Research Article

JOURNAL OF HEPATOLOGY

Sugar-sweetened beverage, diet soda, and fatty liver disease in the Framingham Heart Study cohorts

Jiantao Ma[1], Caroline S. Fox[2,3], Paul F. Jacques[1], Elizabeth K. Speliotes[4], Udo Hoffmann[3,5], Caren E. Smith[1], Edward Saltzman[1], Nicola M. McKeown[1,*]

[1]*USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, United States;* [2]*NHLBI's Framingham Heart Study, Framingham, MA, United States;* [3]*Harvard Medical School, Boston, MA, United States;* [4]*University of Michigan Medical School, Ann Arbor, MI, United States;* [5]*Massachusetts General Hospital, Boston, MA, United States*

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Background & Aims: Non-alcoholic fatty liver disease affects ~30% of US adults, yet the role of sugar-sweetened beverages and diet soda on these diseases remains unknown. We examined the cross-sectional association between intake of sugar-sweetened beverages or diet soda and fatty liver disease in participants of the Framingham Offspring and Third Generation cohorts.

Methods: Fatty liver disease was defined using liver attenuation measurements generated from computed tomography in 2634 participants. Alanine transaminase concentration, a crude marker of fatty liver disease, was measured in 5908 participants. Sugar-sweetened beverage and diet soda intake were estimated using a food frequency questionnaire. Participants were categorized as either non-consumers or consumers (3 categories: 1 serving/month to <1 serving/week, 1 serving/week to <1 serving/-day, and ⩾1 serving/day) of sugar-sweetened beverages or diet soda.

Results: After adjustment for age, sex, smoking status, Framingham cohort, energy intake, alcohol, dietary fiber, fat (% energy), protein (% energy), diet soda intake, and body mass index, the odds ratios of fatty liver disease were 1, 1.16 (0.88, 1.54), 1.32 (0.93, 1.86), and 1.61 (1.04, 2.49) across sugar-sweetened beverage consumption categories (p trend = 0.04). Sugar-sweetened beverage consumption was also positively associated with alanine transaminase levels (p trend = 0.007). We observed no significant association between diet soda intake and measures of fatty liver disease.

Conclusion: In conclusion, we observed that regular sugar-sweetened beverage consumption was associated with greater risk of fatty liver disease, particularly in overweight and obese individuals, whereas diet soda intake was not associated with measures of fatty liver disease.

Keywords: Sugar-sweetened beverages; Diet soda; Alanine transaminase; Fatty liver disease.

Received 9 November 2014; received in revised form 1 March 2015; accepted 27 March 2015; available online 5 June 2015

☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2015.05.021.

* Corresponding author. Address: Jean Mayer USDA HNRCA at Tufts University, 711 Washington Street, Boston, MA 02111-1524, United States. Tel.: +1 (617) 556 3008; fax: +1 (617) 556 3344.

E-mail address: nicola.mckeown@tufts.edu (N.M. McKeown).

Abbreviations: ALT, alanine transaminase; FFQ, food frequency questionnaire; LPR, liver to phantom ratio; MDCT, multidetector computed tomography; NAFLD, nonalcoholic fatty liver disease; SAT, abdominal subcutaneous adipose tissue; SSB, sugar-sweetened beverage; VAT, visceral adipose tissue.

Introduction

Currently, an estimated 30% of the US adult population has non-alcoholic fatty liver disease (NAFLD) [1], a spectrum of pathological disorders that includes simple hepatic steatosis, steatohepatitis, and cirrhosis that arises despite a lack of alcohol consumption [2]. Individuals with NAFLD are at greater risk of developing type 2 diabetes [3] and cardiovascular disease [4]. Hepatic steatosis, or fatty liver, is the defining characteristic of NAFLD [5,6]. Several imaging techniques are able to accurately capture hepatic steatosis [1]. One aspect of diet that has been postulated to increase risk of developing NAFLD is sugars, particularly fructose [7]. While some randomized controlled trials have found high intakes of fructose are linked to greater liver fat [8,9], others have not [10,11]. However, fructose in these studies was excessive (providing 25–60% of energy) and these intakes are rarely consumed at such high amounts in the general population. To date, there is relatively little evidence indicating whether habitual intake of added sugars as typically consumed, i.e. in the form of sucrose or high fructose corn syrup, is associated with fatty liver disease in healthy adults.

Sugar-sweetened beverages (SSB) are the leading source of added sugars in the American diet [12]. The caloric sweeteners in SSB, sucrose and high fructose corn syrup, are also the most commonly used fructose-containing sugars. Diet soda is similar to regular soda; however, it contains no added fructose or other sugars. Our hypothesis was that, independent of generalized adiposity, higher habitual SSB intake would be associated with higher risk of fatty liver disease, whereas no such association would be observed with diet soda. Thus, the objectives of the

present study were to examine the cross-sectional association between habitual SSB and diet soda intake, and liver fat measured by multidetector computed tomography (MDCT), and alanine transaminase (ALT) levels (a crude marker of fatty liver disease in a population based cohort).

Participants and methods

Participants

Study participants were from the Framingham Heart Study's Offspring cohort and Third Generation (Gen3) cohort and have been previously described [13,14]. In brief, the Offspring cohort began in 1971 by enrolling 5124 adults, and the Gen3 cohort was initiated in 2002 with enrollment of 4095 adults. Participants were evaluated approximately every 3–4 years. From 2002 to 2005, 3529 participants were assessed by MDCT scans [3]. The following inclusion criteria were applied for the MDCT study: body weight <160 kg, men $\geqslant$35 years of age, and non-pregnant women >40 years of age. We excluded 323 individuals with non-interpretable MDCT scans. We also excluded 333 individuals with unreliable dietary data and 5 participants who were missing important covariates. Dietary information, as assessed by food frequency questionnaire (FFQ), was considered unreliable if reported energy intake was: <2.5 MJ/d for both men and women; $\geqslant$16.7 MJ/d for women; $\geqslant$17.5 MJ/d for men; or if $\geqslant$13 food items were left blank on the questionnaire. In order to avoid potential confounding from high alcohol consumption, we further excluded 234 individuals who were classified as high alcohol consumers, i.e. men consuming >21 and women consuming >14 alcoholic beverages/week [1]. The final sample size for the analyses using imaging data was 2634 participants, 1075 from the Offspring cohort and 1559 from the Gen3 cohort. After applying the same exclusion criteria among the full cohorts, we identified 5908 individuals who had valid measurements for ALT concentrations and dietary and covariate data: 2593 from Offspring and 3315 from the Gen3 cohort. All participants provided written informed consent before study participation. The Framingham Heart Study protocols and procedures were approved by the Institutional Review Board for Human Research at Boston University Medical Center, and the current analyses were approved by the Tufts Medical Center and Tufts University Health Sciences Institutional Review Board.

Fatty liver disease

The protocols for measuring liver fat and ALT have been described in detail previously [15,16]. In brief, participants underwent an abdominal scan with an 8-slice MDCT scanner (LightSpeed Ultra; General Electric Health Care, Milwaukee, WI) from 2002 to 2005. The Hounsfield Units were estimated for three regions in the liver and one in the calibration control (phantom). The liver fat content was estimated using liver attenuation, which was reflected by multiplying the ratio of the average Hounsfield Units for liver to that for the phantom by 100 [3]. A lower value of the liver to phantom ratio (LPR) represented a higher volume of liver fat. A value of LPR <33.0 indicated the presence of fatty liver [3]. Visceral adipose tissue (VAT, cm^3) and abdominal subcutaneous adipose tissue (SAT, cm^3) were measured using the same MDCT scans [17]. Fasting serum ALT concentrations were measured using the kinetic method [16]. Elevated ALT level was defined using a sex-specific cut-off point, (above 19 U/L for women and 30 U/L for men) [18].

Beverage consumption

SSB and diet soda intakes were assessed using the Harvard semi-quantitative FFQ which was designed to assess the habitual dietary intake for the year preceding the physical and medical examinations [19]. The FFQ consisted of 126 food items with standard serving sizes and a selection of 9 frequency categories ranging from none or <1 serving/month to $\geqslant$6 servings/day. The present study used dietary data collected in the 7th exam cycle (1998–2001) of the Offspring cohort and in the 1st examination (2002–2005) of the Gen3 cohort.

The SSB assessment on the FFQ included the following: (1) caffeinated colas with sugar; (2) caffeine-free colas with sugar; (3) other carbonated beverages with sugar; and (4) fruit punches, lemonade, or other non-carbonated fruit drinks. Diet soda was captured using 3 FFQ items including the following: (1) low calorie cola; (2) low calorie, caffeine-free cola; and (3) other low calorie carbonated beverage. The relative validity of the FFQ has been examined for both nutrients and foods in other cohorts [19–21]. The correlation coefficients between FFQ and 7-day dietary records for SSB and diet soda were 0.51 and 0.66, respectively. Participants were categorized according to the frequency of SSB and diet soda consumption: none to <1 serving/month (non-consumers), 1 serving/month to <1 serving/week, 1 serving/week to 1 serving/day, and $\geqslant$1 serving/day (daily consumers).

To better estimate long-term consumption [22], we calculated the cumulative average intakes of SSB and diet soda using data from three Offspring cohort exam cycles (5th, 6th, and 7th) in 888 participants with imaging data and in 2029 participants with enzyme data, reflecting approximately 7 years of follow-up. Participants were categorized in the same way as described above. The cumulative average intake was not calculated for participants in the Gen3 cohort because dietary data were only available at one examination prior to MDCT scans.

Anthropometry and covariates assessment

Standard protocols were used in physical and medical examinations at each visit. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Physical activity level was calculated based on questionnaire-derived time and intensity of activities in a typical day [23]. Nutrient and food intakes were estimated using the FFQ as described above. The 2005 Dietary Guidelines Adherence Index (DGAI) was used to capture overall diet quality [24]. Fasting plasma glucose and serum lipids were measured after an overnight fast. Blood pressure was calculated as the mean of two blood pressures measured by a physician. Diabetes was defined as a fasting plasma glucose concentration $\geqslant$7 mmol/L or self-reported use of diabetes medicines. Metabolic syndrome was defined according to the ATP III criteria [25].

Statistical analysis

Characteristics of participants who had liver imaging data were evaluated using least-squares means after adjustment for age and sex. Dietary characteristics were additionally adjusted for energy intake. A test for linear trend across categories of SSB intake was performed by assigning the median value of SSB intake to every individual in the category and treating this as a continuous independent variable in linear regression models for continuous response variables, or in logistic regression models for dichotomous response variables.

In the primary analysis using MDCT imaging data, the odd ratios (ORs) of fatty liver disease and least-squares means of LPR across SSB consumption categories were estimated using logistic regression and linear regression models, respectively. Model 1 was adjusted for the following covariates: age (y), sex, smoking status (non-smokers or current smokers), Framingham cohort (Offspring and Gen3), energy intake (kcal/d), alcohol intake (g/d), dietary fiber (g/d), dietary fat (% energy), dietary protein (% energy), and diet soda (serving/wk). Linear trends for both outcomes were tested across categories of SSB intake using the median value approach with adjustment for the same covariates. We further adjusted for BMI to test if associations may be independent of generalized adiposity. Finally, we examined whether VAT and SAT may confound the association between SSB and liver fat.

In secondary analyses, we repeated the above analyses using the cumulative average intake of SSB in the Offspring cohort. We also additionally examined whether diabetes might confound or modify the main association between SSB intake and liver fat. In addition, we tested whether sex, age, or BMI might modify the association between SSB intake and liver fat by including a product term of SSB intake and dichotomous variables of sex, age (< and $\geqslant$ median age of 50 years), or BMI (<25 and $\geqslant$25 kg/m^2) in multiple regression models for linear trend. We examined whether the observed associations might be confounded by DGAI and physical activity level. We also examined the association between SSB intake and liver fat with adjustment for individual food intake (fruits, vegetables, whole grains, red meat, coffee, and nuts) and multivitamin use.

We conducted the same analyses as described above to examine the association between SSB intake and continuous and elevated ALT concentrations. We also conducted primary and secondary analyses for diet soda using the same imaging and enzyme data and same statistical approaches. In the analyses for diet soda, we adjusted for SSB intake. All statistical analyses were conducted using SAS statistical software (version 9.3; SAS Institute, Cary, North Carolina). A two-tailed p <0.05 was considered statistically significant, unless otherwise specified.