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Sponsor-investigator

None

Investigator

Gro Askgaard, email: gask@dadlnet.dk

Section of Gastroenterology and Hepatology, Medical Department, Zealand University Hospital, 4600 Køge, DK-Denmark

Clinical epidemiologist responsible

Matilde Winter-Jensen, email: matilde.winther-jensen.01@regionh.dk

Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, The Capital Region, Denmark

Content

Abbreviations

RCT Randomized controlled trial

Introduction

Individuals with alcohol use disorders are less likely to receive preventive healthcare such as outpatient follow-up and screening examinations compared to the general population.[1] Evidence indicates that information and screening for disease may lead to a positive change in health risk behaviors. For example, a screening for lung cancer with detection of scan abnormalities seems to increase smoking cessation.[2,3] However, if no disease is detected by a screening examination some research indicates a risk for a negative influence on health risk behaviors such as decrease in physical activity.[2] Therefore, it is important to study if and how screening for liver disease influences alcohol consumption among individuals with alcohol use disorders.[4]

Objective

- To evaluate the efficacy of screening for liver disease with liver stiffness measurement on abstinence or light consumption after 6 months in individuals who are receiving treatment for alcohol use disorder and do not have a history of liver disease. We will conduct a randomized controlled trial with concealed allocation and blinded outcome assessment comparing A) an invitation to a liver stiffness measurement, blood sampling and leaflet on alcohol-related disease (intervention) with B) an invitation to blood sampling (control).
- The primary outcome is 'abstinence or light consumption' (≤ 10 units/week) throughout the last 30 days, and with one unit (containing 12 gram of pure alcohol) assessed 6 months after randomization.

Hypotheses, endpoints, and rationale

Hypotheses and endpoints

- Null-hypothesis: We hypothesize that among individuals attending treatment for alcohol use disorders, a screening for liver disease with liver stiffness measurement will not change the proportion that is abstinent or with light controlled consumption throughout the last 30 days after 6 months of follow-up compared to usual care.

- Alternative hypothesis: We hypothesize that among individuals attending treatment for alcohol use disorders, a screening for liver disease with liver stiffness measurement will increase the proportion that are abstinent or with light controlled consumption by at least 15 percentage-points after 6 months of follow-up compared to usual care.

Rationale

Early diagnosis of alcohol-related liver disease is key to survival, in particular if it leads to alcohol abstention.[5] Technological advances have made it possible to detect liver fibrosis as a sign of disease in its early stage by an easy and non-invasive approach called a liver stiffness measurement.[6] Among individuals in alcohol treatment without a history of liver disease, 17% had either significant hepatic fibrosis or cirrhosis identified with a liver stiffness measurement.[6]

Until now, it has not been established whether having a screening for liver disease with liver stiffness measurement, irrespective of its result, could motivate alcohol abstention among individuals with alcohol use disorders. One could fear that a liver scan indicating low likelihood of liver disease could be interpreted as a license to continue drinking alcohol (a phenomenon called the "certificate of health effect" that has been observed for physical activity and weight gain in an RCT of colon cancer screening).[7] No randomized controlled trials have been conducted. We have conducted a successful pilot study (ClinicalTrials.gov identifier NCT05244720) showing that a full study is feasible regarding recruitment and participation.

Study methods

Trial design

This is a randomized controlled study aiming to clarify if a liver stiffness measurement in the spirit of motivational interviewing can increase cutting down to light consumption or abstinence after 6 months among individuals attending treatment for alcohol use disorders. Participants are randomized 2:1 to intervention (invitation to blood samples and liver stiffness measurement and leaflet in addition to usual care) or usual care including an invitation to blood samples (control group). Study participants randomized as controls will be invited to have a screening for liver disease based on blood samples (the Fib-4 index), this is in line with the current recommended

practice from the European Association of the Study of Liver Diseases, describing what participants should be offered from their general practitioner [8]. The study period for recruitment will proceed from May 2023 until November 2026. There is follow-up for each individual participant at 6 months conducted by 1) telephone contact, 2) electronic health record, and 3) information on compliance with and untimely treatment drop-out of specialized treatment for alcohol use disorders. Six-month follow-up for all participants is expected to be finished in May 2027. We plan to conduct follow-up via healthcare registries in about 5 years after study inclusion.

Randomization

The randomization of the sequence of participants to intervention or control group will be computer generated using the webpage "sealedenvelope.com" by the researchers before enrollment to the study begins, so that each participant number/sequence number has a determined randomization outcome before enrollment to the study begins. Participants are block randomized 2:1 to an invitation to blood samples, leaflet and a liver stiffness measurement at Zealands University Hospital (intervention) or to usual care with an invitation to blood samples, using a block size of 24. We will use sequentially numbered opaque sealed envelopes with the sequence number provided. The physician or alcohol therapist will hand this envelope to the participant after obtaining informed consent for study participation and after the collection of the baseline variables, and by this approach assigning participants to randomization group.

Sample size

We plan to include 408 individuals in the study: 272 will be offered the intervention and 138 will be controls. This number is based on a sample size calculation with the assumption of a favourable alcohol outcome at follow-up of abstinence or light consumption in 66% in the intervention group and 51% in the control group and with a power of 80% and a two-sided significance level of 5%.[9] We expect loss to follow-up to be negligible because of the three follow-up methods applied. Further, patients who screen positive may react differently than patients who screen negative, which may affect outcome (the certificate of health effect). The number of 272 in the intervention group will also allow a comparison between those who are screen positive (fibroscan indicates liver fibrosis) and those who are screen negative. About 20% are expected to have indications of liver

fibrosis on fibroscan, while 80% are expected to screen negative (data from pilot trial and this reference: [10]). A difference in the outcome of abstinence or light consumption of 24% is expected (75% vs. 51% will be light drinkers/abstinent at 6 months) based on a prior study in primary care.[4]

Framework, interim analysis and stopping guidance

No interim analyses will be performed.

Timing of final analysis

Analyses will be performed in a blinded data set with treatment allocation labeled as "A" and "B". Prior to this, the statistical analysis plan will be completed, signed, and uploaded at clinicaltrials.gov and the data set locked. Unblinding will not take place until all analyses are performed (expected spring 2027). This means that apart from data on long-term follow up, all analyses will be finalized collectively.

Timing of outcome assessment

Outcome assessment will be performed 6 months after randomization in all participants.

Statistical principles

Confidence and P-values

Level of statistical significance is set at an alpha level of 0.05 with two-sided testing and a confidence interval of 95%.

Adherence and protocol deviation

Protocol deviations will be presented in a table, divided into categories: Eligibility, study procedure and randomization. The deviations "lost to follow-up" (in case of emigration out of Denmark) and "withdrawal" (when study participants withdraw their informed consent) are described in more detail below.

Analysis populations

The primary analysis will be performed by the intention-to-treat approach by including all patients randomized. In a secondary analysis, the primary outcome will be investigated using the per protocol principle, where only those participants randomized to the intervention and who met at the hospital and had the liver stiffness measurement will be included in the analysis in addition to

the controls. Participants who are lost to follow up due to emigration will also be excluded in this analysis. Follow-up will be possible in all other participants (follow-up procedures are described below).

Trial population

Screening data

A CONSORT flow chart will present the flow of study participants.

Eligibility

Inclusion criteria

- Attending outpatient treatment for alcohol use disorder (international classification of disease version 10: F102: alcohol dependence or F101: harmful alcohol use) at Novavi Køge or Novavi Roskilde
- Age ≥ 18 years
- Informed written consent

Exclusion criteria

- Not speaking Danish or English
- Severe liver disease (known by the participant)

Recruitment

May 2023 until November 2026 (or until there are 408 study participants)

Patients will be recruited from the outpatient alcohol treatment centres of Novavi Køge and Novavi Roskilde.

Withdrawal/follow up

See Table 1 for description of follow-up. Three follow-up methods will be applied: Telephone interview, review of medical chart records and records from the alcohol treatment center. If participants are not approachable by telephone, follow-up data will be based on information from records from the hospital and alcohol treatment center alone. Participants who have untimely drop out of the treatment for alcohol use disorder will be regarded as not having a successful primary outcome of 'abstinence or light consumption' (≤ 10 units/week) throughout the last months.

Withdrawal is when a study participant withdraws their informed consent for study participation.

Loss to follow-up is only in the case of emigration out of Denmark.

Baseline characteristics

The following characteristics will be summarized according to intervention:

- Sex
- Age , median and 25-75% percentiles
- Age groups
- Educational level
- Cohabitation status
- Employed
- Duration of current treatment for alcohol abuse disorder (in days or months)
- Days since last alcohol consumption, median
- Heavy drinking days, mean/median last month?
- Heavy drinking days, groups (<4, 5-11, 12-17, 18-23, 24-30)
- Abstinence or light drinking < 10 units/week throughout last month
- Years exceeding 10 units/week, groups (<5, 5-10, 10-15, 15-20, >20)
- Audit-C
- Motivation to cut down on 10 point scale, median and IQR
- Belief in capability to cut down on alcohol, 10 point scale, median and IQR
- smoking (yes/no)
- Sf-12 physical, median
- Sf-12 mental, median

Analysis

Outcome definitions

Primary endpoint

Primary outcome: Alcohol abstinence or light consumption (≤ 10 units/week) throughout the last 30 days (as an average intake) assessed after 6 months since the intervention of an evaluation of liver disease (yes/no).

Table 1. Evaluation of primary outcome of alcohol abstinence or light consumption throughout the last 30 days		
	Interpreted as *not fulfilling* alcohol abstinence/light consumption if indicated by *one or more* of the outcome measures below	**Interpreted as *fulfilling* alcohol abstinence/light consumption the last month if indicated by all three of the outcome measures below**
1) Telephone interview with timeline follow-back method	Interview reveals alcohol intake above the light consumption level the last 30 days as an average intake	Interview reveals alcohol abstinence or light consumption the last 30 days as an average intake
2) Electronic health record	Hospital contact the last 30 days with history that indicates current drinking: alcohol intoxication, ethanol measurement or told by the patient, or death with obvious alcohol involvement.	Either no hospital contacts or hospital contact without mentioning of alcohol consumption above the light consumption level, as an average intake last 30 days. Death with no obvious alcohol involvement.
3) Untimely treatment drop-out of treatment for alcohol use disorder from Novavi	Untimely treatment drop-out since randomization as judged by Novavi alcohol treatment	Not untimely dropout since randomization. Death with no obvious alcohol involvement.

	center, or death with obvious involvement of alcohol during the 6 months since baseline	

Secondary outcomes:

1) Reduction in number of heavy drinking days assessed last 30 days (yes or no).

2) Reduction in AUDIT C score (yes or no).

3) Improvement or no decrease in motivation to cut down on alcohol (yes or no), improvement or no decrease in physical and mental health-related quality of life (yes or no), calculated as the difference between baseline and follow-up.

4) The "certificate-of-health effect" will be evaluated by comparing likelihood of abstinence or light consumption last 30 days at six months between those in the intervention group with a screen negative result (liver stiffness measurement< 8kPa) with those in the control group.

5) Comparison within the intervention group: Whether those screening positives were more likely to cut down on alcohol than those who screen negative.

Supportive outcomes

Supportive outcomes: Evaluation of liver disease by liver stiffness measurement, ultrasound or CT scan at the hospital not as part of the study among participants randomized as controls (cross-over). Also, we will evaluate further investigations at the hospital if a transient elastography measurement result indicates liver fibrosis (significant fibrosis (≥8kPa)) to assess the burden of

extra hospital contacts for the participant and the healthcare institution. Longer follow-up (3 years) is planned to be conducted through health care registries to look for incidence of alcohol-related liver disease and death, other liver disease, visits to general practitioner and hospital contacts.[25,26]

Statistical analysis

Continuous outcomes will be assessed for normality and reported as mean (sd) or median (25th-75th percentile) and analyzed with t-test or Wilcoxon test, as appropriate. Categorical outcomes will be reported as n (%) and analyzed using chi-square test.

The primary outcome (alcohol abstinence or light consumption (≤ 10 units alcohol/week throughout last 30 days) yes/no) will be assessed using logistic regression adjusting for intervention with invitation to fibroscan examination and average number of units per week at inclusion.

The primary outcome will be assessed in the intention-to-treat population, and further, in the per-protocol population. In the latter, inverse probability of treatment weighting will be used to account for measured confounding of age, sex, average number of drinks per week and months in alcohol abuse treatment . Further, we will analyse whether time in treatment for alcohol use disorder is an effect modifier analysed as interaction with randomization group and primary outcome.

Secondary outcomes:

1) Reduction in number of heavy drinking days (yes or no)
   This secondary outcome will be assessed using Logistic regression.
2) Reduction in AUDIT-C score (yes or no, measured on continuous scale),
   linear regression
3) Improvement or no decrease in motivation to cut down on alcohol (yes or no), improvement or no decrease in health-related quality of life (yes or no), calculated as the difference between baseline and follow-up. Linear regression.
4) Staying in alcohol abuse treatment among participants exceeding light drinking levels (yes/no). Logistic regression.

5) Improvement or no decrease in physical or mental health-related quality of life (Sf-12)). Linear regression.
6) Improvement or no decrease in smoking. Logistic regression.
7) Evaluation of liver disease at the hospital not as part of the study among all participants to assess cross-over: whether those randomised as controls had the intervention performed in another occasion (yes/no).
8) Comparison within the intervention group: Whether those screening positives were more likely to cut down on alcohol than those who screen negative.

Assessment of model assumptions

Logistic regression:

The assumption of linearity between log odds of outcome and the predictor is less relevant when the predictor is dichotomous, as in this study.

Linear regression:

Linear relationship between intervention and number of drinking days will be assessed by plotting the fitted values(x) vs. the residuals(y).

Normality of residuals is checked by the QQ-plot, residuals should follow the straight line.

Homoscedascity is assessed plotting standardized residuals vs. fitted values.

Influential values are not as likely, since the intervention is dichotomous, and all numbers of heavy drinking days pr. 30 days are likely.

Sensitivity analysis

Only including those who had the intervention by excluding those in the intervention group who never showed up for the intervention with the fibroscan at the hospital (per protocol analysis). Participants who are lost to follow up due to emigration will also be excluded in this analysis.

Subgroup analysis

To assess certificate of health user effect: Compare outcomes between those who screen negative (fibroscan < 8 mmhg) from the intervention group with that of the control group.

To assess whether those from the intervention group with a screen indicating liver fibrosis (screen positive) have more success with abstinence than controls: Compare outcomes within participants from the intervention group with a fibroscan >8 mmHg with those from the control group.

Time in days of receiving treatment for alcohol use disorder (over/under median, over/under 6 months osv.)

Severity of alcohol abuse disorder, measured by AUDIT-C (over/under median)

By sex (men/women)

By educational level

By age

Motivation to cut down

Site (Novavi Køge vs. Novavi Roskilde)

Assessment of missing data

Missing data will be investigated by producing tables that characterize patients with missing data vs. patients with information for each missing variable, as in table 2 below. There may be missing data in many variables, so variables of interest will be assessed.

Table 2: Assessment of missingness

	Missing (n=xx)	Not missing (n=YY)
Intervention	2%	10%
Primary outcome	12%	5%
Age	69 years	65 years
Male sex	75%	50%

Marital status: Cohabiting/married	33%	80%
Occupation		

Missingness is not expected in intervention assignment or outcome but may be present in confounders. Missingness is likely unrelated to intervention, patterns of missingness will be assessed. If patients with missing data differ from patients without missing data, it is assumed that data is missing not at random and multiple imputation may be redundant. Otherwise, multiple imputation may be used as a sensitivity analysis. Whether imputation can be used will be based on a judgment of the extent of patterns in missingness as well as degree of missingness. Imputation will not be used if missingness should be skewed or if missingness is present in less than 10% of the total dataset including the confounders to be used. All secondary outcomes will be assessed as cross tables with intervention, primary outcome, age, sex, marital status, and occupation. As a rule of thumb, differences should be less than 5% between patients with and without missing data, but the total pattern will be considered.

Tables

Table 3. Baseline demographic and clinical characteristics according to randomization outcome, values are number (%) unless otherwise stated

	Screening for liver disease with liver stiffness measurement (intervention)	Usual care with offer of blood test
Sex, % men		
Age, median		
Exceeding 10 units/week last 30 days (tages fra AUDIT spørgsmål)		
AUDIT-C		
Days since last alcohol consumption, median		
Years with exceeding 10 units/week, median SD		
Phosphatidylethanol		
Motivation to cut down on alcohol, 1 to 10 (median)		
Believe in capability to cut down, 1 to 10 (median)		
Duration of alcohol misuse treatment in months, median		
Smoking, % yes		
Health-related quality of life, physical, median (IQR)		
Health-related quality of life, mental, median (IQR)		

Table 4. Assessment of primary outcome N (%) at 6 months after randomization according to the three follow-up methods

	Intervention		Control	
Alcohol abstinence or light consumption (≤ 10 units/week) throughout the last 30 days	*Yes*	*No*	*Yes*	*No*
At Inclusion				
By Telephone interview				
By Electronic health record				
By Dropout				
In total				

Table 5. Comparison of endpoints at 6 months follow-up according to randomization group

	Screening for liver disease with liver stiffness measurement (intervention)	Usual care with offer of blood test (usual care)	p-value
Exceeding 10 units/week last 30 days			
Exceeding 10 units/week last 30 days (change since randomization)			
AUDIT-C (change since randomization)			
Total alcohol consumption, g/30 days last month			
Days without alcohol last 30 days			
Heavy drinking days last 30 days			
Total alcohol consumption, g/30 days last six month			
Days without alcohol per month last six month			
Heavy drinking days per month last six month			
Motivation to cut down on alcohol, 1 to 10			

(median) (change since randomization)			
Believe in capability to cut down, 1 to 10 (median)			
Smoking, % yes (change since randomization)			
Health-related quality of life, physical (change since randomization)			
Health-related quality of life, mental (change since randomization)			

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