Physical activity as treatment for alcohol use disorders – FitForChange
Analysis protocol for preregistration

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Statistical Analysis Plan

1. Introduction

This statistical analysis plan will go through the methods that will be used to analyse the primary and secondary outcomes of the drinking outcomes from the FitForChange-study. The plan is based on the published study protocol in Trials, 2018 (1). Analyses related to mental- and physical health outcomes will be specified elsewhere.

Objective and hypotheses

Background**:** Alcohol use disorders (AUD) is one of the most common psychiatric diseases. However, there is a large treatment gap between the number of individuals being affected and the number seeking help for their problems. Stigma associated with traditional treatments and the urge to deal with the problem on one's own are factors preventing help-seeking (2). Physical activity (PA) is a non-stigmatizing treatment option that may help those with AUD to reduce their alcohol consumption (3, 4, 5, 6). Previous trials have focused on aerobic exercise training for AUD. In a pilot study (7) we showed that yoga is a feasible alternative, but no trials have investigated the effects of yoga on alcohol consumption. The FitForChange study is a randomised controlled study evaluating physical activity as stand-alone treatment for alcohol use disorders.

Objective: To investigate the effectiveness of PA as treatment option and to compare three types of interventions; aerobic exercise, yoga exercise and treatment as usual (TAU) regarding reduction of alcohol consumption.

Hypothesis: PA interventions will show greater reduction than TAU regarding alcohol consumption and other alcohol related outcomes.

Key research questions:

1. What are the effects of aerobic and yoga exercise on alcohol consumption in AUD patients?
2. What are the effects of yoga and aerobic exercise on severity of dependence?

2. Measurements

Primary outcome measures:

- Timeline Follow Back (TLFB) self-reported questionnaire, assessing total standard drinks past 30 days (1 drink=12g alcohol).

Secondary outcome measures:

- Frequency of heavy drinking days (for men ≥5 drinks and ≥4 standard drinks for women).
- Days of sobriety.
- Diagnose criteria for alcohol use disorder (DSM-5) assessing severity of dependence.
- Alcohol Use Disorders Identification Test (AUDIT) assessing consumption and harms caused by alcohol use.
- Biomarker Phosphatidylethanol (PEth).
- Biomarker Gamma-glutamyltransferase (Gamma GT)

Exposures:

- Aerobic exercise 3 times a week plus 3 support sessions with a personal trainer (PT) at the gym chain SATS.
- Yoga exercise 3 times a week plus 3 support sessions with a personal trainer (PT) at the gym chain SATS. In this trial, the yoga intervention was primarily Hatha yoga, with an emphasis on physical postures (see study protocol for details) (1).
- TAU; up to 3 telephone sessions with the national alcohol helpservice 'Alkoholhjälpen' to motivate help seeking in regular treatment.

Baseline characteristics:

Other participant demographic data collected at baseline are: age, sex, source of income, civil status, smoking, Hospital Anxiety and Depression Sale (HADS), perceived health, International Physical Activity Questionnaire (IPAQ), BMI and cardiorespiratory fitness.

3. Follow up and participant flow

Outcome measures will be assessed at 13 weeks post randomisation. Progression through trial regarding number of individuals screened, included, randomised, attrition and completed outcomes will be presented according to CONSORT flow diagram (8).

4. Statistical analysis

Due to covid-19, study closed in august 2020 with 140 participants included. A revised power calculation was performed based on results from a recent study by Weinstock et al., 2020 (6). Based on the results of this study we assumed a standardized difference (effect size) yoga exercise and aerobic exercise respectively, versus treatment as usual of around 0.5, calculated on the primary outcome (alcohol consumption) at the 12 week follow up. To accomplish 80 % power, at a significance level of 0.05 we needed to enroll 123 participants in the study (i.e. 41 in each group: treatment as usual, yoga, aerobic exercise). Power calculation was performed using G*Power version 3.1.

4.1 *Descriptive analyses*

Baseline characteristics and baseline outcomes in the three groups; TAU, aerobic and yoga will be presented, using Analysis of variance for continuous variables and chi square test for categorical variables. If significant differences between groups this will be discussed and taken in consideration before the inferential analysis. All analyses will be undertaken using SPSS v.25.

4.2 *Inferential analysis*

Inferential analysis will compare the effect of the three interventions on alcohol consumption and other alcohol related outcomes.

Definition of comparison groups:

Intention to treat (ITT), complete case analyses at 13 weeks according to randomised allocation.

Per protocol (PP), complete case analysis will include those randomised to exercise training and exercising minimum 12 times during the intervention period (12 weeks) and those in TAU having a minimum of one contact with Alcohol helpline and have not registered any exercise during the intervention period.

Intention to treat (ITT) imputed, all participants according to randomised allocation.

Primary analysis

Analysis of covariance (ANCOVA) will be used to compare primary and secondary outcomes between groups, according to intention to treat (defined above) and adjusting for baseline outcome values. Age and gender will be analysed by group to assess potential differences on the primary outcome; alcohol consumption.

Secondary analysis

To examine the impact of adherence the secondary analysis will include the per protocol analysis (defined above). Also, in the event of data missing at random (MAR) a secondary intention to treat imputed analysis will be performed. Analysis of covariance (ANCOVA) will be used for all secondary analyses.

4.3 Data cleaning and Missing data

Data will be collected in paper form through participants case report file and thereafter entered manually in the data base (SPSS). Variables and values falling outside the expected range (outliners) will be identified and double checked with the raw data and corrected if not accurate.

If data is missing due to item non-response (1-2 items on a questionnaire), single imputation method by using the individuals mean or median will be used, if not stated different in the description of the specific questionnaire.

Missing data will be defined as absence of data on participants due to drop out or loss to follow up at the 13 weeks follow up for one or more outcomes. A comparison of baseline characteristics of completers and non-completers will be performed. In addition, Little's missing completely at random (MCAR) test will investigate the reason of missingness on the primary and secondary outcomes. If missingness is found to be Missing at random (MAR) or Missing non at random (MNAR) missing values will be replaced by using the multiple imputation method. Complete case ITT is considered valid if missingness is found to be missing completely at random (MCAR).

4.4 Adverse events

Adverse events will be listed, described by group and details of the event will be presented.

5. Data presentation

Within group mean differences and 95% confidence intervals will be analysed using paired t-statistics. P-values will be adjusted for multiple testing. Between group results will be reported with F-statistics. If significant differences, post hoc tests will be performed to identify which mean differences are statistically significant and estimated effect sizes will be presented with partial eta square. Threshold for significant effects will be set at $P<0.05$. The ITT analysis on the primary outcome will be performed prior to other analyses.

6. Model validating

Data will be checked to fit the assumptions of chosen statistical models.

References

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