Title: Authors' Response

The relationship between fructose intake and non-alcoholic fatty liver in obese adolescents: A response to Chiavarioli, Ha, de Souza, Kendall and Sievenpiper (2014)

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To the Editor

We respond to the queries raised by Chiavarioli et al. regarding our paper, which reported associations between fructose and non-alcoholic fatty liver disease (NAFLD). [1]

Although we are confident that our statistical approach was appropriate, we extended our analysis as requested by Chiavarioli et al. To address their concern that the residuals method insufficiently adjusts for total energy intake, the logistic regression model was refitted with additional adjustments for quartiles of total energy intake, aerobic fitness and energy-adjusted saturated fat and dietary fiber.

Notably, the association between fructose intake and NAFLD in obese adolescents remained significant. The odds of NAFLD increase by 8% with each 1 g increase in energy-adjusted fructose after adjustment for sex and total energy intake, and by 25% (OR 1.25, 95% CI 1.002-2.86) after further adjustment (Table 1).

It is important to note that the meta-analysis of controlled feeding trials of fructose, [2] referred to by Chiavarioli et al., consisted predominately of normal and overweight individuals with median BMIs of 24.3-25.9 kg/m^2. Thus, the association between fructose and NAFLD that we noted in obese individuals may not have been detectable.

With regard to alanine transaminase (ALT), one would only expect consistent associations between fructose consumption and NAFLD if liver ultrasound and ALT testing were equivalent diagnostic tests for NAFLD. However, previous research on the Raine adolescents found that “90% of males and 91% of females with fatty liver in our cohort had normal ALT levels, and this indicates that the majority of subjects would have been missed if we relied upon ALT”. [3] The American Association for the Study of Liver Diseases (AASLD) guidelines also state that ALT is less sensitive for fatty liver than ultrasound. [4]

In summary, the additional analyses suggest that our study has not overstated the association between fructose and NAFLD in obese adolescents. However, we acknowledge that the limitations previously described in our paper still apply, [1] and that further research is warranted to explore these concepts further.

References

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TABLE 1. Odds ratio estimates from multivariable logistic regression models of daily fructose (energy adjusted g/day) at 14 years and risk of NAFLD at 17 years in obese adolescents.

	Logistic regression method			
	Asymptotic†		Exact‡	
Model adjusted for:	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex	1.09 (1.01-1.19)	0.030	1.09 (1.02-1.19)	0.008
Plus total energy intake*	1.10 (1.01-1.19)	0.031	1.08 (1.02-1.18)	0.010
Plus saturated fat, dietary fiber, and aerobic fitness*	1.20 (0.995-1.43)	0.056	1.25 (1.002-2.86)	0.041

CI=confidence interval; OR=odds ratio.

* Total energy intakes, saturated fat, dietary fiber and aerobic fitness categorised as quartiles.

† Maximum likelihood estimate.

‡ Estimate from exact conditional analysis (proc logistic procedure, SAS V 9.4).