Official title: Screening for liver disease in individuals attending treatment for alcohol use disorder – a randomized controlled study

Document date: 05th of January 2023

Protocol

0 Title in English and Danish

The Liver Care Trial: Screening for liver disease in individuals attending treatment for alcohol use disorder – a randomized controlled study

(Danish: Screening for leversygdom hos personer i alkoholbehandling – et lodtrækningsstudie)

1 Introduction and objectives

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 influence 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 without 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 months,

and with one unit containing 12 gram of pure alcohol) and assessed 6 months after randomization.

2 Hypotheses, endpoints and rationale

2a 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 after 6 months of follow-up compared to standard 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 with 15% after 6 months of follow-up compared to standard care.

2b The 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 attending treatment for alcohol use disorders 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, irrespectively 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.

3 Scientific background

3a Alcohol-related liver disease is often diagnosed too late

Today, around 35% of patients with alcohol-related liver disease die within the first year after diagnosis.[8] This high mortality is mainly caused by the liver disease being diagnosed in its late stage, when complications of liver failure such as ascites, variceal bleeding or hepatic encephalopathy have developed. Alcohol-related liver disease develops over many years prior to diagnosis, but the disease is usually asymptomatic until complications develop. If alcohol-related liver disease were to be diagnosed before the development of liver disease complications, the liver has the potential to regenerate if alcohol consumption is reduced, which increases the survival associated with alcohol-related liver disease significantly.[5] Early diagnosis of alcohol-related liver disease improves the likelihood for better treatment options for the life-threatening complications of varices and hepatocellular carcinoma.[5]

3b A non-invasive measurement of liver stiffness can detect liver disease in its early stage

Patients with the early stages of alcohol-related liver disease are asymptomatic and they therefore less frequently seek healthcare for liver disease.[5] Blood samples and clinical examination can even be unaffected, so investigations done by general practitioners are not sufficient to detect fibrosis of the liver.[9] Technological advances have made it possible to detect the disease in its early stage by an easy and non-invasive approach called a liver stiffness measurement (FibroScan©).[6] This measurement takes around 10 minutes and is without adverse effects.[9] International guidelines recommend that individuals with long-lasting heavy drinking such as individuals attending alcohol misuse treatment should be offered an evaluation for liver disease such as a liver stiffness measurement.[5,10] Indeed, among Danish asymptomatic individuals attending treatment for alcohol use disorders, 17% had significant alcohol-related liver disease defined as significant liver fibrosis or cirrhosis (liver stiffness measurement ≥8kPa).[6]

3c An evaluation for liver disease is not routinely offered to individuals in treatment for alcohol use disorders

Individuals attending treatment for alcohol use disorders have a much higher risk of several medical conditions such as anemia that can be caused by vitamin deficiencies (folate or B12) or gastrointestinal bleed.[11] The English National Institute for Health and Care Excellence recommends blood sampling to diagnose deficiencies in vitamins and minerals and anemia in individuals with alcohol use disorders to be able to give vitamin supplements to individuals with deficiencies.[12] If anemia is diagnosed, this should be further ruled out with current guidelines and may include endoscopies to look for ulcers, malignancy, or other causes of gastrointestinal bleeding.[13] Today, no

routine blood sampling is done in Danish specialized alcohol treatment centers, although blood sampling may be performed in case of prescriptions of pharmacotherapy.[14]

3d Screening for disease may lead to behavior change – the teachable moment hypothesis

Observational studies have found increased smoking cessation rates after myocardial infarction, cancer diagnosis, and prior to surgery.[15] A similar pattern is seen for alcohol: Health problems and perceived consequences of heavy drinking motivate reduced alcohol consumption in treatment-seeking individuals with alcohol use disorders.[16,17] It remains unknown whether screening for alcohol-related disease before health problems occur is enough to induce a reduction in alcohol consumption. A systematic review of randomized controlled trials from 2011 concluded that the literature was too sparse to draw a conclusion on whether screening for a somatic disease had effects on health behavior.[2] Results from an observational study indicate that appropriate behavioral advice in the context of screening for liver disease can reduce heavy drinking.[4]

However, an important issue to consider is the "certificate-of-health effect" with the observation that individuals who had a negative screening result are more likely than controls to practice an unhealthy lifestyle in the months after their screening. In that sense a negative screening result may be regarded as a "licence to drink/smoke/eat unhealthy". This has been observed for a RCT with a colon cancer screening program in which the screened individuals had a lower improvement in smoking, exercise habits and eating healthy after 3 years compared to the controls.[7]

We believe that 'individuals in alcohol treatment' is a suitable study population to offer an evaluation of liver disease since these people are more likely to be motivated for alcohol abstinence than are, for instance, heavy drinkers in primary care not seeking alcohol treatment.[4]

Motivational interviewing is an evidence-based approach to increase patient compliance and reduce alcohol consumption in individuals with alcohol use disorders.[18] Motivational interviewing is based on empathy and seek to increase patient engagement - and therefore it may be a good approach for patients with alcohol use disorders who often feel stigmatized in the hospital.[19] We therefore developed an intervention with delivering the liver stiffness measurement based on motivational interviewing.

3e Prior studies

No randomized controlled studies of a liver stiffness measurement versus no intervention have been conducted to study if such a liver stiffness measurement could increase abstinence or light controlled consumption, in addition to what can be obtained by motivational interviewing/brief advice.[20,21]

4 Methods

4a Study design

See the study flowchart for a graphical presentation of the study 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) or standard care including an invitation to blood samples. If those in the control group have the liver stiffness measurement performed elsewhere it could introduce a bias because some participants

randomized as controls had the intervention as well. Therefore, 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, at what participants could be offered from their general practitioneer.[22] The study period for recruitment and follow-up will proceed from December 2022 until November 2032. 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.

4b Practicalities

See SPIRIT DIAGRAM below

Baseline assessment

Questionnaires with baseline data will be filled by the participant and collected by the alcohol therapist and include: Severity of alcohol use disorders (AUDIT questionnaire),[23] years with heavy drinking (exceeding the national guidelines for sensible drinking anno 2022: > 10 units/week), current alcohol consumption, day for last alcohol consumption, sociodemographic variables, and smoking. Moreover, we will ask for motivation to decrease alcohol consumption and the belief in this change using ”Spørg til alkoholvaner” from the guideline to general practitioners.[24] A unit of alcohol is equivalent to 12 g of pure alcohol in this study. Further, we will ask for health-related quality of life with the validated Short-form 12 questionnaire, version 2.[25]

Randomization

The randomization of the sequence of participants to intervention or control group will be computer generated using REDCap 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 randomized 2:1 to an invitation to blood samples, leaflet and a liver stiffness measurement at Sjællands Universitetshospital (intervention) or to standard care with an invitation to blood samples. 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.

The intervention: Invitation to a liver stiffness measurement

The intervention will be delivered with motivational interviewing meaning that the researcher delivering the intervention has participated in a course in motivational interviewing for alcohol use disorders. There will be a semi-structured manual to follow for delivering of the intervention and this is prepared in conjunction with a certified motivational interviewing coach. The intervention consists of 1) a liver stiffness measurement using FibroScan©, 2) clinical examination for signs of liver disease, 3) routine blood samples, and 4) leaflet with description of alcohol-related disease and benefits of cutting down and with the result of the liver stiffness measurement (Appendix “spørgeskemaer”).

The researchers will contact the study participants by phone for an appointment within few days after the enrolment and will aim for an appointment for a liver stiffness measurement within 4 weeks and preferably within 2 weeks. If not reached the first time by phone, they will be called up to 10 times until they are reached. The researchers will explain about the liver stiffness measurement (the same information as the "deltagerinformation"). The researchers will explain to the participant that they need to fast for 4 hours before they meet at the hospital for blood sampling and liver stiffness measurement (morning sessions will be prioritized).[26] At the hospital, routine blood samples and optionally blood samples for biobank will be taken. A measurement of liver stiffness will be performed using FibroScan©. The FibroScan© (transient elastography) works by measuring shear wave velocity with an ultrasound probe. A FibroScan© assesses liver stiffness which correlates with liver fibrosis. The FibroScan© is safe, without adverse events and used in daily clinical practice. Early liver disease ("significant liver fibrosis") will be defined as a test result of 8.0-15 kPa with 10 successful measurements and an IQR of the median < 30 %.[27] Late liver disease ("liver cirrhosis") will be defined as a test result of ≥15.1 kPa with 10 successful measurements and an IQR of the median < 30 %. [27]

The participant attending the liver stiffness measurement, will have the test result of the FibroScan© explained promptly by the healthcare professional performing the FibroScan©. Moreover, the result will be written on the leaflet. If the FibroScan© suggests early liver disease or the blood samples reveal anemia or vitamin deficiencies, the participant will be offered routine assessment for this at the hospital department where the study takes place. When the results of the blood samples are available they will be explained to the participant by a physician.

We will collect blood used for routine care analyses (for more details see table 1) and for a research biobank. We will analyse blood for biomarkers of liver disease and inflammation including

apolipoproteinA1, haptoglobin, alpha-2-macroglobulin, and hyaluronate, which are not yet used in daily clinical practice.[22] For example, the Fibrotest is a commercially available algorithm that combines age, gender, alpha-2- macroglobulin, haptoglobin, apolipoprotein, bilirubin, and gamma-glutamyl transferase (GGT).[28] Moreover, The Enhanced Liver Fibrosis (ELF) test is a commercially available algorithm that combines 3 direct serum markers of extracellular matrix remodeling and fibrogenesis: hyaluronic acid, the N-terminal pro-peptide of collagen type III, and tissue inhibitor of metalloproteinase-1.[21,28]

We will also analyse phosphatidyl ethanol, a marker of chronic alcohol consumption.

Control group

Participants randomized as controls will be offered: 1) routine blood samples including AST, ALT and platelet count to calculate the FIB-4 index.[22] Participants randomized as controls will need themselves to call for an appointment for blood samples. If the FIB-4 index suggests early liver disease ($\geq$ 1.30) or the blood samples reveal anemia or vitamin deficiencies, the participant will be offered routine assessment for this at the hospital department where the study takes place. Participants will only be contacted by physicians after blood sampling if the blood samples indicate abnormalities and a need for follow-up.

Follow-up

We offer one follow-up assessment to all participants who were randomized and no matter intervention or not, and no matter the result of the liver stiffness measurement. Follow-up data is collected at 6 months by a research nurse who is blinded to whether or not the participant had the

intervention. Follow-up data include: Severity of alcohol use disorders (AUDIT), motivation to cut down, alcohol consumption/heavy drinking days the last 6 months, smoking status and health-related quality of life (Short-Form 12, version 2).[25]

The follow-up data will be collected by three methods: 1) by phone interview with the validated Timeline Follow-Back method.[29] In these interviews, the research nurse will tell the participant not to reveal the information about if they had a liver stiffness measurement, 2) from participants' electronic health record to look for data on alcohol consumption, and 3) we will obtain information on compliance with and untimely treatment drop-out of treatment for alcohol use disorders from the municipal specialized alcohol treatment center (Novavi Køge and Roskilde). We expect loss to follow-up to be negligible because we include information from medical chart review and compliance with alcohol misuse treatment. However, if study participants emigrate they will be regarded as loss to follow-up.

If participants are unavailable for the telephone-interview on alcohol consumption after 6 months, we will use multiple imputation to construct missing values. In a sensitivity analysis we will analyse whether the results change if unavailability for the telephone-interview is regarded as relapse to heavy drinking (treatment failure).

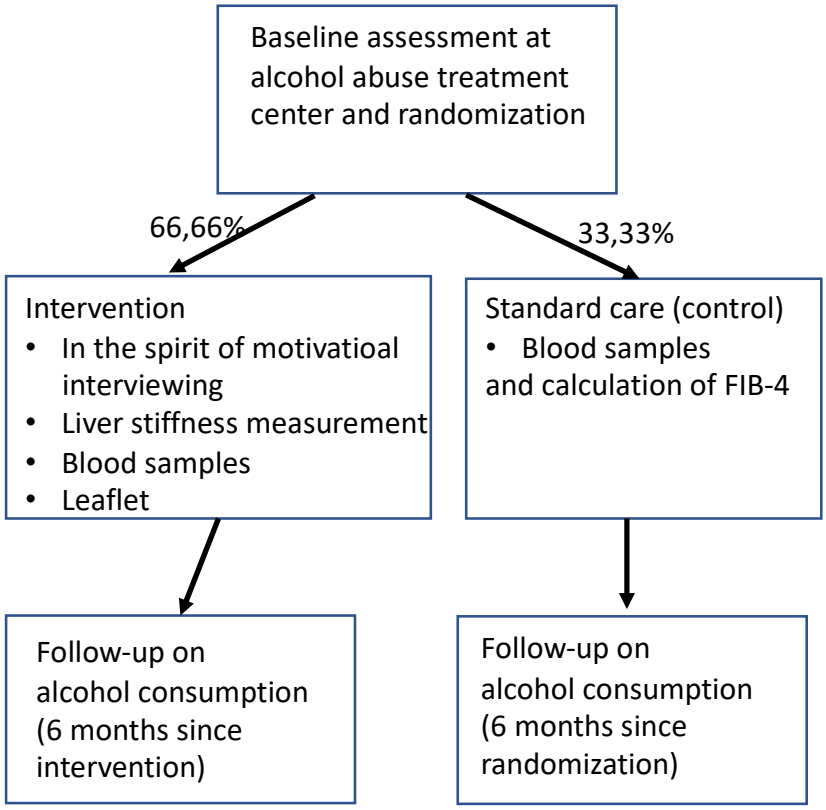
We will also collect information on hospital evaluation of liver disease outside the project, this information will come from medical charts review.

SPIRIT DIAGRAM

	Enrolment	**Allocation**	**Close-out**		
TIMEPOINTS	*-t_1*	Baseline	*Within 1 month*	*6 months*	*>2 years*

ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Liver screening with liver stiffness measurement			X		
Standard care with offer of blood tests			X		
ASSESSMENTS:					
***Baseline:** AUDIT, motivation to cut down, units/week, last alcohol consumption, SF-12, smoking*	X				
***Follow-up:** Alcohol abstinence/light consumption last month, AUDIT, motivation to cut down, SF-12, smoking*				X	
***Longer follow-up**: healthcare use, liver disease incidence, death*			X	X	X

Study flow chart



4c: Deviations from standard care

All participants at the specialized alcohol misuse treatment centers will receive their usual standard treatment for alcohol use disorder. If patients choose to take part in this study they will be offered blood samples with screening for liver fibrosis with the FIB-4 index. If they are randomized to the intervention, they will be offered a liver stiffness measurement and a leaflet in addition to blood samples. The intervention may increase the rate of abstinence in the intervention group compared to the control group, but we don’t know.

5 Statistics and sample size

A final statistical protocol will be uploaded on clinicaltrials.gov before enrolment begins. The analyses of data will be based on the intention-to treat approach meaning that our primary analysis will include all participants who were randomized. The primary outcome (alcohol abstinence or light consumption (≤ 10 units alcohol/week throughout the last month)) will be analyzed using a logistic regression model with adjustment for average number of units per week at inclusion. Multiple imputation will be used to account for missing information on outcome and average number of units per week at inclusion. In addition, the primary outcome will be investigated using the per protocol principle, where only those participants randomized to the intervention who actually met at the hospital and had the liver stiffness measurement will be included in the analysis in addition to the controls. We will use inverse probability of treatment weighting in those analyses to account for measured confounding of age, sex, average number of drinks per week and months in alcohol misuse treatment.[30] Further, we will analyse whether "time on unsuccessful" treatment for alcohol use disorder is an intervention moderator analysed as interaction with randomization group and primary outcome. Secondary and supportive outcomes will be investigated using the same principles used for the primary outcome, however for continuous outcomes linear regression will be used and for count data, Poisson regression models.

We plan to include 408 individuals in the study: 272 will be offered the intervention and 136 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%.[31] The number of 272 in the intervention group will also allow a comparison between those who are screen positive (fibroscan indicate liver fibrosis) that is expected in about 20% (data from pilot trial

and this reference: [32]) and those who are screen negative (80%) with a difference in the outcome of abstinence or light consumption of 24% (75% vs. 51% will be light drinkers/abstinent at 6 months). We expect loss to follow-up to be negligible because of the three follow-up methods applied (described in the follow-up section above). The specialized alcohol treatment center of Novavi Køge has around 200 and Novavi Roskilde around 150 individuals attending treatment for alcohol use disorders every year. We expect to include 408 participants during a period of 30 months.

6 Study outcomes

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

Evaluation of primary outcome of alcohol abstinence or light consumption throughout the last month	**Interpreted as not *fulfilling* alcohol abstinence/light consumption if indicated by just *one* of the outcomes measures below**	**Interpreted as *fulfilling* alcohol abstinence/light consumption the last month if indicated by all three of the outcomes measures below**
1) Telephone interview with timeline follow-back method	Interview reveals alcohol intake above the light consumption level the last month	Interview reveals alcohol abstinence or light consumption the last month
2) Electronic health record	Hospital contact the last month with history that	Either no hospital contacts or hospital contact without

	indicates current drinking: alcohol intoxication, ethanol measurement or told by the patient.	mentioning of alcohol consumption above the light consumption level
3) Untimely treatment drop-out of treatment for alcohol use disorder from Novavi	Untimely treatment drop-out the last month as judged by Novavi alcohol treatment center or death with obvious involvement of alcohol during the 6 months since baseline	Not untimely dropout the last month

Secondary outcomes: 1) Reduction in number of heavy drinking days throughout last month (yes or no), 2) reduction in AUDIT score (yes or no), 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. 4) Continuous treatment for alcohol use disorder among participants exceeding light consumption levels. One could fear that a liver stiffness measurement indicating low likelihood of liver disease could be interpreted as a license to continue drinking alcohol (a phenomenon called the “certificate-of-health effect”). This will be evaluated by comparing likelihood of abstinence or light consumption at six months between those in intervention group with a screen negative result (liver stiffness measurement< 8kPa) with those in the control group.

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 early liver disease (significant fibrosis (≥8kPa)) to assess the health-care burden. 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, visits to general practitioner and hospital contacts.[25,26]

7 Participants

7a 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 Roskilde
- Age ≥ 18 years
- Informed written consent

7b Exclusion criteria

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

8 Risks and adverse effects

The known risks for venepuncture are bleeding and hematoma at the point of puncture. A transient elastography is a non-invasive test and the technique is based on ultrasound. The transient elastography is considered safe without adverse events to the patient.[9] The emotional impact of further clinical investigations seems to be negligible, at least after four weeks.[33]

9 Blood samples and the research biobank

From each participant we will collect blood only one time. All blood samples are outlined in Table 1 and in the following points. Part of the blood is destroyed within few days and is not considered as a research biobank; another part of the blood is stored in a research biobank.

A: Blood samples (not stored)

Section A shows the amount of blood samples taken at inclusion with routine analyses of markers of liver disease, anemia and selected vitamins. These blood samples will be analysed immediately by the laboratory at Zealand University Hospital, Køge. The blood will be destroyed within few days after analysis. This is not considered as a research biobank.

- **B: Phosphatidylethanol (stored in a research biobank for maximum 1 year)**

Section B shows the amount of blood used for the alcohol biomarker analysis (phosphatidylethanol) taken at inclusion. Sygehus Lillebælt, Vejle is the only place in Denmark making this analysis. The blood will be stored in a research biobank at Department of Internal Medicine, Zealand University Hospital, Køge before it is sent to Sygehus Lillebælt. During the study period, the blood will be collected for each study patient, stored in the research biobank and continuously in groups sent to

Sygehus Lillebælt for analysis. The blood will be stored for maximum 1 year and will be destroyed immediately after the analysis in Sygehus Lillebælt.

- **C: The blood for biomarkers of liver disease (stored in research biobank)**

Section C shows the amount of blood used for analyses of biomarkers of liver disese. The blood will be stored in a research biobank at Region Sjællands Biobank i Næstved, Sygehusene i Næstved, Slagelse og Ringsted. The blood samples will be stored in the research biobank during the study period of 10 years. After the end of the study we will apply the Danish Data Protection Agency for permission to store the excess amount of blood from section C in a new biobank for future unspecified research. In case of permission the blood will not be destroyed or anonymized, it will be stored in a new research biobank and still handled according to the Law of Data Protection. In case of rejection we will destroy the blood after 10 years.

The volume of blood collected for blood samples without the research biobank: 17 ml

The volume of blood collected for the research biobank: 29 ml

The total volume of blood collected during the study period: 46 ml

Table 1. Blood samples

	Type of analyses	Sampling time points	Sampling volume and destruction	Location
	Routine blood samples (not a research biobank)			
A	Hæmoglobin;B Erythrocyt middelcellevolume;B MHCH; B	One time	Total amount of blood: 17 ml	Laboratories of clinical biochemistry,

	Ferritin; B Leukocytter;B CRP;P Trombocytter;B Koagulationsfaktor II+VII+X [INR];P Aspartattransaminase [ASAT];P Alanintransaminase (ALAT);P Albumin; P, Bilirubin;P Kreatinin;P Natrium;P Kalium;P Basisk fosfatase;P Gammaglutamyltransferase(GGT); P B12; P Folate; P Glucose; P Insulin; P Cortisol; P		Samples will be destroyed immediately after analysis (maximum 2 days)	Zealand University Hospital, Køge
	Blood samples for the research biobank			
B	Phosphatidylethanol	One time	Total amount of blood: 4 ml	Stored at Laboratories of clinical biochemistry, Zealand University Hospital, Køge

			Samples will be stored and sent to Sygehus Lillebælt for analysis. It will destroyed immediately after analysis (maximum 1 year)	Analysed at Region Midt, Sygehus Lillebælt, Vejle (only place in Denmark who does this analysis)
C	ApolipoproteinA1, haptoglobin, alpha2macroglobulin, hyaluronate and a little extra in case of failure analyses.	One time	Total amount of blood: 25 ml Samples will be stored in the research biobank of Region Sjællands Biobank i Næstved, Sygehusene i Næstved, Slagelse og Ringsted. Samples will be analysed at clinical biochemistry, Sygehusene i Næstved, Slagelse og Ringsted. Afterwards they will be destroyed.	Stored at Region Sjællands Biobank i Næstved, Sygehusene i Næstved, Slagelse og Ringsted.

10 Data obtained from medical records and health registries

We will not obtain information from medical records before informed consent.

Data obtained from medical records after obtained written informed consent:

- Information on alcohol-related hospital contacts: if patients are not responding to our phone call we will investigate whether they have been admitted to the hospital with alcohol problems.
- Results of assessments for liver disease
- Results of blood samples (those mentioned in Table 1)
- Information on death: to clarify if the patient died, including causes of death

We (the researchers) will ask participants for permission to look in participants' medical records to obtain information on health that is necessary in order to conduct the present research project and for quality control, self-control, and monitoring. The information will be collected 6-36 months after study enrolment.

Data obtained from specialized alcohol treatment centers:

From municipal specialized alcohol treatment centers (Novavi Køge and Roskilde), we will obtain data on finishing date of treatment for alcohol use disorder and whether it was untimely (unplanned), after we have obtained written informed consent. The information will be collected 6-12 months after study enrolment.

Data from health registries

Two years after start of inclusion to the study, we will seek permission to get data from Danish nationwide healthcare registries including: Landspatientregisteret (information on hospital contacts, diagnosis of liver disease and other alcohol-related diseases), CPR-registeret (vital status), uddannelsesregisteret (education), registerbaserede arbejdsstyrkestatistik (employment history), familieregisteret (children and cohabitation status) and dødsårsagsregisteret (cause of death). This information will be used to analyse whether there are differences for intervention and control group in this study with regard to: diagnosis of liver disease, hospital contacts for liver disease, survival, cause of death, employment history. Also we will investigate any differences according to educational level and employment status.

11 Processing of personal data

The processing of personal data in the current study will be handled in accordance with the law of data protection (in Danish: Databeskyttelsesforordningen og Databeskyttelsesloven). It is the responsibility of the primary investigator (Lone Galmstrup Madsen) to ensure that handling of personal data will comply with the law of data protection. Baseline information and the informed consent will be handled in paper form at Novavi Køge, and Roskilde where it will be locked safely in a room, where Tine Lunding Bergenhagen (the manager of Novavi Køge) or Tina Skoubo Jensen (the manager of Novavi Roskilde) have access. Afterwards, the baseline information and informed consent will be transferred safely to Medicinsk afdeling, Køge, where the baseline information will be entered into the REDCap (Reserch ELectronic Data Capture) to store the research data safely. The remaining documents in paper form - the informed consent and the trial master file including patient ID list - will always be locked safely in a room where only the researchers and Tine Lunding Bergenhagen (Køge) and Tina Skoubo Jensen (Roskilde) have access.

11 Economy

We, the researchers, have initiated the research project, no companies or institutions have initiated the project and there are no financial or marketing interests associated with the project.

Gro Askgaard, Sjællands Universitetshospital, received funding from ”Den fællesregionale pujle til forskning I forebyggelse (1.198.000 kr.), Fonden Novavi (900.000 kr.) and the Novo Nordisk Foundation (2.998.000 kr.). This funding will cover salary for researchers, project nurse, administrator and pay for analyses of blood samples. The funders have no role in research design or decision to publish. Moreover, the researchers in this project have no commitments to the funders.

12 Economic compensation to participants

Some participants in the study will have their documented transportation expenses covered for up to 200 Danish kr for their visit to Sjællands Universitetshospital Køge . The researchers will make a judgement according to the physical condition and economic situation of the study participant. This judgement will follow the principles of economic compensation given to hospital patients in routine hospital care – it can be given if patients are not able to transport themselves. This means that not all study participants will be offered economic compensation of transportation expenses. The requirements of Appendix 1 from VEK are fulfilled.

13 Recruitment of participants and procedure for obtaining informed consent

The recruitment and oral and written information will be conducted by the staff at the specialized alcohol treatment centers (Novavi Køge and Roskilde). All consecutive individuals attending treatment for alcohol use disorders will be screened for eligibility. Potential participants have the opportunity to contact the researchers for more information about the study, as written in the

recruitment material. We have made a written agreement ("samarbejdsaftale") that both Novavi and Medicinsk Afdeling, SUH Køge have signed. The written agreement includes a statement of which persons at Novavi Køge and Roskilde that will give the oral and written information about the study, obtain the informed consent, and sign that information about the study was provided to the study participant.

The Chief physician at the specialized alcohol treatment center organization (Novavi) is a member of the research team for this study and have agreed to ensure that study participants will receive the oral and written information about the study. Lone Galmstrup Madsen has the overall responsibility to ensure correct oral and written information of study participants at Novavi Køge and Roskilde. Alcohol therapists at Novavi Køge and Roskilde will screen possible participants among individuals attending treatment for alcohol use disorders at Novavi Køge and Roskilde and will do a screeningslog. Written information about the study will be found in Novavi Køge and Roskilde displayed so everyone can see it, and it can be sent by email after agreement with the individual in attending treatment for alcohol use disorders. Alcohol therapists and physicians at the alcohol treatment center will inform potential participants about the study. Physicians and alcohol therapists at the Novavi alcohol treatment center will obtain the oral and written informed consent for study participation. Participants will get oral information about the study in a quiet room. Participants will be invited to bring a relative with them when they receive the oral information about the study. When they are informed oral and written, they will sign an informed consent either immediately or after reflection time. The length of the reflection time is until the study stop for recruitment. The participant will sign an informed consent, where the participant agrees to participate in the study.

14 Publication of results

Results will be published no matter positive, negative, or inconclusive via www.clinicaltrials.gov, and to the research community through one or more papers in peer-reviewed scientific journals, and at conferences. We will present and discuss our results with alcohol therapists and administrators by attending the National alcohol conference (Den Nationale Alkohol Konference). The organization of Alcohol and Society will help us communicate the results to individuals with alcohol problems, their relatives, alcohol workers, and politicians through their magazines, webpage, and "viden om alcohol": https://alkohologsamfund.dk/viden-om-alkohol.

15 Ethics

The study does not involve more harm to participants than a routine outpatient hospital visit does. However, the liver stiffness measurement, like other screening examinations, potentially cause psychological distress for up to 4 weeks.[33] Moreover, we don't know yet if a liver stiffness measurement with a result indicating low risk of liver disease could motivate continuing alcohol consumption. For the individual participant there may be some benefits of participating such as diagnostic testing and patient empowerment, since many patients with alcohol use disorders feel neglected by the healthcare system.[19] The increased awareness on alcohol may motivate alcohol abstinence. Participants of this research project will be covered by Patienterstatningen, since they will be followed by the department until the evaluation of liver disease has been performed.

16 Participating institutions

Novavi Køge: Place for screening, inclusion and randomization of participants.

Novavi Roskilde: Place for screening, inclusion and randomization of participants.

Medicinsk afdeling, Sjællands Universitetshospital Køge: Sponsor of the study together with Lever-, Mave og Tarmsygdomme, Aarhus Universitets Hospital. Place for intervention and follow-up of participants.

Lever-, Mave og Tarmsygdomme, Aarhus Universitetshospital: Expertise in clinical research, data management, and statistical analysis.

Center for Klinisk forskning og forebyggelse: Expertise in randomized controlled studies.

17 Collaborators

Lone Galmstrup Madsen (overordnet forsøgsansvarlig): Work fulltime as a Clinical specialist of liver diseases and chief physician at the Medicinsk afdeling, Sjællands Universitets hospital Køge. Research experience within clinical research. Will contribute to research design, inclusion of patients, and manuscript writing.

Gro Askgaard (primary investigator): Work part-time as researcher (post.doc) and part-time as a medical doctor. Has experience with research into alcohol and liver disease and the collection of clinical data. Contributed with systematic reviews and manuscript drafting for the national guideline on alcohol treatment.

Role: Principal investigator of the project. Carry the overall responsibility for completing the studies, the data-analysis, and manuscript writing.

Peter Jepsen: Work part-time as a senior researcher (professor) and part-time as a clinical specialist in hepatology. Research experience within epidemiology and clinical epidemiology.

Role: Overall responsibility of the research design and methodology. Will supervise data-analysis and manuscript writing.

Signe Wegmann During: Chief Physician at Novavi, post.doc and experience with research into alcohol and psychiatric diseases. Role: supervise the planning and conduct of the study.

Janne Petersen: Chief statistician at Center for Klinisk forksning og forebyggelse. Role: will supervise the statistical analysis of study data.

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