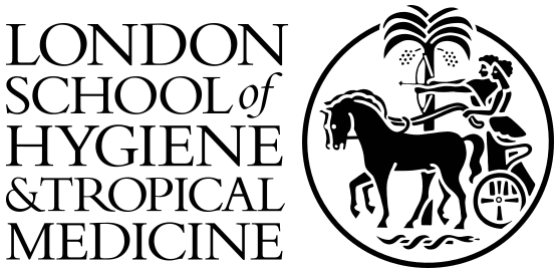

Letter to the editor: A measure of alcohol consumption in late adolescence associated with liver disease after 39 years of follow-up is insufficient to guide alcohol safe limits

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Comment on:

" Alcohol consumption in late adolescence is associated with an increased risk of severe liver disease later in life"
By Hagström H, Hemmingson T, Discacciati A, and Andreasson A. Journal of Hepatology 2018

And

"Managing excessive alcohol consumption at a population level: The earlier the better"
By Krag A, Louvet A. Journal of Hepatology 2018

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We have read with great interest the paper by Hagström et al. [1], and the associated editorial by Louvet and Krag [2], which uses a prospective cohort design to examine the association between a single measure of alcohol consumption and subsequent risk of severe liver disease over a follow-up period of 39 years. The study is based on data on alcohol, smoking, BMI, and other factors collected at conscription to military service for 43,000 Swedish men 18-20 years of age. Follow-up to ascertain a diagnosis of severe liver disease was done by linkage to registries. While this study is of interest, we are concerned that the authors of the study itself, and the editorial comment, have reached erroneous conclusions concerning the relevance of their findings to determining alcohol safe limits.

In contrast to the majority of earlier studies that found no increased risk of severe alcoholic liver disease below 30 g alcohol/day for men [3,4], Hagström et al. state in their abstract that “Importantly, a clear trend pointed towards an increased risk of severe liver disease in men who consumed less than 30 grams of alcohol per day" which led them to conclude: “Alcohol consumption in young men is associated with an increased risk of severe liver disease, up to 39 years later in life. The risk was dose-dependent, with no sign of a [lower] threshold effect.”

Looking more closely at the presented estimates, we think that their results are in line with prior studies demonstrating no increased risk of severe liver disease at levels below 30 g alcohol/day for men. Hagström et al. present estimates for alcohol consumption at 18-20 years of age and risk of severe liver disease over 39 years of follow-up. In analyses unadjusted for established risk factors such as smoking, obesity, and viral hepatitis, alcohol consumption as low as 6-10 g/day was associated with an increased risk of severe liver disease [HR 1.98; 95% CI 1.05–3.72]. But, in adjusted analyses taking the effect of smoking and BMI on risk of liver disease into account, only alcohol consumption at 31-40 g/day and above was associated with increased risk compared to abstention. This indicates that the unadjusted analyses are subject of confounding due to smoking and BMI [5].

Most importantly, the study is based on a single measure of alcohol consumption at age 18-20 years. Alcohol consumption at this age is related to subsequent liver-disease risk because it is predictive of consumption across the life-course, and not because any particular level of consumption at that age constitutes a biological threshold. The importance of alcohol

consumption in all stages of life is underlined by studies that show that risk of alcoholic liver disease is influenced by a change in alcohol consumption [3]. For example, decreasing alcohol use was observed to lower the risk of liver cirrhosis among men with early signs of alcoholic liver disease [6].

Severe alcoholic liver disease is a rare outcome in the general population

We therefore believe that it is incorrect to use the results obtained in the study by Hagström et al. to guide lower safe levels of alcohol consumption for the whole population as Louvet and Krag suggest in the editorial: "….safe levels of alcohol consumption must be revised for the general population and public health policies must be adapted accordingly". Severe alcoholic liver disease is rare in the general population. For example, the incidence of severe liver disease in the study by Hagström et al. was only 234 per million annually (383 cases/1,638,622 person-years) corresponding to 0.9% of the study population experiencing this during the 39 years of follow-up (Table 1). In comparison, 6.5% died without being diagnosed with severe liver disease. Even among drinkers of >30 g alcohol/day in the study, only 3.1% developed severe liver disease. This illustrates that alcoholic liver disease mainly develops in persistent heavy drinkers that constitute a minority of the general population. In a study of 2070 alcoholic liver cirrhosis patients, mean consumption was 115-126 g alcohol/day for > 25 years [7]. In the study by Hagström et al., reflecting a general population sample, only 4.4% drank > 30 g alcohol/day.

Providing the public and professionals with an evidence-based approach to recommended levels of alcohol consumption is vitally important. Such assessments should be based on the full evidence for the diversity of conditions associated with alcohol consumption [8] and not just liver disease [9]. Drawing unsound conclusions in this area should be avoided not least because economic interests who are opposed to reduced consumption will be able to make use of scientific shortcomings for their own purposes. Having said this, it should be noted that the 30 g alcohol/day "limit" identified is almost twice that of the new more soundly based levels recommended by the UK government [10].

Tabel 1. Numbers (percentages) of study participants, study participants who were diagnosed with severe liver disease, and study participants who died without diagnosis of severe liver disease at follow-up according to alcohol consumption at enrollment in 1969-70. Numbers derived from study by Hagström et al. [1].

	Alcohol consumption ≤ 30 g/day	Alcohol consumption > 30 g/day	Overall
Study participants 18-20 years in 1969-70	41,377 (96%)	1919 (5%)	43,296 (100%)
Study participants with severe liver disease during 39 years of follow-up in 2009	323 (0.8%)	60 (3.1%)	383 (0.9%)
Study participants who died without severe liver disease during 39 years of follow-up in 2009	-	-	2816 (6.5%)

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