 (5.4)	34.8 (5.8)	0.08	37.3 (7.7)	36.4 (6.6)	<0.0001
LDL-C, mg/dL	126 (33)	127 (33)	120 (33)	105 (31)	99 (31)	<0.0001	112 (32)	104 (31)	<0.0001
HDL-C, mg/dL	50 (15)	51 (16)	54 (17)	58 (18)	62 (19)	<0.0001	55 (16)	60 (18)	<0.0001
Triglyceride, mg/dL†	125 (92)	119 (89)	117 (87)	104 (69)	103 (63)	<0.0001	97 (73)	97 (66)	0.16
Non–HDL-C	262 (81)	258 (78)	250 (77)	220 (68)	211 (63)	<0.0001	220 (76)	212 (71)	<0.0001
Diabetes mellitus, %	7.1	9.5	10.8	13.2	14.5	<0.0001	2.9	4.7	<0.0001
LDL-C–lowering medication users, %	7.3	13.0	20.7	42.9	50.1	<0.0001	6.8	16.2	<0.0001
Dietary intakes									
Total energy, kcal/d	1862 (612)	1846 (607)	1827 (591)	1866 (626)	NA	0.33	2055 (667)	1990 (628)	<0.0001
Saturated fat, % total energy	10.4 (2.9)	10.1 (2.8)	10.7 (2.9)	11.1 (2.7)	NA	<0.0001	11.5 (2.9)	10.5 (2.5)	<0.0001
Alcohol, g/d†	1.24 (13.3)	1.19 (13)	1.14 (12.9)	1.20 (13.9)	NA	0.001	1.9 (12.8)	2.3 (14.5)	0.006
Whole fruits, servings per d†	0.66 (1.09)	0.77 (1.12)	0.79 (1.13)	0.78 (1.13)	NA	<0.0001	0.64 (1.06)	0.54 (0.92)	<0.0001
Vegetables, servings per d†	1.74 (1.22)	1.75 (1.23)	1.75 (1.26)	1.75 (1.24)	NA	0.28	1.77 (1.37)	1.60 (1.20)	<0.0001
Whole grain, servings per d†	0.62 (1.31)	0.62 (1.25)	0.65 (1.34)	0.83 (1.40)	NA	<0.0001	0.71 (1.21)	0.17 (0.44)	<0.0001
Nuts/seeds, servings per d†	0.16 (0.36)	0.14 (0.36)	0.18 (0.50)	0.36 (0.86)	NA	<0.0001	0.28 (0.64)	0.11 (0.36)	<0.0001
Seafood, servings per d†	0.29 (0.37)	0.27 (0.33)	0.29 (0.37)	0.30 (0.37)	NA	0.68	0.26 (0.38)	0.21 (0.28)	<0.0001
SSBs, servings per d†,‡	0.09 (0.49)	0.09 (0.44)	0.08 (0.42)	0.05 (0.20)	NA	<0.0001	0.12 (0.56)	0.08 (0.42)	<0.0001
100% FJ, servings per d†,‡	0.36 (0.93)	0.37 (0.99)	0.37 (0.92)	0.23 (0.93)	NA	<0.0001	0.31 (0.87)	0.21 (0.79)	<0.0001
LCSBs, servings per d†,‡	0.10 (0.85)	0.09 (0.78)	0.08 (0.70)	0.07 (0.49)	NA	<0.0001	0.08 (0.70)	0.06 (0.42)	<0.0001

Maximum available observations for analyses. Values are means (SDs) unless otherwise indicated. Means are compared with the use of general linear models. BMI indicates body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not available; WC, waist circumference.

**P* trend (Framingham Offspring Study cohort) or *P* value (Generation 3 cohort) for examination follow-up number.

†Geometric mean (interquartile range).

‡One serving of sugar-sweetened beverages (SSBs) or low-calorie sweetened beverages (LCSBs) is equivalent to 12 fluid ounces, and 1 serving of 100% fruit juice (FJ) is equivalent to 8 fluid ounces.

DOI: 10.1161/JAHA.119.014083

fat (percent), and servings of whole fruits, whole grains, and nuts/seeds. Trends were different among GEN3 participants where decreases were observed in total energy intake, percent energy from saturated fat, and consumption of whole fruits, vegetables, whole grains, nuts/seeds, and seafood.

Table 2 shows that after multivariable adjustment for potential confounding factors and change in abdominal adiposity (covariate model 3), participants in the highest category of SSB intake (>1 serving per day) had a 1.6 mg/dL lower mean 4-year change in HDL-C concentrations [β±standard error (SE): −1.6±0.4 mg/dL; *P* for trend <0.0001], and a 4.4 mg/dL higher mean 4-year change in triglyceride concentrations (β±SE: 4.4±2.2 mg/dL; *P* for trend=0.003) than those in the lowest category of SSB intake (<1 serving per month). Participants in the highest category of LCSB consumption had mean 4-year changes in HDL-C concentrations 0.7 mg/dL lower than those in the lowest intake category (β±SE: −0.7±0.2 mg/dL; *P* for trend=0.001). No other significant associations between beverage consumption and lipid concentrations were observed in fully adjusted models after Bonferroni correction. No significant interactions were observed by cohort for analyses of change in lipoprotein concentrations (cohort-specific results found in Table S1). However, the effect size in the association between SSB consumption and mean 4-year changes in triglyceride concentrations was larger in the GEN3 cohort (β±SE: 10.8±3.5 mg/dL; *P* for trend=0.006) compared with the FOS cohort (β±SE: 2.6±2.9 mg/dL; *P* for trend=0.03). No significant interactions were observed between beverage intakes and sex or BMI. Similar results were observed in sensitivity analyses eliminating those who had diabetes mellitus or took LDL-C–lowering medications, when food groups were substituted for the 2015 DGAI, and when the change in WC was replaced with the change in BMI. Additional analyses of the joint effects of SSB and LCSB revealed that the highest categories of both SSB and LCSB intakes had mean 4-year changes in HDL-C concentration (β±SE: −1.6±0.4 mg/dL; *P*<0.0001) and triglyceride concentration (β±SE: 4.3±2.4 mg/dL; *P*=0.07) compared with the nonconsumers, but no significant interaction was observed (*P*>0.01) (Figure 1 and Table S2).

During a mean 12.5 years of follow-up in the FOS cohort, incident cases of dyslipidemia were as follows: 961 cases of high LDL-C, 319 cases of low HDL-C, 457 cases of high triglyceride, and 975 cases of high non–HDL-C. Multivariable-adjusted HRs for the highest category of beverage consumption (>1 serving per day) compared with the lowest category (<1 serving per month), estimated as both recent and cumulative average intakes, are presented in Figure 2. After adjustment for potential confounders, in the FOS cohort the highest recent SSB consumers had 98% higher incidence of low HDL-C (HR, 1.98; 95% CI, 1.20–3.28 [*P* for trend=0.01]) and 53% higher incidence of high triglyceride (HR, 1.53; 95% CI, 1.01–2.31 [*P* for trend=0.004]) compared with the lowest SSB consumers. For cumulative SSB intake, the risk was attenuated to nonsignificant for incidence of low HDL-C (HR, 1.57; 95% CI, 0.97–2.54 [*P* for trend=0.09]) and high triglyceride (HR, 1.52; 95% CI, 1.03–2.25 [*P* for trend=0.03]), but effect sizes remained similar. The highest recent LCSB consumers had a 40% higher incidence of high non–HDL-C (HR, 1.40; 95% CI, 1.17–1.69 [*P* for trend=0.0002]) and 27% higher incidence of high LDL-C (HR, 1.27; 95% CI, 1.05–1.53 [*P* for trend=0.01]) compared with the lowest LCSB consumers. However, using cumulative average LCSB intakes, these associations were attenuated to nonsignificant (HDL-C: HR, 1.06; 95% CI, 0.74–1.52 [*P* for trend=0.79]; Triglyceride: HR, 1.03, 0.76–1.39 [*P* for trend=0.51]), suggesting that reverse causation may explain the observation of increased risk for dyslipidemias related to LDL-C and non–HDL-C among high LCSB consumers. No other significant differences in incidences of dyslipidemia by category of beverage consumption were observed among FOS participants, although there was suggestion of a lower incidence of high non–HDL-C observed among the highest compared with the lowest FJ consumers (HR, 0.75; 95% CI, 0.56–1.00 [*P* for trend=0.34]). Multivariable-adjusted HRs for additional categories of beverage consumption are presented in Tables S3 and S4. During a mean follow-up of 6.1 years in the GEN3 cohort, results for the association between recent SSB and LCSB consumption were nonsignificant. This could suggest that beverage consumption may play less of a role in the development of dyslipidemia in this younger, lower-risk cohort (Table S5), but could also reflect the lower power attributable to smaller number of cases and less follow-up time in the GEN3 cohort. No significant interactions were observed between beverage intakes and sex or BMI in either cohort. Similar results were observed in sensitivity analyses removing individuals with diabetes mellitus, when food groups were substituted for the 2015 DGAI, and when WC was replaced with BMI.

Discussion

In this population-based, prospective cohort study among US adults, greater consumption of SSB was associated with adverse changes in lipid concentrations over time and development of dyslipidemia. Consumption of SSB was adversely associated with mean 4-year changes in HDL-C and triglyceride concentrations, along with increased incidence of low HDL-C and high triglyceride. Mixed results were observed for LCSB consumption, where cumulative LCSB consumption was not significantly associated with development of dyslipidemia, but we observed some adverse changes

Table 2. Mean Difference in 4-Year Changes in Lipid Traits Across Beverage Consumption Groups in Pooled Analysis for the Framingham Offspring Study and Generation 3*

	Beverage Consumption Groups					
	<1 Serving per mo	1 to 4 Servings per mo	1 to 2 Servings per wk	3 to 7 Servings per wk	>1 Serving per d	*P* for Trend
SSB intake						
No. of observations	4360	2215	1804	2281	999	
Median intake, 12-oz servings per wk	0.1	0.7	1.7	3.9	10.2	
LDL-C	Reference	−0.6 (0.6)	0.7 (0.7)	0.1 (0.6)	1.3 (0.9)	0.25
HDL-C, mg/dL	Reference	−0.3 (0.2)	−0.5 (0.2)	−0.8 (0.2)	−1.6 (0.4)	<0.0001
Triglyceride, mg/dL	Reference	2.1 (1.4)	2.4 (1.6)	4.6 (1.5)	4.4 (2.2)	0.003
Non–HDL-C, mg/dL	Reference	−0.2 (0.7)	−0.5 (0.7)	0.7 (0.7)	1.8 (1.0)	0.11
LCSB intake						
No. of observations	5017	1463	1092	2396	1689	
Median intake, 12-oz servings per wk	0.0	0.7	1.7	4.5	12.3	
LDL-C	Reference	0.5 (0.7)	0.8 (0.7)	−0.2 (0.6)	−0.2 (0.6)	0.71
HDL-C, mg/dL	Reference	−0.3 (0.2)	−0.4 (0.3)	−0.5 (0.2)	−0.7 (0.2)	0.001
Triglyceride, mg/dL	Reference	1.5 (1.6)	1.7 (1.8)	1.8 (1.3)	1.3 (1.6)	0.20
Non–HDL-C, mg/dL	Reference	0.5 (0.7)	0.7 (0.8)	0.04 (0.6)	−0.3 (0.7)	0.78
100% FJ intake						
No. of observations	1429	1368	1556	4710	2596	
Median intake, 8-oz servings per wk	0.2	0.9	2.0	5.0	9.8	
LDL-C	Reference	0.4 (0.8)	0.5 (0.8)	−0.7 (0.7)	−0.9 (0.8)	0.05
HDL-C, mg/dL	Reference	0.23 (0.3)	−0.2 (0.3)	−0.4 (0.3)	−0.1 (0.3)	0.20
Triglyceride, mg/dL	Reference	2.0 (2.0)	0.1 (2.0)	0.2 (1.6)	−3.2 (1.9)	0.06
Non–HDL-C, mg/dL	Reference	0.8 (0.9)	0.4 (0.9)	−0.5 (0.8)	−1.5 (0.9)	0.02

HDL-C indicates high-density lipoprotein cholesterol.

*Maximum number of observations available is 11 659 (Framingham Offspring Study cohort: 8859 observations from 3124 participants; Framingham Generation 3 cohort: 2800 participants), but variation in the number of observations exists for each lipoprotein measure. Values are beta-coefficients and standard errors for beverage intake in multivariable adjusted mixed effects models accounting for family structure and multiple observations, and adjusted for age (continuous), sex (male/female), total energy (continuous), baseline for lipid trait (continuous), education (less than high school, graduated high school, some college, or graduated college), current smoking status (yes/no), current diabetes mellitus status (yes/no), physical activity index (continuous), alcohol (grams per day), use of low-density lipoprotein cholesterol (LDL-C)–lowering medication (yes/no; where applicable), servings per day of vegetables, whole fruits, whole grains, nuts/seeds, and seafood, as well as percent energy from saturated fat (continuous), change in waist circumference, and mutual adjustment for sugar-sweetened beverages (SSBs), low-calorie sweetened beverages (LCSBs), and 100% fruit juice (FJ; categorical as continuous).

in lipoprotein concentrations with recent consumption of LCSB. FJ consumption was not significantly associated with the development of dyslipidemia.

Several cross-sectional studies have observed that higher SSB consumption is associated with lower HDL-C concentrations and higher triglyceride concentrations.[13,15,16] In the only other prospective analysis conducted to date among adults, a higher incidence of hypertriglyceridemia and low HDL-C concentrations among adults with higher soft drink consumption (SSB+LCSB) was seen in the FOS cohort during a follow-up period of about 4 years.[17] Our study strengthens this evidence base by providing prospective data that SSB alone is associated with 4-year changes in triglyceride and HDL-C concentrations, along with the incidence of dyslipidemia during up to 23 years of follow-up (mean of 12.5 years). These results also agree with findings from shorter prospective studies among children and young adults that observed an association between higher SSB intake and adverse changes in triglyceride and HDL-C concentrations.[34–36] Animal and human intervention trials corroborate these observational studies and provide evidence that SSBs may influence lipid concentrations.[9–11,37]

We also assessed the association of LCSB consumption and changes in lipoprotein concentrations and development of dyslipidemia. We found that recent LCSB consumption, but not cumulative consumption, was associated with an increased incidence of dyslipidemias related to LDL-C and non–HDL-C, where the latter results are consistent with the

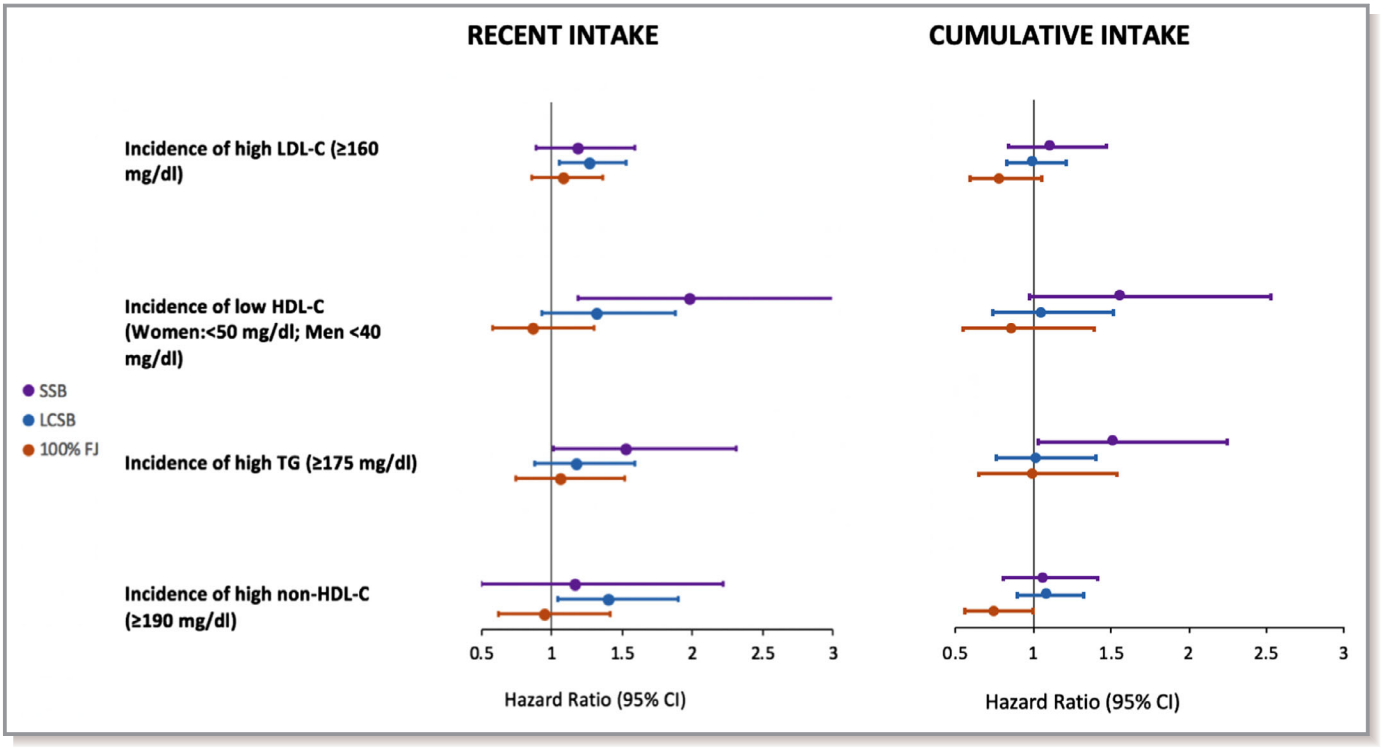

Figure 2. Hazard ratios for development of dyslipidemia among the highest beverage consumers (>1 serving per day) compared with the lowest beverage consumers (<1 serving per month) indicated by recent beverage consumption vs cumulative average of beverage consumption among the Framingham Offspring Study cohort. Participants were followed for a mean of 12.5 years and were free of dyslipidemia at baseline (according to each definition). Thus, maximum sample sizes and case numbers were as follows: low-density lipoprotein cholesterol (LDL-C) (n=2161; 961 cases), high-density lipoprotein cholesterol (HDL-C) (n=1703; 319 cases), triglyceride (TG) (n=2116; 457 cases), and non–HDL-C (n=2205; 975 cases). We defined "recent" beverage intake as intake one examination before development of dyslipidemia and "cumulative" beverage intake as the average beverage intake during the period before development of dyslipidemia. All hazard ratios are adjusted for age, sex, total energy, education, current smoking status, current diabetes mellitus status, physical activity index, waist circumference, alcohol intake, percent energy from saturated fat, and servings per day of vegetables, whole fruits, 100% fruit juice, whole grains, nuts/seeds, and seafood. Horizontal bars indicate 95% CIs. FJ indicates fruit juice; LCSB; low-calorie sweetened beverage; SSB, sugar-sweetened beverage.

null associations observed between LCSB intake and 4-year changes in LDL-C and non–HDL-C concentrations described above. We also observed a modestly larger mean decrease in HDL-C among the highest LCSB consumers compared with the lowest consumers. These findings are consistent with several cross-sectional and short-term randomized control trials that indicate mixed results when examining the association between LCSB intake and lipoprotein concentrations.[15,38–40] A recent meta-analysis of observational studies concluded that LCSB intake was associated with increased risk of metabolic syndrome and cardiovascular events.[21] The potential explanation for these conflicting results is reverse causality, as reported by others,[38,41,42] given that higher consumers of LCSBs may choose to consume these products because they are at a higher risk for disease and switch from SSB to LCSB consumers.[38,42] Additional data examining the joint association of SSB and LCSB consumption in the current study indicate that the association between SSB consumption and mean 4-year changes in triglyceride and HDL-C concentrations is not dependent on LCSB consumption, further supporting the notion that LCSB consumption is not associated with mean changes in lipoprotein concentrations in our data. Thus, the significant association observed between LCSB consumption and incident high non–HDL-C and LDL-C, only observed among recent consumers, is most likely more influenced by reverse causality than LCSB intakes. Because our analysis was limited to examining the relationship between LCSB intake and lipoprotein concentrations and recent research has shown alterations in the gut microbiota and changes in taste preferences[20] with consumption of low-calorie sweeteners, further consideration of the health effects of LCSB is warranted.

The results from our study did not identify a significant relationship between FJ consumption and the risk of dyslipidemia among adults. However, the direction of the association between cumulative FJ consumption and incident dyslipidemia related to non–HDL-C suggests potential risk reduction among the highest consumers compared with the

lowest consumers. This is in contrast to prior work that has identified both positive and negative associations between FJ consumption and risk for cardiometabolic diseases[43–48] and changes in plasma lipoprotein concentrations.[49–51] Dietary patterns high in FJ consumption may be more likely to associate with positive dietary behaviors than dietary patterns high in SSB consumption,[52] which underscores the importance of considering potential residual confounding in interpretation. Additionally, FJs may contain other beneficial nutrients not contained in SSBs or the way people consume FJs may differ from that of SSB (whether it is consumed with meals or not and/or time of consumption). These factors may mitigate potential adverse effects of sugar from FJ on lipids and other cardiometabolic outcomes. Similar to other observations,[23] further research is needed to identify the potential mechanisms by which FJs and SSBs may alter intermediate markers and health outcomes.

Study Limitations

As with all research designs, the proposed study has limitations. The use of self-reported dietary data from a FFQ to infer dietary intakes could potentially lead to misclassification of food and nutrient intakes. While FFQs are able to provide rough estimates of absolute dietary intakes, they are more suited to ranking individuals on relative dietary intakes. Thus, in this study, we categorized individuals based on estimates of beverage consumption. These FFQs did not include an exhaustive list of all potential sources of SSBs, such as consumption of presweetened coffee/tea. Thus, we are not able to capture added sugar intake from these sources in our study. Individuals diagnosed as having high plasma cholesterol concentrations may be advised to change their diet in order to help improve lipid profiles. Thus, this potential reverse causality makes it difficult to infer underlying mechanisms based on results from this study. Even for longitudinal analyses in prospective cohort studies adjusting for a variety of potential demographic, lifestyle, and dietary confounding factors, residual confounding cannot be ruled out. Long-term, randomized controlled intervention studies would be necessary to infer causal mechanisms for how differing beverage consumption patterns might be influencing plasma lipoprotein concentrations. Our assessment of socioeconomic status is limited by our ability to only adjust for education, and not income, which could potentially result in incomplete adjustment for socioeconomic status. Our findings are only generalizable to adults of European descent who are middle-aged or older. It is possible that our findings may be biased because of the differences in age and health status between participants who were excluded from the analyses and those who remained in the study.

Study Strengths

The strengths of the present study include its large sample size, repeated assessments of dietary intakes and covariates, long follow-up period, and prospective design. High-quality observational studies are necessary to inform whether it would be cost-effective to conduct a long-term randomized controlled trial. We were able to account for important lifestyle variables that could confound the association between beverage consumption and lipids such as overall diet quality, physical activity, and alcohol intake. We have also used 2 different types of longitudinal analyses in this study. Because models for the development of dyslipidemia may be biased by reverse causality, the ability to additionally assess the change in lipoprotein concentrations in a larger subset of individuals by beverage consumption category strengthens our findings. Few studies directly compare the health effects of both FJs and LCSBs to those of SSBs, and this comparison can be useful when making recommendations for changes in dietary patterns.

Conclusions

Our findings suggest that SSB consumption is associated with dyslipidemias related to low HDL-C and high triglyceride concentrations. Cumulative LCSB consumption was not associated with risk of dyslipidemia nor was intake of FJ up to 1.5 servings per day. These findings are consistent with current recommendations to limit SSB consumption and emphasize the need for further research to inform recommendations related to LCSB and FJ consumption.

Acknowledgments

Author contributions: The authors' responsibilities were as follows: Haslam, Peloso, Dupuis, Herman, and McKeown: designed research; Haslam, Peloso, Herman, Dupuis, Lichtenstein, Smith, and McKeown: conducted research. Haslam, Peloso, Dupuis, and McKeown: performed statistical analyses; Haslam: wrote the article; Haslam, Peloso, and McKeown had primary responsibility for final content. All authors read and approved the final version of the article.

Sources of Funding

This work is supported by National Institutes of Health (NIH) 5T32HL069772-15 and NIH 2T32CA009001-39 (Haslam), American Heart Association 16CSA28590003 (Haslam, McKeown, and Herman), NIH R01DK100425 (Herman) and K08 HL112845 (Smith), and USDA ARS agreement No. 58-1950-4-003 (McKeown) and 588-1950-9-001 (Lichtenstein). From the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and

Boston University School of Medicine. This project has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. 75N92019D00031.

Disclosures

None.

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Supplemental Material

Table S1. Mean difference in 4-year changes in lipid traits across beverage consumption groups by cohort*

	Beverage Consumption Groups					
	<1 serving/ month	**1-4 servings/ month**	**1-2 servings/ week**	**3-7 servings/ week**	**>1 serving/ day**	***P* for trend**
Sugar-Sweetened Beverage Intake						
Offspring Cohort						
No of Observations	3,497	1,666	1,321	1,705	674	
LDL-C (mg/dl)	Reference	-0.6 (0.7)	1.2 (0.8)	-0.004 (0.8)	0.9 (1.2)	0.44
HDL-C (mg/dl)	Reference	-0.4 (0.3)	-0.5 (0.3)	-0.7 (0.3)	-1.8 (0.4)	0.0002
TG (mg/dl)	Reference	1.8 (1.8)	2.5 (2.0)	4.9 (1.9)	2.6 (2.9)	0.03
Non-HDL-C (mg/dl)	Reference	-0.3 (0.8)	-0.5 (0.9)	0.6 (0.9)	1.0 (1.3)	0.31
Generation 3 Cohort						
No of Observations	867	549	483	576	325	
LDL-C	Reference	0.3 (0.8)	-0.3 (0.9)	1.2 (0.9)	2.4 (1.2)	0.08
HDL-C (mg/dl)	Reference	-0.1 (0.4)	-0.4 (0.4)	-1.0 (0.4)	-0.8 (0.5)	0.01
TG (mg/dl)	Reference	4.5 (2.4)	2.8 (2.6)	5.6 (2.6)	10.8 (3.5)	0.006
Non-HDL-C (mg/dl)	Reference	0.8 (0.9)	-0.6 (1.0)	1.6 (1.0)	3.6 (1.4)	0.02
Low-Calorie Sweetened Beverage Intake						
Offspring Cohort						
No of Observations	3,775	1,112	805	1,890	1,275	
LDL-C (mg/dl)	Reference	0.4 (0.8)	1.1 (0.9)	-0.2 (0.7)	0.1 (0.8)	0.99
HDL-C (mg/dl)	Reference	-0.6 (0.3)	-0.3 (0.3)	-0.5 (0.3)	-0.6 (0.3)	0.03
TG (mg/dl)	Reference	1.0 (2.0)	1.7 (2.3)	1.9 (1.7)	1.3 (2.0)	0.28
Non-HDL-C (mg/dl)	Reference	0.5 (0.9)	1.1 (1.0)	0.1 (0.8)	0.04 (0.9)	0.91
Generation 3 Cohort						
No of Observations	1,242	351	287	506	414	
LDL-C	Reference	0.5 (0.9)	0.3 (1.0)	-0.2 (0.8)	-1.7 (0.9)	0.12
HDL-C (mg/dl)	Reference	0.7 (0.4)	-0.5 (0.4)	-0.4 (0.3)	-0.8 (0.4)	0.01
TG (mg/dl)	Reference	4.4 (2.6)	4.3 (2.8)	3.5 (2.3)	0.2 (2.5)	0.40
Non-HDL-C (mg/dl)	Reference	0.5 (1.0)	0.2 (1.1)	0.2 (0.9)	-2.0 (1.0)	0.17
100% Fruit Juice Intake						
Offspring Cohort						
No of Observations	1,122	991	1,009	3,644	2,093	
LDL-C (mg/dl)	Reference	0.6 (1.0)	0.8 (1.0)	-0.5 (0.8)	-0.9 (0.9)	0.12
HDL-C (mg/dl)	Reference	0.2 (0.4)	-0.3 (0.4)	-0.6 (0.3)	-0.2 (0.3)	0.11
TG (mg/dl)	Reference	2.1 (2.5)	-0.03 (2.5)	0.6 (2.0)	-3.0 (2.3)	0.17
Non-HDL-C (mg/dl)	Reference	1.0 (1.1)	0.2 (1.2)	-0.3 (0.9)	-1.5 (1.0)	0.07
Generation 3 Cohort						
No of Observations	307	377	547	1,066	503	
LDL-C	Reference	0.2 (1.1)	0.4 (1.1)	-0.8 (1.0)	-0.6 (1.1)	0.27
HDL-C (mg/dl)	Reference	0.2 (0.5)	-0.03 (0.5)	0.3 (0.4)	0.3 (0.5)	0.42
TG (mg/dl)	Reference	-1.0 (3.3)	-3.9 (3.1)	-4.4 (2.9)	-6.0 (3.3)	0.04
Non-HDL-C (mg/dl)	Reference	0.9 (1.3)	1.3 (1.2)	-0.7 (1.1)	-0.9 (1.3)	0.11

HDL-C, high density lipoprotein cholesterol concentrations; LDL-C, low-density lipoprotein cholesterol concentrations; mg/dl, milligrams per deciliter; TC, total cholesterol concentrations; TG, triglyceride concentrations.

*Framingham Offspring Cohort: 8,859 observations from 3,124 participants; Framingham Generation 3 Cohort: 2,800 participants. Values are beta-coefficients and standard errors for beverage intake in multivariate mixed effects models accounting for family structure and adjusted for age (continuous), sex (M/F), total energy (continuous), baseline for lipid trait (continuous), education (less than high school, graduated high school, some college, or graduated college), current smoking status (yes/no), current diabetes status (yes/no), physical activity index (continuous), alcohol (grams), use of LDL-lowing medication (yes/no; where applicable), servings per day of vegetables, whole fruits, whole grains, nuts/seeds, and seafood, as well as percent energy from saturated fat (continuous), change in waist circumference, and mutual adjustment for SSB, LCSB, and 100% fruit juice (categorical as continuous).

Table S2. Difference in 4-year changes in lipid traits by SSB and LCSB category*.

					HDL-C (mg/dl)		TG (mg/dl)	
SSB Category	**LCSB Category**	**Median SSB Intake (servings/week)**	**Medan LCSB Intake (servings/week)**	***n***	**β ± SE**	***p***	**β ± SE**	***p***
<1 serv/ month	**<1 serv/ month**	0.1	0.0	1,561	**Reference**		**Reference**	
	1-10 serv/month	0.1	1.3	885	-0.2 (0.3)	0.54	0.4 (2.2)	0.84
	>3 serv/week	0.1	7.1	1,913	-0.5 (0.3)	0.08	0.8 (1.8)	0.66
1-10 serv/month	**<1 serv/ month**	1.2	0.0	1,730	-0.2 (0.3)	0.42	0.3 (1.9)	0.86
	1-10 serv/month	1.1	1.1	1,031	-0.8 (0.3)	0.02	3.7 (2.2)	0.08
	>3 serv/week	1.1	6.2	1,258	-0.7 (0.3)	0.03	4.6 (2.1)	0.03
>3 serv/week	**<1 serv/ month**	5.5	0.0	1,726	-0.9 (0.3)	0.004	4.8 (2.0)	0.02
	1-10 serv/month	4.5	1.2	639	-1.0 (0.4)	0.02	5.4 (2.6)	0.04
	>3 serv/week	4.4	6.2	914	-1.6 (0.4)	<0.0001	4.3 (2.4)	0.07

HDL-C, high density lipoprotein cholesterol concentrations; LDL-C, low-density lipoprotein cholesterol concentrations; mg/dl, milligrams per deciliter; serv, serving(s); TC, total cholesterol concentrations; TG, triglyceride concentrations.

*Framingham Offspring Cohort: 8,857 observations from 3,124 participants; Framingham Generation 3 Cohort: 2,800 participants. Values are pooled beta-coefficients for beverage intake in multivariate mixed effects models accounting for family structure and adjusted for age (continuous), sex (M/F), total energy (continuous), baseline for lipid trait (continuous), education (less than high school, graduated high school, some college, or graduated college), current smoking status (yes/no), current diabetes status (yes/no), physical activity index (continuous), alcohol (grams), use of LDL-lowing medication (yes/no; where applicable), change in waist circumference (continuous), servings per day of vegetables, whole fruits, whole grains, nuts/seeds, and seafood, as well as percent energy from saturated fat (continuous) and mutual adjustment for SSB, LCSB, and 100% fruit juice (categorical as continuous).

Table S3. HRs (95% CIs) for incident dyslipidemia according to recent beverage consumption category (Framingham Offspring Cohort)*

	SSB Intake			LCSB Intake			100% Fruit Juice Intake		
	Incident Cases	**Person-Years**	**HR (95% CI)**	**Incident Cases**	**Person-Years**	**HR (95% CI)**	**Incident Cases**	**Person-Years**	**HR (95% CI)**
Incidence of high LDL-C (≥160 mg/dl)									
<1 serving/month	394	9956	Reference	419	11653	Reference	129	3290	Reference
1-4 servings/month	216	6190	0.99 (0.84-1.17)	138	3830	1.00 (0.83-1.20)	162	4011	1.13 (0.90-1.40)
1-2 servings/week	70	2239	0.98 (0.76-1.28)	42	1336	0.85 (0.63-1.15)	67	2009	0.94 (0.70-1.26)
3-7 servings/week	206	5010	1.22 (1.01-1.47)	216	5162	1.17 (0.99-1.39)	376	10091	0.98 (0.81-1.20)
>1 serving/day	75	2044	1.19 (0.88-1.59)	144	3428	1.27 (1.05-1.53)	227	6033	1.08 (0.86-1.36)
			p_{trend}=0.05			p_{trend}=0.01			p_{trend}=0.94
Incidence of low HDL-C (Women:<50 mg/dl; Men <40 mg/dl)									
<1 serving/month	108	9784	Reference	124	10481	Reference	45	3221	Reference
1-4 servings/month	90	5610	1.47 (1.11-1.95)	51	3495	1.18 (0.85-1.63)	45	3579	0.83 (0.55-1.25)
1-2 servings/week	29	2030	1.24 (0.80-1.92)	9	1240	0.54 (0.25-1.13)	20	1804	0.63 (0.38-1.07)
3-7 servings/week	63	4064	1.43 (1.02-2.01)	85	4823	1.38 (1.04-1.84)	135	9064	0.96 (0.67-1.37)
>1 serving/day	28	1396	1.98 (1.20-3.28)	49	2809	1.32 (0.92-1.88)	74	5215	0.87 (0.58-1.30)
			p_{trend}=0.01			p_{trend}=0.05			p_{trend}=0.98
Incidence of high TG (≥175 mg/dl)									
<1 serving/month	167	11515	Reference	194	12684	Reference	59	3971	Reference
1-4 servings/month	99	6784	1.03 (0.80-1.31)	65	4263	1.04 (0.77-1.39)	75	4398	1.15 (0.82-1.63)
1-2 servings/week	49	2427	1.50 (1.07-2.10)	35	1534	1.43 (0.99-2.04)	44	2184	1.24 (0.83-1.84)
3-7 servings/week	98	5097	1.42 (1.07-1.88)	93	5724	1.07 (0.83-1.37)	179	10823	1.14 (0.83-1.56)
>1 serving/day	43	1937	1.53 (1.01-2.31)	68	3534	1.18 (0.88-1.59)	99	6384	1.06 (0.74-1.52)
			p_{trend}=0.004			p_{trend}=0.23			p_{trend}=0.84
Incidence of high Non-HDL-C (≥190 mg/dl)									
<1 serving/month	402	10351	Reference	404	11864	Reference	145	3435	Reference
1-4 servings/month	222	6298	1.02 (0.87-1.20)	144	3895	1.12 (0.93-1.34)	159	4110	0.99 (0.81-1.23)
1-2 servings/week	82	2367	1.11 (0.87-1.42)	47	1402	0.98 (0.73-1.30)	65	2080	0.84 (0.63-1.12)
3-7 servings/week	193	5021	1.16 (0.96-1.41)	223	5352	1.26 (1.07-1.49)	386	10335	0.92 (0.77-1.12)
>1 serving/day	75	2065	1.17 (0.87-1.57)	155	3565	1.40 (1.17-1.69)	220	6141	0.95 (0.77-1.18)
			p_{trend}=0.10			p_{trend}=0.0002			p_{trend}=0.49

HDL-C, high density lipoprotein cholesterol concentrations; LDL-C, low-density lipoprotein cholesterol concentrations; mg/dl, milligrams per deciliter; TC, total cholesterol concentrations; TG, triglyceride concentrations.

Participants were free of dyslipidemia at baseline (according to each definition), thus sample sizes were as follows LDL-C (n=2,161), HDL-C (n=1,703), TG (n=2,116), and non-HDL-C (n=2,205).

*Models adjusted for age (continuous), sex (M/F), total energy (continuous), education (less than high school, graduated high school, some college, or graduated college), current smoking status (yes/no), physical activity index (continuous), body mass index (BMI), alcohol (grams), servings per day of vegetables, whole fruits, whole grains, nuts/seeds, and seafood, as well as percent energy from saturated fat (continuous) and mutual adjustment for SSB, LCSB, and 100% fruit juice (categorical as continuous).

Table S4. HRs (95% CIs) for incident dyslipidemia according to cumulative beverage consumption category (Framingham Offspring Cohort)[*]

	SSB Intake			LCSB Intake			100% Fruit Juice Intake		
	Incident Cases	**Person-Years**	**HR (95% CI)**	**Incident Cases**	**Person-Years**	**HR (95% CI)**	**Incident Cases**	**Person-Years**	**HR (95% CI)**
Incidence of high LDL-C (≥160 mg/dl)									
<1 serving/month	288	7665	Reference	355	9585	Reference	66	1680	Reference
1-4 servings/month	189	4852	1.01 (0.84-1.22)	100	3165	0.75 (0.60-0.93)	82	2331	0.78 (0.56-1.07)
1-2 servings/week	180	5172	0.92 (0.75-1.11)	109	2944	0.82 (0.66-1.01)	142	3767	0.75 (0.56-1.01)
3-7 servings/week	223	5615	1.05 (0.87-1.28)	231	5856	0.93 (0.77-1.11)	415	10463	0.83 (0.63-1.08)
>1 serving/day	81	2138	1.11 (0.84-1.47)	166	3891	1.00 (0.82-1.21)	256	7202	0.79 (0.59-1.05)
			p_{trend}=0.61			p_{trend}=0.94			p_{trend}=0.47
Incidence of low HDL-C (Women:<50 mg/dl; Men <40 mg/dl)									
<1 serving/month	95	7487	Reference	108	8422	Reference	27	1559	Reference
1-4 servings/month	55	4531	0.91 (0.65-1.27)	45	2962	1.06 (0.74-1.51)	23	1992	0.69 (0.39-1.22)
1-2 servings/week	63	4662	1.03 (0.74-1.44)	35	2725	0.90 (0.59-1.37)	43	3415	0.72 (0.43-1.19)
3-7 servings/week	76	4760	1.17 (0.84-1.63)	80	5445	1.04 (0.77-1.40)	134	9601	0.81 (0.52-1.25)
>1 serving/day	30	1447	1.57 (0.97-2.54)	51	3333	1.06 (0.74-1.52)	92	6320	0.87 (0.54-1.39)
			p_{trend}=0.09			p_{trend}=0.79			p_{trend}=0.88
Incidence of high TG (≥175 mg/dl)									
<1 serving/month	130	8713	Reference	156	10308	Reference	36	2037	Reference
1-4 servings/month	81	5336	1.03 (0.77-1.37)	55	3517	1.01 (0.73-1.39)	50	2522	1.18 (0.77-1.82)
1-2 servings/week	92	5717	1.10 (0.83-1.46)	60	3310	1.14 (0.83-1.56)	62	4064	0.96 (0.62-1.49)
3-7 servings/week	109	5984	1.25 (0.94-1.68)	116	6563	1.12 (0.87-1.45)	192	11369	1.07 (0.72-1.58)
>1 serving/day	45	2019	1.52 (1.03-2.25)	70	4070	1.03 (0.76-1.39)	117	7776	1.00 (0.65-1.54)
			p_{trend}=0.03			p_{trend}=0.51			p_{trend}=0.82
Incidence of high Non-HDL-C (≥3.5)									
<1 serving/month	301	7989	Reference	345	9762	Reference	71	1736	Reference
1-4 servings/month	188	4976	0.98 (0.81-1.18)	104	3209	0.82 (0.66-1.04)	84	2360	0.76 (0.56-1.05)
1-2 servings/week	179	5286	0.90 (0.74-1.09)	106	3029	0.83 (0.66-1.03)	137	3867	0.68 (0.51-0.92)
3-7 servings/week	227	5672	1.07 (0.88-1.30)	248	6079	1.03 (0.87-1.23)	423	10745	0.79 (0.61-1.04)
>1 serving/day	80	2186	1.07 (0.81-1.41)	172	4031	1.09 (0.90-1.32)	260	7402	0.75 (0.56-1.00)
			p_{trend}=0.58			p_{trend}=0.31			p_{trend}=0.34

HDL-C, high density lipoprotein cholesterol concentrations; LDL-C, low-density lipoprotein cholesterol concentrations; mg/dl, milligrams per deciliter; TC, total cholesterol concentrations; TG, triglyceride concentrations.

Participants were free of dyslipidemia at baseline (according to each definition), thus sample sizes were as follows LDL-C (n=2,161), HDL-C (n=1,703), TG (n=2,116), and non-HDL-C (n=2,205).

*Models adjusted for age (continuous), sex (M/F), total energy (continuous), education (less than high school, graduated high school, some college, or graduated college), current smoking status (yes/no), physical activity index (continuous), body mass index (BMI), alcohol (grams), servings per day of vegetables, whole fruits, whole grains, nuts/seeds, and seafood, as well as percent energy from saturated fat (continuous) and mutual adjustment for SSB, LCSB, and 100% fruit juice (categorical as continuous).

Table S5. HRs (95% CIs) for incident dyslipidemia according to recent beverage consumption category (Framingham Generation 3 Cohort)*

	SSB Intake			LCSB Intake			100% Fruit Juice Intake		
	Incident Cases	**Person-Years**	**HR (95% CI)**	**Incident Cases**	**Person-Years**	**HR (95% CI)**	**Incident Cases**	**Person-Years**	**HR (95% CI)**
Incidence of high LDL-C (≥160 mg/dl)									
<1 serving/month	81	4261	Reference	118	6909	Reference	33	1627	Reference
1-4 servings/month	47	3613	0.76 (0.53-1.09)	31	2275	0.84 (0.57-1.26)	52	2667	0.82 (0.52-1.32)
1-2 servings/week	30	1764	1.15 (0.72-1.83)	12	705	1.14 (0.58-2.22)	27	2078	0.72 (0.42-1.24)
3-7 servings/week	56	3046	1.18 (0.80-1.73)	50	2597	1.17 (0.83-1.64)	77	5081	0.69 (0.44-1.08)
>1 serving/day	30	1872	1.04 (0.61-1.76)	33	2064	0.82 (0.53-1.28)	55	3102	0.87 (0.53-1.44)
			p_{trend}=0.32			p_{trend}=0.92			p_{trend}=0.45
Incidence of low HDL-C (Women:<50 mg/dl; Men <40 mg/dl)									
<1 serving/month	25	3851	Reference	44	6010	Reference	14	1495	Reference
1-4 servings/month	27	3316	1.15 (0.64-2.05)	13	1930	0.87 (0.44-1.70)	17	2322	0.67 (0.30-1.47)
1-2 servings/week	15	1555	1.15 (0.54-2.46)	5	617	1.27 (0.44-3.64)	24	1806	1.42 (0.69-2.93)
3-7 servings/week	28	2548	1.55 (0.81-2.95)	25	2324	1.33 (0.78-2.28)	35	4363	0.88 (0.43-1.79)
>1 serving/day	14	1461	1.07 (0.42-2.72)	23	1851	1.55 (0.89-2.72)	20	2753	0.85 (0.39-1.86)
			p_{trend}=0.44			p_{trend}=0.09			p_{trend}=0.88
Incidence of high TG (≥175 mg/dl)									
<1 serving/month	48	4394	Reference	73	7026	Reference	21	1739	Reference
1-4 servings/month	35	3690	0.89 (0.56-1.43)	32	2267	1.24 (0.81-1.90)	39	2767	1.01 (0.56-1.81)
1-2 servings/week	21	1806	0.92 (0.53-1.62)	10	765	1.41 (0.72-2.77)	27	2091	1.08 (0.59-1.97)
3-7 servings/week	40	3090	1.04 (0.63-1.72)	31	2579	1.18 (0.75-1.86)	52	5111	0.80 (0.46-1.42)
>1 serving/day	32	1843	1.49 (0.83-2.69)	30	2187	1.00 (0.62-1.61)	37	3121	1.00 (0.55-1.83)
			p_{trend}=0.30			p_{trend}=0.77			p_{trend}=0.64
Incidence of high Non-HDL-C (≥190 mg/dl)									
<1 serving/month	76	4269	Reference	117	6988	Reference	31	1659	Reference
1-4 servings/month	48	3648	0.86 (0.59-1.25)	31	2267	0.91 (0.61-1.35)	54	2675	0.92 (0.57-1.47)
1-2 servings/week	29	1784	1.28 (0.80-2.04)	12	697	1.51 (0.80-2.85)	27	2102	0.72 (0.42-1.23)
3-7 servings/week	54	3077	1.16 (0.78-1.72)	50	2633	1.25 (0.88-1.76)	85	5168	0.76 (0.49-1.18)
>1 serving/day	43	1909	1.49 (0.92-2.42)	40	2103	1.01 (0.66-1.54)	53	3091	0.80 (0.49-1.31)
			p_{trend}=0.09			p_{trend}=0.46			p_{trend}=0.25

HDL-C, high density lipoprotein cholesterol concentrations; LDL-C, low-density lipoprotein cholesterol concentrations; mg/dl, milligrams per deciliter; TC, total cholesterol concentrations; TG, triglyceride concentrations.

Participants were free of dyslipidemia at baseline (according to each definition), thus sample sizes were as follows LDL-C (n=2,377), HDL-C (n=2,084), TG (n=2,426), and non-HDL-C (n=2,400).

*Models adjusted for age (continuous), sex (M/F), total energy (continuous), education (less than high school, graduated high school, some college, or graduated college), current smoking status (yes/no), physical activity index (continuous), body mass index (BMI), alcohol (grams), servings per day of vegetables, whole fruits, whole grains, nuts/seeds, and seafood, as well as percent energy from saturated fat (continuous) and mutual adjustment for SSB, LCSB, and 100% fruit juice (categorical as continuous).