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# Clinical treatment of patients with substance use disorder: The role of physical health

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine
Department of Circulation and Medical Imaging

Doctoral thesis

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Trondheim, August 2016

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# Betydningen av fysisk helse i rusbehandling

Rusavhengige har en høy forekomst av somatiske sykdommer i tillegg til ulykker og overdoser, og dette gir dem en forventet levealder som er 15-20 år lavere enn friske. Utgangspunktet for denne doktorgradsavhandlingen var å dokumentere den fysiske helsetilstanden til pasientgruppen, og videre å vurdere om et helhetlig behandlingstilbud burde inneholde effektiv trening for å bedre pasientenes fysiske helse. Spesielt var målet med de fire studiene i avhandlingen å:

1. Evaluere hvordan nøkkelfaktorer for fysisk helse, som aerob utholdenhet og muskelstyrke, er hos ruspasienter sammenliknet med friske.
2. Måle hvordan skjeletthelsen er hos amfetaminmisbrukere sammenlignet med friske.
3. Undersøke effekt og gjennomførbarhet av intervalltrening med høy aerob intensitet for ruspasienter i behandling.
4. Undersøke effekt og gjennomførbarhet av styrketrening med høy intensitet for ruspasienter i behandling.

Avhandlingen viser at ruspasienter har redusert aerob utholdenhet, målt som maksimalt oksygenopptak ($VO_{2max}$) og gangøkonomi, sammenlignet med friske. Pasientgruppen har også redusert muskelstyrke og evne til å utvikle muskelkraft hurtig. I tillegg dokumenterer vi at amfetaminavhengige også har en systematisk redusert skjeletthelse i hele kroppen, og at omtrent halvparten av pasientene i studien hadde verdier som kvalifiserer til osteopeni eller osteoporose. Den svekkede skjeletthelsen sammenfaller med reduksjonen i muskelstyrke og evne til å utvikle muskelkraft. Generelt sett kan den fysiske helsen hos ruspasientene sammenliknes med hva som typisk observeres hos personer som er 15-20 år eldre. Resultatene indikerer at pasientgruppen har høy risiko for å utvikle hjerte- og karlidelser, visse typer kreft, skjelettproblemer samt forhøyet risiko for tidlig død. Selv om flere årsaker trolig bidrar til den svekkede fysiske helsen, er det sannsynlig at inaktivitet spiller en viktig rolle. Dette kan begrunnes med at reduksjonen i aerob utholdenhet og muskelstyrke var systematisk til stede i pasientgruppen, uavhengig av alder, kjønn og hovedrusmiddel, samt at koblingen mellom disse nøkkelfaktorene for fysisk helse og inaktivitet tidligere er veldokumentert.

I doktorgradsavhandlingens to siste studier dokumenterer vi at trening med høy intensitet er gjennomførbart i klinikk, og at den fysiske helsen til pasientene kan bedres til et nivå som er på linje med det man ser hos friske innenfor dagens behandlingsperiode på tre måneder. Reduksjonen i risiko for hjerte-kar sykdommer, andre livsstilsykdommer og tidlig død er dermed betydelig redusert. Resultatene viser også at bedringen i den fysiske helsen også kan tenkes å ha en gunstig effekt på pasientenes psykiske helse.

Vi konkluderer med at ruspasienter har systematisk svekket fysisk helse sammenlignet med friske. Videre viser vi at effektiv fysisk trening kan bedre den fysiske helsen til pasientgruppen til et nivå liknende det man ser hos friske. Strukturert og effektiv trening bør derfor bli en del av standard rusbehandling.

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***Finansieringskilde:*** ***Samarbeidsorganet HMN-NTNU***

*Ovennevnte avhandling er funnet verdig å forsvares offentlig*
*for graden PhD i klinisk medisin.*
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## CONTENT


| | |
|---|---|
| ACKNOWLEDGEMENTS | 4 |
| ABBREVIATIONS | 6 |
| LIST OF PAPERS | 7 |
| SUMMARY | 8 |
| INTRODUCTION | 10 |
| Substance use disorder | 10 |
| Physical health status in patients with substance use disorder | 15 |
| Physical training in clinical treatment | 20 |
| Effective physical training | 20 |
| Physical training for patients with substance use disorder | 24 |
| OBJECTIVES AND HYPOTHESES | 26 |
| METHODS | 27 |
| Subjects | 27 |
| Testing | 27 |
| Training | 32 |
| Statistical analysis | 33 |
| SUMMARY OF RESULTS | 35 |
| DISCUSSION | 38 |
| Reduced aerobic capacity among SUD patients | 38 |
| Reduced muscular strength among SUD patients | 39 |
| Bone health among SUD patients with amphetamine as primary drug | 40 |
| Exercise training interventions in SUD patients | 41 |
| Compliance and dropout in the training studies | 44 |
| Associations between physical and mental health | 45 |
| Beneficial effects of physical improvements on mental health | 46 |
| Future perspective | 47 |
| CONCLUSION | 48 |
| REFERENCES | 49 |
| PAPER I-IV | 58 |

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Grete Flemmen
Trondheim, February 2016

## ABBREVIATIONS

| | |
|---|---|
| a-$vO_{2diff}$ | Arterial-venous oxygen difference |
| BPS | Biopsychosocial model |
| BMC | Bone mineral content |
| BMD | Bone mineral density |
| CTX-1 | C-terminal telopeptides of type I collagen |
| DSM-5 | The diagnostic and Statistical manual of mental disorders, Fifth Edition |
| DXA | Dual X-ray absorptiometry |
| EuropASI | European Addiction Severity Index |
| HAD | Hospital anxiety and depression scale |
| $HR_{max}$ | Maximal heart rate |
| ICD-10 | International Classification of Diseases, rev 10 |
| ISI | Insomnia severity index |
| LT | Lactate threshold |
| MET | Metabolic equivalent |
| MST | Maximal strength training |
| M-wave | Direct muscle wave |
| P1NP | Type 1 collagen amino-terminal propeptide |
| PF | Peak force |
| Q | Cardiac output |
| RER | Respiratory exchange ratio |
| RFD | Rate of force development |
| 1RM | One repetition maximum |
| SUD | Substance use disorder |
| TBS | Trabecular bone score |
| $V_E$ | Ventilation |
| $VO_{2max}$ | Maximal oxygen consumption |
| V-wave | The first volitional wave |
| WE | Work economy |
| WHO | World Health Organization |

## LIST OF PAPERS

### Paper I

Grete Flemmen & Eivind Wang. Impaired Aerobic Endurance and Muscular Strength in Substance Use Disorder Patients. Medicine 11/2015; 94(44).

### Paper II

Mats Peder Mosti, Grete Flemmen, Jan Hoff, Astrid Kamilla Stunes, Unni Syversen, Eivind Wang. Impaired skeletal health and neuromuscular function among amphetamine users in clinical treatment. Osteoporosis International 10/2015.

### Paper III

Grete Flemmen, Runar Jakobsen Unhjem, Eivind Wang. High-Intensity Interval training in Patients with Substance Use Disorder. BioMed Research International 03/2014(1).

### Paper IV

Runar Jakobsen Unhjem, Grete Flemmen, Jan Hoff, Eivind Wang. Maximal strength training as physical rehabilitation for patients with substance use disorder; a randomized controlled trial. Accepted for publication, 02/2016. BMC Sports Science, Medicine and Rehabilitation.

## SUMMARY

It has been well documented that substance use disorder (SUD) patients suffer a high prevalence of cardiovascular disease, other lifestyle related diseases and have a decreased life expectancy of 15-20 years. However, their physical health status has been unclear. Furthermore, it has been uncertain if physical training, as a part of clinical treatment, could be a feasible and good strategy to counteract the patient groups' physical as well as mental challenges.

The objectives of this thesis were:

1. To evaluate key components for aerobic endurance and skeletal muscle strength in SUD patients.
2. To assess skeletal properties along with skeletal muscle strength and neuromuscular function in the lower extremities of amphetamine users.
3. Examine the effect and feasibility of high aerobic intensity interval training in SUD patients in clinical treatment.
4. Examine the effect and feasibility of maximal strength training in SUD patients in clinical treatment.

In paper I we observed that SUD patients on average had a reduced aerobic capacity ($VO_{2max}$) (15% for men and 25% for women), walking efficiency (12% for men and 15% for women) and maximal strength (30% for men and 33% for women) compared to healthy individuals. Such reductions are associated with an elevated risk of cardiovascular disease, cancer, mental health and premature death. In paper II we observed that amphetamine users also suffer reduced bone mineral density (BMD) (on average 8% for men and 7% for women) at several skeletal regions compared to healthy individuals. The impairments were accompanied by reduced maximal muscle strength and rate of force development (RFD). In paper III we documented the effect and feasibility of a high aerobic intensity training intervention in clinical treatment. Following the 8 weeks training intervention the SUD patients improved their aerobic capacity by 15 ± 7%, likely resulting in a substantial risk reduction for developing cardiovascular disease and other life style related diseases. Similarly as the aerobic endurance intervention, we documented the effect and feasibility of a strength training intervention in clinical treatment in paper IV. The eight week maximal strength training (MST) resulted in large improvements in maximal muscle strength (88 ± 54%) and RFD (82 ± 29%), likely predominantly due to adaptions in the nervous system. The improvements in muscular strength and function are associated with decreased risk of falls and fractures,

osteopenia and osteoporosis and improved motor function and quality of life. Additionally, both paper III and IV confirmed the attenuation of aerobic endurance and muscular strength in SUD patients, before the training was carried out.

In general, the physical measurements were not associated with the type of primary drug the SUD patients were using. This indicates that the systematic physical health reductions SUD patients suffer may be a consequence of an inactive lifestyle rather than direct damage by the actual drug use. In conclusion, this thesis advocates the importance of effective physical training as a part of clinical treatment of SUD patients.

# INTRODUCTION

## Substance use disorder

When describing persons with a harmful use of substances, both researchers and clinicians apply the terms substance dependency, substance use, substance abuse and addiction interchangeably. However, substance use disorder (SUD) has recently been widely accepted as a collective term (1). Not only an individual's mental and physical health is affected when a person develops SUD. Most likely, both family, friends and the larger society also suffer.

### Definitions and diagnoses of substance use disorder

The precursors to substance use are often benign feelings or motives like sociability, curiosity, and excitement. However, it can also derive from negative life events, when substances are used to distance one-self emotionally from the events. Nevertheless, most people using substances do not develop SUD (2, 3). The exact distinction between use, abuse and dependence has been an ongoing debate within the field for decades. In recent years, SUD has replaced the concepts "abuse" and "dependence" in the diagnostic systems (1, 4). SUD is an overarching disorder; independent of type of substance use, the diagnosis is based on the same classification criteria. SUD is a complex illness and a precise definition is not yet agreed on. It is also unclear at what point the substance use is severe enough to require treatment. Several factors must be taken into consideration. There are two classification systems and diagnostic criteria manuals used to classify the mental disorders and thereby defining the criteria to fulfill the diagnosis of SUD in Europe and USA: ICD-10 and DSM-5 (1).

ICD-10 (International Classification of Diseases, rev. 10) is a classification system developed by the World Health Organization (WHO). The classification system is used in the Norwegian health care systems, including the clinic that the participants in these studies were recruited from, and hence also used in this thesis. Patients with SUD are classified within ICD-10: F10-19: Mental and behavioral disorders due to psychoactive substance use. According to ICD-10 three or more of the following criteria have to be fulfilled, and the criteria must have appeared simultaneously during a one year period, before SUD can be diagnosed:

- A strong desire to take the substance.

- Impaired capacity to control the substance consumption (e.g. time of onset, termination, time of use, failure at reducing or control substance use).
- Abstinence symptoms when intake of substances is reduced.
- Increased tolerance to the effect of the substance.
- Preoccupations with substance use, other activities are reduced because of substance use.
- Despite of harmful consequences the substance use continues.

The classification system DSM-5 (The diagnostic and Statistical manual of mental disorders, Fifth Edition) is a manual published by the American Psychiatric Association. While the DSM-5 is the official diagnostic system for mental disorders in the US, the ICD-10 is used more widely in Europe and other parts of the world and covers all aspects of health. The two classification systems are relatively similar, but awareness of which system is used is important since there are differences that can influence the determination of an exact diagnose.

**A model of development and cause of substance use disorder**

There is a common perception within the field that the interaction between biological, psychological and social factors plays a major role in the development, course and treatment of the disorder. Each of these factors cannot alone account for the development of health or illness. Instead, the interaction between them determines the course of development.

The WHO emphasizes that SUD can be explained and understood by the biopsychosocial model (BPS) (5). The BPS model was first introduced to the medical world by Georg L. Engel (6). The model emphasizes the importance of the interaction between biological, psychological and social factors in the development of illness. With this model Engel challenged the biomedical model of illness by proposing other important factors as cause of disease and its consequences. In line with this model, studies have shown that the combination of pharmacological and psychosocial treatment provides a better outcome than pharmacological treatment alone (7, 8). SUD is a complex illness, and the BPS model provides a good framework for understanding the disorder.

The biological influences are also complex. Among them are genetic factors, which influence the brain reward system and bodily organs (9). Several disorders have a biological origin in an inherited genetic vulnerability or disposition. This is observed in twin studies, among them a study on development of alcoholism by Ducci & Goldman (10), where the authors state that there is a high inheritance factor in vulnerability for developing alcoholism. The effect substances has on the bodily organs and our biology is important to understand the consequences of substance use, and vital in constructing the ideal treatment regime.

The psychological component of the BPS model may include factors such as mental health, identity, personality, social functioning and significant life events (11, 12).

The social part of the BPS model emphasizes how factors such as family, social network, educational and work status, economy, leisure activities and religion can influence health and illness. A childhood characterized by conflicts, bad parent/child relations, violence, substance use and abuse is associated with a high vulnerability for development of SUD. A large number of persons diagnosed with SUD report child abuse or sexual abuse (13). This does not mean that children from stable homes cannot develop SUD, but that other risk factors will be causative for them (14).

**Prevalence of harmful illicit substance use**

According to the UN World Drug Report (15), 27 million people worldwide are estimated to have a SUD due to use of illicit drugs. Approximately 12 million people suffer severe health problems due to the drug use, and ~0.2 million deaths are caused by the drug use each year. In comparison, 2.3 million deaths are associated with alcohol use (16).

An epidemiologic survey in the US documented that 2% of the population met the criteria for SUD ( 9% alcohol use disorder) within the last 12 months (17), while a review including 27 community studies in European countries estimated the prevalence of SUD in the population to be 3% within the last 12 months (18).

Drug overdoses are estimated to be the cause of ~4% of all deaths among European 15-39 year olds, and about 75% of fatal overdoses are caused by opioids. An estimated 1.3 million were opioid users in Europe in 2012 (19).

Surveys show that the use of illicit drugs in Norway is somewhat lower than in most other countries in Europe. An exception is the use of amphetamine, where Norway is at the average European level (20). Although the prevalence is somewhat lower compared to other European countries, the consequences of the illicit drug use in Norway are severe. This is due to a high rate of injection drug users (21, 22); followed by a high risk of infections, infectious diseases (23) and overdoses (24). Between 8600 and 12500 individuals were estimated to inject heroine or amphetamine in Norway in 2007 (22). Cannabis is the most used illicit drug in Norway. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 7% of the 15-34 year old population in Norway have tried cannabis during the last year, and 2% during the last month (20). Amphetamine is the second most used illicit drug in Norway. In the age group 15-34 years 6 % has at some point in life tried amphetamines.

**Substance use disorder treatment in Norway**

Historically SUD was considered to be a social problem in Norway, and substance treatment was part of the social service. Interventions and treatment was given according to the social care law (25), which mainly focused on the social welfare of the users.

In 2004 a reform by the Norwegian government led to a major change in the options given to individuals diagnosed with SUD. The reform sought to give the SUD patients the same right to treatment as patients with other chronic medical diseases (26). The purpose was to emphasize the importance that treatment should evolve into inter-disciplinary specialized services embracing biological, psychological end social needs, based on the theory behind the BPS model.

The reform moved responsibility for the treatment of individuals with SUD from the municipalities to specialist health care. The state has the overall responsibility for the specialist health services, also financially (26). The reform aimed to increase collaboration between health care, social services and specialist health care services.

In 2012; 29 500 patients with SUD received inter-disciplinary services in Norway. Out of these 30% received residential treatment. A survey done by SINTEF (27) on behalf of the Norwegian Directorate of Health showed that among the patients who receive residential treatment in Norway, 35% was treated for alcohol dependency, 17% had amphetamine as their primary drug and 15 % had cannabis as their primary drug. About 70% of the patients in treatment are men, 28% of the patients were in the age group 18-29 yrs., and 49% were between 30-49 yrs.

The gender distribution in Norwegian clinics mirrors the gender distribution globally, both in differences in drug abuse and in treatment. Few gender differences appear in adolescence, they are more apparent in adulthood (28). Gender differences are seen in multiple factors; males and females differ in physiological responses to the drugs (29, 30), the path from drug use to dependency (31), the long term health effects from drugs and vulnerability for comorbid psychiatric diseases (28, 30, 31).

Despite restructured policies, use of a range of different treatment approaches and a growing body of research concerning different treatment methods, the treatment success and recovery rate is low. High relapse rates are common within SUD treatment (32-35). Studies show that despite widely available treatment programs approximately 60% of SUD patients will have relapsed within 12 months after leaving treatment (3, 36). Relapse has severe consequences for SUD patients, abstinence leads to loss of tolerance to the toxic effects, and the risk for overdose is high when returning to drug use (37). These challenges show that there is a need to search for new efficacious methods for SUD treatment (32, 35).

The BPS model of treatment is widely accepted within the field today. However, in today’s treatment programs it has been challenging to find systematic descriptions of actions towards the patients physical health, and the treatment programs does not seem to emphasize this particularly. Considering both the challenge with treatment outcomes, and the patients’ substantial somatic complaints it is surprising how little attention the patients physical health problems receive in a rehabilitation perspective. One possible explanation for this could be the diagnose classification systems. Since SUD is classified within the mental health disorders, physical health problems might simply have been neglected.

### Socioeconomic costs of harmful substance use

Substance use is a major public health problem and causes a large economic burden on the social welfare system (38, 39). To estimate the exact economical costs is challenging. Studies attempting to do so have little coherent methodology and are difficult to compare (39). This also reflects the challenges in defining what costs the substance use leads to from a health and crime perspective, death, drug treatment and prevention initiatives, withdrawal from school and work etc. Whether the costs are caused by alcohol use and/or illicit drugs are also often unclear. Despite these difficulties to calculate the exact cost associated with SUD, estimates claim that of the overall costs on society caused by disease, at least 10% can be attributed to the consequences of SUD (39, 40). Costs associated with residential treatment are high. The patients are often dependent of extensive help from public services both prior to residential treatment and after (41).

Governmental costs associated with SUD treatment are dependent on several factors; including length of treatment, education level of employees, number of employees per patient, facilities etc., and the costs also vary between the public specialist health care system and the private clinics.

Estimates indicate that the average cost per day in a residential SUD treatment clinic (interdisciplinary services) in Norway was NOK 4900 (~ € 560) in 2012. The costs were higher in the public specialist health care than in the private clinics. In 2012 each clinic-stay had an average cost of NOK 195 000 (~ € 2223). For outpatient treatment, an average consultation was estimated to cost NOK 2496 (~ € 285). Here the costs were similar for public and private treatment (27).

Considering the large economic costs associated with SUD treatment, and services following treatment, it is clear that optimizing the rehabilitation programs would not only lead to better outcomes for patients, but also reduce the overall costs on the society.

## Physical health status in patients with substance use disorder

SUD and poor physical conditions are highly related, and a long term substance use is associated with elevated risk of developing physical health problems (36, 42, 43). Persons with SUD are frequent users of medical care systems; emergency services, primary health care, hospitals and treatment clinics. A substantial part of these inquiries are caused by accidents and overdoses (44), but there is also a high prevalence of hypertension, infections, cardiovascular diseases, diabetes (43, 45), cancer (45, 46) and indications of an attenuated bone health (47, 48). Despite the knowledge of SUD's relations to medical challenges there are barely any clinical studies identifying the frequency of somatic illnesses among SUD patients. A study by Keaney et al. (49) found that three out of four SUD patients, mostly heroin addicts, had at least one somatic problem, while another study revealed that the SUD patients in their survey suffered four or more somatic diagnoses in addition to their SUD (42). It is also noteworthy that persons with SUD have a 15-20 years shorter life expectancy than the general population (44, 50). The factors that contribute to the physical health challenges are multiple; both the drugs and the lifestyle following the addiction has negative consequences.

Evidence of SUD patients' physical health status is scarce. Aerobic endurance capacity, measured as maximal oxygen consumption ($VO_{2max}$), is seen as one of the most important and basic components of physical health, and is linked to risk of diseases and premature death (51, 52). Wei et al. (52) observed that a low aerobic endurance capacity resulted in a similar, if not larger, relative risk of mortality compared to more recognized risk factors such as diabetes, high cholesterol, hypertension and cigarette smoking. An improvement of $VO_{2max}$ is shown to reduce the risk of mortality. Myers et al. (51) estimated that an improvement of 1 metabolic equivalent (MET) (~3.5 $mL \cdot min^{-1} \cdot kg^{-1}$) increase in $VO_{2max}$ corresponded to a 12% improvement in survival. This was supported by Kodama et al. (53) who observed a decrease of 1 MET to be associated with a 13-15% higher risk of all-cause mortality and coronary heart disease.

Muscular strength has in recent years also received recognition as being one of the strongest predictors of physical illnesses and premature death (54, 55). Low muscular strength is found to be highly associated to falls and fractures (56, 57), reduced bone health (58, 59) poor walking efficiency (60), elevated risk of cancer (54) and cardiovascular disease (61).

Since there is a high prevalence of premature death, cardiovascular diseases and other lifestyle related diseases among persons with SUD, assessment of their physical health is sought after. If the assessment reveals reduced physical health compared to healthy individuals, and indicate an elevated risk of diseases and premature death, effective exercise training should be part of the clinical treatment of the patient group to reduce their health risks.

### Maximal oxygen consumption

Research on the SUD patient's aerobic endurance capacity is sparse. A few studies have estimated $VO_{2max}$ from submaximal testing, typically applying a cycling or walking modality (62, 63). Mamen et al. (64) measured $VO_{2max}$ in a group of SUD patients in a rehabilitation project, which displayed values of 39 (men) and 23 (women) $mL \cdot min^{-1} \cdot kg^{-1}$, respectively. Dolezal et al. (65) measured $VO_{2max}$ in methamphetamine (a derivate of amphetamine) dependent individuals, and documented values of 31 (men) and 23 (women) $mL \cdot min^{-1} \cdot kg^{-1}$, respectively. These studies are difficult to compare, due to different measurement methods and SUD populations. However, what these studies have in common are low measurement results compared to healthy populations, which indeed indicates a population at high risk of developing cardiovascular disease and other life style diseases.

### Maximal muscle strength and rate of force development

Together with aerobic endurance, the force generating capacity of skeletal muscle is important in assessing an individual's physical health (54). Maximal muscle strength is typically expressed as the one repetition maximum (1RM) a person can attain in a standardized movement (66, 67). 1RM refers to the result of several force producing muscles performing maximally during a single voluntary effort of a task (67).

To our knowledge, only one study can point to measurements of muscular strength in SUD patients. Dolezal et al. (65) assessed 1RM for both leg press and chest press in a study examining the effectiveness and feasibility of an eight week exercise training intervention in methamphetamine dependent individuals in residential treatment. The baseline results in this study indicated that methamphetamine dependents had an impaired muscular strength. Unfortunately, the study lacks comparison with a healthy control group, and because their test method is not described in detail, it is difficult to compare with other studies. For health and performance purposes, not only the maximal strength is shown to be important, but also the ability to develop force rapidly (60, 68). Rate of force development (RFD) is defined as the rate of rise in contractile force at the onset of contraction (69) . The RFD is especially relevant in situations or performance where it is not sufficient time to reach maximal force. I.e. having a high RFD may be preventing falls and improve motor function and balance (69). RFD is typically measured the initial <250ms of a muscle contraction, whilst it may take >300ms to reach maximal force (69, 70). Furthermore, the early (<100ms) and late (>200ms) phase of the RFD has been shown to reflect different physiological parameters. Whilst the early phase is closely linked to the twitch contractile properties of the muscle, the later phase is more linked to the maximal strength (71). Recognizing this difference between the various parts of the RFD, it may be more or less associated with i.e. maximal strength. Despite being a very good measure of functionality and to reflect important factors in the force generating capacity of the muscle, measurement of RFD amongst SUD patients appears, to our knowledge, not to have been conducted before.

**Bone health**

Skeletal health is determined by several factors, including genetics, physical activity, hormonal status, level of calcium and vitamin D and cigarette smoking. Impaired skeletal health increases the risk of osteoporosis and osteoporotic fractures (72, 73).

Osteoporosis is a skeletal disease characterized by low bone mass, reduced bone quality and deteriorated microarchitecture, which causes increased risk of bone fractures (72, 74). Osteoporosis is diagnosed by measurements of bone mineral density (BMD), using Dual X-ray Absorptiometry (DXA), and osteoporosis is defined as a BMD T-score of less than or equal to -2.5 standard deviation below average of a young adult (64). By the WHO and Internationally Society for Clinical Densitometry criterion the level of BMD is categorized into normal, osteopenia and osteoporosis. Osteopenia is an early sign of bone loss, where BMD is lower than normal, causing increased fracture risk compared to normal BMD values. Osteopenia is defined as a T-score between -1,5 and -2,5 (73). The first treatment initiative for persons measured with low BMD is usually lifestyle changes; like increased physical exercise and reduce cigarette smoking along with supplements of calcium and vitamin D (72).

Bone formation and bone resorption are results from slow metabolic processes. Acute changes in bone metabolism are therefore difficult to detect with BMD measurements (75). Biochemical markers of bone formation or bone break-down products in serum, like bone formation marker type 1 collagen amino-terminal propeptide (P1NP) and the bone resorption marker C-terminal telopeptides of type I collagen (CTX-1) can be used to assess acute or short term effects in bone metabolism (75) and also to support findings done by DXA.

***Bone health in amphetamine dependents***

Despite a high prevalence of tooth decay and skeletal fractures among methamphetamine users, there is little evidence regarding amphetamine's effects on the skeletal system (48). A weakened skeletal system may also be associated with a poor muscle strength and neuromuscular function. The high prevalence of fractures may have been attributed to drug related falls and accidents. The possibility that the patients have low BMD is not given much attention in research or clinical settings. A few studies have obtained bone measurements of methamphetamine users. Low bone quality in the calcaneus was observed among male methamphetamine users in a study by Katsuragawa (47), using an achilles ultrasound bone densitometer. Another study among male methamphetamine users revealed high prevalence of osteoporosis at the lumbar spine assessed with DXA (48). About 50% of the participants in this study had osteoporosis or osteopenia in the lumbar spine. These findings indicate that methamphetamine use or/and inactivity may lead to poor bone quality and increased risk of osteoporosis.

**Associations between physical and mental health**

SUD, depression- and anxiety disorders are the most common mental illnesses (76, 77). These disorders often appear together and are closely connected (78). Several associations between mental health and physical health have been shown (43, 55, 79, 80). In the general population, the prevalence of depression is lower among physically active (81). Both aerobic endurance and muscular strength are shown to be associated with mental health. Ortega et al. (55) showed that strong male adolescents were 15-65% less likely to develop any psychiatric diagnosis in a 24-year follow up study than males with low muscular strength. In a study evaluating associations between measures of physical activity and mental health, Galper et al. (80) showed that an increase in aerobic endurance was associated with lower depressive symptomatology for both genders. This was supported in a longitudinal study by Sui et al. (82); participants with low aerobic endurance at baseline were associated with larger risk of depressive symptoms at follow-up. Given the high prevalence of mental illnesses among SUD patients, developing a good physical health should also be emphasized in SUD treatment programs because it may have an effect on the patients' mental health.

## Physical training in clinical treatment

Physical activity has been a supplement to the SUD treatment programs for decades. However, evidence of the efficacy of exercise as an adjunct therapy in SUD treatment is not clear (83, 84). The content and physiological effects of already integrated physical activities are poorly described (85). There is a clear lack of descriptions of the physical activities that are being carried out in clinical treatment, and the intensity and frequency appears to not be reported. The activities seem to be random and unstructured (86, 87). There are many unanswered questions concerning physical training in SUD treatment programs. Important questions that need to be addressed are: What is the rationale for including the training intervention in clinical treatment? What is the physical health status to an average SUD patient arriving in treatment? Are effective training methods feasible in a clinical setting, and how do the SUD patients respond to training? These important questions need to be answered if physical training is to be an integrated part of SUD treatment.

## Effective physical training

High aerobic intensity (85-95% of maximal heart rate ($HR_{max}$)) endurance training has been shown to be more advantageous for improving aerobic endurance than aerobic training with lower intensity. Similarly, strength training with high intensity (85-90% of 1RM) has yielded larger improvements in skeletal muscle strength than strength training with lower intensity (88, 89). When following these methods carefully, paying attention to their recommended frequency, intensity and duration, large improvements are achieved in a few weeks of training. The methods have been shown to be feasible and applicable for a range of different populations; athletes and untrained, young and old, healthy and people from several patient groups (90-94).

**Aerobic endurance**

Pate and Kriska (95) developed a model describing the three most important factors accounting for inter-individual variances in aerobic endurance performance; $VO_{2max}$, lactate threshold (LT) and work economy (WE). Numerous studies have supported this model (66, 96-98). $VO_{2max}$ is argued to be the most important factor of the three, determining physical fitness and success in an aerobic endurance performance (88, 99).

*Maximal oxygen consumption ($VO_{2max}$):*

$VO_{2max}$ is defined as "the highest rate at which oxygen can be taken up and utilized by the body during severe exercise" (95, 100). At increasing work intensities the delivery and use of oxygen must match the amount of work performed (101). $VO_{2max}$ represents the maximum capacity for energy production through oxidative phosphorylation, and is a recognized measure for aerobic capacity (102, 103). The transport of oxygen throughout the circulatory system from air to mitochondria depends on several factors; the Fick principle summarizes both central and peripheral components, and is an exact physiological definition of $VO_{2max}$:

$$VO_{2max} = Q \cdot (a\text{-}vO_{2diff})$$

The Fick's equation shows that $VO_{2max}$ equals the product of cardiac output (Q) and the arterial- venous oxygen difference ($a\text{-}vO_{2diff}$) (101). Q is a product of the heart rate and stroke volume of the heart, which represents the amount of blood pumped out of the heart in a given time. It has been a long lasting debate what primarily limits $VO_{2max}$, and consequently which factor that should be emphasized during effective training. Although each and every factor from air to mitochondria contributes, depending on the situation, it has been argued that Q and locomotor muscle blood flow may be the most important factors at sea level. At least Q is representing the largest differences between trained and untrained, (88, 104, 105).

*Lactate threshold (LT):*

LT reflects the highest working intensity at which the production and elimination of lactate are balanced (67, 88), and is determined by "the fraction of the $VO_{2max}$ that may be sustained over an extended period" (95). Lactate is a product of anaerobic carbohydrate metabolism (88, 96). During continuous exercise above the LT, the concentration of blood lactate starts to increase, and the accumulation of lactate in the blood is larger than the elimination. The higher workload allowed before the threshold is reached, the greater ability to resist fatigue during exercise. This is why the LT, although it is a product of anaerobic metabolism, is a good predictor of aerobic performance (103). Highly trained athletes can have LT values as high as 90% of $VO_{2max}$ (106). It is suggested that LT predominantly changes with alterations of $VO_{2max}$ (106).

*Work economy (WE):*

The measure of WE refers to the oxygen cost of performing work at a standard submaximal workload or the energy expenditure required for a given workload below LT (66, 103). The lower the oxygen costs, the better the WE is (66). WE is also an important predictor of aerobic performance, especially among groups with homogenous $VO_{2max}$. This is important for endurance athletes, but it also has consequences in daily life and tasks for different patient groups where walking the stairs or going to the grocery store might be a challenge. Increased muscular strength and RFD, without changes in body mass has been shown to improve WE (66, 107, 108).

WE may also be expressed in relation to the external work produced, then it is commonly referred to as work efficiency, mechanical efficiency or walking efficiency, and expressed as the percentage of the total chemical energy expended, which contributes to the actual external work output (101). Several different patient groups have been found to perform work/exercise with lower efficiency of movement compared to healthy controls (60, 109, 110). Walking efficiency in humans is approximately 25% in healthy individuals (110).

***Training for maximal oxygen consumption improvements***

Improvements in $VO_{2max}$ are shown to be directly related to the intensity, duration and frequency of training (96). There has been a long lasting discussion about the importance of each factor, different intensity levels, and whether training with low intensity and long duration gives the same effect as high intensity and short duration. However, in the last decade several studies have shown that high aerobic intensity training gives the highest training response in improving $VO_{2max}$ (88, 90, 91, 93). Interval training with high aerobic intensity (85-95% of $HR_{max}$) has in several studies been shown to be an excellent strategy to improve $VO_{2max}$. A well-documented modality to carry out the high aerobic intensity training is four repeated intervals each lasting for four minutes, with three minutes active rest in between. This modality offers a simple, feasible and effective approach to carry out the training sessions, and has also been documented to be superior to training with moderate

($85\%$ of $HR_{max}$) and low intensity ($70\%$ of $HR_{max}$) training across age, pathology and physical capacity (88, 93). It is important to separate training with high aerobic intensity from training with high work intensity when the aim is to target the oxygen taxing organs, and specifically the Q. Intervals between 3-8 minutes have been suggested to represent an ideal length, as the time then will be sufficient to reach a high taxation of Q as well as terminating the interval before the lactate accumulation produced by anaerobic metabolism will be too high.

## Muscular strength

### *Training for strength improvements*

In terms of strength improvements, adaptions to training can be divided in two main categories; muscular and neural adaptions. Muscular adaptations commonly includes muscle hypertrophy, and is typically a result of strength training with a moderate load (~70% 1RM), and moderate number of repetitions (10-12) and 5-6 sets (111). Neural adaptions may also contribute substantially to a muscle strength increase (89, 112). To target neural adaptations the strength training is typically carried out with higher loads and fewer repetitions than if the aim is to stimulate to muscle hypertrophy. Maximal strength training (MST) has been defined as training with loads corresponding to 85-90% of 1RM, resulting in ~5 repetitions until failure. Importantly, the repetitions are carried out with maximal mobilization in the concentric part of the movement. MST is associated with minimal hypertrophy, and the neural adaptions may include alterations in; motor neuron recruitment, firing frequency, synchronization of motor units, coordination, inhibition, co-contractions of antagonist muscles (66, 113). MST has been used by healthy populations and multiple patient populations with excellent results; it is shown to give large gains in 1RM and RFD and has low risk of injuries, likely due to the slow and controlled eccentric phase (59, 114, 115). One previous study showed that MST was superior to hypertrophy (conventional) strength training with regards to 1RM and exhibited a clear tendency to also yield a larger improvement in functionally relevant RFD (115). A vast number of studies have applied MST as a strategy for treatment in various patient populations, suggesting that the training indeed should be feasible in a clinical setting (59, 60, 109, 114, 116-122). 1RM improvements following a two month training intervention, training 3 x week, have typically been in the range of 30-45% increase (109, 114, 116-118) accompanied with a 100-150% increase in RFD (109, 114, 117). It is likely that the large percentage improvements that are observed in RFD in some of these studies are due to the emphasis on high-intended velocity in the concentric phase, and thus maximal firing in the neural system, when carrying out the MST. However, it is not known if the large adaptations have taken place in the earlier or later phase of the RFD, as these studies have made an average observation from 10% to 90% of peak force. Consequently it remains elusive if the training adaptation is more caused by twitch contractile properties or maximal strength (71) .

### Effects of maximal strength training on aerobic endurance

Not only has MST shown to yield large improvements in 1RM and RFD, it has also been shown in several studies with trained (66, 94, 107) and untrained (115, 123) that it can improve aerobic endurance by altering the WE. MST interventions of 8 weeks have typically resulted in ~5% improvements in WE (107). The mechanisms responsible for the reduced oxygen cost have been shown to be solely in the skeletal muscle, lowering blood flow, but leaving the a-$vO_{2diff}$ unaltered (124). Thus, the application of MST should be advocated with the potential to both improve the force generating capacity of skeletal muscles and to improve the aerobic endurance.

## Physical training for patients with substance use disorder

Recognizing the indications that patients with SUD may have a poor physical health, evident as a wide range of life-style related diseases, medical conditions and high risk of premature death, using effective physical training may likely reverse, and even restore, some of these conditions. However, since the activities in clinical treatment today appear unstructured and the effects are scarcely documented, a systematic research approach to evaluate the effects, as well as the feasibility, is sought after. Additionally the synergetic effect between physical health improvements and mental health improvements appears to be an interesting topic for investigation. Importantly, regardless of potential effects on substance use or mental health, SUD patients should receive a good clinical treatment for a potential impaired physical health. Thus, the aim of this thesis was to evaluate the SUD patients' physical status, specifically through direct assessment of key factors for aerobic endurance, muscular strength and bone health. Furthermore the aim was to introduce effective physical training in a clinical setting, and finally consider the overall effects on mental health and implications for various life style related diseases.

## OBJECTIVES AND HYPOTHESES

**In paper I** the objective was to evaluate $VO_{2max}$, walking efficiency, 1RM and RFD.

Our hypotheses were that SUD patients had significantly reduced $VO_{2max}$, walking efficiency, 1RM and RFD, compared to an age and gender matched healthy control group.

**In paper II** the objective was to assess skeletal properties along with muscle strength and neuromuscular force generating capacity in the lower extremities of amphetamine users.

Our hypotheses were that amphetamine users would have lower bone mass and altered bone metabolism compared to healthy age- matched controls. Furthermore, we hypothesized the reductions in bone mass would be accompanied with lower 1RM and RFD.

**In paper III** the objective was to examine the effect and feasibility of high aerobic intensity interval training in SUD patients in clinical treatment.

Our hypotheses were that SUD patients would improve their $VO_{2max}$ and walking efficiency more than a SUD control group receiving conventional rehabilitation.

**In paper IV,** the objective was to examine the effect and feasibility of a MST intervention for SUD patients in clinical treatment.

Our hypotheses were that SUD patients would improve 1RM, RFD and efferent neural drive more than a SUD control group receiving conventional treatment.

# METHODS

## Subjects

Patients were recruited from residential long term treatment in a substance use treatment clinic over a period of 2 years. All patients that volunteered to participate were diagnosed with SUD (ICD-10, F10-F19: Mental and behavioral disorders due to psychoactive substance use). In paper I 44 patients, 31 males and 13 women, were included. In paper II 36 patients, 25 males and 11 females, were included. In these two cross sectional studies the subjects were compared with two healthy age- and sex matched reference groups consisting of 25 and 37 subjects, respectively. Paper I evaluated the SUD patients' aerobic endurance and muscular strength, whilst paper II evaluated the patient groups' skeletal health. Paper III and IV were training studies, investigating the effects of high aerobic intensity interval training and MST, respectively. In each of these two training studies, 24 subjects were randomized between a training group and a control group receiving conventional treatment. Inclusion criteria are described in detail in the respective papers. No injuries or complications were noted in any of the studies. The regional ethics committee (REK) approved all four studies, and they were carried out in accordance with the Declaration of Helsinki.

## Testing

Measurements of physiological key factors and a battery of psychological questionnaires were used for the four papers in the current thesis.

## Physiological testing

### *Endurance*

Oxygen uptake was measured in SUD patients in paper I and III. Oxygen uptake was continuously measured from the start of the warm up until the termination of the $VO_{2max}$ test. The oxygen uptake measurements were obtained using the Cortex metamax II portable metabolic test system (Cortex Biophysic GmbH, Leipzig, Germany), walking or running on a treadmill (Woodway Weil am Rhein, Germany). Oxygen uptake, $HR_{max}$, respiratory exchange ratio (RER) and ventilation ($V_E$) were monitored in 10 second intervals. For heart rate assessment Polar F6$^{TM}$ heart rate monitors were used (Polar Electro, Finland).

*Oxygen uptake at submaximal workload*

To measure WE and walking efficiency, oxygen consumption at a standard submaximal workload was measured. After a 10 minute warm up period, the subjects walked at 4.5 km · $h^{-1}$ at 5% inclination on the treadmill for a period of 5 minutes. This workload was chosen to target a submaximal load for all participants; they all showed steady state oxygen uptake values at this load.

In paper I we calculated the energy input and output to determine the net walking efficiency, while in paper III the average oxygen consumption at a given workload for the last minute of this period was recorded as the WE. The measurement procedures are described in detail in paper I and III.

*Maximal oxygen consumption*

Immediately after the submaximal workload, the subjects progressed into the $VO_{2max}$ test. The incline was kept at 5% while velocity was increased by 1 km · $h^{-1}$ every minute until exhaustion. Encouragement was given towards the end of the test. $VO_{2max}$, RER, and $V_E$ were calculated averaging the three highest continuous ten second values. One or more of the following criteria for reaching $VO_{2max}$ were used: 1) If the oxygen consumption reached a plateau despite further increases in workload, 2) A RER above 1.10 and 3) Lactate concentration in blood > 7mmol. These criteria have previously been used in $VO_{2max}$ testing (125).

*Lactate concentration in blood*

Lactate concentration in blood was measured using a Biosen C_line (EKF Diagnostics GmbH, Barleben, Germany) analyzer. Blood from the patient's fingertip was sampled for analysis of blood lactate within one minute after the end of the $VO_{2max}$ test.

**Muscle strength**

1RM and RFD were measured in paper I, II and IV. Additionally, the strength testing in paper IV also included measurements of efferent drive.

*Maximal muscle strength*

1RM was predominantly measured in a hack squat apparatus. Paper IV also included a 1RM test in a plantar flexion apparatus. In the hack squat machine (impulse Fitness IT7006, Shandong, China) the subjects were in a standing position angled 45° to vertical. From the standing position the participants moved eccentrically down to 90° knee angle position before the concentric movement (figure 1). The hack squat was chosen because, in contrast to leg press, the resistance would be on the participants shoulders. Thus, following training it would include stress not only on the SUD patients lower extremity, but also on the spine and lower back in the upper body. In the plantar flexion test, the participants had a seated position in a calf rise machine (Impulse Health Tech IT7005, Shandong, China), and performed their lifts from an ankle joint angle of ~20° dorsiflexion in the lower position, up to ~30° plantar flexion in the upper position, respectively. Before the test started, the subjects were familiarized with the lifting procedures and performed two warm-up sets. For both hack squat and plantar flexion, 1RM was achieved by increasing the load by five to ten kg until the subject was not able to complete the lift. A three to four minutes rest was given between each trial, and correct joint angles were ensured by marking the respective joint angle positions on the apparatus with a tape. 1RM was achieved within six to nine trials, and the highest load completed was recorded as 1RM. Importantly, only the last three to four lifts were higher than 80% of 1RM to prevent fatigue.

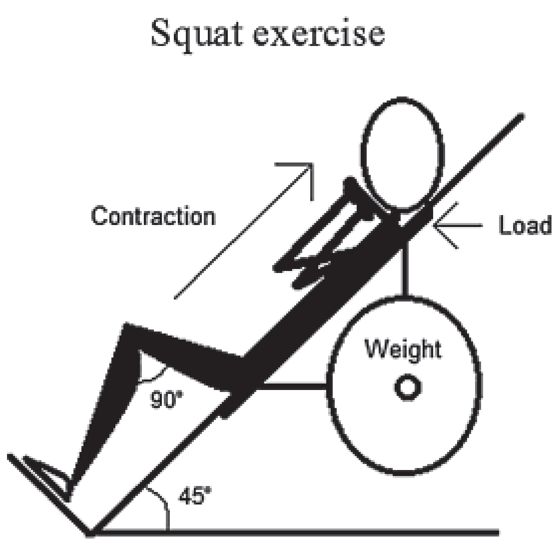


Figure 1. Hack squat exercise machine and the positioning during testing and training. Reprint with permission from Mosti et al. 2013 (59).

*Rate of force development (RFD)*

RFD was recorded using the hack squat machine and a force platform at 2000Hz (9286AA, Kistler, Switzerland) attached to the foot plate. Each subject was given three attempts with a load corresponding to 80% of pretest 1RM, only the best trial was used for analyzes. The subjects were instructed to move slowly down to a knee joint angle of 90°, and then mobilize maximally in the concentric phase of the movement. These instructions were given to ensure maximal mobilization of the nervous system. Three minutes rest was given between each trial. The highest concentric force was recorded as peak force and RFD was calculated between 10% and 90% of peak force.

*Efferent drive*

Since MST was primarily applied to induce neural adaptions, measurements of the first volitional waves (V-waves) (to indicate possible efferent drive adaptions) were assessed before and after training intervention in paper III. With the subjects seated in a fixed version of the plantar flexion apparatus for isometric muscle contractions, reflex potentials were evoked by a current stimulator (DS7AH, Digitimer, Welwyn Garden City, UK), in the tibial nerve, in the popliteal fossa. The electrical current was delivered by gel-coated (Lectron 2 conductive gel, Pharmaceutical innovations INC, Newark, NJ, USA) bipolar felt pad electrodes, 25 mm between tips, 8 mm diameter (Digitimer, Welwyn Garden City, UK). Evoked potentials were recorded through self-adhesive AG/AgCI electrodes (Ambu, M-00-S/50, Ballerup, Denmark) placed as recommended by SENIAM (126) on muscle soleus, m. gastrocnemius medialis and m. gastrocnemius lateralis.

For explicit details on the assessment of V-waves and the search for maximal M-wave amplitude see paper IV.

**Skeletal properties and body composition**

*Dual X-ray absorptiometry (DXA)*

The most widely used measurement technique for evaluating bone mass is DXA. The technique is used both in research and in clinical settings, and serves as the primary diagnostic tool of osteoporosis (127, 128). The regions for measurements in study II were lumbar spine (L1-L4), the hip region and whole body, which are clinically relevant sites for BMD measurements. DXA is based on areal quantification of bone mass, therefore accuracy in subject positioning during the scan is important to minimize data variance. The DXA measurements of BMD and bone mineral content (BMC) were all performed in the same DXA machine (Hologic Discovery, S/N 83817). All DXA scans were carried out by the same certified technician to ensure standardized procedures between subjects.

*Trabecular bone score (TBS)*

TBS reflects the structural condition of the bone microarchitecture and is an estimate of bone quality (129). Since TBS data are estimates of trabecular bone structure within the cortical bone envelope, they provide supplemental information to traditional bone mass parameters. TBS is measured at the lumbar spine, and because DXA does not directly measure TBS, the estimates are performed by using the TBS iNsight® Software version 1.8 (Med-Imaps, Pessac, France).

*Muscle mass and fat percentage*

The whole body DXA scans enables calculation of soft-tissue composition, such as fat mass and lean mass. During the DXA scan, two x-ray beams at two different energy levels passes through body tissues and the beams distinct each elemental composition. The distinctive profile of bone, fat, and lean tissue allows the DXA scans to visualize and separate each tissue (130).

*Markers of bone metabolism*

Blood samples (5 ml) were drawn by venipuncture with stasis and collected on vacuum tubes for serum. Serum level of the bone formation marker P1NP was determined by radioimmunoassay (Orion Diagnostica, Espoo, Finland). Concentration of the bone resorption marker CTX was determined by a Serum CrossLaps enzyme-linked immunosorbent assay (ELISA) (Nordic Bioscience Diagnostics A/S, Herlev, Denmark). Serum levels of 25-hydroxy vitamin $D_3$ were determined by radioimmunoassay (RIA) (DIAsource, Louvain-la-Neuve, Belgium), using the manufacturer's procedure and controls. The timing of the blood sample collection and the participants fasting state can interfere with the experimental results. The bone resorption marker CTX is particularly sensitive to such variations. Standardizes procedures was used in order to prevent such errors.

**Psychometric variables**

*EuropASI addiction severity index*

EuropASI (131) was used to get an overview of the extent of drug use. The index quantifies which substances the subject has used, age of debut and years of use.

*Insomnia severity index (ISI)*

ISI is composed of 7 items targeting different categories of sleep disturbance severity. The items are rated at a five-point Likert scale (0-4) and summed up to provide a total score ranging from 0-28, where a higher score indicate more severe insomnia. The score categories are 0-7 (no clinically significant insomnia), 8-14 (subthreshold insomnia), 15-21 (clinical insomnia, moderate severity) and 22-28 (clinical insomnia, severe) (132).

*Hospital anxiety and depression scale (HAD)*

The HAD self-assessment scale consists of a fourteen item scale, where seven items relate to anxiety and seven relate to depression. On the subscales for anxiety and depression a score of 0-7 is regarded to be within the normal range, a score of 8-10 is considered signs of a mood disorder, while a score of 11 or higher implies a probable presence of a mood disorder (133).

**Training**

*High aerobic intensity interval training:*

In paper III the training intervention group performed high aerobic intensity interval training on a treadmill. The training group trained three times a week for eight weeks and all training sessions were supervised. The training sessions were organized in intervals: after a ten minute warm up, the patients performed four intervals of four minutes duration at a high aerobic intensity (90-95% of $HR_{max}$), interrupted by three minutes recovery periods (~70% of $HR_{max}$). As the subjects improved, velocity and incline were increased to meet the targeted heart rate. The subjects were required to attend at least 20 out of 24 training sessions in order to be included in the data analyzes.

*Maximal strength training:*

The MST intervention in paper IV consisted of two exercises, hack squat and plantar flexion. Both exercises consisted of four sets of four to five repetitions, corresponding to 85-90% of 1RM. If the participants were able to complete five repetitions or more in one set, the training load was increased with five kg in the following set. Since the intended velocity of the concentric phase of movement is known to be of importance for the training adaptions (66), both exercises were conducted with a slow controlled movement in eccentric phase, a short, less than a second stop, and then maximal mobilization of force in the concentric movement. As for the testing, hack squat was performed with 90° knee joint angle, while the plantar flexion exercise was performed from an ankle joint angle of ~20° dorsiflexion up to ~30° plantar flexion. Every training session was supervised to ensure proper technique and progression during the exercises. The MST procedure has been described previously (66, 113).

**Statistical analysis**

All statistical analyses were performed using the software program IBM SPSS version 20 or 21 (Statistical Package for Social Science, Chicago, USA). All figures were created using GraphPad Prism 5 (San Diego, USA).

Paper I: To determine if the data was normally distributed a Q-Q plot was used. Independent samples T-test was used to compare differences between the SUD patient group and the healthy reference group. Correlations between primary substance use, gender, age, substance use history and physical capacity were analyzed using linear Pearson correlation regression analyses.

Paper II: Levene's test of homogeneity of variance was used to test the data for normal distribution. One-way analysis of variance (ANOVA) was used to detect between group differences, using the Tukey post hoc test to correct for multiple testing or by Mann-Whitney *U* test when normal distribution could not be assumed. Correlations between groups were established using linear Pearson correlation regression analysis.

Paper III: To determine if the data was normally distributed a Q-Q plot was used. Repeated measures ANOVAs (2 (group) x 2 training status) were used to determine differences between groups following training. Unpaired and paired t-tests were used to detect differences between groups at baseline and within group following training, respectively.

Paper IV: To determine if the data was normally distributed a Q-Q plot was used. Independent t-tests were used to detect between groups differences before training, whilst paired t-tests were used to detect within group differences with training. Between groups differences following training were identified using two-way repeated ANOVAS. Linear correlations were identified with the use of the Pearson test for linear regression.

All studies used two tailed significance levels of $p < 0.05$. Data are reported as mean values and standard deviations (SD), unless otherwise stated.

## SUMMARY OF RESULTS

Paper I

- SUD patients had a significantly ($p<0.01$) reduced $VO_{2max}$ compared to the healthy reference group; females and males displayed group average reductions of 25% and 15%, respectively.
- The SUD patients WE was significantly ($p<0.05$) reduced compared to the healthy reference group; apparent as a 12% higher oxygen cost of walking at 4.5 $km \cdot h^{-1}$ at 5% inclination. This was accompanied by a concomitant significant ($p<0.05$) reduction of 13% in walking efficiency.
- SUD patients had significantly ($p<0.05$) lower maximal muscle strength compared to the healthy reference group, exhibited as 30% and 33% lower group average 1RM in male and females, respectively. The reduced 1RM was accompanied by a tendency ($p=0.09$) towards reduced RFD (20%) in SUD males compared to male references.
- The reductions in aerobic endurance and muscular strength were consistently present in all age groups, with no significant differences observed between patients who had amphetamine or cannabis as their primary drug. Finally, $VO_{2max}$ correlated significantly with years of drug use; however, this correlation was not present when adjusted for age.

Paper II

- Male amphetamine users displayed lower whole body, total hip and femoral neck BMD of 8% ($p<0.001$), 10% ($p<0.001$) and 9% ($p<0.05$), respectively, compared to the healthy reference group. Female amphetamine patients showed significantly lower total hip and whole body BMD of 11% ($p<0.001$) and 7% ($p<0.05$), respectively.
- The male amphetamine users had significantly lower TBS (4%) at the lumbar spine compared to healthy controls, whilst female users tended ($p=0.07$) to have lower TBS (5%).
- The male amphetamine users had a 48% ($p<0.05$) higher serum level of the bone formation marker P1NP compared to the reference group. P1NP tended to be higher (23%, $p= 0.10$) also in females.

- Male patients had a 30% significantly ($p<0.001$) lower 1RM compared to the reference group and a 27% significantly ($p<0.01$) lower RFD. Female patients displayed a 25% significantly ($p<0.05$) lower 1RM than the healthy reference group.

Paper III

- $VO_{2max}$ significantly ($p<0.01$) improved by 15 ± 7% for the 9 SUD subjects that completed the training intervention. The improvement was also significantly ($p<0.01$) different from the SUD control group receiving only conventional treatment. No within group improvement in $VO_{2max}$ was observed in the SUD control group following the 8 weeks period.
- 9 of the 12 SUD patients completed the high aerobic intensity training. 1 participant dropped out from both the training study and the clinical treatment and 2 of the patients dropped out from the training only.
- A significant ($p<0.05$) within group reduction in depression was seen in the high aerobic intensity training group

Paper IV

- MST in SUD patients significantly ($p<0.01$) improved hack squat 1RM by 88±54% and plantar flexion 1RM increased 26±20%. Hack squat RFD significantly ($p<0.01$) increased with 82±28%. No changes were observed in the SUD control group receiving only conventional treatment for any of the strength parameters.
- 9 out of 12 SUD patients completed the MST. The 3 patients that dropped out from the strength training also dropped out of the clinical treatment at the same time.

For the psychological variables, there were no between groups difference on level of anxiety and depression after the training intervention. Both groups displayed significant within groups reduction in anxiety level ($p<0.05$), while level of depression tended to decrease ($p=0.11$ for the MST group and $p= 0.10$ for the SUD control group). The insomnia score decreased significantly ($p<0.05$) in the MST group, which according to the ISI changed the insomnia level from the category of “subthreshold insomnia” to “no clinically significant insomnia”.

Results across papers

- Female SUD patients with a low muscular strength had a significantly ($p<0.05$) higher anxiety level (12.0 ± 3.9) compared to female SUD patients with moderate strength (7.4 ± 4.8, Table 1).
- Male SUD patients with a low muscular strength had a significantly ($p<0.05$) higher depression level 8.6 ± 4.0 compared to male SUD patients with moderate strength (6.2 ± 3.7, Table 1).

**Table 1.** Psychological measurements and muscular strength level (one repetition maximum)

| | **Male (n=49)** | | **Female (n=21)** | |
|---|---|---|---|---|
| | Moderate strength | Low strength | Moderate strength | Low strength |
| Anxiety (0-21) | 9.6 ± 4.9 | 12.0 ± 3.9 | 7.4 ± 4.8 | 12.0 ± 3.7* |
| Depression (0-21) | 6.2 ± 3.7 | 8.6 ± 4.0* | 4.7 ± 3.7 | 5.8 ± 2.2 |
| Insomnia (0-28) | 10.3 ± 7.3 | 13.5 ± 5.9 | 8.7 ± 5.8 | 11.1 ± 7.4 |

Average hack squat 1RM for SUD is 121 kg and 70 kg for men and women respectively (Paper 1). Moderate strength: Male 1RM=≥120 kg, female 1RM≥70. Low strength: Male 1RM= <120 kg, female 1RM<70 kg. Anxiety and depression scores; 0-7: normal, 8-10: signs of anxiety/depression disorder, 11 or higher: probable presence of disorder. Insomnia scores; 0-7: normal, 8-14: threshold insomnia, 15-21: clinical insomnia (moderate severity), 22-28: clinical severity (severe). **p< 0.05.*

## DISCUSSION

There is a high prevalence of cardiovascular disease, other life-style related diseases and premature death among SUD patients. This may be a direct consequence of their substance use, but may also indicate that they have a poor physical health. Since little is known, through direct assessment of physiological key factors, of this patient groups' aerobic endurance, muscular strength and bone mass, we sought to evaluate if the patient groups' physical health was indeed attenuated compared to what is typically observed in the healthy population. Furthermore, if the SUD patients had an impaired physical health, we sought to investigate if it would be feasible to implement effective physical training as a part of the clinical treatment, and if the patients would exhibit similar adaptations to training as what previously had been shown in healthy subjects and other patient groups. Finally, since synergistic effects have been shown between physical and mental health, we wanted to examine if an improvement in the patients' physical health lead to an improvement also in their mental health. The main findings of this thesis' four papers were that SUD patients had a reduced $VO_{2max}$ , walking efficiency, 1RM, RFD, and BMD compared to healthy. Furthermore, the SUD patients were able to improve these aerobic endurance and muscle strength components following training, to a level similar to what is observed in the healthy population. In contrast, somewhat surprisingly, the conventional SUD treatment did not lead to any alterations the patients' physical health. Finally, the papers revealed indications that muscle strength and aerobic endurance status and improvement may have an effect on the patients' anxiety, depression and insomnia. Combined, these results imply that effective aerobic endurance training and strength training should be implemented as part of clinical treatment.

### Reduced aerobic capacity among SUD patients

$VO_{2max}$ measurements in paper I and III demonstrated that the SUD patients have a reduced aerobic capacity compared with healthy controls. The reductions are comparable to what is observed with ~20 years of aging (134, 135), and implies an increased risk of developing a wide range of lifestyle related diseases and early death (51, 53). Compared to the healthy controls these measures were 15% and 25% lower on average for male and female SUD patients, respectively. Our results are in line with observations on SUD methamphetamine patients (65), and SUD patients in a rehabilitation project (64) which both revealed even lower $VO_{2max}$ results than in our studies. There are some challenges comparing these studies with regards to drug use severity in the SUD populations in each study, possible differences in test methods and protocols may explain some of this discrepancy. The criteria for reaching $VO_{2max}$ in the two studies referred to above are not precisely explained; and it is thereby difficult to decide if the same criteria were used for reaching $VO_{2max}$. However, collectively, our results and the results from the studies by Dolezal et al. (65) and Mamen et al. (64) are in line showing an impaired aerobic endurance, and consequently an elevated risk of diseases and early death.

**Reduced muscular strength among SUD patients**

To our knowledge, this is the first time strength measurements among SUD patients have been compared with a healthy control group. Paper I, II and IV reports that the reductions in aerobic capacity were accompanied by a low force generating capacity. In paper I the SUD patients showed average reductions in hack squat 1RM of 30% (male) and 33% (female) compared to healthy controls. These reductions elevates the patients' risk for falls and fractures (136), premature death (137, 138) and can be compared to 30-35 years of aging (139). Several studies have shown a relationship between maximal strength and RFD (59, 71, 109, 114, 140, 141), which we also observed in our studies (paper I, II and IV). In paper I, RFD also showed a clear tendency to be 20% and 15% reduced in SUD males and females, respectively, compared to the healthy controls.

RFD and its effect on walking economy and walking efficiency have previously been shown (124, 142). Indeed, also in this thesis, the reduced RFD observed in paper I was associated with reduced walking efficiency. These observations demonstrate that an attenuated muscular force development affects both the strength and endurance sides of the physical health spectrum. Combined, this may contribute to extra challenges performing physical work, and may lead the SUD patients in a downward spiral, where the reductions in physical capacity lead to reduced functionality and probably even more inactivity (60, 143).

The patients' physical capacity scores in paper I were not associated with type of primary drug, which implies that the chemical composition of the different drugs does not appear to influence physical capacity. This suggests that the reduced aerobic capacity and force generating capacity may be caused by an inactive lifestyle rather than the actual drug use. Taken together, a reduced 1RM and RFD will result in daily tasks being relatively heavier to carry out for the SUD patients than for healthy individuals, adding weight to an already challenging situation.

**Bone health among SUD patients with amphetamine as primary drug**

A few previous studies have indicated that amphetamine use may lead to reduced bone quality and increased risk of osteoporosis (47, 48, 144), and an association between amphetamine use and reduced bone health has been reported (47, 48, 144). These studies build their evidence up on measurements of the calcaneus (47) and BMD in the lumbar spine (48). Paper II in the current thesis was the first to report evidence that amphetamine users have impaired bone health at several skeletal regions, along with reduced bone quality in the lumbar spine. Almost half of the patients in our study had a T-score within the classification osteopenia, meaning lower BMD than normal, but not to the extent of osteoporosis.

Observations such as tooth decay and increased fracture rate among amphetamine users have led to the assumption that amphetamines have a negative effect on bone health. Although one study demonstrated that amphetamines might have a direct effect on bone metabolism (144) we cannot distinguish such an effect from the results in paper II. We found associations between bone quality and muscular strength in this study, which is in line with earlier studies on several different populations (145-147). In paper II we measured lower hack squat 1RM (30% in males and 25% in females) amongst amphetamine users than in healthy controls. Hack squat RFD was also reduced by 27% in the male amphetamine group. These findings expand the results from the SUD patients in paper I, and their association to an inactive lifestyle. It is likely that the reduced muscular function, possibly caused by inactivity, could be a mediator for the impaired bone health found in paper II. In paper I there were no differences on the physical capacity measurements observed between patients who had amphetamine or cannabis as their primary drug. Additionally, in paper II, the whole body scans revealed that the patients had a higher fat mass and less lean mass than the reference group. Low lean mass is usually caused by low levels of muscle activity (148, 149). It remains unclear which proportion of bone mass deterioration that may be caused by the amphetamine use, and which proportion that may be a result of inactivity. However, the results from paper I and paper II collectively suggest that lifestyle related alterations in muscle function may be an important factor contributing to impaired skeletal health. This topic should be addressed in future research.

Among the SUD patients with amphetamine as their primary drug and a history of extensive amphetamine use in paper II, impaired BMD and altered bone metabolism was observed. Despite the reduced bone mass, the serum levels of the bone formation marker P1NP was higher than both the healthy reference group and values typically expected among men and women at similar age. It is unlikely that this reflects an advantageous effect on bone turnover, and might therefore be a manifestation of a compensatory response (144). The bone resorption marker CTX did not differ between the groups. The amphetamine users in paper II showed relatively low levels of vitamin D, with serum 25-ODH level of 68 ± 24 (males) and 63 ± 17 (females). Serum concentrations of 25-OHD at 75 nmol/liter or higher are considered as optimal and desirable (150, 151). There is no standard definition of vitamin D deficiency. According to the WHO (2003), a serum 25-ODH level below 50 nmol/liter is considered as vitamin D insufficiency (152). In patients with osteomalacia, low levels of vitamin D has been associated with increased level of P1NP (153, 154). However, since the level of vitamin D was not significantly lower in the amphetamine group than the reference group we cannot assume that this alone explains the increased level of the bone formation marker.

**Exercise training interventions in SUD patients**

Paper I and II documented that SUD patients had attenuated physical health, and their physical health may be interrelated with their mental health. Therefore, in paper III and IV, we used well-established aerobic endurance (88, 90, 91, 93) and strength training (66, 109, 124, 155) interventions, respectively, to improve the SUD patients' physical health. Specifically, high aerobic intensity interval training was used to improve the patients $VO_{2max}$ in paper III, whilst MST was applied to improve maximal muscle strength, RFD and walking efficiency in paper IV. Additionally, we used a battery of questionnaires to evaluate the effect on mental health variables. Importantly, since SUD patients certainly represent a challenging patient population, we also aimed to evaluate not only the patients' physiological responses, but also the feasibility of the training interventions in a clinical setting.

**High aerobic intensity interval training in patients with SUD**

In paper III, 75% of the patients completed the training intervention. Although the applied intensity in the intervention in paper III may be somewhat strenuous, it is important to recognize that the intensity is not maximal. The high aerobic intensity training is organized to specifically target the stroke volume of the heart. The four minutes intervals are selected as a middle way between the time necessary to reach a sufficient blood flow, and the time resulting in too much lactate accumulation. Due to sluggishness of the blood flow, it takes ~1-2 minutes before a sufficient shear stress is placed on the heart (156). On the other hand, the upper end of the time spectrum is limited by the continuous lactate accumulation, resulting in about ~8 minutes as the maximal time at this given intensity (88). If several intervals are to be carried out, 4 minutes should be a simple and good strategy. The active rests at low intensity in the three minutes bouts between the high intensity intervals ensure the removal of lactate before the next 4 minute interval. Since the intervals are carried out walking or running uphill, they also place a very benign force on the joints, and thus represent a minimal risk for injuries. In accordance with this notion, no injuries or complications were reported in the current study.

Following the interval training, SUD patients improved $VO_{2max}$ by 15 ± 7%, which is in accordance with improvements observed in healthy (88), elderly (157), cardiovascular disease patients (90, 93), metabolic syndrome patients (158) and schizophrenic patients (92). The magnitude of the improvement is dependent on the fitness level at baseline; for a higher $VO_{2max}$ starting point, a lower improvement should be expected (159). For several patient populations the baseline values are very low (160-162), like in paper III. The large improvements following training should thus be expected to yield substantial health benefits. The 6.5 $ml \cdot min^{-1} \cdot kg^{-1}$ improvement in $VO_{2max}$ in paper III may be associated as much as a ~20% increase in survival and ~25% reduced chance of developing cardiovascular disease, as 3.5 $ml \cdot min^{-1} \cdot kg^{-1}$ differences in $VO_{2max}$ previously have been associated with 12% improved chance of survival (51) and a 15% reduced risk of developing cardiovascular disease (53). In addition to likely having large health benefits, the improved aerobic capacity in paper III likely also resulted in improved performance during daily activities. An improved aerobic endurance could either yield the potential to carry out more work throughout the day, or may cause the daily tasks to be less strenuous since the relative intensity is lower compared to before training (160, 163, 164). Notably, the SUD patients in the control group receiving conventional treatment did not improve $VO_{2max}$, despite of participating in the treatment clinics' mandatory activity program. One plausible explanation for this result might have been that the activities were carried out with too low aerobic intensity, since aerobic intensity is considered to be the most important factor for $VO_{2max}$ improvements (88, 165).

Paper III demonstrated that SUD patients' $VO_{2max}$ values can be restored to a level similar to an age-matched healthy population (166), and that the intervention was feasible in a clinical setting. Also the socioeconomic gain from these health improvements should be expected to be substantial, considering the reduced risk for this patient group to develop severe lifestyle diseases that acquire medical health care.

**Maximal strength training in SUD patients**

SUD patients exhibited large improvements in all strength measurements following the MST intervention in paper IV. Especially the improvement in 1RM was large (88 ± 54%) compared to other studies with the same training intervention (60, 109). However, the magnitude of improvement is likely exercise specific, and whereas most previous MST training studies (60, 109) have used a horizontal leg press, a hack squat apparatus was used in paper IV in the current thesis. This makes it difficult to compare the magnitude of improvement between studies.

The improvements in 1RM in paper IV were accompanied by large improvements in RFD (82 ± 28%). This is in accordance with previous studies (60, 107, 109), which also report similar improvements in RFD after 8 weeks of MST. The large improvements in 1RM and RFD without any alteration in body weight indicates that the strength gain is only minimally due to increased muscle mass, and may predominantly be caused by neural factors (107, 114).

The V-wave method applied in paper IV is a useful technique for expressing efferent neural drive to maximally contracting skeletal muscles. The method utilizes modulations of the muscle spindle reflex of the soleus muscle (H-reflex). More specifically, it reflects the amount of reflex potentials recorded in the muscle during supramaximal electrical stimulation, and depends largely on the magnitude of voluntary efferent drive. To allow comparisons between and within groups, the V-wave is normalized to the maximal M-wave (V/M-ratio). The V-wave potential origins from the reflex potential evoked during supramaximal electrical stimulation. While the amplitude of the V-wave is shown to increase following strength training (69, 167), the amplitude of the H-reflex is repeatedly reported to not change with strength training (167, 168). On this basis, any change in V-wave amplitude is argued to reflect a change in efferent drive, as it will allow more or less of the reflex to pass through to the muscle. Although the V/M-ratio cannot determine the influence from pre/post synaptic inhibition, it closely reflects any training-induced changes in efferent drive. In paper IV the

SUD patients exhibited large improvements in V/M-ratio (88%), suggesting that MST was indeed very effective in targeting neural adaptations. The improvements are in accordance with previous studies applying the V-wave method (169, 170), adding weight to the trainability of SUD-patients, also neurologically.

Importantly, as a result of the MST intervention, the SUD patients achieved large improvements in force generating capacity, restoring the SUD patients 1RM and RFD to a level that is similar to what was observed in the healthy age matched population. As a consequence, we can expect that the risk for falls and fractures (136) and premature death (137, 138) was counteracted, and that balance and body control was improved (171). The 8 week MST intervention was clearly very effective and feasible to carry out in the clinic. However, the large improvement in force generating capacity in untrained subjects is subject to detraining, especially in the functionally important concentric part of the muscular contractions (172). As this patient group may suffer a lack of initiative to continue exercising, clinical treatment should preferably offer a follow-up of the patients after their 3 month residence in the clinic. A follow-up training clinic may be a cost effective way to maintain, and even improve, the endurance and muscular strength capacities of the patient group.

**Compliance and dropout in the training studies**

One of the objectives in paper III and IV was to examine the feasibility of high intensity training in the clinic, and if the patient population were able to follow the two training regimes for eight weeks. In paper III, 9 out of 12 patients completed the high aerobic intensity endurance training. Two dropped out due to personal reasons, but completed their clinical treatment. One patient dropped out from the clinical treatment and thereby also from the training group. Whilst the two first drop outs may be ascribed to the training itself, the latter is difficult to determine if the reason is due to the clinical stay, the exercise training or other causes. However, a dropout rate of 2-3/10 has also been present in a healthy young population (88), indicating that this training modality and intensity is as feasible in SUD patients as in healthy subjects. Notably, the number dropping out from the SUD control group receiving conventional treatment was higher. Five patients, in contrast to one in the interval group, dropped out of the clinical treatment during the time of the intervention period. This certainly indicates that the high aerobic intensity endurance training is feasible, and may even be beneficial for completion of the clinical treatment.

As in paper III, 9 out of 12 patients completed the MST in paper IV. All 3 patients that dropped out from MST, also dropped out of clinical treatment. In combination, paper III and IV suggests that SUD patients indeed are capable of fairly strenuous endurance and strength training. Interestingly, 5 patients dropped out from the SUD control group also in paper IV. Although the number of participants in these two training study is relatively low, a ~67% higher dropout rate from the SUD control groups receiving conventional treatment is thought-provoking. Given that the conventional treatment also had no effect on the SUD patients' aerobic endurance or muscular strength, our results strongly suggests that the effective training in paper III and IV should be implemented as a part of clinical treatment. Since both high aerobic intensity endurance training and MST separately gave large improvements in different physiological key factors, we will argue that they should be carried out concurrently in a clinical treatment. Although it may be somewhat more challenging to do both the training modalities in one session, it is noteworthy that it takes less than one hour to complete a single concurrent training session. It is also possible that the patients may be more motivated by the "double effect". This should be a topic for future evaluation. Previously it has been shown that concurrent high aerobic intensity endurance training and MST appears to have similar effects as when the respective interventions are carried out alone (117, 173).

**Associations between physical and mental health**

In the current thesis, data on psychological variables were collected in paper I and II. Our results are in line with previous studies documenting that SUD, depression and anxiety are closely associated (78, 174, 175). The SUD patients scores in this thesis was "moderately severe insomnia" according to ISI and showed presence or signs of anxiety and depression on the HAD scale. Interestingly, when data from both cross sectional studies were combined we observed that female SUD patients with lower muscle strength than average had a higher anxiety level compared with female patients with higher muscle strength than average. Similarly, male SUD patients with lower strength than average had higher depression level than male patients with higher muscle strength than average. This association between muscle strength and anxiety and depression is in accordance with a cohort study by Ortega et al (55) where a large sample of 1 142 599 Swedish male adolescents, age 16-19 years, were followed over a 24 year period. In the Ortega et al. study (55) it was documented that muscular strength was associated with a psychiatric diagnosis as well as premature death (caused by diseases and suicide). Loss of muscular strength is shown to appear with aging, disease or inactivity.

Inactivity, which is proposed as a possible cause of the high risk of illness and early death among SUD patients earlier in this thesis, is in several studies also associated with mental illness (80, 176).

**Beneficial effects of physical health improvements on mental health**

Given the large improvements in aerobic endurance and muscular strength the SUD patients achieved in the two training interventions (paper III and IV), it was somehow unexpected that we were not able to detect between-group differences in the psychological variables between the SUD training groups and the SUD control groups. However, following the high aerobic intensity training (paper III) we did find reductions in depression level in the training group at posttest, but between-group differences on these two variables were not found. In paper IV both groups displayed reduced anxiety level after the MST intervention and the level of insomnia was decreased in the MST group, but again no between group differences were observed. There are several possible explanations for the lack of differences in the psychological variables in our studies. Firstly, the intervention studies have quite small sample sizes. Secondly, it is reasonable to question whether the self-report questionnaires used are appropriate tools for detecting the mental health benefits from a physical training intervention. A third possibility is that the improvements of the psychological variables within the groups were more related to the physical activity in general (both the training interventions and the physical activities in the conventional treatment), and not necessarily to the training interventions (79). There is a broad agreement that physical activity has a positive influence on mental health (79, 177, 178). However, the knowledge about physical capacities' importance for mental health is scarce (177). A few studies have documented that improved aerobic endurance have beneficial effects on psychological outcomes as depression and anxiety (80, 179, 180). With the large improvements in physical capacity, and subsequent reduced risk of developing lifestyle diseases and early death, further investigation is needed to find possible effects on mental health.

**Future perspective**

Although all patients were diagnosed within the same diagnostic criteria system (ICD-10) for SUD, it might be a limitation that all patients in this thesis were recruited from the same treatment clinic. Thus, it would be beneficial in future research if our results were confirmed from other clinics as treatment programs may be different. Furthermore, although the sample size in our studies was sufficient with regards to the main physiological variables and hypothesis, the mental variables, assessed by questionnaires, would likely have benefitted from a larger sample size. Nevertheless, the observations in the four papers in this thesis suggest that exercise should be an essential part of clinical treatment programs. If carried out in accordance with procedures described in papers III and IV, exercise will likely give substantial health and performance benefits, reduce the risk of developing comorbid diseases in addition to the SUD, reduce socioeconomic costs and perhaps improve mental health. Although physical activity is not novel in SUD treatment, the activities seem random and unstructured and typically involve only low to moderate intensity exercise with regards to both endurance and strength. Paper III and IV documented no improvements in $VO_{2max}$ or muscular strength in the SUD control groups after eight weeks in treatment, despite a wide activity program included in the weekly treatment program. Approximately one hour, four days a week, was set aside for activities like yoga, stretching and low resistance strength training. In this thesis we have shown how it is feasible to obtain substantial improvements from high aerobic intensity interval training and MST in this population within eight weeks, and that it is feasible both among the SUD patients and within the clinical frame. Thus, this should also be advocated as a part of a standard future clinical treatment.

Implementing effective physical training in the clinical treatment program certainly had its challenges. Completing these projects was rewarding and demanding in several ways. Although supervising, training and testing were time consuming, it was typically easy to collaborate with the patients and they were appreciative of the training. In contrast, somewhat surprisingly, although the studies were supported by the clinic, it was difficult to administer and coordinate the logistics revolving around the patients' training with the employees in the clinic. This may represent a challenge for implementing the effective training in similar clinics in the future, and detailed explanation of the purpose and potential effect of the training should be emphasized. The papers in this thesis clearly documents that not only is it feasible, the SUD patients also appear to appreciate the initiative, and it does not interfere with their daily routines. The patients also reported that they liked the challenge that the training and testing amounted. Finally, a question that should be posed is why should we have lower expectations to SUD patients to care about own health and capability of completing a training intervention than other patient populations? When recruiting patients to the project, we were clear about the expectations from them as participants, and that the expectations were the same as from other populations. This seemed to motivate them for committing to the project. We recognize that these are only non-documented observations from the researchers, but it may still be an important notion if the aim is to implement effective training in clinics. Systematic information to, and support from, all employees in the clinic may facilitate the training implementation.

## CONCLUSION

SUD patients exhibited a systematically attenuated physical health compared to what is typically observed in the healthy population. Specifically, this was evident as a reduced $VO_{2max}$, walking efficiency, 1RM, RFD and BMD. These reductions imply that the patient group suffers a higher risk of developing cardiovascular disease, other lifestyle diseases and early death compared to the healthy population. The aerobic endurance and muscular strength impairments were systematically present regardless kind of primary drug, which indicate that the reductions may rather be caused by an inactive lifestyle than the direct effects of the various drugs. In contrast, high aerobic intensity interval training- and MST restored the SUD patients' physical health to a level similar to what is observed in the healthy population. Although challenging, the training interventions were feasible in the clinic, with a low drop-out rate. In combination, our results suggest that the training interventions carried out in this thesis should be advocated as a part of SUD treatment programs. This may not only have beneficial effects on the SUD patient's physical and mental health, but may also reduce socioeconomic costs.

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# Paper I

Medicine®

Observational Study

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# Impaired Aerobic Endurance and Muscular Strength in Substance Use Disorder Patients

## *Implications for Health and Premature Death*

*Grete Flemmen, MSc and Eivind Wang, PhD*

**Abstract:** Although substance use disorder (SUD) patients are documented to have an inactive lifestyle, which is associated with cardiovascular disease, other lifestyle-related diseases and premature death, evidence regarding their aerobic endurance and muscular strength is limited. Therefore, the authors aimed to evaluate directly assessed maximal oxygen consumption, walking efficiency, as well as maximal strength in a group of SUD patients.

A total of 44 SUD patients in residential treatment, 31 men (31 ± 8 years) and 13 women (34 ± 10 years), were included and completed the physical testing. The patients were compared with an age- and sex-matched reference group.

Male and female SUD patients exhibited a maximal oxygen consumption of 44.6 ± 6.2 and 33.8 ± 6.6 mL· $min^{-1}$ $kg^{-1}$, respectively. This was significantly lower than the reference group, 15% ($P = 0.03$) for men and 25% ($P = 0.001$) for women. In addition, the SUD patients had a 13% significantly reduced walking efficiency ($P = 0.02$), compared with healthy controls. The impairments in aerobic endurance were accompanied by significant reductions in maximal strength of 30% ($P = 0.001$) and 33% ($P = 0.01$) for men and women, respectively. In combination, these results imply that SUD patients have impaired endurance and muscular strength compared with what is typically observed in the population, and consequently suffer a higher risk of developing cardiovascular and other lifestyle-related diseases and early death. Effective physical exercise should be advocated as an essential part of the clinical practice of SUD treatment to improve the patient's health and consequently reduce the costs because of the high use of emergency departments, hospital, and medical care.

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**Abbreviations**: $HR_{max}$ = maximal heart rate, ICD-10 = International Classification of Diseases rev 10, $[La^-]_b$ = lactate concentration in blood, MET = maximal metabolic equivalent, 1RM = one repetition maximum, Q = cardiac output, RER = respiratory exchange ratio, RFD = rate of force development, SUD = substance use disorder, $V_E$ = ventilation, $VO_{2max}$ = maximal oxygen consumption.

## INTRODUCTION

Patients with substance use disorder (SUD), classified within International Classification of Diseases rev 10; F10–19 (World Health Organization's classification 1990) have in addition to their mental and behavioral disorders an increased prevalence of cardiovascular disease,[1] cancer,[1] attenuated bone health,[2] and a decreased life expectancy of 15 to 20 years, the lowest among patients with different mental illnesses.[3] Undoubtedly, various causes contribute to the mental as well as physical problems that substance users suffer.[3] Evidence, however, is limited regarding the patient groups' physical health status and its likely influence on their overall health problems, cardiovascular system, and muscle strength and function, especially through direct assessment of key factors, such as maximal oxygen consumption ($VO_{2max}$), walking efficiency, maximal strength, and muscle force development characteristics.

$VO_{2max}$, commonly also referred to as cardiorespiratory fitness and given in maximal metabolic equivalents (METs), is one of the strongest predictors for mortality from cardiovascular disease and other causes.[4–6] Analyzing several risk factors, Wei et al[4] observed that a low $VO_{2max}$ resulted in a similar, if not greater, relative risk of mortality compared with established risk factors, such as diabetes mellitus, high cholesterol levels, hypertension, and cigarette smoking. The relative risk of mortality has been quantified from estimated $VO_{2max}$ showing that a reduction of 1 MET (~3.5 mL· $min^{-1}$ $kg^{-1}$) corresponded to a 12% increase in mortality.[5] More recently, this was confirmed by Kodama et al[6] who observed a decrease of 1 MET to be associated with a 13% to 15% higher risk of all-cause mortality and coronary heart disease.

Not only $VO_{2max}$, but also skeletal muscle strength has been increasingly recognized as a considerable risk factor for mortality,[7,8] cardiovascular disease,[8] and cancer.[7] The mortality risk from impaired muscle strength is comparable with the elevated risk from hypertension and obesity.[8] Reduced muscle strength is also shown to result in poor bone health[9] and an absence of sufficient muscular overload, through lack of physical activity or resistance training, will consequently induce bone loss.[10] Thus, the synergetic effect between muscular strength and $VO_{2max}$ should be emphasized in clinical practice as prevention and treatment of cardiovascular disease as they in combination represent a substantial risk reduction.[11]

Importantly, both a reduced $VO_{2max}$ and low muscular strength are also shown to be associated with a poor mental health.[8,12] $VO_{2max}$ is in several studies associated with diagnosis of psychosis or schizophrenia,[13,14] and a low muscular strength is associated with a 20% to 30% increase in suicide rate in young adults.[8] The number of suicides in SUD patients may be even higher than in the general young population as a significant part of deaths are because of drug overdose,[1,3] and it is difficult to determine if this is because of accidents or suicide. Although causality is difficult to interpret from these findings, a low physical fitness typically leads to loss of daily functions, which in turn are associated with depressive symptoms. In contrast, physical activity is documented to be an effective countermeasure.[15]

Although documentation of SUD patients' physical health, through direct assessment of $VO_{2max}$ and muscular strength is limited, a few studies are indicating that the patient group is indeed at risk. Recent research has evaluated the effects of aerobic endurance training and shown that SUD patients had a ~20% lower $VO_{2max}$ than what is typically seen in the population.[16] Our results were in line with observations from methamphetamine dependents, revealing severely reduced $VO_{2max}$ values,[17] and SUD patients in a rehabilitation project, which displayed values of $39 \pm 10$ (men) and $31 \pm 8$ (women) $mL \cdot min^{-1} kg^{-1}$ in ~30-year-old patients.[18] Although it lacks a comparison with healthy individuals, one recent study[17] documented that SUD patients' reduced $VO_{2max}$ may be accompanied by reductions in maximal muscle strength with reported values as low as ~60 kg in leg press and ~40 kg in chest press. It, however, is difficult to interpret these findings because joint angle are not reported and apparatus construction is not known, and these factors are clearly relevant for comparison with other populations. Despite that, muscular strength reductions often accompany inactivity-related reductions in $VO_{2max}$; this is to our knowledge the only study that has indicated that SUD patients may have an impaired muscular strength.

Although a few studies imply that SUD patients may be at risk for cardiovascular disease, other lifestyle-related diseases and premature death because of their reduced cardiorespiratory and muscular fitness, there is a clear need for a more robust assessment of the SUD patients' physical health across sex, age, and primary drug dependence. Therefore, the aim of this study was to directly assess the patients' muscular strength as well as aerobic endurance. Specifically, our hypothesis was that SUD patients had a significantly reduced $VO_{2max}$, walking efficiency, maximal muscle strength, and muscle rate of force development (RFD) compared with an age- and sex-matched control group.

## METHODS

### Patients

We included 44 patients, 13 women (age $34 \pm 10$ years; weight $80.0 \pm 20.3$ kg; and height $165 \pm 6$ cm) and 31 males (age $31 \pm 8$ years; weight $85.1 \pm 15.9$ kg; and height $181 \pm 7$ cm), with a diagnosis of SUD; International Classification of Diseases rev 10: F10–F19 (mental and behavioral disorders because of psychoactive substance use). Twenty-two of the men and 9 of the women were current smokers, respectively. Patients' medical use is given in Table 1. Patients were all in a ~3 months' full-time residential treatment program. All patients agreed voluntarily to participate in the study and signed a written informed consent. Patients were excluded if they had been abstinent from drugs for the last 6 months or if they had impairments or injuries that prevented them from completing the treadmill and/or strength tests. All patients who fulfilled the inclusion criteria who arrived in the treatment clinic in a 6 months period were included in the study. The patients' physical performance was compared with a healthy age- and sex-matched reference group, targeted to exhibit what is typically observed in the population, consisting of 14 women (age $34 \pm 8$ years; weight $68.8 \pm 7.9$ kg; and height $171 \pm 5$ cm) and 11 men (age $37 \pm 9$ years; weight $89.3 \pm 10.9$ kg; and height $183 \pm 6$ cm), recruited among students and employees at the local University Hospital. A total of 20% of the controls (one of the men and 4 of the women, respectively) were current smokers. The regional medical ethics committee approved the study and it was carried out in accordance with the Helsinki Declaration.

**TABLE 1.** Substance Use Disorder Patients' Drug Use and Prescribed Medicine

| | Man (n = 31) | Woman (n = 13) |
|---|---|---|
| Primary Drug | | |
| Heroin | 2 | — |
| Benzodiazepines, Sed, hypnotic | 1 | 1 |
| Amphetamine | 20 | 10 |
| Cannabis | 8 | 2 |
| Secondary Drug | | |
| Alcohol | 1 | 3 |
| Heroin | 5 | 1 |
| Opiates, painkillers | 4 | — |
| Cocaine | 2 | — |
| Amphetamine | 4 | 1 |
| Cannabis | 14 | 8 |
| Hallucinogens | 1 | — |
| Prescribed Medicines for Symptoms | | |
| Attention deficit hyperactivity disorder | 3 | 2 |
| Allergies | 4 | 4 |
| Anxiety | 4 | 2 |
| Arthritis | 4 | 1 |
| Asthma/chronic obstructive pulmonary disease | 4 | 2 |
| Depression | 5 | 2 |
| Epilepsy | 6 | 1 |
| Hypertension | 3 | 1 |
| Infections | 1 | 3 |
| Schizophrenia/bipolar | 9 | 5 |
| Skin disorder | 2 | 2 |
| Substitutional treatment | 4 | 2 |
| Other | 8 | 3 |

Data are presented as mean ± SD. Prescribed medicines in substitutional treatment are methadone and suboxone. Other prescribed medicines: skin disorder, pain, and inflammation. Sed = sedatives.

### Testing Procedures

#### Maximal Oxygen Consumption and Walking Efficiency

After a warm-up period of 10 minutes, patients started the 5 minutes walking efficiency test at 5% inclination and $4.5 km \cdot h^{-1}$. Oxygen consumption was obtained every 10 seconds (Metamax II Cortex Biophysik GmbH, Leipzig, Germany), and net walking efficiency was calculated as an average of the last minute as

$$\text{Net waliking efficiency} = \frac{\text{External work accomplished (Kcal·min}^{-1}\text{)}}{\text{Energy expenditure (Kcal·min}^{-1}\text{)}} \cdot 100$$

where oxygen consumption and work both were expressed as kcal to express walking percentage efficiency.[19] Continuously from the walking efficiency test, the patients progressed to the $VO_{2max}$ test, which consisted of an incremental ramped protocol till exhaustion, where velocity was increased by 1 km·h$^{-1}$ every minute and inclination kept constant at 5%. Maximal oxygen consumption was calculated as an average of the highest 30-second window. Pulmonary ventilation and respiratory exchange ratio were averaged in the same period as the $VO_{2max}$. Criteria for reaching $VO_{2max}$ were used in accordance with previous literature.[20] Heart rate measurements were obtained using heart rate monitors (Polar Electro, Finland), and maximal heart rate was estimated as 3 to 5 beats·min$^{-1}$ added to the highest heart rate during the last minute.[20] After completion of the $VO_{2max}$ test, a fingertip blood sample was taken for measurements of lactate concentration in blood (Biosen C_line, EKF Diagnostics GmbH, Barleben, Germany).

### Maximal Strength and Rate of Force Development Measurements

After 2 warm-up sets, one repetition maximum (1RM) was performed in a hack squat machine (Impulse Fitness IT7006, Shandong, China). The patients started in a standing position and then moved eccentrically down to a 90° knee angle position. After a fraction of a second stop, the patient then moved concentrically with a fast intended velocity. The correct knee angle position was assessed with a goniometer. The load was increased with increments of 10 kg, and 1RM was achieved within 4 to 8 lifts. The patients had rest periods of 4 minutes between their attempts. After completion of the 1RM test, RFD was measured using a force plate (9286AA, Kistler, Switzerland) in the same apparatus with a weight corresponding to 75% of 1RM. Measurements were obtained with a 2000 Hz frequency (Bioware v3.06b, Kistler, Switzerland). As for the 1RM test, the patients were instructed to try and lift the weight as fast as possible in the concentric movement. The highest RFD among 3 attempts was used for the data analysis, and patients had 3 minutes rest periods between their attempts.

### Statistical Analysis

Statistical analyses were performed using the SPSS, version 20, software program (Chicago, IL), and figures were made using the software GraphPad Prism 5 (San Diego, CA). Independent samples *t* test were used to compare differences between the SUD patient group and the reference group. Correlations between primary substance use, sex, age, substance use history, and physical capacity were analyzed using linear Pearson correlation regression analysis. Results were considered statistically significant at a 2-tailed level of $P < 0.05$. Data are presented as mean ± SD unless otherwise stated.

## RESULTS

All 44 SUD patients [21–30 years (n = 23); 31–40 years (n = 14); and 41–50 years (n = 7)] in residential treatment and the 25 control age- and sex-matched patients [21–30 years (n = 10); 31–40 years (n = 7); and 41–50 years (n = 8)] completed the $VO_{2max}$ test, walking efficiency test, and strength tests. No differences were observed in body mass between the 2 groups, but female SUD patients tended ($P = 0.08$) to be heavier than the controls.

### Aerobic Endurance

Maximal oxygen consumption was significantly lower in SUD patients compared with the reference group (Table 2), this was apparent for both sexes (Fig. 1A). Women and men displayed reductions of 25% ($P = 0.001$) and 15% ($P = 0.03$), respectively. The lower aerobic power was consistently present in all age groups (Fig. 1B). No significant differences were observed between patients who had amphetamine (n = 30) or cannabis (n = 10) as their primary drug (Fig. 2). Maximal oxygen consumption correlated significantly with years of drug use; however, this correlation was not present when it was adjusted for age.

As for the maximal aerobic power, the SUD patients' aerobic endurance at a submaximal level below anaerobic threshold was also impaired. No differences were observed between women and men in walking efficiency and as a consequence, data were collapsed (Table 3; Fig. 3). The impairment was apparent as a 12% ($P = 0.05$) higher oxygen cost of walking at 4.5 km/h at 5% inclination (Fig. 3A), and this was mirrored by a 13% ($P = 0.02$) reduction in walking efficiency (Fig. 3B). This was further accompanied by a significant increase in ventilation ($P = 0.042$) and respiratory exchange

**TABLE 2.** Physiological Variables Measured During a Maximal Oxygen Uptake Test

| | SUD Patients (n = 44) | | Reference Group (n = 25) | |
|---|---|---|---|---|
| | Male (n = 31) | Female (n = 13) | Male (n = 11) | Female (n = 13) |
| $VO_{2max}$, L·min$^{-1}$ | 3.74 ± 0.62** | 2.60 ± 0.35** | 4.56 ± 0.44 | 3.10 ± 0.31 |
| VE, L·min$^{-1}$ | 113.6 ± 19.5* | 77.4 ± 13.7** | 131.5 ± 17.5 | 95.9 ± 11.5 |
| RER | 1.15 ± 0.07 | 1.13 ± 0.07 | 1.13 ± 0.04 | 1.11 ± 0.03 |
| $HR_{max}$, beat·min$^{-1}$ | 185 ± 10 | 181 ± 13* | 192 ± 11 | 190 ± 10 |
| $[La^-]_b$, mM | 9.98 ± 2.8 | 7.37 ± 2.12* | 12.03 ± 3.23 | 8.82 ± 1.31 |

Data are presented as mean ± SD. $HR_{max}$ = maximal heart rate, $[La^-]_b$ = lactate concentration in blood, RER = respiratory exchange ratio, SUD = substance use disorder; VE = ventilation, $VO_{2max}$ = maximal oxygen uptake.

* $P < 0.05$.

** $P < 0.01$. Significant differences between patient group and reference group.

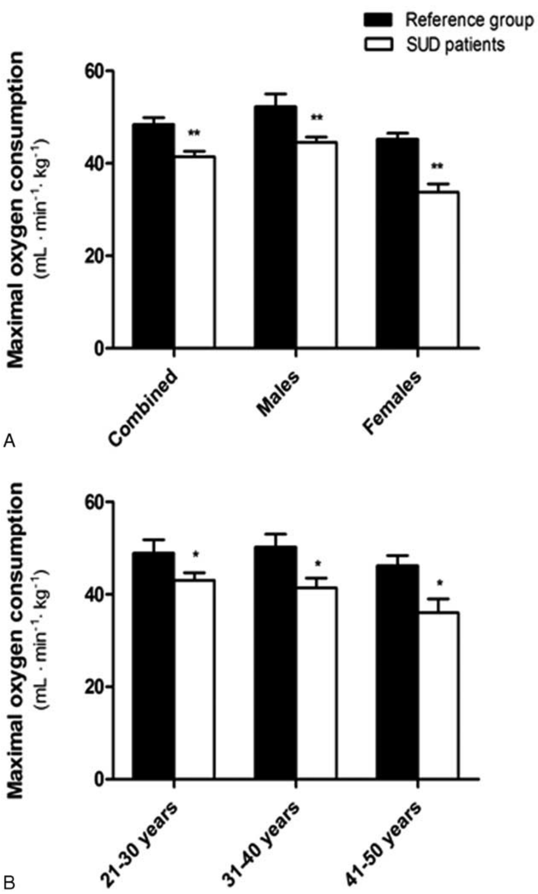


**FIGURE 1.** A, Substance use disorder patients' maximal oxygen consumption were compared with the reference group, both sexes and combined. Data are presented as mean ± SE. **Significant difference between the reference group and SUD patients ($P < 0.01$). B, Maximal oxygen consumption, comparing SUD patients and reference group, all age groups. Data are presented as mean ± SE. *Significant difference between the groups ($P < 0.05$). SUD = substance use disorder.

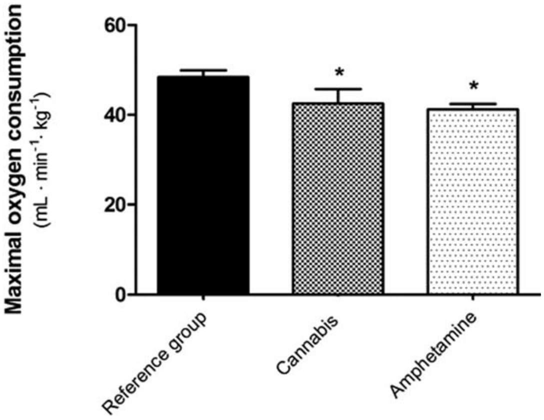


**FIGURE 2.** Maximal oxygen consumption in patients with amphetamine or cannabis as their primary drug, was compared with reference group. Data are presented as mean ± SE. *Significant difference between the groups ($P < 0.05$). No significant differences between the 2 drug categories.

ratio ($P = 0.001$) among the SUD patients. Systematically, the impairments were exhibited in both women and men and across age.

## Muscular Strength

Substance use disorder patients had a significantly lower maximal muscle strength compared with the reference group, with 1RM reductions of 30% ($P = 0.001$) and 33% ($P = 0.010$) in men and women, respectively (Fig. 4A). A significant $r = 0.36$ correlation between 1RM and RFD was observed ($y = 4.0x + 874$; 95% confidence interval: 1.4–6.5 and 555–1193; $P < 0.01$), and the reductions in 1RM were accompanied by a clear tendency toward a reduced RFD (Fig. 4B), expressing 20% and 15% reductions in men and women, respectively, compared with healthy controls. Because an association between muscular strength and walking efficiency, has been established previously, the strength parameters and walking efficiency were tested against each other, revealing that the RFD significantly correlated ($r = 0.38$) with walking efficiency ($y = 0.0037x + 17.9$; 95% confidence interval: 0.0013–0.0062 and 14.3–21.4; $P < 0.01$), whereas 1RM did not. Furthermore, the differences in maximal strength and RFD between SUD patients and the reference group were consistently present for all age groups, but were not affected by the drug type dependency.

## DISCUSSION

Because $VO_{2max}$ and muscular strength are strong predictors for physical and mental health, but evidence of directly assessed aerobic endurance and strength components rarely has been presented, our aim was to present such components and evaluate their implications for health in SUD patients. The main findings of the current study were that SUD patients have a reduced $VO_{2max}$ compared with what is typically observed in the population; aerobic endurance is further reduced because of reductions in walking efficiency; the aerobic endurance impairments were accompanied by reduced maximal strength and ability to perform rapid muscle contractions; and the

**TABLE 3.** Walking Economy at 4.5 km/h, 5% Inclination on a Treadmill

| | SUD Patients (n = 44) | Reference Group (n = 25) |
|---|---|---|
| $VO_2$, mL·min$^{-1}$·kg$^{-1}$ | 19.1 ± 1.6* | 18.0 ± 1.6 |
| VE, L·min$^{-1}$ | 36.4 ± 7.6* | 32.2 ± 6.5 |
| RER | 0.91 ± 0.04** | 0.87 ± 0.04 |
| %$HR_{max}$ | 64 ± 8 | 61 ± 8 |

Data are presented as mean ± SD. %$HR_{max}$ = percentage of maximal heart rate, RER = respiratory exchange ratio, SUD = substance use disorder, VE = ventilation, $VO_2$ = oxygen uptake.
* $P < 0.05$.
** $P < 0.01$. Significant differences between patient group and reference group.

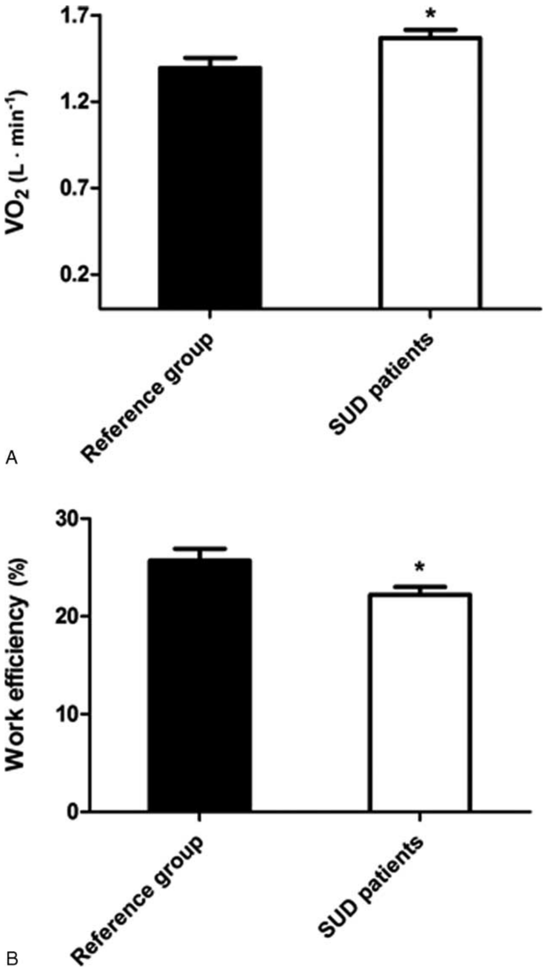


**FIGURE 3.** A, Oxygen cost of walking at 4.5 km·h$^{-1}$ at 5% inclination on the treadmill, comparing reference group with substance use disorder patients. Data are presented as mean ± SE. *Significant difference between the groups ($P < 0.05$). B, Walking efficiency at 4.5 km/h at 5% inclination on the treadmill, comparing reference group with substance use disorder patients. Data are presented as mean ± SE. *Significant difference between the groups ($P < 0.05$).

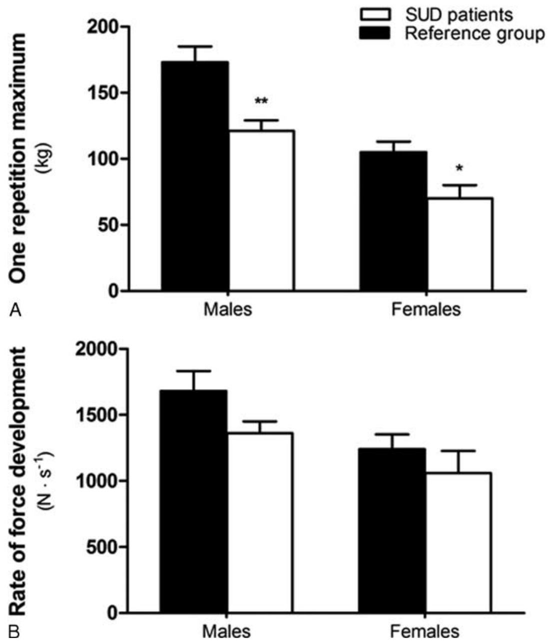


**FIGURE 4.** A, Muscular strength (one repetition maximum) in substance use disorder patients and reference group. Data are presented as mean ± SE. *Significant difference between the groups ($P < 0.05$) and **($P < 0.01$). B, Rate of force development in substance use disorder patients and reference group. Data are presented as mean ± SE.

impairments in aerobic endurance and muscular strength were systematically present across age, sex, primary drug, and history of substance use. In combination, these findings imply that SUD patients indeed are at risk for developing cardiovascular disease, cancer, attenuated bone health, and premature death, and that inactivity may be responsible, at least in part, for the physical health reductions.

## Maximal Oxygen Consumption and Substance Use Disorder

Substance use disorder patients in the current study exhibited a systematically reduced $VO_{2max}$ compared with healthy controls. The values of the patients in this study are also below what recently was reported as reference data for the Norwegian population.[21] Specifically, the women in our study showed a large attenuation in aerobic power, equivalent to what is observed with ~25 years of aging,[22] and associated with a ~25% increased risk of mortality.[5,6] The reduction in $VO_{2max}$ was not related to the patients' drug type dependency (Fig. 2), and was present for all age groups (Fig. 1B). Although well below what is typically observed in the population, our $VO_{2max}$ results are somewhat higher than previous studies that have observed values of 39 (men) and 31 (women) mL· min$^{-1}$ kg$^{-1}$,[18] 32 (indirectly estimated for men and women combined) mL· min$^{-1}$ kg$^{-1}$,[23] and 31 (men) and 23 (women) mL· min$^{-1}$ kg$^{-1}$.[17] The discrepancy between these results may be because of the different populations tested, indirect or direct measurements of oxygen uptake, testing modality (i.e., bicycle or treadmill), and protocol. In combination, our study and previous studies are in agreement, observing that SUD patients, however, have a reduced $VO_{2max}$, and thus have an elevated risk for cardiovascular disease, other lifestyle-related diseases and premature death. Alterations in $VO_{2max}$ is suggested to primarily be caused by changes in cardiac output and function,[24] and a causality has been shown both with training[25] and detraining.[26] This implies that the very low $VO_{2max}$ that is observed in SUD patients is likely accompanied by a severely reduced cardiac output, and that this may be one of the factors that can explain the high prevalence of cardiovascular disease within the patient group.

## Walking Efficiency

Contributing to an overall reduced aerobic endurance in SUD patients in the current study was also a reduction in walking efficiency. Walking efficiency is approximately 25% in healthy individuals,[27] and our observation of 26% among the healthy controls was in line with this. In contrast, the SUD patients exhibited a 13% lower efficiency, meaning that not only do they have to work on a higher percentage of their $VO_{2max}$ when carrying out daily tasks, but they also have to do the certain amount of work with a larger cost of energy compared with healthy individuals. This is adding weight to an already challenging situation and certainly contributes to the negative spiral toward even more inactivity, and an aggravation of the calamitous lifestyle. The decreased walking efficiency has to our knowledge not been documented in SUD patients before, and was present for both men and women in all age groups (Fig. 3). Thought provoking, their walking efficiency is similar to an efficiency that is observed among 50-year-old men and women.[28] Again, as for the $VO_{2max}$ measurements, the reduced efficiency was not associated with the substance use history or drug type dependency, and advocates that the SUD patients' lifestyle, and absence of sufficient activity, may be the explanation for their weakened aerobic energy production.

## Maximal Muscle Strength, Force Development Characteristics and Substance Use Disorder Patients

In addition to endurance, skeletal muscle strength is important for the assessment of an individuals' physical health. The current study show that SUD patients exhibited significant maximal strength reductions compared with the healthy controls. Although strength training has previously been applied on SUD patients in residential treatment,[17] it has, to our knowledge, not been known how their strength relates to what is observed in healthy patients. The 33% (men) and 30% (man) reduced strength in SUD patients in our study corresponds to what is observed with 30 to 40 years of aging,[29] and puts the patients at an elevated risk for falls and fractures,[30] premature death,[8,31] and possibly cancer.[31] Importantly, reductions in maximal strength are usually accompanied by reductions in muscle RFD.[19,32] Therefore, it was not surprising that in the current study, RFD was correlated with 1RM. Rate of force development may be an even more important predictor for physical function[30] compared with maximal strength because it is more related to functional tasks, balance adjustments, and prevention of falls, where the time to reach maximal strength is limited. The 15% to 20% lower RFD among the SUD patients in this study may contribute to more challenging everyday situations and risk of injuries.

A relationship between muscular strength and aerobic endurance has also been established, specifically through the effects of RFD on aerobic work and walking efficiency.[33,34] It is suggested that alterations in RFD will lead to changes in the force–velocity curve,[33] resulting in changes in oxygen demand in the working muscle, and consequently changes in blood flow.[34] Indeed, a correlation between RFD and walking efficiency was documented in this study, and it is likely that a poor RFD in the SUD patients have resulted in a worsening of their aerobic endurance in accordance with previous literature.[19,32]

## Physical Health in Substance Use Disorder Patients: Implications for Mental Health

Previously, both $VO_{2max}$ and muscular strength have been observed to be predictors for mental health.[8,12] A weakened aerobic endurance has been associated with depression[12] and psychosis,[13] whereas muscular strength have been associated with psychiatric diagnoses and even suicide.[8] Although it is often difficult to establish a cause–effect relationship, it has been demonstrated that aerobic endurance training can decrease depression.[16] Enhanced physical health may lead to an improved mental health because of changes in the individual's perception of physical as well as social factors. Because SUD patients in the current study display large reductions in both endurance and muscular capacity and function, it is likely that this is associated with their mental health. It is an interesting topic of future research if effective physical training may be able to improve their mental state, and thus ultimately also have an effect on their substance use.

## Reduced Physical Health in Substance Use Disorder Patients: Clinical Treatment Perspectives

Although the sample size in the current study is relatively small, our results indicate that SUD patients have a reduced aerobic endurance and muscular strength, consequently putting them at risk for diseases, premature death, and an aggravation of their mental health. The SUD patients' attenuated physical health likely has multifactorial causes. Drug use and cigarette smoking may directly have contributed to the reduced physical health observed in the current study. Indeed, especially cigarette smoking is well documented to effect cardiorespiratory function and consequently reduce exercise capacity[35,36] as well as increase the risk of cardiorespiratory diseases.[37] In addition, the patient groups' inactivity-related lifestyle may indirectly have affected their aerobic endurance and muscular strength as the lack of activity previously has been shown to dramatically reduce both aerobic endurance[26] and muscular strength.[38] Exercise training is shown to work as an effective countermeasure for reduced endurance and strength, and should be emphasized as a part of the clinical treatment. Although today's treatment of SUD patients commonly includes physical activity, it appears random and unstructured, without the sufficient training intensity to have a robust effect.[16] Importantly, high intensity is favorable to yield the most optimal effects both for endurance[25] and muscular strength,[39] and documented to be feasible and effective also for untrained patient populations.[16,32] Therefore, as one element to counteract the SUD patients from spiraling down the physical and mental cascade toward more inactivity and substance dependence, effective training for improving aerobic endurance, muscular strength, and function should be applied in the clinics, preferably targeting the optimal exercise intensity and modality.

# CONCLUSIONS

Applying direct assessment of physiological variables, our findings show that SUD patients have a reduced $VO_{2max}$, walking efficiency, maximal strength, and ability to rapid force development compared with healthy individuals. Because reductions in these physiological factors are associated with an elevated risk of cardiovascular disease, cancer, poor bone quality, premature death, and mental health, effective exercise training should be a part of the clinical treatment of the patient group. This may not only have a beneficial effect on the patients' physical and mental health, but could also reduce socioeconomic costs.

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# Paper II

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# Paper III

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*Clinical Study*

# High-Intensity Interval Training in Patients with Substance Use Disorder

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Patients with substance use disorder (SUD) suffer a higher risk of cardiovascular disease and other lifestyle diseases compared to the general population. High intensity training has been shown to effectively reduce this risk, and therefore we aimed to examine the feasibility and effect of such training in SUD patients in clinical treatment in the present study. 17 males and 7 females (32 ± 8 yr) in treatment were randomized to either a training group (TG), treadmill interval training in 4 × 4 minutes at 90–95% of maximal heart rate, 3 days a week for 8 weeks, or a conventional rehabilitation control group (CG). Baseline values for both groups combined at inclusion were 44 ± 8 (males) and 34 ± 9 (females) $mL \cdot min^{-1} \cdot kg^{-1}$, respectively. 9/12 and 7/12 patients completed the TG and CG, respectively. Only the TG significantly improved (15 ± 7%) their maximal oxygen consumption ($VO_{2max}$), from 42.3 ± 7.2 $mL \cdot min^{-1} \cdot kg^{-1}$ at pretest to 48.7 ± 9.2 $mL \cdot min^{-1} \cdot kg^{-1}$ at posttest. No between-group differences were observed in work economy, and level of insomnia (ISI) or anxiety and depression (HAD), but a significant within-group improvement in depression was apparent for the TG. High intensity training was feasible for SUD patients in treatment. This training form should be implemented as a part of the rehabilitation since it, in contrast to the conventional treatment, represents a risk reduction for cardiovascular disease and premature death.

## 1. Introduction

Patients with substance use disorder (SUD), classified within ICD-10: F10-19 (mental and behavioral disorders due to psychoactive substance use) at the World Health Organization's mental and behavioral disorders classification, have a high prevalence of health and psychosocial problems in addition to their substance use disorder [1]. Although this patient group's disorder indeed has multifactorial causes, the evidence of how their physical capacity may be related to their calamitous lifestyle is sparse. Contributing to a decreased life expectancy of 15–20 years, the lowest among patients with different mental illnesses [2, 3] is an increased prevalence of cardiovascular disease [4–6]. The high risk of developing cardiovascular disease is associated with the population's drug use, poor nutrition, and obesity but is also likely a direct result of the patient group's inactivity [3].

Endurance training, especially with emphasis on high intensity, is shown to increase aerobic power and reduce the risk of cardiovascular disease [7–10]. Improvements of 10–30% in maximal oxygen consumption ($VO_{2\,max}$) have typically been observed in these studies, after training interventions of 2-3 months. These improvements may also be associated with large reductions in the risk of mortality, as an improvement of 1MET (~3.5 $mL \cdot min^{-1} \cdot kg^{-1}$) is shown to reduce the mortality rate by 12% [11]. Adding to the physical benefits of exercise are also possible effects on mental health. Although little is known about the effects of high-intensity interval training in SUD patients, exercise has been documented to have an overall beneficial effect on mental health and quality of life in patients with mental illnesses [12].

Despite the well-documented effect on cardiovascular disease risk reduction [7, 8, 10], decreased mortality rate [11, 13, 14], and improved mental health [15–19], effective

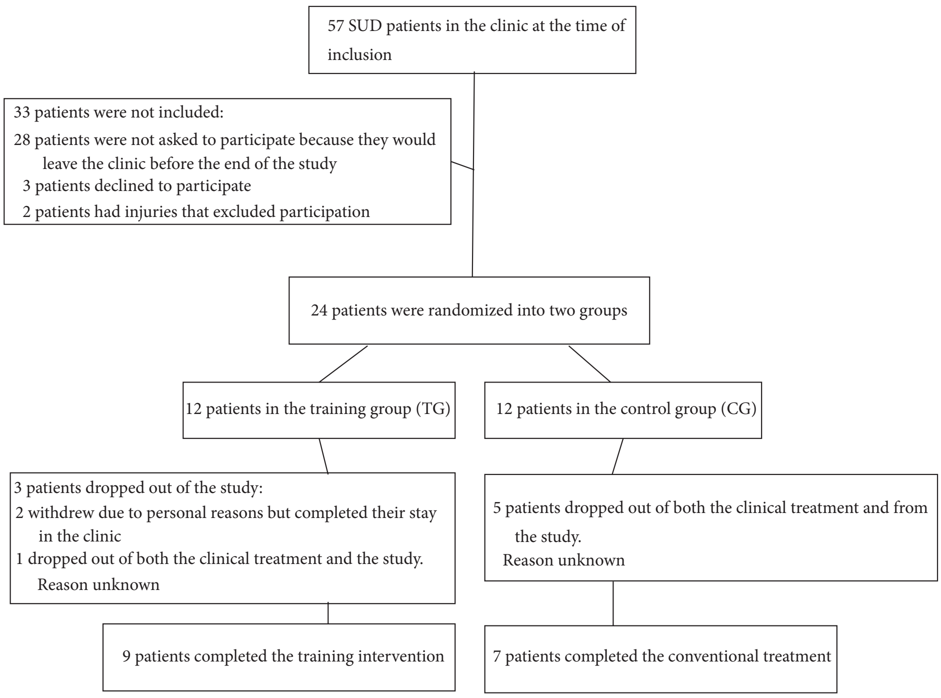


Figure 1: Recruitment, randomization, and withdrawal of SUD patients throughout the study.

physical training appears not to be a part of the conventional treatment for SUD patients. There has certainly been physical activities in the clinics for more than 30 years [20], but in general this activity seems random and unstructured and the frequency and intensity of the activities are often unknown. Indeed the activities may vary between clinics, but to our knowledge, it has not been documented that whole body exercise with a high intensity (≥85% of $HR_{max}$) constitutes a part of the clinical program. As physiological parameters rarely are documented, knowledge of physical status or improvements remains uncertain. Therefore, the aim of the present study was to examine if high-intensity interval training was feasible for SUD patients in treatment. Further, we aimed to document their aerobic power and compare the training group, if they were able to adhere, with patients receiving conventional treatment in the same clinic. Our hypotheses were that SUD patients (1) are able to complete a high-intensity interval training program, (2) have a decreased aerobic power at baseline compared to the average population, and (3) improve their $VO_{2\,max}$ and work economy more than the control group receiving conventional rehabilitation.

## 2. Methods

*2.1. Subjects.* 24 patients with a diagnosis of substance use disorder, ICD-10: F10-F19, were included in this study. All subjects participated in residential long term treatment in a substance abuse treatment clinic at the time of the study, due to abuse of illegal drugs. The long term treatment program at the clinic lasts for ~3 months. Subjects were excluded if they had been abstinent or/and systematically participated in endurance training for the last six months. Subjects were also excluded if they had cardiovascular disease or chronic obstructive pulmonary disease or were not able to perform treadmill testing and training. After signing the written informed consent, patients were randomized to either a high intensity training group (TG) or a conventional rehabilitation control group (CG) (Figure 1). Patient characteristics and medical use are given in Table 1. The regional ethical committee did approve the study, and it was carried out in accordance with the Declaration of Helsinki.

*2.2. Testing*

*2.2.1. Maximal Oxygen Consumption and Work Economy.* Measurements of $VO_{2\,max}$, work economy, and ventilatory parameters were obtained using the Cortex Metamax II portable metabolic test system (Cortex Biophysik GmbH, Leipzig, Germany), walking/running on a treadmill (Woodway Weil am Rhein, Germany). After a 10-minute warm-up period, the subjects walked at $4.5\,km \cdot h^{-1}$ at 5% inclination for a period of 5 minutes. The average oxygen consumption for the last minute of this period was recorded as the work economy. Immediately following the work economy test, the

Table 1: Patient characteristics and medical use.

| | TG ($n$ = 9) | CG ($n$ = 7) | Combined ($n$ = 16) |
|---|---|---|---|
| Men/women ($n$) | 8/1 | 5/2 | 13/3 |
| Age (yr) | 33 ± 11 | 31 ± 8 | 32 ± 9 |
| Height (cm) | 177 ± 10 | 175 ± 10 | 176 ± 10 |
| Weight (kg) | 84.1 ± 14.9 | 87.9 ± 20.8 | 85.8 ± 17.2 |
| Current smoker | 8 | 6 | 14 |
| Drug use debut (age) | 15 ± 6 | 17 ± 4 | 16 ± 5 |
| Duration of abuse (yr) | 17 ± 8 | 12 ± 4 | 15 ± 7 |
| Primary drug | | | |
| Heroin | 1 | 1 | 2 |
| BZD, Sed, Hypn | 1 | 1 | 2 |
| Amphetamine | 4 | 4 | 8 |
| Cannabis | 3 | 1 | 4 |
| Secondary drug | | | |
| Alcohol | 2 | 0 | 2 |
| Heroin | 1 | 1 | 2 |
| Opiates, painkillers | 2 | 1 | 3 |
| Amphetamine | 1 | 0 | 1 |
| Cannabis | 3 | 5 | 8 |
| Symptoms for medicine prescription: | | | |
| ADHD | 0 | 1 | 1 |
| Allergies | 1 | 2 | 3 |
| Anxiety | 2 | 1 | 3 |
| Arthritis | 0 | 1 | 1 |
| Asthma/COPD | 0 | 1 | 1 |
| Depression | 1 | 2 | 3 |
| Epilepsy | 0 | 1 | 1 |
| Hypertension | 3 | 1 | 4 |
| Schizophrenia/bipolar | 1 | 2 | 3 |
| Substitutional treatment | 1 | 1 | 2 |
| Other | 0 | 3 | 3 |

Data are presented as mean ± SD; TG: training group; CG: control group, Type of medication is reported on indication of symptoms according to common directory. The prescribed medicines in substitutional treatment are methadone and suboxone. Others: skin disorder, pain, and inflammation.

subjects continued to the $VO_{2\,max}$ test. The incline was kept at 5% while velocity was increased by 1 km $\cdot$ $h^{-1}$ every minute until exhaustion. $VO_{2\,max}$, respiratory exchange ratio (RER) and ventilation were calculated averaging the three highest continuous 10 second values. One or more of the following criteria for reaching $VO_{2\,max}$ were considered [21]: (1) if the oxygen consumption reached a plateau despite further increases in workload, (2) a RER above 1.05, and (3) lactate concentration in blood ($[La^-]_b$) > 7 mmol. Maximal heart rate ($HR_{max}$) was calculated as 4 beats $\cdot$ $min^{-1}$ added to the highest heart rate during the last minute [22]. For heart rate assessment Polar F6 heart rate monitors were used (Polar Electro, Finland). $[La^-]_b$ were measured using the Biosen C_line (EKF Diagnostics GmbH, Barleben, Germany) analyzer. Blood from the patient's fingertip was sampled for analysis of blood lactate within 1 min after the $VO_{2\,max}$ test. As an expression of maximal aerobic power, inclination and velocity at $VO_{2\,max}$ were registered.

*2.2.2. Identification of Drug Use.* For identification of the extent of drug use the first page of EuropASI was applied (Addiction Severity Index, European adaption of The American 5th edition [23]). This index quantifies which substances have been used, when the patients started their use, and for how long the dependency has lasted. Further, the medical use for the patients participating in the study is given in Table 1.

*2.2.3. Insomnia, Anxiety, and Depression Questionnaires.* In addition to the physical testing two questionnaires were implemented; Insomnia Severity Index (ISI) to detect possible cases of insomnia and Hospital Anxiety and Depression Scale (HAD) which is used to estimate the levels of anxiety and depression. These self-report questionnaires were answered before and after the training intervention as measures of psychological changes during the period of the study. The ISI has been evaluated to be a clinically useful tool for screening and quantifying perceived insomnia severity [24]. It is composed of 7 items targeting different categories of sleep disturbance severity. The items are rated at a five-point Likert scale (0–4) summed up to a total score ranging from 0 to 28, where a higher score indicates more severe insomnia. The score categories are 0–7 (no clinically significant insomnia), 8–14 (subthreshold insomnia), 15–21 (clinical insomnia, moderate severity), and 22–28 (clinical insomnia, severe). The HAD self-assessment scale is consisting of a fourteen item scale, seven items related to anxiety and seven related to depression. On the subscales for anxiety and depression a score of 0–7 for either subscale is estimated within the normal range, while a score of 11 or higher implies a probable presence of a mood disorder. A score of 8–10 is considered signs of a mood disorder [25].

*2.3. Training Intervention.* Both the TG and the CG participated in the clinic treatment activities throughout the 8-week intervention period. These activities included: Ball-games (indoor-soccer and volleyball), yoga, stretching, outdoor walking, low resistance strength training, ceramics, TV games, and card games. Additionally,the TG received supervised training 3 times a week for a period of 8 weeks. The training was performed as inclined walking or running on a treadmill, using the same heart rate monitor as during the $VO_{2\,max}$ testing, to ensure correct intensity of every training session. The training sessions were organized as interval training, with 4 × 4 minutes of high aerobic intensity (90–95% of $HR_{max}$), interrupted by 3-minute recovery periods (~70% of $HR_{max}$) [21]. All training sessions were supervised. As the subjects improved, velocity and incline were increased to meet the targeted heart rate. The subjects needed to have an adherence of at least 20 out of 24 training sessions in order to be included in the data analyses. Within the same time period as the TG performed their high-intensity interval training on a treadmill, the patients in the CG chose to participate

Table 2: Changes in physiological parameters from pre- to posttest.

| | TG ($N$ = 9) | | CG ($N$ = 7) | |
|---|---|---|---|---|
| | Pre | Post | Pre | Post |
| $VO_{2\,max}$ | | | | |
| ($L{\cdot}min^{-1}$) | 3.60 ± 0.91 | $4.15 \pm 1.03^{**\#}$ | 3.43 ± 0.66 | 3.54 ± 0.65 |
| ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) | 42.3 ± 7.2 | $48.7 \pm 9.2^{**\#}$ | 41.8 ± 12.3 | 42.6 ± 12.1 |
| $V_E$ ($L{\cdot}min^{-1}$) | 109.2 ± 28.6 | $125.9 \pm 36.8^{**\#}$ | 103.5 ± 24.4 | 103.2 ± 23.9 |
| RER | 1.09 ± 0.03 | 1.10 ± 0.02 | 1.17 ± 0.11 | 1.14 ± 0.06 |
| $HR_{max}$ ($beats{\cdot}min^{-1}$) | 180 ± 11 | 181 ± 14 | 189 ± 7 | 188 ± 7 |
| $[La^-]_b$ | 9.12 ± 2.41 | 10.65 ± 1.69 | 8.04 ± 3.54 | 9.21 ± 2.01 |

Data are presented as mean ± SD. TG: training group; CG: control group; $VO_{2\,max}$: maximal oxygen uptake; $V_E$: ventilation; RER: respiratory exchange ratio; $HR_{max}$: maximal heart rate; $[La^-]_b$: lactate concentration in blood, $^{**}P < 0.01$, difference within group from pre- to posttest, $^{\#}P < 0.05$, differences in changes from pre- to posttest between groups.

in a self-elected activity among the offered sports or games in the clinical treatment program. Although representing a wide range of different activities, they all shared a measured or estimated intensity level of <70% of $HR_{max}$.

*2.4. Statistics.* Statistical analyses were performed using the software SPSS, version 20 (Chicago, USA), and figures were made using the software GraphPad Prism 5 (San Diego, USA). Relative improvements are given as mean percentage change. To determine if the data was normal distributed a Q-Q plot was used. Repeated measures ANOVAs (2 (group) × 2 training status) were used to determine differences between groups following training. If appropriate, a Tukey post hoc analysis was used. Unpaired and paired $t$-tests were used to detect differences between groups at baseline and within group following training, respectively. Statistical significance was accepted at an $\alpha$-level of $P < 0.05$. Data are reported as mean ± SD, unless otherwise noted. Additionally, using similar statistics, an intention to treat analysis with the use of last observation carried forward for missing data was carried out for all the 24 subjects that were randomized to the two groups. To achieve a statistical power of 80%, 8 patients in each group needed to complete the study period in order to observe a $0.375\,L \cdot min^{-1}$ improvement difference in mean $VO_{2\,max}$ between TG and CG, assuming a SD of $0.25\,L{\cdot}min^{-1}$. These values were based on previous studies from our group using the same training intervention in other populations. The drop-out rate in previous studies has been ~2/10 subjects. However, considering that this patient population may be more challenging than average, a higher drop-out rate is expected. Thus 12 subjects were randomized to each group to ensure observation of the assumed efficacy difference between the two groups.

## 3. Results

11 of the 12 SUD patients in the TG and 7 out of 12 patients in the CG, respectively, completed their overall intended stay at the substance use disorder clinic. With regard to the high intensity training, 3 subjects withdrew from the TG. Two withdrew due to personal reasons but remained in the clinical treatment, while one dropped out from both the clinical treatment and the TG. In the CG 5 subjects dropped out of the clinical treatment and thus withdrew from the study without giving any reasons (Figure 1). The SUD patients that completed the training period carried out 22 ± 1 of the scheduled supervised training sessions. The targeted intensity (90–95% of $HR_{max}$) was reached in all completed sessions. None of the subjects reported any problems or discomfort completing the training sessions, other than the normal strain following high intensity exercise.

At baseline, before the withdrawal of subjects from the study, values for both groups combined were 44 ± 8 (males) and 34 ± 9 (females) $mL \cdot min^{-1} \cdot kg^{-1}$, respectively. $VO_{2\,max}$ significantly ($P < 0.01$) improved by 15±7% for the 9 subjects that completed the TG (Table 2). This improvement was also significantly ($P < 0.01$) different from the CG (Figure 2). In accordance with the improvement in aerobic power, the TG also increased velocity and inclination at $VO_{2\,max}$ from 9.2 ± $2.3\,km \cdot h^{-1}$ and 5.6 ± 1.1% at pretest to 9.3 ± $2.2\,km \cdot h^{-1}$ and 8.3 ± 2.4% at posttest. The CG showed no within-group improvement in neither $VO_{2\,max}$ nor maximal workload. The TG increased ventilation at $VO_{2\,max}$ by 14 ± 10%, while there were no differences within or between groups in RER or $[La^-]_b$ at $VO_{2\,max}$ from pre- to posttest. An intention to treat analysis, including all 24 participants that were randomized to either the TG or the CG, did not show different results for the primary outcomes compared to analysis including only subjects that completed the study.

Work economy, measured at 5% inclination and $4.5\,km \cdot h^{-1}$ on the treadmill, showed no significant differences between or within the two groups following the training period (Table 3). However, the heart rate at the work economy workload significantly ($P < 0.05$) decreased by 9 ± 12% in the TG, but this within-group change was only apparent as a trend ($P = 0.158$) when compared to the CG.

For psychological variables, the TG displayed a significant ($P < 0.05$) decrease in depression level following the training period, whereas the CG had a significant decrease ($P < 0.05$) in anxiety level from pre- to posttest (Table 4). However, neither of these within-group differences, measured by the Hospital Anxiety and Depression questionnaire, was apparent as between-group differences.

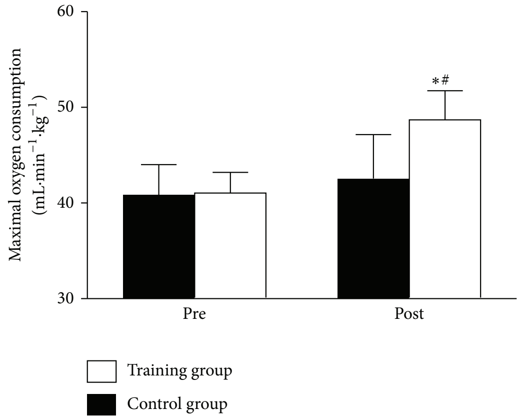


Figure 2: Maximal oxygen consumption before and after the training intervention. Data are presented as mean ± SE. $^{*}P < 0.01$, difference within group from pre- to posttest, $^{\#}P < 0.05$, differences in changes from pre- to posttest between groups.

Table 3: Work economy measured at 4.5 km·h$^{-1}$ and 5% inclination at pre- and posttest.

| | TG ($N$ = 9) | | CG ($N$ = 7) | |
|---|---|---|---|---|
| | Pre | Post | Pre | Post |
| $VO_2$ | | | | |
| (L·min$^{-1}$) | 1.54 ± 0.24 | 1.61 ± 0.28 | 1.70 ± 0.36 | 1.77 ± 0.43 |
| (ML·kg$^{-1}$·min$^{-1}$) | 18.5 ± 1.1 | 18.9 ± 1.3 | 19.6 ± 2.3 | 20.2 ± 1.4 |
| $V_E$ (L·min$^{-1}$) | 35.1 ± 4.4 | 33.3 ± 5.3 | 38.3 ± 9.3 | 41.1 ± 9.0 |
| RER | 0.90 ± 0.04 | 0.89 ± 0.08 | 0.93 ± 0.05 | 0.94 ± 0.07 |
| $HR_{max}$ (beats·min$^{-1}$) | 116 ± 17 | 105 ± 18 | 116 ± 18 | 119 ± 9 |

Data are presented as mean ± SD. TG: training group; CG: control group; $VO_2$: oxygen uptake; $V_E$: ventilation; RER: respiratory exchange ratio; $HR_{max}$: maximal heart rate.

Table 4: Psychological changes from pre- to posttest (scores from the insomnia severity index and hospital anxiety and depression scale questionnaires).

| | TG ($n$ = 9) | | CG ($n$ = 7) | |
|---|---|---|---|---|
| | Pre | Post | Pre | Post |
| Anxiety | 9.4 ± 3.5 | 8.6 ± 2.5 | 9.1 ± 5.3 | 6.3 ± 3.4* |
| Depression | 8.5 ± 4.8 | 5.3 ± 3.9* | 6.0 ± 3.5 | 4.6 ± 3.5 |
| Insomnia | 10.6 ± 5.4 | 8.9 ± 5.1 | 10.9 ± 10.1 | 9.1 ± 5.0 |

Data are presented as means ± SD. TG: training group; CG: control group. $^{*}P < 0.05$, difference within group from pre- to posttest.

## 4. Discussion

Since little is known about the aerobic power of SUD patients in treatment and their lifestyle indicates that they may suffer a high risk of cardiovascular and lifestyle diseases, this study sought to investigate the aerobic power of this group of patients and their response to exercise training of high intensity. The main findings of the study were as follows (1) the initial aerobic power at baseline is lower than what is typically seen in the average population, (2) the SUD patients improved their aerobic power and work performance following the training intervention, thus decreasing the risk factors for lifestyle diseases, and (3) the training intervention is applicable as a part of the clinical treatment.

*4.1. Reduced Aerobic Power in Patients with Substance Use Disorder.* At inclusion, the SUD patients in the present study had a baseline $VO_{2\,max}$ of 44 ± 8 (males) and 34 ± 9 (females) mL · min$^{-1}$ · kg$^{-1}$. This is well below age-matched reference data from the average population [26]. The 10% and 16% lower baselines for the ~30 year old males and females, respectively, are comparable to the average values observed among 50–59-year-old healthy subjects [26]. The low aerobic power, as documented in the current study, is in line with a previous study displaying $VO_{2\,max}$ values of 39 (males) and 31 mL · min$^{-1}$·kg$^{-1}$ (females) in SUD patients [27]. Our study and the Mamen and Martinsen [27] study are to our knowledge the only studies to directly assess aerobic power in SUD patients. However, the assumption of a health-related critical low aerobic power is also supported by several studies applying estimations of $VO_{2\,max}$ [17, 28–31]. Since low aerobic power is a well-established risk factor for cardiovascular disease and all-cause mortality [11, 13, 14, 32], it is likely that the low $VO_{2\,max}$ observed among SUD patients may, at least in part, be responsible for the elevated prevalence of cardiovascular disease and premature death observed in this patient group.

It is therefore surprising that aerobic power commonly is not listed as one of the major causes for illnesses, medical conditions, and early death in SUD patients [3, 4, 6].

*4.2. Exercise-Induced Effect on Aerobic Power, Work Load, and Risk Reduction.* As expected, the SUD patients that completed the supervised eight week treadmill training period in the current study improved $VO_{2\,max}$. In accordance with the $15 \pm 7\%$ improvement in $VO_{2\,max}$, the TG increased maximal velocity and inclination at $VO_{2\,max}$ from $9.2 \pm 2.3\,km \cdot h^{-1}$ and $5.6 \pm 1.1\%$ at pretest to $9.3 \pm 2.2\,km \cdot h^{-1}$ and $8.3 \pm 2.4\%$ at posttest. For patient groups with low aerobic capacities, daily activities are often perceived as strenuous. An improvement in work capacity is therefore typically associated with an increased wellbeing in everyday life, since it reduces the relative intensity on the daily tasks [10, 33, 34]. The improvement in $VO_{2\,max}$ observed in our study is similar to what have previously been reported following a whole body high intensity (>85% of $HR_{max}$) training intervention in a wide range of patient groups [7–10, 35, 36], as well as and in healthy subjects [21, 37] and old subjects [37]. The magnitude of $VO_{2\,max}$ improvement may be influenced by training status, age, or pathology [7–10]. Subjects with a low baseline are, both mathematically and physiologically, susceptible to larger percentage improvements (~15–35%) than subjects with a higher baseline (~6%–13%) [21, 37].

Considering the elevated risk of mortality [3] and cardiovascular incidents in SUD patients [4], $VO_{2\,max}$ improvements as demonstrated in the present study are beneficial. A $3.5\,mL \cdot min^{-1} \cdot kg^{-1}$ improvement in $VO_{2\,max}$ has been shown to be associated with a 12% improved chance of survival [11] and a 15% reduced risk for developing cardiovascular disease [32]. The SUD patients in the present study improved their $VO_{2\,max}$ by $6.6\,mL \cdot min^{-1} \cdot kg^{-1}$, indicating that not only will they have a strongly decreased mortality rate, but also a considerable reduced risk of developing cardiovascular disease. After the relatively short-duration training period the SUD patients restored their $VO_{2\,max}$ values to a level similar to the age-matched healthy population [26]. In contrast, it is thought provoking that conventional clinical treatment did not improve $VO_{2\,max}$. Physical activity is certainly applied in today's treatment [20], but clearly this physical activity is not sufficient to induce improvements in $VO_{2\,max}$. Since the conventional activities are all reported to be carried out with a low intensity, this may explain the lack of improvement, as intensity is suggested to be the key factor for $VO_{2\,max}$ improvements [21, 38]. Recognizing the high risk for cardiovascular disease and mortality in these patients, it is critical that today's treatment may have no effect on one of the most important factors for these conditions.

The exercise-induced improvement in $VO_{2\,max}$ that was observed in the TG is likely due to an improvement in maximal cardiac output, and more specific is the stroke volume of the heart since no changes were observed in $HR_{max}$. Previously the stroke volume has been shown to be the decisive factor that explains the adaptations to high intensity training, both in moderately trained healthy subjects [21] and in untrained coronary artery disease patients [39]. The $\sim 42\,mL \cdot min^{-1} \cdot kg^{-1}$ (males and females combined) baseline $VO_{2\,max}$ in the current study falls between an aerobic power of ~55 (young, healthy) and ~27 (coronary artery disease) $mL \cdot min^{-1} \cdot kg^{-1}$. Although the SUD patients indeed represent a different group of subjects, it is likely, since the stroke volume adaptations appear to be similar across different populations, that also their improvements in $VO_{2\,max}$ originate from training-induced changes in maximal stroke volume.

*4.3. Training Effect on Insomnia, Anxiety, and Depression.* A positive relationship between exercise and mood disorders is well-documented [20, 40–44] specifically apparent as insomnia [40, 45], anxiety [44], and depression disorder [41, 43, 46] reductions. Therefore, it is surprising that the large difference between the TG and the CG in aerobic power and work load following the study period did not induce detectable differences between groups in any of these variables. At baseline, the level of mental distress in both the TG and the CG group was ranged as moderately severe according to the Insomnia Severity Index and the Hospital Anxiety and Depression Scale. Both groups scored within subthreshold for insomnia and within signs of mood disorder. Following the study period there was a reduction of the depression variable within the TG, as well as a reduction of the anxiety variable within the CG, but these reductions were not different between the two groups. It is possible that psychological benefits, as measured by the questionnaires in our study, are more related to physical activity per se and not necessarily to aerobic exercise training. Although reduced depression symptoms may be associated with exercise in general and not necessarily restricted to the aerobic form of exercise [15], it should undoubtedly be expected that a risk reduction of cardiovascular disease and mortality would cause an improvement of mood disorders and quality of life [42]. Thus the commonly applied questionnaires that were used in our study should be able to detect such an improvement. Our results indicate that a supplement, expansion, or replacement to/of the questionnaires are sought for, although it is recognized that the relatively small sample size in the current study may be, in part, responsible for the nondetectable differences in mood disorders.

*4.4. High-Intensity Interval Training: Clinical Implications.* Considering their high rate of nonattendance and discontinuation [47, 48], reflected in the high relapse rates from clinical treatment [49], an important question in the current study was whether the SUD patients were able to carry out the scheduled period of training. To our knowledge there have not been any previous reports of SUD patients participating in such an intensive training intervention. The SUD patients were in our study capable of managing the intensive training, reflected in the high attendance ($22 \pm 1$ of the total 24 scheduled training sessions) for the 9 subjects that completed the training period. Interestingly, the completion rate was higher for the TG, both in the current study and in the clinical treatment, compared to the CG. Only 1 out of 12 patients in the TG dropped out from clinical treatment (5 subjects in the CG) and 3 from the training study (5 subjects in the

CG). Certainly these withdrawals could be due to chance, but the completion rate is nevertheless a testament to the feasibility of high-intensity interval training as part of the clinical treatment. An intention to treat analysis showed no differences in the main findings of the current study and thus strengthens the result of an overall beneficial effectiveness of high-intensity interval training in a clinical setting. Not only was it feasible to apply this intervention in the clinic, but additionally the subjects that completed the training reported no discomfort or pain during the training sessions other than what should be expected with high intensity training, and not one single commenced training session was aborted.

Our findings are in line with a previous study applying a similar training intervention in patients with schizophrenia [10]. In the Heggelund et al. study [10] the training was reported to be challenging but feasible. In our study, as well as in the Heggelund et al. study [10], all trainings were conducted in presence of a supervisor. This may be favorable when implementing a training intervention in mentally ill patients. Mamen et al. [50] emphasized that the relationship between the patient and the supervisor can prove essential for the patients motivation and commitment to the project. Our experience throughout this study supports this notion. The present study exemplifies that high intensity training can be applicable for SUD patients in treatment and that the intensive training is manageable also for this patient group. Considering the health benefits associated with this training, it should be implemented as a complementary treatment for SUD patients.

## 5. Conclusion

In the present study SUD patients are shown to have a low aerobic power, and thus they are at risk for developing cardiovascular disease. As it is important that SUD patients receive both a physical and psychological treatments in the clinic and our results indicate that the conventional treatment is not sufficient to reduce the risk of cardiovascular disease, high-intensity interval training should be implemented as part of the clinical treatment to effectively improve the patient groups' aerobic power.

## Conflict of Interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

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# Paper IV

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RESEARCH ARTICLE Open Access

# Maximal strength training as physical rehabilitation for patients with substance use disorder; a randomized controlled trial

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## Abstract

**Background:** Patients with substance use disorder (SUD) suffer from multiple health and psychosocial problems. Because poor physical capacities following an inactive lifestyle may indeed contribute to these problems, physical training is often suggested as an attractive supplement to conventional SUD treatment. Strength training is shown to increase muscle strength and effectively improve health and longevity. Therefore we investigated the feasibility and effect of a maximal strength training intervention for SUD patients in clinical treatment.

**Methods:** 16 males and 8 females were randomized into a training group (TG) and a control group (CG). The TG performed lower extremities maximal strength training (85-90 % of 1 repetition maximum (1RM)) 3 times a week for 8 weeks, while the CG participated in conventional clinical activities.

**Results:** The TG increased hack squat 1RM (88 ± 54 %), plantar flexion 1RM (26 ± 20 %), hack squat rate of force development (82 ± 29 %) and peak force (11 ± 5 %). Additionally, the TG improved neural function, expressed as voluntary V-wave (88 ± 83 %). The CG displayed no change in any physical parameters. The TG also reduced anxiety and insomnia, while the CG reduced anxiety.

**Conclusion:** Maximal strength training was feasible for SUD patients in treatment, and improved multiple risk factors for falls, fractures and lifestyle related diseases. As conventional treatment appears to have no effect on muscle strength, systematic strength training should be implemented as part of clinical practice.

**Trial regestration:** ClinicalTrials.gov Identifier: NCT02218970 (August 14, 2014).

**Keywords:** Muscle strength, One repetition maximum, Rate of force development, V-wave, Physical health, Mental health

## Background

In addition to their drug abuse, patients with substance use disorder (SUD) suffer from multiple health and psychosocial comorbidities, resulting in a life expectancy 20–30 years less than the general population [1, 2]. Compared to the average population these patients are more frequently represented in medical care, with an elevated incidence of cardiovascular disease [1, 2], diabetes [1, 2], cancer [1, 2], suicide [1, 2], as well as traumas, falls and fractures [3–5]. Recent findings in our laboratory show that muscle strength and aerobic fitness are markedly reduced in SUD patients compared to healthy age-matched individuals [6]. Low muscle strength is associated with increased incidence of falls and fractures [7, 8], poor mechanical efficiency [9], elevated risk of cancer [10] and cardiovascular disease [11], and is even shown to be an independent predictor of all-cause mortality in both patient populations and healthy [12–14].

Strength training has become an increasingly common measure to improve muscle strength in different patient populations, and effectively reduce the risk of medical conditions and mortality. Maximal strength training, with heavy loads (>85 % of 1 repetition maximum (1RM)) and emphasis on intended concentric velocity has been successfully applied in multiple patient

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populations in our labs, and is shown to induce particularly large improvements in rate of force development (RFD) and muscle strength [15–19]. The improvements in maximal strength and RFD are suggested to predominantly rely on neural factors, with little or no change in body mass [9, 18, 20], which results in the training being even more suitable in populations where gains in weight are not sought after. Importantly, no injuries have been reported following these interventions, indicating that the training is not only effective, but also safe. Perhaps even more than the maximal strength, rapid force development is shown to be important for functional status, mechanical efficiency, balance adjustments and the prevention of falls and fractures [21–23]. Because the RFD relies mainly on neuromuscular properties [24], strength training applied to induce functional gain in patient populations should target neural adaptations. Assessed by the use of evoked reflex recordings, our research group has previously documented neural adaptations in both patient and healthy populations following maximal strength training [17, 25].

Although SUD patients are reported to have low muscle strength and aerobic capacity [6], there are few studies of systematic physical training as a part of clinical SUD treatment [26]. While physical activity is commonly used in conventional treatment [27], it appears not to apply a sufficient overload for taxing the muscular strength. Thus, maximal strength training would likely offer additional health benefits, and effectively reduce the risk of medical conditions. In addition to physical benefits, strength training is shown to have a positive effect on mental health, reducing anxiety and depression levels [28–30]. A low muscle strength has even been shown to independently be associated with an elevated rate of suicide [31]. In general, adherence to an exercise regime is also suggested to improve treatment outcomes and possibly reduce relapse rates in patients suffering from alcohol and substance abuse [26, 32].

Since physical activity in clinical treatment often appear random and unstructured [33], without the sufficient overload to produce gains in muscular strength, the aim of this study was to assess if a maximal strength training intervention was feasible for SUD patients, and would yield the previously documented beneficial physical and mental effects of such a training regime. We hypothesized that (1) SUD patients would be able to carry out the 8 week maximal strength training intervention, and (2) that the training group would improve maximal strength, RFD, efferent neural drive, depression, anxiety and insomnia more than the control group that participated in conventional treatment.

## Methods

### Subjects

24 patients diagnosed with SUD, classified within ICD-10: F10-F19 (mental and behavioral disorders due to psychoactive substance use), were included in the study from February to March 2013. All subjects participated in a ~3 month residential long term treatment at a substance abuse clinic at the University hospital, and had amphetamine as their primary drug. After providing their informed consents subjects were randomized to either a maximal strength training group (TG) or a control group (CG) participating in conventional activities (Fig. 1). Subjects were assigned a number between 1 and 24, and randomization was performed using a publicly accessible official website designed for research randomization (https://www.randomizer.org). Subjects were excluded if they had been abstinent and/or systematically participated in strength training for the last six months. Other exclusion criteria were cardiovascular or respiratory disease, not being able to carry out the testing procedure or failure to participate in at least 20/24 training sessions. Patient characteristics and medical use are shown in Table 1. The study was approved by the regional ethical committee (REK-nord) and conducted in accordance with the declaration of Helsinki.

### Extent of drug use

To get an overview of the extent of drug use the first page of EuropASI was applied [34]. The index quantifies which substances the subject has used, age at first time drug use and years of use. Further the clinic provided information of prescribed medicine for the overall participating group of patients. Patient characteristics and medical use are given in Table 1.

### Testing procedure

All subjects conducted the testing procedure before and after the 8 week training intervention. On the day of testing, neuromuscular measurements (V-wave) were carried out first, followed by 1RM hack squat, 1RM plantar flexion and hack squat RFD. After the strength measurements, psychological questionnaires were filled out to assess levels of insomnia, anxiety and depression. Subjects were asked to not engage in any physical training on the day of testing or the day before.

### Strength measurements

One repetition maximum (1RM) was measured in hack squat and plantar flexion. Hack squat 1RM was obtained in a hack squat machine (Impulse Fitness IT7006, Shandong, China) angled 45° to vertical. For the plantar flexion test, the participants were seated in a calf rise machine (Impulse Health Tech IT7005, Shandong, China),

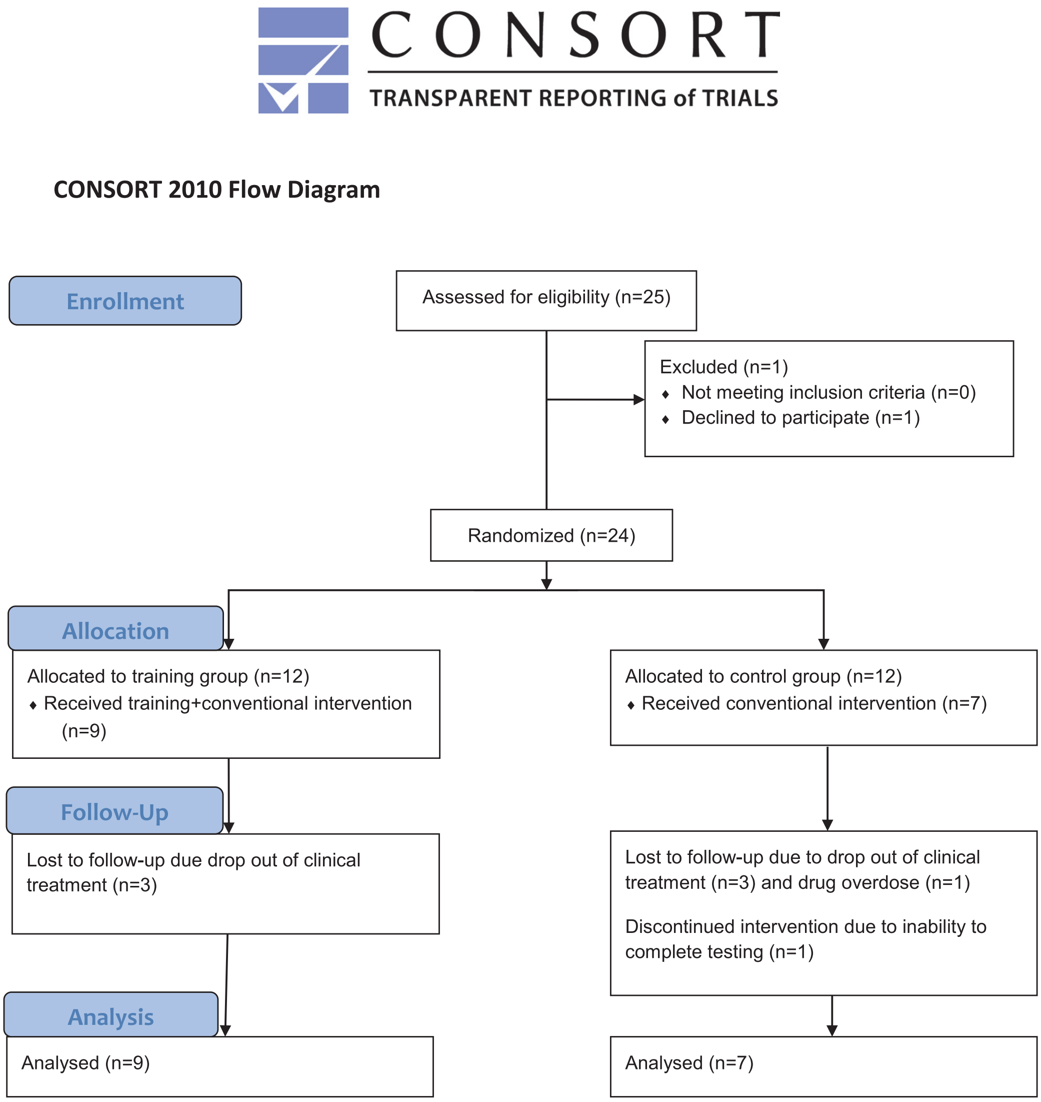


**Fig. 1** CONSORT flow diagram of study design

with a knee joint angle of ~90°, and performed their lifts from an ankle joint angle of ~20° dorsiflexion in the lower position, up to ~30° plantar flexion in the upper position. Before testing the subjects were familiarized with the testing apparatus during an extensive warm up procedure, however no additional familiarization session was arranged. For both hack squat and plantar flexion, 1RM was achieved by increasing the load by 5-10 kg until the subject was not able to complete the lift. A three minutes rest was given between each trial, and correct joint angles were ensured. 1RM was achieved within 6–9 trials, and the highest load completed was recorded as 1RM.

RFD was recorded in the hack squat machine with a force platform at 2000Hz (9286AA, Kistler, Switzerland) attached to the foot plate. Each subject was given three attempts with a load corresponding to 80 % of pretest 1RM. Only the best trial was used for analyzes. The subjects were instructed to move slowly down to a knee

**Table 1** Patient characteristics and medical use

| | TG ($n = 9$) | CG ($n = 7$) | Combined ($n = 16$) |
|---|---|---|---|
| Men/Women (n) | 6/3 | 7/0 | 13/3 |
| Age (yr) | 33 ± 9 | 29 ± 5 | 32 ± 8 |
| Weight (kg) | 80.2 ± 18.2 | 81.8 ± 9.6 | 80.9 ± 14.3 |
| Height (cm) | 173 ± 10 | 181 ± 5 | 177 ± 9 |
| First time drug use (age) | 14 ± 2 | 15 ± 2 | 14 ± 2 |
| Duration of abuse (yr) | 13 ± 10 | 11 ± 4 | 12 ± 8 |
| Current Smoker | 7 | 6 | 13 |
| Primary drug: | | | |
| Amphetamine | 9 | 7 | 16 |
| Secondary drug: | | | |
| Alcohol | 4 | 1 | 5 |
| Cocaine | | 1 | 1 |
| Cannabis | 5 | 5 | 10 |
| Symptoms for medicine prescription: | | | |
| ADHD | 1 | 1 | 2 |
| Allergies | 3 | 4 | 7 |
| Anxiety | | 3 | 3 |
| Arthiritis | 2 | | 2 |
| Asthma/COPD | 3 | 1 | 4 |
| Depression | 3 | 1 | 4 |
| Epilepsy | | 1 | 1 |
| Hypertension | 5 | | 5 |
| Schizofenia/Bipolar | 4 | 1 | 5 |
| Migrene | 3 | | 3 |
| Substitutional treatment | | 1 | 1 |
| Other | 5 | 1 | 6 |

Data are presented as mean ± SD, *TG*; training group, *CG*; control group. Type of medication is reported on indication of symptoms according to common directory. The prescribed medicine in substitutional treatment is subuxone. Others: atherothrombosis, diabetes, infections

joint angle of 90°, have a short stop to avoid eccentric action involvement, and then mobilize maximally in the concentric phase of the movement. Three minutes rest was given between each trial. The highest concentric force was recorded as peak force and RFD was calculated as Δforce between 10 % and 90 % of peak force [9].

#### Neuromuscular measurements

Neuromuscular measurements were assessed by voluntary V-waves, with the subjects seated in a fixed version of the plantar flexion apparatus used for dynamic strength measurements. The V-wave method involves electrical stimulation of the tibial nerve, applied to evoke reflex potentials and motor potentials in afferent and efferent nerves. During supramaximal electrical stimulations all afferent and efferent nerve fibers are recruited simultaneously, and the reflex volley traveling the muscle spindle reflex circuit will collide with electrically evoked action potentials traveling antidromically in the efferent axons. Because of these collisions the reflex volley will be completely abolished during rest and not reach the muscle. In contrast, during maximal voluntary contraction (MVC) the efferent drive to the muscle will collide with the antidromic potentials, leaving some efferent axons open for transmission of the reflex. A higher efferent drive will clear more axons for reflex transmission, and will thus allow more of the reflex volley to pass through to the muscle, where it is recorded as a V-wave. Based on this, the amplitude of V-wave is used to express the efferent neural drive during MVC.

Reflex potentials were evoked by a current stimulator (DS7AH, Digitimer, Welwyn Garden City, UK), in the tibial nerve, in the popliteal fossa. The electrical current was delivered by gel-coated (Lectron 2 conductive gel, Pharmaceutical innovations INC, Newark, NJ, USA) bipolar felt pad electrodes, 25 mm between tips, 8 mm diameter (Digitimer, Welwyn Garden City, UK). The electrodes were held by hand throughout the testing procedure, and positioned at the site evoking the largest reflex amplitude. Evoked potentials were recorded through self-adhesive AG/AgCI electrodes (Ambu, M-00-S/50, Ballerup, Denmark) placed as recommended by SENIAM [35] on m. soleus. Before electrode attachment the skin was carefully preparated to minimize the inter-electrode impedance; impedance level <5 kΩ were required. To provide equal conditions from pre- to post-test, pictures were taken of the electrode placement at pretest, and used for identical positioning at posttest.

Searching for the maximal direct motor potential ($M_{max}$) the current intensity was gradually increased by 2–5 mA until the M-wave reached a plateau. Between 70 and 180 mA was needed to evoke $M_{max}$. To validate the $M_{max}$ three supramaximal stimuli at 150 % of the current intensity needed to reach the plateau were given. Eight V-waves were evoked during MVC by delivering a supramaximal (150 %) stimulus at the point where the subject reached ~90 % of MVC force. Each MVC was separated by 1 min rest. Only V-wave recordings, in which the M-wave was > 90 % of $M_{max,}$ were used for analyzes. The maximal V-wave amplitude ($V_{max}$) was expressed relative to $M_{max}$ (V/M-ratio), to allow between subjects comparisons. Changes in V/M-ratio are used to express changes in efferent drive following training.

#### Psychological questionnaires

In addition to the physical testing two questionnaires were implemented; Insomnia Severity Index (ISI) to measure level of insomnia, and Hospital Anxiety & Depression Scale (HAD), used to estimate symptoms of anxiety and depression. These self-report questionnaires were answered in conjunction with the pre- and posttest of muscular strength, as measures of psychological changes during the period of the study. The ISI has been evaluated to be a clinically useful tool for screening and quantifying perceived insomnia severity [36]. It is composed of 7 items targeting different categories of sleep disturbance severity. The items are rated at a five-point Likert scale (0–4) summed up to provide a total score ranging from 0–28, where a higher score indicates more severe insomnia. The score categories are 0–7 (no clinically significant insomnia), 8–14 (subthreshold insomnia), 15–21 (clinical insomnia, moderate severity) and 22–28 (clinical insomnia, severe). The HAD self-assessment scale consists of a fourteen item scale, seven items relate to anxiety and seven relate to depression. On the seven item HADS subscales a score of 0–7 for either subscale is estimated within the normal range, a score of 11 or higher implies a probable presence of a mood disorder. A score of 8–10 is considered signs of a mood disorder [37].

### Training intervention

Both the TG and the CG attended the regular treatment program at the substance abuse clinic during the intervention period. The treatment program activities included: Ballgames (indoor-soccer, bandy and volleyball), yoga, stretching, outdoor walking, low resistance strength training (estimated <50 % of 1RM), ceramics, TV games and card games. Together this resulted in a total of ~3 h of physical activity per week. In addition, the TG received maximal strength training 3 times a week for a period of 8 weeks. The training intervention consisted of two exercises; hack squat and plantar flexion. Both exercises consisted of 4 sets of 4–5 repetitions, corresponding to 85-90 % of 1RM. The training load was increased with 5 kg if 5 repetitions were accomplished in the last set. Both exercises were conducted with a slow controlled movement in the eccentric phase, a short stop, and then maximal mobilization of force in the concentric movement. Hack squat was performed with 90° knee joint angle, while the plantar flexion exercise was performed from an ankle joint angle of ~20° dorsiflexion up to ~30° plantar flexion. Every training session was supervised to ensure proper technique and progression throughout the training period. While the TG participated in the supervised strength training, the CG chose to participate in self-elected supervised activities among the offered sports or games in the clinical treatment program.

### Statistical analyzes

Statistical analyzes were done using IBM SPSS Statistics 21 (Chicago, IL, USA), while figures were created using GraphPad Prism 5 (San Diego, USA). Independent and paired t tests were used to examine differences between groups at baseline and within groups following training, respectively. Between group differences following training were determined by use of two-way repeated ANOVAS. The Pearson test for linear regression was applied to assess correlations. Statistical significance level was set to $p < 0.05$. All variables exhibited normal distribution, as confirmed by quantile-quantile plots. Data are presented as mean ± SD unless otherwise noted.

## Results

### Completion

Of the 24 patients that were included in the study, 16 subjects completed the study period. 3 patients in the TG dropped out of the clinical treatment, and hence also dropped out of the study. In the CG 5 subjects dropped out; 3 patients dropped out of clinical treatment, 1 patient were not able to complete the testing procedure and 1 patient died from drug overdose. The withdrawal in the two groups resulted in an uneven distribution of genders, leaving no females in the CG at posttest. The participants in the TG adhered to 23 ± 1 of the 24 scheduled training sessions during the training period. The patients completed all commenced training sessions and the targeted intensity (85–90 % of 1RM) was reached in all sessions.

### Muscle strength measurements

For the 16 subjects that completed the study, there was no significant difference between the TG and the CG in any of the measured strength parameters at pretest. After 8 weeks of maximal strength training the TG increased 1RM hack squat by 88 ± 54 % ($p < 0.01$) (Fig. 2), whereas plantar flexion 1RM increased from 98 ± 23 kg to 121 ± 17 kg (26 ± 20 %, $p < 0.01$). The TG also increased RFD by 82 ± 28 % ($p < 0.01$) (Fig. 3), whereas peak force increased from 1846 ± 357 N to 2045 ± 415 N (11 ± 5 %, $p < 0.01$). No significant changes were observed in the CG for any of the strength parameters.

### Neuromuscular measurements

Maximal strength training led to an enhanced efferent neural drive in the TG. Following the 8 week training intervention the TG increased m. soleus $V_{max}$ from 1583 ± 1596μv to 2189 ± 1375μv (92 ± 95 % ($p < 0.01$)). As there was no observed change in m. soleus $M_{max}$ (6379 ± 2188μv vs. 6332 ± 2244μv), this resulted in an 88 ± 83 % ($p < 0.01$) increase in m. soleus V/M-ratio (Fig. 4). No significant changes were observed for the CG. Finally, ΔV/M-ratio correlated with Δhack squat 1RM (r = 0.44, $p < 0.05$) and Δplantar flexion 1RM (r = 0.57, $p < 0.05$).

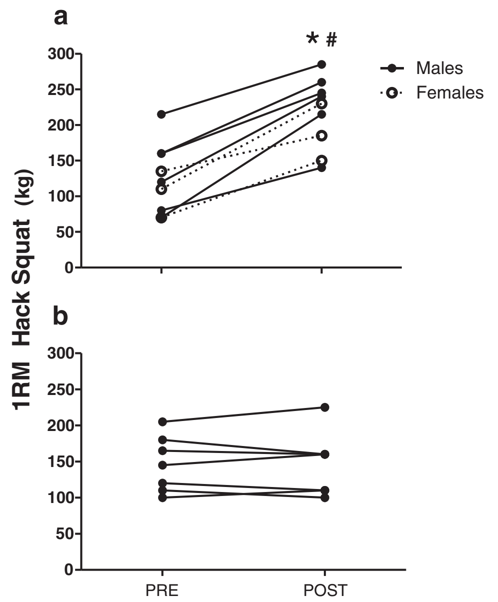


**Fig. 2** Hack squat one repetition maximum (1RM) for (**a**) the training group and (**b**) the control group from pre- to posttest. * $p < 0.01$, difference within group from pre- to posttest. # $p < 0.01$, difference between groups from pre- to posttest

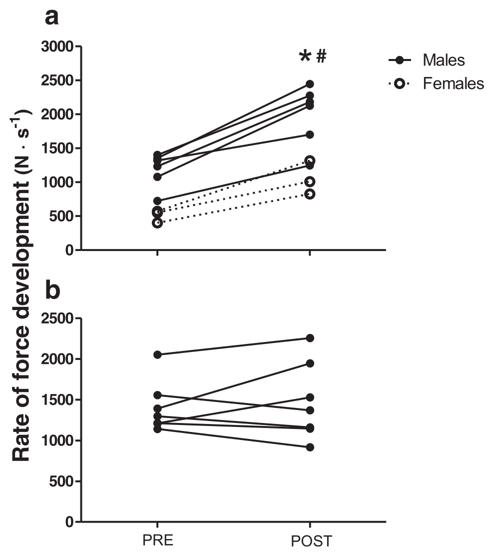


**Fig. 3** Hack squat rate of force development for (**a**) the training group and (**b**) the control group from pre- to posttest. * $p < 0.01$, difference within group from pre- to posttest. # $p < 0.01$, difference between groups from pre- to posttest

### Psychosocial variables

Both the TG and the CG scored within “probable presence of mood disorder” at inclusion, with elevated scores of anxiety and insomnia. Following the study period both the TG and the CG displayed significant within group reductions in anxiety level ($p < 0.05$), while the level of insomnia significantly decreased only in the TG ($p < 0.05$) (Table 2). Also the level of depression tended to decrease in both groups ($p = 0.11$ for the TG and $p = 0.10$ for the CG). Neither of the within group differences were apparent as between-group differences.

## Discussion

### Main findings

SUD patients suffer from physical and psychological deconditioning as a consequence of their detrimental lifestyle. Since strength training is documented to improve both physical and mental health, we sought to investigate the feasibility and efficiency of a maximal strength training regime for a group of SUD patients in residential treatment. The main findings were that 1) A maximal strength training intervention was feasible for SUD patients in treatment, 2) Maximal strength training effectively improved maximal strength and muscle force development characteristics, likely caused by alterations in the central nervous system, 3) Anxiety and insomnia were improved following the clinical treatment period.

### Improved maximal strength and muscle force development characteristics

As expected the SUD patients that completed the strength training intervention displayed large improvements in all the measured strength parameters. The 88 % increase in hack squat 1 RM after 8 weeks of

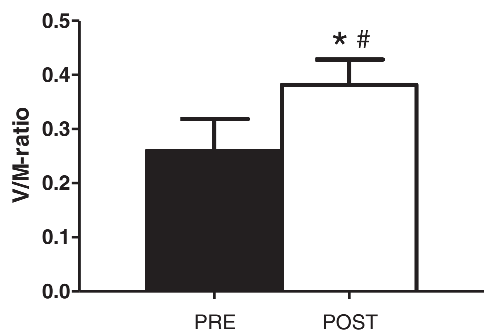


**Fig. 4** Data are presented as mean ± SE. Maximal V-wave/maximal M-wave (V/M-ratio) for the training group at pre- and posttest. * $p < 0.01$, difference within group from pre- to posttest. # $p < 0.01$, different from the control group from pre- to posttest

**Table 2** Psychological measurements, changes from pre- to posttest (scores from insomnia severity index and hospital anxiety and depression scale questionnaires)

| | TG (*n* = 9) | | CG (*n* = 7) | |
|---|---|---|---|---|
| | Pre | Post | Pre | Post |
| Anxiety (0–21) | 12.3 ± 5.8 | 6.3 ± 3.9 * | 11.1 ± 4.5 | 8.0 ± 4.8 * |
| Depression (0–21) | 5.2 ± 2.1 | 3.0 ± 1.6 | 7.4 ± 4.7 | 4.9 ± 3.8 |
| Insomnia (0–28) | 9.2 ± 6.5 | 3.0 ± 2.0 * | 13.3 ± 6.2 | 10.1 ± 5.3 |

Data are presented as mean ± SD, *TG*; Training group, *CG*; Control group. Score categories anxiety and depression: Normal (0–7); signs of mood disorder (8–10); probable presence of mood disorder (11–21). Score categories insomnia: No clinically significant insomnia (0–7); subthreshold insomnia (8–14); clinical insomnia, moderate severity (15–21); clinical insomnia, severe (22–28). * $p < 0.05$, difference within group pre- to posttest

training is even somewhat higher than most previous maximal strength training studies, typically ranging between 25–45 % [9, 18, 19, 38, 39]. Since familiarization was included as a part of the training intervention in this study, this likely contributed to the large strength gain. Additionally, the very low baseline of the weakest subject, which allowed for a very large percentage improvement of ~200 %, also contributed to the high percentage improvement of the TG. Nevertheless, our findings demonstrate the large strength gain achievable when heavy loads and maximal intended concentric velocity are emphasized in strength training. Recognizing that the low physical baseline of the patients in the current study allows large training adaptations, both physiologically and mathematically, the large increase in hack squat 1RM highlights the clinical benefit of a high intensity training intervention in effective physical rehabilitation. The health benefits from an 88 % improvement in leg muscle strength are unquestionable. Ortega et al. [31] reported that Swedish men with high muscular strength had 35 % lower risk of developing cardiovascular disease, 15–65 % lower risk of having any psychiatric diagnosis and 20 % lower risk of all cause mortality when compared to men with low muscle strength. Also Ruiz et al. [10, 12] found the risk of mortality from cancer, cardiovascular disease and other causes to be inversely correlated with muscle strength. Both the Ortega et al. (2012) study and the Ruiz et al. [10, 12] studies emphasize that subjects with low and very low muscle strength particularly suffer an increased risk of medical complications. Considering this, increasing the strength of the weakest individuals would provide the largest health benefit. Although we did not compare our subjects with a reference group some of the patients in the current study stood out as particularly weak. Interestingly it was these patients who apparently seemed to benefit the most from the training. This visual observation was also reflected in the psychosocial questionnaires, where the three weakest subjects exhibited substantial improvements in the psychosocial variables following the training period.

High muscle strength is also associated with lower risk of falls and fractures [7, 8]. Moreland et al. [40] reported that subjects with low and very low muscle strength exhibited elevated risk of single and recurrent falling (Odds ratio: 1.31–5.06). Considering the high incidence of non-drug related hospitalizations among SUD-patients, typically including traumas, falls and fractures [3–5], it is likely that the improved muscle strength would have a preventive effect on these high injury- and hospitalization rates. Balance adjustments and fall prevention do not only require maximal strength; the ability of rapid muscle contractions is often just as important, since the time frame to avoid a fall is short [21, 22, 41]. Because strength training with heavy loads and maximal concentric mobilization is associated with large gain in explosive strength, maximal strength training is argued to be particularly beneficial to induce gain in motor function. The 82 % increase in RFD in the current study adds evidence of the large improvements in explosive strength following maximal strength training regimes, and is similar to previous reports from our research group [18, 38, 39].

### Neuromuscular alterations and maximal strength training

The ~ twofold increase in V/M-ratio highlights that neuromuscular changes largely contributed to the gain in muscle strength. Although there is agreement that training-induced changes in muscle strength relies on a combination of neuromuscular and anabolic adaptations [42], studies involving maximal strength training have often claimed that the improvements were mainly of neuromuscular origin, due to large improvements in 1RM and RFD, with no change in body weight [9, 18, 20]. Based on the comparable large improvements in V/M-ratio and maximal strength, as well as the lack of change in body weight, our findings are in line with this notion. It is unlikely that the low number of repetitions, and thus low anabolic effect, was sufficient to induce any significant muscle growth, while the heavy loads and maximal mobilization seems to be optimal for neural adaptations [20, 43]. The 88 % increase in V/M-ratio is slightly higher compared to other strength training studies, typically displaying improvements of 50–80 % [44, 45]. However, these interventions have been conducted with a lower training intensity than the current, consequently also resulting in smaller improvements maximal strength. Therefore, in combination, our findings and previous studies, exhibits corresponding improvements in neuromuscular adaptations and muscular strength. Specifically, the changes in V-wave amplitude in the current study likely reflects an enhanced efferent neural drive to the muscle, probably due to increased motor unit firing frequency and/or increased motoneuron recruitment [44, 46]. This is because a higher efferent drive would allow more of the electrically evoked reflex volley to pass through to the muscle, hence resulting in the increased amplitude of the V-wave.

#### Feasibility of maximal strength training in substance use clinical treatment

The 75 % completion rate of the TG in the current study exemplifies that although maximal strength training may be considered strenuous, SUD patients are in general capable of engaging in physically demanding training regimes. To date there have been few studies examining intensive physical training in SUD patients, but we have recently shown that also intensive endurance training is feasible for this patient group [33]. In agreement with our findings from the endurance training study, the SUD patients reported no difficulties carrying out the strength training, and the targeted intensity (85–90 % of 1 RM) was reached in all commenced training sessions, without any reports of pain or discomfort. Importantly, most of the subjects that participated reported that they found the simple and robust training motivating, and that they enjoyed observing their own steady and impressing large progression throughout the study. Although SUD is commonly associated with high rates of nonattendance and relapse [47, 48], we experienced no issues regarding subject compliance and attendance to the scheduled training sessions. None of the participating subjects in clinical treatment dropped out solely from the training intervention. Despite being simple and time-efficient to carry out, the training intervention likely benefits from supervision from a trained professional to provide commitment to, and understanding of, the training regime. This notion is also in agreement with previous studies employing training interventions in SUD-patients [33, 49]. Notably, our experience involves only patients participating in residential treatment. It should therefore be considered that the same feasibility and completion rates may not apply for outpatients.

#### Maximal strength training and psychosocial health

The SUD patients in the current study revealed significant signs of mood disorder at inclusion, reflected in elevated scores of anxiety and insomnia. The TG showed a reduction in both anxiety and insomnia scores, as well as a trend towards less depression. However, a reduction in depression following endurance training has previously been reported [33]. In combination, this is evidence that effective, intensive exercise training is not mentally harmful but, again, feasible. Since these improvements in this study are not significantly different from the CG it is difficult to conclude whether the mental health improvements were related to the clinical treatment itself or if they were a result of the improvements in muscle strength. Physical activity is in general shown to positively affect mental health [29], and it may therefore be that the mental health improvements are more related to physical activity performed by both groups, rather than the improvements in muscle strength. However, given the large beneficial effect of an improved physical capacity, and the substantial risk-reduction for diseases and thus likely improvement in quality of life, a clinical treatment including effective physical training should be advocated. Indeed, a close association between physical training and mental health has previously been reported [50–52]. Furthermore, it should be questioned whether self-reporting questionnaires that are not able to detect large training-induced decreases in risk of lifestyle-related diseases are good enough.

#### Clinical considerations for effective physical training in clinical treatment

Recognizing the close relationship between physical capacities, life style related diseases and mortality [10, 53], it is likely that implementation of effective physical training as standard part of the treatment for SUD patients would decrease the high rates of non-drug related hospitalizations. This study shows that maximal strength training not only is feasible as a part of the treatment, it also has a large effect size and is time efficient. Previously we have shown similar findings for endurance training [33]. Adding to the arguments for implementation of effective physical training in the clinic is also the poor rehabilitation results observed in the CG participating in conventional physical activity. The current study observed that the muscular strength and force characteristics in the CG remained unchanged following the 8 week period. In a previous study similar observations were also reported for endurance capacity [33]. Although SUD patients suffer from many challenges, it is important to recognize that their physical health constitutes an important part of the overall health. Since muscle strength and aerobic capacity are known to be important contributors to the physical health, we would argue that strength- and endurance training should be carried out concurrently in clinical SUD treatment. Not only are these physical characteristics shown to be very low in SUD patients [6], today's treatment also appears to have very limited, if any endurance and strength effects. Importantly, this study, as well as a recent endurance training study [33] suggests that effective strength- and endurance training regimes are feasible and safe to carry out within this patient group.

Interestingly, the dropout rate in the TG (3 subjects) in the current study was lower than in the CG (5 subjects). Again, a similar finding was documented following endurance training (3 subjects) vs. conventional treatment (5 subjects) [33]. It is also of importance that the three subjects that dropped out of this study dropped out of the general clinical treatment, and not solely the adherence to the maximal strength training intervention. In support of this notion, it has previously been suggested that participation and adherence to an exercise program may have a positive effect on the relapse rates during alcohol recovery [32]. In combination, these findings suggest that implementation of effective physical training will improve the patients' physical health more than conventional treatment, and it is likely that it may also lead to gains in psychosocial health.

### Study limitations

The training-induced changes of the main physiological variables were statistical significant in this study. However, a larger sample size may have been beneficial for the psychosocial variables, or perhaps a replacement by more detailed psychosocial questionnaires. While this study exemplifies that high intensity strength training is effective and feasible in SUD treatment, it should be noted that all patients in the current study had amphetamine as their primary drug, and that they were all recruited from the same clinic. While the conventional treatment in this clinic did not have any effect on the physical variables, it cannot be excluded that other clinics may have more effective treatment programs. Similarly, it can also be questioned whether our results would have been different if we had included patients with other primary drugs than amphetamine. As both patient characteristics and clinical treatment programs may vary between clinics, future studies should aim to investigate the effect of effective physical training in multiple clinics, and also aim for larger sample sizes to target psychosocial variables and include patients with different primary drugs.

## Conclusion

This study shows that maximal strength training is a feasible, safe and effective method to improve muscle strength and function during SUD treatment. The large improvements in maximal strength and RFD that were observed following two months of training seemed to rely largely on neuromuscular adaptations. The improvements in physical health implies that the SUD patients have reduced their risk for traumas, falls and fractures, life style related diseases and all-cause mortality. Recognizing the poor physical condition of SUD patients, effective physical training, targeting muscle strength and aerobic capacity should be implemented in clinical treatment to improve physical and mental health.

#### Abbreviations

1RM: one repetition maximum; CG: control group; HAD: hospital anxiety & depression scale; ISI: insomnia severity index; $M_{max}$: maximal M-wave amplitude; MVC: maximal voluntary contraction; RFD: rate of force development; SUD: substance use disorder; TG: training group; $V_{max}$: maximal V-wave amplitude; V/M- ratio: maximal V-wave amplitude / maximal M-wave amplitude.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

RU has contributed as main author of the paper as well as physical testing. GF has contributed with subject recruitment, training and physical testing. JH has contributed with study design and writing of the paper. EW has contributed with study design and writing of the paper. All authors have read and approved the final version of the manuscript.

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