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# INCREASED FRUCTOSE CONSUMPTION IS ASSOCIATED WITH FIBROSIS SEVERITY IN PATIENTS WITH NAFLD

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## Abstract

**Background and Aims—**The rising incidence of obesity and diabetes coincides with a marked increase in fructose consumption. Fructose consumption is higher in individuals with nonalcoholic fatty liver disease (NAFLD) than age- and BMI-matched controls. Because fructose elicits metabolic perturbations that may be hepatotoxic, we investigated the relationship between fructose consumption and disease severity in NAFLD.

**Methods—**We studied 341 adults enrolled in the NASH Clinical Research Network for whom Block food questionnaire data were collected within 3 months of a liver biopsy. Fructose consumption was estimated based on reporting (frequency × amount) of kool-aid, fruit juices, and non-dietary soda intake, expressed as servings per week, and classified into none, occasional (< 7 servings/week), and daily (> = 7 servings/week). The association of fructose intake with metabolic and histologic features of NAFLD was analyzed using multiple linear and logistic regression analyses with and without controlling for other confounding factors.

**Results—**Increased fructose consumption was univariately associated with decreased age ($p < 0.0001$), male gender ($p < 0.0001$), hypertriglyceridemia ($p < 0.04$), low HDL cholesterol (< 0.0001), decreased serum glucose ($p < 0.001$), increased calorie intake ($p < 0.0001$) and hyperuricemia ($p < 0.0001$). After controlling for age, gender, BMI, and total calorie intake, daily fructose consumption was associated with lower steatosis grade and higher fibrosis stage ($p < 0.05$ for each). In older adults (age > 48 years), daily fructose consumption was associated with increased hepatic inflammation ($p < 0.05$) and hepatocyte ballooning ($p = 0.05$).

**Conclusions—**In patients with NAFLD, daily fructose ingestion is associated with reduced hepatic steatosis but increased fibrosis. These results identify a readily modifiable environmental risk factor that may ameliorate disease progression in patients with NAFLD.

## INTRODUCTION

The prevalence of obesity in the United States is rising, and with it, the frequency of fatty liver, nonalcoholic steatohepatitis (NASH), “cryptogenic” cirrhosis, hepatocellular

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carcinoma, and other end-organ complications of the metabolic syndrome (1,2). The health-care burden and associated economic implication of the epidemic of obesity, diabetes, and the hepatic complications of the metabolic syndrome are tremendous (3). Unfortunately, no therapy for NAFLD currently exists. Therefore, a rigorous search for modifiable risk-factors and/or environmental exposures which may increase the risk of developing NASH or its transition to cirrhosis is essential.

The rapid rise in NAFLD supports a role for environmental factors in the pathogenesis of this condition. In this regard, recent studies suggest that overconsumption high fructose corn syrup (HFCS) primarily in the form of soft-drink consumption, is linked to weight gain and the rise in obesity, particularly in children and adolescents (4–6) and increases the risk for NAFLD. Table sugar (sucrose) and HFCS are the two major dietary sources of fructose. Intake of dietary fructose, either as a free monosaccharide or bound to glucose in the form of sucrose, has increased 1,000% during the past 40 years (5). First introduced into the human diet around 1970, HFCS consumption during the past decade accounts for 10% of caloric food intake (7).

Dietary fructose is a major candidate for causing NAFLD. Unlike glucose, fructose ingestion can rapidly cause fatty liver in animals, in association with the development of leptin resistance (8), microvascular disease, and vascular inflammation (9,10). Recent data suggest that increased fructose consumption increases fat mass, *de novo* lipogenesis and inflammation and induces insulin resistance and post-prandial hypertriglyceridemia, particularly in overweight individuals (10–15). Further, studies have indicated that the development of NAFLD may be associated with excessive dietary fructose consumption (16,17). Whether increased fructose consumption correlates merely with the development of NAFLD or promote the transition from NAFLD to NASH and more advanced stages of liver damage remains unclear. In view of the global increase in fructose consumption and its association with NAFLD, we sought to evaluate the influence of fructose consumption on liver histology in patients with NAFLD.

## METHODS

### Study design and population

We performed cross-sectional analyses using data from the NASH Clinical Research Network (NASH CRN) (18,19) of patients diagnosed with NAFLD who were enrolled from September 2004 to March 2007. Patients enrolled in the NAFLD Database Study or in the PIVENS trial who met the following criteria were used for our analysis (N = 427): 1) age ≥18 years, 2) available liver histology data, 3) no significant alcohol consumption (> 14 drinks/week in men or > 7 drinks/week in women on average within the past 2 years) or other coexisting etiologies for chronic liver disease and 4) dietary information available from the Block food questionnaire (20) within 3 months of the liver biopsy. The NASH CRN studies were approved by the Institutional Review Boards at each participating center.

### Liver histology

The primary outcome in this study was the impact of fructose consumption on liver histology in patients with NAFLD. All liver biopsies were stained with hematoxylin-eosin and Masson's trichrome stains, and reviewed and scored centrally by the Pathology Committee according to the published NASH CRN scoring system (21). For the analyses, fibrosis stage 1a 1b, and 1c were combined and treated as stage 1.

### Dietary information

Although sugar-sweetened beverages and fruit or fruit juices account for approximately 50% of total fructose consumption (22), we elected to remain conservative in our data acquisition by limiting our dietary assessment of fructose intake to beverage intake only. Dietary information was obtained via a validated dietary questionnaire (Block food questionnaire, version 1998) as self-reported usual eating habits over the prior year. For the calculation of fructose consumption, we first retrieved frequency (per week) and numbers of servings (per day) of fructose-containing beverages. The number of weekly servings of each drink were calculated as a product of frequency per week and number of servings per day and expressed as servings per week. The number of servings were then combined as total servings of fructose-containing drinks per week and used to estimate individual fructose consumption levels. For the analyses, total weekly servings of fructose-containing drinks were classified into three categories: 'non-consumers' (0 servings per week), 'minimum to moderate consumers' (> 0 and < 7 servings per week), and 'daily consumers' (≥7 servings per week) of fructose. The amount of fructose consumed was the primary predictor in this study. Estimates of total calories, carbohydrates, protein, and fat intake from the food frequency questionnaire were performed as previously published by Block *et al* (20).

### Other study variables

Age, gender, ethnicity, race, body mass index (BMI), fasting lipid profiles (triglycerides, HDL-cholesterol, and LDL-cholesterol), serum uric acid, fasting serum glucose and insulin as well as data regarding the use of insulin and/or insulin sensitizing agents were collected at study enrollment. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as [fasting glucose (g/dl) × fasting insulin (μU/ml)]/405.

### Statistical analyses

Data are reported as mean ± standard deviation or number (proportion) of patients with a condition. The clinical characteristics between the three categories of fructose consumption were compared using ANOVA with Tukey's Post Hoc Test or Chi-square tests. The associations between fructose consumption and metabolic features were assessed after adjusting for other potential confounders using multiple linear regression models with two dummy variables ('no fructose consumers' as a reference group) and other potential confounders. The associations between fructose consumption and histologic features of NAFLD were assessed using ordinal logistic regression models with and without adjusting for other potential confounders. In the models, four binary logistic curves with different cut-offs (stage 0 vs. 1–4, 0–1 vs. 2–4, 0–2 vs. 3–4, 0–3 vs. 4) were modeled and cumulative odds were computed by pooling a set of β estimates. Three multiple ordinal logistic regression models were developed to assess the associations between fructose consumption and each histologic features: 1) only dummy variables of fructose consumption (unadjusted), 2) the variables in 1) plus, age, gender, ethnicity, BMI, and total calorie intake (Model 1), and 3) the variables in 2) plus triglycerides, HDL-cholesterol, LDL-cholesterol, serum uric acid, and HOMA-IR (Model 2). Further, to investigate whether the influence of fructose consumption on liver histology in NAFLD differs depending on age, we assessed the associations between fructose consumption and histologic features of NAFLD in different age groups. The study population was divided into two age groups by using a median age value (48 years old). Multiple ordinal logistic regression models (Model 1 and 2) were then separately developed in each group. For the analyses in the age subgroups, fructose consumption was classified into two groups, 'daily consumers' vs. others. For analyses, we used JMP statistical software version 7.0 (SAS institute Inc.) and considered differences statistically significant when the p-value(s) were less than 0.05. Due to the preliminary nature of this subgroup analysis and small sample size, correction for multiple comparisons was not performed.

# RESULTS

## Clinical characteristics of the study population

The clinical characteristics associated with different levels of fructose consumption are summarized in Table 1. Median fructose consumption of the study population was one serving per week (first and the third quartiles 0 and 7, respectively). When the study population was classified into the following three fructose consumption categories: 'no', 'minimum to moderate' and 'daily' fructose consumers, it became apparent that a significant subpopulation (27.9%) consumed the equivalent of at least one fructose-containing beverage per day. The remaining patients consumed either no fructose-containing beverages (84 individuals, 19.7%), or between 1 and 6 servings/week (224 individuals, 52.5%). Higher fructose consumption was univariately associated with younger age, male gender, higher BMI, hypertriglyceridemia, lower HDL-cholesterol, hyperuricemia, and higher total calorie intake (as well as calorie intake of all three different nutrients). Fructose consumption was not associated with fasting serum insulin levels or HOMA-IR; however, 'minimum to moderate fructose consumers' were associated with lower fasting serum glucose compared to 'no fructose consumers'. In the univariate analyses, no difference in histologic features was observed among the fructose consumption groups.

## Associations between fructose consumption and metabolic parameters

Since there were significant differences in age, gender, and BMI among the fructose consumption categories, we assessed the associations between fructose consumption and metabolic parameters after adjusting for these factors (Table 2a). After adjusting for age, gender, and BMI, daily fructose consumption was significantly associated with lower HDL-cholesterol and higher serum uric acid, compared to no fructose consumption; the estimated differences in mean values of these parameters between 'no fructose consumers' and 'daily consumers' (i.e., $\beta \pm SE$) were $-5.5 \pm 1.8$ mg/dl ($p = 0.002$) for HDL-cholesterol and $0.5 \pm 0.2$ mg/dl ($p = 0.03$) for uric acid. Compared to the no fructose consumer group, 'minimum to moderate fructose consumers' had lower fasting serum glucoses, triglycerides and HDL-cholesterol; the estimated differences in means between 'no fructose consumers' and 'minimum to moderate consumers' were $-12.2 \pm 3.9$ g/dl ($p = 0.002$) for fasting serum glucose, $-37.0 \pm 18.8$ mg/dl ($p = 0.05$) for triglycerides, and $-2.7 \pm 1.5$ mg/dl ($p = 0.07$) for HDL-cholesterol. After adjustment for total calorie intake, the difference in serum uric acid between groups ('no fructose consumers' vs. 'daily consumers') was no longer significant. However, the differences in serum glucose and lipids persisted (data are not shown). We repeated the same analyses after excluding subjects who were on insulin or insulin sensitizing agents ($n = 70$). With the adjustment for age, gender, and BMI, the association between blood glucose levels and fructose consumption was diminished; however, daily fructose consumption remained associated with lower HDL-cholesterol ($p < 0.001$) compared to no fructose consumption (Table 2b)

## Associations between fructose consumption and histologic severity of NAFLD

To investigate relationships between fructose consumption and histologic features of NAFLD, we first assessed the associations in the entire study population with and without adjustment for age, gender, Hispanic ethnicity, BMI, total calorie intake, and metabolic parameters. The cumulative odds ratios with 95% confidence intervals of the fructose consumption categories for steatosis, lobular inflammation, ballooning, and fibrosis are summarized in Table 3. Higher fructose consumption was less likely to be associated with higher histologic grades of steatosis; cumulative odds ratios with 95% confidence intervals of 'minimum to moderate consumers' and 'daily consumers' vs. 'no fructose consumers' were 0.7 [0.4, 1.1] ($p = 0.10$) and 0.4 [0.2, 0.9] ($p = 0.02$) respectively (in the full models/ Model 2). On the other hand, daily fructose consumption was more likely associated with

higher histologic stages of fibrosis; cumulative odds ratios with 95% confidence intervals of 'daily consumption' vs. 'no fructose consumption' were 2.6 [1.4, 5.0] (p = 0.004) (in the full models/Model 2).

### Associations between fructose consumption and histologic severity of NAFLD in different age groups

Age and/or aging-related mitochondrial dysfunction is associated with a decline in the intrinsic metabolic activity of the liver and fibrosis progression (23,24). Therefore, we further evaluated the association between fructose consumption and histologic severity of NAFLD in different age groups to see whether the influence of fructose consumption on liver histology in NAFLD differs depending on age. The adjusted cumulative odds ratios with 95% confidence intervals of 'daily consumption' vs. higher levels of fructose consumption for steatosis, lobular inflammation, ballooning, and fibrosis are summarized in Table 4. Among older subjects, 'daily consumers' were less likely to have higher grades of steatosis (adjusted cumulative OR [95% CI] = 0.2 [0.1, 0.5], p = 0.0008 in Model 2) and were more likely to have higher grades of lobular inflammation (adjusted cumulative OR [95% CI] = 2.5 [1.0, 6.2], p < 0.05 in Model 2) and ballooning (adjusted cumulative OR [95% CI] = 2.5 [1.0, 6.0], p = 0.05 in Model 2). Compared to non-consumers of fructose beverages, both older and younger 'daily fructose consumers' were more likely to have higher stages of liver fibrosis; adjusted cumulative OR and 95% confidence intervals in Model 2 were 3.2 [1.7, 6.1], p = 0.0003 for the younger groups and 3.2 [1.4,7.4], p = 0.006 for the older groups.

## DISCUSSION

Recent data suggest that intake of more simple carbohydrates and less saturated fat is higher in patients with NAFLD compared with the general population, suggesting that dietary imbalances play a role in the development and progression of NAFLD (25). The ideal diet for NAFLD should reduce fat mass and inflammation in the adipose tissue, restore insulin sensitivity, and provide low amounts of substrates for *de-novo* lipogenesis (26), but scientific evidence to recommend specific diets is currently lacking. Although prior studies suggest an association between increased fructose consumption with NAFLD, no study to date has implicated a dietary risk factor in NAFLD progression. Defining modifiable risk factor(s) for liver disease progression in NAFLD would have significant public health implications for the development of strategies which may decrease risk for liver fibrosis and associated health-related complications. Evidence that childhood obesity and pediatric NALFD are becoming epidemic, particularly in young boys who tend to consume soft drinks (27,28), suggests that there is a significant opportunity to improve risk factors for progressive liver damage at early stages of life.

In this study we investigated the impact of increased fructose consumption on the metabolic syndrome and histologic features of NAFLD. In patients with established NAFLD, increased consumption of fructose was associated with younger age, male gender, increased BMI, increased serum triglycerides, lower HDL cholesterol, and higher uric acid levels. To our surprise, increased fructose consumption appeared to improve systemic insulin sensitivity (i.e. lowered fasting serum glucose, slight decrease in serum insulin and HOMA-IR). Although this observation was diminished when excluding all subjects requiring insulin or insulin-sensitizing agents, this finding is particularly notable as it was observed despite evidence that daily fructose ingestion was accompanied by a significant increase in daily consumption of total calories, carbohydrates, proteins, and fats, as well as increased BMI. Further, based on our extended analysis, such associations still appeared to exist among subjects who were on insulin or insulin sensitizing agents (data are not shown). The limited sample size in the subgroup and the cross-sectional nature of this analysis limits the ability

to draw any conclusions regarding causality and/or the impact of increased fructose consumption on the natural history of NAFLD. Further studies are required to delineate potential differential influences of fructose consumption on insulin sensitivity. Also, from the time of diagnosis of NAFLD to the time of study participation, patients may have spontaneously initiated life-style modification (ie. decreased sugar consumption, dietary modification, and/or increased exercise) which led to improved insulin sensitivity. Although, we attempted to decrease the window between liver biopsy and study participation to only 3 months, even a modest dietary change or weight loss could improve insulin sensitivity. Although a dose response relationship between fructose and low HDL cholesterol was observed, the apparent lack of a dose-response relationship between fructose intake and insulin resistance may potentially be explained by other confounders (ie. use of insulin sensitizing agents or lipid lowering agents) which may alter peripheral and/or hepatic insulin sensitivity and decrease hepatic steatosis.

Despite our inability to link increased fructose consumption to worsened insulin resistance, daily fructose consumption was associated with metabolic abnormalities that typically accompany insulin resistance, including lower HDL-cholesterol and higher serum uric acid, even after adjusting for age, gender, and BMI. In this regard, our findings reproduce other reports that have linked such metabolic derangements with increased consumption of fructose (4,5,29–34). Moreover, after controlling for factors that have been shown to influence NAFLD (e.g., age, gender, BMI, Hispanic ethnicity, and total calorie intake), we found that increased fructose consumption was associated with *decreased* hepatic steatosis and *increased* fibrosis. When lipid parameters (triglycerides, HDL- and LDL cholesterol), uric acid, and HOMA-IR were incorporated into the analytical model, the association of increased fructose intake with decreased steatosis and increased fibrosis persisted. In addition, older subjects (age > 48 years old) with NAFLD who consumed increased amounts of fructose (> 7 servings/week) had increased lobular inflammation and ballooned hepatocytes. Other studies have also identified older age as an independent predictor of NAFLD severity (35). Together with those data, our results raise the possibility that habitual ingestion of fructose exacerbates liver injury and promotes fibrosis progression in NAFLD. However, the research tools utilized to collect dietary fructose consumption do not allow us to ascertain whether or not some other dietary constituent for which fructose is simply a “marker” accounts for our findings.

The concept that excessive consumption of fructose might promote progression of NAFLD is biologically plausible given experimental evidence that high fructose corn syrup-55 (HFCS-55) increases ER stress, promotes activation of the stress-related kinase, Jun N-terminal Kinase (JNK), induces mitochondrial dysfunction, and increases apoptotic activity (36–40) in liver cells. Further, a link between dietary fructose intake, gut-derived endotoxemia, toll-like receptor 4 and NAFLD has been suggested by the results of human and animal studies (17,41). Mice fed water enriched with 30% fructose develop hepatic triglyceride accumulation, altered markers of insulin resistance, portal endotoxemia, and increased hepatic lipid peroxidation, MyD88, and TNF-alpha levels. Such data suggest that fructose-induced NAFLD or NASH associated with intestinal bacterial overgrowth and increased intestinal permeability, subsequently leading to an endotoxin-dependent activation of hepatic Kupffer cells (41). As discussed subsequently, habitual fructose consumption may also lead to an unfavorable energy balance in the liver which enhances the susceptibility of hepatocytes to injury (42).

The lipogenic and proinflammatory effects of fructose appear to be due to its unique metabolism, which involves a period of transient ATP depletion due to its rapid phosphorylation within the cell and from its unique ability among sugars to raise intracellular and serum uric acid. In experimental animals, lowering uric acid concentrations

ameliorated features of the metabolic syndrome induced by fructose, including weight gain, hypertriglyceridemia, hyperinsulinemia and insulin resistance, and hypertension (34). These findings were surprising, because most authorities had considered uric acid to be either biologically inert or an important antioxidant in the plasma (43). However, uric acid was found to have numerous deleterious biologic functions. Uric acid stimulates both vascular smooth muscle cell proliferation and the release of chemotactic and inflammatory substances, induces monocyte chemotaxis, inhibits endothelial cell proliferation and migration and causes oxidative stress in adipocytes, which results in the impaired secretion of adiponectin (1,44–48). Fructose-related reductions in hepatic ATP may also help to explain why we observed a relationship between chronic ingestion of fructose, hyperuricemia, and NAFLD severity in our patients. However, after adjusting for total calorie intake and other metabolic features, the association between increased fructose consumption and liver injury persisted suggesting that an alternative mechanism other than hyperuricemia may be involved.

During hepatic fructose metabolism, two molecules of ATP are consumed per each fructose molecule that is metabolized. The resultant ADP is then further degraded to AMP. The fate of this AMP, in turn, is dictated by the relative activities of two competing enzymes, AMP kinase (AMPK) and xanthine dehydrogenase. When AMPK is more active than xanthine dehydrogenase, AMP is “re-cycled” to restore hepatocyte ATP content. Conversely, when xanthine dehydrogenase is more active than AMPK, AMP is converted to uric acid, delaying recovery of hepatic ATP stores [Figure 1]. Intravenous administration of fructose to healthy subjects increases blood levels of uric acid, the urinary excretion of urate and xanthine, and acutely reduces hepatic ATP (49,50). Further, obese patients with NASH were less efficient than healthy controls at recovering from fructose-induced depletion of hepatic ATP stores (51). Exercise, metformin, thiazolidinediones, and adiponectin (12,52–54), all of which have been shown to improve NASH, activate AMPK. Together, these data support the concept that hepatic AMPK activity is relatively inhibited in NASH, rendering hepatocytes more vulnerable to ATP depletion when ATP is consumed during fructose metabolism. Hence, the presence of hyperuricemia may be a surrogate measure of chronic hepatic ATP depletion in habitual fructose consumers (55). In addition, hyperuricemia has long been recognized as a marker of advanced liver disease (49,56). More recently, multivariate analysis demonstrated that hyperuricemia is also an independent risk factor for NASH (57). Thus, studies in animals and humans suggest a mechanism by which habitual fructose consumption promotes progression of liver damage by exacerbating underlying abnormalities in hepatic energy homeostasis. Impaired hepatic energy homeostasis (i.e., ATP depletion) may also explain the observed associations of increased fructose consumption with decreased steatosis and increased hepatic inflammation; inability to supply ATP for the triglyceride synthesis may fail to transform toxic free fatty acids to a safer form of lipids (i.e., triglycerides), constrain accumulated free fatty acids in the liver and exacerbate lipotoxicity.

Although further research is necessary to confirm these results and evaluate this hypothesis directly, data from the current cross-sectional analysis are exciting because they not only lend credence to this concept, but suggest both a novel biomarker (serum uric acid) and a modifiable risk factor (dietary fructose) for liver fibrosis in patients with NAFLD. Given the latter, well-designed prospective controlled dietary intervention studies are necessary to evaluate whether a low-fructose diet improves the metabolic disturbances associated with NAFLD, but also alters the natural history of NAFLD in those at risk of disease progression.

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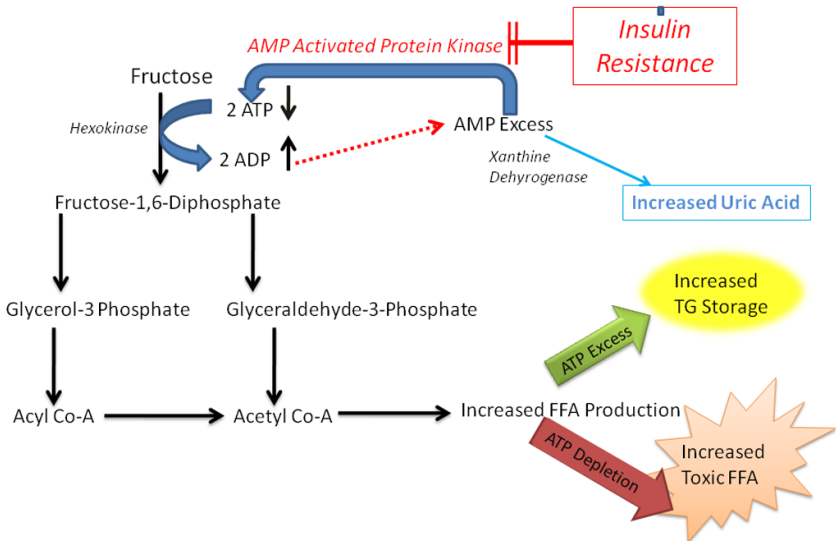


**Figure 1.**

Fructose Associated Hepatic ATP Depletion

For each fructose molecule that is metabolized, two molecules of ATP are consumed.. The resultant ADP is then further degraded to AMP. The fate of this AMP is dictated by the relative activities of two competing enzymes, AMP kinase (AMPK) and xanthine dehydrogenase. When AMPK is more active than xanthine dehydrogenase, AMP is “re-cycled” to restore hepatocyte ATP content. Conversely, when xanthine dehydrogenase is more active than AMPK, AMP is converted to uric acid, delaying recovery of hepatic ATP stores. Insulin resistance, which decreases AMPK activity, further augments the effect of fructose metabolism, resulting in hepatic ATP depletion.

## Table 1

Associations between fructose consumption and clinical characteristics

| | Fructose consumption (reported servings) per week | | | P-value |
|---|---|---|---|---|
| | 0 servings N = 84 | > 0 and < 7 servings N = 224 | ≥7 servings N = 119 | |
| Age | 53.9 ± 1.2 | 47.5 ± 0.8* | 41.4 ± 1.0*# | < 0.0001 |
| Gender (Male, %) | 22.6 | 38.4 | 56.3 | < 0.0001§ |
| Ethnicity (Hispanic, %) | 10.7 | 14.7 | 16.0 | 0.55§ |
| Race, (White, %) | 88.1 | 79.9 | 80.7 | 0.24§ |
| BMI, kg/m$^2$ | 33.7 ± 0.7 | 33.6 ± 0.4 | 35.8 ± 0.6# | 0.008 |
| Triglycerides, mg/dl | 190.9 ± 15.7 | 162.9 ± 9.6 | 203.2 ± 13.2# | 0.03 |
| HDL-cholesterol, mg/dl | 47.8 ± 1.3 | 44.0 ± 0.8* | 39.4 ± 1.1*# | < 0.0001 |
| LDL-cholesterol, mg/dl | 120.0 ± 3.8 | 118.9 ± 2.3 | 122.0 ± 3.2 | 0.75 |
| Serum uric acid, mg/dl | 5.9 ± 0.2 | 6.1 ± 0.1 | 6.8 ± 0.1*# | < 0.0001 |
| Fasting serum glucose, g/dl | 111.9 ± 3.2 | 97.7 ± 2.0* | 101.6 ± 2.7 | 0.0009 |
| Fasting serum insulin, μU/ml | 26.4 ± 3.2 | 23.7 ± 2.0 | 25.7 ± 2.7 | 0.71 |
| HOMA-IR | 7.5 ± 0.8 | 5.8 ± 0.5 | 6.5 ± 0.7 | 0.19 |
| Total calorie intake, Cal/day | 1315 ± 94 | 1727 ± 58* | 2600 ± 79*# | < 0.0001 |
| Carbohydrate, Cal/day | 600 ± 45 | 786 ± 27* | 1310 ± 38*# | < 0.0001 |
| Protein, Cal/day | 224 ± 16 | 276 ± 10* | 366 ± 14*# | < 0.0001 |
| Fat, Cal/day | 513 ± 43 | 690 ± 26* | 951 ± 36*# | < 0.0001 |
| Liver histology | | | | 0.27§ |
| Steatosis | | | | |
| Grade 0 | 6.0 | 3.1 | 5.0 | |
| Grade 1 | 26.2 | 37.1 | 37.8 | |
| Grade 2 | 31.0 | 34.8 | 31.9 | |
| Grade 3 | 36.9 | 25.0 | 25.2 | |
| Lobular inflammation | | | | 0.16§ |
| Grade 0 | 0 | 0 | 0 | |
| Grade 1 | 39.3 | 45.5 | 54.6 | |
| Grade 2 | 47.6 | 44.2 | 32.8 | |
| Grade 3 | 13.1 | 10.3 | 12.6 | |
| Ballooning | | | | 0.44§ |
| Grade 0 | 23.8 | 29.0 | 31.1 | |
| Grade 1 | 29.8 | 34.8 | 28.6 | |
| Grade 2 | 46.4 | 36.2 | 40.3 | |
| Fibrosis | | | | 0.23§ |
| Stage 0 | 20.5 | 28.6 | 22.2 | |
| Stage 1 | 26.5 | 32.6 | 33.3 | |

| | Fructose consumption (reported servings) per week | | | P-value |
|---|---|---|---|---|
| | 0 servings N = 84 | > 0 and < 7 servings N = 224 | ≥7 servings N = 119 | |
| Stage 2 | 21.7 | 19.2 | 24.8 | |
| Stage 3 | 21.7 | 14.7 | 11.1 | |
| Stage 4 | 9.6 | 4.9 | 8.6 | |

p-values from Chi-square test or ANOVA

§ Chi-square test.

* p < 0.05 vs. “0 serving per week”;

# p < 0.05 vs. “> 0 and < 7 serving per week”

**Table 2a**

Associations between fructose consumption and metabolic features after adjusting for age, gender, and BMI in entire study population (n = 427)

| | Fructose consumption (reported servings per week) | | | | |
|---|---|---|---|---|---|
| | 0 servings | > 0 and < 7 servings | | ≥ 7 servings | |
| | | β ± SE | p-value | β ± SE | p-value |
| Triglycerides, mg/dl | - | −37.0 ± 18.8 | 0.05 | −1.4 ± 22.0 | 0.95 |
| HDL-cholesterol, mg/dl | - | −2.7 ± 1.5 | 0.07 | −5.5 ± 1.8 | 0.002 |
| LDL-cholesterol, mg/dl | - | −0.2 ± 4.6 | 0.97 | 4.6 ± 5.5 | 0.40 |
| Serum uric acid, mg/dl | - | 0.1 ± 0.2 | 0.60 | 0.5 ± 0.2 | 0.03 |
| Fasting serum glucose, g/dl | - | −12.2 + 3.9 | 0.002 | −6.7 + 4.6 | 0.15 |
| Fasting serum insulin, μU/ml | - | −2.5 + 3.9 | 0.52 | −1.2 + 4.6 | 0.79 |
| HOMA-IR | - | −1.5 ± 1.0 | 0.13 | −0.8 ± 1.2 | 0.51 |

Multiple lineal regression models were used to compute adjusted mean differences (vs. 0 servings). Adjusted means are presented as β-coefficient ± SE (p-value) in the table.

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**Table 2b**

Associations between fructose consumption and metabolic features after adjusting for age, gender, and BMI in subjects not on insulin or insulin sensitizing agents.

| | Fructose consumption (reported servings per week) | | | | |
|---|---|---|---|---|---|
| | 0 servings | > 0 and < 7 servings | | ≥ 7 servings | |
| | | β ± SE | p-value | β ± SE | p-value |
| Triglycerides, mg/dl | - | −20.6 ± 19.5 | 0.29 | 9.4 ± 22.7 | 0.68 |
| HDL-cholesterol, mg/dl | - | −3.6 ± 1.7 | 0.04 | −6.5 ± 2.0 | 0.001 |
| LDL-cholesterol, mg/dl | - | −1.4 ± 5.3 | 0.79 | 1.5 ± 6.2 | 0.81 |
| Serum uric acid, mg/dl | - | −0.06 ± 0.21 | 0.77 | 0.45 ± 0.24 | 0.06 |
| Fasting serum glucose, g/dl | - | −1.9 ± 2.8 | 0.50 | −0.8 ± 3.2 | 0.81 |
| Fasting serum insulin, μU/ml | - | 1.9 + 4.4 | 0.67 | 3.7 + 5.1 | 0.47 |
| HOMA-IR | - | 0.38 ± 1.01 | 0.71 | 0.96 ± 1.18 | 0.42 |

Multiple lineal regression models were used to compute adjusted mean differences (vs. 0 servings). Adjusted means are presented as β-coefficient ± SE (p-value) in the table.

**Table 3**

Association between fructose consumption and histologic feature of NAFLD in the entire study population

| | Unadjusted | | Adjusted (Model 1) | | Adjusted (Model 2) | |
|---|---|---|---|---|---|---|
| | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** |
| Steatosis | | | | | | |
| Fructose consumption | | | | | | |
| 0 serving | - | - | - | - | - | - |
| 0–7 servings | 0.7 [0.4, 1.1] | 0.09 | 0.6 [0.4, 0.9] | 0.02 | 0.7 [0.4, 1.1] | 0.10 |
| > = 7 servings | 0.6 [0.4, 1.0] | 0.06 | 0.4 [0.2, 0.8] | 0.007 | 0.4 [0.2, 0.9] | 0.02 |
| Lobular inflammation | | | | | | |
| Fructose consumption | | | | | | |
| 0 serving | - | - | - | - | - | - |
| 0–7 servings | 0.8 [0.5, 1.3] | 0.30 | 0.9 [0.5, 1.4] | 0.55 | 0.8 [0.5, 1.4] | 0.53 |
| > = 7 servings | 0.6 [0.4, 1.0] | 0.06 | 0.9 [0.5, 1.8] | 0.86 | 1.1 [0.6, 2.3] | 0.70 |
| Ballooning | | | | | | |
| Fructose consumption | | | | | | |
| 0 serving | - | - | - | - | - | - |
| 0–7 servings | 0.7 [0.4, 1.1] | 0.13 | 0.9 [0.5, 1.4] | 0.62 | 0.9 [0.5, 1.5] | 0.73 |
| > = 7 servings | 0.7 [0.4, 1.2] | 0.25 | 1.3 [0.7, 2.4] | 0.44 | 1.4 [0.7, 2.7] | 0.32 |
| Fibrosis | | | | | | |
| Fructose consumption | | | | | | |
| 0 serving | - | - | - | - | - | - |
| 0–7 servings | 0.6 [0.4, 0.9] | 0.01 | 0.8 [0.5, 1.3] | 0.44 | 0.9 [0.6, 1.5] | 0.78 |
| > = 7 servings | 0.7 [0.4, 1.2] | 0.19 | 1.7 [1.0, 3.2] | 0.07 | 2.6 [1.4, 5.0] | 0.004 |

Fructose consumption is expresses as reported servings per week. OR (cumulative odds ratio) and p-values were derived from ordinal logistic regression models (Model 1: adjusted for age, gender, BMI, Hispanic ethnicity, and total calorie intake; Model 2: adjusted for age, gender, BMI, Hispanic ethnicity, total calorie intake, triglycerides, HDL-cholesterol, LDL-cholesterol, uric acid, and HOMA-IR).

**Table 4**

Association between fructose consumption and liver histology of NAFLD in different age groups

| | Younger group (< 48 years old) | | | | Older group (> = 48 years old) | | | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted (Model 1) | | Adjusted (Model 2) | | Adjusted (Model 1) | | Adjusted (Model 2) | |
| | OR [95% CI] | p-value | OR [95% CI] | p-value | OR [95% CI] | p-value | OR [95% CI] | p-value |
| Steatosis | | | | | | | | |
| Fructose consumption | | | | | | | | |
| < 7 servings | - | - | - | - | - | - | - | - |
| > = 7 servings | 1.1 [0.6, 2.0] | 0.72 | 1.0 [0.6, 1.9] | 0.95 | 0.3 [0.1, 0.6] | 0.0009 | 0.2 [0.1, 0.5] | 0.0008 |
| Lobular inflammation | | | | | | | | |
| Fructose consumption | | | | | | | | |
| < 7 servings | - | - | - | - | - | - | - | - |
| > = 7 servings | 0.7 [0.4, 1.3] | 0.24 | 0.9 [0.5, 1.8] | 0.83 | 2.1 [1.0, 4.8] | 0.07 | 2.5 [1.0, 6.2] | 0.05 |
| Ballooning | | | | | | | | |
| Fructose consumption | | | | | | | | |
| < 7 servings | - | - | - | - | - | - | - | - |
| > = 7 servings | 1.3 [0.7, 2.3] | 0.40 | 1.5 [0.8, 2.8] | 0.19 | 2.1 [0.9, 4.5] | 0.07 | 2.5 [1.0, 6.0] | 0.05 |
| Fibrosis | | | | | | | | |
| Fructose consumption | | | | | | | | |
| < 7 servings | - | - | - | - | - | - | - | - |
| > = 7 servings | 2.5 [1.4, 4.4] | 0.003 | 3.2 [1.7, 6.1] | 0.0003 | 2.1 [0.1, 4.3] | 0.05 | 3.2 [1.4, 7.4] | 0.006 |

Fructose consumption is expresses as reported servings per week. OR (cumulative odds ratio) and p-values were derived from ordinal logistic regression models (Model 1: adjusted for age, gender, BMI, Hispanic ethnicity, and total calorie intake; Model 2: adjusted for age, gender, BMI, Hispanic ethnicity, total calorie intake, triglycerides, HDL-cholesterol, LDL-cholesterol, uric acid, and HOMA-IR.