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# Industrial, not fruit fructose intake is associated with the severity of liver fibrosis in genotype 1 chronic hepatitis C patients

*To the Editor:*

In their study recently published in the *Journal of Hepatology*, Petta *et al.* reported an independent association between advanced liver fibrosis in chronic hepatitis C virus (HCV) genotype 1 infection and 'industrial', but not fruit fructose intake [1]. While these findings are novel we believe this cross-sectional study has significant limitations that need to be addressed before the results can be applied to the broader HCV community.

Firstly, the use of an American web-based calculator (www.health-diet.us/fructose) to quantify the fructose content of specific foods requires validation in an Italian population consuming locally produced and marketed food. The United States uses high fructose corn syrup as an additive sweetener to food and carbonated beverages to a much higher extent than many other countries. Hence the methodology used to calculate 'industrial' fructose intake may have resulted in significant bias being introduced into the study. The authors have not given any specific information of the use of high fructose corn syrup as a sweetener in Italy, but solely relied on extrapolation from American data and practices. Furthermore, the methodology of use of a three-day food diary is questionable when the progression of fibrosis in HCV infection occurs over years.

Secondly, the very low overall fructose intake by study participants (18.0 ± 8.7 g/day) limits the generalizability of the study. This low value is likely reflective of the regional dietary differences many Italians have when compared with other developed countries, including the United States of America. National dietary intake survey data shows that >95% of American residents consume <100 g of fructose per day from all sources [2], while Australian adults consume <60 g total fructose per day [3]. These values are markedly higher than this study's population. Moreover, as those with advanced fibrosis only had 2.3 g higher mean intake of 'industrial' fructose per day than those without advanced fibrosis and the clinical relevance of such a small increase in this form of fructose is questionable.

Thirdly, this study did not find any relationship between insulin resistance and advanced fibrosis. Insulin resistance is a marker of glycaemic control and has been identified by a number of investigators, including Petta's group, to be an important cofactor in the development of advanced liver fibrosis in genotype 1 infection [4–7]. The lack of an association between insulin resistance and advanced fibrosis, as well as steatosis, in both univariate and multivariate analysis in this study cohort raises concern about the internal validity of the study's findings. Of particular note diabetes, insulin resistance, HOMA score, blood glucose levels, insulin levels, body mass index, and other anthropometric measures were not included in the same multivariate analysis. The authors state that this method was employed to 'avoid colinearity', but their statistical methodology may explain why no association between insulin resistance and fibrosis was seen.

Most importantly however, is the lack of a plausible explanation given by the authors as to why the specific source of fructose, whether from 'natural' apples or 'industrial' cola, would have an impact on liver fibrosis rather than the degree of consumption of the monosaccharide itself. Indeed, fructose is the same compound regardless of the source, with 'industrial' derived fructose unlikely to have a differential unfavorable impact on caloric intake and metabolic profile. A more credible explanation is that those who have higher 'industrial' fructose intake are likely to have a less healthy diet and lifestyle, resulting in higher rates of obesity and insulin resistance. Our suggestion is that the key findings of this study are likely to represent a confounding relationship, brought about by gaping methodologic flaws. Our viewpoint is further supported by the independent association between 'industrial' fructose intake and obesity that the study describes.


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## Conflict of interest

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

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# Reply to: "Industrial, not fruit fructose intake is associated with the severity of liver fibrosis in genotype 1 chronic hepatitis C patients"

## Fructose intake and liver damage in chronic hepatitis C

*To the Editor:*

Prof. Kitson's comments give us the opportunity to clarify some issues that were not completely dealt with in our manuscript. In the study we reported a link between fructose intake and the severity of liver fibrosis in a cohort of Italian patients with genotype 1 chronic hepatitis C (CHC) [1], with an association found for industrial, but not for fruit fructose intake. Our results were in keeping with data already reported in patients with non-alcoholic fatty liver disease [2,3].

Prof. Kitson and his colleagues question firstly the appropriateness of using a web-based calculator of U.S. origin (www.healthdiet.us/fructose) to assess fructose intake in the Italian population, due to a presumed much lower fructose consumption in the latter. Actually, we considered industrial fructose as any amount of fructose derived from food sources containing high fructose corn syrup (beverages like soft drink and fruit juices, processed foods like fast-food, especially when enriched with industrial sauces). The U.S. database for the calculation of fructose intake is most likely valid also for use in Italian patients, since the majority of foods and beverages with added fructose are produced by multinational companies, and the concentration of fructose does not change among countries. In addition, our data on fructose consumption are in keeping with another Italian report [4]. Prof. Kitson and colleagues also question the validity of a three-day food diary. It has been reported that a three-day diary record correlates closely with a longer 9-day diary [5], providing a solid dietary assessment. In a cross-sectional analysis no inference can be made regarding a possible causal relationship, but this possibility may be postulated. We have simply described the positive association between industrial fructose and advanced fibrosis, but the two conditions might also share common pathogenic mechanisms.

As a second point, our study was performed in an Italian population, not in an Australian or U.S. population, where much higher rates of fructose consumption are recorded. The accuracy of our computation of fructose intake is in keeping with the industrial fructose intake reported in the Italian population [4], but lower than in the U.S. population. In the participants of the LOOK Ahead study consuming $\geqslant$15 g/day of fructose (high-fructose consumers), a fructose challenge identified metabolic abnormalities potentially responsible for NAFLD progression [6]. This threshold was observed in most of our cases with fibrosis, and the higher industrial fructose intake was the major source of difference between cases with advanced *vs.* mild hepatic fibrosis. When industrial fructose intake as continuous variable was replaced in the model by industrial fructose as categorical variable, 14/25 patients consuming $\geqslant$8 g/day industrial fructose had F3-F4 fibrosis *vs.* 18/89 in the group with lower intake ($p = 0.01$).

Thirdly, Kitson *et al.* remark the lack of association between severe liver fibrosis and both insulin resistance (IR) and steatosis in this specific population. In the present series, steatosis was linked to fibrosis at both univariate and multivariate analysis. Both IR and steatosis, the phenotypic hepatic expression of IR, are risk factors for fibrosis; they both might play an important role in fibrosis progression and are likely to be variably combined in different settings [7,8]. As to the possible reason(s) why industrial, not fruit fructose intake, is associated with the severity of liver fibrosis in CHC, several tentative hypotheses may be suggested. In fresh fruit the deleterious effects of fructose might be counterbalanced by the positive effects of other nutrients (e.g., fibers) and antioxidants, not present in industrial fructose. In processed food, the glucose of high-fructose corn syrup might accelerate fructose absorption, making industrial sugars unhealthy. Finally, even if the link between industrial fructose and the clinico-pathological features (i.e., liver fibrosis and obesity) was independent of energy intake on a statistical basis, we cannot rule out a pivotal role of calories and/or of a less healthy diet and lifestyle in the reported association, considering that higher amounts of industrial fructose were associated with high-calorie diets.

Hence we are confident that our study provides reliable evidence, albeit of an associative nature. Further research is clearly needed to provide external validation and to eventually elucidate the pathophysiological basis, aiming to a healthy diet as an additional tool to manage patients with HCV-induced chronic liver disease.