Fructose Intake From Fruit Juice and Sugar-Sweetened Beverages Is Associated With Higher Intrahepatic Lipid Content

Fructose Intake From Fruit Juice and Sugar-Sweetened Beverages Is Associated With Higher Intrahepatic Lipid Content: The Maastricht Study

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OBJECTIVE

Epidemiological evidence regarding the relationship between fructose intake and intrahepatic lipid (IHL) content is inconclusive. We, therefore, assessed the relationship between different sources of fructose and IHL at the population level.

RESEARCH DESIGN AND METHODS

We used cross-sectional data from The Maastricht Study, a population-based cohort study (n = 3,981; mean ± SD age: 60 ± 9 years; 50% women). We assessed the relationship between fructose intake (assessed with a food-frequency questionnaire)—total and derived from fruit, fruit juice, and sugar-sweetened beverages (SSB)—and IHL (quantified with 3T Dixon MRI) with adjustment for age, sex, type 2 diabetes, education, smoking status, physical activity, and intakes of total energy, alcohol, saturated fat, protein, vitamin E, and dietary fiber.

RESULTS

Energy-adjusted total fructose intake and energy-adjusted fructose from fruit were not associated with IHL in the fully adjusted models (P = 0.647 and P = 0.767). In contrast, energy-adjusted intake of fructose from fruit juice and SSB was associated with higher IHL in the fully adjusted models (P = 0.019 and P = 0.009). Individuals in the highest tertile of energy-adjusted intake of fructose from fruit juice and SSB had a 1.04-fold (95% CI 0.99; 1.11) and 1.09-fold (95% CI 1.03; 1.16) higher IHL, respectively, in comparison with the lowest tertile in the fully adjusted models. Finally, the association for fructose from fruit juice was stronger in individuals with type 2 diabetes (P for interaction = 0.071).

CONCLUSIONS

Fructose from fruit juice and SSB is independently associated with higher IHL. These cross-sectional findings contribute to current knowledge in support of measures to reduce the intake of fructose-containing beverages as a means to prevent nonalcoholic fatty liver disease at the population level.

Nonalcoholic fatty liver disease (NAFLD) is highly prevalent among people with type 2 diabetes and emerging as the principal cause of liver transplantation in Western society (1,2). Furthermore, epidemiological evidence is accumulating that

NAFLD per se is a risk factor for type 2 diabetes (2–4). Currently, a myriad of pharmacological agents that target NAFLD have entered phase II–III clinical trials (5). However, given the high global prevalence of NAFLD (~25% [6]), it is also desirable to use nonpharmacological measures to reduce the burden of NAFLD and its sequela at the population level.

There has been a long debate on whether dietary fructose is a modifiable risk factor of NAFLD. Despite convincing evidence derived from animal studies (7), there have been inconsistent experimental data in humans (8,9). Furthermore, the findings from observational studies that addressed the relationship between fructose intake and intrahepatic lipid (IHL) accumulation, the first stage of NAFLD, vary from positive (10,11) to inverse (12) and divergent (13) associations. Of note, some of these studies have been conducted in selected (pediatric) groups (10), did not use histology or imaging to quantify IHL (12,13), or did not sufficiently adjust for potential confounders (10–13). In addition, only one of these studies made a distinction between multiple sources of dietary fructose (13).

The aim of the current study was, therefore, to assess the independent relationship between habitual fructose intake—total and derived from fruit, fruit juice, and sugar-sweetened beverages (SSB)—and IHL, quantified with use of 3T Dixon MRI, in The Maastricht Study, an extensively phenotyped population-based cohort (14).

RESEARCH DESIGN AND METHODS

Study Population

The Maastricht Study is a population-based cohort study with an oversampling of individuals with type 2 diabetes (14). In brief, the focus of The Maastricht Study is on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes. All individuals between 40 and 75 years old who lived in the southern part of the Netherlands were eligible for participation.

The current study includes cross-sectional data from 7,689 participants who completed the baseline measurements from November 2010 until December 2017. MRI measurements of the liver were implemented from December 2013 onward (available for $n = 5,180$). Participants with invalid MRI measurements, missing data on dietary intake, implausible energy intake, and missing data on covariates were excluded from all analyses, resulting in a study population of 3,981 participants (Supplementary Fig. 1).

The Maastricht Study has been approved by the institutional medical ethics committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (permit 131088-105234-PG). All participants gave written informed consent.

Assessment of Dietary Intake

Assessment of dietary intake has previously been reported in detail (15). In brief, habitual dietary intake over the past 12 months was estimated with use of a tailor-made and validated food-frequency questionnaire, with assessment of the frequency of consumption and the amount of consumed food and nutrients. Intakes of total energy and individual mono- and disaccharides were calculated with use of the Dutch Food Composition Database (and, in the case of missing values in this composition database, this information was complemented with values obtained from other relevant food composition databases).

For the current study, fructose intake (grams per day) was defined as the sum of 50% sucrose intake plus free fructose intake. Further, fructose-containing food items were categorized as follows: *1*) total fructose (grams per day), *2*) fructose from fruit (fresh and dried fruit [grams per day]), *3*) fructose from fruit juice (grams per day), and *4*) fructose from SSB, including sugar-containing fruit drinks and syrups (grams per day).

Assessment of Intrahepatic Lipid Content

IHL was assessed through Dixon MRI using a 3.0 Tesla MRI system (MAGNETOM Prismafit; Siemens Healthineers, Erlangen, Germany) with body matrix and supine radiofrequency coils. After a scout scan, transversal two-dimensional T2-weighted true fast imaging with steady-state free precession (T2w TRUFI) images were acquired through the liver with the following parameters: voxel size 1.2 × 1.2 × 5.0 mm^3, repetition time (TR) 422 ms, echo time (TE) 1.65 ms, flip angle 60°, number of signal averages = 1, and parallel imaging (GeneRalized Autocalibrating Partial Parallel Acquisition [GRAPPA]) factor 2. Next, transversal two-dimensional turbo spin-echo Dixon magnetic resonance images were acquired through the liver during a breathhold with the following parameters: voxel size 2.0 × 2.0 × 6.0 mm^3, number of slices = 4, TR 500 ms, TE 31 ms, turbo factor 5, number of signal averages = 1, and parallel imaging (GRAPPA) factor 3. Three regions of interest were drawn in the liver by trained observers on the T2w TRUFI images. Subsequently, these regions of interest were copied to the water and fat Dixon magnetic resonance images for calculation of the IHL fraction.

This method was validated and calibrated against proton MRS (^{1}H-MRS), the gold standard to noninvasively quantify IHL, in 36 participants. After calibration, the intraclass correlation coefficient between Dixon MRI and ^{1}H-MRS was 0.989 (95% CI 0.979; 0.994). IHL was expressed as the ratio of CH_2 to H_2O (*100%).

Measurement of Covariates

All participants completed questionnaires regarding age, sex, educational level (low, medium, high), smoking status (never, former, current smoker), and history of cardiovascular disease (CVD) (14). Use of medication was assessed during medication interviews. Weight, height, waist circumference, and office systolic and diastolic blood pressure were measured during a physical examination. Fasting levels of glucose, HbA_{1c}, and lipid profile were measured in venous blood samples. Daily physical activity levels were measured during eight consecutive days with the activPAL3 physical activity monitor (PAL Technologies, Glasgow, U.K.) (16).

Alanine aminotransferase (ALT) was measured enzymatically on a cobas 8000 modular analyzer (Roche Diagnostics, Basel, Switzerland).

All participants underwent a standardized 2-h 75-g oral glucose tolerance test (OGTT) after an overnight fast (14). Use of insulin or fasting capillary glucose levels >11.0 mmol/L were considered as contraindications for an OGTT. Participants fulfilling either of these criteria were automatically classified as having diabetes. Glucose metabolism status, i.e., normal glucose metabolism, prediabetes (i.e., impaired fasting glucose or impaired glucose tolerance), and

diabetes, was categorized based on venous plasma glucose levels obtained during an OGTT according to the World Health Organization 2006 criteria in all other participants.

The Matsuda index ($10{,}000/\sqrt{G0 \times I0 \times \text{mean G} \times \text{mean I}}$, where G0 = fasting glucose, I0 = fasting insulin, mean G = mean glucose during OGTT, and mean I = mean serum insulin levels during an OGTT) was used as a measure of insulin sensitivity (14).

Statistical Analyses

Continuous data are presented as mean ± SD or as median (interquartile range) in case of nonnormal distribution. Categorical data are presented as *n* (%).

All nutrient variables were adjusted for total energy intake with the residual method (17).

Multivariable linear regression models were constructed for studying the associations between the energy-adjusted intake of *1*) total fructose, *2*) fructose from fruit, *3*) fructose from fruit juice, and *4*) fructose from SSB and IHL, independent of confounders. Energy-adjusted fructose intake was entered as either a continuous variable (for deriving a *P* for trend) or a category. Based on the distribution of energy-adjusted intake of fructose from fruit, fruit juice, and SSB, with a high number of low consumers in the latter two groups (Supplementary Fig. 2), we decided to categorize the participants according to tertiles of energy-adjusted fructose intake to obtain discriminative categories of intake. The tertiles of energy-adjusted fructose intake were entered in the models as independent variables (with the lowest tertile as a reference). The following regression models were used: model 1, crude; model 2, with adjustment for age, sex, and type 2 diabetes, the latter because of the oversampling of type 2 diabetes in The Maastricht Study; model 3, with additional adjustment for (proxies of) lifestyle, i.e., educational level, smoking status, physical activity, and total energy intake; model 4, with additional adjustment for nutritional factors that have been associated with IHL in randomized controlled trials, i.e., energy-adjusted intakes of alcohol, saturated fat, protein, and vitamin E (18–21); and model 5, with additional adjustment for energy-adjusted dietary fiber, which has been associated with IHL in observational studies (22).

IHL was ^{10}log transformed to fulfill the assumption of normality for linear regression. To obtain interpretable results we back transformed the regression coefficients, which should be interpreted as the fold change (and not the additive change) in IHL that is associated with the difference between the tertile of fructose intake and the reference group (i.e., lowest tertile of energy-adjusted fructose intake), as can be deduced from the following:

$$Log(y) = \beta_0 + \beta_1 x$$
$$Exp\big(log(y)\big) = exp(\beta_0 + \beta_1 x)$$
$$y = exp(\beta_0)exp(\beta_1 x)$$

For instance, a regression coefficient of 0.019 implies that for every unit increase in fructose intake, (^{10}log) IHL increases with 0.019. After backtransformation, the interpretation should be that for every unit increase in fructose intake, IHL increases 1.04-fold (= $10^{0.019}$), i.e., by 4%.

Additional analyses were performed to test for the effect of an interaction between energy-adjusted fructose intake and type 2 diabetes or sex on IHL in the fully adjusted model.

Several sensitivity analyses were performed. First, multivariable logistic regression analyses were conducted with hepatic steatosis as a dependent, dichotomous variable, defined as IHL ≥5.56% (23). This cutoff value, originally expressed as (CH_2 / (H_2O + CH_2)) (23), corresponds to 5.89% (= 0.0556/(1 − 0.0556)) when IHL is expressed as CH_2/H_2O, as was done in the current study. Second, the original analyses were repeated with replacement of *1*) the covariate type 2 diabetes in models 2–5 by the Matsuda index (available for n = 1,415) for exploration of the role of insulin sensitivity in the relationship between fructose intake and IHL and *2*) IHL by (^{10}log transformed) serum ALT levels (available for n = 1,602).

Statistical analyses were performed with the use of SPSS (version 25.0; IBM, Chicago, IL). A P value of <0.05 was considered statistically significant in all analyses, except for interaction tests where a less stringent significance threshold of $P < 0.10$ was applied.

Data and Resource Availability

The data of this study derive from The Maastricht Study, but restrictions apply to the availability of these data, which were used under license for the current study. Data are, however, available from the authors on reasonable request and with permission of The Maastricht Study management team.

RESULTS

Study Population

Table 1 shows the characteristics of the overall population with stratification according to IHL tertiles. Mean ± SD age of the study population was 60 ± 9 years, 50% were female, 20% were diagnosed with type 2 diabetes, and the median IHL was 3.2% (interquartile range 2.0–6.1). Participants in the highest IHL tertile more often were men, older, had a lower educational level, were less physically active, and had a higher BMI compared with those in the lowest IHL tertile. Compared with participants in the lowest IHL tertile, those in the highest were metabolically unhealthy, as reflected by lower HDL cholesterol and higher serum triglycerides, HbA_{1c}, prevalence of prediabetes, and systolic and diastolic blood pressure. Further, the prevalence of CVD and the use of medication (including lipid-modifying, glucose-lowering, and antihypertensive medication) were higher in the highest IHL tertile. Finally, intakes of total fructose, fructose from fruit, and dietary fiber were lower, while intakes of total energy and saturated fat were greater, in the highest IHL tertile.

Relationship Between Fructose Intake and Intrahepatic Lipid Content

Total fructose intake was associated with lower IHL ($P < 0.001$) (Table 2, models 1–3), but this association was lost after adjustment for nutritional factors that are associated with IHL (P = 0.903) (Table 2, model 4).

When fructose intake was categorized according to different sources of fructose, a similar association was observed between intake of fructose from fruit and lower IHL ($P < 0.001$) (Table 2, models 1–3). Again, the strength of association was attenuated after adjustment for nutritional factors that are associated with IHL (P = 0.044) (Table 2, model 4) and was completely lost after additional

Table 1—Characteristics of the overall population with stratification according to IHL tertiles

	Total (n = 3,981)	First tertile (n = 1,327)	Second tertile (n = 1,327)	Third tertile (n = 1,327)
IHL, %	3.2 (2.0–6.1)	1.7 (1.3–2.0)	3.2 (2.7–3.9)	8.3 (6.1–12.6)
ALT, units/L	26.0 (21.0–34.0)	22.0 (19.0–28.0)	26.0 (21.0–33.0)	31.0 (24.0–42.0)
Age, years	60 ± 9	57 ± 9	60 ± 8	61 ± 8
Women, %	50	62	46	40
Education, % low/medium/high	32/28/40	26/30/44	32/27/41	38/27/35
Smoking, % never/former/current	40/49/12	44/44/12	39/49/12	35/53/12
Physical activity, min/day	51.4 (36.6–69.6)	56.0 (40.6–73.6)	52.7 (38.6–72.0)	45.1 (31.9–62.1)
BMI, kg/m^2	26.5 ± 4.1	24.3 ± 3.0	26.3 ± 3.6	28.9 ± 4.1
Waist circumference, cm	93.7 ± 12.6	85.6 ± 9.6	93.6 ± 11.0	101.8 ± 11.4
Total cholesterol, mmol/L	5.3 ± 1.1	5.3 ± 1.0	5.3 ± 1.1	5.2 ± 1.2
HDL cholesterol, mmol/L	1.6 ± 0.5	1.8 ± 0.5	1.6 ± 0.5	1.4 ± 0.4
LDL cholesterol, mmol/L	3.1 ± 1.0	3.1 ± 0.9	3.1 ± 1.0	3.0 ± 1.1
Triglycerides, mmol/L	1.2 (0.9–1.7)	1.0 (0.8–1.2)	1.2 (0.9–1.6)	1.5 (1.1–2.1)
Lipid-modifying medication, %	28	17	28	39
HbA_{1c}, % and mmol/mol	5.5 (5.2–5.9)/37	5.4 (5.1–5.6)/35	5.5 (5.3–5.8)/36	5.7 (5.4–6.4)/39
Matsuda index of insulin sensitivity	3.56 (2.14–5.34)	4.87 (3.63–6.72)	3.81 (2.60–5.42)	2.31 (1.52–3.40)
GMS, % NGM/prediabetes/type 2 diabetes/other type of diabetes	65/15/20/1	82/9/8/1	71/13/15/1	41/21/38/0
Glucose-lowering medication, %	15	7	12	27
Office SBP, mmHg	133 ± 17	128 ± 17	133 ± 17	138 ± 16
Office DBP, mmHg	75 ± 10	73 ± 10	76 ± 9	78 ± 9
Antihypertensive medication, %	33	20	31	48
History of CVD, %	13	10	13	16
Total fructose, g/day	35.9 (26.2–47.5)	36.7 (27.0–47.6)	36.3 (26.3–47.6)	34.8 (25.1–47.2)
Fructose from fruit, g/day	9.1 (4.7–14.8)	9.6 (5.3–15.5)	9.1 (5.0–15.6)	8.2 (3.9–13.4)
Fructose from fruit juice, g/day	0.9 (0.1–3.8)	1.0 (1.2–3.8)	0.9 (0.1–3.8)	0.9 (0.1–3.9)
Fructose from SSB, g/day	0.4 (0.0–2.8)	0.3 (0.0–2.1)	0.3 (0.0–2.4)	0.6 (0.0–3.8)
Total energy, kcal/day	2,074 (1,721–2,486)	2,027 (1,699–2,446)	2,087 (1,748–2,515)	2,105 (1,703–2,500)
Alcohol, g/day	8.6 (1.8–18.7)	7.8 (1.5–15.7)	9.6 (2.5–19.5)	8.3 (1.6–21.0)
Carbohydrates, g/day	222 (179–272)	223 (179–273)	224 (181–273)	219 (178–269)
Saturated fat, g/day	27.3 (20.5–35.3)	26.2 (20.2–34.3)	27.6 (20.4–35.8)	28.1 (20.8–36.1)
Protein, g/day	82.0 (68.9–96.9)	80.8 (68.0–94.8)	82.7 (69.5–98.1)	82.5 (69.3–97.6)
Vitamin E, mg/day	12.5 (9.7–16.0)	12.5 (9.8–16.0)	12.5 (9.8–16.2)	12.5 (9.6–15.8)
Dietary fiber, g/day	26.1 (21.3–31.8)	26.4 (21.4–32.0)	26.6 (21.7–32.2)	25.5 (21.1–30.9)

Data are means ± SD, median (interquartile range), median (interquartile range)/median, or n (%) unless otherwise indicated. Nutrient variables represent absolute intake values. DBP, diastolic blood pressure; GMS, glucose metabolism status; NGM, normal glucose metabolism; SBP, systolic blood pressure.

adjustment for dietary fiber (P = 0.767) (Table 2, model 5).

In contrast, intake of fructose from fruit juice was associated with higher IHL, also after full adjustment for potential confounders (P = 0.019) (Table 2, model 5). Individuals in the highest tertile of energy-adjusted intake of fructose from fruit juice had a 1.04-fold (95% CI 0.99; 1.11) (Table 2, model 5) higher IHL in comparison with the lowest tertile in the fully adjusted model.

Similarly, intake of fructose from SSB was associated with higher IHL in the fully adjusted model (P = 0.009) (Table 2, model 5). Individuals in the highest tertile of energy-adjusted intake of fructose from SSB had a 1.09-fold (95% CI 1.03; 1.16) (Table 2, model 5) higher IHL in comparison with the lowest tertile in the fully adjusted model.

Table 2—Multivariable-adjusted associations of energy-adjusted fructose intake and IHL (n = 3,981)

	Energy-adjusted fructose intake tertiles			
	T1	T2	T3	P_{trend}
Total fructose, median g/day*	24.4	35.1	47.6	
Model 1	1	0.89 (0.84; 0.95)	0.83 (0.78; 0.88)	**<0.001**
Model 2	1	0.94 (0.89; 0.99)	0.90 (0.85; 0.96)	**<0.001**
Model 3	1	0.95 (0.90; 1.00)	0.91 (0.86; 0.97)	**<0.001**
Model 4	1	1.01 (0.95; 1.07)	1.01 (0.95; 1.08)	0.903
Model 5	1	1.01 (0.95; 1.07)	1.02 (0.95; 1.09)	0.647
Fructose from fruit, median g/day*	3.1	9.0	17.8	
Model 1	1	0.88 (0.83; 0.94)	0.82 (0.77; 0.87)	**<0.001**
Model 2	1	0.90 (0.85; 0.95)	0.84 (0.80; 0.90)	**<0.001**
Model 3	1	0.91 (0.86; 0.97)	0.87 (0.82; 0.92)	**<0.001**
Model 4	1	0.94 (0.89; 1.00)	0.91 (0.86; 0.97)	**0.044**
Model 5	1	0.96 (0.90; 1.01)	0.95 (0.89; 1.02)	0.767
Fructose from fruit juice, median g/day*	0.1	0.9	5.3	
Model 1	1	0.95 (0.90; 1.02)	0.96 (0.90; 1.02)	0.512
Model 2	1	1.01 (0.96; 1.08)	1.02 (0.96; 1.08)	0.078
Model 3	1	1.02 (0.96; 1.08)	1.03 (0.97; 1.09)	0.082
Model 4	1	1.03 (0.97; 1.09)	1.05 (1.00; 1.12)	**0.008**
Model 5	1	1.02 (0.96; 1.08)	1.04 (0.99; 1.11)	**0.019**
Fructose from SSB, median g/day*	0.0	0.5	4.5	
Model 1	1	1.00 (0.94; 1.07)	1.09 (1.02; 1.16)	**<0.001**
Model 2	1	1.02 (0.96; 1.08)	1.11 (1.04; 1.17)	**0.001**
Model 3	1	1.02 (0.96; 1.08)	1.08 (1.02; 1.14)	**0.024**
Model 4	1	1.03 (0.97; 1.09)	1.12 (1.06; 1.19)	**<0.001**
Model 5	1	1.02 (0.96; 1.08)	1.09 (1.03; 1.16)	**0.009**

Regression coefficients should be interpreted as the fold change in IHL that is associated with the difference between the tertile of fructose intake and the reference group (see *Research Design and Methods*). Data in parentheses are 95% CI. P_{trend} values were obtained from linear regression with fructose as continuous variables (see *Research Design and Methods*). Model 1: energy-adjusted intake of fructose. Model 2: additional adjustment for age, sex, and type 2 diabetes. Model 3: additional adjustment for educational level, smoking status, physical activity, and intake of total energy. Model 4: additional adjustment for energy-adjusted intakes of alcohol, saturated fat, protein, and vitamin E. Model 5: additional adjustment for energy-adjusted intake of dietary fiber. T, tertile. *Energy-adjusted fructose by means of the residual method.

There was a statistically significant interaction between type 2 diabetes and total fructose, fructose from fruit, and fructose from fruit juice in the effect on IHL (P for interaction = 0.089, 0.058, and 0.071, respectively), and the associations were more pronounced among individuals with type 2 diabetes (Supplementary Table 1). Furthermore, individuals with type 2 diabetes in the second and third tertile of intake of fructose from SSB had a statistically significantly higher IHL in comparison with individuals without type 2 diabetes (P = 0.001 and P = 0.020) (Supplementary Table 1). Of note, the strength of these associations did not differ between individuals with newly diagnosed type 2 diabetes (based on an OGTT) and individuals with prior diagnosed type 2 diabetes (data not shown).

Sex did not modify the association between fructose intake and IHL (P for interaction >0.10; data not shown).

Sensitivity Analyses

First, when hepatic steatosis, defined as IHL ≥5.56% (CH_2 / (H_2O + CH_2)), was considered as a dichotomous variable, associations were generally similar (Fig. 1). In the fully adjusted model, individuals in the highest tertile of intake of fructose from SSB were more likely to have hepatic steatosis in comparison with the lowest tertile (odds ratio [OR] 1.37 [95% CI 1.12; 1.68]) (Fig. 1). Again, individuals with type 2 diabetes in the highest tertile of intake of fructose from fruit juice had a numerically higher risk of hepatic steatosis in comparison with individuals without type 2 diabetes (OR 1.33 [95% CI 0.93; 1.90] vs. OR 1.06 [95% CI 0.85; 1.34], respectively; P for interaction = 0.097) (Fig. 1).

Second, replacement of the covariate type 2 diabetes by the Matsuda index in the fully adjusted model showed a robust, positive association between fructose from SSB and IHL, whereas the association between fructose from fruit juice and IHL was attenuated toward the null (Supplementary Table 2).

Last, repeated analyses with ALT as an outcome variable resulted in null associations (Supplementary Table 3).

CONCLUSIONS

In the current study, we found that the intake of fructose from fruit juice and SSB is independently associated with higher IHL in a large, extensively phenotyped, population-based cohort. The strength of the association between fructose from fruit juice and IHL appeared to be stronger among individuals with type 2 diabetes.

Only a few studies have addressed the relationship between dietary fructose and IHL at the population level. Kanerva et al. (12) previously reported a surprisingly inverse association between total fructose intake and prevalence of NAFLD in a Finnish population-based

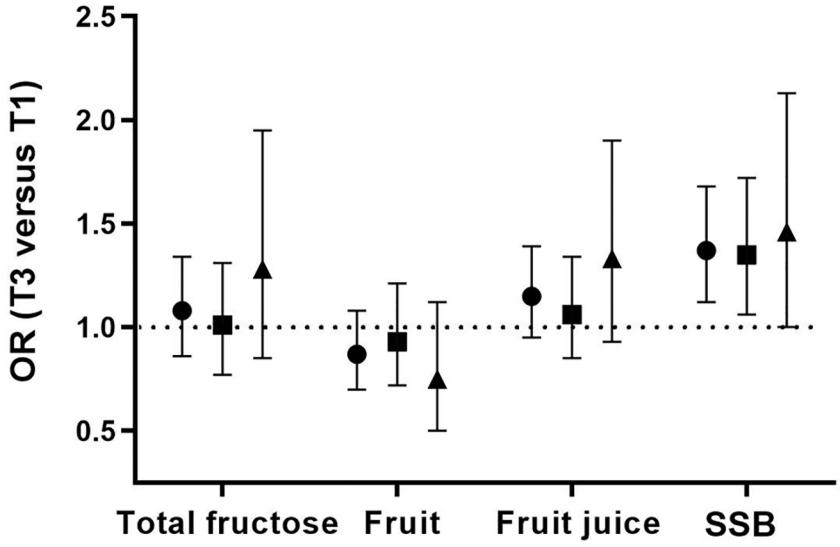

Figure 1—Association between energy-adjusted fructose intake (highest vs. lowest tertile) and hepatic steatosis among the overall population (n = 3,981) (●), individuals without type 2 diabetes (n = 3,171) (■), and individuals with type 2 diabetes (n = 810) (▲). Data are presented for the fully adjusted model. T, tertile.

cohort. However, this study was limited by the use of surrogate outcome measures, i.e., the fatty liver index and the NAFLD liver fat score, and, in particular, incomplete adjustment for potential confounders. Indeed, although we observed a similar crude, inverse association between total fructose intake and IHL, quantified by MRI, this association was completely abrogated after additional adjustment for nutritional factors that previously have been reported to be associated with IHL (18–21).

Further, we were able to differentiate between sources of dietary fructose in relation to IHL. For fructose from fruit, we found that the crude, inverse association with IHL was attenuated toward the null after additional adjustments including dietary fiber. It is possible that overadjustment has occurred, since fruits are rich in dietary fiber. In agreement, in a previous study in Chinese adults investigators found an inverse association between fruit intake and the presence of NAFLD but did not adjust for dietary fiber (and other relevant confounders) (24).

In contrast to the findings for fructose from fruit, we observed an association between fructose from fruit juice and SSB and higher IHL, even after adjustment for nutritional factors that are associated with IHL. The role of SSB in the development of NAFLD and type 2 diabetes has extensively been studied, however, with inconsistent results for NAFLD (25,26). Of note, when this relationship was examined in a large cohort (n = 2,634) and IHL was accurately assessed (by computed tomography), a positive association was observed, even after adjustment for confounders (27). To date, only one study addressed the association of fructose from fruit juice and a surrogate marker of NAFLD, in a relatively small cohort of healthy individuals and individuals with type 2 diabetes, and did not find an association (13). Of note, in a recent meta-analysis ($n \approx$ 35,000) investigators did find a positive association between fruit juice consumption and incident type 2 diabetes (26).

The divergent associations of fructose from fruit and fructose from fruit juice and SSB with IHL may be explained by the food matrix, i.e., "the physical domain that contains and/or interacts with specific constituents of a food (e.g., a nutrient) providing functionalities and behaviors which are different from those exhibited by the components in isolation or a free state" (28). For instance, the presence of fiber, vitamins, flavonoids, and antioxidants might counteract the deleterious effects of fructose (29,30). The abrogation of the inverse association of fructose from fruit with IHL after adjustment for dietary fiber supports the concept of the food matrix. Alternatively, consumption of fruit could be a proxy of a healthy lifestyle (and vice versa for fruit juice and SSB). Although we extensively corrected for lifestyle variables, residual confounding may still be present and (partly) account for the current observations.

We generally observed stronger associations for individuals with type 2 diabetes, which warrant further investigation. One potential biological explanation could be a gene-environment interaction. Gene-environment interactions have been reported for NAFLD susceptibility genes that also predispose to type 2 diabetes (31,32). Alternatively, the observed interactions may be methodologically flawed due to underreporting bias by specific subgroups, e.g., with higher BMI or type 2 diabetes, which is a limitation inherent to nutritional epidemiology (33). Adjustment for total energy intake can overcome this source of bias, except when there is differential bias in the reporting of macronutrient intake (33). However, we did not find differences in the strength of the associations between individuals with prior diagnosed type 2 diabetes and those with newly diagnosed type 2 diabetes (i.e., who were unaware of the diagnosis), which further reduces the likelihood of underreporting bias and suggests that the associations are truly stronger among individuals with type 2 diabetes.

Previous studies have shown that advanced liver fibrosis is particularly prevalent in type 2 diabetes (34,35). In the current study we did not find any association between fructose intake and ALT, used as a marker of hepatocyte damage. This may be explained by a lack of power (serum ALT was available for n = 1,602) and/or the fairly normal ALT levels in this population. Future studies are, therefore, warranted for further investigation of (different sources of) dietary fructose in relation to liver damage and fibrosis.

The current study has several strengths and limitations. We used a large population-based cohort, enriched with individuals with type 2 diabetes, extensively phenotyped with state-of-the-art methods (e.g., 3T Dixon MRI of the liver and physical activity monitoring by an accelerometer). This allowed for an accurate estimation of the dependent variable and the adjustment for a wide range of potential confounders. Our study also has specific limitations. First, dietary intake was

assessed by means of a food-frequency questionnaire, which has been validated against 24-h dietary recalls for intakes of mono- and disaccharides and fruit but not for fruit juice and SSB (15). Further, we could not differentiate between intakes of fresh fruit juice and packed fruit juice, which warrants further study. Second, although the self-reported intake of total fructose in our cohort was comparable with that of the general Dutch population (36), self-reported intakes of fructose from fruit juice and particularly from SSB were low (consistent with reduced intakes of fruit juice and SSB with increasing age in the Dutch population [36]). Our results may, therefore, not be extrapolated to populations with high fructose consumption, such as the U.S. (25), although the effects of fructose restriction, in the case of any difference, are expected to be even greater in such populations. Third, similar to a previous study (13), we only calculated intakes of fructose from homogeneous and relatively easily quantifiable food products, such as fruit, fruit juice, and SSB. We did not specifically assess the association of other dietary sources of fructose, such as vegetables and processed foods (which are more difficult to quantify), with IHL. Fourth, this is a cross-sectional study, which, by design, does not allow inference of causality. We do, however, believe that reverse causality, i.e., high IHL leads to more intake of fructose from fruit juice and SSB, is less likely. Finally, we adjusted for type 2 diabetes in the regression models because of the oversampling of type 2 diabetes in The Maastricht Study. It is likely that overadjustment has occurred, since type 2 diabetes is believed to be a consequence of IHL (3). We, therefore, performed stratified analyses and generally observed stronger associations for individuals with type 2 diabetes. The role of insulin resistance is even more complicated, as it may be the consequence of both fructose intake (= exposure) and IHL (= outcome) (37). Adjustment for the Matsuda index may, therefore, have introduced collider bias and should be interpreted cautiously (38).

In view of implications for public health, we found that individuals in the highest tertile of intake of SSB may reduce their risk of hepatic steatosis by 37% by lowering their fructose intake to the lowest tertile of intake (i.e., a reduction of ~4.5 g fructose from SSB/day). The corresponding absolute reduction of 0.3 percentage points in IHL (9%-fold change [Table 2, model 5] multiplied by the population median of 3.2% [Table 1]), is small, yet in line with our recently conducted double-blind randomized controlled trial showing that fructose restriction per se resulted in a reduction of 0.7 percentage points in IHL (9). Moreover, this seemingly small reduction in IHL should be viewed in the context of the global epidemic of NAFLD. It has been estimated that one-quarter of the worldwide adult population (approximately five billion people) is affected by NAFLD. Moreover, NAFLD is more frequently observed in type 2 diabetes and, in fact, is currently viewed as a risk factor of type 2 diabetes (2–4). It is, therefore, expected that a relatively easily implementable change in lifestyle, i.e., reduction of fruit juice and SSB intake, will have major beneficial health effects at the population level. This finding is of particular interest, since there is growing evidence that an excise tax on SSB—as already implemented in U.K. and U.S. cities including Berkeley (California)—has a beneficial, reducing effect on SSB consumption (39,40). Of note, fruit juice (without added sugar) is currently exempted from all these levies (39,40).

In conclusion, our population-based cohort study shows that fructose from fruit juice and SSB is associated with higher IHL, independent of confounders. These cross-sectional findings contribute to current knowledge in support of measures to reduce the intake of fructose-containing beverages as a means to prevent hepatic steatosis at the population level.

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