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Alcohol and cirrhosis: dose–response or threshold effect?

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***Background/Aims*: General population studies have shown a strong association between alcohol intake and death from alcoholic cirrhosis, but whether this is a dose–response or a threshold effect remains unknown, and the relation among alcohol misusers has not been studied.**

***Methods*: A cohort of 6152 alcohol misusing men and women aged 15–83 were interviewed about drinking pattern and social issues and followed for 84,257 person-years. Outcome was alcoholic cirrhosis mortality. Data was analyzed by means of Cox-regression models.**

***Results*: In this large prospective cohort study of alcohol misusers there was a 27 fold increased mortality from alcoholic cirrhosis in men and a 35 fold increased mortality from alcoholic cirrhosis in women compared to the Danish population. Number of drinks per day was not significantly associated with death from alcoholic cirrhosis, since there was no additional risk of death from alcoholic cirrhosis when exceeding an average daily number of five drinks (>60 g/alcohol) in neither men nor women.**

***Conclusions*: The results indicate that alcohol has a threshold effect rather than a dose–response effect on mortality from alcoholic cirrhosis in alcohol misusers.**

***Keywords*: Alcohol; Misuse; Cirrhosis; Mortality; Epidemiology**

1. Introduction

The most consistent finding from epidemiological studies on alcohol and cirrhosis in the general population has been that of an increasing risk of cirrhosis with increasing intake of alcohol [1–6]. In some studies, this relation was modified by duration of alcohol misuse [4], type of alcohol consumed [3] and frequency of alcohol intake [7,8]. Despite the elevated risk, only a minority of alcohol misusers develops alcoholic cirrhosis [9,10]. One hypothesis is that alcohol has a permissive rather than a dose-dependent effect on development of liver disease, i.e. if alcohol intake at some point in time is higher than some threshold level, the risk of developing cirrhosis is constant over time [9]. This hypothesis is best investigated in populations of alcohol misusers, but only a few small studies regarding alcohol and alcoholic cirrhosis have been carried out in men and not in women [9–11]. The purpose of this study is therefore, in a prospective study design to investigate whether average daily number of drinks, duration of alcohol misuse, predominant type of alcohol consumed and frequency of alcohol intake respectively, is associated with alcoholic cirrhosis mortality in a large cohort of alcohol misusing men and women.

2. Materials and methods

2.1. Sample

The Copenhagen Alcohol Cohort consists of men and women between 15 and 83 years of age (median age = 38 years) who attended Copenhagen Hospital Corporation's outpatient clinic for alcohol misusers in the period 1977–1992. Through interview with a nurse trained as alcohol therapist, recordings of alcohol related, social issues, frequency of alcohol use and duration of alcohol misuse were obtained for each subject. These data were recorded on structured data sheets at the time of first admission to the alcohol outpatient clinic. Information on average number of drinks per day and predominant type of alcohol was only recorded in medical records at the same time as the interview was carried out. By review of these medical records, data on average number of drinks per day and type of alcohol was extracted and added to the dataset. By linkage to The Danish National Hospital Discharge Register, all hospital discharges of the 9150 subjects attending the alcohol clinic were recorded. The Danish National Discharge

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Register was established on January 1 1977. Due to inadequate information of one or more of the variables of interest, 2858 subjects were excluded from analysis (2688 with missing alcohol information and 170 with missing other information). A further 112 subjects with a liver disease at baseline (ICD-8 code: 570, 571, 573) and 28 subjects reporting not to drink any alcohol were excluded. Eventually a total of 6152 subjects (4500 men and 1652 women) were included in this study.

2.2. Alcohol intake

Subjects were asked about the average number of drinks 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. Duration of alcohol misuse, defined as years since onset of alcohol misuse at time of interview, was recorded. Predominant type of alcohol consumed within the last month was recorded with four possibilities: beer, wine, spirits or mixed type of alcohol. Information regarding frequency of alcohol intake, defined as frequency of alcohol intake within the last month, was collected and categorized as either daily (every day) or periodic (with pauses of one or more days). Mean number of drinks per day was 22 in men corresponding to 240 g/alcohol per day and 17 per day in women corresponding to 204 g/alcohol per day.

2.3. Covariates

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). Subjects reported housing status, which was categorized as either owner of property (house or apartment) or not owner of property (including tenants, occupiers of shelters and homeless). Work situation was categorized as either working (currently working at time of interview) or not working (including subjects absent owing to illness).

2.4. Follow-up

Subjects were followed from date of first attendance to the outpatient clinic to December 31 1998 (58%), date of death (40%) or loss to follow-up (2%), whichever came first. The vital status of subjects was identified using each participant's unique identification number by record linkage to the national Central Person Register. End point was alcoholic cirrhosis mortality (ICD-8 code 571.09 and ICD-10 code K70.3 in the International Classification of Diseases) and date of death and cause of death was obtained from the death certificates.

2.5. Statistical analysis

Data was analyzed by means of Cox proportional hazards regression models [12] with age as underlying time scale and delayed entry implemented, separately for the two sexes by using SAS/stat software [13]. Cox-regression models generate estimates of relative risk (hazard ratio) adjusted for confounders.

The main effects of relevant variables were estimated through multivariate analyses. By backward elimination, insignificant variables were removed by log-likelihood test at the 5% level separately for the two sexes. All variables were included as categorical variables in the model. Estimated relative risks are given with 95% confidence limits, using the category containing the most subjects as reference category. We excluded all patients with a liver disease at baseline ($n = 112$). In separate analyses we excluded all deaths from alcoholic cirrhosis that occurred during the first 5 years after baseline (9 men and 1 woman). Given the long sub clinical phase that often characterizes patients with alcoholic cirrhosis, we performed these analyses to test whether subjects reporting a low daily intake was suffering from undiagnosed alcoholic cirrhosis, which could affect their daily intake (the sickquitter hypothesis). 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. Sex and age adjusted mortality rate ratios were calculated to compare alcoholic cirrhosis mortality in subjects in the Copenhagen Alcohol Cohort and the Danish population. To test whether eligible subjects differed from excluded subjects, we performed χ^2 analysis on distribution of sex and t-test analysis for differences in age.

3. Results

Baseline characteristics of The Copenhagen Alcohol Cohort on categories of average number of drinks per day are shown in Table 1. The study population comprised 4500 men and 1652 women with a complete set of data and a total observation time of 84,257 person-years (mean follow-up time = 14 years). During follow-up, 285 subjects (205 men and 80 women) died from alcoholic cirrhosis, while a total of 2177 subjects (1681 men and 496 women) died from other causes. Sex and age adjusted mortality rate proved a 27 fold excessive mortality from alcoholic cirrhosis in men and a 35 fold excessive mortality from alcoholic cirrhosis in women in The Copenhagen Alcohol Cohort compared to the Danish population [14]. The percent of men, mean duration of alcohol misuse, percent of mixed drinkers and percent of subjects owning property was positively associated with average number of drinks per day. Mean age at first attendance, percent of wine drinkers, percent of married subjects, and percent of working subjects was negatively

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

	5–9	10–14	15–19	20–24	25–29	30–34	35 +
Number of individuals	439	1134	1284	1192	846	535	722
Number of deaths from alcoholic cirrhosis	32	64	59	47	30	18	35
Men, percent	49	59	72	75	83	86	89
Mean age at first attendance, years	45	42	39	38	37	37	36
Mean duration of misuse, years	11	12	13	13	14	14	15
Beer drinkers, percent	50	53	57	52	49	44	31
Spirits drinkers, percent	10	11	7	9	6	7	9
Wine drinkers, percent	19	11	7	4	2	2	3
Mixed drinkers, percent	21	25	29	35	43	47	57
Daily drinkers, percent	77	77	78	78	81	83	80
Married, percent	31	25	20	17	12	13	11
Owner of property, percent	16	19	23	28	30	34	36
Working, percent	31	32	29	22	21	17	16

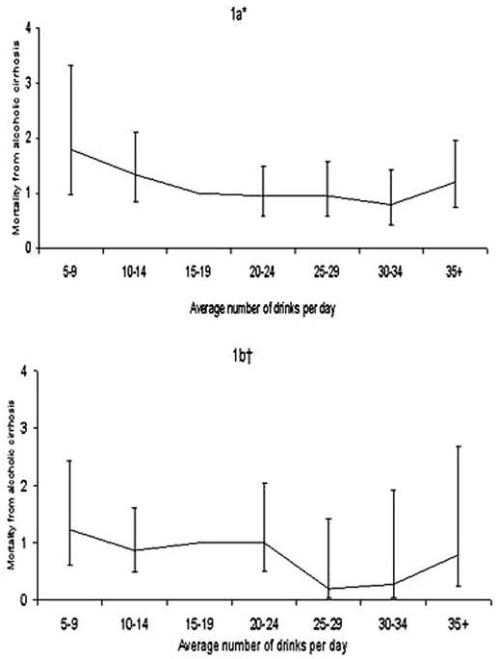

Fig. 1. Relative risks of alcoholic cirrhosis mortality by categories of average number of drinks per day in men (a) and women (b). Subjects drinking 15–19 drinks per day were used as a reference group (RR = 1). Vertical bars are 95% confidence limits. ∗ Adjusted for age, duration of alcohol misuse, predominant type of alcohol consumed and frequency of alcohol intake. †Adjusted for age, duration of alcohol misuse, predominant type of alcohol consumed, frequency of alcohol intake, marital status, housing status and work situation.

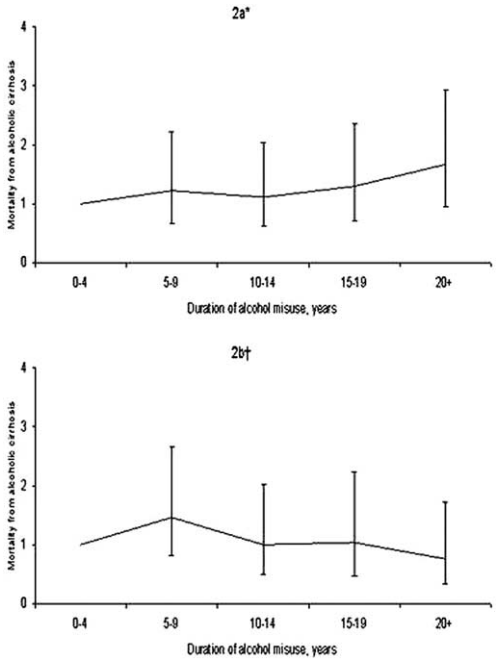

Fig. 2. Relative risks of alcoholic cirrhosis mortality by categories of duration of alcohol misuse in men (a) and women (b). Subjects with an alcohol misuse of 4 or less years were used as a reference group (RR = 1). Vertical bars are 95% confidence limits. ∗ Adjusted for age, average number of drinks per day, predominant type of alcohol consumed and frequency of alcohol intake. †Adjusted for age, average number of drinks per day, predominant type of alcohol consumed, frequency of alcohol intake, marital status, housing status and work situation.

associated with average number of drinks per day. Excluding the first 5 years of observation time did not influence the results (data not shown). There was no difference in the age distribution in excluded compared to eligible subjects ($P = 0.11$). The excluded cohort comprised 75% men, while the eligible subjects comprised 73% men ($P = 0.04$).

3.1. Average number of drinks per day

The risk of death from alcoholic cirrhosis was independent of average number of drinks per day. Men (Fig. 1a) who drank 35 or more drinks (>420 g/alcohol) per day, had a RR of 1.20 (CL 0.74;1.95) compared to the reference group who drank 15–19 drinks (180–228 g/alcohol) per day (RR = 1). Women (Fig. 1b) who drank 35 or more drinks per day had a RR of 0.78 (CL 0.23;2.67) compared to the reference group who drank 15–19 drinks per day. Adjustment for confounders and exclusion of all deaths from alcoholic cirrhosis within the first 5 years implied no significant change of these results (data not shown).

3.2. Duration of alcohol misuse

In both men (Fig. 2a) and women (Fig. 2b), no significant associations between duration of alcohol misuse and alcoholic cirrhosis mortality were found. Men who had had a misuse for 20 years or more had a RR of 1.67 (CL 0.95;2.92) compared to the reference group with a misuse of 4 years or less (RR = 1). Women with a misuse of 20 years or more had a RR of 0.76 (CL 0.33;1.73) compared to women with an alcohol misuse of 4 years or less. The association was the same when both adjusting for and not adjusting for confounders and when excluding all deaths from alcoholic cirrhosis within the first 5 years (data not shown).

3.3. Predominant type of alcohol consumed

No significant association was observed between predominant type of alcohol consumed and risk of alcoholic cirrhosis mortality, in neither men nor women (Table 2). Men who predominantly drank wine had a RR of 1.69 (CL 0.82;3.48) compared to men who drank beer (RR = 1), while women who predominantly drank wine had a RR of 1.49 (CL 0.76;2.91) compared to women who drank beer (RR = 1). The association was the same when both adjusting for and not adjusting for confounders and when excluding all deaths from alcoholic cirrhosis within the first 5 years (data not shown).

Table 2
Relative risk (95% confidence limits) of alcoholic cirrhosis mortality by sex and predominant type of alcohol consumed

Type of alcohol	Men[a]	Women[b]
Beer	1 (reference)	1 (reference)
Wine	1.69 (0.82;3.48)	1.49 (0.76;2.91)
Spirits	1.22 (0.71;2.11)	0.93 (0.46;1.88)
Mixed	1.04 (0.76;1.43)	1.61 (0.91;2.86)

[a] Adjusted for age, average number of drinks per day, duration of alcohol misuse and frequency of alcohol intake.
[b] Adjusted for age, average number of drinks per day, duration of alcohol misuse, frequency of alcohol intake, marital status, housing status and work situation.

Table 3
Relative risk (95% confidence limits) of alcoholic cirrhosis mortality by sex and frequency of alcohol intake

Frequency	Men[a]	Women[b]
Daily drinking	1 (reference)	1 (reference)
Periodic drinking	0.56 (0.37;0.85)	0.55 (0.29;1.02)

[a] Adjusted for age, average number of drinks per day, duration of alcohol misuse and predominant type of alcohol consumed.
[b] Adjusted for age, average number of drinks per day, duration of alcohol misuse, predominant type of alcohol consumed, marital status, housing status and work situation.

3.4. Frequency of alcohol intake

Men who drank periodically were found to have a significantly lower RR of 0.56 (CL 0.37;0.85) compared to the reference group of men who drank daily with a RR of 1 (Table 3). In women, periodic drinking was associated with a RR of 0.55 (CL 0.29;1.02) compared to women who drank daily (RR = 1). Not adjusting for confounders and exclusion of all deaths from alcoholic cirrhosis within the first 5 years did not change the results (data not shown).

3.5. Covariates

In men, we found no significant associations between any of the covariates and alcoholic cirrhosis mortality. In women however, marital status, housing status and working situation were significantly associated with alcoholic cirrhosis mortality. Married women had a RR of 0.55 (CL 0.34;0.89) compared to unmarried women (RR = 1). Compared to women who owned property (RR = 1), women who did not own property had a relative risk of 3.13 (CL 1.72;5.69). Non-working women had a relative risk of 3.54 (CL 1.61;7.81) compared to working women (RR = 1).

4. Discussion

In this cohort of alcohol misusers, men had a 27 fold and women a 35 fold increased mortality from alcoholic cirrhosis compared to the Danish population. No association between average number of drinks per day and alcoholic cirrhosis mortality was found. Periodically drinking was associated with lower risk than daily drinking. Predominant type of alcohol and duration of alcohol misuse was not associated with risk of alcoholic cirrhosis mortality.

In Denmark the five most frequent non alcohol-related causes of death are ischaemic heart disease, lung cancer, stroke, COPD and colorectal cancer. Only two studies concerning alcohol misusing men have evaluated the relation between risk of alcoholic cirrhosis and quantitative alcohol intake [9,10]. The findings of the studies are diverging. The small prospective cohort study by Sørensen et al. [9] found risk of developing alcoholic cirrhosis to be independent of quantitative alcohol intake, while the retrospective cohort study by Lelbach [10] found a linear increasing dose dependent risk with increasing intake. Our study must be interpreted differently than previous studies on normal consuming populations [1–6], showing an unquestionable relationship between alcohol intake and development of alcoholic cirrhosis. The findings in this study are compatible with the hypothesis, previously suggested in a study by Sørensen et al. [9], that alcohol may have a permissive rather than a dose-dependent effect on alcoholic cirrhosis mortality in men. From other cross-sectional, case control and prospective cohort studies a threshold, above which an increased risk of alcoholic liver disease is observed has been estimated to 20–40 g/day [15], 30 g/day [16], 12–24 g/day (women) and 24–36 g per day (men) [1], 40 g/day [17,18], 40–80 g/day (fatty liver and alcoholic hepatitis) and 80–160 g/day (fibrosis and cirrhosis) [19], <50 g/day [20,21]. In the meta-analysis by Corrao et al. (1998) even low levels resulted in a significantly increased risk of liver disease [22].

Quantitative alcohol intake may not be a good predictor for alcoholic cirrhosis mortality in alcohol misusing men and women who have all exceeded the threshold of 50–75 g of alcohol per day as suggested by Sørensen et al. [9]. The percentage of subjects in this study with a daily alcohol intake exceeding 50 and 75 g was 100 and 97, respectively.

Regarding duration of alcohol misuse, the findings of our study support previous findings in men [9,10]. Cirrhosis is often preceded by a period with fatty liver and/or alcoholic hepatitis. Especially alcoholic hepatitis is predictive of a high risk of later developing cirrhosis, while fatty liver is usually a benign condition with low risk of cirrhosis in abstinent patients. The increase in risk of cirrhosis with increasing duration of alcohol misuse in men may reflect an association with cumulated alcohol intake (life-time) or may reflect a time-dependent risk of being exposed to other risk factors as for example hepatitis C or other unknown risk factors. Concomitant viral hepatitis, especially hepatitis C, may be an additional risk factor for developing alcoholic cirrhosis. We have no information on serologic status of the

participants, but Denmark is a low prevalence area for hepatitis B and C (frequencies among blood donors 50–60 per 100.000) [23]. Variation in prevalence of viral hepatitis with beverage choice to such extent that it may bias results is very unlikely, although it cannot be ruled out.

The initial dataset comprised 9150 subjects, which by exclusion of subjects with inadequate information, liver disease at baseline or no alcohol intake, were reduced to 6152 subjects. If this reduction has excluded subjects unequally with regard to any of the variables of interest, our estimates may not apply to alcohol misusers in general. Since the cohort included in this study is large and no differences were found in age distribution between the excluded cohort and the eligible subjects, we do not consider the exclusion of the 2998 subjects a source of error. The difference in sex distribution between the excluded cohort and the eligible subjects should not affect our results, since analyses were performed separately for the sexes. Still we cannot exclude that groups may differ in respect to drinking habits.

Underreporting of deaths from alcoholic cirrhosis may have occurred, but the validity of alcoholic cirrhosis mortality in Denmark has previously been validated by Prytz and Anderson [24] and underreporting was found to be low in the period of interest. Besides subjects diagnosed with a liver disease in The Danish National Discharge Register, subjects with undiagnosed liver disease must be expected to appear in the remaining cohort. If diagnosis of liver disease is dependent on exposure status, for example more often recognized in the heaviest drinking subjects, this could have affected which subjects we excluded at baseline. To avoid this we excluded all deaths within the first 5 years, but as no differences was observed between the results of the analyses including and excluding these deaths respectively, we concluded that subjects with undiagnosed liver disease had no effect on our estimates. Hamberg et al. [25] concluded that by using only clinical and biochemical data cirrhosis may be diagnosed with a high accuracy in alcohol misusing men. Register based information on alcoholic liver disease in Denmark has previously been validated, and more than 85% of cirrhosis cases fulfill accepted diagnostic criteria [26].

Information on smoking and body mass index was not obtained. Different studies have different conclusions regarding smoking and cirrhosis. Bourliere et al. [27] found no effect from smoking while Klatsky et al. [5] and Becker et al. [3] found smoking to be an independent risk factor for developing cirrhosis. Klatsky et al. [5] and Bourliere et al. [27] found no effect of body mass index (BMI), while Becker et al. [3] found subjects with low (<20) and high (>30) BMI respectively, to have significantly increased relative risk of alcoholic cirrhosis. If either smoking or BMI is independent risk factors for death from alcoholic cirrhosis, and the risk factors are unequally distributed on different levels of the independent variable, our estimates can be confounded. Since the above studies imply that smoking, and maybe BMI, are independent risk factors, we consider the lack of information on smoking and BMI a weakness in this study. Furthermore, information on genetic predisposition was not obtained, which may have confounded our results. Genetic factors undoubtedly play a role in the development of alcoholic liver disease. This is known from twin studies where a higher concordance between monozygotic twins than in dizygotic twins in relation to alcoholic cirrhosis [28]. Several studies have shown that women have a higher risk of liver disease for a given alcohol intake [6]. Several genetic polymorphisms have been implicated in the development of alcoholic and non-alcoholic chronic liver disease [29]. In recent studies an association between a mutation in the promoter region of the tumor necrosis factor (TNF-α) and alcoholic hepatitis has been observed [30], although an association between TNF-α polymorphism and development of alcoholic liver disease was not confirmed in an Italian study of 158 heavy drinkers [31]. Furthermore, an association between a polymorphism in the interleukin (IL-10) promoter gene and alcoholic liver disease has been observed [32].

This study comprises a large cohort of alcohol misusers containing both men and women followed prospectively, which distinguish this study from most of the previous studies on alcohol misusers in terms of both study design and cohort size. The results of this study indicate that alcohol has a threshold effect rather than a dose–response effect on mortality from alcoholic cirrhosis in alcohol misusers.

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