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Sørensen, Holger J; Holst, Charlotte; Knop, Joachim; Mortensen, Erik L; Tolstrup, Janne S; Becker, Ulrik

DR HOLGER JELLING SØRENSEN (Orcid ID : 0000-0003-2268-1735)

MRS CHARLOTTE HOLST (Orcid ID : 0000-0003-1189-038X)

Alcohol and delirium tremens: effects of average number of drinks per day and beverage type

Authors: Holger J. Sørensen[.1,2], Charlotte Holst[1], Joachim Knop[4], Erik L. Mortensen[5], Janne S. Tolstrup[1] & Ulrik Becker[1,3]

[1] National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark.

[2] Mental Health Centre Copenhagen, The Capital Region, Copenhagen, Denmark

[3] Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

[4] Dept. of Clinical Epidemiology, Frederiksberg & Bispebjerg Hospital, Copenhagen, Denmark

[5] Dept. of Public Health and Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark

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Corresponding author and reprint requests:
Holger J. Sørensen
E-mail: holger.jelling.soerensen@regionh.dk
Mental Health Centre Copenhagen & Copenhagen University
Kildegaardsvej 28, 4
2900 Hellerup, Denmark

ABSTRACT

Objective: Associations of amount of alcohol intake and beverage type with the risk of delirium tremens (DT) have not been studied. This longitudinal study investigated if the average number of drinks per day and beverage type predict DT.

Methods: A cohort of 3 582 alcohol dependent men and women aged 19-82 without previous DT were interviewed about alcohol intake and beverage type at baseline in 1994-2005 and followed through record linkage in Danish nationwide registers to identify incident DT. Data was analyzed by means of Cox regression models.

Results: An average number of drinks per day of 20-30 or > 30 was associated with hazard ratios (HRs) of 1.38 (95% CI 1.03-1.84) and 1.64 (95% CI 1.19-2.27) relative to the reference category (1-9 drinks). Independently of amount consumed and covariates (age, gender, civil status and work status), beverage type (spirits vs. mixed alcohol) was associated with a HR of 1.63 (95% CI 1.08-2.46). Male gender was robustly associated with increased risk (HR= 1.62 (95% CI 1.25-2.08)

Conclusions: In alcohol dependent men and women, daily alcohol intake above a threshold of 20 beverages or 240 gram alcohol and a preference for spirits increase the risk of developing DT.

Significant outcomes

• In alcohol dependent men and women, many of which had been alcohol dependent for years, individuals who reported a daily alcohol intake above 20 beverages had a significantly increased risk of incident delirium tremens.

• Amount of alcohol intake and drinking spirits (relative to mixed alcohol) were independently associated with increased risk of delirium tremens.

• Of other baseline predictors of incident delirium tremens, male gender emerged as the strongest.

Limitations

• We had only information about amount of alcohol and beverage type at baseline when individuals sought alcohol treatment.

• Information on incident delirium tremens were based on information from nationwide Danish registers and the validity of a register-based diagnosis of delirium tremens is uncertain at present.

• Despite attempts to adjust for sociodemographic factors, we cannot rule out residual confounding by unmeasured factors including social factors.

Introduction

Delirium tremens (DT) is a severe condition characterized by confusion and fluctuating disturbance of attention and cognition. DT is included among the alcohol-psychoses but has its own clinically distinguishing features.[1] It often presents acutely when alcohol dependent persons reduce or discontinue their alcohol consumption. Individuals with symptoms of alcohol withdrawal have a 3-6% risk of developing DT. [2,3] Once developed, DT confers a markedly higher mortality risk than the general population. [4] Risk factors include a previous DT episode, [5,6] but relatively little is known about other risk factors, especially those that are potentially modifiable such as the average quantity of alcohol intake and the preferred type of beverage intake. Furthermore, findings on predictors of DT have shown mixed results; perhaps partly due to possible heterogeneity of the existing literature and publication bias. [6]

Both total amount of alcohol consumed [7] and the type of alcohol preferred (i.e. beverage choice) [8,9] has been linked with alcohol psychosis rates. With respect to amount of alcohol consumed and the type of alcohol preferred in relation to risk of DT, the literature has not been updated for years. About 4 decades ago, Hemmingsen, reviewed the evidence that beverage type (spirits) was associated with a particularly high risk of DT.[10] Briefly, Nielsen [11] and Strømgren [12] had reflected upon the most likely reasons for an earlier era decrease in

number of admissions with DT when a steep taxation of spirits was introduced in Denmark in 1917. However, despite efforts, it has remained difficult to disentangle whether the reduction in DT rates was associated with altered type of alcohol preferred (i.e. from largely spirits to largely beer drinking) or whether there was a concurrent reduction in total amount of alcohol consumed that could have accounted for the falling DT rates.[10] Remarkably, it continues to be an open question whether total alcohol intake and preferred type of alcohol are independent risk factors for DT. If an association between higher quantitative alcohol consumption and increased DT risk is indeed confirmed, it will be important to examine if there is a threshold of alcohol intake above which the risk is especially salient. Furthermore, an association with total alcohol intake could be modified by beverage choice (i.e. alcohol type).[9] Thirdly, studies suggesting a special risk-increasing role of alcohol type such as spirits for DT have not used individual-specific data and have drawn their conclusions from ecological associations. [11] It is therefore necessary to extend the earlier literature on the subject with longitudinal data where information about individual-specific data including the average number of drinks consumed per day and beverage type are available. These questions are best investigated in populations of with alcohol dependence and with access to individual-specific data on alcohol consumption. Therefore, we undertook the current study to examine if the number of drinks consumed daily and the beverage type were associated with DT, based on a large cohort of men and women seeking treatment for alcohol dependence. [13]

Aims of the study

In a clinical setting where men and women sought alcohol treatment for alcohol dependence, we aimed at investigating if the self-reported average number of drinks per day and beverage type at baseline predicted later development of DT. We hypothesized that alcohol dependent treatment seekers with the highest self-reported alcohol intake would be at higher risk for DT

than those with lower alcohol intake. We also hypothesized that alcohol treatment seekers with a beverage preference of spirits would be at higher risk of DT when beverage type of mixed alcohol was used as reference category.

Methods

Data sources

The Copenhagen Alcohol Cohort (COPAC) consists of men and women attending alcohol treatment, covering the greater Copenhagen area in Denmark from 1954 to 2009. [13] In the period 1994–2005, information about alcohol consumption was obtained from interviews at baseline.

Alcohol variables

Individuals were asked about the average number of drinks consumed per day within the last month.

A Danish standard drink contains 12 g of alcohol, corresponding to one beer, one glass (one sixth of a bottle) of table wine or four centiliters of 40% proof spirits. Predominant type of alcohol consumed within the last month was recorded with four possibilities: beer, wine, spirits or mixed type of alcohol. Mean number of drinks per day was 17 in men corresponding to 204 g/alcohol per day and 12 per day in women corresponding to 144 g/alcohol per day. Duration of alcohol dependence, defined as years since onset of alcohol dependence at time of interview, was recorded. Information on duration of alcohol dependence was collected through interview and data was available in 2,946 subjects (17.8% missing).

Covariates

Covariates were gender and age at registration in COPAC. Information on marital status was collected and categorized as either married (currently married at time of interview) or unmarried (including separated, widow(er)s and divorced). Information on work situation was categorized as either working (currently working at time of interview) or not working (including subjects absent owing to illness).

Study sample

Individuals were included if they had data on spirits, beer, and wine consumption. Using nationwide registers, we excluded individuals who had any registered mental disorder compatible with DT (International Classification of Diseases (ICD), 8th (ICD-8) code 291.0 or 10th edition (ICD-10) code 10.4) before baseline. Information on nationwide somatic hospital contacts is available from 1977 onwards,[14] and the Danish Psychiatric Central Research Register[15] contains information on all psychiatric inpatient contacts since 1969 and out-patients since 1995. [16] Vital status was identified using each participant's unique identification number by record linkage to the Danish Civil Registration System

Follow-up

Participants were followed from baseline (date of first attendance in COPAC between January 1st, 1994 and December 31st, 2005) to March 31, 2018, date of first registration with DT (10.8%) or loss to follow-up (1.6%), or death (47.7%) whichever came first. End-point was a principal or secondary diagnosis of DT (ICD-10 code 10.4).[17]

Statistical analyses

Data was analyzed by means of Cox proportional hazards regression models using SPSS version 24. Exposures were average amount of drinks per day and beverage type according to interviews at baseline and duration of alcohol dependence. Number of drinks per day at baseline was estimated as the sum of spirits, beer and wine, and was categorized into 1-9, 10-14, 15-19, 20-30, and 30+. Beverage choice was a categorical variable with 4 categories1) spirits only, 2) wine only, 3) beer only and 4) mixed type of alcohol. The largest category (mixed alcohol) was used as reference. The independent effects of the exposures were estimated through multivariate analyses. First order interactions between relevant variables were tested by log-likelihood test for significance at the 5% level, but since none of the interactions included implied significant improvement of the fit of the models, we concluded that there was no evidence of interaction.

To test whether eligible participants with data on alcohol consumption and beverage choice differed from excluded subjects, we performed chi-square analysis on the distribution of gender and t test on mean differences in age.

Results

Sample characteristics

The sample consisted of 3,582 individuals of which 2,547 (71%) were men and 1,035 (29%) women. Mean age at registration was 45 years (range 19-82 years)). The mean duration of alcohol dependence was 9.9 (SD 8.4) years; − higher in men (mean 10.7 years) than in women (mean 7.9 years) (p<0.01). A total of 387 (10.8%) developed DT during follow-up at a mean age of 49 years. A total of 80 (20.7%) of all DT cases were exclusively identified in psychiatric departments using data from the Danish Psychiatric Register. Overall, the risk of DT was significantly higher in men (11.9%) than in women (7.9%) (p<0.001).

Table 1 shows baseline sociodemographic characteristics according to average amount of drinks. The proportion of men, mean duration of alcohol dependence, percent of mixed drinkers was positively associated with average number of drinks per day. In the 30+ category (relative to the 1-9 category), 89.2 % (59.5%) were men, 59.6 % (42.1%) were mixed drinkers and the mean duration of alcohol dependence was 12.6 (9.1) years. Mean age at first attendance, percent of wine drinkers, percent of married subjects, and percent of working subjects was negatively associated with average number of drinks per day. Thus, in the 30+ category 30.5 % reported that they were working while this was the case for 39.0 % in the 1-9 drink per day category.

At baseline, men consumed on average significantly (p<0.0001) more beer and had higher total alcohol intake (p<0.0001) than women. The mean beer consumption was 11.4 vs. 4.6 drinks/day for men vs women and the mean total alcohol consumption was 16.8 vs 11.6 drinks/day. Women consumed significantly (p<0.001) more drinks of wine than men (means 4.4 vs 2.6 per day). There was no significant gender difference for the average number of spirits drinks per day (2.8 vs 2.6 per day). For type of alcohol, both men and women preferred mixed alcohol. In men, beer constituted the second largest category and in women, it was wine.

Average number of drinks per day and beverage type

Table 2 shows the relative risk (HR) and 95% confidence intervals for developing DT as a function of the number of drinks per day and the preferred beverage type at baseline and gender. The basic model of table 2 (model 1) was adjusted for age and shows multivariate effects of three risk factors for DT: average number of drinks per day, beverage type and gender. Model 2 is additionally adjusted for civil status and working status at baseline. The

results of table 2 indicate that amount of alcohol was significantly associated with higher risk

of DT above 20 drinks per day. Compared to the reference category, drinking 20-30

beverages per day was associated with a HR of 1.42 (95% CI 1.06-1.91) and this estimate

was only slightly attenuated when adjusting for civil status and working status at baseline.

Amount of alcohol above 30 drinks per day was also significantly associated with higher risk

of DT. Compared to the reference category, drinking > 30 beverages per day was associated

with a HR of 1.73 (95 % CI 1.25-2.40). Table 2 (model 2) also shows that further adjustment

for civil status and work status at baseline had some attenuating effects on these risk

estimates for amount of alcohol, but the significant effects of alcohol consumption in the

interval 20-30 and > 30 drinks per day remained statistically significant.

Beverage type (spirits vs mixed alcohol as reference category) was significantly associated

with increased risk of DT in model 1 (HR= 1.64 with 95% CI 1.09-2.47) and model 2

(HR=1.63 with 95% CI 1.08-2.46). There was no significant predictive effect of wine or beer

(relative to mixed alcohol)

Most of the covariates emerged as significant baseline predictors of DT independently of

amount of alcohol and beverage type (model 2). The most robust independent predictive

effect was observed for male gender (model 2) (HR =1.62 (95% CI 1.25-2.08). Subjects who

reported being married at baseline had a lower hazard of developing DT in unadjusted

analyses, but effects were attenuated in the multivariate analyses shown in table 2 (model 2)

(HR= 0.79; 95% CI 0.63-0.99). Furthermore, table 2 (model 2) indicates that subjects who

reported that they had work at baseline had a marginally lower hazard of developing DT

(HR=0.81 (95% CI 0.65-1.01).

There was no significant interaction between amount of alcohol and gender. This suggests

that amount of alcohol was similarly associated with risk of DT in both genders. There was

no significant first order interaction between amount of alcohol and beverage type. This suggests that the association between amount of alcohol per day and risk for DT was not significantly modified by beverage choice (i.e. alcohol type).

Further analyses

When we selected a high-risk group (N=47) based on 3 criteria: 1) consuming > 20 beverages/day, 2) being male, and 3) drinking spirits, the absolute risk of DT was 21.3%.

Results in table 2 suggest that beer drinkers had a statistically non-significant lower risk (HR 0.93; 95% CI 0.75-1.17) of developing DT than the reference group of mixed alcohol. Thus, after adjustment for confounders, we found no evidence of a protective effect of beer drinking relative to mixed alcohol. When we selected "beer drinkers only," there was a significant (P<0.05) effect of increasing amount of alcohol (i.e. drinks of beer) per day on the risk of developing DT.

In individuals with data on duration of alcohol dependence, - and when data were categorized into quartiles, - longer duration predicted later DT. Using the lowest quartile (<3 years) as the reference, the HR was 1.15 (95% CI 0.83-1.59) for the next quartile (3-8 years), 1.40 (95% CI 1.01-1.93) for duration between 8 and 15 years and 1.12 (0.78-1.60) for duration above 15 years.

Comparisons of the study sample with data on alcohol consumption and beverage type (n=3,582) with the rest of the cohort without data on at least one of the variables on alcohol

consumption and beverage type (n=7,337) yielded significantly (P<0.01) higher proportion of men (71.1 vs 69.0%) in the group with alcohol data while there was no age difference between the two groups.

Discussion

Main findings

In this large cohort study of alcohol dependent men and women, the average number of drinks per day was associated with DT. Above a threshold of 20 beverages per day (240 gram pure alcohol), the risk was significantly elevated. Independently of average number of drinks per day, alcohol type also predicted DT; - thus, predominant alcohol type of spirits was associated with a HR of 1.63 (95% CI 1.08-2.46) when compared to the reference group of mixed alcohol users. There was no interaction between average number of drinks per day and alcohol type. Male gender also predicted DT (HR=1.62 (95% CI 1.25-2.08).

This is the first longitudinal study suggesting that both amount of alcohol and alcohol type are independently associated with the risk for DT among alcohol dependent men and women. In Sweden, Rommelsjo et al. earlier linked a fall in alcohol consumption at population level with reduced rates of inpatient treatment of alcohol psychosis.[7] In Poland, Wald et al. found a correlation between total alcohol consumption and the incidence of alcohol psychosis. In Russia, beverage type in the form of vodka sales was found to correlate with the incidence of alcohol psychosis.[9] As far as we are aware of, there has been no previous study linking alcohol consumption above a threshold of 20 beverages per day to risk of DT. Our findings are in keeping with what has been found for unprovoked seizures. In a Study from New York using a case-control design, Stephen et al.[18] examined alcohol use before the onset of a first seizure in 308 patients with seizures and 294 controls. The risk, which was independent of

alcohol withdrawal, increased with higher consumption of spirits (liquor) and with increasing current alcohol use. The relative risk rose from 3-fold at intakes of 51 to 100 g of ethanol per day to 8-fold at 101 to 200 g and to almost 20-fold at 201 to 300 g per day.[18] Using the same Danish alcohol cohort as in the current study, Kamper-Jørgensen et al. found no association between quantitative alcohol intake, type of alcohol or duration of alcohol abuse and alcoholic cirrhosis mortality in alcohol misusing men and women.[19] This lack of a dose effect of quantitative alcohol intake was considered due to a possible threshold effect,[20] since men and women in this particular cohort had all exceeded the threshold (of 50–75 g of alcohol per day) considered of importance for elevated alcohol cirrhosis risk.

Alcohol's detrimental effects depend upon the dose, duration and pattern of exposure with binge drinking as one of the most common, but most damaging, patterns of intake.[21] In this study, alcohol dependent individuals who later developed DT were more likely to be men, drinking above a threshold of 20 beverages/day and preferring spirits. The possible mechanisms behind the elevated risk in spirits users are not clear, but drinking pattern of spirits users might be associated with binge drinking. [22] Unfortunately, data on binge drinking was not available in the current study, but emerging evidence indicate that binge drinking has profound effects on neurobiological processes in the brain and amplifies the risk of brain damage.[23] However, it is also possible that spirits-drinkers more frequently reach the blood alcohol concentrations necessary to develop physical dependence than beer drinkers. [10] Additionally, when self-poured, spirit drinkers may underestimate the size of drinks and may therefore have larger drinks on average. [24,25]

The cumulative effects of high alcohol-percent beverages could mean that the threshold to develop DT gradually becomes lower. We did not find significant interaction between the

average daily alcohol intake and beverage type and found no evidence that amount of alcohol *did no*t increase risk for DT for an alcohol type with relatively low alcohol-percent (i.e. beer). Nevertheless, the critical "alcohol threshold" may be higher for beer. Our findings clearly dismiss earlier claims of a possible protective role of beer drinking in the development of DT.[26] Perhaps as a result more statistical power in the beer drinking group, we observed a more dose-response like pattern between amount of alcohol and risk of DT than for wine or spirits.

Compared to the reference category, beverage choice of wine was close to being significantly associated with elevated risk for DT. This could have clinical significance as such borderline-significant findings might be explained by limited statistical power. On average, alcohol dependent women consumed more wine than alcohol dependent men, and this should probably be read into a Northern European cultural context where, in the general population, overall alcohol intake in women is to a high extent derived from wine.[27] We cannot rule out that wine plays a stronger role in the development of DT in alcohol dependent women than in alcohol dependent men. A factor that could have contributed and perhaps exacerbated a marginally elevated risk of DT among wine drinkers is that fortified wine such as port wine or liqueur wine is classified as wine here.

Contrary to the findings of a recent systematic review and meta-analysis, [6] our findings suggest a significantly higher risk of DT in alcohol misusing men than in women. The higher risk in men was not simply due to men's larger total alcohol consumption (and larger beer) consumption. Unmeasured factors such as response to alcohol treatment, treatment compliance, social network, and physical or mental illness comorbidity could be mediators of this rather robust gender difference. Generally, we believe that our findings are in agreement

with others suggesting that women seeking alcohol treatment fare better under treatment and receive a better long-term drinking outcome.[28]

Strength and limitations

With timely and appropriate treatment, DT episodes are potentially preventable. In this regard, it is a major limitation of our study that data on inpatient psychopharmacological treatment was not available. This limitation is perhaps especially important for inpatient treatment of conditions such as DT and for severe withdrawal symptoms (without DT). The fairly high proportion that developed DT in this cohort could suggest possible inadequate treatment (e.g. withdrawal symptoms that were not adequately and timely treated). The higher percentage (10.8 %) of DT in this large alcohol cohort than in previous studies in alcohol settings[2] may, however, also reflect that this was a comprehensive follow-up study utilizing national registers on both somatic and psychiatric hospital contacts. A total of 80 (20.7%) of all DT cases were exclusively identified in the Danish Psychiatric Register. This likely prevented bias from excluding cases with psychiatric comorbidity and may have contributed to better generalizability of our results. To our knowledge, no validity study of a register-based DT diagnosis exists. Obviously, this is a limitation and it is possible that an explanation for the high rate would be inaccurate coding of individuals with mild-moderate withdrawal as having DT episodes. However, we would expect virtually all severe cases with DT to lead to acute somatic or psychiatric contact. And we would expect most clinical diagnoses to be correct, in particular for cases of some severity. Furthermore, the fact that baseline total alcohol consumption (i.e. a proxy of severity of alcohol use disorder) predicted DT incidence strengthens the external validity of register-based DT diagnoses. Earlier case series studies suggest that a more severe drinking history can help separate those developing DT from alcohol dependent individuals who do not develop DT.[29] Other limitations include

that "duration of alcohol dependence" does not express a person's cumulative (lifetime) number of alcohol dependent years until the date of the DT episode. Furthermore, our findings regarding spirits are probably not applicable to other populations (with different preferences to spirits). Also, alcohol consumption was only assessed at one single point and measures on consumption levels over time would have been preferable. No data were available on intake of other psychoactive substances than alcohol. Furthermore, our adjustment for socioeconomic variables at baseline is rather crude.

Study strengths include the large sample of men and women with alcohol dependence and hence the statistical power to examine new aspects of the epidemiology of DT. Furthermore, the relatively extended period of follow-up constitutes an advantage along with the ability to use self-reported alcohol consumption at baseline, even though self-report information may be unreliable in this patient group. Additionally, participants were asked about the intake of beer, wine and spirits separately, which usually gives the most realistic levels of intake.[30]

Conclusion and clinical implications

To conclude, the average number of drinks per day significantly increased the risk of DT above a threshold of 20 beverages per day (240 gram). Spirits was independently associated with DT (HR 1.63 95% CI 1.08-2.46) relative to mixed alcohol and men had a 61% higher risk of DT than women. In a clinical high-risk group (men who drank>20 beverages a day and preferred spirits), the absolute risk of subsequently developing DT exceeded 20%. If clinicians and individuals with alcohol misuse had ready access to the information that the average number of drinks per day, spirits and male gender all predict DT, this information could permit more tailored interventions and better psycho-education about self-management.

Role of the funding source

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Table 1. Baseline characteristics of The Copenhagen Alcohol Cohort by categories of average number of drinks per day

	category of average number of drinks per day				
	1-9	10-14	15-19	20-30	30+
N of individuals	1228	778	473	687	416
Men, percent	59.5	69.4	74.8	80.2	89.2
Mean age, (SD) years	45.6 (11.5)	45.9 (11.4)	44.7 (10.3)	44.1 (10.0)	42.1 (9.5)
Mean duration of alcohol dependence, (SD) years	9.1 (7.8)	10.0 (8.3)	9.6 (7.9)	10.8 (8.8)	12.6 (9.3)
Beverage type					
Beer drinkers, percent	36.2	41.1	40.3	41.6	32.5
Spirit drinkers, percent	4.5	6.4	3.2	7.6	3.4
Wine drinkers, percent	17.1	12.5	10.4	4.7	4.6
Mixed alcohol, percent	42.1	40.0	46.1	46.1	59.6
Married, percent	29.1	32.4	35.9	24.6	19.7
Working, percent	39.0	38.5	35.3	32.4	30.5

Table 2: Relative risk (HR) and 95% confidence intervals of DT according the number of drinks per day and beverage type. The basic model (model 1) is adjusted for age and shows multivariate effects of 3 risk factors for DT: average number of drinks per day, beverage type and gender. Model 2 is additionally adjusted for civil status and working status at baseline

	HR (95% CI)	
	Model 1	Model 2
Average number of drinks per day		
1-9 (reference)	1.00	1.00
10-14	1.28 (0.96-1.71)	1.30 (0.97-1.73)
15-19	1.31 (0.94-1.83)	1.30 (0.93-1.82)
20-30	1.42 (1.06-1.91)	1.38 (1.03-1.84)
30+	1.73 (1.25-2.40)	1.64 (1.19-2.27)
Beverage type		
Beer	0.93 (0.74-1.16)	0.82 (0.71-1.12)
Spirits	1.64 (1.09-2.47)	1.63 (1.08-2.46)
Wine	1.33 (0.94-1.89)	1.34 (0.94-1.90)
Mixed alcohol (reference)	1.00	1.00
Sociodemographic risk factors		
Men vs. women (reference)	1.61 (1.24-2.09)	1.62 (1.25-2.08)
Married vs. other (reference)	--------------------	0.79 (0.63-0.99)
Work vs. other (reference)	---------------------	0.81 (0.65-1.01)

Model 1 is adjusted for age and shows multivariate effects of number of drinks per day and beverage type and gender. Model 2 is additionally adjusted for civil status and working status