Word count=399

To define alcohol consumption thresholds associated with lowest risk for all-cause mortality and cardiovascular disease subtypes, we analysed individual-participant data from 599 912 current drinkers without previous cardiovascular disease.[1] Among current drinkers, the threshold for lowest risk of all-cause mortality was about 100g/week. For cardiovascular disease subtypes other than myocardial infarction, there were no clear risk-based thresholds below which lower alcohol consumption stopped being associated with lower disease risk. These data challenge the concept that moderate alcohol consumption is universally associated with lower cardiovascular disease risk, and suggest implications for low-risk limits in guidelines.

In response to Astrup et al and Eva Schernhammer, our paper stated the scientific rationale to focus on current alcohol drinkers. First, guidelines provide recommendations about low-risk limits only for drinkers; we are unaware of any guidelines that encourage non-drinkers to consume alcohol. Second, a focus on current drinkers should limit potential biases that are difficult to control in observational studies (eg, reverse causality, residual confounding, and unmeasured effect modification) because ex-drinkers include people who might have abstained from alcohol owing to poor health itself,[2] as well as those who have changed their habits to achieve a healthier lifestyle. Third, never-drinkers might differ systematically from drinkers in ways that are difficult to measure, but which might be relevant to disease causation.[3] For example, our study found important differences between never drinkers and current drinkers in key baseline characteristics (e.g., sex, ethnicity, smoking, diabetes status), but other differences are also likely to exist for relevant characteristics we did not record.[4]

Our analysis, therefore, aimed to minimise the scope for residual bias by comparing different levels of alcohol consumption among current drinkers. A complementary approach to minimising such bias involves studying genetic proxies for drinking habits. For example, data from large studies in East Asian populations, where common genetic variants predict 20-fold differences in drinking prevalence, have yielded results concordant with those of our study.[5]

In response to Warren Thompson's query, our consortium could not powerfully study binge drinking as a primary hypothesis due to limited information available on the frequency of alcohol consumption (e.g., fewer than half of the deaths had frequency information). Furthermore, only partial information was available on important confounding factors (e.g., socioeconomic characteristics) in this subset of participants. We found wide confidence limits for hazard ratios for association of binge-drinking and disease outcomes, reinforcing the need to interpret these exploratory analyses with caution.

Angela Wood, Stephen Kaptoge, Ellie Paige, Emanuele Di Angelantonio, John Danesh

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