Measure, modesty, and mechanism: Alcohol in non-alcoholic steatohepatitis

To the Editor:
We studied the association of modest alcohol consumption and steatohepatitis in a large sample of well-characterized study participants with biopsy-proven non-alcoholic fatty liver disease (NAFLD) from referral centers across the United States. Modest alcohol consumption was associated with significantly lower odds of non-alcoholic steatohepatitis (NASH). Feng et al. raise questions about diabetes and soft drink consumption as potential confounders.

The first question about diabetes speaks to one possible mechanism by which alcohol could lower the odds for NASH. Diabetes has consistently been shown to be a major risk factor for steatohepatitis. In order to be considered a confounder, a factor must be associated with both the exposure and outcome, but cannot be in the causal pathway. Therefore, our main analysis did not include the diagnosis of diabetes as a confounder because diabetes is thought to be in the causal pathway. We did, however, perform a series of sensitivity analyses to address such issues. Sensitivity analysis #4 adjusted for the diagnosis of diabetes and showed that the odds ratio between modest alcohol and NASH was attenuated from 0.52 (95% CI 0.36–0.76) to 0.58 (95% CI 0.41–0.84). Thus as evidenced by this small attenuation, the effect of modest alcohol on steatohepatitis may in part be manifested through reduced prevalence of diabetes, but this is not likely to be the major explanation for the lower odds of steatohepatitis.

While we adjusted for an extensive list of social, demographic and lifestyle covariates, the possibility remains for any epidemiology study that the exposure of interest is a surrogate marker of other unmeasured factors. The second question posed by Feng et al. was whether non-drinkers may consume greater amounts of soft drinks, especially those containing fructose. Thus, soft drink consumption could be one of the unmeasured factors, because previous data has suggested an association between fructose consumption and an increased risk for NAFLD and [1,2] and NASH. We performed a literature search, but were unable to find published studies comparing soft drink consumption between non-drinkers and modest drinkers. Thus it is unclear whether the amount of soft drink consumption was different between our two groups. However, in our main analysis we did adjust for total calories per day and percent calories from carbohydrates. Neither of these adjustments attenuated the association between modest alcohol and lower odds of having NASH.

Beyond issues of mechanism and statistical analyses, the question of whether or not to permit adult patients with NAFLD to drink alcohol in modest amounts remains controversial. As opposed to being harmful, many studies now support the belief that modest alcohol consumption in adults with NAFLD could be beneficial. However, to date no studies can definitively support nor refute this contention. Therefore, hepatologists are not unified on this issue and thus fall into one of three camps: (1) those that continue to recommend strict avoidance; (2) those that counsel their patients that heavy drinking is bad, but that there is not enough evidence to know whether modest alcohol is good or bad; and (3) those that have taken to proactively recommending one alcoholic beverage a few times per week. In order to move past the controversy and know how to best counsel our patients will require collaborations to further build the evidence than can support a clinical consensus.

Conflict of interest
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References

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