

Cardiopulmonary and muscular effects of different doses of high-intensity physical training in substance use disorder patients: study protocol for a block allocated controlled endurance and strength training trial in an inpatient setting

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ABSTRACT

Introduction Patients with substance use disorder (SUD) have high prevalence of lifestyle-related comorbidities. Physical exercise is known to yield substantial prophylactic impact on disease and premature mortality, and there seems to be an inverse association between physical fitness and adverse health outcomes. High-intensity training is regarded as most effective for improving physical fitness, but less is known concerning the ideal training dose necessary to achieve clinically relevant effects in these patients. The aim of this study is to compare the effect of low-dose and high-dose, high-intensity training, on physical fitness in patients diagnosed with SUD.

Methods and analysis This study will recruit 40 inpatients of mixed genders, aged 18–70 years. Participants will be block allocated to low-dose or high-dose training, encompassing 24 high-intensity interval and maximal strength training sessions (3/week × 8 weeks). After a 10 min warm-up, the low-dose group will perform 1×4 min intervals at ~90% of maximal heart rate and 2×4 repetitions strength training at ~90% of 1 repetition maximum. The high-dose group will perform 4×4 min intervals at ~90% of maximal heart rate and 4×4 repetitions strength training at ~90% of 1 repetition maximum. Clinical measurements and physical tests will be conducted at baseline, midway and on completion and a questionnaire on physical activity will be administered at baseline.

Ethics and dissemination This protocol is in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement. All participants will sign a written informed consent. The Regional Committee of Medical Research Ethics, Norway has approved the study. A study of this kind is warranted, and the results will be published in an open access journal to ensure public access, and presented at national and international conferences.

Trial registration number NCT04065334.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This will be the first controlled trial aiming to optimise training dose for improving physical fitness in substance use disorder patients.
- ⇒ We apply evidence-based effective interventions, carefully supervised and accurately intensity monitored.
- ⇒ The intervention and testing is colocated with the in-patients in our clinic, which can strengthen recruitment, compliance and feasibility, and reduce the burden on the patients.
- ⇒ The low sample size complicates stratification for subgroup analysis.
- ⇒ The study uses block allocation of study groups instead of traditional randomisation procedure.

BACKGROUND

Substance use disorder (SUD) is a collective term encompassing detrimental use of substances,¹ including, but not limited to illicit drugs. SUD has consistently demonstrated to have debilitating impact on both somatic- and mental health.² At present, there is no consensus of a precise definition of SUD, largely attributed the complexity of the illness. International Classification of Diseases 10th Edition (ICD-10) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders 4th Edition) are two comparatively similar classification systems, with a widespread use of the former in Europe (eg, the Norwegian health system) and other parts of the world, whereas the latter is used in the USA.¹ However, judicious use is imperative since there exist diverging diagnostic criteria.

The ICD-10 system subclassifies SUD as F10-19: Mental and behavioural disorders due to psychoactive substance use, with the simultaneous presence of ≥ 3 ICD-10 criteria for the duration of a 12 months period as a precondition for a SUD diagnosis (WHO's classification 1992).³

Findings suggest a substantial number of people with SUD lead a sedentary lifestyle,⁴ and consequently being insufficiently physically active.⁵ Epidemiological studies signal a general inverse relationship between level of physical activity and severity of SUD.⁶ This is supported by previous results from our group, demonstrating distinctly lower cardiorespiratory fitness (CRF) and muscular strength among patients with SUD,⁷ compared with age-matched healthy controls.^{8,9} Their physical fitness is consistent with being 20–40 years older than their actual age.^{9,10} Such a poor physical fitness status heralds an increased risk of adverse health effects and premature death.^{11–14} This is in line with patients with SUD exhibiting an increased occurrence of lifestyle-related diseases (ie, diabetes, hypertension and cardiovascular disease and some types of cancer).^{4,15–17} Moreover, having SUD is associated with a 15–30 years shorter life expectancy compared with the general population, attributed to poor mental and somatic health in addition to psychosocial comorbidities.^{4,17,18} It is noteworthy that premature mortality is commonly caused by lifestyle-related diseases. Among the youngest (15–24 years), suicide and accidents are common causes of death, whereas cardiovascular disease and cancer constitute the predominant causes of death among the older (≥ 55 years).¹⁷

Connection between ill health, mortality and physical fitness

A plethora of epidemiological studies, provide unequivocal evidence in support of an apparent link between physical activity and positive health outcomes. Contemporary findings, published over the last three decades, offer a consistent indication of a robust inverse association between CRF and lifestyle-related diseases such as certain types of cancer,^{19–22} cardiovascular disease,^{23–28} hypertension,^{29,30} type II diabetes,^{31,32} metabolic syndrome^{33–36} and all-cause mortality.^{11,12,23,37–42} Maximal CRF is commonly and more accurately measured and labelled as maximal oxygen uptake ($VO_{2\max}$), which is defined as the maximal ability, or highest rate at which oxygen can be transported by the cardiovascular and respiratory system, and used by the tissues. Reaching $VO_{2\max}$ requires vigorous exercise using large muscle mass.^{43–45} CRF will in the following be referred to as $VO_{2\max}$.

More recently, salient findings also identify functional muscular strength as a prominent predictor of physical health. Muscular strength is inversely linked to the prevalence of somatic illness such as cancer,¹⁴ cardiovascular disease,^{46,47} type II diabetes,⁴⁸ impaired skeletal health⁴⁹ and being an independent predictor of all-cause mortality.^{13,47,50,51} Muscular strength is typically measured as 1-repetition maximum (1RM) in a defined concentric task, which denotes the highest possible force or torque generated in one muscle contraction. Also, muscular

strength is commonly measured using large muscle mass with dynamic movement patterns (eg, bench press or leg press), but single joint movements (eg, arm flexion or knee extension) or static contractions (eg, hand grip) are also used.^{13,14,46–48,50,51}

High-intensity physical training

Physical endurance and strength training at higher intensities are shown to elicit larger increases in $VO_{2\max}$ and 1RM than low-intensity or moderate-intensity training, in both healthy and patient populations.^{36,52–58} High-intensity physical training denotes endurance and strength workloads of 85%–95% of maximum heart rate (HR_{\max}) and 85%–90% of 1RM, respectively.

Limitations to existing research

SUD treatment clinics have used physical activity and/or physical exercise for more than four decades.⁵⁹ Nonetheless, there are still apparent limitations in existing research regarding physical training in patients with SUD, as well as implementation of scientific results into standard care. Despite existing evidence in support of the health promoting effect of physical training aiming to boost $VO_{2\max}$ and 1RM in functional muscle groups,^{12,14,23,36,47,51,58} it is not sufficiently appreciated in conventional SUD treatment.⁶⁰

With few exceptions, there is a general paucity of research deploying high-intensity physical training in the field of SUD. Generally, physical activity has been offered as an adjunctive treatment, but suffer from insufficient adherence and high attrition rates.^{6,61} Additionally, the physical activity used in clinical settings seems unstructured and random,⁶⁰ and does neither tax the aerobic nor the neuromuscular system sufficiently to elicit clinically relevant improvements in physical fitness. Of interest, previous research from our clinic,^{60,62} using high-intensity physical training in patients with SUD, resulted in large improvements in both $VO_{2\max}$ and 1RM in functional muscle groups, restoring their physical fitness level to that of age-matched healthy controls after 8 weeks of training. The high-intensity training intervention consisted of treadmill training with four intervals of 4 min at 90%–95% of $VO_{2\max}$, and hack squat with four series of four repetitions at 85%–90% of 1RM.

Research question

While the most effective training intensity for optimal improvement of physical fitness is well established (ie, 90%–95% of HR_{\max} and 85%–90% of 1RM), less is known about the ideal training volume and total workload per session (ie, number of bouts and sets) needed to obtain clinically relevant effects in many patient groups.

Sedentary people, typically characterised by exhibiting lower levels of physical fitness, may experience substantial improvements in physical fitness (ie, $VO_{2\max}$ and 1RM) during the initial part of a training intervention, even with relatively low workloads.⁶³ One study reported similar improvements in $VO_{2\max}$ in two moderately

trained healthy cohorts, performing high-dose (HD) (four bouts \times 4 min at 90% of HR_{max}) and low-dose (LD) (one bout \times 4 min at 90% of HR_{max}) high-intensity endurance training, respectively.⁶⁴ Considering these findings, and that patients with SUD generally display a poor physical fitness, it seems reasonable to expect a low workload to produce similar augmentations in physical fitness as a high workload over the course of a training intervention.

Objectives and hypothesis

The purpose of this study is to compare two different physical training interventions, both using a high-intensity training modality. The primary aim is to compare the effects of HD training with LD training on VO_{2max} and lower extremity 1RM in patients with SUD. We hypothesise that LD and HD physical training will elicit similar improvements in VO_{2max} and 1RM. Primary outcomes are VO_{2max} and 1RM following high intensity physical training.

METHODS AND ANALYSES

Study design

This clinical study is a two-group controlled trial designed to compare the effect of HD and LD training interventions on VO_{2max} and lower extremity 1RM. A block allocated controlled trial design (1:1) will be used to expedite recruitment, with the completion of the HD intervention prior to the LD intervention. This is to avoid discrimination in treatment form among patients in concurrent residential stay at the in-patient clinic, which in our experience may cause conflict and compromise feasibility. It is often challenging to get patients with SUD to participate in physical training to start with. We anticipate low feasibility using parallel recruitment, with potential high dropout in the HD group. Both groups will perform 24 supervised training sessions (three sessions/week) of similar high-intensity endurance and muscular strength training. The intervention group will use LD training and the HD group will function as control group. The LD group will perform 25% and 50% of the endurance and strength training workload, respectively, compared with the controls in the HD group. Also, physical tests will be conducted at three different time points during the trial period. A training compliance of 80% (ie, completing 19 training sessions) is required for inclusion of test data in analysis. On account of the nature of the study (ie, supervised training intervention) no blinding will be implemented. Data will be collected at the three test points, and anonymised and stored in a password-protected computer and in a locked filing cabinet, both located in a restricted office area. Data will be stored for 10 years to allow for follow-up analysis. Data may be subject to quality control by the Norwegian health inspectorate. For information about data contact corresponding author.

Settings and participants

Participants will be patients diagnosed with SUD applying the (ICD-10, F10-F19).³ Men and women aged 18–70

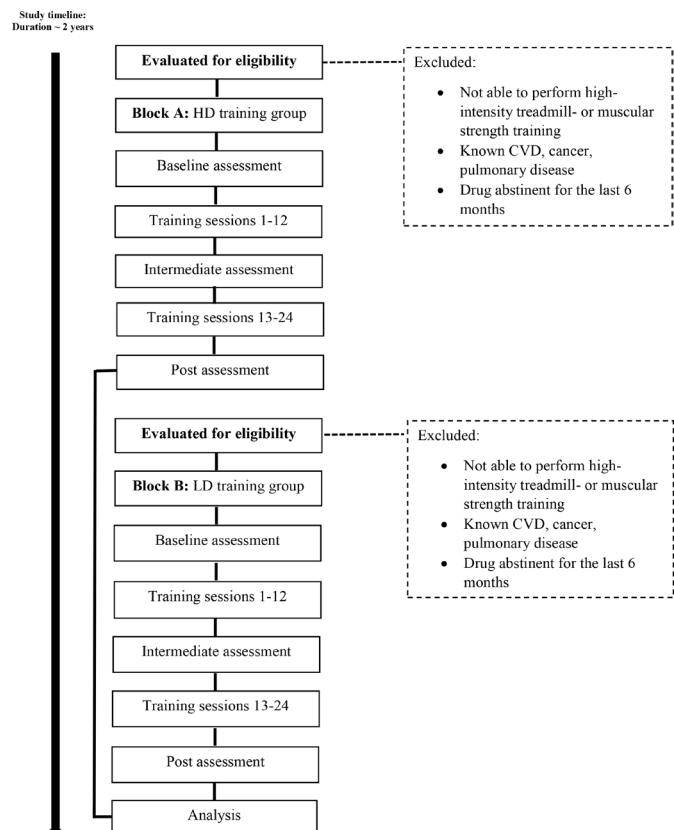


Figure 1 Participant flow chart. CVD, cardiovascular disease; HD training group: high-dose training group; LD training group, low-dose training group.

years will be included. Recruitment will take place in the Clinic of Substance Use and Addiction Medicine, St. Olavs University Hospital, Trondheim, Norway. Participants will be included successively as they are admitted, until intended sample size is cumulated. The duration of the training intervention and testing will be ~10 weeks for each patient (Training: 3/week \times 8 weeks; testing: 2 weeks total for baseline, intermediate and post-tests). However, unforeseen factors could prolong trial duration to enable accumulation of 24 training sessions, but should not exceed 12 weeks. An expected inclusion rate (\times) of $1 \leq x \leq 3$ /monthly admissions, entails a timeframe of approximately 2 years (to include, train and test) to conclude the trial period (figure 1). The time frame is based on a posteriori experience from SUD training interventions,^{60 62} as well as complications regarding COVID-19. Testing and physical training will be executed on site in our laboratory and training clinic. Participation is voluntary and assumes being an in-patient at the clinic. Exclusion criteria are not being able to perform strenuous endurance and strength training, not being able to complete the all-out treadmill and strength tests, having been abstinent from drugs for the last 6 months, as well as having known cancer, cardiovascular or pulmonary disease (figure 1). Research staff will secure informed consent after providing a detailed study description, both oral and written. Recruitment commenced in October 2020 and will conclude in November 2022.

COVID-19

All participants from both study groups are recruited from our in-patient cohorts adhering to the same conditions and restrictions. In-patients are prohibited from leaving the clinic unattended by staff, and all home visitations are cancelled to enforce contagion- and quarantine regulations decreed by St. Olavs University Hospital. Curfew is lifted successively as patients are vaccinated, re-enabling in-patients to leave the clinic and arrange for home visitations. Notably, despite restrictions we are still able to provide identical training treatment as pre COVID-19.

Examinations

Participants will submit to clinical measurements and physical tests at three separate points in time: at baseline, midway and on completion of the training intervention (posttest).

Clinical measurements

We will measure blood pressure (BP) and HR using a SunTech Tango M2 (SunTech Medical, Morrisville, North Carolina, USA)) following a 5 min resting period sitting in an upright position. The BP cuff is fixed on the right arm and positioned at heart level. The average of two successive systolic and diastolic measurements will be used in analysis, as well as an orthostatic measurement after standing up for 1 min. Participants must refrain from smoking, eating and drinking 30 min prior to measurements.

Cardiopulmonary exercise testing

All participants will perform a maximal physical performance cardiopulmonary exercise testing (CPET) on a PPS 55 Med treadmill (Woodway USA, Waukesha, Wisconsin, USA), wearing a HR sensor Polar H7 (Polar Electro Oy, Kempele, Finland) and a properly fitted face-mask (Hans Rudolph, Germany). The face mask connects to a Vyntus CPX with a mixing chamber module (Jaeger, Hoechberg, Germany) recording respiratory kinetics data during task load. Preceding the all-out performance test, participants will undertake a 10 min familiarisation phase during warmup and be encouraged not to grab the treadmill handrails as it will impact the measurements through decreased oxygen cost at a given workload. Workload during warmup will be individually adjusted to evoke a moderately increased HR and minute ventilation (~60%–70% of HR_{\max}). Prior to the CPET, participants will also receive detailed instructions on the test procedure. VO_2 and HR will be measured continuously during the personalised incremental test protocol. During the first phase of the CPET a 5 min submaximal steady state⁶⁵ walking economy (C_r) measurement will be attained at a fixed workload (ie, velocity: 4.5 km/hour, slope inclination: 5%) from all participants. On completion of the first phase there is an immediate transition onto phase two: the all-out performance test. Treadmill velocity will be set based on the participant's anticipated physical fitness and warmup workload, and increased with 1 km/hour every

minute until test completion. The 5% treadmill slope inclination will remain constant throughout the test. The test is terminated when the participant reaches volitional exhaustion. $\text{VO}_{2\max}/\text{peak VO}_2$ ($\text{VO}_{2\max/\text{peak}}$) will be registered as the mean of the three highest successively 10 s VO_2 recordings. $\text{VO}_{2\max}$ is established if the following criteria are met: (1) Demonstration of a plateau in the VO_2 recordings that remain stable despite increased workload. A plateau is viewed as stable if VO_2 does not increase more than 2 mL/kg/min (ie, $\leq 2 \text{ mL/kg/min}$ between any of the three consecutive highest measurements), even if the workload is increased,⁶⁶ (2) Respiratory exchange ratio (R) is >1.05 ,⁶⁷ (3) participant reaching volitional exhaustion (eg, shortness of breath or/and leg fatigue).⁶⁷ HR_{\max} is denoted as adding four beats to the highest recorded HR during the CPET. Attaining HR_{\max} is essential to establish optimal workload during the training intervention.

Although CPET is considered a safe practice, adverse outcomes and complications can occur.⁶⁸ In a review the American Heart Association (AHA) reported that sudden cardiac death, in a mixed population of healthy and high-risk patients, occurred at a rate of 0–5 for every 100 000 tests.⁶⁹ A French study reported one death for every 76 000 tests, based on 458 000 exercise tests.⁷⁰ Including other adverse outcomes (eg, myocardial infarction, ventricular fibrillation and other dysrhythmia) in addition to death, the overall hazard of using CPET, among seemingly healthy and high-risk patients rose to ~6 cardiac events per 10 000 tests.⁷¹ Overall, adverse events are strongly linked to underlying disease.⁶⁸ Even in populations with high risk cardiovascular pathology, CPET is considered safe.⁷² The AHA and the American College of Sports Medicine clearly state that potential adverse health effects caused by vigorous exercise should not be exaggerated, as the health benefits by far outweigh the risks,⁷³ which is further supported by contemporary opinion.⁷⁴ Yet, test staff should be attentive of symptoms indicative of termination of CPET (eg, great dyspnoea, acute chest pain, mental confusion, sudden pallor and loss of coordination).⁶⁸ Trained personnel, with immediate access to defibrillator and medical assistance, conduct CPET and supervise all training sessions.

The Vyntus CPX (Jaeger, Hoechberg, Germany) used for CPET has been evaluated against an iron lung (Metabolic Simulator with mass flow controller, VacuMed, Ventura, California, USA). All parameters were within acceptable range, with the exception of a discrepancy in minute ventilations (V_E) $>180 \text{ L/min}$. A 5.46% error was detected for this ventilation volume, which is higher than the predefined accepted error of 5.0%. However, previous findings demonstrate that patients with SUD rarely, if ever, reach these ventilation volumes (n=44, mean \pm SD of V_E : men 113.6 ± 19.5 , women 77.4 ± 13.7).⁷ Velocity (km/hour) and slope inclination (%) on the PPS 55 Med treadmill (Woodway USA, Waukesha, Wisconsin, USA) will be calibrated prior to testing. In daily operations, the Vyntus CPX will be routinely calibrated prior to the first test of each day. This multistep process consist

Hack squat

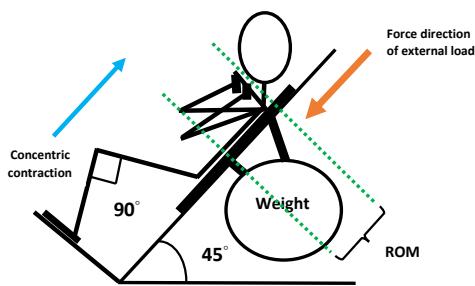


Figure 2: joint angles, range of motion (ROM), movement and force directions (modified from Mosti and colleagues).⁴⁸

Figure 2 Joint angles, range of motion (ROM), movement and force directions (modified figure from Mosti *et al*).⁴⁹

of calibrating the Digital Volume Transducer (DVT) and measuring of a gas mix of known content (15.99% O₂ and 5.00% CO₂ mixed with N₂) and ambient air, with the DVT docked in the parking and calibration position in the Vyntus CPX. Subsequently, the two-point gas calibration will be performed every fifth test. By default, a mandatory volume calibration will be carried out between each test.

Maximal muscular strength test

We will test maximal muscular strength, in the lower extremities, using a hack squat machine (Impulse Fitness IT7006, Impulse (Qingdao) Health Tech, Shandong, China). 1RM concentrically will be measured in a specific range of motion (from an upright position-down to a knee joint angle of 90°, **figure 2**). Warmup will be executed using two sets consisting of five repetitions at 50% of anticipated 1RM and one set of two repetitions at 70% of expected 1RM, followed by a 3 min resting period. The test is started slightly below expected 1RM load, increasing load of 5–10 kg for each new attempt. True 1RM is expected to be established within 6–9 attempts allowing ~3 min to recover between each attempt.⁶² The test is terminated when the participant is not able to complete the lift, and 1RM is determined as the highest successfully achieved lift.

International Physical Activity Questionnaire

Participants will answer the short version of the International Physical Activity Questionnaire (IPAQ) at baseline to determine the level of physical activity, categorised by volume and intensity. The short version is derived from the initial IPAQ,⁷⁵ and was previously tested for reliability and validity in a Norwegian population.⁷⁶

Physical training intervention

All participants will complete three familiarisation training sessions, at moderate intensity, prior to the training intervention.

HD training: control group

Treadmill

The control group will receive training treatment as usual, consisting of ten minutes individualised treadmill warmup followed by four bouts of 4 min of high-intensity treadmill workloads at 90%–95% HR_{max}, reaching ~90% HR_{max} within the first 2 min. Each bout is interspersed by a 3 min active resting period performing at 70% of HR_{max}.⁵⁴ The session will end with a 5 min cool-down period of low-intensity workload. Total treadmill time per session is 40 min.

Hack squat

Following a warmup of two sets at 50% of 1RM, four sets of four repetitions at 90% of 1RM will be performed in a hack squat (from an upright position-down to a knee joint angle of 90°, **figure 2**), with focus on maximal mobilisation in the execution of movement,⁷⁷ interspersed with a ~3 min resting period between sets.⁶²

LD training: intervention group

Treadmill

The LD group follows an identical warmup, training intensity and cool-down procedure as the HD group. However, the LD group performs only one bout of 4 min of high-intensity treadmill workloads per training session. Total treadmill time per session is 19 min.

Hack squat

The LD group follows an identical warmup, training intensity and resting procedure as the HD group. However, the LD group performs only two sets of four repetitions per training session.

When training adaptations, in one or the other intervention, reduce HR at a given treadmill workload and/or participants are being able to successfully perform all hack squat lifts without assistance, it is imperative to increase the workload to maintain training intensity to further optimise both endurance and strength improvements. Treadmill velocity will be increased by increments 0.5–1.0 km/hour or slope angle with 1%, and hack squat workload will be increased by 2.5–5 kg.

Methodological considerations

Cardiorespiratory data will be collected through continuous recordings of respiratory kinetics in a direct test to volitional exhaustion using gas analysis, which is regarded the gold standard.^{63 78} Qualified staff will execute all tests, applying standardised equipment and procedures. Consequently, the information bias is expected to be minuscule, with minor measurement irregularities and errors.

The IPAQ will be used to attain level of physical activity. It should be taken into account that the questionnaire is based on self-report, thus carries the inherent possibility of inaccurate reporting, as well as being prone to misclassification.^{8 79–81} Nonetheless, the use of self-reporting has long been preferred in the field of epidemiology as opposed to more accurate objective measurements.⁸² Judicious and appropriate use of the IPAQ will provide a



rough estimate of physical activity. Also, we cannot reject the possibility of a selection bias where those who partake prove fitter (ie, higher $\text{VO}_{\text{2max/peak}}$ and 1RM) than those who decline participation. However, there are no indications suggesting that the study population will not be representative for (Norwegian) patients with SUD.

Sample size and statistical analyses

Power calculations are based on VO_{2max} as primary endpoint, with a difference of ≥ 1 MET (3.5 mL/kg/min) between the LD and HD groups considered as clinically relevant.¹² A previous study with healthy participants, applying a similar design, reported a 10% and 13% improvement in VO_{2max} subsequent LD and HD training, respectively.⁶⁴ The effect size is in line with findings from patients with SUD, where a 15% ($\pm 7\%$ SD) improvement in VO_{2max} (following a HD intervention) has been reported.⁶⁰ Adhering to these preconditions, with a statistical power of 80 ($1 - \beta=0.8$, $\alpha=0.05$), the power calculation suggests a minimum of 16 participants included in each group to detect a clinically relevant difference between groups. A sample of 20 participants is selected to allow for a 20% drop-out rate. Linear mixed models will be employed to test differences between groups, and to provide robust analysis despite possible missing values, $p<0.05$ is considered statistically significant. Between groups (ie, HD and LD) and within groups (ie, baseline, midway and post-test) changes will be analysed. Analyses will be based on per protocol. Descriptive data will be displayed as arithmetic mean \pm SD. SPSS V.25 and GraphPad Prism V.4.01 (GraphPad Software, San Diego, California, USA) will be used for data analysis and graphic presentation of data, respectively.

Patient and public involvement

Two previous in-patients, experienced with high-intensity endurance and strength training from our clinic were consulted regarding the feasibility of the high-intensity training modality among patients with SUD. Other than that, patients had no further involvement in developing the research question or study design. Participants will get their personal test results immediately after each test.

Ethics and dissemination

This protocol is in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement, and the study was approved by REK-Regional Committee for Medical and Health Research Ethics (2019/502/REK midt), registered in Clinical Trials (NCT04065334) and in compliance with the Declaration of Helsinki (WMA Declaration of Helsinki 2013). All participants receive both oral and written information prior to inclusion, and signed a written informed consent. Given the possibility of a less effective, and thus less health promoting treatment in the intervention group a power calculation was used to establish the minimum sample size necessary to detect significant differences between groups. Participants will be covered by the Norwegian

patient compensation claim insurance, and consecutively receive their personal test results. Results from this study will be published in an open access journal to ensure widespread and easy access, as well as being presented at national and international conferences. Author eligibility will adhere to the Vancouver Declaration.

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Contributors All authors meet the ICMJE criteria for authorship. HL, MPM, UW, CH and GF were involved in study concept and design. The manuscript was drafted by HL and revised critically for important intellectual content by MPM, UW, CH and GF. The final draft was approved by all authors. All authors agreed to be accountable for all aspects of the work related to the accuracy and integrity, and that all parts of the work are appropriately investigated and resolved. HL and GF will have access to the final dataset. There is currently no agreement of limited access for other involved investigators.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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