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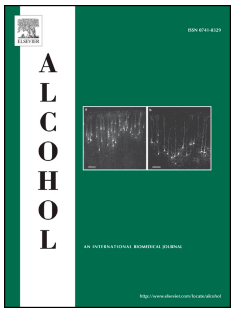

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Liver enzymes in alcohol consumers with or without binge drinking

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ABSTRACT

Background: While alcohol use is linked with a wide variety of health problems, the question whether differences in drinking patterns could yield different outcomes has remained unclear.

Patients and methods: We measured liver enzymes (ALT, GGT) from alcohol consumers with or without binge drinking from a population-based sample in Finland, where binge-type drinking is common. Data on alcohol use, diet, body weight, lifestyle (smoking, coffee consumption, physical activity) and health status were collected from 19,225 subjects (9,492 men, 9,733 women), aged 25–74 years. The participants were subsequently classified to subgroups both according to the frequencies of binge drinking and the amounts of regular alcohol intake (low, medium and high risk drinking).

Results: The quantity of regular alcohol use was roughly linearly related with GGT and ALT activities. ANOVA analyses of the trends according to the frequency of binge drinking showed a significant GGT increase in both men ($p < 0.0005$) and women ($p < 0.0005$) and ALT in men ($p < 0.0005$). In those with low risk overall consumption, markedly higher GGT ($p < 0.0005$) and ALT ($p < 0.0005$) occurred in those with binge drinking more than once a month compared with those with no such occasions. Binge drinking occurring ≤ 1/month also resulted in higher GGT ($p < 0.0005$) and ALT ($p < 0.05$) activities.

Conclusions: These results emphasize possible adverse consequences of binge drinking on hepatic function even in those with low-risk overall consumption. The pattern of drinking should be more systematically implicated in clinical recommendations on drinking reduction.

Key words: ALT, ethanol, drinking pattern, GGT, harm reduction

INTRODUCTION

Alcohol use is a leading cause of addiction and disease throughout the world (Lim et al., 2012; Wittchen, 2012; Spanagel et al., 2013; Connor, Haber & Hall, 2016; GBD 2016 Alcohol and Drug Use Collaborators, 2018). While the relationships between total cumulative alcohol consumption and adverse health effects have been well established, only few studies have separately investigated the specific characteristics of the ethanol effects brought about by different patterns of intake. Therefore, especially the contribution of repeated episodes of binge-type drinking when several drinks are consumed within short periods of time have remained poorly defined (Rehm, Samokhvalov & Shield, 2013).

Recent studies have supported the view that regular alcohol consumption in amounts exceeding 100 grams of ethanol per week leads to an increase in all-cause mortality and signs of hepatotoxicity (Niemelä, Niemelä, Bloigu, Aalto & Laatikainen, 2017; Wood et al., 2018). It may, however, be hypothesized that repeated heavy drinking occasions could further potentiate the risks for negative health effects since binge drinking have been suggested to readily lead to stimulation of inflammatory cascades and oxidative stress (Hillbom, Saloheimo & Juvela, 2011; Rehm & Shield, 2013; Li et al., 2017; Orio et al., 2017). Current guidelines define binge drinking as a pattern of drinking, which typically consists of occasional heavy drinking which exceeds 60 grams of alcohol for men or 40 grams of alcohol for women on one occasion (World Health Organization, 2000; National Institute of Alcohol Abuse and Alcoholism, 2004). On the other hand, chronic drinking can be classified to categories of low, medium or high risk drinking based on mean ethanol consumption defined in grams of ethanol per day with gender-specific cut-offs, as recently recommended by World Health Organization (Witkiewitz et al., 2017). In the latter protocol low risk drinking represents drinking in amounts below 40 grams (men) or 20 grams (women) per day.

In the present work we explored the joint and individual effects of heavy drinking occasions and regular alcohol consumption on biomarkers of liver status in a large population health survey, the National FINRISK Study. The patterns of alcohol drinking are known to show a notable variation between communities. Since Finland represents a country with a high prevalence of binge drinking (Levola & Aalto, 2015), the FINRISK survey of individuals including detailed records on alcohol consumption, diet and other health-related

behavior affords an excellent opportunity to examine the associations between the different patterns of drinking and health outcomes.

MATERIALS AND METHODS

Study design, data sources and participants

Data was collected from a cross-sectional population health survey (The National FINRISK Study) carried out in Finland every five years since 1972. In this study, data from surveys between 1997 and 2007 were used, as previously described (Niemelä, Niemelä, Bloigu, Aalto & Laatikainen, 2017). A nationally representative age- and gender stratified random sample was drawn from the population register following an international protocol (The World Health Organization MONICA project (monitoring trends and determinants in cardiovascular disease): A major international collaboration. WHO MONICA project principal investigators.1988) (World Health Organization, 1988). Clinical examinations included physical measurements, laboratory tests and detailed questionnaires on the amounts and patterns of alcohol intake, current health status, diet, smoking, physical activity, medical history and socioeconomic factors (Kuulasmaa et al., 2006). Data was available from 19,225 apparently healthy individuals: 9,492 men and 9,733 women (mean age 45 ± 13 years, range 25–74 years) who completed the questionnaires, attended the medical examination, and were devoid of any apparent clinical signs of liver disease, ischemic heart or brain disease or active infection at the time of the study.

Data on self-reported alcohol consumption was recorded from the past 12 months prior to blood sampling using structured questionnaires on the types of beverages consumed, the frequency of consumption, and the amounts of ethanol-containing drinks. The amount of ethanol in different beverages was quantitated in grams of ethanol based on defined portion sizes as follows: regular beer 12 grams (1/3 L), strong beer 15.5 grams (1/3 L), long drink 15.5 grams (1/3 L), spirit 12 grams (4 cL), wine 12 grams (12 cL) and cider 12 grams (1/3 L). Binge drinking was defined as a pattern of drinking, which typically had consisted of occasional heavy drinking exceeding 60 grams of alcohol for men or 40 grams of alcohol for women on one occasion (World Health Organization, 2000; National Institute of Alcohol Abuse and Alcoholism, 2004). Such drinking

within a relatively short period of time typically results in blood alcohol levels above 0.8 per mill. Based on the frequency of such episodes the material was divided to subgroups of those with no episodes of binge drinking and to those with different numbers of binge episodes, as indicated. Data on total alcohol consumption from the period of 12 months prior to sampling was used to further categorize the material according to the recently established WHO risk drinking protocol (Witkiewitz et al., 2017) as follows: 1. those who consumed between 1 to 40 grams (men) or 1 to 20 grams (women) per day represented low risk drinkers, 2. medium risk drinkers consumed 41 to 60 grams (men) or 21 to 40 grams (women) per day, 3. high risk drinkers consumed 61–100 grams (men) or 41–60 grams (women) per day. Individuals exceeding the levels of high risk drinking (very high risk drinkers) (n = 245, 167 men, 78 women) were excluded due to the fact that they all represented individuals with high levels of both total alcohol consumption and numbers of binge drinking occasions.

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI, kg/m^2) was calculated as a measure of relative body weight. Waist circumference was measured to the nearest 0.5 cm between the lowest rib and the iliac crest while exhaling. Smoking and coffee consumption were assessed with a set of standardized questions and expressed as the amounts of cigarettes per day and as the intake of standard servings of coffee (cups) per day, respectively. For statistical analyses, smoking habits were classified to subgroups as follows: 1, no smoking; 2, smoking 1–19 cigarettes per day and 3, smoking ≥ 20 cigarettes per day. For coffee consumption, the subgroups were the following: 1, no consumption; 2, coffee consumption 1–4 cups per day and 3, coffee consumption ≥ 4 cups per day. Leisure-time physical activity and the number and total time used for physical exercises were registered using structured questionnaires and the data was used to classify the population into the subgroups of 1, moderate or vigorous activity (over 4 hours of activity per week) 2, light (0.5–4 hours per week), and 3, sedentary activity (less than 0.5 hours per week).

The approval for this study was received from the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District. All surveys were conducted in accordance with the Declaration of Helsinki according to the ethical rules of the National Public Health Institute.

Laboratory analyses

Serum ALT and GGT were measured by standard clinical chemical methods following the recommendations of the assay manufacturer on an Abbott Architect clinical chemistry analyzer (Abbott Laboratories, Abbott Park, IL, USA). High-sensitivity C-reactive protein (CRP), an index of inflammation, was determined using a latex immunoassay (Sentinel Diagnostics, Milan, Italy) with the Abbott Architect c8000 clinical chemistry analyzer. The upper normal limits for the assays were as follows: ALT (50 U/L men; 35 U/L women), GGT (60 U/L men; 40 U/L women), CRP (3.0 mg/L).

Statistical methods

Values are expressed as mean ± SD or mean ± 95% confidence interval (CI). The main characteristics were compared using analysis of variance (ANOVA). A logarithmic transformation of GGT and ALT was used to obtain non-skewed distributions. ANOVA was performed to assess the trend in GGT and ALT activities across the ordered groups of heavy drinking occasions. Comparisons of GGT and ALT activities between the groups representing the different drinking patterns were carried out using analysis of covariance (ANCOVA). As covariates we used age and BMI as continuous variables and smoking, physical activity and coffee consumption as categorical variables (categories as described above). The association between GGT and ALT levels above the upper normal limit and the different drinking patterns was evaluated by means of logistic regression, while simultaneously adjusting for aforementioned covariates. The Breslow-Day test was used to assess whether the effect of binge drinking was homogenous across the different BMI categories (< 25, 25-24.99 and ≥ 30). For the analyses, IBM SPSS Statistics 22.0 (Armonk, NY: IBM Corp.) software was used. A p-value < 0.05 was considered statistically significant.

RESULTS

The main demographic and lifestyle characteristics of the participants classified to subgroups according to gender, the amounts of regular alcohol consumption and the frequencies of heavy drinking occasions are summarized in Table 1. The data on regular alcohol consumption indicated that among the 19,225

participants, 90.6 % of men (n = 8597) were low risk drinkers consuming an average of below 40 grams of ethanol per day, 6.0 % (n = 570) were moderate risk drinkers and 3.4 % (n = 325) represented high risk drinkers. In women (n = 9,733), the corresponding percentages in the different alcohol drinking risk groups were 93.8%, 5.1%, and 1.1%. Those with higher numbers of heavy drinking occasions were younger than those with low numbers of such occasions ($p < 0.001$ for both genders). Smoking was also more common in those with higher levels of alcohol consumption ($p < 0.001$ for both genders) and higher numbers of heavy drinking occasions ($p < 0.001$ for both genders), whereas for body weight, coffee consumption and physical activity no clear patterns were seen in the corresponding comparisons.

Figure 1 demonstrates the medians and interquartile ranges of GGT and ALT activities in the total study population classified according to the frequency of heavy drinking occasions. The ANOVA analyses of the trends across the subgroups showed significant increases for GGT in both men ($p < 0.0005$) and women ($p < 0.0005$) in association with increasing frequencies of binge drinking. For ALT, a significant trend was observed in men ($p < 0.0005$) whereas not for women. In individual comparisons of each group with binge episodes to those reporting no such episodes, a significant increase in GGT and ALT in men was first observed in the group reporting heavy drinking occasions 2–3 times per year ($p < 0.05$ for both comparisons). A notable increase in liver enzymes was found in those with heavy drinking occasions at least once a month ($p < 0.0005$ for both GGT and ALT). For women a significant increase in GGT values was noted in subgroups reporting heavy drinking occasions once a week or more often ($p < 0.0005$).

Figure 2 shows the adjusted geometric means of GGT and ALT in the different study subgroups classified both according to the total alcohol consumption and the frequency of heavy drinking occasions. The activities of the liver enzymes increased in a rather linear manner as a function of total regular alcohol consumption, the individuals with the highest amounts of total ethanol intake showing the highest activities. The patterns of drinking were found to further influence the activities such that among individuals with low-risk total alcohol consumption, the individuals reporting heavy drinking occasions more than once a month showed elevated GGT ($p < 0.0005$) and ALT ($p < 0.0005$) activities significantly more often than those reporting no such occasions. Episodes of heavy drinking once a month or less was also associated with

significantly higher GGT ($p < 0.0005$) and ALT ($p < 0.05$) values than those in individuals without any such episodes. In subgroups representing medium or high risk drinkers such differences were not evident.

Table 2 summarizes the ORs of GGT and ALT activities exceeding the upper normal limits according to the different drinking categories following adjustment for age, BMI, smoking, physical activity and coffee consumption. When compared with those reporting no episodes of binge drinking, GGT ($p < 0.0005$ for both genders) and ALT ($p < 0.02$ for men) showed significantly higher odds for exceeding the upper thresholds in low risk drinkers with a history of binge drinking. The effect of binge drinking on GGT and ALT levels above the upper normal limit was also found to be homogeneous across BMI categories for both genders (p values varying from 0.18 to 0.94). In additional logistic regression analyses by adding alcohol consumption reported from the past one week (reflecting recent drinking) to our previous model as adjusting variable (categorized as with or without recent drinking), we reached similar conclusions on higher odds for elevated liver enzymes in those with binge drinking than in those without binge drinking (data not shown).

In men with low overall levels of alcohol consumption, the levels of C-reactive protein (CRP), a marker of inflammation, were also slightly higher in those with binge drinking (1.36; 1.29-1.44 mg/l) than in those without such episodes (1.25; 1.17-1.34 mg/l) ($p < 0.05$) whereas in women, no significant differences were observed. In the present population, total alcohol consumption recorded from the past 12 months correlated positively with GGT (r= 0.224, $p < 0.01$), ALT (r= 0.132, $p < 0.01$) and CRP (r=0.037, $p < 0.01$). The number of binge drinking episodes was also found to correlate with GGT (r = 0.158, $p < 0.01$) and ALT (r = 0.115, $p < 0.01$) activities.

DISCUSSION

While excessive alcohol consumption is known to cause both addiction and substantial health loss, comparisons between the health effects brought about by repeated episodes of heavy drinking or regular total alcohol consumption have been limited. Therefore, the present data from a large cross-sectional population-

based health survey is unique and demonstrates that even in individuals with low risk overall alcohol consumption occasions of heavy drinking may lead to an extra burden in hepatic tissue and increased activities of liver-derived enzymes.

Recent findings from large international collaborations have indicated that all-cause mortality increases significantly when regular alcohol consumption exceeds the levels of 100 grams (~8 drinks) per week (GBD 2016 Alcohol and Drug Use Collaborators, 2018; Wood et al., 2018). Therefore, many national guidelines currently recommend lowering of the thresholds for risk alcohol consumption. Based on the present data individuals who habitually engage in heavy drinking occasions may need separate attention in alcohol control policies, and the frequency of alcohol binge episodes should also be recorded in a more systematic manner in the follow-up of alcohol consuming patients. Those engaged in heavy drinking occasions appear to show increased activities of both GGT and ALT despite of relatively low total alcohol consumption levels. It remains to be established whether the increases in liver enzymes could also be related with higher odds for incident liver disease (Alatalo et al., 2008; Lawlor et al., 2014) or possible extrahepatic disease risks (Kazemi-Shirazi et al., 2007; Sundell, Salomaa, Vartiainen, Poikolainen & Laatikainen, 2008; Hillbom, Saloheimo & Juvela, 2011) in individual patients.

Based on current findings it is tempting to speculate that differences in the prevalence of heavy drinking occasions in different societies could also explain some previous findings on the alcohol-attributable health outcomes with notable differences in dose-response curves (Connor, Haber & Hall, 2016; Wood et al., 2018). For instance, several studies from populations following Mediterranean diets have proposed cardio-protective properties for light to moderate drinking (Di Castelnuovo et al., 2006), whereas a number of other studies have found no evidence of such benefits (Holmes et al., 2014; Klatsky, 2015; Sipilä, Rose & Kaprio, 2016; Stockwell et al., 2016; Niemelä, Niemelä, Bloigu, Aalto & Laatikainen, 2017; Topiwala et al., 2017; Wood et al., 2018). Therefore, it is of interest to note that the possible beneficial health effects related to light to moderate drinking have been observed primarily from societies with a low prevalence of binge drinking (Renaud & de Lorgeril, 1992; Di Castelnuovo et al., 2006).

Alcohol exerts its toxic effects through multiple biochemical mechanisms (Lieber, 1995). So far, relatively little has, however, been known on the specific pathogenic features of binge-type drinking. Recent studies have demonstrated that even young binge drinkers show elevated levels of blood endotoxin, activation of inflammatory cascades, enhanced oxidative stress and lipid peroxidation (Guerri & Pascual, 2010; Orio et al., 2017) as well as increased markers of neuroinflammation (Ezquer et al., 2018) . Generation of oxidative stress has been linked with activation of GGT enzyme and several lines of evidence have also suggested a role for GGT as a biomarker of oxidative stress (Speisky, Shackel, Varghese, Wade & Israel, 1990; Lee, Blomhoff & Jacobs, 2004; Kazemi-Shirazi et al., 2007). Its activation seems to be related with the development of superoxide ion, unintended oxidation of lipoproteins and generation of pro-inflammatory status in the body (Emdin, Pompella & Paolicchi, 2005; Kozakova et al., 2012; Danielsson, Kangastupa, Laatikainen, Aalto & Niemelä, 2014). Alcoholics with recent drinking have been shown to present with higher levels of circulating neutrophils which also correlate with serum liver enzyme activities (Li et al., 2017). Chronic plus binge type drinking also markedly induces liver inflammation and injury through upregulation of pro-inflammatory cytokines and induction of E-selectin (Bertola, Park & Gao, 2013; Cai et al., 2017).

Based on current data the changes in the activities of GGT and ALT enzymes could also be used as biomarkers for detecting the individuals needing the closest monitoring in the assessment of alcohol-related health risks. Follow-up of liver enzyme activities may also prove to be of value in monitoring both hepatic and extra-hepatic health risks, including cardio- or cerebrovascular events and metabolic syndrome (Ruttmann et al., 2005; Kazemi-Shirazi et al., 2007; Kim, Flamm, Di Bisceglie, Bodenheimer & Public Policy Committee of the American Association for the Study of Liver Disease, 2008; Ruhl & Everhart, 2009; Niemelä, 2016). A more systematic use of liver enzyme measurements in addition to alcohol self-reports in the follow-up of alcohol patients could thus help to yield a more comprehensive approach for improving treatment adherence and for offering specifically targeted support aimed at drinking reduction. In clinical settings, more emphasis should also be placed to changes occurring in the low range of liver enzyme activities.

While the overall biomarker responses to episodes of binge drinking appeared relatively similar between genders, men seem to show relatively greater sensitivities for elevations in liver enzymes in response to heavy drinking occasions. Although the primary mechanisms underlying such observations remain unknown at this time it is possible that alcohol use stimulates oxidative stress in a gender-dependent manner (Finkel & Holbrook, 2000; Zhang & Forman, 2009). GGT plays a pivotal role in the metabolism of glutathione (GSH), and elevated activities could be related to an attempt to maintain intracellular GSH levels during oxidative stress, which could also be considered as a protective mechanism towards alcohol toxicity (Speisky, Shackel, Varghese, Wade & Israel, 1990; Emdin, Pompella & Paolicchi, 2005; Zhang & Forman, 2009). Women seem to, however, show elevated liver enzyme activities following smaller actual quantities of total alcohol consumption. Women are also known to be more vulnerable to alcohol addiction, alcohol-induced liver disease and central nervous system effects (Liu, Balkwill, Reeves, Beral & Million Women Study Collaborators., 2010; Hillbom, Saloheimo & Juvela, 2011; Alfonso-Loeches, Pascual & Guerri, 2013; Schwarzinger et al., 2018). Previous studies have also suggested that the immune and inflammatory consequences of binge drinking may be more pronounced among women (Orio et al., 2017; Pascual et al., 2017). In the present work, the responses in CRP, an acute inflammatory protein, to binge drinking was, however, found to occur in a slightly more sensitive manner among men.

Not surprisingly, those engaged more frequently in heavy drinking occasions were younger than those with a lower number of such episodes. In accordance with previous observations heavy drinking occasions and smoking also appeared to be highly concomitant behaviors especially in young adults (Harrison, Desai & McKee, 2008; Woolard et al., 2015). There may also be significant synergistic effects between alcohol use and smoking in creating hepatotoxic effects (Breitling, Raum, Müller, Rothenbacher & Brenner, 2009; Park et al., 2013). It may therefore be assumed that interventions aimed at reducing smoking could also affect binge drinking and vice versa. While physical activity, the presence or absence of obesity (Alatalo et al., 2008), and coffee consumption (Goh, Chow, Wang, Yuan & Koh, 2014; Xiao, Sinha, Graubard & Freedman, 2014) have also been suggested as factors influencing liver enzyme activities in alcohol consumers, in the present material such variables were not found to affect the conclusion reached on the effects of binge drinking on liver enzyme activities.

The strengths of this study include the large number of study subjects and separate assessments for men and women. The questionnaire used in this study covered the evaluation of both regular alcohol consumption and the frequencies of heavy drinking occasions from the past one year allowing the assessment of single and joint effects of regular or binge-type drinking on liver outcomes. Various possible covariates, such as age, smoking, waist circumference, BMI, physical activity or coffee consumption were also included in the multivariable analyses. Nevertheless, our study has some potential limitations. Self-reports are prone to the shortcomings of this memory-dependent channel and it is possible that the alcohol recall techniques overestimate the proportion of those not drinking alcohol at all. This could also lead to underestimation of the true dose-response associations (Livingston & Callinan, 2015). The cross-sectional setting of the survey and lack of follow-up data can also be kept as a limitation of this study.

Taken together, our study demonstrates distinct differences in liver enzyme responses in alcohol consumers with or without binge drinking. This data should be considered in health guidelines related to the amounts and patterns of alcohol drinking and in efforts aimed at reduction of population-level alcohol consumption.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

ON, TL and MA designed the study, UN, AB and RB performed data analyses. UN and ON drafted the manuscript, and all authors revised and approved the final version.

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Table 1. Main characteristics of the study population, as classified according to the amounts and patterns of drinking.

Men							
Amount of drinking	≤ 40 grams/day (low risk)			41–60 grams/day (medium risk)		61–100 grams/day (high risk)	
Binge drinking episodes	None	≤ 1/month	> 1/month	≤ 1/month	> 1/month	≤ 1/month	> 1/month
n (%)	1248 (13.1)	5249 (55.3)	2100 (22.1)	174 (1.8)	396 (4.2)	53 (0.6)	272 (2.9)
Age, years, mean ± SD	58.6 ± 11.8	48.9 ± 13.1	45.0 ± 12.7	51.7 ± 11.3	44.6 ± 11.1	54.7 ± 10.8	45.4 ± 11.7
BMI	27.3 ± 4.0	27.1 ± 3.9	27.1 ± 4.2	27.9 ± 4.1	27.2 ± 4.1	27.5 ± 3.7	27.5 ± 4.5
Waist circumference, cm	96.7 ± 11.5	95.4 ± 11.3	95.4 ± 12.2	99.0 ± 10.9	96.4 ± 12.0	98.8 ± 11.4	97.5 ± 12.7
Smoking, cigarettes/day	2.1 ± 6.8	4.1 ± 8.1	7.2 ± 10.0	7.4 ± 11.2	8.9 ± 10.4	8.5 ± 12.1	10.0 ± 11.9
Coffee, cups/day	4.1 ± 3.3	4.7 ± 3.2	4.7 ± 3.1	4.2 ± 3.2	4.9 ± 3.3	4.6 ± 3.4	4.5 ± 3.4
Physical activity, number of exercises per week	2.7 ± 2.3	2.4 ± 2.1	2.3 ± 2.2	2.0 ± 1.8	1.9 ± 2.1	1.8 ± 1.9	2.0 ± 2.1
Women							
Amount of drinking	≤ 20 grams/day (low risk)			21–40 grams/day (medium risk)		41–60 grams/day (high risk)	
Binge drinking episodes	None	≤ 1/month	> 1/month	≤ 1/month	> 1/month	≤ 1/month	> 1/month
n (%)	3152 (32.4)	5439 (55.9)	535 (5.5)	274 (2.8)	224 (2.3)	42 (0.4)	67 (0.7)
Age, years, mean ± SD	53.8 ± 12.0	43.2 ± 11.7	40.1 ± 11.4	46.7 ± 10.9	40.7 ± 11.7	49.1 ± 9.9	44.7 ± 10.8
BMI	27.3 ± 5.2	25.7 ± 4.8	25.6 ± 5.0	26.2 ± 5.1	25.9 ± 4.9	27.3 ± 4.9	25.6 ± 4.5
Waist circumference, cm	85.8 ± 13.3	82.2 ± 12.3	82.1 ± 13.0	84.6 ± 13.1	83.9 ± 13.0	88.8 ± 12.1	83.6 ± 10.9
Smoking, cigarettes/day	1.1 ± 3.8	2.7 ± 5.9	5.5 ± 7.2	4.6 ± 7.4	5.6 ± 6.6	7.2 ± 9.3	9.8 ± 10.9
Coffee, cups/day	3.6 ± 2.3	3.7 ± 2.5	4.1 ± 2.8	3.8 ± 2.4	3.9 ± 2.5	3.9 ± 2.6	4.2 ± 3.5
Physical activity, number of exercises per week	2.5 ± 2.2	2.5 ± 2.0	2.3 ± 1.8	2.5 ± 2.0	2.3 ± 1.8	1.9 ± 1.9	1.8 ± 2.0

BMI, body mass index.

Table 2. Odds ratios (OR) for liver enzymes exceeding the upper normal limits in individuals with low, medium or high risk drinking and different levels of binge drinking (as adjusted for age, BMI, smoking, physical activity and coffee consumption).

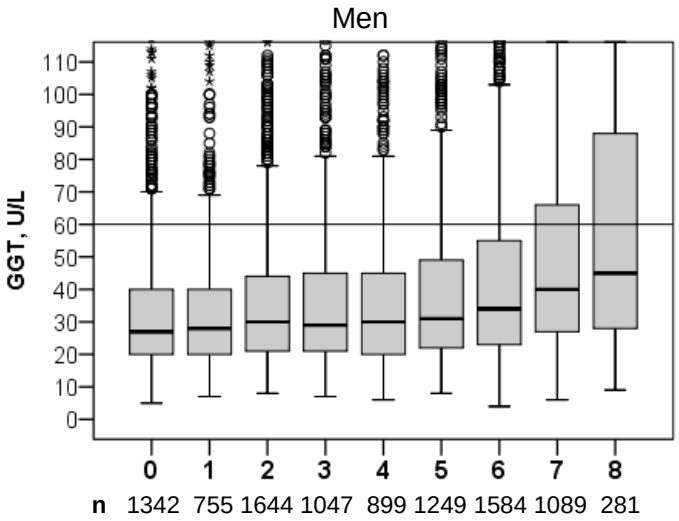
		Low risk		**Medium risk**		**High risk**	
	Binge drinking episodes	OR (95 % CI)	*p*-value*	OR (95 % CI)	*p*-value*	OR (95 % CI)	*p*-value*
Men							
GGT							
	None	1.00	< 0.0005				
	≤ 1/month	1.49 (1.21–1.83)		1.00	0.791	1.00	0.347
	> 1/month	2.63 (2.09–3.30)		1.06 (0.69–1.62)		0.71 (0.35–1.45)	
ALT							
	None	1.00	0.015				
	≤ 1/month	1.49 (0.92–2.44)		1.00	0.524	1.00	0.802
	> 1/month	1.99 (1.18–3.34)		1.28 (0.60–2.72)		1.21 (0.26–5.57)	
Women							
GGT							
	None	1.00	< 0.0005				
	≤ 1/month	1.48 (1.25–1.74)		1.00	0.597	1.00	0.874
	> 1/month	2.41 (1.78–3.26)		1.15 (0.68–1.94)		0.93 (0.37–2.31)	
ALT							
	None	1.00	0.272				
	≤ 1/month	1.16 (0.86–1.56)		1.00	0.085	1.00	0.174
	> 1/month	1.56 (0.91–2.67)		0.47 (0.19–1.14)		0.26 (0.03–2.05)	

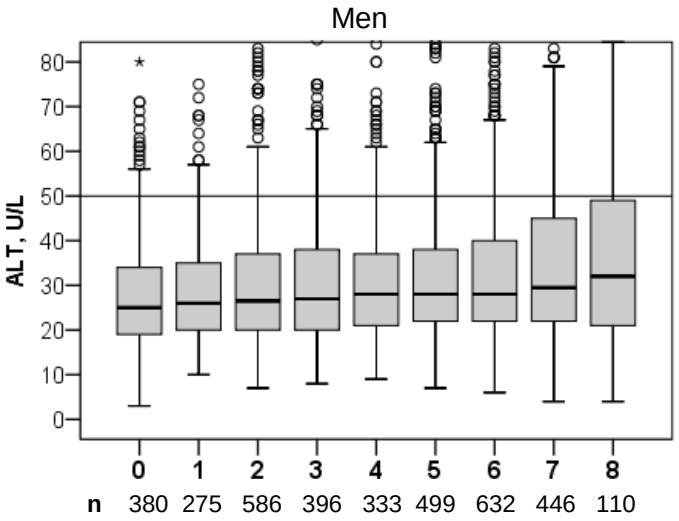
* Likelihood Ratio test

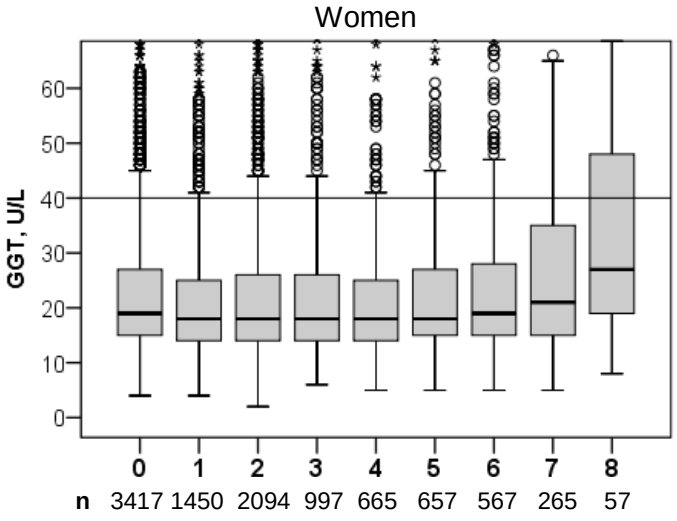
FIGURE LEGENDS

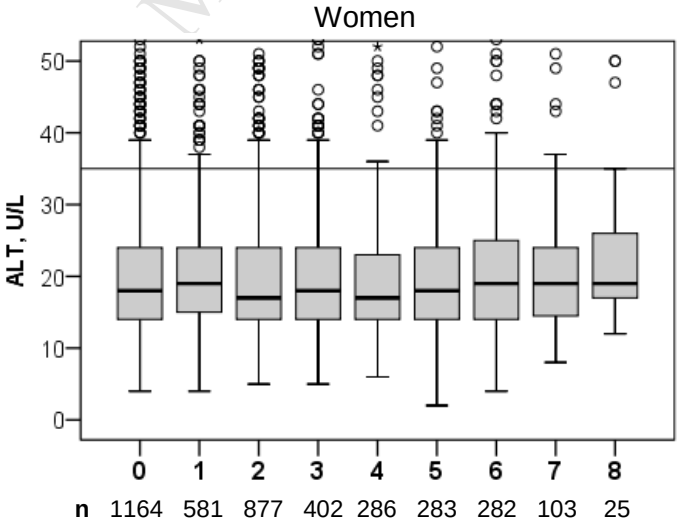
Figure 1. Median and interquartile ranges of liver enzyme activities in the study population classified according to the number of heavy drinking occasions as follows: 0 = no episodes, 1 = once a year; 2 = 2–3 times per year; 3 = 4–5 times per year; 4 = once per two months; 5 = once a month; 6 = two times per month; 7 = once per week; 8 = two times per week or more. The ANOVA analyses of the trends across the subgroups with different levels of binge drinking showed significant GGT increases in both men ($p < 0.0005$) and women ($p < 0.0005$) and increased ALT activities in men ($p < 0.0005$). In individual comparisons of each binge drinking subgroup with those reporting no binge drinking, a significant increase in GGT and ALT in men was first observed in group 2 (reporting heavy drinking occasions 2–3 times per year) ($p < 0.05$ for both comparisons). In women, a significant increase in GGT values was noted in subgroups 7-8 reporting heavy drinking occasions once a week or more often ($p < 0.0005$ for both comparisons). The upper normal limits (ALT: 50 U/L men; 35 U/L women), (GGT: 60 U/L men; 40 U/L women) are indicated by solid lines in each figure. n, number of observations in each subgroup.

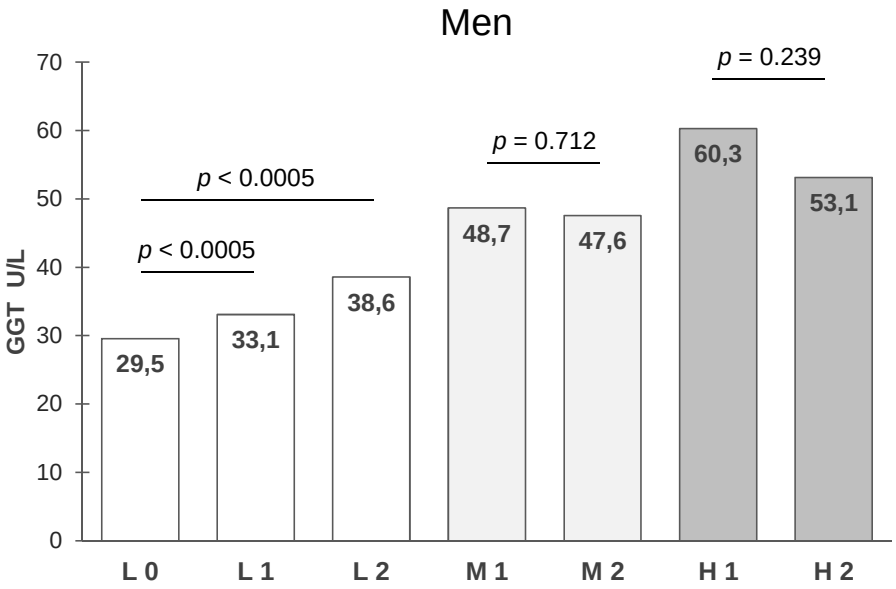
Figure 2. Geometric mean values of GGT and ALT (adjusted for age, BMI, smoking, physical activity and coffee consumption) in groups classified according to both alcohol drinking levels and episodes of binge drinking. L = low risk drinking, 1–40 grams (men) or 1–20 grams (women) per day; M = medium risk drinking, 41–60 grams (men) or 21–40 grams (women) per day; H = high risk drinking, 61–100 grams (men) or 41–60 grams (women) per day. Episodes of binge drinking were classified to: 0, those with no episodes of heavy drinking; 1, those with heavy drinking occasions once a month or less and 2, those with heavy drinking more than once a month.

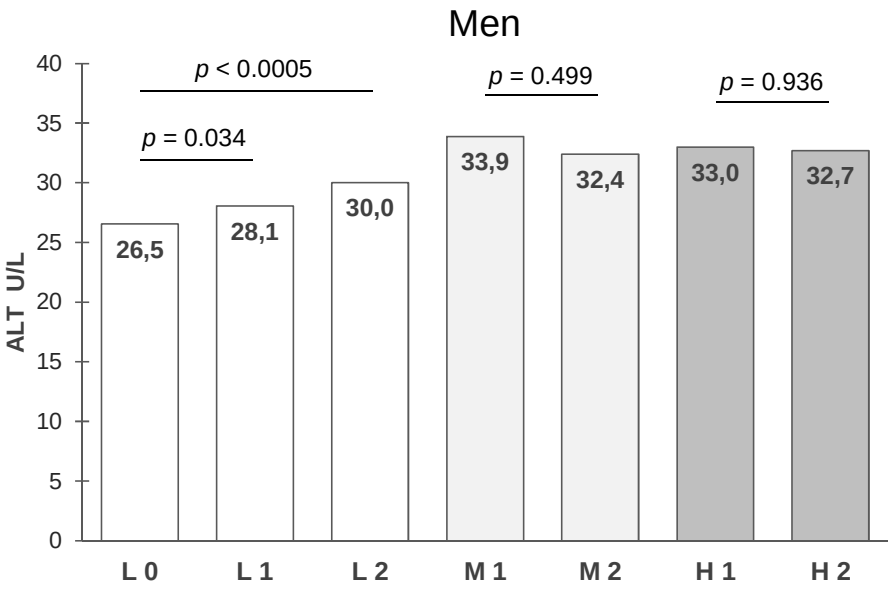

Men
GGT, U/L
0 10 20 30 40 50 60 70 80 90 100 110
0 1 2 3 4 5 6 7 8
n 1342 755 1644 1047 899 1249 1584 1089 281

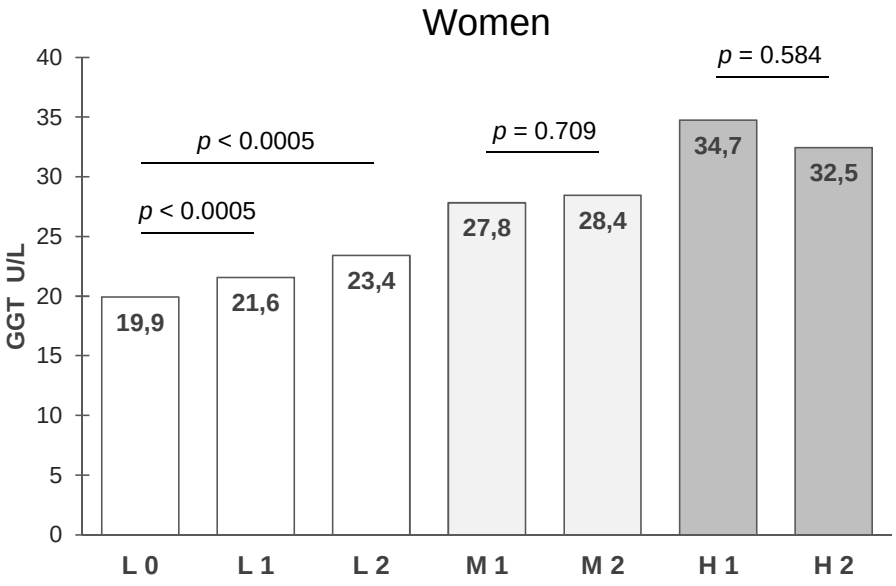

Men
ALT, U/L
0 10 20 30 40 50 60 70 80
0 1 2 3 4 5 6 7 8
n 380 275 586 396 333 499 632 446 110

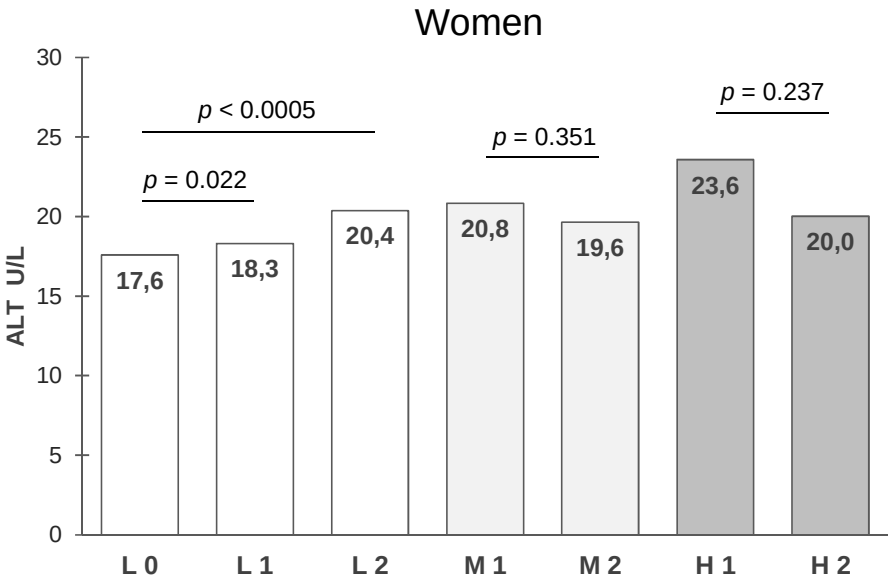

Women
GGT, U/L
0 10 20 30 40 50 60
0 1 2 3 4 5 6 7 8
n 3417 1450 2094 997 665 657 567 265 57


Women
ALT, U/L
0 10 20 30 40 50
0 1 2 3 4 5 6 7 8
n 1164 581 877 402 286 283 282 103 25


Men
GGT U/L
70
60
50
40
30
20
10
0
p < 0.0005
p < 0.0005
p = 0.712
p = 0.239
29,5
33,1
38,6
48,7
47,6
60,3
53,1
L 0
L 1
L 2
M 1
M 2
H 1
H 2


Men
ALT U/L
40
35
30
25
20
15
10
5
0
p < 0.0005
p = 0.034
p = 0.499
p = 0.936
26,5
28,1
30,0
33,9
32,4
33,0
32,7
L 0
L 1
L 2
M 1
M 2
H 1
H 2


Women
GGT U/L
40
35
30
25
20
15
10
5
0
p < 0.0005
p < 0.0005
p = 0.709
p = 0.584
19,9
21,6
23,4
27,8
28,4
34,7
32,5
L 0
L 1
L 2
M 1
M 2
H 1
H 2


Women
ALT U/L
30
25
20
15
10
5
0
p < 0.0005
p = 0.022
p = 0.351
p = 0.237
17,6
18,3
20,4
20,8
19,6
23,6
20,0
L 0
L 1
L 2
M 1
M 2
H 1
H 2

Highlights

- Patterns of alcohol drinking and low-risk thresholds suggested for alcohol use vary between different communities.
- The question whether differences in drinking patterns could yield different health outcomes has remained unclear.
- This work among a large population-based sample of apparently healthy individuals shows that in individuals with low risk overall alcohol consumption levels, heavy session drinking is associated with higher activities of liver-derived enzymes than in those without such episodes.
- The pattern of drinking should be more systematically incorporated in clinical recommendations on drinking reduction.