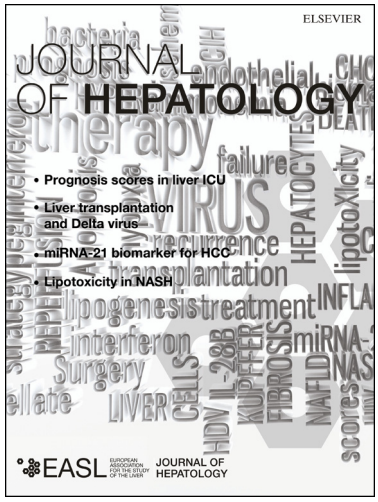

Letter to the Editor

Reply to: Is industrial fructose just a marker of an unhealthy dietary pattern?

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Reply to: Is industrial fructose just a marker of an unhealthy dietary pattern?

To the Editor,

We recently reported a link between fructose intake and the severity of liver fibrosis in a cohort of Italian patients with genotype 1 (G1) chronic hepatitis C (CHC) [1]. In particular, the association holds true for "industrial" only, not for "fruit" fructose intake.

We thank Chiavaroli and colleagues for their comments that give us the opportunity to further strength data from our analyses.

Firstly, they question the approach we used for the multivariate model assessing variables independently associated with severe liver fibrosis. Specifically, they raised concerns about the lack of adjustment for energy intake, a variable associated in our analysis with industrial fructose intake, not with liver fibrosis. From a methodological point of view the choice of independent variables included in the final multivariate analysis is not a simple task, particularly in relatively small databases. To enhance the accuracy of the model, the number of independent variables must be reduced or the model must be simplified. In order to include in the model the maximum number of variables with a potential prognostic significance, we choose a bivariate confirmation, so called "univariate", at the p threshold of ≤0.10 [2,3]. Accordingly, in our model the variable "energy intake" was not included because not significantly associated with the severity of fibrosis. In any case, because candidate variables may be also chosen from previous research or from clinical experience, and considering the well-known relation between industrial fructose and total energy intake, we repeated our analyses adding "energy intake" in the model. This issue, probably missed by Dr Chiavaroli and colleagues, was reported at page 173 of the article [1] as follows "The association between industrial fructose intake and severe liver fibrosis did not change when the presence of hypercaloric diet was forced into the model as independent variable (OR 1.158, 95% CI 1.045-1.283, $p = 0.005$)."

Second, the authors also question that the analyses were not corrected for other parameters not significant at univariate analysis, but also known to be associated with metabolic alterations, NAFLD, and unhealthy lifestyle, like several dietary nutrients, smoking and exercise. Unfortunately in our population we did not collect data on smoking and exercise, while data on nutrients were available. After correction for an extensive panel of dietary variables, industrial fructose intake remained significant associated with severe liver fibrosis (Table 1).

In conclusion, our study supports the association between industrial fructose intake and the severity of liver fibrosis in CHC patients. Along this line, while some studies attribute

a key pathogenic role for fibrosis to energy intake [4-7], others reported an association between fructose intake and the severity of possibly associated metabolic disorders, including NAFLD [8-12]. We are confident that the available evidence, including our own data, will stimulate future research in this area to provide external validation based on prospective studies.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Table 1. Multivariate analysis of risk factors associated with severe fibrosis (F3-F4) in 147 patients with chronic hepatitis C by logistic regression analysis.

Variable	Non-severe fibrosis n = 114	Severe fibrosis n = 33	Univariate analysis *p* value	Multivariate analysis	
				OR (95% CI)	*p* value
Age, yr	54.7 ± 11.0	59.1 ± 10.4	0.04	1.046 (0.993-1.100)	0.08
Waist circumference, cm	94.6 ± 11.4	98.7 ± 10.4	0.06	1.019 (0.974-1.067)	0.41
Histology at biopsy					
Severe grading	28/86	19/14	<0.0001	3.616 (1.373-9.526)	0.009
Moderate-severe steatosis	28/86	17/16	0.003	2.462 (0.861-7.045)	0.09
Features of NASH	6/108	7/26	0.004	4.185 (1.010-17.676)	0.04
kCal*	1910.8 ± 695.9	1987.3 ± 561.8	0.56	1.001 (0.998-1.002)	0.44
Proteins amount*, %	16.6 ± 2.9	16.9 ± 3.5	0.60	1.156 (0.988-1.354)	0.07
Cholesterol*, mg	223.9 ± 115.1	215.0 ± 98.9	0.69	0.999 (0.994-1.006)	0.86
Saturated fats*, g	19.9 ± 9.9	18.9 ± 8.4	0.60	0.938 (0.838-1.050)	0.26
Monounsaturated fats*, g	28.6 ± 10.1	28.3 ± 9.3	0.89	1.029 (0.935-1.132)	0.56
Polyunsaturated fats*, g	7.6 ± 3.9	7.3 ± 2.5	0.64	0.997 (0.708-1.403)	0.98
Fibers*, g	22.5 ± 9.4	24.9 ± 8.8	0.18	1.008 (0.920-1.104)	0.87
Industrial fructose*, g	5.5 ± 4.2	7.8 ± 6.0	0.01	1.205 (1.065-1.364)	0.003

yr, years.

Data are given as mean ± standard deviation or as number of case (%).

*Mean value of three-day dietary intake