A dose-response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults

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Introduction

This study investigates the impact increasing levels of high fructose corn syrup (HFCS) consumption has on cholesterol, triglycerides, and weight in healthy, young men and women.

Conclusions

HFCS with normal diet, leading to likely weight gain, increases LDL, non-HDL cholesterol, and triglycerides.

HFCS seems to negatively affect (increasing cholesterol, triglycerides) men more than women.

Amendments

Study Design & Additional Information

The researchers recruited 85 participants, roughly equal number of healthy, young (24-28 years) men and women, and purposefully put them into groups of equal health, weight, etc. (so, this study was not randomized). They were then given one drink per meal, for 2 weeks, that contained 0% high fructose corn syrup (HFCS-55), so this group consumed no HFCS; another group received drinks with 10% HFCS; another group received 17.5% HFCS; and the final group received drinks with 25% HFCS. They were told to maintain their diet, but cut out all other sugary drinks (juice, soda, etc.). Blood was taken in the first three days of the study, as well as in the final three days of the study (with meals controlled, supplied in those total 6 days, as determined by a calorie calculator). Blood was taken before consuming food (fasted), as well as 30 and 60 minutes after eating food (post prandial).

A dose-response study of consuming high-fructose corn syrup–sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults[1–6]

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ABSTRACT

Background: National Health and Nutrition Examination Survey data show an increased risk of cardiovascular disease (CVD) mortality with an increased intake of added sugar.

Objective: We determined the dose-response effects of consuming beverages sweetened with high-fructose corn syrup (HFCS) at zero, low, medium, and high proportions of energy requirements (Ereq) on circulating lipid/lipoprotein risk factors for CVD and uric acid in adults [age: 18–40 y; body mass index (in kg/m^2): 18–35].

Design: We conducted a parallel-arm, nonrandomized, double-blinded intervention study in which adults participated in 3.5 inpatient days of baseline testing at the University of California Davis Clinical and Translational Science Center's Clinical Research Center. Participants then consumed beverages sweetened with HFCS at 0% (aspartame sweetened, $n = 23$), 10% ($n = 18$), 17.5% ($n = 16$), or 25% ($n = 28$) of Ereq during 13 outpatient days and during 3.5 inpatient days of intervention testing at the research center. We conducted 24-h serial blood collections during the baseline and intervention testing periods.

Results: Consuming beverages containing 10%, 17.5%, or 25% Ereq from HFCS produced significant linear dose-response increases of lipid/lipoprotein risk factors for CVD and uric acid: postprandial triglyceride (0%: 0 ± 4; 10%: 22 ± 8; 17.5%: 25 ± 5: 25%: 37 ± 5 mg/dL, mean of Δ ± SE, $P < 0.0001$ effect of HFCS-dose), fasting LDL cholesterol (0%: −1.0 ± 3.1; 10%: 7.4 ± 3.2; 17.5%: 8.2 ± 3.1; 25%: 15.9 ± 3.1 mg/dL, $P < 0.0001$), and 24-h mean uric acid concentrations (0%: −0.13 ± 0.07; 10%: 0.15 ± 0.06; 17.5%: 0.30 ± 0.07; 25%: 0.59 ± 0.09 mg/dL, $P < 0.0001$). Compared with beverages containing 0% HFCS, all 3 doses of HFCS-containing beverages increased concentrations of postprandial triglyceride, and the 2 higher doses increased fasting and/or postprandial concentrations of non–HDL cholesterol, LDL cholesterol, apolipoprotein B, apolipoprotein CIII, and uric acid.

Conclusions: Consuming beverages containing 10%, 17.5%, or 25% Ereq from HFCS produced dose-dependent increases in circulating lipid/lipoprotein risk factors for CVD and uric acid within 2 wk. These results provide mechanistic support for the epidemiologic evidence that the risk of cardiovascular mortality is positively associated with consumption of increasing amounts of added sugars. This trial was registered at clinicaltrials.gov as NCT01103921. *Am J Clin Nutr* 2015;101:1144–54.

Keywords: apolipoprotein CIII, fructose, risk factors, sugar, uric acid

INTRODUCTION

Considerable epidemiologic evidence suggests that increased intake of added sugars, sucrose and/or high-fructose corn syrup (HFCS),[7] or sugar-sweetened beverages is associated with dyslipidemia, cardiovascular disease (CVD), and metabolic syndrome (1). Recent evidence from National Health and Nutrition Examination Survey III suggests that the higher the intake of added sugar, the greater the risk (2). The adjusted HRs of CVD mortality across quintiles of percentage of daily calories consumed from added sugar (quintile 1: 0–9.59%; quintile 2: 9.6–13.09%; quintile 3: 13.1–16.69%; quintile 4: 16.7–21.29%; quintile 5: ≥21.3% of daily calories) were 1.00 (reference) for

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[4] Supplemental Tables 1–3, Supplemental Figures 1–5, and Supplemental Discussion are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[7] Abbreviations used: apoB, apolipoprotein B; apoCIII, apolipoprotein CIII; CCRC, University of California Davis Clinical and Translational Science Center's Clinical Research Center; CVD, cardiovascular disease; Ereq, energy requirement; HFCS, high-fructose corn syrup; Δ, absolute change.

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quintile 1, 1.07 (95% CI: 1.02–1.12) for quintile 2, 1.18 (95% CI: 1.06–1.31) for quintile 3, 1.38 (95% CI: 1.11–1.70) for quintile 4, and 2.03 (95% CI: 1.26–3.27) for quintile 5 (P = 0.004; n = 11,733) (2). These data suggest that the average amount of added sugar consumption in the United States, ~13–14% of daily calories for adults 20–60 y of age (3) and 16% for children and adolescents (4), is associated with an 18% increase in CVD mortality risk (2). However, investigators of a recent dose-response study, in which ad libitum diets of men and women were supplemented with beverages containing 8%, 18%, or 30% energy requirement (Ereq) from sucrose or HFCS for 10 wk (5, 6), have reported that consumption of added sugar does not increase fasting cholesterol and LDL cholesterol (5) and that there were no differences between the 3 doses of sugar in 24-h circulating triglyceride and uric acid concentrations (6). We have conducted a dose-response study in which the ad libitum diets of young men and women were supplemented with HFCS-sweetened beverages for 2 wk. Our objective was to determine the dose-response effects of consuming of beverages providing 0%, 10%, 17.5%, or 25% Ereq from HFCS (Ereq-HFCS) on circulating concentrations of lipid/lipoprotein risk factors for CVD and uric acid.

METHODS

Participants in this study are a subgroup from an NIH-funded investigation in which a total of 187 participants assigned to 8 experimental groups were studied. A primary objective of this 5-y investigation was to compare the metabolic effects of consuming beverages containing fructose, glucose, or HFCS at 25% Ereq, and the results from the first 48 subjects to complete the study protocol in these experimental groups (n = 16/group) have been reported (7). The current article reports the results from 85 participants consuming beverages containing 0% (n = 23), 10% (n = 18), 17.5% (n = 16), and 25% (n = 28) Ereq from HFCS.

Participants, who were recruited through an Internet listing (craigslist.com) and local postings of flyers, underwent telephone and in-person interviews with medical history, complete blood count, and serum biochemistry panel to assess eligibility. Inclusion criteria included age 18–40 y and BMI 18–35 kg/m^2 with a self-report of stable body weight during the prior 6 months. Exclusion criteria included diabetes (fasting glucose >125 mg/dL), evidence of renal or hepatic disease, fasting plasma triglyceride >400 mg/dL, hypertension (>140/90 mm Hg), hemoglobin <8.5 g/dL, and surgery for weight loss. Individuals who smoked, habitually ingested >2 alcoholic beverages/d, exercised >3.5 h/wk at a level more vigorous than walking, or used thyroid, lipid-lowering, glucose-lowering, antihypertensive, antidepressant, or weight loss medications were also excluded. Assignment to the experimental groups was not randomized; by design, the experimental groups were matched for sex, BMI, and concentrations of fasting triglyceride, cholesterol, HDL cholesterol, and insulin in plasma collected during the in-person interviews.

For the 5 wk before study, subjects who were scheduled for participation were asked to limit daily consumption of sugar-containing beverages to no more than one 8-oz serving of fruit juice and to discontinue consumption of any vitamin, mineral, dietary, or herbal supplements. Ninety-seven subjects were enrolled in the experimental groups consuming 0%, 10%, 17.5%, or 25% Ereq-HFCS. Five subjects withdrew or were dismissed from the study before the start of the intervention for reasons that included scheduling problems, new job, dissatisfaction with inpatient meals, family emergency, and personal anxiety. Of the 7 subjects who participated in intervention, one (0% group) withdrew due to job-related conflict, one (10% group) was lost to follow-up due to loss of contact, one (17.5% group) withdrew due to a family emergency, and 4 (25% group) did not complete the study for other reasons [one withdrew due to back pain (one fasting intervention sample was collected from this subject), one withdrew due to personal anxiety, one was dismissed for medical issues not apparent during screening, and one was dismissed for illness (e.g., flu-like symptoms)]. A sensitivity analysis was conducted, which demonstrated that the higher number of noncompleters in the 25% group did not influence the results (see **Supplemental Figure 1**). A total of 85 subjects completed the dose-response study. The data from one subject (17.5% group) were included in the fasting analyses but not postprandial analyses because a family emergency prevented completion of the 24-h serial blood collection during the intervention period. The sample size calculation, based on the fasting apolipoprotein B (apoB) results generated during a previous study (8), indicated that 25 subjects per group would be sufficient to detect differences between the 25% Ereq and 0% Ereq groups. This number was not achieved in all groups due to insufficient funding. The larger number of subjects in the 25% group is due to additional funding (R01 HL107256) being obtained to conduct mechanistic studies in participants from this group. The 28 participants who consumed 25% Ereq-HFCS included 16 participants whose results were previously reported (7). A comparison of these 16 subjects with the 12 additional subjects in the 25% group is provided in **Supplemental Table 1** and reveals no differences in baseline parameters and outcome responses.

This was a parallel-arm, double-blinded diet intervention study with 3 phases: *1*) a 3.5-d inpatient baseline period during which subjects resided at the University of California Davis Clinical and Translational Science Center's Clinical Research Center (CCRC), consumed a standardized baseline diet, and participated in experimental procedures; *2*) a 12-d outpatient intervention period during which subjects consumed their assigned sweetened beverages providing 0% (aspartame sweetened) or 10%, 17.5%, or 25% Ereq-HFCS along with their usual ad libitum diets; and *3*) a 3.5-d inpatient intervention period during which subjects resided at the CCRC and consumed standardized diets that included the sweetened beverages, and all experimental procedures were repeated.

Inpatient diets

During days 2 and 3 of the baseline and intervention inpatient periods, subjects consumed energy-balanced meals consisting of conventional foods. Daily energy requirements were calculated by the Mifflin equation (9), with adjustment of 1.3 for activity on the days of the 24-h serial blood collections and adjustment of 1.5 for the other days. The baseline diet contained 55% Ereq mainly as low-fiber complex carbohydrate (i.e., white bread, white rice, regular pasta), 30% from fat, and 15% from protein. The meals during the inpatient intervention period included the assigned study beverages and were as identical as possible to baseline meals, except for the substitution of the sugar-sweetened

beverage in place of isocaloric amounts of complex carbohydrate. The intervention meals contained 19–20 g fiber/2000 kcal fiber, and the baseline meals contained 22 g fiber/2000 kcal. The timing of inpatient meals and the energy distribution were as follows: breakfast, 0900 (25%); lunch, 1300 (35%); and dinner, 1800 (40%).

Study beverages and outpatient diet

HFCS-containing beverages were sweetened with HFCS-55 (Isosweet 5500, 55% fructose, 45% glucose; Skidmore Sales and Distributing), flavored with an unsweetened drink mix (Kool-Aid; Kraft Inc.). A fruit-flavored aspartame drink mix (Market Pantry) was used to prepare the 0% Ereq-HFCS beverages and to augment the sweetness of the 10% Ereq-HFCS beverages. Participants were blinded to their beverage assignment, as were all CCRC and study personnel who interacted with participants or analyzed samples. Voluntary feedback from participants indicated that they were unable to distinguish between beverages containing aspartame or HFCS. The amount (grams) of beverage provided was standardized among the 4 groups and based on energy requirements [calculated with the Mifflin equation (9) plus 1.5 activity adjustment]. During the 12-d outpatient phase of the study, participants were instructed to drink one serving of study beverage with each meal, to consume their usual diet, and to not consume other sugar-sweetened beverages, including fruit juice. To monitor compliance of beverage consumption (10, 11), the study beverages contained a biomarker (riboflavin) that was measured fluorimetrically in urine samples collected at the times of beverage pickup. Subjects were informed about the biomarker but were not provided information regarding its identity. Fasting urinary riboflavin concentrations (**Supplemental Figure 2**) following 9 d and 13 d of unmonitored beverage consumption were not different from those following one day of monitored beverage consumption at the CCRC, suggesting good and comparable compliance in all groups.

Procedures

The 24-h serial blood collections (7) were conducted on the third day of the baseline (0 wk) and intervention (2 wk) inpatient periods. Three fasting blood samples were collected at 0800, 0830, and 0900 h. Twenty-nine postprandial blood samples were collected at 30- to 60-min intervals until 0800 the following morning. Additional 6-mL blood samples were collected at the fasting time points (0800, 0830, and 0900 h) and also at the late-evening time points (2200, 2300, and 2400 h). The additional plasma from the 3 fasting samples was pooled, as was that from the 3 late-evening postprandial samples; multiple aliquots of each pooled sample were stored at −80°C. The plasma concentrations of triglyceride and uric acid were measured at all time points and calculated for mean 24-h concentration and for 24-h AUC by the trapezoidal method. The concentrations of non–HDL cholesterol, LDL cholesterol, apoB, apolipoprotein CIII (apoCIII), and apolipoprotein AI were measured during the fasting and late-evening postprandial period. These postprandial measures were conducted on samples collected or pooled from the 2200, 2300, and 2400 h time points because this was the period during which peak postprandial triglyceride concentrations were observed in our previous study (8). Lipid, lipoprotein, and uric acid concentrations were measured with a Polychem Chemistry Analyzer (PolyMedCo Inc.) with reagents from MedTest DX. The intra- and interassay CVs during the time period when these measurements were conducted (2010–2014) were as follows: triglyceride: 3.1%, 7.6% (intra-assay, inter-assay); total cholesterol: 2.3%, 4.4%; HDL cholesterol: 3.0%, 5.5%; direct LDL cholesterol: 2.4%, 4.7%; apoB: 3.5%, 6.9%; apoCIII: 2.0%, 6.5%; and uric acid: 1.9, 5.6%.

Ethics

The study was conducted in accordance with an experimental protocol that was approved by the UC Davis Institutional Review Board, and participants provided written informed consent.

Statistical analyses

The absolute change (Δ) at 2 wk of intervention compared with the 0-wk baseline value for each outcome was tested for a dose-response trend in a general linear model (SAS 9.3; SAS Institute), adjusted for sex, BMI, and outcome concentration [outcome] at baseline by using HFCS dose (0%, 10%, 17.5%, 25%) as a continuous variable. Departures from linearity were tested with polynomial terms by using the same model. The proportion of variance explained by each covariate was calculated as follows: (type III sum of squares/corrected total sum of squares) × 100 (**Supplemental Table 2**). A secondary trend-testing general linear model that also included Δbody weight as a continuous covariate was conducted. The Δ for each outcome was also analyzed in a general linear model (SAS 9.3), adjusted for sex, BMI, and [outcome] at baseline, with HFCS-group (1, 2, 3, 4) as a categorical variable. This model allowed for testing of outcomes that were significantly changed from baseline concentrations as least squares means of Δ different from zero and identified significant differences between groups by Tukey's multiple-comparisons test. The Δnon–HDL cholesterol, LDL cholesterol, and apoB concentrations were further investigated in the adjusted general linear model that included HFCS dose (0%, 10%, 17.5%, 25%) as a continuous variable and Δpostprandial triglyceride, apoCIII, and uric acid as continuous covariates, singly and in combination. This model was also used to test for relations between Δpostprandial triglyceride, apoCIII, and uric acid. Sixteen outcomes were tested for nominal significance ($P < 0.05$) and notated when the effect of HFCS-dose did not obtain a level of significance corrected for 16 comparisons ($P < 0.0031$). Data presented in **Table 1** are means ± SDs; all other data are means ± SEs.

RESULTS

There were no significant differences between the 4 experimental groups in anthropomorphic or metabolic parameters at baseline (Table 1).

Effect of HFCS-dose

The outcome means at 0 wk and at the end of the 2-wk intervention by group, as well as the P values for the effects of HFCS-dose, are presented in **Table 2**. The consumption of beverages containing 0%, 10%, 17.5%, and 25% Ereq-HFCS produced positive dose-response effects that did not deviate

TABLE 1
Description of participants at baseline by HFCS content of beverage[1]

	HFCS 0%	HFCS 10%	HFCS 17.5%	HFCS 25%
Men/women, *n*	11/12	9/9	7/9	15/13
Age, y	25 ± 6[2]	28 ± 6	24 ± 5	27 ± 7
BMI, kg/m^2	24.8 ± 3.3	24.9 ± 3.8	24.2 ± 3.3	24.9 ± 4.0
Body fat, %	27.1 ± 9.8	26.8 ± 7.4	26.3 ± 9.6	25.9 ± 9.9
Energy requirement,[3] kcal/d	2354 ± 322	2323 ± 247	2326 ± 375	2390 ± 350
Waist circumference, cm	74.8 ± 6.2	75.3 ± 8.7	73.1 ± 8.0	76.3 ± 9.7
Systolic blood pressure, mm Hg	112 ± 12	115 ± 10	115 ± 8	117 ± 10
Diastolic blood pressure, mm Hg	69 ± 9	73 ± 8	71 ± 5	74 ± 9
Fasting glucose, mg/dL	91.3 ± 7.1	89.2 ± 8.0	87.2 ± 6.5	89.9 ± 6.5
Fasting insulin, μU/mL	12.8 ± 5.5	11.8 ± 3.4	11.7 ± 3.0	13.0 ± 5.2
Fasting triglyceride, mg/dL	101 ± 53	122 ± 70	97 ± 34	108 ± 50
Fasting cholesterol, mg/dL	149 ± 25	162 ± 27	165 ± 35	158 ± 34
Fasting HDL cholesterol,[4] mg/dL	36 ± 7/43 ± 7	42 ± 11/46 ± 12	44 ± 7/48 ± 11	42 ± 8/50 ± 18
HFCS provided in beverage, g/d	0 ± 0	63 ± 7	111 ± 18	162 ± 24

[1]Values are means ± SDs. HFCS, high-fructose corn syrup.
[2]All variables (excepting HFCS in beverage): $P > 0.05$ for differences among groups at baseline (general linear model ANOVA with HFCS-group as categorical variable: SAS 9.3).
[3]Energy requirement calculated by the Mifflin equation with 1.5 adjustment for physical activity.
[4]Data from men/women.

significantly from linear in all outcomes presented. All outcomes, except Δbody weight, fasting triglyceride, and fasting apoCIII, retained significance after correction for multiple comparisons ($P < 0.0031$). Supplemental Table 2 shows the variance explained by HFCS-dose, sex, BMI, [outcome] at baseline, and the complete model for each outcome. The Δ24-h mean uric acid concentration was the outcome most affected by HFCS-dose (proportion of variance: 36%; $P < 0.0001$) and Δfasting triglyceride was the least affected (proportion of variance: 6%; $P = 0.019$). When tested in the general linear model that included adjustment for the Δbody weight, the effect of HFCS-dose remained significant for all outcomes with the exception of fasting triglyceride (**Supplemental Table 3**).

Effect of HFCS-group

The least squares means of each Δoutcome (2 wk minus 0 wk with adjustment for sex, BMI, and [outcome] at baseline) are presented in **Figure 1**A–D and labeled for significant effect of HFCS-group and differences between groups and from baseline [significance notations in red indicate that difference did not retain significance after correction for multiple comparisons ($P < 0.0031$)]. With the exception of Δbody weight and fasting triglyceride, all outcomes presented in Figure 1A–D were significantly affected by HFCS-group. Compared with 0% Ereq-HFCS, consumption of beverages containing 25% Ereq-HFCS resulted in significantly higher concentrations of postprandial non–HDL cholesterol, LDL cholesterol, and triglyceride, as well as fasting and 24-h mean uric acid (all $P < 0.0001$, Tukey's multiple-comparisons test); fasting non-HDL-C and LDL and postprandial apoB and apoCIII (all $P < 0.001$); fasting apoB ($P < 0.01$); and 24-h mean triglyceride ($P < 0.05$). The changes measured during consumption of 17% Ereq-HFCS were significantly higher compared with those induced by 0% Ereq-HFCS for postprandial apoCIII ($P < 0.001$); postprandial non–HDL cholesterol and triglycerides, as well as 24-h mean uric acid (all $P < 0.01$); and fasting non–HDL cholesterol and uric acid, as well as postprandial LDL cholesterol and apoB (all $P < 0.05$). Consumption of the 10% Ereq-HFCS beverages, which is comparable to consuming slightly more than half of a 12-oz (355 mL) can of soda (40 g sugar/can) with each of the 3 major meals, increased concentrations of postprandial triglyceride compared with 0% Ereq-HFCS beverages ($P < 0.05$). The increases of non–HDL cholesterol, LDL cholesterol, apoB, and 24-h mean uric acid were larger in men than in women ($P = 0.0025 - P = 0.038$, effect of sex; **Supplemental Figure 3**A–C). As shown in **Figure 2**A–D, consumption of HFCS resulted in increases of uric acid concentrations that were consistent throughout the 24-h collection period within each dose group. The 24-h uric acid AUC was significantly increased in the 25% group compared with both the 0% and 10% groups (Figure 2E). The differential effects of HFCS compared with complex carbohydrate on 24-h circulating triglyceride concentrations (**Figure 3**) were most marked during the late-evening postprandial period (Figure 1D). HFCS consumption consistently resulted in a third triglyceride peak 4–6 h after dinner, whereas consumption of 55% Ereq complex carbohydrate at baseline or along with aspartame-sweetened beverages did not (Figure 3A–D).

Relations between outcomes

ΔPostprandial triglyceride, apoCIII, and uric acid concentrations were tested in the adjusted general linear regression model for their relation to each other (data not shown) and for their potential contributions to Δfasting and postprandial non–HDL cholesterol, LDL cholesterol, and apoB. The Δuric acid was not significantly related to ΔapoCIII or postprandial triglyceride (data not shown). The Δpostprandial triglyceride and Δfasting or postprandial apoCIII were highly correlated, especially Δpostprandial apoCIII and Δ24-h mean triglyceride concentrations (data not shown). The Δpostprandial apoCIII was a highly significant covariate (proportion of variance = 35%, $P < 0.0001$) in the adjusted model testing the effects of HFCS dose on Δ24-h mean triglyceride, and Δ24-h mean triglyceride was an almost

Table 1

This is a table showing the baseline (pre-study beginning) values of the four groups being compared. HFCS 0% is the group that consumed a beverage with aspartame, no high fructose corn syrup (HFCS). HFCS 10% had a beverage with 10% HFCS. And so on…

Primary Results

- There are no significant differences between the four groups before the study begins.

Take Away: Before the study, all participants were even, which stands to reason as they weren't randomized and were purposefully put into groups to be equal.

TABLE 2
Body weight and plasma concentrations of risk factors before and 2 wk after consuming 0%, 10%, 17.5%, or 25% Ereq as HFCS-sweetened beverages in young men and women[1]

	HFCS dose				
Outcome	0% (n = 23)	10% (n = 18)	17.5% (n = 16)	25% (n = 28)	Effect of dose[2] (P value)
Body weight, kg					
0 wk	71.8 ± 2.2	70.9 ± 2.4	69.9 ± 3.6	72.9 ± 2.7	0.014[3]
2 wk	71.7 ± 2.2	70.9 ± 2.4	70.2 ± 3.7	73.7 ± 2.8	
FST non–HDL cholesterol, mg/dL					
0 wk	110 ± 5	118 ± 6	119 ± 8	112 ± 6	<0.0001
2 wk	107 ± 5	126 ± 7	126 ± 7	128 ± 6	
PP non–HDL cholesterol, mg/dL					
0 wk	101 ± 5	111 ± 5	113 ± 8	103 ± 5	<0.0001
2 wk	99 ± 5	120 ± 7	126 ± 8	124 ± 6	
FST LDL cholesterol, mg/dL					
0 wk	84 ± 5	95 ± 5	93 ± 8	91 ± 5	<0.0001
2 wk	83 ± 6	102 ± 6	102 ± 6	107 ± 6	
PP LDL cholesterol, mg/dL					
0 wk	81 ± 5	89 ± 4	89 ± 7	86 ± 5	<0.0001
2 wk	80 ± 4	99 ± 7	99 ± 7	105 ± 6	
FST apoB, mg/dL					
0 wk	64.8 ± 3.6	69.0 ± 3.3	69.4 ± 5.6	69.6 ± 3.5	0.0002
2 wk	65.1 ± 3.0	73.6 ± 3.9	73.2 ± 4.4	80.0 ± 4.1	
PP apoB, mg/dL					
0 wk	62.0 ± 3.6	65.3 ± 3.1	66.0 ± 4.9	65.3 ± 3.4	<0.0001
2 wk	61.3 ± 3.0	70.1 ± 4.0	73.7 ± 4.7	77.4 ± 4.2	
FST apoCIII, mg/dL					
0 wk	7.31 ± 0.52	8.63 ± 0.65	8.08 ± 0.48	8.20 ± 0.50	0.0054[3]
2 wk	7.25 ± 0.47	8.34 ± 0.55	8.55 ± 0.52	8.84 ± 0.52	
PP apoCIII, mg/dL					
0 wk	6.71 ± 0.62	7.82 ± 0.58	7.48 ± 0.52	7.40 ± 0.46	<0.0001
2 wk	6.55 ± 0.51	8.13 ± 0.53	8.65 ± 0.55	8.48 ± 0.55	
FST uric acid, mg/dL					
0 wk	4.57 ± 0.22	4.27 ± 0.29	4.40 ± 0.20	4.55 ± 0.22	<0.0001
2 wk	4.51 ± 0.20	4.42 ± 0.30	4.70 ± 0.23	5.03 ± 0.24	
24-h Mean uric acid, mg/dL					
0 wk	4.35 ± 0.21	4.10 ± 0.29	4.22 ± 0.21	4.27 ± 0.21	<0.0001
2 wk	4.22 ± 0.19	4.25 ± 0.31	4.56 ± 0.23	4.86 ± 0.24	
FST triglyceride, mg/dL					
0 wk	101 ± 11	122 ± 17	97 ± 9	108 ± 9	0.019[3]
2 wk	98 ± 10	114 ± 14	97 ± 9	119 ± 10	
24-h Mean triglyceride, mg/dL					
0 wk	109 ± 14	134 ± 19	109 ± 10	119 ± 10	0.0014
2 wk	104 ± 12	135 ± 20	119 ± 12	131 ± 12	
PP triglyceride, mg/dL					
0 wk	94 ± 14	125 ± 23	100 ± 11	108 ± 11	<0.0001
2 wk	94 ± 13	147 ± 25	125 ± 14	145 ± 14	

[1]Values are means ± SEs. apoB, apolipoprotein B; apoCIII, apolipoprotein CIII; Ereq, energy requirement; FST, fasting; HFCS, high-fructose corn syrup; PP, postprandial; Δ, absolute change.
[2]The absolute change (Δ from 2-wk intervention with sweetened beverage compared with 0 wk baseline) for each outcome was analyzed in a general linear model (SAS 9.3) with dose of HFCS in beverage as a continuous variable (0%, 10%, 17.5%, 25%) and adjustment for sex, BMI, and [outcome] at baseline; departures from linearity were tested with polynomial terms in the same model. All outcomes exhibited trends that did not significantly deviate from linear.
[3]Nominally significant outcome that is not significant ($P < 0.0031$) when corrected for 16 comparisons.

equally significant covariate (proportion of variance = 30%, $P < 0.0001$) in the model testing the effects of HFCS dose on Δpostprandial apoCIII.

Despite their strong correlation, Δpostprandial triglyceride, whether indexed as the 24-h mean or the late-evening postprandial peak (or mean of postmeal peaks), was not a significant covariate in the models testing the effects of HFCS dose on Δnon–HDL cholesterol, LDL, or apoB (data not shown), whereas ΔapoCIII was highly related. In **Table 3**, we present the proportion of variances and P values for 4 adjusted models that tested the effects of HFCS dose, HFCS dose and Δuric acid, HFCS dose and ΔapoCIII, and HFCS dose with Δuric acid and ΔapoCIII together on the Δfasting and postprandial non–HDL cholesterol, LDL cholesterol, and apoB. Singly, Δuric acid and ΔapoCIII were significant covariates for all 6 outcomes and reduced the proportion of variance for the effect of HFCS dose

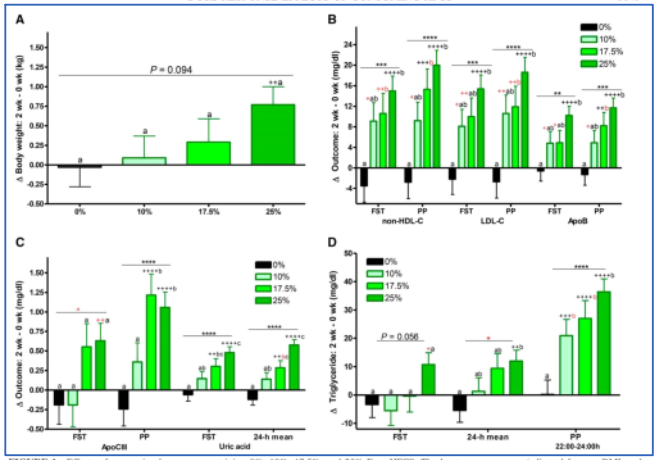

FIGURE 1 Effects of consuming beverages containing 0%, 10%, 17.5%, and 25% Ereq-HFCS. The least squares means (adjusted for sex, BMI, and [outcome] at baseline) ± SEs of (A) Δbody weight; (B) ΔFST and PP plasma non–HDL cholesterol, LDL cholesterol, and apoB concentrations; (C) ΔFST and PP plasma apoCIII concentrations and ΔFST and 24-h mean plasma uric acid concentrations; and (D) ΔFST, 24-h mean, and PP plasma triglyceride concentrations in young men and women after consuming beverages providing 0% (n = 23), 10% (n = 18), 17.5% (n = 16), or 25% (n = 28) of Ereq from HFCS for 2 wk. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$, effect of HFCS group; 2-factor (HFCS group, sex) ANCOVA of Δ with adjustment for BMI and [outcome] at baseline. ^{a}Δ different from ^{b}Δ or ^{bc}Δ and ^{ab}Δ different from ^{c}Δ, Tukey's multiple-comparisons test. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$, least squares mean different from zero. Significance notations in red indicate that difference did not retain significance after correction for multiple comparisons ($P < 0.0031$). apoB, apolipoprotein B; apoCIII, apolipoprotein CIII; Ereq, energy requirement; FST, fasting; HFCS, high-fructose corn syrup; PP, postprandial; Δ, absolute change.

by 33–77%. In combination, both Δuric acid and ΔapoCIII remained significant covariates and reduced the proportion of variance estimates for the effect of HFCS dose by 76–95%.

DISCUSSION

This study demonstrates for the first time that established risk factors for CVD, plasma concentrations of non–HDL cholesterol, LDL cholesterol, and apoB (12), increase in a dose-dependent manner in young adults consuming beverages providing 10%, 17.5%, or 25% Ereq from HFCS for 2 wk. The dose-dependent increases of these risk factors for CVD, which were shown to be statistically independent of body weight gain, provide mechanistic support for the recent epidemiologic findings that there is increased risk of CVD mortality with increased intake of added sugar across quintiles (2). The significant and independent correlations of both ΔapoCIII and uric acid with Δnon–HDL cholesterol, LDL cholesterol, and apoB (see **Supplemental Discussion** for more details) suggest the potential for 2 separate pathways by which consumption of HFCS increases these risk factors for CVD.

The increases of late-night postprandial triglyceride concentrations during consumption of all 3 doses of HFCS compared with 0% Ereq-HFCS support our previous work (7, 8) but do not support a meta-analysis concluding that fructose in isocaloric exchange for other carbohydrate does not increase postprandial triglyceride (13) (see Supplemental Discussion for details and also **Supplemental Figure 4**A,C). Consumption of fructose-containing sugars increases circulating triglyceride because fructokinase, which catalyzes the initial phosphorylation of dietary fructose, is not regulated by hepatic energy status (14). This results in unregulated hepatic fructose uptake (15–17), with most of the ingested fructose being metabolized in the liver and little reaching the systemic circulation (18). The excess substrate leads to increased de novo lipogenesis (8), which may increase the intrahepatic lipid supply directly (19, 20), via synthesis of fatty acids, and indirectly, by inhibiting fatty acid oxidation (21, 22). Increased intrahepatic lipid content promotes VLDL production and secretion (23, 24), leading to increased concentrations of postprandial triglyceride (25). Postprandial hypertriglyceridemia has been recently reviewed as an important risk factor for CVD (26) (see Supplemental Discussion).

Figure 1

These graphs show the health parameters like body weight [1A], cholesterol [1B], triglycerides [1D], and body weight in a fasted state (FST) or after eating (PP), before and after the 2 weeks of consumption of each HFCS dose drink (0-25%).

Primary Results

- Body weight did not increase in a statistically significant manner [1A].
- Highest (25%) HFCS conditions saw increases in non-HDL, LDL, and ApoB.
- Highest (25%) HFCS elevated triglycerides after eating only.

Take Away: Body weight would have likely become significantly increased with more time, but as it stands, HFCS did not have an effect (after 2 weeks), but high levels of HFCS did increase cholesterol and triglycerides.

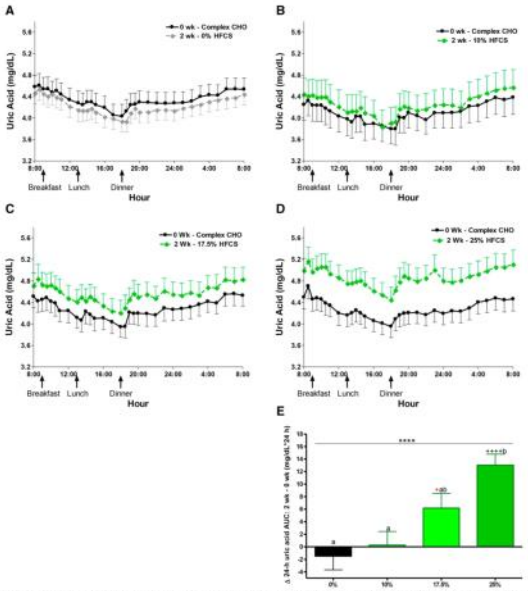

FIGURE 2 The 24-h circulating uric acid concentrations during consumption of complex carbohydrate and during consumption of sweetened beverages containing 0%, 10%, 17.5%, and 25% of Ereq-HFCS. Circulating 24-h uric acid plasma concentrations during consumption of energy-balanced baseline diets containing 55% Ereq complex carbohydrate at 0 wk and during consumption of energy-balanced intervention diets containing isocaloric amounts of carbohydrate as complex carbohydrate and (A) 0% Ereq-HFCS (n = 23), (B) 10% Ereq-HFCS (n = 18), (C) 17.5% Ereq-HFCS (n = 15), or (D) 25% Ereq-HFCS (n = 28) at 2 wk. (E) The change in circulating 24-h uric acid plasma concentrations (2 wk − 0 wk) quantified for each group as Δ24-h uric acid AUC. $^{****}P < 0.0001$, effect of HFCS group; 2-factor (HFCS group, sex) ANCOVA of Δ with adjustment for BMI and [outcome] at baseline. "Δ different from ^{b}Δ, Tukey's multiple-comparisons test. $^{*}P < 0.05$, $^{****}P < 0.0001$, least squares mean different from zero. Significance notations in red indicate that difference did not retain significance after correction for multiple comparisons ($P < 0.0031$). Data are means ± SEs. CHO, carbohydrate; Ereq, energy requirement; HFCS, high-fructose corn syrup; Δ, absolute change.

This is the first report to our knowledge that consumption of HFCS, or any sugar, increases plasma concentrations of apoCIII in humans. We have, however, reported that plasma apoCIII increased in rhesus monkeys provided with fructose-sweetened beverages for 6 mo (27). The current increases of apoCIII may simply reflect the effect of HFCS to increase VLDL production, because most VLDL particles are secreted as apoCIII-containing VLDL (28). However, glucose induces apoCIII transcription in rat and human hepatocytes via a mechanism involving the transcription factor, carbohydrate response element-binding protein (29). This mechanism could be relevant to consumption of HFCS because a significant proportion of a large fructose dose is converted into glucose (30) and because HFCS contains glucose. In addition, fructose-fed rats treated with carbohydrate response element-binding protein antisense exhibited a decreased rate of hepatic triglyceride secretion (31), suggesting a role for carbohydrate response element-binding protein in the lipogenic effects of fructose feeding. Plasma apoCIII strongly predicts

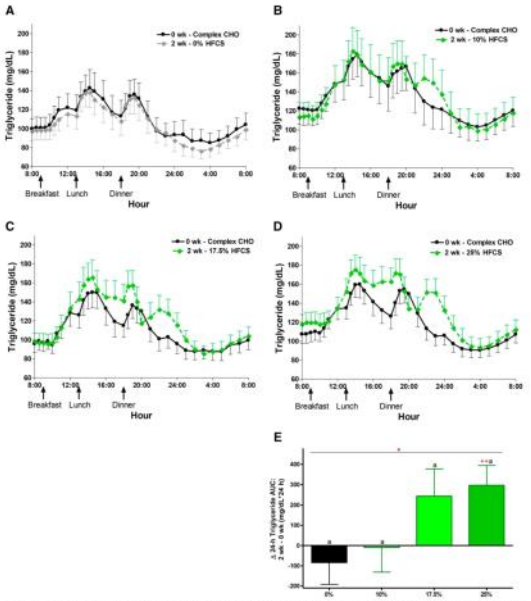

FIGURE 3 The 24-h circulating triglyceride concentrations during consumption of complex carbohydrate and during consumption of sweetened beverages containing 0%, 10%, 17.5%, and 25% of Ereq-HFCS. Circulating 24-h triglyceride plasma concentrations during consumption of energy-balanced baseline diets containing 55% Ereq complex carbohydrate at 0 wk and during consumption of energy-balanced intervention diets containing isocaloric amounts of carbohydrate as complex carbohydrate and (A) 0% Ereq-HFCS ($n = 23$), (B) 10% Ereq-HFCS ($n = 18$), (C) 17.5% Ereq-HFCS ($n = 15$), or (D) 25% Ereq-HFCS ($n = 28$) at 2 wk. (E) The change in circulating 24-h triglyceride plasma concentrations (2 wk – 0 wk) quantified for each group as Δ24-h uric acid AUC. *$P < 0.05$, effect of HFCS group; 2-factor (HFCS group, sex) ANCOVA of Δ with adjustment for BMI and [outcome] at baseline. [a]Δ different from [b]Δ, Tukey's multiple-comparisons test. **$P < 0.01$, least squares mean different from zero. Significance notations in red indicate that difference did not retain significance after correction for multiple comparisons ($P < 0.0031$). Data are means ± SEs. CHO, carbohydrate; Ereq, energy requirement; HFCS, high-fructose corn syrup; Δ, absolute change.

CVD (32) and loss-of-function mutations in the apoCIII gene are associated with lower triglyceride concentrations and reduced risk of ischemic CVD (33).

The unregulated phosphorylation of fructose to fructose-1-phosphate by fructokinase, which results in conversion of ATP to AMP and a depletion of inorganic phosphate, leads to uric acid production via the purine degradation pathway (17). It has also been reported that a high-fructose diet increases de novo purine biosynthesis in humans, and this also contributes to increased uric acid production (34). Our results regarding the proportion of variation explained by HFCS-dose suggest that these pathways are highly sensitive to the dose of fructose. These results do not support the conclusion from a meta-analysis that isocaloric exchange of fructose for other carbohydrate does not affect serum uric acid concentrations in nondiabetic subjects (35) (see Supplemental Discussion for details and **Supplemental Figure 5**A, C). Uric acid is also a potential mediator of metabolic disease, with most recent studies, but not all (36), showing that it is

TABLE 3
Relation of Δuric acid and apoCIII with the HFCS-induced increases in non–HDL cholesterol, LDL cholesterol, and apoB[1]

		Model 2[3]		Model 3[4]		Model 4[5]		
Risk factor/index	Model 1[2]: dose	Dose	Δuric acid[6]	Dose	ΔapoCIII	Dose	Δuric acid[6]	ΔapoCIII
ΔFST non–HDL cholesterol								
% Variance[7]: covariate	15	4	8	8	13[8]	2	6	11[8]
P value	<0.0001	0.033	0.0017	0.0016	<0.0001	0.11	0.0025	<0.0001
% Variance: model	29		38		43		49	
ΔPP non–HDL cholesterol								
% Variance: covariate	24	9	7	8	12[9]	2	6	11[9]
P value	<0.0001	0.0007	0.0036	0.0010	<0.0001	0.063	0.0022	<0.0001
% Variance: model	37		43		49		55	
ΔFST LDL cholesterol								
% Variance: covariate	18	4	11	12	7[8]	2	9	5[8]
P value	<0.0001	0.023	0.0003	0.0003	0.0051	0.066	0.0005	0.0080
% Variance: model	28		39		35		44	
ΔPP LDL cholesterol								
% Variance: covariate	20	7	6	12	8[9]	4	5	6[9]
P value	<0.0001	0.0051	0.0066	0.0002	0.0026	0.018	0.0043	0.011
% Variance: model	35		38		39		44	
ΔFST apoB								
% Variance: covariate	14	3	8	7	10[8]	1	7	8[8]
P value	0.0002	0.050	0.0017	0.0030	0.0006	0.16	0.0026	0.0009
% Variance: model	28		37		38		45	
ΔPP apoB								
% Variance: covariate	20	5	10	7	8[9]	1	9	7[9]
P value	<0.0001	0.0097	0.0006	0.0033	0.0026	0.19	0.0005	0.0019
% Variance: model	30		37		38		47	

[1] apoB, apolipoprotein B; apoCIII, apolipoprotein CIII; FST, fasting; HFCS, high-fructose corn syrup; PP, postprandial; Δ, absolute change.
[2] Model 1: general linear model with dose (0%, 10%, 17.5%, 25%) as a continuous covariate and adjustment for sex, BMI, and [outcome] at baseline.
[3] Model 2: model 1 plus Δuric acid as a continuous covariate.
[4] Model 3: model 1 plus ΔapoCIII as a continuous covariate.
[5] Model 4: model 1 plus Δuric acid and ΔapoCIII as continuous covariates.
[6] ΔFST and Δ24-h mean uric acid yielded nearly identical results in models 2 and 4. Only FST uric acid results are presented.
[7] % Variance: proportion of variance explained by variable or model = (type III sum of squares/corrected total sum of squares) × 100.
[8] Results shown for ΔFST apoCIII.
[9] Results shown for ΔPP apoCIII.

strongly associated and predictive of metabolic syndrome, fatty liver, and CVD (37–39). In one study, an HR of 1.14 for coronary heart disease events was documented for every 0.5-mg/dL increase of uric acid concentrations (40). The similar increases induced by the 25% Ereq-HFCS dose in just 2 wk [+0.5 ± 0.1 (fasting), +0.6 ± 0.1 mg/dL (24-h mean)] suggest that consumption of HFCS can have clinically relevant effects to increase circulating uric acid.

Our results do not support the recent reports that adults consuming beverages containing 8%, 18%, or 30% Ereq as sucrose or HFCS for 10 wk exhibited no differences of total cholesterol or LDL cholesterol (5) and 24-h uric acid and triglyceride AUC responses (6) between doses. The results from these studies (6) and the present study are starkly contrasting. For example, although Yu et al. (6) reported no differences in the 24-h uric acid AUC "response to the 6 different interventions at baseline or post-testing," we report that consumption of the 25% Ereq-HFCS dose increased 24-h uric acid AUC over baseline (Figure 2E: 14.0 ± 2.2 mg/dL × 24 h, $P < 0.0001$, least squares mean significantly different from zero, ANCOVA) and compared with 10% Ereq-HFCS (+12.8 mg/dL × 24 h, $P < 0.0001$, Tukey's multiple-comparisons test). Possible explanations for the contrasting results include the use of milk as a vehicle for the sugars, lack of a control group, the statistical analyses employed, and lack of an objective measure of compliance (see Supplemental Discussion) (6).

A strength of the current study was the presence of a biomarker in the study beverages, which provided an objective measure of compliance. Furthermore, the participants' knowledge of the biomarker likely contributed to the excellent degree of compliance, as evidenced by the highly significant dose-response effects obtained for most of the outcomes. The 3.5-d inpatient periods during baseline and at the end of intervention, which ensured that the study results were not confounded by noncompliance or variations in diet or physical activity during the days immediately preceding the blood collection procedures, are an additional strength.

A limitation of the study was that it was not randomized, thus potentially introducing bias in the assignment of subjects to the

experimental groups. Another limitation is that that the participants consumed ad libitum diets with the study beverages during the 12-d outpatient period, which precludes our drawing conclusions concerning the effects of precise amounts of sugar consumption. Also, in interventions studies lasting 3–10 wk, subjects consumed significantly more energy and gained more weight when consuming sugar-sweetened beverage/snacks compared with artificially sweetened beverages/snacks (41–43). Therefore, variations in outpatient energy intake likely explain the nominally significant dose-response effect of HFCS consumption on body weight gain. This dose-dependent body weight gain could have mediated the dose-dependent increases in the other outcomes. However, the highly significant effects of HFCS-dose in the statistical models adjusted for body weight gain suggest that the dose-dependent effects of HFCS on risk factors were largely independent of body weight gain. This suggestion is supported by reports of increases of risk factors in subjects who consumed high-sugar diets as part of energy-balanced diet protocols and, therefore, did not gain weight (44–47).

The added sugar component of the typical US diet consists of at least as much sucrose as HFCS (48); therefore, a limitation of this study is that we did not also investigate the dose-response effects of sucrose consumption. However, older and recent studies suggest that consumption of sucrose beverages also increases risk factors for CVD (19, 47, 49, 50). The duration of the 2-wk intervention could be considered a potential limitation. It also, however, indicates how quickly excess sugar consumption can initiate metabolic dysregulation. Certainly, the results from sucrose intervention studies ranging from 6 wk to 6 mo (19, 44, 47, 51) and the numerous epidemiologic studies demonstrating associations between CVD risk factors and sugar consumption (1, 2) provide evidence that the highly significant results reported here would unlikely be transient during a longer intervention period.

In conclusion, this study demonstrates that consumption of beverages providing 10%, 17.5%, or 25% Ereq from HFCS results in dose-dependent increases of established risk factors for CVD within 2 wk in young men and women. Concentrations of non–HDL cholesterol, LDL cholesterol, apoB, uric acid, postprandial apoCIII, and postprandial triglyceride increased as the dose of HFCS consumed increased, and they were significant compared with consumption of 0% Ereq-HFCS beverages for most outcomes (12 of 16) in the 25% Ereq-HFCS group, for half (8 of 16) of the outcomes in the 17% Ereq-HFCS group, and for postprandial triglyceride in the 10% Ereq-HFCS group. These results provide a plausible mechanistic link to the results of the recent report that there is increased risk of CVD mortality with increased intake of added sugar across quintiles (2). Both studies suggest that humans are sensitive to the adverse effects of sustained sugar consumption at a relatively wide range of intake and highlight the need for carefully controlled diet intervention studies to determine prudent amounts of added sugar consumption.

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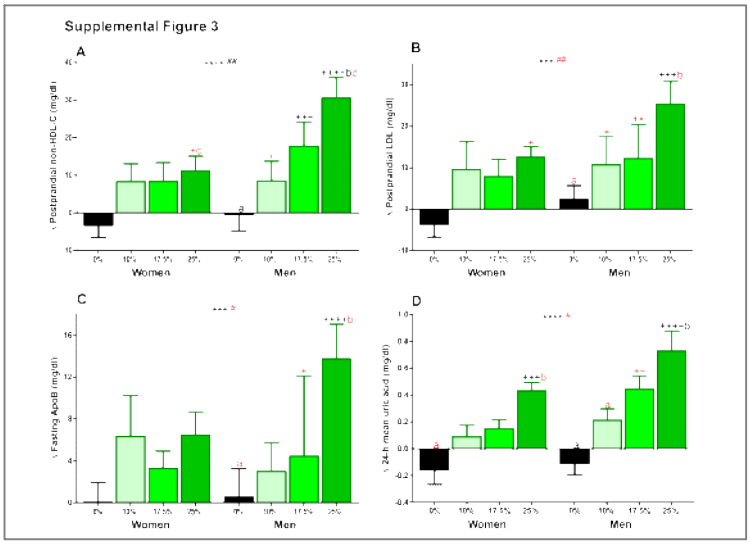

Supplemental Figure 3: Sex-specific effects of consuming aspartame- or HFCS-sweetened beverages on non-HDL-C, LDL-C, apoB and uric acid. The sex-specific least squares (LS) mean (adjusted for sex, BMI and outcome at baseline) ± SE of Δ PP non-HDL-C (**A**), PP LDL-C (**B**), FST apoB (**C**) and 24-h mean uric acid (**D**) plasma concentrations in women and in men after consuming beverages providing 0% (n = 12 women/11 men), 10% (n = 9 women/9 men), 17.5% (n = 9 women/7 men) or 25% (n = 13 women/15 men) of Ereq from HFCS for 2 weeks. ***$P < 0.001$, ****$P < 0.0001$, effect of HFCS-group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, effect of sex, 2-factor (HFCS group, sex) analysis of covariance of Δ with adjustment for BMI and outcome at baseline. Within sex comparison: ^{a}Δ different from ^{b}Δ; within HFCS-group comparison: ^{c}Δ different from ^{d}Δ, Tukey's. $^{+}P<0.05$, $^{++}P<0.01$, $^{+++}P<0.001$, $^{++++}P<0.0001$, LS mean different from zero. Significance notations in red indicate that difference did not retain significance after correction for multiple comparisons ($P < 0.0031$).

Supplemental Figure 3

This is the same as Figure 1, except split between women and men, [1A] Non-HDL cholesterol (after eating); [1B] LDL-cholesterol (after eating)

Primary Results

- Non-HDL and LDL cholesterols increase significantly for men.
- Non-HDL and LDL cholesterols do not increase significantly.

Take Away: Men experience greater increases in cholesterol from 25% HFCS than women.