

STUDY PROTOCOL

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# Physical exercise as a supplement to outpatient treatment of alcohol use disorders – a randomized controlled trial

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## Abstract

**Background:** Alcohol use disorder is a widespread problem in Denmark and has severe impacts on health and quality of life of each individual. The clinical treatment of alcohol use disorder involves evidence-based knowledge on medical treatment, physical training, and psychological management. The aim of this study is to investigate the effect of physical exercise on alcohol intake, cardio-respiratory fitness and socio-psychological outcomes.

**Methods/design:** The study is a randomized controlled trial with three arms: (A) Standard treatment alone, (B) Standard treatment and physical exercise in groups, or (C) Standard treatment and physical exercise on an individual basis. The patients will fill a questionnaire and they will be tested at baseline, and after 6 and 12 months.

**Discussion:** If this study detects a positive relationship between exercise as a supplement to alcohol treatment and patients' alcohol intake, quality of life, fitness, well-being, anxiety, depression and interpersonal problems, it will be recommended to implement exercise as an offer to users of the outpatient clinic in the future.

**Trial registration:** Current Controlled Trials ISRCTN74889852.

## Background

In Denmark, alcohol leads to at least 3,000 potentially preventable deaths annually, representing 5.2% of total deaths. Furthermore, alcohol contributes to a large number of contacts with the health care system (Juel et al, 2006).

The vast majority of services offered to patients suffering from alcohol use disorders are publicly funded. Those who seek treatment represent dependent drinkers. The duration of the alcohol problem is on average ten years at the time of initial contact to the treatment system (Sogaard Nielsen et al. 2006).

Evidence-based treatment of alcohol dependence includes different psychological interventions and pharmacological treatment (National Institute for Health & Excellence 2001). The outcome of current alcohol treatment is modest (Cutler & Fishbain, 2005); relapse in the first year after treatment ranges between 60 and 90% (Miller and Willbourne 2002). There is a strong need for

developing interventions that can increase the effectiveness of treatment.

Methods that foster healthy lifestyle changes are likely to contribute to the long-term maintenance of recovery of alcohol abuse. Interventions targeting physical activity in particular, may be especially valuable as adjunct to alcohol treatment.

Physical exercise is known to produce health-related benefits for different target groups (Pedersen & Saltin, 2006), for example improved fitness or weight control (Chaput et al., 2011; Cornellisen & Fagard, 2005). For substance abuse, exercise is a quite new and promising treatment option (Moore and Werch 2005). Physical exercise can be used both as early prevention, and as part of a continuous treatment process (Collingwood et al. 2000; Biddle & Mutrie, 2005).

With regard to alcohol abusers, several mechanisms can be pointed out. Exercise, especially moderate exercise (Monti et al., 2000), can decrease the *urge* to drink. Exercise may offer positive alternatives to alcohol by triggering *pleasurable states*, for example through *dopaminergic reinforcement* (Read & Brown, 2003). Exercise also improves psychosocial outcomes in the areas

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of *mood management* (Lane & Lovejoy, 2005) and reduces *depression* and *anxiety* (Martinsen, 2008; Babyak et al., 2000; DiLorenzo et al., 1999). In addition, resilience factors such as individual and *social resources* (for example self-confidence) are strengthened by regular physical activity, especially as group activity (Brown et al., 2009; Read & Brown, 2003).

Despite the potential benefits of exercise interventions, only few studies have tested the impact of exercise as an adjunct to alcohol treatment (Trivedi et al., 2011; Murphy et al., 1986; Sinyor et al., 1982; Brown et al., 2009). Findings from the studies support a positive relationship between physical exercise and drinking outcome. However, most of the studies suffer from methodological limitations such as small sample sizes or high dropout.

The overall purpose of the present study is to evaluate the effect of adding exercise to treatment of outpatients with alcohol use disorder.

#### **Aim and hypothesis**

The specific objectives of this study are to examine whether physical activity done alone or in groups as an adjunct to outpatient alcohol treatment has an effect on:

1. Alcohol intake 6 months and 12 months after initiation treatment
2. Patients wellbeing, fitness, anxiety, depression and interpersonal problems

We hypothesize that physical exercise with moderate intensity yields significant clinical improvements.

#### **Methods/design**

The study is a randomized controlled study with three arms: (A) Patients allocated to treatment as usual (B) Patients allocated to treatment as usual + physical exercise in groups, and (C) Patients allocated to treatment as usual + individual exercise.

#### **Participants**

300 consecutive patients entering the alcohol outpatient clinic in Odense and suffering from alcohol use disorder, abuse or dependence according to DSM-IV-TR are enrolled in the study if they meet the following inclusion criteria: Age between 18 and 60 years, Native Danish speaking, have no severe psychosis or cognitive impairment, have no severe physical disabilities or medical problems and accept participating in the study. All new patients who start psychosocial treatment at the alcohol outpatient clinic in Odense will be referred to a research assistant, who will give oral and written information about the study.

If the research assistant has any doubt whether the patients fulfil the inclusion criteria, she will refer them to

one of the outpatient clinics psychiatrists who – according to a clinical evaluation – will decide if they fulfil the inclusion and exclusion criteria. Patients who refuse to participate in the study will not be asked to give a reason. The patients are informed, before the meeting to take a family member by the information meeting about the project.

When patients wish to participate, the research assistant performs a baseline interview in accordance with the evaluation instruments. After the patients have provided a written and an oral consent the baseline interview is carried out. Then the patients are randomized to (A) Treatment as usual (B) Treatment as usual and physical exercise in groups, or (C) Treatment as usual and physical exercise alone.

#### **Randomization**

Patients are randomized by block randomization by the Institute of Public Health, University of Southern Denmark. The research team is not blinded to which intervention the patients receive. However, they do not know the outcome of the randomization in advance.

A case report form for each participant will be prepared, and labelled only with the participant number. Consent and identification list with number will be stored in a locked cabinet out of reach for the research group. The two intervention groups will be coded, for example, “x” and “y”, throughout the analysis phase and when drawing the conclusions.

#### **Interventions**

Treatment as usual (TAU): All patients will receive the normal outpatient treatment for alcohol use disorder at the clinic. Treatment is carried out by an interdisciplinary team of nurses, psychiatrists and social work professionals (Nielsen et al., 2000). On submission, the patient may receive treatment for withdrawal symptoms. Subsequently, the clinical staff, using the Addiction Severity Index (ASI) (McLellan et al, 1980), carries out a screening interview. The attached psychiatrists make assignment to the individual treatment offer. The assignment is based on results of ASI and the psychiatrists' experience as to which patients will benefit the most from the various treatment offers.

Current treatment offers include family therapy, cognitive behavioural therapy, contract therapy and supportive consultations. After psychiatric evaluation, the patient may be offered pharmacological treatment consisting of Disulfiram, Naltrexone, Acamprosate or antidepressant medication. (Nielsen and Nielsen 2001).

The duration of the TAU and the frequency of sessions follow the usual guidelines for outpatient alcohol treatment in Denmark. The therapists are well educated and have received training in the treatment methods that

they offer. Frequent staff supervision takes place. For all treatment modalities, clinical guidelines are available.

### Physical exercise

Patients in the two intervention groups will receive physical exercise and the outpatient treatment as described above (treatment as usual). The exercise training will be accomplished in cooperation with the Institute of Sports Science and Clinical Biomechanics in cooperation with the Department of Psychology at the University of Southern Denmark.

The distinction into individual and group exercise is chosen in order to investigate compliance to the treatment. The heart-rate monitors with USB sticks allow for every patient to transmit running distance and time directly to the computer system.

Patients in the intervention groups will follow a 24-week programme, either alone or in a training group. The exercise involves brisk walking or running. After a ramp-up period of two weeks with only 30 minutes training sessions to minimize the risk of injury, the exercise sessions increase to two one hour exercise training sessions per week for a period of ten weeks. The walking or running ramp-up period consists of 25 min brisk walking including a number of 30 s running intervals all depending on individual fitness level. The duration of the running or walking intervals increases each week as the participants improve their fitness level. The intensity also increases to reach 45 min with 3–5 min running/brisk walking intervals (Heart Rate (HR) corresponding to 80–90% of HR<sub>max</sub>) and 1 min rest (moderate walking HR increase by 50–60%). All patients are requested to use heart rate monitors during exercising with USB sticks to monitor, measure and transmit heart rate and running distance directly into the computer system.

### Exercise alone

Patients will receive an individual program and running instructions during two individual sessions prior to start after first testing. These sessions will be followed up by two more sessions, after 4 weeks and 12 weeks, respectively.

### Exercise in groups

Patients will receive an individual program and running instructions depending on their level of experience. They will exercise in a group with an exercise frequency during the first 12 weeks of 2 hours per week (including a ramp-up period of two weeks), followed by 12 weeks with a supervised training frequency of one hour per week. The patients are asked to exercise at least twice a week and to continue on their own upon completion of the supervised exercise programme.

### Exercise safety

Prior to each exercise session, participants will sit undisturbed for 5 minutes before assessment of their resting HR and blood pressure (BP). If a participant's resting HR is  $\geq 100$ , it will be re-measured after an additional 5-minute rest period. If a participant's resting HR remains  $\geq 100$ , the exercise session will be rescheduled for another day. Likewise, if a participant's resting BP is  $\geq 160/100$ , it will be re-measured after an additional 5-minute rest period. If a participant's resting BP remains  $\geq 160/100$ , the exercise session will be rescheduled for another day. Guidelines are also presented for referral to appropriate medical care and additional physician clearance based on blood pressure readings.

### Evaluation instruments

Evaluation instruments applied in the study are:

*The Addiction Severity Index (ASI)* provides a multidimensional image of the patient's situation within the last month before the interview. The interview concentrates on the following seven areas in the patient's life: medicine, employment, alcohol, drug, legal status, family/social network, and psychiatric health. ASI contains two different scores: the interviewer score and the composite score. The scores give a mathematical estimate of each problem area based on symptoms within the 30-day period preceding the interview. Each composite score consists of the sum of various questions from the ASI. Final scores are reported as 0 to 1, where 0 denotes no problems and 1 denotes severe problems.

*The time-line-follow-back method (TLFB)* is used to describe alcohol-free days as well as number of drinks per day. By use of TLFB patients describe the daily number of standard drinks 30 days before the basic interview and 30 days before the 6 and 12-month follow-up interview.

### Cardio respiratory fitness

The Bruce treadmill protocol (Bruce et al. 1963) is used. According to the protocol, the subjects walk/run on a treadmill until exhaustion. The speed (2,7 km/h, 4,0 km/h, 5,5 km/h, 6,8 km/h) and grade (10%, 12%, 14%, 16%) increase every 3 minutes. Oxygen uptake is measured online with a metabolic unit (Amis2001, Innovision, Odense, DK), and the heart rate by a heart rate monitor (Polar Sportstester, Finland). Blood lactate concentration is measured 2 min after the completion of the test by a Lactate Pro (LP, Arkrey KDK, Japan) and a Borg scale (1–20) to express the subjective exhaustion. The maximal oxygen uptake (VO<sub>2max</sub>) is taken as the highest value over 30 sec periods during the last part of the test.

To avoid discomfort with the testing a standardised written and oral information is applied.

### **Physical activity**

- 1) Prior to treatment: The level of physical activity is assessed using the International Physical Activity Questionnaire (IPAQ), a 27-item self-completion questionnaire. It measures activities taken in each of the four domains: leisure-time physical activity; domestic and gardening activities; work-related physical activity and transport-related physical activity.
- 2) During treatment: HR monitors will measure the physical activity with possibility for valid registration of activity.

*Well-being* is assessed by EuroQuol-5D (EQ-5D), a standardized instrument for use as a measure of health outcome, functioning and health status.

*Anxiety and depression*: is assessed by Common Mental Disorders – Screening Questionnaire (CMD-SQ) consisting of 34 items in validated subscales (SCL-SOM, Whiteley-7, SCL-ANX-4, SCL-8, SCL-DEF-6) measuring anxiety, depression, use of alcohol, and somatisation. The patients respond on a five point Likert scale. A normal score is  $\leq 4$  in somatisation (SCL-SOM) and 0 in the other scales.

*Interpersonal problems*: are assessed by the IIP (Inventory of Interpersonal Problems). The measurement of interpersonal problems allows a differentiation of interpersonal and non-interpersonal sources of distress (e.g. depressed mood, anxiety). The IIP (short form) consists of 64 items scored on eight scales. The scales include areas that may be hard for a person and areas that indicate things a person may do too much. The eight scales (domineering, vindictive, cold, socially avoidant, non-assertive, exploitable, overly nurturing and intrusive) are scored on a five-point scale.

At the 12-month follow-up interview, information regarding treatment is recorded – in addition to the evaluation instruments mentioned above. Disclosure of case notes describes number of treatment sessions, discontinuation of treatment and treatment period.

### **Outcomes**

#### **Primary outcome**

The primary endpoint analysis (6 months) will be a comparison of outcomes for patients assigned to TAU (A) versus the combined physical exercise experimental groups TAU and group exercise (B) and TAU and individual exercise (C). The outcome will be measured by the proportion of patients with sensible drinking according to the limits by the Danish National Board of Health (Sensible drinking is defined as drinking maximum 14/21 drinks/week

among women/men, one drink contain 12 grams of pure alcohol). The primary outcome will be in the intention to treat group using last observation carried forward.

#### **Secondary outcome**

1. 12 months analysis
2. The health status
3. The percent of patient with reduced depression, anxiety and interpersonal problems
4. Maximum oxygen uptake

For each outcome goal, two analyses will be carried out:

1. Intention-to-treat analyses will be carried out for all patients, irrespective of whether they completed the interventions or were re-interviewed. With regard to incomplete data, “last observation carried forward” and multiple imputations will be used.
2. Completer (on-treatment) analyses will be carried out for patients who completed the interventions.

In addition, non-completer (on-treatment) analysis will be carried out by interviews. These will be mentioned as drop-out interviews, as participants who drop-out of the study will continue the treatment at the alcohol out-patient clinic.

#### **Sample size and statistical analyses**

To our knowledge no similar studies have been conducted. Therefore, the power calculation is estimated from quality assurance data and research data of the participating alcohol clinic in Odense. Currently 65% of the patients have sensible drinking 6 months after starting treatment with the current treatment regime (Data from Alkoholbehandlingen i Odense, 2011).

In this study we compare both TAU (A) with TAU and group running (B) and TAU (A) versus TAU and individual running (C). A sample of 100 patients in each group is needed to have 90% power of detecting a difference corresponding to an improvement of 18 percentage points using a 5% level of statistical significance. Since the two primary endpoints are the comparison of each of the additional exercise groups to the regular TAU treatment, the sample size is relevant for all three treatment-arms. Should the data subsequently show that individual and group exercises are comparable then the total power will be increased.

The data will be analysed by a logistic regression model to model the proportion of patients with sensible drinking. The logistic regression modelling allows for inclusion of additional confounders. A backward elimination strategy will be employed to identify significant

explanatory variables, using a significance level of 0.05. Generally, two-sided alternative will be considered except when comparing TAU and physical exercise to TAU without physical exercise, where a one-side alternative is used. Explanatory variables considered will include age, gender, as well as other relevant variables available.

### Ethics statements

The study is presented and approved of The Regional Scientific Ethical Committee for Southern Denmark (J.nr. S-20130031) and the Danish Data Protection Agency. All procedures in the study are in accordance with the second Declaration of Helsinki.

### Discussion

The specific objectives of this study are to examine whether physical activity done alone or in groups as an adjunct to outpatient alcohol treatment has an effect on alcohol intake 6 months and 12 months after initiation treatment and patients wellbeing, fitness, anxiety, depression and interpersonal problems.

Only few studies have tested the impact of exercise as an adjunct to alcohol treatment (Trivedi et al., 2011; Murphy et al., 1986; Sinyor et al., 1982; Brown et al., 2009). Findings from these studies support a positive relationship between physical exercise and drinking outcome. However, most of the studies suffer from methodological limitations such as small sample sizes or high dropout.

The first challenge that this study faces is the number of participants required. If it shows to be difficult to recruit all 300 participants from the outpatient clinic in Odense during the specific time of inclusion, we have two alternatives. One is to prolong the inclusion time; another is to include participants from two more outpatient clinics in the region of Southern Denmark (Svendborg and Aabenraa) to the study. Due to the power calculation and the high dropout experiences from earlier studies, it is necessary to include all 300 patients in the study.

Drop out is a well-known risk in studies that test the impact of exercise as a supplement to alcohol treatment (Murphy et al., 1986; Sinyor et al., 1982; Brown et al., 2009). To avoid this risk we have to put some effort in motivating the participants during the whole study. There might be a possibility that exercise itself will become a motivator for the participants, because they experience physical benefits such as fitness. They also may feel some psychological benefits of physical activity, as for example improved mood or reduced depression and anxiety which some earlier studies have shown (Martinsen, 2008; Lane and Lovejoy 2005; Biddle and Mutrie 2005; Babyak et al., 2000; DiLorenzo et al., 1999).

We hypothesize that physical exercise with moderate intensity yields significant clinical improvements. If this study detects a positive relationship between exercise as

a supplement to alcohol treatment and patients' alcohol intake, fitness, well-being, anxiety, depression and interpersonal problems, it will be relevant to recommend implementation of exercise as an offer to users of the outpatient clinic in the future.

### Abbreviations

DSM-IV-TR: Diagnostic and statistical manual of mental disorders-fourth edition (Text Revision); TAU: Treatment as usual; HRmax: Maximum heart rate; ASI: Addiction severity index; TLFB: Time-line-follow-back;  $VO_{2max}$ : Maximal oxygen uptake; IPAQ: International physical activity questionnaire; EQ-5D: EuroQuol-5D, A standardized instrument for use as a measure of health outcome, functioning and health status; CMD-SQ: Common mental disorders – screening questionnaire; SCL-SOM: Symptom check list, somatization subscale; Whiteley-7: A rating scale for illness worry and conviction; SCL-ANX-4: Symptom check list, subscale for anxiety; SCL-8: Symptom check list, subscale for mental illness; SCL-DEF-6: Symptom check list, depression subscale; IIP: Inventory of interpersonal problems.

### Competing interests

The authors declare that they have no competing interests. This study has received external funding from The Lundbeck Foundation and The Tryg Foundation.

### Authors' contributions

All the authors have contributed to the article, but SS is the main responsible for the article. SS: Data collection, data analysis, drafting of manuscript. KR, AS, BN: Study conception and design. KR, RB: Critical revisions of manuscript for important intellectual content. KR: Obtaining funding. KR: Supervision. All authors read and approved the final manuscript.

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