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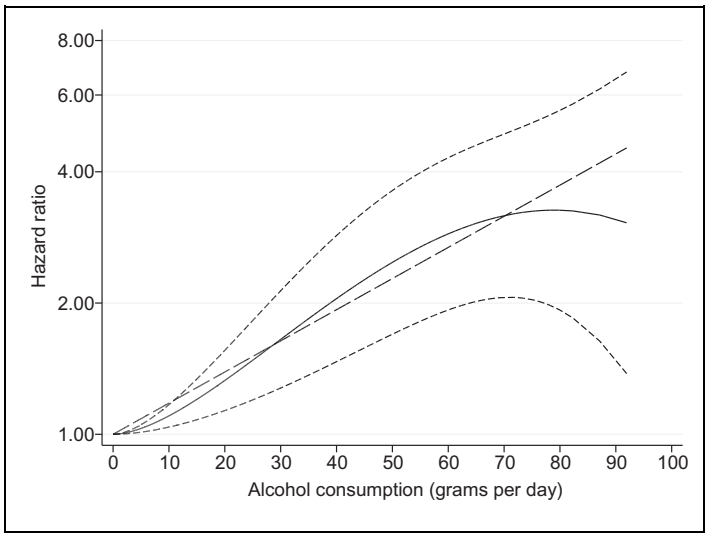
Research Article
Genetic and Metabolic Diseases

Alcohol consumption in late adolescence is associated with an increased risk of severe liver disease later in life

Graphical abstract



Highlights

- Alcohol consumption early in life was associated with an increased risk for development of severe liver disease after 39 years of follow-up.
- The risk increased in a dose-response pattern, with no evidence of a threshold effect.
- Trend towards an increased risk of severe liver disease in men consuming less than current recommendations for a safe alcohol intake.

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Lay summary

We investigated more than 43,000 Swedish men in their late teens enlisted for conscription in 1969–1970. After almost 40 years of follow-up, we found that alcohol consumption was a significant risk factor for developing severe liver disease, independent of confounders. This risk was dose-dependent, and was most pronounced in men consuming two drinks per day or more.

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Alcohol consumption in late adolescence is associated with an increased risk of severe liver disease later in life

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Background & Aims: High alcohol consumption is associated with an increased risk of severe liver disease. Current recommendations suggest it is safe for men to consume 30 grams of alcohol per day. We investigated the association between alcohol consumption early in life and later development of severe liver disease.

Methods: We used data on alcohol consumption at conscription to military service from 43,296 men (18–20 years) in Sweden between 1969 and 1970. Outcomes were defined as incident diagnoses of severe liver disease from systematic national registration of clinical events until the end of 2009. A Cox regression model adjusted for body mass index, smoking, use of narcotics, cognitive ability and cardiovascular capacity was applied.

Results: During a mean follow-up of 37.8 years, 383 men developed severe liver disease. Alcohol consumption was associated with an increased risk of development of severe liver disease in a dose-response pattern (adjusted hazard ratio for every one gram/day increase 1.02; 95% CI 1.01–1.02). No evidence of a threshold effect was found. 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.

Conclusion: 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 threshold effect. Current guidelines for safe alcohol intake in men might have to be revised.

Lay summary: We investigated more than 43,000 Swedish men in their late teens enlisted for conscription in 1969–1970. After almost 40 years of follow-up, we found that alcohol consumption was a significant risk factor for developing severe liver disease, independent of confounders. This risk was dose-dependent, and was most pronounced in men consuming two drinks per day or more.

Keywords: Alcohol; Long-term follow-up; Epidemiology; Decompensated liver disease; Cirrhosis.
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Introduction

Alcohol consumption is a known risk factor for the development of cirrhosis.[1,2] Alcohol has been reported to account for 85,000 deaths per year in the US[3] and as many as 50% of all deaths from liver cirrhosis on a global scale.[4] The exact amount of alcohol needed to inflict liver damage is unclear and is affected by internal factors including genetics[5] and external factors including drinking patterns, type of alcohol and diet.[6] Some evidence points to a cut-off around 30 grams of pure alcohol per day for men and 20 grams per day for women,[1,6–8] although data from two meta-analyses indicate that the cut-off might be lower at 20–25 grams per day.[9,10] This uncertainty is noted in guidelines for alcoholic liver disease.[11,12]

Much of the current evidence on the risk of liver disease progression attributable to alcohol comes from studies with selected populations, short follow-up periods or from cross-sectional or case-control studies, where cases with manifest liver disease might be prone to under report past alcohol consumption, leading to misclassification bias. Thus, the role of alcohol consumption early in life needs to be investigated in studies where alcohol consumption is measured before liver disease has developed, with adequate follow-up and data on possible confounders.

We examined if alcohol consumption in late adolescence in a population of well-characterized adolescent men was associated with an increased risk of severe liver disease later in life, and if a cut-off level could be identified.

Material and methods

Study population

We used data from a nationwide population-based study conducted during 1969–1970 of all Swedish men compulsorily enlisted for conscription. During that time, conscription was mandatory in Sweden, and only 2–3% of men were exempted from conscription, mostly due to severe disabilities or diseases. This study was based on 49,321 Swedish men, age 18–20, conscripted during that period.

Variables

Baseline

All conscripts underwent an extensive health examination with height and weight measurements, and personal interviews.

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They also filled in questionnaires on alcohol consumption, smoking and use of narcotics.

Alcohol consumption
Questionnaires with items regarding the amounts consumed (number of cans or bottles, or centiliters of beer, wine and spirits), and frequency of consumption (daily, once a week, less than once a week, never) were completed during the conscription examination. Information on typical alcohol content for the different kinds of beverages during the period when the examinations were conducted was retrieved from the Swedish alcohol retailing monopoly. Grams of 100% alcohol consumed per day were estimated for each individual.[13]

Body mass index
We used data on height and weight taken at the physical examination to calculate body mass index (BMI) (kg/m^2).

Smoking and use of narcotics
Smoking at the time of conscription was classified as either 0 (non-smoker), 1–5, 6–10, 11–20, or more than 20 cigarettes per day. Use of narcotics was defined as having tried or actively using any drugs, except for alcohol and tobacco, at the time of conscription.

Cognitive ability and cardiovascular fitness
A test of cognitive ability was performed as described elsewhere.[14,15] Cardiovascular fitness using an ergometer cycle was tested at baseline when the men's maximum work capacity divided by body weight was assessed and transformed into a numeric scale.[16] For both tests, the men received a score of one to nine, a higher number indicates a better result. Both tests have been found to be predictors of severe liver disease in the cohort.[17]

Follow-up
All Swedish citizens are assigned a personal identity number a few days after immigration or birth,[18] this data was available at the time of conscription.

The National Patient Register (NPR) was established in 1964. It includes information on dates of hospital admissions, discharges, and diagnoses classified according to International Classification of Diseases (ICD) codes, versions 7-10. The register also includes information on hospital-based outpatient visits since 2001. The coverage of the register is approximately 99% of all somatic discharge diagnoses since 1987, and the validity of hospital discharge diagnoses is between 85–95% depending on diagnosis.[19]

The Causes of Death Register (CDR) contains data from 1952 regarding the causes of death of all Swedish citizens, including if the person died abroad. It is mandatory for the responsible physician to report the underlying cause of death (*e.g.* stroke) and any disease that could have contributed to the death of the individual (*e.g.* atrial fibrillation).

Severe liver disease
We used diagnoses of liver cirrhosis, decompensated liver disease (hepatocellular carcinoma [HCC], ascites, esophageal varices (bleeding or not bleeding), hepatorenal syndrome or hepatic encephalopathy), specific coding for liver failure from the NPR, or death from any of the above in the CDR as our primary end point variable *severe liver disease*. ICD codes for the diagnoses used in the present study are listed (Table S1).

Alcohol abuse and viral hepatitis
Additionally, we obtained ICD codes for any alcohol abuse related diagnosis as well as all ICD codes for viral hepatitis. ICD codes for these diagnoses are listed (Table S1).

Statistical analysis
We excluded 6,025 men due to missing data regarding any of the covariates, leaving a final sample of 43,296 men. All analyses were performed in STATA 13.0 (StataCorp, College Station, Texas, USA) and a two-sided alpha value of 0.05 was used to test for statistical significance.

Descriptive data
Descriptive data are presented per alcohol consumption category. Dichotomous and categorical variables are presented as percentages, and continuous variables are presented as mean values.

Survival analysis
Men were followed up from conscription until the first registered diagnosis of severe liver disease. Follow-up times were censored at the time of death due to any cause, emigration or end of the follow-up period (31 December 2009).

Cox regression was used to assess the association between alcohol consumption and the hazard of severe liver disease. Alcohol consumption was modeled both as a categorical and a continuous variable. Categories were defined as 0 (abstainers, reference), 1–5, 6–10, 11–15, 16–20, 21–25, 26–30, 31–40, 41–50, 51–60 and above 60 grams of pure alcohol per day. Second-degree fractional polynomials[20] were used to explore a potential nonlinear dose-response relationship between alcohol consumption and severe linear disease. A p value for nonlinearity was calculated as proposed in Royston and Altman.[21]

We constructed one crude univariate model and one multivariate model. The multivariate model was adjusted for BMI, smoking, use of narcotics, cognitive ability and cardiovascular fitness at conscription.

Estimates of the final models are presented as hazard ratios (HRs) and 95% CIs. We checked the assumption of proportionality of the hazards using Schoenfeld residuals. We observed no evidence of departure from this assumption.

Sensitivity analyses
Firstly, a competing risk regression method[22,23] was used to estimate the association with the risk of severe liver disease using overall mortality as competing risk, while adjusting for the confounders previously mentioned. Secondly, all men who received an ICD-code for viral hepatitis during follow-up were excluded from the analysis.

Ethical considerations
This study was approved by the regional ethics committee at Karolinska Institutet (dnr 2004/5:9 – 639/5). Due to the character of the database and the anonymization of all data, no written informed consent was needed.

For further details regarding the materials used, please refer to the Supplementary material and the CTAT table.

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Results

Mean daily alcohol consumption among the 43,296 men included in the analyses was 8.6 grams (SD 11.2). Categorized, 6.1% men were abstainers, a large proportion, 43.2%, reported a consumption between 1–5 grams per day and 4.6% reported a consumption of more than 60 grams per day (Table 1). Smoking was common at the time of the conscription with 58.4% reporting being a smoker, with a significantly correlation between smoking and higher consumption of alcohol. Mean BMI was 21.0 kg/m^2, with 6.7% of individuals being overweight or obese. Baseline descriptive data per alcohol consumption category are presented (Table 1).

Severe liver disease

The men were followed for a mean period of 37.8 years (SD 4.9, range 0.1–39) or 1,638,622 person-years. During this time, 3,024 men died and 419 men, 0.97%, emigrated and were censored. A total of 383 men were diagnosed with severe liver disease. Out of these 383 men, 208 (54.3%) died during the follow-up period. Mean time from conscription to the first diagnosis of severe liver disease was 25.5 years (SD ± 11.2, range 3–39).

Alcohol abuse disorder and viral hepatitis

During follow-up, 2,661 men received an alcohol abuse diagnosis. Of these, 243 were subsequently diagnosed with severe liver disease (9.1%). Alcohol consumption at baseline was a strong predictor of a diagnosis of an alcohol abuse diagnosis during follow-up. Compared to abstainers, the hazard of obtaining an alcohol abuse diagnosis was moderately elevated among men who reported a consumption of between 1–5 grams of alcohol per day at baseline (HR 1.48; 95% CI 1.13–1.95; $p = 0.005$) and was highly elevated among men who reported a consumption of more than 60 grams per day at baseline (HR 5.22; 95% CI 3.72–7.32; $p < 0.001$).

A total of 386 men were diagnosed with viral hepatitis during follow-up, of which 22.3% were later diagnosed with severe liver disease. The prevalence increased with alcohol consumption, corresponding to an HR of 3.81 (95% CI 1.59–9.12; $p = 0.003$) for those who consumed more than 60 grams of alcohol per day at time of conscription compared to abstainers. Adjusted HRs for alcohol abuse diagnosis and viral hepatitis per alcohol consumption category are presented (Table S3a and S3b).

Alcohol consumption as a predictor of severe liver disease

In univariate analysis, alcohol consumption was associated with development of severe liver disease later in life, both when tested as a continuous variable (HR 1.03 for each additional gram of alcohol per day, 95% CI 1.03–1.04), and as a categorical variable. Here, a close association between alcohol consumption and increased risk of severe liver disease was seen in a dose-dependent pattern that first became statistically significant in the category of 6–10 grams of alcohol per day (HR 2.01; 95% CI 1.03–3.91), with the highest risk seen in men who consumed more than 60 grams per day (HR 11.05; 95% CI 5.22–23.40) compared to abstainers (Table 2).

When adjusting for body mass index, smoking, use of narcotics, cognitive ability and cardiovascular capacity, a significant association was observed for alcohol as a continuous variable (HR 1.017; 95% CI 1.010–1.023 for every one gram per day increase). When we modeled alcohol consumption using fractional polynomials, we observed no evidence of nonlinearity ($p = 0.82$) (Fig. 1). The association followed a dose-dependent pattern similar to the crude analyses and became statistically significant beginning with the category of 31–40 grams of alcohol per day (HR 2.31; 95% CI 1.06–5.05, [Table 2]). HRs for development of severe liver disease for included covariates, adjusted for alcohol consumption as a continuous variable are presented (Table S2).

A graph of the cumulative incidence for the development of severe liver disease, stratified on alcohol consumption categories is presented (Fig. 2).

Sensitivity analyses

Alcohol consumption at baseline was significantly associated with development of severe liver disease in the competing risk regression (subhazard ratio for alcohol consumption as a continuous variable 1.02; 95% CI 1.01–1.02; $p < 0.001$).

Removing the 386 men diagnosed with viral hepatitis during follow-up from the Cox regression analysis yielded lower but significant estimates on the risk of alcohol consumption (HR for alcohol as a continuous variable 1.01; 95% CI 1.01–1.02; $p = 0.001$).

Table 1. Participant characteristics.

Daily alcohol consumption, n (%)	0 g 2,630 (6.1)	1–5 g 18,717 (43.2)	6–10 g 9,872 (22.8)	11–15 g 4,826 (11.2)	16–20 g 2,642 (6.1)	21–25 g 1,676 (3.9)	26–30 g 954 (2.2)	31–40 g 883 (2.0)	41–50 g 402 (0.9)	51–60 g 267 (0.6)	>60 g 427 (1.0)
BMI (kg/m^2)	21.0	20.9	21.0	21.0	21.1	21.2	21.2	21.1	21.4	21.1	21.1
Smoking											
Non–smoking (%)	85.7	52.2	33.9	26.2	22.8	18.6	18.5	17.4	14.2	13.5	10.8
1–5 cig/day (%)	3.8	12.8	12.6	11.0	9.3	9.3	6.8	7.47	5.0	7.1	4.0
6–10 cig/day (%)	5.6	19.1	25.7	25.5	23.2	22.9	19.9	17.8	14.4	16.5	9.1
11–20 cig/day (%)	4.1	14.5	25.3	33.4	39.0	41.7	44.4	43.8	47.3	42.3	45.0
>20 cig/day (%)	0.8	1.4	2.5	4.0	5.7	7.6	10.4	13.5	19.2	20.6	31.2
Use of narcotics (%)	1.7	4.8	11.0	17.4	23.2	23.6	30.4	36.8	41.3	42.0	53.9
Cognitive ability (1–9)	5.4	5.4	5.5	5.4	5.4	5.1	5.0	5.0	4.8	4.6	4.5
Cardiovascular fitness (1–9)	6.1	6.2	6.1	6.1	6.0	5.9	5.9	5.7	5.7	5.7	5.5
Severe liver disease during follow–up, n (%)	11 (0.4)	128 (0.7)	88 (0.9)	44 (0.9)	33 (1.3)	26 (1.6)	17 (1.8)	18 (2.0)	12 (3.0)	12 (4.2)	18 (4.2)

Characteristics of the cohort, stratified on alcohol consumption. Dichotomous and categorical variables are presented as percentage and continuous variables are presented as mean values. Associations between variables and alcohol consumption were tested using Mann-Whitney rank sum test for dichotomous variables and Spearman rank correlation for ordinal and continuous variables. BMI, body mass index. Cig, cigarettes.

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Table 2. Alcohol consumption as a predictor for severe liver disease.

			Univariate		Multivariate[1]	
Alcohol consumption	**Cases**	**n**	**Crude HR**	***p* value**	**Adjusted HR**	***p* value**
Continuous (g/day)	383	43,296	1.032 (1.026–1.037)	<0.001	1.017 (1.010–1.023)	<0.001
Categorized (g/day)						
0	11	2,630	1	(ref)	1	(ref)
1–5	122	18,717	1.56 (0.84–2.90)	0.16	1.39 (0.74–2.59)	0.31
6–10	81	9,872	1.98 (1.05–3.72)	0.033	1.50 (0.79–2.87)	0.22
11–15	40	4,826	2.01 (1.03–3.91)	0.041	1.33 (0.67–2.65)	0.42
16–20	29	2,642	2.67 (1.34–5.35)	0.005	1.58 (0.77–3.24)	0.21
21–25	25	1,676	3.66 (1.80–7.43)	<0.001	2.03 (0.98–4.23)	0.058
26–30	15	954	3.87 (1.78–8.42)	0.001	1.95 (0.87–4.35)	0.10
31–40	18	865	5.02 (2.37–10.62)	<0.001	2.32 (1.06–5.05)	0.034
41–50	12	390	7.45 (3.29–16.89)	<0.001	2.99 (1.28–7.00)	0.011
51–60	12	255	11.68 (5.15–26.46)	<0.001	4.83 (2.07–11.29)	<0.001
>60	18	409	11.05 (5.22–23.40)	<0.001	3.66 (1.65–8.11)	0.001

Crude and adjusted hazard ratios with 95% CIs for development of severe liver disease depending on alcohol consumption at time of conscription.
[1] Adjusted for BMI, smoking, use of narcotics, cardiovascular fitness and cognitive ability at conscription. BMI, body mass index. HR, hazard ratio.

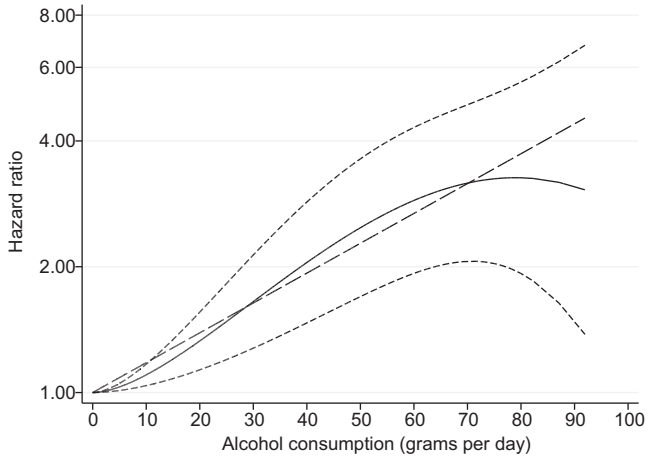

Fig. 1. Hazard ratios (HRs) during 39 years of follow-up. For individuals with severe liver disease by alcohol consumption (grams per day) at the time of conscription in 43,296 Swedish men in 1969–70. The solid line represents HRs and the short-dashed lines the 95% CIs estimated from multivariable Cox models modeling alcohol consumption using fractional polynomials. The long-dashed lines represent HRs from linear-response Cox models.

Fig. 2. Cumulative incidence graph for the development of severe liver disease. Stratified on a mean daily alcohol consumption (<30 *vs.* ≥30 grams per day) in 43,296 Swedish men at the time of enlistment for conscription in 1969–70, and followed for up to 39 years.

Discussion

Herein, we show that consumption of alcohol early in life is associated with an increased risk of developing severe liver disease in men after 39 years of follow-up, independent of established confounders. This is, to the best of our knowledge, the longest follow-up time ever documented in a population-based cohort. The association increased in a dose-response pattern, with no evidence of a threshold effect. Importantly, consumption of lower levels of alcohol than the currently used "safe" cut-off of 30 grams of alcohol per day, down to 20 grams of alcohol per day, were borderline statistical significant in the adjusted model. In the univariate model, men consuming as little as one to five grams of alcohol per day had an increased risk of severe liver disease compared to abstainers, indicating that the increased risk of severe liver disease might be present even at very low doses of alcohol. Importantly, we could ascertain cases that during follow-up were diagnosed with alcohol use disorder, as well as viral hepatitis. Men with a high consumption of alcohol at baseline were more likely to receive an alcohol use disorder diagnosis during follow-up, which has been shown previously.[24]

The association between alcohol consumption and liver disease remained after removing cases with viral hepatitis from the model, although the estimates were slightly reduced, indicating that the excess risk of a high consumption of alcohol early in life cannot be explained by a risk-behaviour and later contracting viral hepatitis.

Our results are consistent with previous large-scale epidemiological studies, although the follow-up period in this study is unmatched. Specifically, in the landmark Dionysos study, a cut-off of around 30 grams of alcohol per day was found to differentiate between high and low risk of cirrhosis.[6] In persons who consumed more than 30 grams per day, 2.2% of men were diagnosed with alcoholic cirrhosis, which is comparable to the 2.7% of men that consumed 30 to 60 grams of alcohol in our study who later developed severe liver disease. In fact, our estimates are higher, and include only register-captured cases of severe liver disease, why we will likely have missed cases of subclinical cirrhosis indicating that the estimates might be falsely low. However, the long follow-up time in our study can likely explain our somewhat higher estimates, as it allows more time to experience an outcome. Although well designed and executed, the cross-sectional methodology of the Dionysos

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study will have led to missing of cases that died from liver disease prior to the examination, possibly underestimating the detrimental effect of alcohol, a limitation not present in our study.

The present study only included men. It is, however, known that alcohol has detrimental effects on liver health in women as well. In data from the Million Women Study on more than 1.3 million middle-aged women followed for a mean time of 6.2 years, a consumption of more than 150 grams of alcohol per week increased the risk of a future diagnosis of cirrhosis (RR 3.44; 95% CI 2.70–4.37) compared to consuming less than 70 grams per week.[25] These estimates are slightly higher than ours, which could be explained by older age at baseline and an increased susceptibility of liver damage in women from alcohol. Indeed, in a study of 13,295 Danish men and women, the risk of death or hospitalization due to liver cirrhosis increased from a consumption of 7–13 units of alcohol per week in women, while this risk was only significant at 14–27 drinks per week for men.[26]

In a study of 6,152 alcohol misusing men and women from Denmark,[27] a threshold effect rather than a dose-response effect was seen. This differs from our results, and could possibly be explained by our much larger sample size that allows for categorization of narrower ranges of alcohol consumption, and the fact that we examined the entire male population at the time, not focusing on at-risk individuals.

Many liver diseases progress slowly[28–30] and outcomes are relatively rare, and a long follow-up period in a large cohort is needed to obtain accurate estimates. Given that risk factors for severe liver disease such as diabetes type 2[31] and obesity[17] are increasing,[32] there might be more cases of severe liver disease in the near future. The current study provides long-term estimates for the risk of alcohol consumption early in life on the development of severe liver disease, and can be used to guide future public health decisions.

The strengths of this study are the large population-based cohort (n = 43,296), very long follow-up time (39 years) and low (1%) loss to follow-up, which minimizes the risk of selection bias. Also, investigating men of a relatively low age as in the present study minimizes the risk for misclassification bias, since none of the men had experienced a liver-related event prior to baseline.

We had access to detailed and credible baseline data regarding the exposure status on almost the entire male population from the study period, as well as on a multitude of possible confounders such as BMI[17,33] and use of narcotics. The national, population-based registers used for ascertaining outcome status are validated and a source of very high-quality data. The use of liver decompensation and cirrhosis, which in almost all cases leads to hospitalization at some point, and liver-related death as a joint outcome variable allowed us to minimize bias regarding the outcome status. However, there were too few disease-specific cases, such as HCC, to allow for analyses of specific disease outcomes. As discussed above, another limitation is that the present study only includes men and the results may not be generalizable to women.

Although the stability of alcohol consumption over time in this cohort is uncertain, previous studies have shown that alcohol consumption as reported at conscription is strongly associated with alcohol problems many years later.[34] Nevertheless, there could be residual confounding in the current study, most importantly regarding changes in alcohol consumption during follow-up. Also, people with high consumption of alcohol were more likely to have tried drugs, and are thus more likely to contract viral hepatitis during follow-up, which would affect the estimates. However, we controlled for this by excluding cases with viral hepatitis during follow-up. It was also evident that men that consumed high amounts of alcohol at baseline to a greater proportion were subsequently diagnosed with an alcohol abuse disorder, suggesting that consuming high amounts of alcohol early in life is associated with continued drinking, and later a higher risk of developing severe liver disease.

Another limitation is that we did not have access to more detailed data on alcohol consumption, such as relation to meals and binge drinking, which may influence the effect of consumption on the development of severe liver disease. Indeed, daily drinking has been associated with an increased risk of alcoholic cirrhosis compared to drinking less frequently, independent of the total amount of consumption.[35]

The current study suggests that the risk of alcohol consumption on the development of severe liver disease later in life is already present from an early age. It is likely that this increased risk is caused by a longer exposure to alcohol, compared to starting to drink later in life, and that individuals with a longer history of alcohol consumption have increased risk of severe liver disease. The risk was significantly elevated for men who consumed more than 30 grams per day, and importantly approaching significance for men who consumed more than 20 grams per day in the adjusted model. However, this model might be over-adjusted, and we cannot exclude the possibility of a type 2 error.

Although national variances in the recommended level of safe intake of alcohol differ, these data indicate that the risk of severe liver disease might already be present at 20 grams of alcohol per day or lower, and that some countries current cut-off levels might be set too high. This has clear implications for public health decision-making, and should be further explored in future studies. Ideally, a prospective study on the risk of alcohol on liver outcomes should include a large population-based cohort composed of both women and men starting from a young age, with repeated measurements of quantity, mode and type of alcohol consumption. Further, a long enough follow-up time should be used, as progression to cirrhosis is slow. Such studies, although difficult to orchestrate, are highly warranted.

Conclusion

Alcohol consumption in late adolescent men is associated with an increased risk of developing severe liver disease later in life, after 39 years of follow-up. The risk increased in a dose-dependent pattern with no evidence of a threshold effect. Current recommendations for safe alcohol consumption regarding the risk for development of severe liver disease in men might be set too high.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work. Please refer to the accompanying ICMJE disclosure forms for further details.

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Authors' contributions

Study conception and design: HH, TH, AA. Acquisition of data: TH. Statistical analysis: HH, AA, AD. Analysis and interpretation of data: HH, TH, AA, AD. Drafting of manuscript: HH. Critical revision: HH, TH, AA, AD. Guarantor of article: Hannes Hagström. All authors approved the final version of the article, including the authorship list.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2017.11.019.

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