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Letter to the Editor : Moderate Alcohol Use in Fatty Liver  
Disease: Don't Throw the Cabernet Out With the Bathwater REPLY

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## **Reply: Alcohol and mortality in NAFLD: Is the cabernet causal or confounder?**

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**List of abbreviations:** CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; GBD, Global Burden of Disease

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To the editor:

We thank doctors Gow, Testro, Hey, and Sinclair for their interest in our study and for sharing their views on the potential benefits of alcohol.

Indeed, we found an association between light alcohol use and reduced all-cause mortality and reduced incidence of cardiovascular disease (CVD) in never smokers with non-alcoholic fatty liver disease (NAFLD) (1). However, this observation does not necessarily translate into a benefit of alcohol as a therapeutic approach in (CVD) prevention, mainly because of potential residual confounding from, for instance, an imbalance in dietary patterns between light drinkers and abstainers.

The J-shaped association between alcohol and mortality observed in several population studies was recently challenged by the Global Burden of Disease (GBD) study (2), and by a large Asian Mendelian randomization study analyzing genetic proxies for drinking habits (3). Controversy also exists in NAFLD regarding the effect of alcohol on CVD risk (4).

One of the methodological issues introduced by the GBD investigators to better overcome difficult-to-control bias from residual confounding and reverse causation was the exclusion of all abstainers. In our study, we excluded former drinkers, but not lifetime abstainers. When re-analyzed in our population NAFLD cohort after the additional exclusion of lifetime abstainers, similar to the GBD study, the apparent mortality-benefit of light alcohol use diminishes (Figure).

Gow et al also argue that wine could be beneficial for the liver in NAFLD. Although we found wine possibly less harmful than other alcoholic beverages at moderate-level consumption, no liver-protective effect was observed in neither our study nor in the only published randomized controlled trial to date (5), in which light red wine consumption, compared to abstinence, tended to increase liver fat content rather than protect from it.

Additional concerns with alcohol as a therapeutic approach include a substantial individual variation as to when alcohol starts to become harmful, probably dependent on gender, drinking pattern, genetics, obesity, and the gut microbiome.

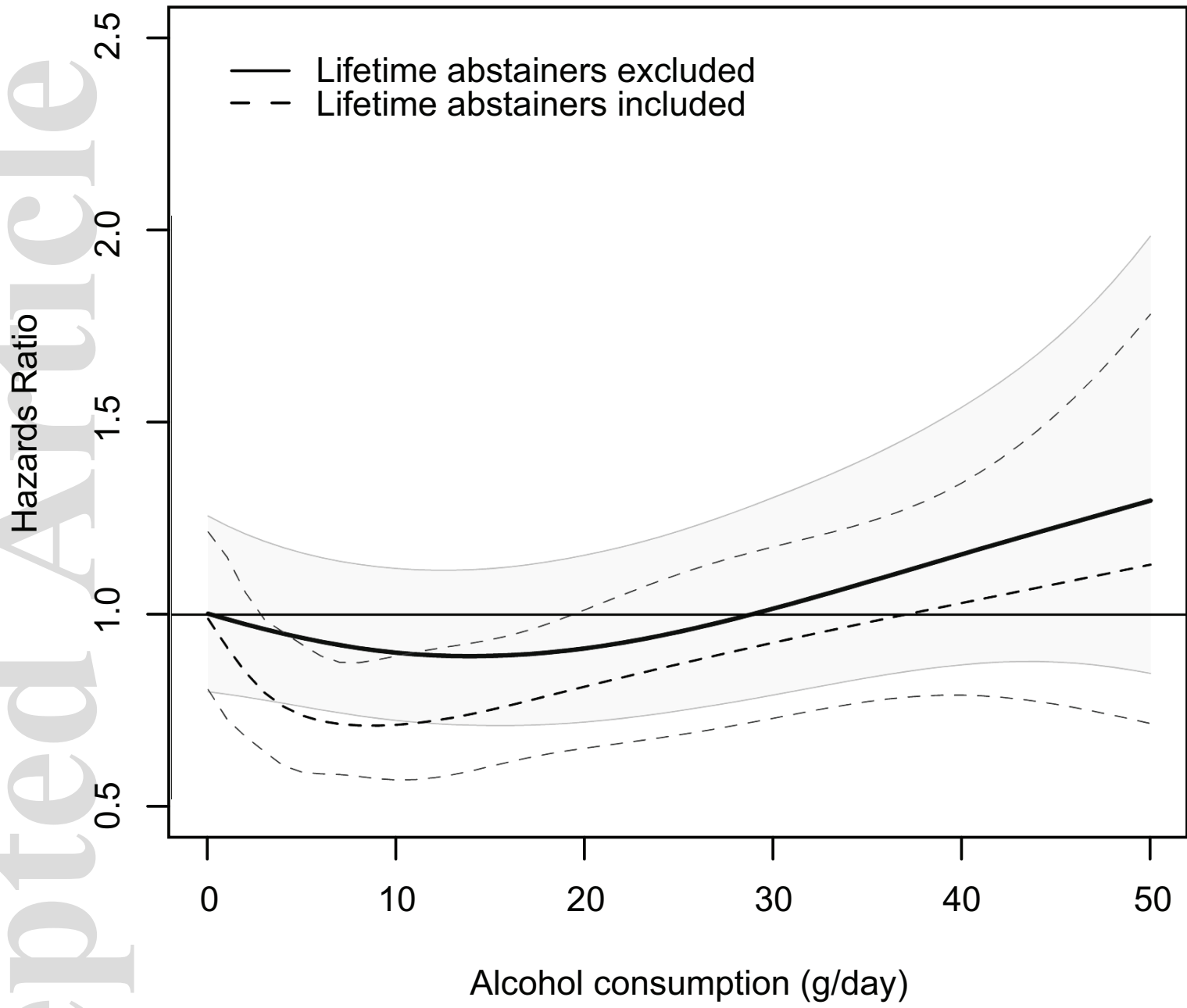
The debate over the risk-benefit of light alcohol use remains open, awaiting further prospective long-term studies with objective measurements of cumulative alcohol consumption. In the meantime, caution with the cabernet consumption, and keep the cork closed in cirrhosis!

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### **Figure legend**

Figure. The relationship between daily alcohol consumption and risk for incident advanced liver disease when either including or excluding lifetime alcohol abstainers, by multivariate Cox regression analysis adjusted for age, sex, marital status, education, employment, smoking, exercise, body mass index, waist circumference, diabetes, systolic blood pressure, ASA use, serum glutamyltransferase, history of cancer, and history of CVD. Former drinkers (abstainers at baseline) are excluded in both analyses.



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