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Fitness, health and exercise training therapy in patients with schizophrenia

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
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Sammendrag på norsk / Summary in Norwegian

Norsk tittel: Fysisk arbeidskapasitet og helse; Trening som behandling for pasienter med schizofreni

Pasienter med schizofreni dør tidlig på grunn av hjertekarsykdom (HK) og har redusert gangfunksjon. Redusert fysisk arbeidskapasitet er nært knyttet til risiko for HK og til gangfunksjon målt som mekanisk nytteeffekt men har vært mangelfullt beskrevet for schizofreni gruppen. Få har undersøkt om trening kan normalisere fysisk arbeidskapasitet hos pasienter med schizofreni.

I denne PhD avhandlingen har vi; **I)** sammenlignet utholdenhet (peak oksygenopptak) hos pasienter med schizofreni med normalverdier fra befolkningen, og evaluert sammenheng mellom utholdenhet, risikofaktorer for HK og livskvalitet, **II)** undersøkt effekten av effektiv utholdenhetstrening på mekanisk nytteeffekt for gange, risikofaktorer for HK, psykiatriske symptomer og livskvalitet, **III)** sammenlignet effekter av maksimal styrketrening og konvensjonell styrketrening hos friske, og **IV)** undersøkt effekten av maksimal styrketrening på maksimal styrke, mekanisk nytteeffekt for gange, psykiatriske symptomer og livskvalitet hos pasienter med schizofreni.

I artikkel **I**, fant vi at utholdenheten til menn med schizofreni er 74 % av det normale. Forskjellen tilsvarer nærmere 30 år med aldring. For kvinner er utholdenheten 89 % av det normale, men ikke signifikant redusert. Kontrollert for alder, kjønn og røyking er det er 28 ganger mer sannsynlig at pasienter har en eller flere risikofaktorer for HK, hvis utholdenheten er redusert. Opplevelsen av god fysisk funksjon, generell helse, vitalitet og sosial funksjon øker med økende utholdenhet i pasientgruppen. 33 pasienter deltok i studien.

I artikkel **II**, fant vi at 8 uker med intensiv aerob intervalltrening økte utholdenheten med 12 % og mekanisk nytteeffekt for gange med 12 % sammenlignet med ingen effekt i kontrollgruppen som spilte dataspill (Tetris). Ingen av gruppene endret psykiatriske symptomer eller risikofaktorer for HK.

I artikkel **III**, fant vi at maksimal styrketrening gir større endring i maksimal styrke, eksplosiv styrke og arbeidsøkonomi sammenlignet med konvensjonell styrketrening som ofte benyttes av begynnere og i trening av pasienter.

I artikkel **IV**, fant vi at 8 uker med maksimal styrketrening økte maksimal styrke med 38 % og mekanisk nytteeffekt med 20 % hos pasienter med schizofreni sammenlignet med ingen effekt i kontrollgruppen som trente på å spille Tetris.

Konklusjonen på avhandlingen er at pasienter med schizofreni har redusert fysisk arbeidskapasitet og at det trolig bidrar til økt risiko for HK og redusert livskvalitet. Intensiv aerob intervalltrening og maksimal styrketrening øker utholdenhet, styrke og gangfunksjon og bør bli en del av standard behandling.

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Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden PhD i klinisk medisin.
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Contents

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Trondheim, January 2013
Jørn Heggelund

List of original papers

The four individual studies (papers) listed below construct the framework for this PhD thesis. In the following text, I refer to this series of studies as **papers** with individual Roman numerals. The papers are the result of the collaboration between Department of Neuroscience, and Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology; Department of Østmarka, and Department of Research and Development (AFFU), Division of Psychiatry, St. Olavs University Hospital.

Paper I

Heggelund J, Hoff J,Helgerud J, Nilsberg GE, Morken G. **Reduced peak oxygen uptake and implications for cardiovascular health and quality of life in patients with schizophrenia.** BMC Psychiatry. 2011 Dec 5;11(1):188.

Paper II

Heggelund J, Nilsberg GE, Hoff J, Morken G, Helgerud J. **Effects of high aerobic intensity training in patients with schizophrenia: a controlled trial.** Nord J Psychiatry. 2011 Sep;65(4):269-75.

Paper III

Heggelund J, Fimland MS, Helgerud J, Hoff J. **Maximal strength training improves work economy, rate of force development and maximal strength more than conventional strength training.** Eur J Appl Physiol. 2013 Jan 11 Epub ahead of print.

Paper IV

Heggelund J, Morken G, Helgerud J, Nilsberg GE, Hoff J. **Therapeutic effects of maximal strength training on walking efficiency in patients with schizophrenia - a pilot study.** BMC Res Notes. 2012 Jul 3;5(1):344.

Abbreviations

BF	Body fat
BMI	Body mass index
CDSS	Calgary Depression Scale for Schizophrenia
CG	Computer game training (Tetris)
$\mathbf{C_{ke}}$	Work economy during single leg knee-extension
CON	Conventional strength training
CVD	Cardiovascular disease
ε_{net}	Net mechanical efficiency of walking
HDL	High-density lipoprotein
HIT	High aerobic intensity training
$\mathbf{HR_{peak}}$	Peak heart rate
HUNT	The epidemiological Nord-Trøndelag health study
$\mathbf{kg_m}$	Quadriceps femoris muscle mass
$\mathbf{la^-}$	Lactate
$\mathbf{[la^-]_{bl}}$	Concentration of lactate in blood
LDL	Low-density lipoprotein
$\mathbf{L_m}$	Quadriceps femoris muscle length
LT	Lactate threshold
$\mathbf{M_b}$	Body mass
MET	One MET is the approximate oxygen consumption at rest
min	Minutes
µl	Micro liter
$\mathbf{mL \cdot kg^{-1} \cdot min^{-1}}$	$\text{Milliliters} \cdot \text{kg}^{-1} \cdot \text{minute}^{-1}$
mmol	Millimol

N	Newton
O1, O2, O3	Thigh circumferences; 10 cm above, at the middle thigh and 10 cm below
PANSS	Positive and negative syndrome scale
PF	Peak force
PF_d	Dynamic peak force
PF_i	Isometric peak force
QOL	Quality of life
RER	Respiratory exchange ratio
RFD	Rate of force development
RFD_d	Dynamic rate of force development
RFD_i	Isometric rate of force development
RM	Repetition maximum
rpm	Revolutions per minute
s	Seconds
S_{fold}	Skin fold
SF-36	The SF-36® Health Survey
TPF	Time to peak force
TTE	Time to exhaustion
V	Anthropometric thigh volume
V_E	Total pulmonary ventilation
VO_2	Oxygen uptake
VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen uptake
W	Watt

Summary

Schizophrenia is a severe, chronic and debilitating mental illness. Patients often suffer a high risk of cardiovascular disease (CVD) and neurological abnormalities such as walking deficits. These physical symptoms reduce quality of life (QOL), the ability to carry out day-to-day activities and adherence to treatment. They are also closely related to inactivity and poor physical fitness, but just a few studies have explored these relationships in patients with schizophrenia.

The aims of this thesis were:

1. To evaluate peak oxygen uptake (VO_{2peak}) in patients with schizophrenia (F20 to 29, ICD-10) compared to healthy individuals.
2. To evaluate the relationships between VO_{2peak} and the risk factors of CVD and QOL in patients with schizophrenia.
3. To compare maximal strength training (MST) with conventional strength training (CON) based on the effects on maximal strength, explosive strength and work economy (i.e. net mechanical efficiency of walking [ε_{net}]).
4. To investigate the effects of high aerobic intensity interval training (HIT) and MST on VO_{2peak}, maximal strength, ε_{net}, the risk factors of CVD, psychiatric symptoms and QOL in patients with schizophrenia.

In paper I, 33 patients were included to evaluate baseline fitness characteristics. Patients' VO_{2peak} were compared with normative VO_{2peak} in healthy individuals from the Nord-Trøndelag Health Study (HUNT). VO_{2peak} was 37.1 ± 9.2 $ml \cdot kg^{-1} \cdot min^{-1}$ in men with schizophrenia; 74 ± 19 % of normative levels in healthy men ($p < 0.001$). VO_{2peak} was 35.6 ± 10.7 $ml \cdot kg^{-1} \cdot min^{-1}$ in women with schizophrenia; 89 ± 25 % of normative levels in healthy women (n.s.). Based on the odds ratio, patients were 28.3 (95 % CI=1.6-505.6) times more likely to have ≥1 CVD risk factors if they were below the VO_{2peak} thresholds (44.2 and 35.1 $ml \cdot kg^{-1} \cdot min^{-1}$ in men and women, respectively). VO_{2peak} correlated with The SF-36® Health Survey (SF-36) physical functioning (r = 0.58), general health (r = 0.53), vitality (r = 0.47), social function (r = 0.41) and physical component (r = 0.51) scores.

In paper II, 25 patients were allocated to groups either completing HIT or playing computer games (CG) on three days per week for eight weeks. HIT consisted of 4 x 4 minutes intervals at 85 to 95 % of peak heart rate (HR_{peak}). The HIT group improved VO_{2peak} by 12 % from 3.17 ± 0.59 $L \cdot min^{-1}$ to 3.56 ± 0.68 $L \cdot min^{-1}$ ($p <$ 0.001), more than the CG group ($p = 0.014$). ε_{net} of walking improved by 12 % in the HIT group from 19.8 ± 3.0 % to 22.2 ± 4.5 % ($p = 0.005$), more than the CG group (p = 0.031). The psychiatric symptoms, expressed as Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS), did not improve in either group.

In paper III, we compared MST with equal training volume (kg × sets × repetitions) of CON primarily with regard to work economy, and secondly one repetition maximum (1RM) and rate of force development (RFD) of single leg knee-extension. In an intraindividual design, one leg was randomised to knee-extension MST (4 or 5RM) and the other leg CON (3 × 10 RM) three times per week for 8 weeks. The gross work economy was improved with -0.10 ± 0.08 $L \cdot min^{-1}$ more after MST compared to CON ($p = 0.011$, between legs). From pre- to post-test the MST and CON improved net work economy with 31 % ($p < 0.001$) and 18 % ($p = 0.01$), respectively. MST also improved 1RM ($p = 0.002$) and dynamic RFD ($p = 0.044$) more than CON did.

In paper IV, we investigated whether MST improved ε_{net} in patients with schizophrenia. Patients were assigned to one of two groups: 1) MST consisting of 4 x 4RM performed in a leg press apparatus or 2) playing computer games (CG). The baseline ε_{net} was 17.3 % ± 1.2 % and 19.4 % ± 3.0 % in the MST (n=6) and CG groups (n=7), respectively, both of which can be is categorised as mechanical inefficiency. The MST group improved 1RM by 79 kg ($p = 0.006$) and ε_{net} by 3.4 % ($p = 0.046$) more than the CG group. The MST group improved 1RM and ε_{net}, by means of 83 kg (i.e. 38 % change) ($p = 0.028$) and 3.4 % (i.e. 20 % change) (p = 0.028), respectively. No change was observed in PANSS and the SF-36 ($p > 0.05$).

In general, we concluded that men with schizophrenia have lower VO_{2peak} levels than the general population. Patients with the lowest VO_{2peak} have higher odds of having ≥1 risk factors for CVD. VO_{2peak} correlates with particular aspects of perceived QOL. VO_{2peak} and ε_{net} improve significantly after 8 weeks of HIT. MST is more effective than CON for improving work economy, 1RM and RFD in untrained and moderately trained men. MST improves 1RM and ε_{net} in patients with schizophrenia. Neither HIT nor MST appears to influence symptoms of schizophrenia and QOL.

HIT and MST could be used as therapeutic interventions for patients with schizophrenia to improve physical capacity, contribute to reducing the risk of CVD and to normalise a reduced ε_{net}.

“*For the first time in my life, I’m completing*
a task lasting as long as eight weeks”

Patient’s statement

1. Background

Schizophrenia

Schizophrenia is a severe, chronic and debilitating mental illness. Main characteristics include personality disorganisation, distortion of reality and dysfunction in social activities, domestic chores and occupational performance (World Health Organization 2010). Patients suffering from schizophrenia often experience symptoms as "*thought echo, thought insertion or withdrawal, thought broadcasting, delusional perception and delusion of control, influence or passivity, hallucinatory voices commenting or discussing the patient in third person, thought disorders and negative symptoms"* (World Health Organization 2010). Symptoms like delusions and hallucinations and thought disorders are prominent in many patients with schizophrenia (World Health Organization 2010) and reflect an excess or distortion of normal function often referred to as **positive symptoms**. In contrast, **negative symptoms** reflect a weakening or loss of normal functions and represent symptoms such as affective flattening, apathy, social withdrawal, isolation, poor communication and cognitive impairments (Makinen et al. 2008; Faulkner 2005). Negative symptoms also appear as lack of motivation, initiative, drive and perseverance to carry out daily activities (Makinen et al. 2008).

Lack of function in independent living, employment and social functioning are common in patients with schizophrenia (World Health Organization 2010). It is mainly problems carrying out activities of daily living that keep patients in hospital (Gunatilake et al. 2004). People with schizophrenia comprise about 10 % of the Norwegian recipients of disability benefit (McGlashan and Johannessen 1996).

The course of illness may be either continuous or episodic with complete or incomplete remission (Hafner and an der Heiden 1999). The median lifetime prevalence is about 7 per 1000 (McGrath et al. 2008), and the first episode is at median age 22 and 24 years in men and women, respectively (Johannessen 2002). The specific causes of schizophrenia have not been determined, but both genetic and environmental factors seem to influence the development (Picchioni and Murray 2007). Modern neuroimaging techniques have revealed abnormal brain structures and neurochemical composition in schizophrenia (van Os and Kapur 2009). Many researchers believe that schizophrenia result from problems during neural development that leads to improper function of synaptic transition and plasticity (Yin et al. 2012). However, the relationship between biological alterations and actual experience are not fully understood (van Os and Kapur 2009).

Pharmacological treatment, psychoeducation, family based therapy, cognitive therapy and other psychosocial interventions are recommended in the treatment guidelines (The Norwegian Directorate of Health 2012). Treatment may provide control over the symptoms, although it may not cure the illness (Gunatilake et al. 2004). Maintenance treatment is regularly needed, but many patients still have residual symptoms, maladaptive behaviour and impaired social function (Gunatilake et al. 2004). In 2012, physical activity and training was included in "the national clinical guidelines for the management of psychotic disorders" (The Norwegian Directorate of Health 2012). Exercise training therapy may have distinct treatment benefits, but is not a stand-alone treatment option for schizophrenia (Faulkner 2005).

Cardiovascular disease

Schizophrenia and increased risk of cardiovascular disease (CVD). Patients suffering from schizophrenia have a mortality risk that is 2-3 times higher than the general population and a 12-15 years reduced life-expectancy (Saha et al. 2007). Schizophrenia causes a greater loss of lives than most other illnesses do (van Os and Kapur 2009). The leading cause of death is CVD (Brown et al. 2010; Osby et al. 2000). Patients with schizophrenia are twice as likely to die of CVD as the general population (Brown et al. 2000; Hennekens et al. 2005) and they have higher rates of major risk factors for CVD (Birkenaes, Sogaard et al. 2006). The prevalence of metabolic syndrome is as high as 50 % in women and 35 % in men (Cohn et al. 2004; McEvoy et al. 2005). Other risk factors for CVD, that also constitute part of the metabolic syndrome, are also more frequent in populations with schizophrenia. High prevalence of hypertension, diabetes type 2, diminished glucose tolerance and insulin resistance have been reported (Dixon et al. 2000). Overweight and obesity are prevalent in both genders, but especially in women (Kurzthaler and Fleischhacker 2001). This high risk of CVD could likely both be ascribed to genetics, unhealthy lifestyle (e.g., smoking, diet and inactivity), poor fitness, and adverse effects of antipsychotic medication (Brown et al. 2000; Ryan and Thakore 2002; Strassnig et al. 2011).

Antipsychotic medication is currently an indispensable treatment option in most patients with schizophrenia. However, antipsychotic medication may result in hypertriglyceridemia, insuline recistence and/or weight gain with reduced treatment adherence and increased risk of CVD as consequence (McIntyre et al. 2001; Stahl et al. 2009). Therefore, prioritising modifiable risk factors such as increasing physical activity and fitness may have particular importance in patients with schizophrenia. The majority of patients with schizophrenia have a potential to improve CVD risk profile.

Lifestyles that increase risk of CVD in patients with schizophrenia. Individuals with schizophrenia are vulnerable to adopt harmful lifestyles. Poor diets, high rates of smoking, drug abuse and a sedentary lifestyle are commonly observed (McCreadie 2003). Their diets are high in fat and sugar and low in fibre (Brown et al. 1999; Ratliff et al. 2012). They are less likely than the general population to reach acceptable levels for consumption of fruit, vegetables, milk and potatoes (McCreadie 2003). Moreover, individuals with schizophrenia eat more full-fat cream, sweet drinks and hydrogenated fats than healthy controls (Amani 2007). Many people with schizophrenia are also heavy smokers. A study from Scotland found that 58 % of the patients were smokers compared to 28 % in the general population (Kelly and McCreadie 1999). Sixty-eight percent of the smokers had more than 25 cigarettes per day. The smokers were younger than non-smokers, more often men, had more hospitalisations and more contact with psychiatric services (Kelly and McCreadie 1999). Patients with schizophrenia are also more likely to be inactive and less involved in sport activities (Vancampfort et al. 2011; Daumit et al. 2005). A low physical activity were almost three and a half times more prevalent in patients with schizophrenia compared to matched healthy controls (Vancampfort et al. 2012). Both the total amount of physical activity and the intensity are significantly lower than in controls (Vancampfort et al. 2012; Ratliff et al. 2012). Walking is the prominent physical activity and activities such as jogging, running, biking, gardening and yard work are less common (Daumit et al. 2005).

An important observation is at that more patients than controls are overweight even if both groups have a similar physical activity level (McLeod et al. 2009).

McLeod et al. (2009) suggested the physical activity recommendations for people with schizophrenia should exceed those that apply for the general population to counteract the weight gain.

Gait deficit

A wide range of motor symptoms are consistently reported in patients with schizophrenia (Walther and Strik 2012). Gait deficits are part of these motor symptoms and are reflected by findings suggesting patients may walk slower than healthy controls due to shorter stride length (Putzhammer et al. 2004; Putzhammer et al. 2005b; Lallart et al. 2012). First-episode patients with schizophrenia walk with less arm swing but greater thorax lateral movements (sideways) compared to healthy controls (Stensdotter et al. 2012). The gait deficits seem to be independent of antipsychotic medication usage. However, gait deficits were less pronounced in young first-episode patients (Stensdotter et al. 2012) but more pronounced in patients treated with conventional antipsychotics (Putzhammer et al. 2004). The reduced stride length is particularly evident at a slow walking velocity and tends to normalise with increasing treadmill speed (Putzhammer et al. 2005b). Gait deficits are considered to be related to neurodevelopmental disturbances but the neurobiological cause is not agreed on (Walther and Strik 2012).

Patients with gait deficits such as patients with Parkinson’s disease spend excessive metabolic energy during walking (i.e. reduced walking economy/mechanical efficiency of walking) (Christiansen et al. 2009). This overconsumption of energy reduces their endurance and their capacity to perform day-to-day activities. Surprisingly, the metabolic consequences of gait deficits in schizophrenia are unexplored. Gait deficits may influence the patients’ well-being, quality of life (QOL), and adherence to antipsychotic treatment (Putzhammer et al. 2005a; Robinson et al. 2002). Thus, interventions to improve walking economy/mechanical efficiency of walking may be especially important in patients with schizophrenia.

QOL

The World Health Organization (WHO) (1995) defines QOL as *"individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"*. QOL depends on *"the person's physical health, psychological state, level of independence, social relationship, personal beliefs and relationship to their environment"* (World Health Organization 1995).

Several aspects of schizophrenia illness may affect patients' QOL. However, QOL is subjective and patients with schizophrenia may not report/or perceive low QOL contrary to ratings given by experienced staff (Linaker and Moe 2005).

High levels of cardio respiratory fitness are associated with high levels of QOL in healthy young adults (Sloan et al. 2009). QOL was also found to improve in a dose dependent manner in sedentary women when they increased their physical activity level (Martin et al. 2009). The physical activity level of patients with schizophrenia is a significant predictor of health related QOL (Vancampfort et al. 2011). Moreover, obesity and physical fitness may be perceived as a physical health problem, not mental (Strassnig et al. 2003).

Physical fitness and exercise training

The term "**physical fitness**" embraces a broad range of physiological characteristics such as cardio-respiratory fitness, body composition, muscular strength, endurance, and flexibility (Lamonte and Blair 2012). These attributes relate to an individual's ability to perform physical activity as well as being outcomes of physical activity (Lamonte and Blair 2012).

"**Physical activity**" refers to behaviour and is defined as *"any bodily movement produced by skeletal muscles that requires energy expenditure"* (World Health Organization 2012). This comprehensive definition incorporates physical activities ranging from top-level athletics to everyday life activities.

Physical activity generally refers to movements that enhances health (U.S. Department of Health and Human Services 2008) and even as little as 15 minutes per day may provide significant reductions in all-cause mortality, cancer mortality and CVD mortality (Wen et al. 2011). The relationship between physical activity and health is, however, more complex. Physical activity, fitness and health are interactions that mutually influence each other and separately they are influenced by both genetic and environmental factors (Bouchard et al. 2012). Some studies suggest that fitness level is a stronger predictor of all-cause mortality than actual physical activity level (Blair et al. 2001; Lee et al. 2011). The term "**exercise training**" is used to describe methods of the physical activity that are known to improve specific aspects of physical fitness. Thus, exercise training and physical fitness are more suitable terms that comply with the aim of medical treatments to improve specific health variables.

This thesis focuses on the type and amount of physical activity, or exercise training that improves fitness to provide significant health benefits.

Physical fitness variables

Physical fitness in terms of maximal strength and aerobic endurance has a significant relationship to health and longevity (Kodama et al. 2009; Ruiz et al. 2008). This section provides an overview of the main fitness variables resulting from maximal strength training and aerobic endurance training.

Three factors explain the variance between individuals in aerobic endurance performance; maximal oxygen uptake (VO_{2max}), lactate threshold (LT) and work economy (otherwise known as mechanical efficiency) (Pate and Kriska 1984).

Maximal and peak oxygen uptake. Oxygen comprises 20.93 per cent of the air at sea level and plays a vital role in cell respiration and energy metabolism. During aerobic exercise, oxygen uptake closely mirrors energy consumption and each litre of oxygen consumed corresponds to approximately 5 kcal of energy. At rest the human body require 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ of oxygen to sustain its vital processes. During exercise, the pulmonary oxygen uptake increases to meet the increasing energy demand. The VO_{2max} is defined as *"the highest rate at which oxygen can be taken up and utilised by the body during severe exercise"* (Bassett and Howley 2000). In healthy subjects, this may be observed as a plateau, where the oxygen uptake settles even though the workload is further increased. Maximal tests are often confirmed by a respiratory exchange ratio (RER, the ratio between the amount of carbon dioxide exhaled and oxygen inhaled in one breath) above 1.15 and a blood lactic acid level above 8-9 mmol. Patients may not manage to reach these criteria therefore the term peak oxygen uptake (VO_{2peak}) is often used. VO_{2peak} is also used to describe the highest oxygen uptake during maximal work with small muscle mass such as single leg knee-extension. Conversely, the VO_{2max} is measured during work with large muscle groups, such as walking or running, by gradual and stepwise increasing workload until exhaustion. Elite male endurance athletes may reach a VO_{2max} as high as >90 $ml \cdot kg^{-1} \cdot min^{-1}$. Normative VO_{2peak} for 30-39 year olds are 39.8 $ml \cdot kg^{-1} \cdot min^{-1}$ and 48.8 $ml \cdot kg^{-1} \cdot min^{-1}$ in women and men, respectively (Aspenes et al. 2011). VO_{2peak} are often presented as $ml \cdot kg^{-0.75} \cdot min^{-1}$ (e.g. running) or $ml \cdot kg^{-0.67} \cdot min^{-1}$ (e.g. knee extension) to normalise inter-individual differences and intra-individual changes in bodyweight (Rogers et al. 1995; Helgerud 1994).

VO_{2max} uptake sets the upper limit for performance in an aerobic endurance event (Bassett and Howley 2000; Kodama et al. 2009). Reduced VO_{2max} or VO_{2peak} is also a strong predictor of CVD and all-cause mortality (Blair et al. 1996; Kodama et al. 2009).

Lactate threshold. Lactate (La^-) is a product of anaerobic carbohydrate metabolism. La^- is formed from glucose breakdown when the oxygen supply is not sufficient to allow complete oxidation. La^- is not a waste product but an important source of energy. During rest and moderate exercise, the removal of La^- exceeds the production and blood La^- is always balanced at a sustainable level. Some of the blood La^- is consumed as fuel by the heart and working oxidative muscle fibres and some is used for gluconeogenesis by the liver. The rate of La^- removal depends on the metabolic rate of resting and exercising muscles. However, during short-term intense exercise, the La^- level may increase to an unsustainable level and prevents intermediary metabolism being accomplished. Further exercise intensity must thereafter be reduced to allow La^- removal. The LT is the threshold for lactate built-up, commonly described as *"the highest working intensity at which the lactate production equals its elimination"* (Helgerud 1994). The LT may differ between individuals in terms of oxygen uptake, but not when expressed as a percentage of VO_{2max} (Helgerud 1994).

Work economy. Work economy is the oxygen uptake required to maintain a constant power output or velocity of movement (McArdle et al. 2010, p. 207). Walking or running economy is typically measured during steady rate treadmill walking or running at a standard inclination and speed. Work economy may also be measured at a set watt load during cycling or during work with small muscle mass such as single leg knee-extension, plantar flexion or arm curl exercise (Wang et al. 2008; Kemi et al. 2011; Heggelund et al. 2013). Lower oxygen cost at a standardised workload means better economy.

Mechanical efficiency. Mechanical efficiency denotes the ratio between energy expenditure (energy input) of exercise and the fraction of energy expenditure that appear as external work (energy output) (McArdle et al. 2010, p. 207). The **net** mechanical efficiency (ε_{net}) of walking differs from mechanical efficiency of walking in that the energy input term is the net rate of metabolic energy expenditure (i.e. leave out resting metabolic rate and the horizontal component walking). Contrary to walking economy, ε_{net} is measured at a given watt load, thus taking into account the bodyweight of each individual. The concept of ε_{net} also considers the relationship between energy input and output unlike work economy, which only measures the energy input (viz. pulmonary oxygen uptake). ε_{net} in healthy individuals is typically about 25 % (Hoydal et al. 2007) and may reach 30 % at best (Perrault 2006). A lower percentage means poorer efficiency.

Work economy or ε_{net} becomes progressively more important as the duration of the endurance exercise increases as success depends on the ability to perform work with the lowest possible oxygen uptake (McArdle et al. 2010, p. 207). For many patients, a poor walking economy/ε_{net} in addition to a low VO_{2peak} could be a limiting factor for performance of daily physical activities including domestic chores, work and leisure time physical activity.

Maximal strength. Strength is defined as the maximal force (in Newton) or torque (in Newton metre) a muscle or muscle group can generate at a specified or determined velocity (Komi 2003, p. xiv). Strength is specific to the given action and the velocity of its performance. Maximal strength are typically measured as one repetition maximum (1RM) which denotes the heaviest weight that can be lifted in 1 repetition in a specific dynamic exercise (e.g., bench press, leg press, squat or knee-extension). Strength may also be measured as the maximal force in an isometric muscle action.

Power and rate of force development (RFD). Work is performed as force is applied to an object and displacement occurs. Power is the rate of performing work, that is the product of force and velocity (Komi 2003, p. xiii). RFD is typically calculated from a force-time curve, as the force difference between 10 % to 90 % of the peak force divided by the elapsed time interval (Weiss 2000). This ratio is often termed explosive strength (Zatsiorsky 2003).

Exercise training

The objective of exercise training is to stimulate structural and functional adaptations that improve performance in a specific task (McArdle et al. 2010, p. 452). These adaptations are achieved by adhering to carefully planned training programs with attention to principles such as specificity and overload in frequency, intensity and duration (McArdle et al. 2010, p. 452). The same principles are applicable for both athletes and untrained individuals.

Aerobic endurance training. Aerobic endurance training aims to improve endurance performance through improving VO_{2peak}, LT and work economy (or ε_{net}) (Bassett and Howley 2000). Trainings sessions are often specific and target one of those variables. The LT tends to improve in absolute terms with training that improves VO_{2max} (Londeree 1997), but the LT does not appear to change when reported as a percentage of VO_{2peak} (Helgerud 1994; Helgerud et al. 2007). Thus, aerobic endurance training programs are frequently focused on improve VO_{2peak} and work economy (Helgerud et al. 2007).

Having a high VO_{2peak} is dependent on having a well-developed system for transportation of oxygen from the environment to the mitochondria. The oxygen transport pathway includes the lungs, the heart and vasculature, the blood and the muscles (Wagner 2005). This system of oxygen transport and utilisation is a highly integrated system through the body (Wagner 2008). Aerobic endurance training enhances every part of this system except the lungs (Wagner 2005). The cardiac output and the heart's stroke volume are particularly important (Wagner 2000). There is now considerable experimental support suggesting that training oxygen transport and utilisation to improve VO_{2peak} is most successfully carried out training at a high oxygen uptake. Several studies have compared different training intensities ranging from long slow distance training (at 70 % peak heart rate) to high aerobic intensity training (intervals at 85-95 % peak heart rate). Their overall conclusion is that the critical stimulus is the total amount of time spent at 85-95 % peak heart rate (Helgerud et al. 2007; Rognmo et al. 2004; Wisloff et al. 2007). Although several strategies may be utilised to achieve this goal, the high aerobic intensity training (HIT) performed as 4 times 4 minutes intervals are a close to optimal combination of intensities, length of intervals and rest periods to improve VO_{2peak} (Helgerud et al.

2007; Rognmo et al. 2004; Wisloff et al. 2007). HIT also significantly improves work economy (Helgerud et al. 2007).

Strength training. Increased maximal strength and RFD occur because of adaptations in the skeletal muscles morphology, architecture and nervous system (Folland and Williams 2007; Aagaard 2003). The most pronounced morphological changes are increased cross-sectional area of whole muscle and individual muscle fibres due to hypertrophy (Folland and Williams 2007). However, a large proportion of strength and RFD improvements may be explained by improved neural function. The neural changes include increased motor unit firing rates, increased motoneuron excitability, decreased neural inhibition and increased central descending motor drive (Aagaard 2003). Training programs aimed to maximise neural adaptations (e.g. maximal strength training [MST]) may improve maximal strength and RFD with no or minor changes in muscle mass (Aagaard 2003).

Resistance exercise can be performed in various ways by manipulating variables such as loading, repetition velocity, rest periods and volume (kg × sets × repetitions) (Bird et al. 2005). Based on unequal neural, morphological, metabolic, strength and power adaptations to these acute program variables, different training methods have been developed (Bird et al. 2005; Campos et al. 2002). MST aim to improve maximal strength and RFD (Hoff and Almåsbakk 1995) while training programs applied by body builders primarily aim to increase muscle fibre hypertrophy and secondly strength (Bird et al. 2005). Although these training methods overlap in their subsequent adaptations, the principle of specificity (Sale and MacDougall 1981) suggest that it is possible to manipulate variables to achieve greater adaptations in selected outcomes. To improve maximal strength and RFD, training programs utilising heavy loads (>85 % of 1RM), few repetitions (≤5), maximal mobilisation of force in the concentric part of the movement and long resting periods (>3 minutes) are beneficial (Bird et al. 2005; Campos et al. 2002; Cormie et al. 2011; Hoff and Almåsbakk 1995). Conversely, training programs to induce muscular hypertrophy regularly involve a higher number of repetitions and sets using a moderate load (70-75 % 1RM) as well as intentional slow repetition velocity (concentric and eccentric) and shorter rest periods (Bird et al. 2005; Schoenfeld 2010; Wernbom et al. 2007). Conventional resistance training programs (CON) employ moderate loads corresponding to 60-70 % of 1RM for a repetition range of 8-12 performed with slow to moderate velocities (Ratamess et al. 2009). The conventional resistance training programs are considered safe for novice training and effective to improve strength and rapid force characteristics for untrained and moderately trained individuals (Ratamess et al. 2009).

Strength training, and MST in particular, improves work economy (Hoff et al. 1999) and ε_{net} (Hoff et al. 2007). The exact mechanism behind this improvement are still somewhat blurred but the improved efficiency of the legs occurs in the skeletal muscle and reduces the muscle's blood flow with no change in arterial-venous oxygen difference (a-vO_{2diff}) (Barrett-O'Keefe et al. 2012). The exact program variables of a resistance-training program that improve work economy/efficiency are not determined.

Relationships between fitness and health in patients with schizophrenia

VO_{2peak}

Cardiorespiratory fitness, measured as VO_{2peak} is a strong predictor of CVD and all-cause mortality (Blair et al. 1996; Kodama et al. 2009; Barlow et al. 2012). Higher VO_{2peak} levels reduces the risk of CVD, coronary heart disease and all cause mortality (Kodama et al. 2009). VO_{2peak} is often a stronger predictor of mortality than conventional risk factors for CVD (Myers et al. 2002). McAuley and Blair (2011) identified reduced VO_{2peak} as a greater health threat than obesity and suggested that more emphasis should be put on increasing VO_{2peak}. This might be especially important considering that higher levels of VO_{2peak} seem to offset the increased health risk associated with obesity (Lee et al. 2005). Findings from the epidemiological Nord-Trøndelag Health Study (the HUNT Study) demonstrate that physically active people with a clustering of cardiovascular risk factors appear to have a comparable risk of premature death as inactive individuals without risk factors (Tjonna et al. 2010). In the same cohort, men with VO_{2peak} below 44.2 $ml \cdot kg^{-1} \cdot min^{-1}$ were eight times more likely to have a cluster of CVD risk factors compared with men above 50.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (Aspenes et al. 2011).

Low aerobic capacity is usually a result of inactivity and lack of overload on the cardiovascular system. Thus, aerobic capacity is a modifiable risk factor and prognosis likely improves through increasing VO_{2peak}.

1RM

Muscular strength is a risk factor that is inversely associated with all-cause mortality, CVD mortality, suicide and the prevalence of metabolic syndrome (Jurca et al. 2004; Ruiz et al. 2008; Ortega et al. 2012). Several important health benefits have been identified, including increased muscle mass, increased resting metabolic rate, increased mobilisation of adipose tissue, enhanced insulin sensitivity, improved glucose tolerance and decreased diastolic blood pressure (Tresierras and Balady

2009). These adaptations are associated with reduced risk of CVD and prevalence of metabolic syndrome (Williams et al. 2007).

ε_{net} and walking economy

Walking constitutes an important part of the ability to function in daily life. This ability may include daily activities such as domestic chores, walking to the shops, picking up the post and attending to medical services. Walking deficits in patients with schizophrenia are related to a reduced QOL (Putzhammer et al. 2005a), and a similar relationship may apply to reduced walking economy/ε_{net}.

Patients with chronic obstructive pulmonary disease and patients with coronary artery disease walk with mechanical inefficiency (Hoff et al. 2007; Hoydal et al. 2007). Walking economy/ε_{net} has not yet been investigated in patients with schizophrenia, to the knowledge of the author.

Mental health effects of exercise

Several factors must be considered when exploring the effects of exercise on mental health in schizophrenia. Exercise could have an impact a number of aspects of the patients' mental health, including symptoms of schizophrenia, depression and QOL. The effects could be either temporary or long-lasting. Moreover, there are different methods of exploring and measuring these symptoms, such as interview, observation of patients and questionnaires. There are also numerous individual or group based exercise interventions of different lengths, type and intensity that hold the potential of having distinct effects on mental health. Furthermore, several confounding variables from participating in exercise, such as the social interaction and distraction, might have significant benefits on mental health variables (Martinsen et al. 1989a; Martinsen et al. 1989b).

Whether improved mental health results from physical activity alone or improved fitness has not received much attention. Reductions in depression scores and anxiety in clinical depression and anxiety disorders are found independently of improved VO_{2peak} (Martinsen et al. 1989a; Martinsen et al. 1989b). However, results from the Aerobics Centre Longitudinal Study suggested that people with a low VO_{2peak} are characterised by depressive symptoms and low emotional well being

(Galper et al. 2006). High levels of VO_{2peak} are associated with high levels of QOL (Sloan et al. 2009). Body mass index (BMI) is inversely related to QOL in patients with schizophrenia (Strassnig et al. 2003) but the relationship between VO_{2peak} and perceived QOL has not been evaluated systematically.

Pajonk and colleagues (2010) found a greater hippocampus volume after three months endurance training in eight patients with schizophrenia. They also found that the hippocampus volume change correlated with the improved VO_{2peak}. Another study disagreed with this finding, although they found increased VO_{2peak} to be associated with an increase in total cerebral matter volume, an attenuated increase in lateral and third ventricle volume, and cortical thickening in the left hemisphere (Scheewe et al. 2012c).

It has been suggested that physical activity can alleviate some of the negative symptoms and can be used as a coping strategy to control positive symptoms in schizophrenia (Faulkner 2005). Patients may have less psychotic features on days of physical activity suggesting an acute effect (Chamove 1986). Regular training may lead to a reduction in overall psychopathology (Lukoff et al. 1986). Recently, a larger randomised trial found a significant improvement in symptoms of schizophrenia as well as depression and need of care (Scheewe et al. 2012a). The trial included mostly outpatients and the training period was 6 months.

Methodological considerations of experimental studies in schizophrenia

Patients with schizophrenia tend to have problems with attending randomised controlled trials (Abbott et al. 2005; Beebe et al. 2005). In one study trying to recruit patients to a health promoting trial, 25 out of 36 eligible patients agreed to meet the researchers. The researchers then made 123 visits before 12 of those ultimately provided informed consent (Abbott et al. 2005). After randomisation, 9 patients declined to participate and they were left with 3. The authors suggested that randomised controlled trials have limitations for patients with schizophrenia. One of these limitations may be that only the less severely ill patients attend with a selection bias so that is harder to generalise the results to the wider population of schizophrenia patients (Correll et al. 2011).

A randomised controlled trial is the most powerful experimental study design and the most strict method to determine whether a cause-effect relation exists between a treatment and an outcome (Stolberg et al. 2004). By definition, randomisation is the process of assigning patients to treatment and control groups, under the assumption that each patient has an equal probability of being assigned to any of the groups (Hulley 2001). The randomisation procedure ensures that characteristics are approximately equally distributed between the groups so that the groups do not differ in any systematic way in the confounding variables and the dependent variable. Therefore, any significant differences in outcome measures could be attributed to the intervention. Proper randomisation ensures no previous knowledge (intentional nor unintentional) of group assignment (Hulley 2001).

Non-randomised controlled trials are experimental studies in which patients are allocated to interventions using methods that are not random (Deeks et al. 2003). The most clear difference between randomised and non-randomised trials is the potential for selection bias in terms of biased allocation of patients to a given intervention (Deeks et al. 2003). Selection bias is introduced when patients allocated to one intervention have different characteristics from those in the alternative intervention (Deeks et al. 2003). Non-randomised controlled trials are able to identify associations between an intervention and an outcome (Sibbald and Roland 1998). However, bias may exist and might be difficult to detect (Kadar 1997).

2. Aims and Hypotheses

The overall aim of this thesis was **to evaluate fitness, health and exercise training therapy in patients with schizophrenia**. This aim was examined in four studies (paper I-IV) with distinct aims and hypotheses:

Paper I

- To evaluate VO_{2peak} during walking or running in men and women with schizophrenia compared to VO_{2peak} in healthy individuals from the Nord-Trøndelag Health Study (HUNT).
- To evaluate relationships between VO_{2peak}, risk factors for CVD, and QOL.
- We hypothesised that patients with schizophrenia had reduced VO_{2peak} compared to normative healthy individuals.

Paper II

- To investigate the effects of HIT compared with physical inactivity in the form of playing computer games (CG), in patients suffering from schizophrenia. The outcome variables were VO_{2peak}, ε_{net} of walking, CVD risk factors and symptoms of schizophrenia.
- We hypothesised that >80 % adherence to 24 training sessions with HIT during 8 weeks would improve the VO_{2peak} and ε_{net} more than the same amount of time spent on CG.

Paper III

- The aim of this study was to compare maximal strength training (MST) with conventional strength training (CON) based on effects on maximal strength, explosive strength and work economy (otherwise known as ε_{net})
- Our hypotheses were that MST improves work economy, maximal strength and RFD more than CON does.

Paper IV

- To evaluate the effects of 8 weeks MST on 1RM, work economy (viz. ε_{net} of walking), symptoms of schizophrenia and QOL. We chose to compare the MST with CG.
- We hypothesised that the MST would improve 1RM and work economy (viz. ε_{net} of walking) more than the CG

3. Methods

Subjects

Paper I, II and IV. Paper I is based on data from 33 patients with ICD-10 schizophrenia, schizotypal or delusional disorders (F20 to F29) (figure 1). Paper II and IV together (figure 1) are based on data from 32 patients at the University Hospital. All patients were treated with antipsychotic medication. Exclusion criteria were known coronary artery disease, known chronic obstructive pulmonary disease, and not being able to perform physical treadmill testing and exercise. A physician examined patients at inclusion to the study and reviewed medical records for potential exclusion criterions. The first patients were allocated to HIT, the next group to CG and the last patients to MST. The allocations to the groups were non-randomised but the patients were not able to choose group themselves. Neither patients nor staff achieved information that could influence their preference to a particular intervention. Testing was performed the week before and the week after the 8-week intervention (figure 2).

Paper III. We included ten healthy, non-smoking men. They were moderately trained or untrained and did not participate in concurrent strength training during the study period.

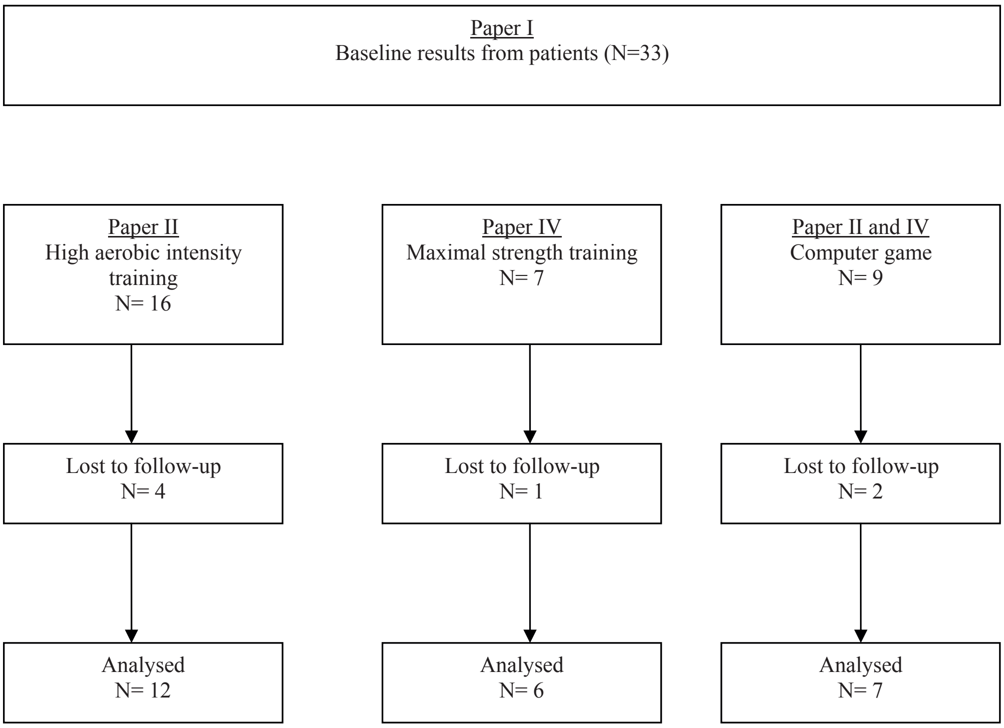

Figure 1. Patients with schizophrenia included in studies (papers I, II and IV). Paper I used baseline results from 33 patients. 32 patients were allocated to three non-randomised groups (paper II and IV) (Heggelund et al. 2011a; Heggelund et al. 2012; Heggelund et al. 2011b).

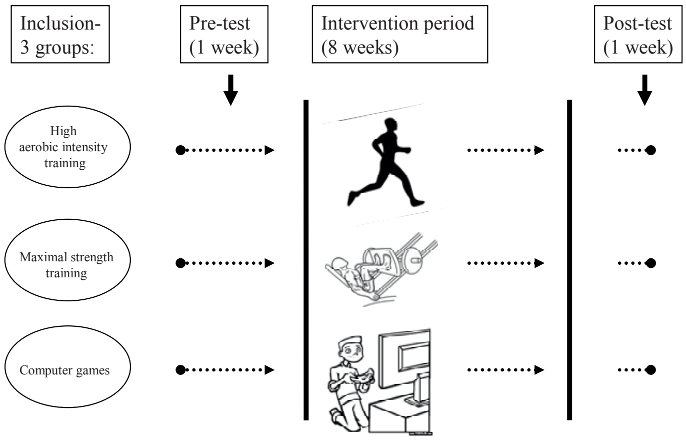

Figure 2. Designs presented in paper II and IV. Paper II (Heggelund et al. 2011b) present effects of high aerobic intensity training and paper IV (Heggelund et al. 2012) present effects of maximal strength training. The computer game group served as a control group in both papers II and IV. Pre- and post-test measurements were made the week before and after the 8 weeks intervention period. The groups were non-randomised.

Experimental designs

In paper I, we evaluated baseline VO_{2peak} measures from 33 patients with schizophrenia and compared them with age and sex specific strata from the Nord-Trøndelag Health Study (the HUNT Study). We also evaluated risk factors for CVD as well as QOL in patients above/below the mean VO_{2peak} thresholds defined by Aspenes, Nilsen et al. (2011). The design resembles a cross-sectional study, but the sample size is low and patients were not randomly selected from the population.

In papers II and IV we performed 8 week non-randomised controlled trials to evaluate the effects of HIT and MST in patients with schizophrenia. The control group spent an equivalent amount of time being physical inactive playing computer games.

Paper III is a randomised controlled trial. Using an intraindividual design, one leg was randomised to 8-weeks MST and the other to equal volume CON in a counterbalanced fashion.

Measurements

Oxygen uptake

Peak exercise testing. We applied an individualised incremental protocol to measure VO_{2peak} and peak heart rate (HR_{peak}). In papers I, II and IV we used the Cortex Metamax II portable ergospirometry system (Cortex Biophysik GmbH, Leipzig, Germany). In paper III we used a Cortex Metamax 3x. We measured HR_{peak} using a heart rate monitor (Polar Electro, Finland) and in study we also drew blood samples to measure lactate concentration ($[La^-]_b$) using a YSI Sport Lactate Analyzer (Yellow Springs Instruments Co, USA). The treadmill protocol has previously been described (Helgerud et al. 2007). The same principles of increasing workload to exhaustion were applied during single-leg knee extension in paper III.

Sub-maximal exercise testing. Subjects performed continuous steady rate submaximal work through a period of 6 minutes (5 minutes in paper III). The respiratory measurements made through the first half of the last minute of the bout were used to evaluate the submaximal performance. In paper III, the workload was 20 watt and determined by the Monark Ergomedic 839E electrical braked cycle ergometer (Monark Exercise AB, Varberg, Sweden). In papers I, II and IV the subjects walked at an individually adjusted speed and incline corresponding to 60 watt at pre- and post-test. In paper III, we present these measures in terms of work economy. In paper III and IV, we further calculated the energy input and output to determine the ε_{net} of walking. The procedures are properly described in paper IV.

Knee-extension. To perform testing in paper III we built the single leg knee-extension apparatus according to a model described by (Andersen et al. 1985; Andersen and Saltin 1985; Richardson et al. 1995). Subjects were sitting in the Felax HG-5114 knee extension machine with the leg fastened to an aluminium-brace that was connected via a bar to the pedal arm of a Monark Ergomedic 839E electrical braked cycle ergometer (Monark Exercise AB, Varberg, Sweden) (figure 3). The knee-extension apparatus were adjusted to produce a 90° -170° arc of the lower leg. Subjects were not strapped to the seat. We instructed the subjects to hold their hands in their lap and to perform the exercise by using the knee-extensors only. Subjects were corrected if unwanted movements occurred. The bicycle ergometer was calibrated before each test and the friction made by the crank was subtracted in order to give a valid watt load. One week before pre-testing the subjects spent 20 min training with each leg to become familiarised with the test (Andersen et al. 1985; Richardson et al. 1995).

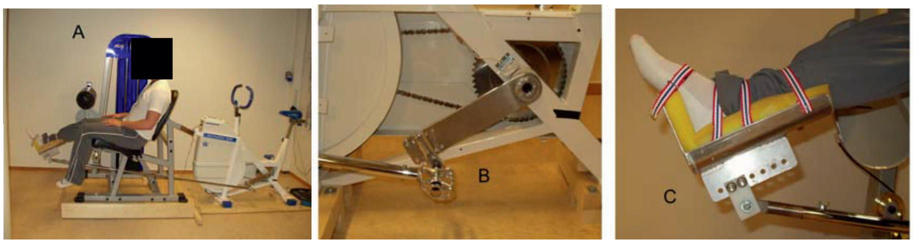

Figure 3. The knee-extension apparatus.

Normative VO_{2peak}

In paper I, we compared the patients' VO_{2peak} with age and sex specific strata from the Nord-Trøndelag Health Study (the HUNT Study) (Aspenes et al. 2011). The HUNT study is an epidemiological study of the general population in the neighbouring county to the university hospital. The HUNT Fitness study tested VO_{2peak} in 4 631 healthy individuals (20 to 90 years old) using mixing chamber gas-analyzer ergospirometry (Cortex MetaMax II, Cortex, Leipzig, Germany) and an individualised protocol that has close resemblance to the protocol used in the present study. 14.1 % of the participants reported to be inactive, defined as no activity or exercising less than once per week. For each patient with schizophrenia, we estimated a normative VO_{2peak}, namely the mean value defined in the HUNT Fitness study strata for the corresponding sex and age. We called the VO_{2peak} estimated from sex and age strata independent of physical activity level the HUNT general. The VO_{2peak} from age and sex strata for healthy inactive men and women was called HUNT inactive. The patients' VO_{2peak} as a percent of HUNT general and HUNT inactive VO_{2peak} was calculated as: (achieved VO_{2peak} ÷ age predicted VO_{2peak}) · 100.

Table 1. Reference intervals for CVD risk factors.

Risk factor	Reference intervals
Hypertension	Diastolic pressure ≥90 mmHg and/or Systolic pressure ≥140 mmHg
Elevated blood glucose	>6.0 $mmol \cdot L^{-1}$
Elevated total cholesterol	>6.1 $mmol \cdot L^{-1}$ in patients <30 years old
	>6.9 $mmol \cdot L^{-1}$ in patients 30-49 years old
	>7.8 $mmol \cdot L^{-1}$ in patients ≥50 years old
Elevated LDL-cholesterol	>4.3 $mmol \cdot L^{-1}$ in patients <30 years old
	>4.7 $mmol \cdot L^{-1}$ in patients 30-49 years old
	>5.3 $mmol \cdot L^{-1}$ in patients ≥50 years old
Reduced HDL-cholesterol	<1.0 $mmol \cdot L^{-1}$
Elevated triglyceride	>2.6 $mmol \cdot L^{-1}$
Obesity	BMI ≥30.0 $kg \cdot m^{-1}$

Taken from the "Nordic Reference Interval Project 2000" and the "2007 Guidelines for the management of Arterial Hypertension" (Mancia et al. 2007; Rustad et al. 2004).

Conventional CVD risk factors

In papers I and II, morning fasting blood levels were taken. Serum glucose was analysed using the Reflotron Plus system (Roche Diagnostics, Mannheim, Germany). HDL (high-density-lipoprotein) cholesterol, total cholesterol and triglyceride concentrations in serum were measured using a Modular P chemistry analyser (Roche Diagnostics, Mannheim, Germany). LDL cholesterol was calculated using the Friedewald, Levy et al. (1972) equation. BP (blood pressure) was measured using a Maxi-Stabil 3 (Welch Allyn, Jungingen, Germany). Patients were sitting and had rested for at least 5 minutes. In paper I, risk factors were classified according to reference intervals (Mancia et al. 2007; Rustad et al. 2004) presented in table 1.

In the HUNT study men and women below 44.2 $ml \cdot kg^{-1} \cdot min^{-1}$ and 35.1 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively, were more likely to have CVD risk factors (Aspenes et al. 2011). These VO_{2peak} values were used as threshold values. Thus, we evaluated the occurrence of conventional CVD risk factors in patients below versus patients above these VO_{2peak} thresholds (paper I).

1RM

In paper IV 1RM was measured in the leg press machine using Olympic weights (Eleiko, Sweden). The lift was performed from complete extension to 90 degrees angle in the knee joint and back to complete extension. In paper III 1RM was measured as single leg knee extension. Approved lifts had to reach 160° in the knee joint. In all three studies/papers, the load was increased successively until the patients or subjects were not able to lift the weight. Rest periods were 2-3 minutes between each trial (American College of Sports Medicine 2010).

RFD

Measures of rate of force development were performed in paper III. Testing of RFD was carried out in the leg extension machine. Force parameters were measured using a SHB×R force transducer (Revere Transducers, California, USA). All tests were performed with 90° flexion in the knee joint. Dynamic peak force (PF_d) and dynamic rate of force development (RFD_d) were measured using a 27.6 kg standard load. Isometric peak force (PF_i) and isometric rate of force development (RFD_i) were measured during a 6 seconds maximal isometric contraction. All subjects held their buttocks on the seat, the hip angle steady and the back against the backrest. All procedures were repeated 2 or 3 times with 3 minutes rest between each trial and alternating between the left and right leg. RFD was calculated as the force difference between 10-70 % of PF divided by the time needed to achieve this difference (i.e. Δforce/Δtime).

Anthropometry

Body fat (BF) was measured using the anthropometric techniques described by Norton, Whittingham et al. (2002) using a Holtain Skinfold calipers (Holtain Ltd, Crosswell, Crymych, United Kingdom). The same exercise physiologist performed all measurements. Measurements were made on the right side of the upper body, at four sites (biceps, triceps, sub scapular and supra-iliac areas). Procedures are described by Durnin and Womersley (1974) and Norton (2002).

Quadriceps femoris muscle volume and mass was calculated for both legs by procedures described by Andersen and Saltin (1985) and Radegran, Blomstrand et al. (1999).

Equations are presented in paper III (Heggelund et al. 2013).

Psychometric variables

Possible changes in positive and negative symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987). The test was performed by two psychiatric nurses, trained in using PANSS, working in the ward and had a personal knowledge of the patient. The Calgary Depression Scale for Schizophrenia (CDSS) was used to assess depressive symptoms (Addington et al. 1990). The SF-36® Health Survey (SF-36) was used to assess the physical health and mental health aspect of health related QOL (Ware et al. 2000). The SF-36 is a 36-item self-report instrument.

Interventions

Treadmill interval training

The HIT group trained 4x4 minutes interval training on a treadmill (Tung Keng Enterprise CO., LTD. Taiwan) at 85 to 95 % HR_{peak} interspersed with 3 min of active resting periods at a work load corresponding to 70 % HR_{peak} between each interval, previously shown to be highly effective (Helgerud et al. 2007; Rognmo et al. 2004; Tjonna et al. 2008; Wisloff et al. 2007). Patients performed the intervals walking or running with a minimum of 5 % inclination. Heart rate was assessed continuously during exercise, using a Polar S610i heart rate monitor (Polar Electro, Finland). The exercise physiologist ensured that the patients performed intervals at the scheduled intensity.

Strength training

Knee extension. Training sessions (paper III) started with a 5 min warm-up on a bicycle ergometer followed by 3 sets of 8-10 repetitions with a weight load approximately 40-50 % of 1RM in the knee-extension machine (Felax, Healthlife HG-5114, China).

All subjects started each training session with their dominant leg, that is, half of the subjects started with MST and half of the subjects with CON. After finishing the training in their dominant leg, subjects performed the other intervention using their non-dominant leg. The two training programs were equal with respect to training volume, hence the CON training was 3 sets of 10RM and the MST alternated each training session between 4 and 5 sets of 5RM (i.e. 85-95 % 1RM). MST was carried out using maximal mobilisation of force in the concentric muscle action. Subjects rested for 3 minutes between each set. CON was performed according to the American College of Sports Medicine (ACSM) guidelines (Ratamess et al. 2009) with 10RM (i.e. 60-70 % of 1RM) which is considered a moderate intensity for 3 consecutive sets with moderate velocity and 1 minute between each set. When a subject successfully executed the determined number of repetitions, the load was increased with approximately 1.25 – 2.5 kg the next training session. An experienced exercise physiologist supervised all training sessions.

Leg press. All MST sessions started with a 5-minute warm-up on the treadmill at a workload corresponding to 70 % of HR_{peak}. MST was then performed at a 54° incline leg press machine (Technogym, Italy). The weight was lowered in a controlled manner in the eccentric phase until the patient reached 90 degrees in the knee joint. Then the patients had a short stop (~0.5 second) before the weight was moved as rapidly as possible to complete extension. The training volume was 4 sets of 4RM (i.e. 85-90 % 1RM). An exercise physiologist supervised the training sessions and ensured that the training load was increased with 2.5-5 kg each time patients managed to perform 4 sets with the determined load or each training session. Rest periods were 3 minutes between each set.

Computer games

The CG group spent 36 minutes three times per week training to improve their ability in the computer game Tetris (THQ Inc. Calabasas Hills, CA), using an Xbox Video Game Systems (Microsoft Corporation, Redmond, USA). All sessions were monitored and patients were encouraged to improve performance.

Statistical analysis

In paper I, we used an independent samples T-test to compare differences between men and women, between patients below and above the VO_{2peak} thresholds as well as between measured VO_{2peak} and HUNT general and HUNT inactive VO_{2peak}. In paper II, an independent samples T-test was performed to test differences at baseline and changes from pre- to post-test between the two groups. Due to the nature of the design in paper III, we used paired samples t-test to evaluate difference in pre- to post-changes between the MST leg and CON leg. Paired samples t-tests were also used to determine changes from pre- to post-test in paper II and III. The normality of the distribution of scores was assessed using the Kolmogorov-Smirnov test and by evaluating the skewness and kurtosis values.

In paper IV, a related samples Wilcoxon test was used to determine changes from pre- to post-intervention. Independent samples Mann-Whitney U tests were used to evaluate the changes and differences between groups. Categorical variables were tested using Fisher's exact test.

In paper I, we used Pearson's chi-square tests to detect whether there was a significant association between patients above/below the VO_{2peak} threshold and prevalence of risk factors. We calculated the odds ratio for having ≥1 risk factors in the patients below threshold. The analysis was adjusted for age and sex. In multiadjusted analysis, we also took into account the potential confounding effect of smoking. We used Pearson r to analyse correlations between VO_{2peak} ($ml \cdot kg^{-0.75} \cdot min^{-1}$) and each domain of the SF-36.

The significance level was set at $p < 0.05$ (2-tailed). Data are described as mean and standard deviation (SD), unless otherwise noted. SPSS statistical package, version 17.0 or 18.0 (SPSS Inc.), was used to analyse results.

4. Summary of results

Paper I. Reduced peak oxygen uptake and implications for cardiovascular health and quality of life in patients with schizophrenia (Heggelund et al. 2011a).

Background. VO_{2peak} is a strong predictor of CVD and all-cause mortality, but is inadequately described in patients with schizophrenia.
Aims. To evaluate treadmill VO_{2peak}, CVD risk factors and QOL in patients with schizophrenia (ICD-10, F20-29).
Methods. 33 patients, 22 men (33.7 ± 10.4 years) and 11 women (35.9 ± 11.5 years), were included. Patients' VO_{2peak} were compared with normative VO_{2peak} in healthy individuals from the Nord-Trøndelag Health Study (HUNT). Risk factors were compared above and below the VO_{2peak} thresholds; 44.2 and 35.1 $ml \cdot kg^{-1} \cdot min^{-1}$ in men and women, respectively.
Results

1. VO_{2peak} was 37.1 ± 9.2 $ml \cdot kg^{-1} \cdot min^{-1}$ in men with schizophrenia; 74 ± 19 % of normative healthy men ($p < 0.001$; figure 4).
2. VO_{2peak} was 35.6 ± 10.7 $ml \cdot kg^{-1} \cdot min^{-1}$ in women with schizophrenia; 89 ± 25 % of normative healthy women (n.s.; figure 4).

Based on the odds ratio patients were 28.3 (95 % CI=1.6-505.6) times more likely to have ≥1 CVD risk factors if they were below the VO_{2peak} thresholds. VO_{2peak} correlated with the SF-36 physical functioning (r = 0.58), general health (r = 0.53), vitality (r = 0.47), social function (r = 0.41) and physical component (r = 0.51) scores.
Conclusion. Men with schizophrenia have lower VO_{2peak} than the general population. Patients with the lowest VO_{2peak} have higher odds of having ≥1 risk factors for CVD. VO_{2peak} should be regarded as at least as important as the conventional risk factors for CVD and evaluation of VO_{2peak} should be incorporated into clinical practice.

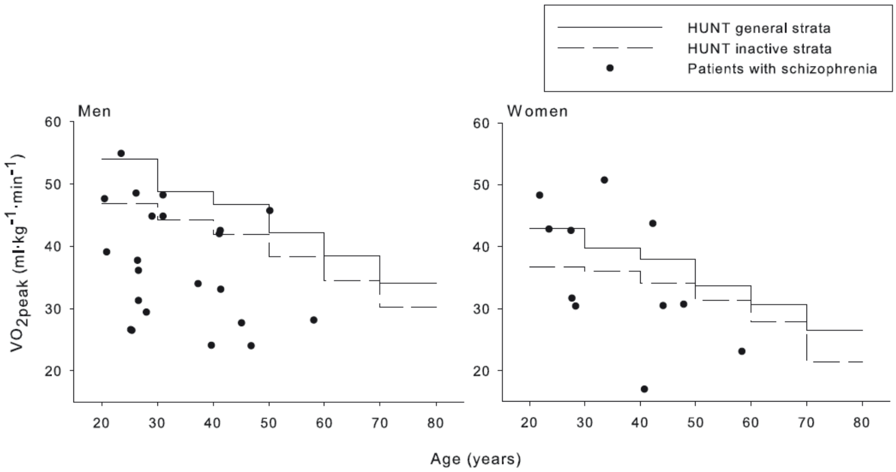

Figure 4. Peak oxygen uptake in patients with schizophrenia and normative healthy men and women. Normative strata are taken from the HUNT fitness study (Aspenes et al. 2011). HUNT general strata are age and sex specific strata regardless of physical activity level. Figure taken from paper I (Heggelund et al. 2011a).

Paper II. Effects of high aerobic intensity training in patients with schizophrenia: a controlled trial (Heggelund et al. 2011b).

Background. Patients with schizophrenia have a high risk of CVD. HIT improves VO_{2peak}, ε_{net} of walking and risk factors for CVD, but these are not investigated in patients with schizophrenia.
Aims. To investigate the effects of HIT on VO_{2peak}, ε_{net} and the risk factors for CVD in patients with schizophrenia.
Methods. 25 inpatients (F20 to 29, ICD-10) were allocated to either HIT or CG, three days per week for eight weeks. HIT consisted of 4x4 minutes intervals with 3 minute rest periods at 85 to 95 % and 70 % of peak heart rate, respectively.
Results.

1. 12 and 7 patients completed HIT and CG respectively.
2. The HIT group improved VO_{2peak} by 12 % from 3.17 ± 0.59 $L \cdot min^{-1}$ to 3.56 ± 0.68 $L \cdot min^{-1}$ ($p < 0.001$; figure 5), more than the CG group ($p = 0.014$).
3. ε_{net} improved by 12 % in the HIT group from 19.8 ± 3.0 % to 22.2 ± 4.5 % ($p = 0.005$; figure 5), more than the CG group ($p = 0.031$).
4. The psychiatric symptoms, expressed as PANSS and CDSS, did not improve in either group.

Conclusions: VO_{2peak} and ε_{net} improved significantly from 8 weeks of HIT. HIT should be included in rehabilitation in order to improve physical capacity and contribute to reducing the risk of CVD.

Paper III. Maximal strength training improves work economy, rate of force development and maximal strength more than conventional strength training (Heggelund et al. 2013).

Background. MST improves work economy but it is not known whether CON would result in the same improvements.
Aims. To compare MST with equal training volume of CON primarily with regard to work economy, and secondly 1RM and RFD of single leg knee-extension.
Methods. In an intraindividual design, one leg was randomized to knee-extension MST (4 or 5×5 repetitions, 85-90 % 1RM) and the other leg CON (3×10 repetitions, 70-75 % 1RM) 3 times per week for 8 weeks. MST was performed with maximal concentric mobilisation of force while CON was performed with moderate velocity.
Results.

1. A significant difference in change were noted between training conditions in C_{ke} ($ml \cdot kg_m^{-1} \cdot min^{-1}$; $p < 0.024$). Cohens'd was >0.8 or higher for between groups differences, indicating a large effect in favour of the MST.
2. The gross work economy was improved with -0.10 ± 0.08 $L \cdot min^{-1}$ more after MST compared to CON ($p = 0.011$, between legs).
3. From pre-to post-test the MST and CON improved work economy with 31 % ($p < 0.001$) and 18 % ($p = 0.01$) respectively.
4. Compared to CON, the improvement in 1RM and RFD_d was 13.7 ± 8.4 kg ($p = 0.002$) and 587 ± 679 $N \cdot s^{-1}$ ($p = 0.044$) larger after MST whereas the improvement in RFD_i was of borderline significance 3028 ± 3674 $N \cdot s^{-1}$ ($p = 0.053$).
5. MST improved 1RM and RFD_i from pre- to post-test by 50 % ($p < 0.001$) and 155 % ($p < 0.001$) respectively.
6. CON improved 1RM and RFD_i with 35 % ($p < 0.001$) and 83 % ($p = 0.028$) respectively.
7. Anthropometric measures of quadriceps femoris muscle mass and VO_{2peak} did not change.

Conclusions. Eight weeks of MST was more effective than CON for improving work economy, 1RM and RFD in untrained and moderately trained men. The advantageous effect of MST on improvements in work economy could be due to a larger improvement in 1RM and RFD.

Paper IV. Therapeutic effects of maximal strength training on walking efficiency in patients with schizophrenia (Heggelund et al. 2012).

Background. Patients with schizophrenia frequently have disabling gait deficits. ε_{net} is an accurate measure often used to evaluate walking performance. Patients with gait deficits have a reduced ε_{net} with excessive energy expenditure during sub-maximal walking. MST improves ε_{net} in healthy individuals and is associated with a reduced risk of mortality.

Aims. The aim of this study was to investigate whether MST improves ε_{net} in patients with schizophrenia.

Methods. Patients (ICD-10 schizophrenia, schizotypal or delusional disorders [F20-F29]) were included in a non-randomised trial. Patients were assigned to one of two groups: 1) MST consisting of 4 x 4RM performed in a leg press apparatus or 2) CG. Both groups carried out their activity three days per week for eight weeks. 1RM, ε_{net} at 60 watt walking, VO_{2peak}, PANSS and the SF-36 were measured pre- and post-intervention.

Results.

1. The baseline ε_{net} was 17.3 % ± 1.2 % and 19.4 % ± 3.0 % in the MST (n = 6) and CG groups (n = 7), respectively, which is categorised as mechanical inefficiency.
2. The MST group improved 1RM by 79 kg ($p = 0.006$) and ε_{net} by 3.4 % ($p = 0.046$) more than the CG group.
3. The MST group improved 1RM and ε_{net}, by a mean of 83 kg (i.e. 38 % change) ($p = 0.028$) and 3.4 % (i.e. 20 % change) ($p = 0.028$) respectively (figure 5).
4. VO_{2peak} at baseline was 34.2 ± 10.2 and 38.3 ± 9.8 $ml \cdot kg^{-1} \cdot min^{-1}$ in the MST and CG groups respectively, and did not change ($p > 0.05$; figure 5).
5. No change was observed in PANSS or SF-36 ($p > 0.05$).

Conclusions. MST improves 1RM and ε_{net} in patients with schizophrenia. MST could be used as a therapeutic intervention for patients with schizophrenia to normalise their reduced ε_{net}.

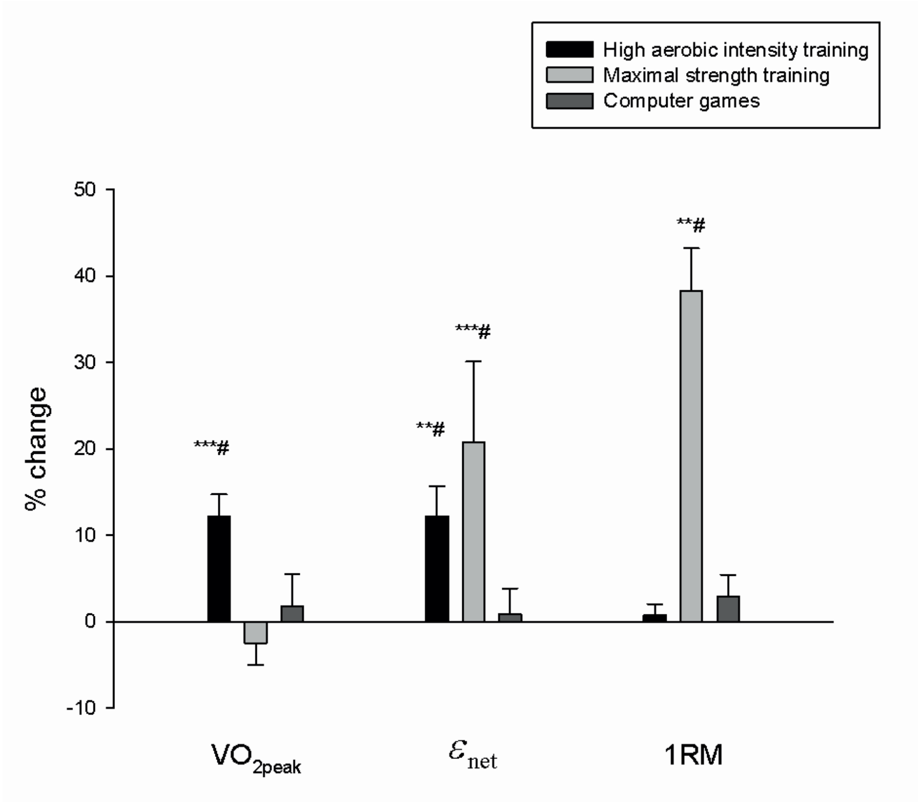

Figure 5. Percent pre-to post-changes of peak oxygen uptake (VO_{2peak}), net mechanical efficiency of walking (ε_{net}) and one repetition maximum (1RM) across interventions in study II and IV. [#]different from CG group; $p < 0.05$, **difference between pre- and post-test $p < 0.01$, *** difference between pre- and post-test $p < 0.001$. Values are mean ± standard error (SE).

5. Discussion across papers

The main findings of the thesis are;

1. Men and women with schizophrenia have only 74 % and 89 % of the VO_{2peak} of normative men and women, respectively (paper I).
2. Patients with a VO_{2peak} below 44.2 $ml \cdot kg^{-1} \cdot min^{-1}$ (men) and 35.1 $ml \cdot kg^{-1} \cdot min^{-1}$ (women) were 28.3 times more likely to have ≥1 risk factors for CVD (paper I).
3. VO_{2peak} correlates with the patients' perception of physical function, general health, vitality, social function and SF-36 physical component score (paper I).
4. The patients with schizophrenia had a ε_{net} of walking that is categorised as mechanical inefficiency (i.e. reduced) (paper II and IV).
5. High aerobic intensity training improved VO_{2peak} (12 %) and ε_{net} (12 %) in patients with schizophrenia (paper II).
6. MST was superior to CON in improving work economy (otherwise known as ε_{net}) (paper III).
7. MST improved 1RM (38 %) as well as ε_{net} (20 %) in patients with schizophrenia (paper IV).

Reduced physical fitness as a predictor of CVD and premature mortality

In paper I we found that VO_{2peak} in men with schizophrenia was 74 ± 19 % of healthy men ($p < 0.001$), whereas women with schizophrenia had a VO_{2peak} that was 89 ± 25 % of healthy women (n.s.). Even more importantly, based on the odds ratio patients were 28.3 (95 % CI=1.6-505.6) times more likely to have ≥1 CVD risk factors if they were below the VO_{2peak} thresholds presented by Aspenes et al. (2011) in the HUNT fitness study. The present study found a very low VO_{2peak} in patients with schizophrenia and a high frequency of risk factors for CVD among patients with low VO_{2peak}. Two resent studies confirmed this finding (Scheewe et al. 2012b; Strassnig et al. 2011).

High risk of CVD in patients with schizophrenia has been consistently reported during the latest decades. The evidence is mainly derived from epidemiological studies concentrated on the high mortality and the causes of the excess mortality as an outcome (Osby et al. 2000; Brown et al. 2000).

It is well known that exercise cause beneficial adaptations that reduce the risk of CVD. Though, early exercise research was often concentrated on the hypotheses as to whether exercise could improve mental health variables and seldom applied high quality measures of physical fitness and cardiovascular risk factors (Adams 1995; Belcher 1988; Carter-Morris and Faulkner 2003; Chamove 1986; Faulkner and Sparkes 1999; Gimino and Levin 1984; Hatlova and Basny sen 1995; Lukoff et al. 1986; Mrazek and Hatlova 1995; Pelham et al. 1993; Rosenthal and Beutell 1981). These studies did not incorporate highly effective training interventions to improve fitness (Wildgust et al. 2010) and they had methodological issues that reduced the quality (Faulkner 2005). This trend has changed during the recent years. Now a number of exercise studies in patients with schizophrenia have been conducted, some have a high methodological quality and the studies' aims are often to reduce the high risk of CVD (Scheewe et al. 2012c; Scheewe et al. 2012b; Strassnig et al. 2011; Pajonk et al. 2010; Blouin et al. 2009; Pajonk et al. 2008; Heggelund et al. 2011a; Heggelund et al. 2012; Heggelund et al. 2011b).

The epidemiological studies of CVD risk in patients with schizophrenia point at obesity and overweight, hyperglycemia, dyslipidemia, hypertension and smoking as major risk factors (Hennekens et al. 2005). Although these are indisputable contributors to the high CVD risk, several studies now suggest that these variables are indirect manifestations of poor exercise capacity (Kavanagh et al. 2002; Kodama et al. 2009; Myers et al. 2002). VO_{2peak} is often a stronger predictor of mortality than conventional risk factors for CVD (Myers et al. 2002). McAuley and Blair (2011) recently pointed out that reduced cardiorespiratory fitness is as a greater health threat than obesity and suggested that more emphasis should be put on increasing VO_{2peak}. Higher levels of VO_{2peak} seem to attenuate or eliminate the increased health risk associated with obesity (Lee et al. 2005). Findings from the HUNT study demonstrate that physical active people with a clustering of cardiovascular risk factors appear to have comparable risk of premature death as inactive individuals without risk factors (Tjonna et al. 2010). In the same cohort, men with VO_{2peak} below 44.2 $ml \cdot kg^{-1} \cdot min^{-1}$

were eight times more likely to have a cluster of CVD risk factors, compared to men above 50.5 ml·kg^{-1}·min^{-1} (Aspenes et al. 2011).

The association between physical fitness and risk of CVD is often described in relation to VO_{2peak}. However, muscular strength is an additional risk factor and its relationship to the risk of CVD is independent of VO_{2peak} and body mass index (Jurca et al. 2004; Ortega et al. 2012; Ruiz et al. 2008). Muscular strength is inversely associated with CVD and all-cause mortality (Ruiz et al. 2008; Ortega et al. 2012) and the prevalence of metabolic syndrome (Jurca et al. 2004). Stronger individuals likely have increase resting metabolic rate, increase muscle mass and reduced total and abdominal fat (Tresierras and Balady 2009). Strength is also associated with insulin sensitivity, glucose tolerance and diastolic blood pressure (Pollock and Vincent 1996). The data collected in this thesis do not allow for comparison with 1RM levels in the general population.

Reduced physical fitness associated with low QOL

In paper I, we reported that the VO_{2peak} correlated with the patient' perceptions of physical function, general health, vitality, social function, and physical component score. With some exceptions, these findings are consistent with correlations between SF-36 variables and BMI in patients with schizophrenia (Strassnig et al. 2003). In line with Strassnig, Brar et al. (2003) we found a significant correlation with the physical component score but not the mental component score, suggesting that reduced VO_{2peak} mainly is perceived as a physical health problem, not mental. Conversely, both the mental and physical health components of QOL are found to be related to estimated VO_{2peak} in healthy men (Sloan et al. 2009). Interestingly, the patients with lower VO_{2peak} seemed to experience lower vitality and social functioning. A sedentary lifestyle is associated with greater risk of low vitality (Puetz 2006).

The patients' perceptions of their QOL in the SF-36 self report measure tended to be better than expected. Severely ill patients with schizophrenia are said to have problems in evaluating QOL and their scores tend to differ from those of their carer (Linaker and Moe 2005).

Walking inefficiency in patients with schizophrenia

Papers II and IV are the first published studies that have measured ε_{net} of walking in patients with schizophrenia. Poor ε_{net} is analogous with excessive energy expenditure and physical fatigue. The findings revealed a mechanical inefficiency of walking in patients with schizophrenia. The mechanism for this walking inefficiency is not known, but it may likely be related to the gait deficits observed in schizophrenia. The fact that gait deficits such as those in Parkinson's disease reduce ε_{net}, suggests a similar relationship for those with schizophrenia (Christiansen et al. 2009).

Effects from HIT and MST on VO_{2peak} in patients with schizophrenia

In paper II we evaluated the effects of HIT in patients with schizophrenia. The HIT training program was developed with the distinct aim of improving VO_{2peak}. The comparisons of HIT with other endurance training regimes are documented elsewhere (Helgerud et al. 2007; Rognmo et al. 2004; Wisloff et al. 2007), but the effect of this particular program was not tested in patients with schizophrenia. In paper II, the HIT group improved VO_{2peak} by 12 % by adhering to 85 ± 9 % of the scheduled training sessions. Similar sizes of improvement are found in healthy controls and in patients with CVD (Helgerud et al. 2007; Rognmo et al. 2004; Wisloff et al. 2007). However, neither CG nor MST (in paper IV) improved VO_{2peak} (figure 2). Although this was not surprising, it illustrates that HIT should be given particular attention in the treatment program to improve VO_{2peak}. Neither CG nor MST overloads the oxygen transport system sufficiently to give any adaptations in VO_{2peak}.

It seems fair to conclude that VO_{2peak} is a trainable property in patients with schizophrenia as for healthy individuals. For patients with schizophrenia the trainability of VO_{2peak} is largely related to their ability to adhere to the HIT. The patients included in the present study were inpatients that suffered from severe schizophrenia. The majority of the patients had several years of hospitalisation and some were described as treatment resistant. In spite of the severity of their illness, they managed to participate in HIT and improve VO_{2peak} within a short period.

Other types of endurance training programs may also improve VO_{2peak}, at least in the first months of a training program (Pajonk et al. 2010; Scheewe et al. 2012a; Scheewe et al. 2012b). The benefit of HIT is the larger improvement, due to training at a high aerobic intensity. Considering the high risk of CVD and the challenging task of motivating patients with schizophrenia to exercise, the effectiveness of the intervention ought to be considered. Additionally, training with intervals at a high aerobic intensity is found to be more enjoyable than moderate intensity at a constant pace (Bartlett et al. 2011). These issues could have important implications for the adherence to exercise training and the long-term prevention of low VO_{2peak} in patients with schizophrenia.

Strength training to improve 1RM, RFD and work economy (or ε_{net})

In paper III we compared two 8-weeks resistance training programs on effects on work economy, maximal strength and explosive strength. Paper III is part of the strategy to develop the resistance training program that we planned to use in paper IV. To compare these two resistance training programs we used an intraindividual design and an equivalent volume of training. The main finding was that MST was superior to CON based on the primary outcome variables.

MST improved 1RM and RFD and work economy, by using heavy loads (>85 % of 1RM), few repetitions (≤5), maximal mobilisation of force in the concentric part of the movement in combination interspersed with long resting periods (>3 minutes) (Bird et al. 2005; Campos et al. 2002; Cormie et al. 2011). For untrained and moderately trained individuals, it is generally recommended to apply CON; i.e. moderate loads corresponding to 60-70 % of 1RM for a repetition range of 8-12 performed with slow to moderate velocities (Ratamess et al. 2009). Paper III is the first study that aimed to clarify whether CON could attain the same profitable benefits (in work economy, 1RM, RFD) as found after heavy, explosive strength training (i.e. MST).

Work economy improved by 31 % and 18 % after MST and CON respectively. The improvements were large but they were in agreement with others (Hoff et al. 2002; Hoff et al. 1999; Osteras et al. 2002; Storen et al. 2008; Sunde et al. 2010; Wang et al. 2010). 1RM improved in MST and CON by 50 % and 35 % respectively. MST improved maximal strength substantially and statistically significantly more than CON. This is in agreement with the findings from Campos, Luecke et al. (2002) that 3-5RM in 4 sets and 3 minutes rest periods was more effective than 9-11RM for 3 sets and 2 minutes rest periods. Both groups also improved PF and RFD in both the dynamic and isometric muscle actions. The change was larger after MST for all variables apart from the RFD_i, which was of borderline significance, and the effect sizes are favourable towards MST. This is in line with Behm and Sale (1993) who suggested that the intentional velocity is more important than the actual velocity. However, CON, with moderate repetition velocity also improved RFD, although to a lesser extent than MST.

Paper III indicates that a resistance-training program that is most effective in improving maximal strength and RFD is superior for improving work economy. As all variables improved in both conditions, it seems reasonable that mechanisms responsible for the underlying improvement in work economy were similar for the two interventions although of a greater magnitude with MST.

From the findings of paper III, we choose to apply the MST program in patients with schizophrenia (paper IV). This option was based on the suggestion that the findings from paper III also would apply to patients with schizophrenia. Paper III also suggested that CON would have beneficial responses in patients with schizophrenia, but these were not pursued further. The empirical rationale suggests that a broader range of strength training methods is beneficial. Thus, trainers have some freedom when gradually introducing the most effective intervention to patients that might struggle to accommodate an optimal training regimen.

Effects from HIT and MST on 1RM and work economy (or ε_{net}) in patients with schizophrenia

In this thesis, we applied two interventional strategies to improve ε_{net}. In paper II, we found that HIT improved ε_{net} by 12 % whereas maximal strength was not affected (figure 2). On the contrary, in paper IV we found that MST improved ε_{net} by 20 % along with a large improvement in maximal strength (figure 2). As HIT improves ε_{net}, part of the walking inefficiency in schizophrenia must be caused by inactivity. However, MST seems to improve ε_{net} more than HIT, in absolute terms. As suggested in paper III, this favourable change may be elicited by improved maximal strength and explosive strength.

Our findings are similar to those found with other patients who suffer from poor ε_{net}, such as those with coronary artery disease, peripheral arterial disease, chronic obstructive pulmonary disease and patients operated with total hip arthroplasty, that have derived benefit from lower limb MST (Husby et al. 2009;

Karlsen et al. 2009; Wang et al. 2010; Hoff et al. 2007). Improved maximal strength and explosive strength have significant carry-over effects on walking performance measured as ε_{net} (Karlsen et al. 2009; Wang et al. 2010; Husby et al. 2009; Hoff et al. 2007).

HIT and MST to reducing the risk of CVD

Improved VO_{2peak} and 1RM confirmed the reduced risk of CVD in papers II and IV. There were no changes in the conventional risk factors for CVD during the intervention (paper II). The mean blood pressure, triglyceride, hs-CRP, total-cholesterol and glucose were within normal values. While targeting this risk factor of CVD it may be important to emphasise improvements in 1RM and VO_{2peak} even if the conventional risk factors do not respond in the short term (Lee et al. 2005). Fitness in terms of 1RM and VO_{2peak} offer a protective effect from other risk factors that independently would reduce the risk of CVD and all cause mortality (Lee et al. 2005).

Physical activity and exercise training are considered effective therapies for improving the cardiovascular risk factor profile in patients with CVD, hypertension, metabolic syndrome and diabetes (Regensteiner and Hiatt 2002; Leon et al. 2005; Gordon et al. 2004; Khan et al. 2009). The general benefits of aerobic exercise training include reduced blood pressure, improved blood lipid profile, decreased systemic inflammation with accompanying reduction in atherosclerosis (Janssen 2012, p. 190). Aerobic exercise also improves endothelial function, vasoconstriction properties and has an antithrombotic effect (Janssen 2012, p. 190). These improvements are considered plausible mechanisms by which exercise reduced the risk of CVD. Similarly, strength training promotes metabolic health (Magyari and Churilla 2012). Strength training improves glucose metabolism, cholesterol levels, blood pressure and basal metabolic rate (Pollock and Vincent 1996). These changes are thought to reduce the CVD risk factors and the prevalence of metabolic syndrome (Williams et al. 2007). The strength training program is however probably dependent on higher total training volume (several exercises) than that in paper IV to allow significant adaptations to the CVD risk factor profile. A combination of HIT and MST may be an overall effective strategy to affect both strength and cardiovascular mechanisms in patients with schizophrenia (Stensvold et al. 2010). Both training modalities independently benefit cardiovascular risk (Schjerve et al. 2008; Stensvold et al. 2010). Therefore, program design would allow some individual adjustments to assist patients struggling with motivation to exercise.

Training intensity, as in HIT, tends to be crucial to reverse risk factors. HIT is found to elicit greater improvements in endothelial function, insulin signalling, skeletal muscle biogenesis, blood glucose and lipogenesis than that found after moderate intensity endurance training (Tjonna et al. 2008; Wisloff et al. 2007; Schjerve et al. 2008).

Effects of HIT and MST on symptoms and QOL in patients with schizophrenia

In paper II and IV, no significant changes in PANSS, CDSS or in SF-36 were found after HIT, MST or CG. Thus, our findings do not support the idea of exercise as a treatment for symptoms of schizophrenia. In absolute terms, there was an increase of 10 points in the MST group (paper IV), a decrease of 2 points in the HIT group (paper II) and a decrease of 2 points in the CG group (papers II and IV) on the total PANSS score. We suggested this tendency of a change is due to natural variations in the course of the illness and is probably expected for patients with schizophrenia.

The hypothesis of whether exercise training has an impact on symptoms of schizophrenia has been discussed in the literature. Although, with some limitations in methodology in early studies, Faulkner (2005) concluded in his review that exercise could alleviate some of the positive and negative symptoms of schizophrenia. Moreover, important psychological benefits may be observed in patients in addition to those of a diagnostic character (Faulkner 2005). In brief, patients may: display less psychotic features on days of exercise (Chamove 1986), use exercise as a coping strategy to control auditory hallucinations (Carter-Morris and Faulkner 2003; Faulkner and Sparkes 1999), improve social interest and self-esteem (Adams 1995; Carter-Morris and Faulkner 2003; Chamove 1986), improve body image (Rosenthal and Beutell 1981), improve sleep pattern (Faulkner and Sparkes 1999), and reduce depression and anxiety (Chamove 1986; Faulkner and Sparkes 1999; Gimino and Levin 1984; Pelham et al. 1993). Patients may also improve their daily functioning level expressed as hygiene and pursuit of appropriate independence (Perham and Accordino 2007). The conclusion by Faulkner (2005) that exercise may improve chronic symptoms of schizophrenia recently achieved support from a larger randomised trial (Scheewe et al. 2012a). Scheewe and colleagues (2012a) found that the patients participating an a 6 months exercise therapy reduced their total PANSS score (-20.7 %) compared to occupational therapy (+3.3 %). Only a small proportion of these patients were inpatients. Another study found that total PANSS improved somewhat in a cycling exercise group (-9 %) and worsened in a nonexercise group (+13 %) after 3 months (Pajonk et al. 2010). Additionally, Beebe and colleagues (2005) reported an absolute improvement (non-significant) in the total PANSS score after 16 weeks of exercise. Beside slight differences between interventions and sample characteristics, these three latter studies lasted for a longer period than our 8 week interventions.

The effects of resistance training in patients with schizophrenia are poorly investigated. A single-group study found that patients reported improvement in a questionnaire that measured perceived psychological well being, but no improvement in the Zung Self Rating Depression Scale, after weight lifting therapy (Auchus and Kaslow 1994). A case study described some improvements in Brief Psychiatric Rating Scale (BPRS) and the Nurses' Observational Scale for In-Patient Evaluation (Adams 1995). Clearly, there is a need for larger scale and longitudinal intervention studies on the impact of resistance training exercise in patients with schizophrenia.

In patients with chronic schizophrenia already receiving much psychosocial support, it might be difficult to demonstrate improvement in symptoms or in psychosocial function with an 8-week physical training intervention. The patients included in our studies (papers I, II and IV) had severe schizophrenia, the majority of the patients had several years of hospitalisation and some were described as treatment resistant. In spite of the severity of their illness, they managed to complete the 8-week exercise training periods.

Thesis limitations

In two studies (papers II and IV), the allocation of patients to groups were non-randomised. Non-randomised trials might overestimate changes (Schulz et al. 1995). The decision was a trade-off between accepting the limitations of the non-randomised groups design and achieving the benefits of including more patients. Many patients, and particularly those with a high level of negative symptoms, might have difficulties in attending randomised trials (Abbott et al. 2005; Beebe et al. 2005; Correll et al. 2011).

To reduce the selection bias we ensured that all patients were eligible for all three interventions. None of the patients were selected because they fitted one of the groups more than they fitted the other. Moreover, the patients were not able to choose a particular group. It was not possible to control for potential unknown confounders such as months since last hospitalisation (outpatients), fluctuating symptoms, previous exercise experience, drug abuse, type and/or amount of psychiatric services et cetera. Nevertheless, there were no statistically differences between groups on demographic variables at baseline.

It is appropriate to discuss whether a randomised controlled trial on exercise can be performed in seriously ill patients with schizophrenia. In the recruitment process, we noticed that patients were insecure about attending the study. To make them feel confident, we had to explain into detail what they were supposed to do during tests and exercise. These explanations were vital in helping patients to feel secure and finally consent to participate in the study. Without giving them this security, many would not participate or withdraw from the study. We had to tell them about the intervention and therefore, the studies (paper II and IV) were not randomised. Two other research groups managed to carry out a randomised controlled trial in patients with schizophrenia (Pajonk et al. 2010; Scheewe et al. 2012b). Contrary to the present studies (papers II and IV), a large proportion of the patients were outpatients.

The short 8-week interventions (paper II and IV) might be too short a period, particularly for patients suffering from schizophrenia, to induce change in certain psychiatric and metabolic parameters.

Employing an intraindividual design (paper III) with unilateral training may obviously have caused cross education. Cross education is at least partly caused by enhanced neural drive to the contra lateral agonist muscle (Fimland et al. 2009). This could have been precluded by using a control group. However, we consider this disadvantage to be outweighed by the fact that there is a considerable inter-individual variation to strength training adaptations. In addition, the magnitude of the cross-education depends on the improvement in the trained leg. Hence, the improvements after CON might have been increased by the greater improvements of the MST leg.

Future perspectives

The benefits of exercise training therapy in patients with severe mental illnesses are substantially documented but many may be unexploited. Exercise combines the physiological and psychological aspect of health and holds the potential to prevent and cure many of the illnesses related to inactivity. Exercise influences the body-mind connection through many known mechanisms and improves several aspects of mental health (Faulkner 2005). Moreover, the improved exercise capacity provides a basis that renders possible the performance of day-to-day activities.

Exercise therapy is not a stand-alone treatment for patients with schizophrenia but a therapy that should be integrated in the conventional treatment to achieve the quality of care in terms of preventive, curative, palliative treatment and disease management. Exercise therapy has distinct adaptations that patients may not achieve through other treatment modalities. However, there is a lack of knowledge on how exercise can be combined and adapted with the conventional treatments.

The distinct benefits of exercise, including the reduction of CVD risk, need further address. There are multiple risk factors for CVD in schizophrenia and the particular role of exercise appears to be an effective strategy. Theoretically, we assume that participation in exercise therapy with resulting improvement in fitness increases the likelihood to sustain good health, but how this translates into CVD prevalence and mortality rates should be investigated in a longitudinal study.

The potential influence of exercise therapy on general psychopathology, and positive, negative and cognitive symptoms of schizophrenia should be further addressed. Whether the described effect in some studies is a result of a specific intervention, confounding variables or natural variation, is worthy of further study/investigation. Effects of longitudinal exercise therapy interventions on symptoms of schizophrenia could be tested in a prospective design. HIT and MST should be compared to other exercise modalities to define effective interventions and dose-response relationships. Moreover, there are rather conflicting results on whether the physical activity level or the fitness level contributes the most to the mental health benefits. The improvements in certain fitness variables tend to be central for physical health improvements. It is possible that the relationship to mental health variables follows a similar pattern.

Regardless of the potential treatment effect on symptoms of schizophrenia, probably the most important aspect for the patients is how they can manage to cope with their illness, integrate to community and ensure a lower risk of CVD. Whether these effects are possible with exercise interventions is due to be addressed in a larger prospective study. Low aerobic capacity might have adverse effects that could hamper the reintegration into the community, reduce adherence to other treatment regimens, and have harmful effects on QOL and physical functioning (Faulkner 2005). Thus, HIT might help the patients to function better and cope with their illness.

The difficulty of recruiting patients to randomised controlled trials is an obstacle that ought to be considered when planning a randomised controlled trial. Randomisation has been shown to be possible in patients with schizophrenia referred to exercise. In addition, adherence to exercise is another obstacle. Separate interventions to improve adherence such as motivational interviewing, may be worth exploring.

In paper IV, we found that MST improved 1RM along with a corresponding improvement in walking economy/ε_{net}. However, we did not measure explosive strength (e.g. RFD). Explosive strength may have particular benefits in patients with schizophrenia considering the motor symptoms and walking deficit. Still, the responsiveness of resistance training on explosive strength in patients with schizophrenia is unknown. A smaller improvement in explosive strength may explain why the improvement in ε_{net} in paper IV was not as large as the improvements reported in healthy individuals.

Practical implications

Patients with schizophrenia suffer a high risk of CVD and neurological abnormalities such as walking deficits. These physical illnesses reduce QOL, the ability to carry out day-to-day activities and comply with treatment. From this thesis, it is evident that a reduced VO_{2peak} in part explains the high risk of CVD. Reduced VO_{2peak} is a strong predictor of CVD and all-cause mortality. By taking part in HIT and MST, patients with schizophrenia could improve health and reduce the risk of CVD. Furthermore, VO_{2peak} and ε_{net} are major determinants of endurance performances. In real life, these performances may range from athletic competitions and all out performances to day-to-day activities in patients with reduced physical fitness. In patients with schizophrenia, the VO_{2peak} and ε_{net} is at a level that challenges the performance of physical activities and may lead to reduced QOL. This thesis clearly advocates HIT and MST to improve VO_{2peak} and ε_{net}. Importantly, after a training period, a patient with schizophrenia would have the ability to perform more work or to perform the same amount of work with reduced effort. This would likely have significant practical implications for the reintegration into community, adherence to medical treatments and therapy, and normalisation of physical health and fitness.

HIT and MST are safe and effective interventions to improve VO_{2peak}, 1RM and ε_{net} in patients with schizophrenia

6. Conclusions

Men with schizophrenia have lower VO_{2peak} than men in the general population. Patients with a VO_{2peak} below 44.2 ml·kg^{-1}·min^{-1} (men) and 35.1 ml·kg^{-1}·min^{-1} (women) have higher odds of having ≥1 risk factors for CVD than patients above the 44.2 and 35.1 ml·kg^{-1}·min^{-1} thresholds. Low VO_{2peak} also compromises patients' perceived physical health. Therefore, VO_{2peak} should be regarded as at least as important as the conventional risk factors for CVD and evaluation of VO_{2peak} should be incorporated in clinical practice.

The patients with schizophrenia have poor ε_{net} and spend excessive energy during walking.

HIT can effectively improve VO_{2peak} and net ε_{net} during 8 weeks in patients that adhere to training.

MST is more efficient than CON in improving work economy of single leg knee-extension, maximal strength and RFD for moderately trained healthy men in an eight-week intervention.

Those patients with schizophrenia who adhere to MST improve their 1RM to the same level as has been observed in other patient groups and in healthy controls. MST also improves ε_{net} and thus the patients' ability to normalise their walking.

No significant changes in symptoms of schizophrenia or QOL were found after 8 weeks of HIT or MST.

Treatment for schizophrenia should include HIT and MST to contribute to reduce the risk associated with poor physical ability such as inactivity related mortality.

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Attachments (papers 1-4)

Paper I

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RESEARCH ARTICLE Open Access

Reduced peak oxygen uptake and implications for cardiovascular health and quality of life in patients with schizophrenia

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Abstract

Background: Peak oxygen uptake (VO_{2peak}) is a strong predictor of cardiovascular disease (CVD) and all-cause mortality, but is inadequately described in patients with schizophrenia. The aim of this study was to evaluate treadmill VO_{2peak}, CVD risk factors and quality of life (QOL) in patients with schizophrenia (ICD-10, F20-29).

Methods: 33 patients, 22 men (33.7 ± 10.4 years) and 11 women (35.9 ± 11.5 years), were included. Patients VO_{2peak} were compared with normative VO_{2peak} in healthy individuals from the Nord-Trøndelag Health Study (HUNT). Risk factors were compared above and below the VO_{2peak} thresholds; 44.2 and 35.1 $ml \cdot kg^{-1} \cdot min^{-1}$ in men and women, respectively.

Results: VO_{2peak} was 37.1 ± 9.2 $ml \cdot kg^{-1} \cdot min^{-1}$ in men with schizophrenia; 74 ± 19% of normative healthy men ($p < 0.001$). VO_{2peak} was 35.6 ± 10.7 $ml \cdot kg^{-1} \cdot min^{-1}$ in women with schizophrenia; 89 ± 25% of normative healthy women (n.s.). Based on odds ratio patients were 28.3 (95% CI = 1.6-505.6) times more likely to have one or more CVD risk factors if they were below the VO_{2peak} thresholds. VO_{2peak} correlated with the SF-36 physical functioning ($r = 0.58$), general health ($r = 0.53$), vitality ($r = 0.47$), social function ($r = 0.41$) and physical component score ($r = 0.51$).

Conclusion: Men with schizophrenia have lower VO_{2peak} than the general population. Patients with the lowest VO_{2peak} have higher odds of having one or more risk factors for cardiovascular disease. VO_{2peak} should be regarded as least as important as the conventional risk factors for CVD and evaluation of VO_{2peak} should be incorporated in clinical practice.

Background

Patients suffering from schizophrenia have a mortality risk that is two to three times that of the general population and the leading cause of death is cardiovascular disease (CVD) [1,2]. Although, multifactor causes have been identified, reduced cardiorespiratory fitness has probably been overlooked as a risk factor for CVD in patients with schizophrenia [3].

Cardiorespiratory fitness, measured as peak oxygen uptake (VO_{2peak}) is a strong predictor of CVD and all-cause mortality [4,5]. Improvements in VO_{2peak} have indicated reduced risk of CVD, coronary heart disease and all cause mortality [5]. VO_{2peak} is often a stronger predictor of mortality than conventional risk factors for CVD [6]. McAuley and Blair [7] recently pointed out reduced cardiorespiratory fitness as a greater health threat than obesity and suggested that more emphasis should be put on increasing VO_{2peak}. This might be especially important considering that higher levels of VO_{2peak} seems to attenuate or eliminate the increased health risk associated with obesity [8]. Findings from the epidemiological Nord-Trøndelag Health Study (the HUNT Study) demonstrate that physical active people with a clustering of cardiovascular risk factors appears to have comparable risk of premature death as inactive individuals without risk factors [9]. In the same cohort men with VO_{2peak} below 44.2 $ml \cdot kg^{-1} \cdot min^{-1}$ were eight times more likely to have a cluster of CVD risk factors, compared to men above 50.5 $ml \cdot kg^{-1} \cdot min^{-1}$ [10].

Results from the Aerobics Center Longitudinal Study further suggest that people with low VO_{2peak} is

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characterized by depressive symptoms and low emotional well being [11]. High levels of VO_{2peak} are associated with high levels of quality of life (QOL) [12]. Body mass index (BMI) are found inversely related to QOL in patients with schizophrenia [3] but the relation between VO_{2peak} and perceived QOL are not evaluated.

Objective measures of VO_{2peak} have rarely been presented in patients with schizophrenia. The classical study by Carlson et al. [13] were the first to describe oxygen uptake in patients with schizophrenia, but many of their patients did not reach values close to maximal oxygen uptake. Our research group revealed significant changes in VO_{2peak} after eight weeks of high aerobic intensity training in patients with schizophrenia [14]. Recently, Strassnig et al. [3] published measures of oxygen uptake in 117 patients with schizophrenia that were exceedingly low (4.4 metabolic equivalents ≈ 15.4 $ml \cdot kg^{-1} \cdot min^{-1}$). This VO_{2peak} value are much lower than the VO_2 required for walking in patients with schizophrenia [14], and at a level that may indicate a need for heart transplant in heart failure patients [15].

The primary aim of this study was to evaluate objectively measured VO_{2peak} during walking or running in men and women with schizophrenia compared to VO_{2peak} in healthy individuals from the Nord-Trøndelag Health Study (HUNT). We hypothesized that patients with schizophrenia had reduced VO_{2peak} compared to normative healthy individuals. The secondary aim was to evaluate relationships between VO_{2peak}, risk factors for cardiovascular disease, and quality of life.

Methods

Subjects

We included 33 patients, 11 women and 22 men, with ICD-10 schizophrenia, schizotypal or delusional disorders (F20 to F29) in the study. Patients were in- and out-patients at a University hospital and had agreed to take part in exercise interventions studies. All patients were under antipsychotic medical treatment. 24 patients were smokers. Exclusion criteria were known coronary artery disease, known chronic obstructive pulmonary disease, and not being able to perform physical treadmill testing and exercise. Patients were examined by a physician at inclusion to the study and the exclusion criterions were confirmed by medical records.

Assessments

An individualized protocol was applied to measure VO_{2peak} and peak heart rate (HR_{peak}), using the Cortex Metamax II portable metabolic test system (Cortex Biophysik GmbH, Leipzig, Germany) and the Polar S610i heart rate monitor (Polar Electro, Finland), respectively. The protocol has previously been described in patients with schizophrenia as well as in healthy individuals [14,16].

The patients were carefully familiarized with the test procedures and the treadmill when entering the laboratory. Warm-up was ten minute walking or running on the treadmill at an intensity corresponding to 60-70% HR_{peak}. The test started from warm-up speed (with minimum 5% inclination) after which the speed or the inclination was increased every minute (0.5-1 $km \cdot h^{-1}$ and 1-2%, respectively) to a level that brought the patient to exhaustion. The highest oxygen uptake and heart rate (HR) recorded during the last minute of the test were determined as VO_{2peak} and HR_{peak}, respectively. VO_{2peak} where also presented as $ml \cdot kg^{-0.75} \cdot min^{-1}$ to normalise for the differences in bodyweight between the patients [17].

We compared the patients VO_{2peak} with age and sex specific strata from the Nord-Trøndelag Health Study (the HUNT Study) [10]. The HUNT study is an epidemiological study of the general population in the neighbouring county to the university hospital. The HUNT Fitness study tested VO_{2peak} in 4 631 healthy individuals (20 to 90 years) using mixing chamber gas-analyzer ergospirometry (Cortex MetaMax II, Cortex, Leipzig, Germany) and an individualised protocol that has close resemblance to the protocol used in the present study. 14.1% of the participants reported to be inactive, defined as no activity or exercising less than once per week. For each patient with schizophrenia, we estimated a normative VO_{2peak}, namely the mean value defined in the HUNT Fitness study strata for the corresponding sex and age. We titled the VO_{2peak} estimated from sex and age strata independent of physical activity level, as HUNT general. The VO_{2peak} from age and sex strata for healthy inactive men and women were titled HUNT inactive. The percent of HUNT general and HUNT inactive VO_{2peak} was calculated as: (achieved VO_{2peak} ÷ age predicted VO_{2peak}) · 100.

In the HUNT Fitness study men and women below 44.2 $ml \cdot kg^{-1} \cdot min^{-1}$ and 35.1 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively, were associated with higher cardiovascular risk factor profile [10]. The same VO_{2peak} values were used as threshold values when evaluating conventional CVD risk factors.

Morning fasting blood levels were taken. Serum glucose was analysed using Reflotron Plus system (Roche Diagnostics, Mannheim, Germany). HDL (high-density-lipoprotein) cholesterol, total cholesterol and triglyceride concentrations in serum were measured using a Modular P chemistry analyzer (Roche Diagnostics, Mannheim, Germany). LDL cholesterol was calculated using the Friedewald equation [18]. BP (blood pressure) was measured using a Maxi-Stabil 3 (Welch Allyn, Jungingen, Germany). Patients were sitting and had rested for at least 5 minutes. Risk factors were classified as follows: hypertension, diastolic pressure ≥ 90 mmHg and/or systolic pressure ≥ 140 mmHg; elevated blood glucose, > 6.0 $mmol \cdot L^{-1}$; elevated total cholesterol, > 6.1 $mmol \cdot L^{-1}$ in patients < 30 years old, > 6.9 $mmol \cdot L^{-1}$ in patients 30-49 years old and > 7.8 $mmol \cdot L^{-1}$ in patients ≥ 50 years old; elevated LDL-cholesterol, 4.3 > $mmol \cdot L^{-1}$ in patients < 30 years old, 4.7 > $mmol \cdot L^{-1}$ in patients 30-49 years old and > 5.3 $mmol \cdot L^{-1}$ in patients ≥ 50 years old; reduced HDL-cholesterol, < 1.0 $mmol \cdot L^{-1}$; elevated triglyceride, > 2.6 $mmol \cdot L^{-1}$; obesity, BMI ≥ 30.0 $kg \cdot m^{-1}$ [19,20].

The short form (SF-36) was used to assess the physical health and mental health aspects of health related quality of life [21]. SF-36 consists of eight sub scores and can also be divided into a physical component score (PCS) and mental component score (MCS). 0 reflect the poorest health whereas 100 reflect the best health.

The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the severity of symptoms of schizophrenia [22]. PANSS constitutes three scales measuring positive (productive symptoms), negative symptoms (deficit features) and general severity of illness. A total of 30 items are evaluated on a likert scale ranging from 1 (absent) to 7 (extreme) and added up to a total score as well as the three sub scores. In this study we used the positive and negative sub scores (7 items each) as well as the total score (30 items).

Analyses

We used the independent samples T-test to compare differences between men and women, between patients below and above the VO_{2peak} thresholds as well as between measured VO_{2peak} and HUNT general and HUNT inactive VO_{2peak}. We used the Pearson chi-square test to detect whether there was a significant association between patients above/below the VO_{2peak} threshold and prevalence of risk factors. We calculated the odds ratio for having one or more risk factors in the patients below threshold. The analysis was adjusted for age and sex. In multiadjusted analysis we also adjusted for the potential cofounding effect of smoking.

We used Pearson r to analyse correlations between VO_{2peak} ($ml \cdot kg^{-0.75} \cdot min^{-1}$) and each domain of the SF-36. The significance level (α) was set at $p < 0.05$ (2-tailed). Data are described as mean and standard deviation (SD), unless otherwise noted. SPSS statistical package, version 18.0 (SPSS Inc.), was applied to analyse results.

The study was approved by the regional committees for medical and health research ethics, middle Norway and conducted according to the Helsinki declaration. Written informed consent was obtained from all the included patients after the procedures were fully explained.

Results

Demographics

Age was 33.7 ± 10.4 years and 35.9 ± 11.5 years in men and women, respectively. The total PANSS, total positive PANSS and total negative PANSS score was 65 ± 17, 15 ± 6 and 17 ± 8 in men, and 68 ± 23, 16 ± 6 and 18 ± 8 in women, respectively.

Peak oxygen uptake

The VO_{2peak} for the men and women with schizophrenia are presented in Table 1. Individual VO_{2peak} values are plotted against age as well as normative VO_{2peak} strata from the HUNT Fitness study in Figure 1. VO_{2peak} in the men with schizophrenia was 84 ± 21% of age predicted HUNT inactive ($p < 0.001$) and 74 ± 19% of HUNT general ($p < 0.001$). The VO_{2peak} in the women with schizophrenia was not different from HUNT inactive (101 ± 28%) and HUNT general (89 ± 25%; n.s.). Age predicted VO_{2peak} was 44.5 ± 2.9 in HUNT inactive men, 50.3 ± 4.1 $ml \cdot kg^{-1} \cdot min^{-1}$ in HUNT general men, 35.2 ± 1.8 in HUNT inactive women and 40.0 ± 3.2 $ml \cdot kg^{-1} \cdot min^{-1}$ in HUNT general women.

Conventional risk factors

Risk factor assessment was lost in one male patient. Risk factors were present in 24 of 32 patients and of these five were above and 19 were below the thresholds. Among the eight patients without risk factors, six were above and two were below the thresholds ($\chi^2 = 7.6$, df = 1, $p = 0.006$). Based on the odds ratio adjusted for age and sex patients were 24.2 (95% CI = 1.5-505.6) times more likely to have one or more risk factors if they were below the VO_{2peak} threshold. When we also adjusted for smoking the odds ratio was 28.3 (95% CI = 1.6-505.6). Among the patients below the VO_{2peak} thresholds 10 patients had hypertension, 11 elevated glucose, 12 reduced HDL-cholesterol, 11 elevated triglyceride and 14 had obesity. Above the thresholds 2 patients had hypertension, 2 elevated glucose and 1 was obese. There were 8 smokers above the thresholds and 16 below. Differences in mean levels are presented in Table 2.

Quality of life

Results from the SF-36 questionnaire and correlations between SF-36 variables and VO_{2peak} are presented in Table 3.

Discussion

Peak oxygen uptake

The present results highlight reduced VO_{2peak} as a major risk factor for CVD in patients suffering from schizophrenia. The VO_{2peak} was 37.1 ± 9.2 and 35.6 ± 10.7 $ml \cdot kg^{-1} \cdot min^{-1}$ in men and women, respectively.

Table 1 Individual characteristics from the peak oxygen uptake test

Patient nr	Age years	BW Kg	VO_{2peak} $L{\cdot}min^{-1}$	VO_{2peak} $ml{\cdot}kg^{-1}{\cdot}min^{-1}$	VO_{2peak} $ml{\cdot}kg^{-0.75}{\cdot}min^{-1}$	V_E $L{\cdot}min^{-1}$	RER	HR Beats $\cdot min^{-1}$
Men								
1	21	76.5	3.64	47.6	140.7	126.1	1.07	186
2	21	95.3	3.72	39.1	122.0	107.7	1.09	175
3	24	66.6	3.65	54.9	156.6	138.1	1.19	211
4	25	159.5	4.25	26.6	94.7	134.0	1.19	154
5	25	120.9	3.21	26.5	88.0	115.8	1.09	160
6	26	65.0	3.15	48.5	137.6	100.4	1.22	185
7	26	107.9	4.07	37.7	121.6	126.3	1.23	177
8	27	96.7	3.50	36.1	113.5	102.4	1.11	186
9	27	107.2	3.36	31.3	100.9	94.7	1.04	180
10	28	100.6	2.96	29.4	93.2	69.2	1.00	190
11	29	66.7	2.99	44.8	128.1	121.7	1.13	183
12	31	78.0	3.76	48.2	143.3	118.6	1.41	188
13	31	70.1	3.14	44.8	129.6	106.9	1.10	165
14	37	114.0	3.87	34.0	110.9	109.2	1.10	153
15	40	98.7	2.38	24.1	76.0	65.2	1.00	143
16	41	77.4	3.29	42.0	126.1	110.4	1.21	153
17	41	89.5	3.80	42.5	130.6	105.7	1.22	164
18	41	117.1	3.88	33.1	109.0	118.6	1.06	165
19	45	122.3	3.38	27.7	91.9	125.4	1.08	150
20	47	122.7	2.94	24.0	79.7	89.2	1.00	153
21	50	75.7	3.46	45.7	134.8	90.8	1.08	156
22	58	109.6	3.07	28.1	90.6	91.2	1.07	160
Mean ± SD	33.7 ± 10.4	97.2 ± 24.0	3.43 ± 0.44	37.1 ± 9.2	114.5 ± 22.6	107.6 ± 19.0	1.12 ± 0.10	170 ± 17
Women								
1	22	61.7	2.98	48.3	135.4	94.1	1.18	180
2	24	53.3	2.28	42.8	115.6	54.0	0.99	173
3	28	66.4	2.82	42.6	121.2	97.1	1.14	169
4	28	73.5	2.33	31.7	92.8	66.4	1.20	176
5	28	80.3	2.44	30.4	91.0	93.0	1.20	188
6	34	51.6	2.61	50.7	135.6	79.8	1.27	194
7	41	144.5	2.46	17.0	59.0	71.0	1.02	150
8	42	75.5	3.30	43.7	128.8	108.0	1.20	163
9	44	64.9	1.98	30.5	86.6	56.0	1.16	175
10	48	55.5	1.70	30.7	83.6	73.2	1.10	168
11	58	91.8	2.12	23.1	71.5	74.1	1.13	151
Mean ± SD	35.9 ± 11.5	74.5 ± 26.3	2.46 ± 0.46	35.6 ± 10.7	101.9 ± 26.6	78.8 ± 17.4	1.15 ± 0.08	172 ± 14

BW, body weight; VO_{2peak}, peak oxygen uptake; HR, heart rate; V_E, total pulmonary ventilation; RER, respiratory exchange ratio; SD, standard deviation

These values are considerable higher than previous assumptions [3,13]. Strassnig et al. [3] reported VO_2 values of 18.7 ± 6.8 and 13.4 ± 4.6 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$in the men and women, respectively (mean age of 45.1 ± 10.1 years). These low VO_{2peak} values is to some degree explained by the high body weight (mean BMI of 36.7 ± 7.5 $m{\cdot}kg^2$). However, there are some indications of an underrating of these patients' VO_{2peak}. First, the patients only reached a low peak heart rate (142 ± 21 $beats{\cdot}min^{-1}$). Secondly, both Carlsson et al. [13] and Strassnig et al. [3] applied a cycle ergometer test which is known to depend more on the patients motivation than a treadmill test. Patients with schizophrenia terminate cycle tests already at submaximal work loads, in contrast to health subjects [23]. Thirdly, subjects tested on a cycle ergometer achieve 7-16% lower VO_{2max} compared with a maximal treadmill test, even when HR_{peak} is not significantly different [24,25].

In contrast to Strassnig et al. [3], the present results demonstrate that the mean VO_{2peak} in the women was similar to the men with schizophrenia, even though the age was similar (36 years in women versus 34 years in

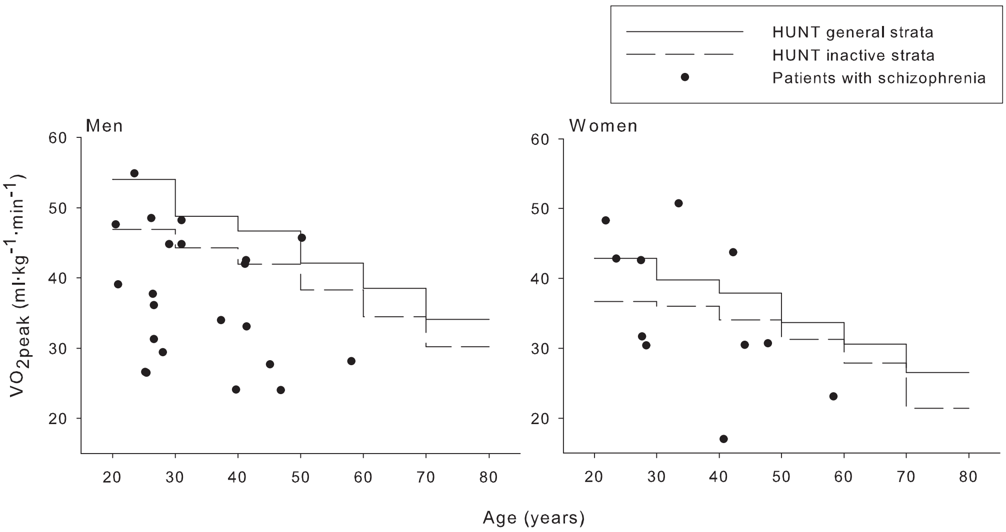

Figure 1 Peak oxygen uptake in patients with schizophrenia and normative healthy men and women. Normative strata are adopted from the HUNT fitness study [10]. HUNT general strata are age and sex specific strata regardless of physical activity level.

men). Women normally have about 10 ml·kg^{-1}·min^{-1} lower VO_{2peak} compared to men at the same age [10]. The mean body weight was 97.2 and 74.5 kg in men and women, respectively, which partially explain the difference in VO_{2peak}.

Comparison with healthy individuals

The comparison with normalised VO_{2peak} from the HUNT Fitness study, confirm our hypothesis that VO_{2peak} is reduced in men with schizophrenia. The VO_{2peak} in the women with schizophrenia was almost identical (101%) to inactive healthy HUNT women. Even lower VO_{2peak} in men with schizophrenia compared to normative inactive men might suggest that more than just inactivity contribute the reduced VO_{2peak}. The VO_{2peak} in the men with schizophrenia is similar to normative healthy men aged 60-69 years [10]. In other words, the VO_{2peak} in the men with schizophrenia is comparable to healthy men that are about 30 years older. Patients with schizophrenia actually have 15-25 years shorter life expectancy than the general population [26,27]. It is noteworthy that the VO_{2peak} presented in the HUNT Fitness study is somewhat higher than previous described populations with regard to objectively measured VO_{2peak} [28-31].

Cardiovascular risk

People with reduced VO_{2peak} are consistently being associated with increased risk of cardiovascular and all-cause mortality. Kodama et al. [5] found that 3.5 ml·kg^{-1}·min^{-1} (1 MET) increases were associated with 13% and 15% reductions in all-cause mortality and CVD/coronary heart disease, respectively. Aspenes et al. [10] found that 5 ml·kg^{-1}·min^{-1} lower VO_{2peak} correspond to 56% higher odds of having a cluster of cardiovascular risk factors.

The comparison of patients with schizophrenia below and above the VO_{2peak} thresholds suggested by Aspenes et al. [10] confirm that patients below these thresholds have higher prevalence of risk factors compared with patients above the thresholds. Based on the odds ratio patients were 28.3 times more likely to have one or more risk factors if they were below the VO_{2peak} thresholds. When comparing mean levels above and below thresholds, all risk factors, except glucose, was better in the patients above the thresholds. These findings suggest a strong connection between the patients VO_{2peak} and the conventional risk factors for CVD, as confirmed in other populations [10,32].

Our data are not quite consistent with findings from US suggesting that especially women with schizophrenia are at high risk of developing metabolic syndrome [33].

Table 2 Characteristics[a] in patients below and above the threshold peak oxygen uptake (VO_{2peak})[b]

	Men		
	VO_{2peak} (< 44.2) (n = 15)	VO_{2peak} (≥ 44.2) (n = 6)	Mean difference (95% CI)
Systolic pressure (mm Hg)	139.4 ± 16.8	125.7 ± 11.0	-13.8 (-29.6 to 2.0)
Diastolic pressure (mm Hg)	87.4 ± 7.0	84.3 ± 5.0	-3.0 (-9.7 to 3.6)
Total cholesterol ($mmol·L^{-1}$)	5.2 ± 0.7	4.5 ± 0.5	-0.7 (-1.3 to -0.0)
HDL cholesterol ($mmol·L^{-1}$)	1.0 ± 0.3	1.6 ± 0.4	0.5 (0.2 to 0.9)
LDL cholesterol ($mmol·L^{-1}$)	3.2 ± 0.6	2.5 ± 0.6	-0.7 (-1.3 to -0.1)
Triglyceride ($mmol·L^{-1}$)	2.1 ± 1.1	0.9 ± 0.2	-1.2 (-1.8 to -0.6)
Glucose ($mmol·L^{-1}$)	6.4 ± 2.0	5.8 ± 0.6	-0.6 (-2.4 to 1.1)
BMI ($kg·m^{-2}$)	33.0 ± 5.5	23.6 ± 2.4	-9.5 (-14.5 to -4.5)
	Women		
	VO_{2peak} (<35.1) (n=6)	VO_{2peak} (≥35.1) (n=5)	
Systolic pressure (mm Hg)	121.6 ± 7.9	103.8 ± 11.9	-17.8 (-32.6 to -3.0)
Diastolic pressure (mm Hg)	80.8 ± 4.4	68.8 ± 8.8	-12 (-22.1 to -1.9)
Total cholesterol ($mmol·L^{-1}$)	5.0 ± 0.7	4.6 ± 1.0	-0.4 (-1.5 to 0.8)
HDL cholesterol ($mmol·L^{-1}$)	1.3 ± 0.3	1.8 ± 0.3	0.5 (0.1 to 0.9)
LDL cholesterol ($mmol·L^{-1}$)	2.9 ± 0.9	2.5 ± 1.1	-0.4 (-1.8 to 1.0)
Triglyceride ($mmol·L^{-1}$)	1.8 ± 0.7	0.8 ± 0.3	-1.0 (-1.7 to -0.3)
Glucose ($mmol·L^{-1}$)	6.1 ± 1.5	4.8 ± 0.4	-1.3 (-2.9 to 0.2)
BMI ($kg·m^{-2}$)	31.2 ± 10.9	23.6 ± 4.5	-7.5 (-19.5 to 4.4)
	All		
	< threshold (n = 21)	≥ threshold (n = 11)	
Systolic pressure (mm Hg)	134.7 ± 16.8	115.7 ± 15.7	-19.0 (-31.8 to -6.3)
Diastolic pressure (mm Hg)	85.63 ± 6.9	77.3 ± 10.4	-8.4 (-14.9 to -1.9)
Total cholesterol ($mmol·L^{-1}$)	5.1 ± 0.7	4.6 ± 0.7	-0.6 (-1.1 to -0.0)
HDL cholesterol ($mmol·L^{-1}$)	1.1 ± 0.3	1.6 ± 0.3	0.5 (0.0 to 0.1)
LDL cholesterol ($mmol·L^{-1}$)	3.1 ± 0.7	2.5 ± 0.8	-0.6 (-1.2 to -0.1)
Triglyceride ($mmol·L^{-1}$)	2.0 ± 1.0	0.9 ± 0.3	-1.1 (-1.6 to -0.7)
Glucose ($mmol·L^{-1}$)	6.3 ± 1.8	5.3 ± 0.7	-1.0 (-2.2 to 0.2)
BMI ($kg·m^{-2}$)	32.4 ± 7.5	23.6 ± 3.3	-8.8 (-13.7 to -3.9)

[a]mean ± SD.
[b]44.2 $ml·kg^{-1}·min^{-1}$ in men and 35.1 in women based on the results from Aspenes et al. [10].
HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

Table 3 SF-36 items scores[a] and Pearson correlation coefficient between SF-36 items and peak oxygen uptake[b]

	Women (N = 11)		Men (N = 19)		All (N = 30)	
SF-36 items	**Mean ± SD**	***r***	**Mean ± SD**	***r***	**Mean ± SD**	***r***
Physical function (PF)	76.4 ± 28.1	0.68*	82.6 ± 20.2	0.48*	80.3 ± 23.1	0.58***
Role physical (RP)	56.8 ± 35.5	0.61*	67.1 ± 30.1	0.10	63.3 ± 32.0	0.34
Bodily pain (BP)	77.5 ± 24.7	0.06	73.8 ± 26.1	0.11	75.2 ± 25.2	0.26
General health (GH)	58.1 ± 17.6	0.72*	63.6 ± 19.9	0.42	61.6 ± 19.0	0.53**
Vitality (VT)	52.7 ± 22.8	0.71*	51.8 ± 18.6	0.30	52.2 ± 19.9	0.47*
Social function (SF)	51.1 ± 29.8†	0.41	74.3 ± 17.4	0.34	65.8 ± 25.9	0.41*
Role emotional (RE)	42.4 ± 33.7†	0.39	73.7 ± 37.8	0.25	62.2 ± 38.9	0.35
Mental health (MH)	55.3 ± 15.1	0.68*	67.0 ± 16.5	0.08	62.7 ± 16.7	0.34
Physical component (PCS)	49.1 ± 10.3	0.72*	48.2 ± 7.6	0.37	48.6 ± 8.6	0.51**
Mental component (MCS)	36.5 ± 8.4†	0.52	45.6 ± 10.2	0.16	42.2 ± 10.4	0.34

[a]Patients with schizophrenia
[b]$ml·kg^{-0.75}·min^{-1}$.
* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ Pearsons r. † $p < 0.05$ compared to men, independent T-test.

This is most likely caused by the women's fitness level in the present study, as VO_{2peak} have been described as a strong independent predictor of metabolic syndrome [32].

These results emphasize that evaluation of VO_{2peak} should be incorporated into routine clinical practice for risk prediction. The prognostic value of VO_{2peak} is beyond that predicted from other conventional risk factors [6,34]. Even in individuals with present risk factors, the higher levels of VO_{2peak} seem to confer a significant protective effect [4]. Reduced VO_{2peak} is a modifiable risk factor, and eight weeks aerobic high intensity interval training has provided significant improvements of VO_{2peak} both in healthy populations [16] and in patients with schizophrenia [14]. Furthermore, to reduce the risk of CVD, the interventions are probably more dependent on improving VO_{2peak} than increasing physical activity level alone [35,36].

Quality of life

Our findings of lower SF-36 social function, role emotion and mental component score among women than among men might reflect a sex difference in the general population. Lower scores for women than for men have been identified in normative adults [37]. The gender-specific correlations between items of SF-36 and VO_{2peak} suggest major gender differences in self-perception. Only the correlation with between SF-36 physical functioning and VO_{2peak} was significant in men, whereas six correlations with the SF-36 were significant in women. In all subjects together the VO_{2peak} correlated with the patient's perception of physical function, general health, vitality, social function, and physical component score. With some exceptions, these findings are consistent with correlations between SF-36 variables and BMI in patients with schizophrenia [38]. In line with Strassnig et al. [38] we found a significant correlation with the physical component score but not the mental component score, suggesting that reduced VO_{2peak} mainly is perceived as a physical health problem, not mental. Contrary, both the mental and physical health components of QOL are found related to estimated VO_{2peak} in healthy men [12]. An interesting note is, however, that the patients with lower VO_{2peak} seemed to experience lower vitality and social functioning. Sedentary people are associated with greater risk of low vitality [39]. QOL are found to improve in a dose dependent manner in sedentary women when increasing physical activity level [40].

Limitations

There are some limitations of the study. First, the sample size is low. Secondly, the patients were included in the study based on request to take part in exercise intervention studies. However, all eligible patients at the department were asked to participate in these studies. Thirdly, severe ill patients with schizophrenia, with poor insight to their illness, might have difficulties to evaluate their perception of QOL.

Conclusions

Men with schizophrenia have lower VO_{2peak} than men in the general population. Patients with a VO_{2peak} below 44.2 $ml \cdot kg^{-1} \cdot min^{-1}$ (men) and 35.1 $ml \cdot kg^{-1} \cdot min^{-1}$ (women) have higher odds of having one or more risk factors for cardiovascular disease. Low VO_{2peak} compromise patients' perceived physical health. VO_{2peak} should be regarded as least as important as the conventional risk factors for CVD and evaluation of VO_{2peak} should be incorporated in clinical practice. Finally, these finding represent an urging need for developing effective physical training interventions for patients with schizophrenia.

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Authors' contributions
GM, JH, JH and JH designed the study. JH and GEN recruited patients, performed VO_{2peak} testing and other data acquisition. GM and JH undertook the statistical analysis and JH wrote the first draft of the paper. All authors have contributed to and have approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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Paper II

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healthcare

Effects of high aerobic intensity training in patients with schizophrenia—A controlled trial

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Heggelund J, Nilsberg GE, Hoff J, Morken G, Helgerud J. Effects of high aerobic intensity training in patients with schizophrenia—A controlled trial. Nord J Psychiatry 2011;65:269–275.

Background: Patients with schizophrenia have a high risk of cardiovascular disease (CVD). High aerobic intensity training (HIT) improve peak oxygen uptake (VO_{2peak}), net mechanical efficiency of walking and risk factors for CVD but has not been investigated in patients with schizophrenia. *Aims:* To investigate effects from HIT on VO_{2peak}, net mechanical efficiency of walking and risk factors for CVD in patients with schizophrenia. *Methods:* 25 inpatients (F20–29, ICD-10) were allocated to either HIT or playing computer games (CG), 3 days per week for 8 weeks. HIT consisted of 4 × 4-min intervals with 3-min break periods, at 85–95% and 70% of peak heart rate, respectively. *Results:* 12 and seven patients completed HIT and CG, respectively. The baseline VO_{2peak} in both groups combined ($n = 19$) was 36.8 ± 8.2 ml/kg/min and 3.12 ± 0.55 l/min. The HIT group improved VO_{2peak} by 12% from 3.17 ± 0.59 to 3.56 ± 0.68 l/min ($P < 0.001$), more than the CG group ($P = 0.014$). Net mechanical efficiency of walking improved by 12% in the HIT group from 19.8 ± 3.0% to 22.2 ± 4.5% ($P = 0.005$), more than the CG group ($P = 0.031$). The psychiatric symptoms, expressed as the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS), did not improve in either group. *Conclusions:* VO_{2peak} and net mechanical efficiency of walking improved significantly by 8 weeks of HIT. HIT should be included in rehabilitation in order to improve physical capacity and contribute risk reduction of CVD.

• *Cardiovascular disease, Exercise, Oxygen consumption, Schizophrenia.*

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Patients suffering from schizophrenia have an illness-related vulnerability to adopt deleterious lifestyles in addition to a congestion of cardiovascular and metabolic risk factors from antipsychotics and a genetic vulnerability for developing cardiovascular disease (CVD) (1). The combination of these factors causes impaired physical fitness, weight gain, obesity, hyperglycemia, type 2 diabetes, hyperlipidemia and ultimately increased risk of CVD (2, 3). Although these risk factors are related to the physical fitness level and are improvable with aerobic endurance training, there has not been much attention to the contribution of poor physical fitness to the risk of CVD in schizophrenia. Reduced physical fitness also compromises the ability to perform lifestyle physical activity that is necessary for social rehabilitation and integration into the community. Effective aerobic endurance training has the potential to reduce the high risk of CVD, and improve functional ability and quality of life for patients with schizophrenia, as have been reported in other populations with reduced physical fitness (4). Positive psychological effects on mental health and well-being are also reported in patients with schizophrenia (5).

Physical fitness, measured as peak oxygen uptake (VO_{2peak}), appears to have more influence on risk of CVD compared with the physical activity level (6). Relatively small improvement in VO_{2peak} is associated with a fair-sized decrement in risk of all-cause mortality and CVD (7). This effect might be induced by an improvement in major risk factors for CVD (8), but physically active people have reduced cardiovascular mortality even when CVD risk factors are present (9).

High aerobic intensity training (HIT) performed as 4 × 4-min intervals are found to be an effective training method to improve VO_{2peak} for healthy individuals, patients with CVD and metabolic syndrome (10–13). Studies on patients with schizophrenia have usually

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investigated low-intensity exercise corresponding to <70% peak heart rate (HR_{peak}) (14–17). Only a few studies have applied direct measurements of oxygen uptake (18–20), but the exact level of VO_{2peak} are not described.

A major concern over the cardiovascular health in people with schizophrenia is their ability to engage in and participate in physical training. In addition, inherent difficulties in recruitment to randomized controlled trials and distrust in methodological issues such as randomization has been described (15, 21).

Aims

The objectives of the study were to investigate effects from HIT, compared with physical inactivity in the form of playing computer games (CG), in patients suffering from schizophrenia. The primary outcome was changes in VO_{2peak} and net mechanical efficiency of walking. The secondary outcome was effects on other CVD risk factors and symptoms of schizophrenia. We hypothesized that >80% adherence to 24 training sessions with HIT during 8 weeks would improve the primary outcome variables more than the same amount of time spend on CG.

Materials and Methods

All inpatients at three wards in a University hospital that fulfilled the inclusion criteria were evaluated for eligibility for the study by the medical doctor. In total 38 patients were evaluated, one did not meet the inclusion criteria, five did not want to participate and seven did not participate for other reasons. The first 16 consecutive patients were included in the HIT group and the next nine consecutive patients were included in the CG group. The inclusion criteria were ICD-10 schizophrenia, schizotypal and delusional disorders (F20–F29). Patients were on stable antipsychotic medication for 6 weeks prior to inclusion. Exclusion criteria were coronary artery disease, chronic obstructive pulmonary disease, unstable pharmacological treatment during the intervention period, and not being able to perform physical treadmill testing and exercise.

Interventions

The HIT group trained 4 × 4-min interval training on a treadmill (Tung Keng Enterprise CO., Ltd, Taiwan) at 85–95% HR_{peak} interspersed with 3 min of active resting periods at a work load corresponding to 70% HR_{peak} between each interval, previously shown to be highly effective (10–13). Patients performed the intervals walking or running with a minimum of 5% inclination. Heart rate was assessed continuously during exercise, using a Polar S610i heart rate monitor (Polar Electro, Finland). The exercise physiologist ensured that the patients performed intervals at the scheduled intensity.

The CG group spent the same amount of time, 36 min three times per week, training to improve their ability in the computer game, Tetris (THQ Inc. Calabasas Hills, CA) using an Xbox Video Game Systems (Microsoft Corporation, Redmond, USA).

Patients performed the training sessions three times per week for 8 weeks. In both groups, training sessions were lead and monitored by the same exercise physiologist. Adherence to at least 19 training sessions (80%) during the 8-week period was required to be included in the effect analyses.

Testing

The test started with a 10-min warm-up at approximately 50–60% of VO_{2peak}. Patients then walked for 6 min on the treadmill at an inclination and speed corresponding to 60 Watt (22, 23). We obtained the measurements of pulmonary gas exchange and heart rate between 5 and 5½ min walking, using the Cortex Metamax II portable metabolic test system (Cortex Biophysik GmbH, Leipzig, Germany) and the Polar S610i heart rate monitor, respectively. Net mechanical efficiency of walking is defined as the percentage of the work input (kilocalories) that is converted into work output. The equation for this calculation is described elsewhere (22, 23).

After testing net mechanical efficiency of walking the patient immediately proceeded with the VO_{2peak} testing protocol. The speed or the inclination was increased every minute to a level that brought the patient to exhaustion in 3–6 min. VO_{2peak} was accepted when VO_2 leveled off, despite further increases in speed and when respiratory exchange ratio (RER) was above 1.10 (24). The highest heart rate recorded during the last minute of the test was determined as HR_{peak}.

The patients took the pre and post-test fasting blood samples in the morning and we calculated low-density lipoprotein (LDL)-cholesterol using the Friedewald equation (25).

Possible changes in positive and negative symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (26). The test was performed by two psychiatric nurses, trained in using PANSS, working in the ward and had a personal knowledge of the patient. The Calgary Depression Scale for Schizophrenia (CDSS) was used to assess depressive symptoms (27). The 36-item short form (SF-36) was used to assess the physical health and mental health aspect of health-related quality of life (HRQOL) (28). The SF-36 is a 36-item self-report instrument.

Patients were given 10-min to learn the Tetris computer game before testing. Thereafter patients had three attempts, and the best of three trials were used in the results. We measured performance as total number of lines achieved during a game,

We accomplished this test for the CG, but not for HIT patients. Testing was not done blinded to allocation.

The study was approved by the National Committee for Medical and Health Research Ethics, Middle Norway. The approval number is: 4.2005.1507. ClinicalTrials.gov Identifier: NCT00286299.

Statistics

We suggested a change in VO_{2peak} from pre- to post-test of 4 ± 3 ml/kg/min for use in the sample size estimation; 18 patients was needed in the study for 80% power to detect a between group difference at $P < 0.05$. Data are expressed as mean and standard deviation (s). Difference in changes from pre- to post-test between groups is expressed as mean difference and 95% confidence intervals (CI). Paired samples *t*-test was performed to determine changes from pre- to post-intervention. Independent sample *t*-test was performed to test differences at baseline and changes from pre- to post-test between the two groups. The significance level (α) was set at $P < 0.05$ (two-tailed).

Results

During the training period, six of the 25 included patients did not complete the study and are not included in the results: one HIT and one CG patient were discharged from the hospital before completion and one HIT patient was lost because of ankle pains during running. One CG patient disappeared. In addition, two of the HIT patients were excluded because they completed less than 80% of the training sessions. The patients that discontinued the study were not significantly different in any of the measured baseline variables, compared with the patients that completed the study. Patients in the HIT (n = 12) and CG (n = 7) groups performed 85 ± 9% and 83 ± 6% of the scheduled training sessions, respectively. Characteristics of the patients are presented in Table 1.

After 8 weeks of training, the HIT group improved VO_{2peak} more than the CG group (Table 2). VO_{2peak} increased in the HIT group from pre- to post-test (12%, $P < 0.001$), but no change was apparent in the CG group. In both groups combined (n = 19), VO_{2peak} was 36.8 ± 8.2 ml/kg/min and 3.12 ± 0.55 l/min at baseline.

The HIT group improved net mechanical efficiency of walking more than the CG group (P = 0.031, Table 3). The net mechanical efficiency of walking improved from pre- to post-test in the HIT group (12%, P = 0.005), but no change was apparent in the CG group. In both groups combined (n = 19), the net mechanical efficiency of walking was 19.6 ± 2.9% at baseline.

A between group change in high-density lipoprotein (HDL)-cholesterol was observed (0.18 mmol/l, P = 0.007; Table 4). HDL-cholesterol decreased by 8 ± 8% in the CG group (0.13 mmol/l, P = 0.044).

No significant changes were observed between or within the two groups in PANSS, CDSS and SF-36 (Table 5). The CG group improved their performance in Tetris, measured as total number of lines achieved, from 10 ± 11 lines at pre-test to 83 ± 41 lines at post-test (P = 0.003).

Discussion

The primary finding is that the patients suffering from schizophrenia were able to participate in high aerobic intensity training and improve their VO_{2peak}. The HIT group improved VO_{2peak} by 12%. The size of the improvement in VO_{2peak} is in line with effects of 8 weeks of training in healthy controls and in patients with CVD (10–12, 29). It seems fair to conclude that, in line with what has been shown for healthy subjects, patients suffering from schizophrenia also benefit from 8 weeks with HIT.

The ability to improve VO_{2peak} is highly related to the ability to adhere to the exercise training, which is considered challenging for patients suffering from schizophrenia. The patients included in the present study were inpatients that suffered from severe schizophrenia, the majority of

Table 1. Characteristics of the patients.

	High aerobic intensity training (n = 12)	Computer game training (n = 7)	All (n = 19)
Men/women, n	9/3	4/3	13/6
Age (years), mean ± s	30.5 ± 8.7	38.9 ± 11.4	33.6 ± 10.3
Age at first contact with psychiatric services (years), mean ± s	24.8 ± 9.0	25.2 ± 6.3	24.9 ± 7.9
Months of hospitalization, mean ± s	35.2 ± 19.6	70.1 ± 62.9	48.0 ± 43.0
ICD-10 diagnosis, n			
Schizophrenia	11	6	17
Delusional disorder	1	0	1
Schizoaffective disorder	0	1	1

s, standard deviation.
No significant differences between the groups ($P < 0.05$).

Table 2. Physiological variables measured during peak treadmill exercise.

	High aerobic intensity training (n = 12)		Computer game training (n = 7)		Difference pre-post between groups
	Pre	Post	Pre	Post	Mean (95% CI)
VO_{2peak} (l/min), mean ± s	3.17 ± 0.59	3.56 ± 0.68***	3.03 ± 0.51	3.09 ± 0.57	0.33 (0.07 to 0.58)†
VO_{2peak} (ml/kg/min), mean ± s	36.0 ± 7.4	40.2 ± 6.6***	38.3 ± 9.8	37.9 ± 9.9	4.7 (1.8 to 7.6)††
HR (beats/min), mean ± s	175 ± 14	172 ± 15	166 ± 14	167 ± 14	−4 (−11 to 3)
V_E (l/min), mean ± s	95.8 ± 21.0	103.0 ± 17.1	91.2 ± 19.9	94.7 ± 22.1	3.7 (−6.5 to 13.9)
RER, mean ± s	1.11 ± 0.08	1.12 ± 0.06	1.10 ± 0.10	1.12 ± 0.10	0.00 (−0.06 to 0.05)

s, standard deviation; VO_{2peak}, peak oxygen uptake; HR, heart rate; V_E, total pulmonary ventilation; RER, respiratory exchange ratio; CI, confidence interval.
***$P < 0.001$, changes from pre- to post-test.
†$P < 0.05$, ††$P < 0.01$ differences in changes from pre- to post-test between groups.

the patients had several years of hospitalization and some were described as treatment resistant. In spite of the severity of their illness, they managed to participate in HIT and improve VO_{2peak} within a short period. This effectiveness could have important implications for the long-term treatment and prevention of low VO_{2peak}.

In both groups combined, the VO_{2peak} at inclusion was low and can be considered close to normative VO_{2peak} for sedentary people of the same age but well below normative values for active healthy people that participate in occasional aerobic exercise ≤2 times per week (30, 31). Low VO_{2peak} is associated with higher risk of cardiovascular morbidity, obesity, high blood pressure, high total- and LDL-cholesterol levels, and reduced glycemic control. A resent meta-analysis defined 28 ml/kg/min (7.9 MET) as a critical level, as those with lower than 28 ml/kg/min had substantial higher rates of all-cause mortality and CVD events compared with those with higher VO_{2peak} (7). Fortunately, only a modest level of improvement in VO_{2peak} appears to confer a significant protective effect from CVD risk factors. Kodama et al. (7) found that every 3.5 ml/kg/min increase in VO_{2peak} was associated with 13% and 15% decrements in risk of all-cause mortality and CVD, respectively. These benefits may result from an improvement in CVD risk factors, but could also be related to other indirect protective mechanisms. The present study found an improvement of 4.2 ml/kg/min after 8 weeks with HIT, and theoretically a considerable reduction in the CVD risk.

VO_{2peak} values are seldom reported in patients suffering from schizophrenia. Carlsson et al. (18, 19) measured oxygen uptake (VO_2) in people with schizophrenia in the late 1960s. Carlsson et al. (18) presented VO_2 values that did not seem to reach VO_{2peak} in all patients and are therefore considerable lower than the current VO_{2peak} findings. A recent 3-month intervention study found +5% and −3% change in VO_{2peak} in the exercise group and non-exercise group, respectively (20). The exact level of VO_{2peak} was not reported.

Participation in HIT was associated with improved net mechanical efficiency of walking, compared with the CG. The HIT group improved net mechanical efficiency of walking from 19.8 ± 3.1% to 21.9 ± 4.4%, whereas no significant change was observed within the CG group. This is in line with studies reporting improved work

Table 3. Physiological variables measured during 60-Watt submaximal treadmill walking.

	High aerobic intensity training (n = 12)		Computer game training (n = 7)		Difference pre-post between groups
	Pre	Post	Pre	Post	Mean (95% CI)
ε_{net} (%), mean ± s	19.8 ± 3.0	22.2 ± 4.5**	19.4 ± 3.0	19.4 ± 2.5	2.4 (0.3 to 4.6)†
VO_2 (l/min), mean ± s	1.79 ± 0.32	1.70 ± 0.31**	1.77 ± 0.49	1.77 ± 0.45	−0.09 (−0.17 to −0.01)†
VO_2 (ml/kg/min), mean ± s	20.0 ± 2.6	19.3 ± 2.5**	21.5 ± 3.5	21.1 ± 3.2	−0.3 (−1.2 to 0.5)
HR (beats/min), mean ± s	140 ± 16	133 ± 15**	136 ± 17	133 ± 11	−4 (−12 to 4)
V_E (l/min), mean ± s	43.9 ± 10.0	40.9 ± 8.4	45.5 ± 15.7	44.8 ± 12.8	−2.4 (−7.4 to 2.7)
RER, mean ± s	0.89 ± 0.06	0.91 ± 0.05	0.93 ± 0.04	0.92 ± 0.04	0.03 (−0.03 to 0.08)

s, standard deviation; VO_2, oxygen uptake; HR, heart rate; V_E, total pulmonary ventilation; RER, respiratory exchange ratio; ε_{net}, net mechanical efficiency of walking; CI, confidence interval.
**$P < 0.01$, changes from pre- to post-test.
†$P < 0.05$ difference in changes from pre- to post-test between groups.

Table 4. Hematological values and blood pressure.

	High aerobic intensity training ($n = 12$)		Computer game training ($n = 7$)		Difference pre-post between groups
	Pre	Post	Pre	Post	Mean (95% CI)
Body weight pretest (kg), mean ± *s*	90.1 ± 17.9	89.1 ± 16.6	85.3 ± 29.7	87.1 ± 29.9	−2.8 (− .2 to 0.5)
BMI (kg/m^2), mean ± *s*	28.8 ± 4.7	28.5 ± 4.5	27.6 ± 8.5	28.2 ± 8.8	−0.9 (−2.0 to 0.1)
Systolic pressure (mmHg), mean ± *s*	131 ± 22	135 ± 21	124 ± 22	128 ± 28	0 (−15 to 16)
Diastolic pressure (mmHg), mean ± *s*	82 ± 10	84 ± 12	80 ± 12	79 ± 12	3 (−5 to 12)
Triglyceride (mmol/l), mean ± *s*	1.5 ± 0.9	1.9 ± 1.3	1.8 ± 1.3	1.8 ± 1.2	0.3 (−0.3 to 1.0)
HDL-cholesterol (mmol/l), mean ± *s*	1.21 ± 0.38	1.26 ± 0.30	1.37 ± 0.38	1.24 ± 0.28*	0.18 (0.06 to 0.31)††
LDL-cholesterol (mmol/l), mean ± *s*	3.15 ± 0.86	2.82 ± 0.73	3.10 ± 0.67	2.95 ± 0.84	−0.17 (−0.67 to 0.33)
Hs-CRP (mg/l), mean ± *s*	8.09 ± 18.15	2.67 ± 2.11	4.41 ± 5.34	4.26 ± 5.09	−5.28 (−18.83 to 8.28)
Total cholesterol (mmol/l), mean ± *s*	5.0 ± 0.8	4.9 ± 1.0	5.3 ± 0.4	5.0 ± 0.7	0.1 (−0.5 to 0.7)
Glucose (mmol/l), mean ± *s*	5.5 ± 0.8	5.6 ± 0.6	6.4 ± 2.8	6.8 ± 3.7	−0.3 (−1.1 to 0.5)

s, standard deviation; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity serum C-reactive protein; CI, confidence interval.
**$P < 0.01$, changes from pre- to post-test.
††$P < 0.01$ difference in changes from pre- to post-test between groups.

economy both in students and in patients with post-infarction heart failure after participation in walking and running interventions (10, 12). Walking is an important part of daily function and interventions that improve net mechanical efficiency of walking might have great impact in the performance on daily tasks and physical activity in general.

The baseline value for net mechanical efficiency of walking in all patients ($n = 19$) was 19.6%. This is similar to values found in patients with coronary artery disease (19.2%) and lower than in healthy controls (24.7%) (32). It could be assumed that patients with schizophrenia walk with mechanical inefficiency. Psychomotor slowing has been recognized as a feature in people with schizophrenia and probably contributes to walking mechanical inefficiency (33). However, it also seems connected to inactivity, as we found that net mechanical efficiency of walking could be improved after participation in HIT.

The poor VO_{2peak} and net mechanical efficiency of walking described in this study might have adverse effects that could hamper rehabilitation and reintegration into the community, reduce compliance to other treatment regimens, increase stigmatization and discrimination, have harmful effects on quality of life and physical functioning, and increase financial burden (4, 34). Poor VO_{2peak} and net mechanical efficiency of walking involves that lifestyle physical activity, such as walking and household chores will demand a higher percentage of the patients VO_{2peak}, making lifestyle physical activity less pleasant. Improved endurance performance is shown to improve functional status in other populations (4). Effective HIT might help the patients to better function in general and cope better with their illness.

The baseline BMI score in all patients was 28.3 kg/m^2, which is classified as overweight with increased health risk. Blood pressure, triglyceride, hs-CRP, total cholesterol and glucose were within normal values. During

Table 5. Psychiatric symptoms and quality of life before and after interventions.

	High aerobic intensity training ($n = 12$)		Computer game training ($n = 7$)		Difference pre-post between groups
	Pre	Post	Pre	Post	Mean (95% CI)
Total PANSS	74.7 ± 20.9	73.3 ± 24.3	63.4 ± 20.4	61.4 ± 18.9	2.4 (−13.2 to 18.1)
Total positive, mean ± *s*	16.5 ± 6.9	15.2 ± 6.3	14.6 ± 6.1	13.7 ± 7.4	1.4 (−1.7 to 4.5)
Total negative, mean ± *s*	20.3 ± 8.2	23.1 ± 10.0	15.9 ± 10.3	15.3 ± 9.8	3.3 (−2.7 to 9.3)
Total global psychopathology, mean ± *s*	37.8 ± 10.3	35.0 ± 10.7	33.0 ± 7.2	32.4 ± 7.2	−2.2 (−10.7 to 6.4)
Total CDSS, mean ± *s*	2.0 ± 2.3	1.9 ± 3.4	4.2 ± 2.4	3.7 ± 1.6	0.4 (−1.6 to 2.4)
SF-36					
Physical health, mean ± *s*	52.8 ± 7.7	52.3 ± 7.7	45.7 ± 8.3	47.6 ± 5.6	−2.4 (−6.8 to 2.1)
Mental health, mean ± *s*	45.8 ± 10.2	44.9 ± 10.9	44.5 ± 10.5	47.7 ± 2.2	−4.1 (−13.9 to 5.8)

s, standard deviation; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; SF-36, 36-item short form; CI, confidence interval. No significant differences in changes from pre- to post-test between or within the two groups.

the intervention period, HDL-cholesterol changed significantly between the groups.

No significant changes in PANSS, CDSS or in SF-36 in either group or between groups were found in the present study. A few exercise studies have applied the same instruments in patients with schizophrenia. In a study by Beebe et al. (15) the patients participated in less strenuous training that continued for twice as long (16 weeks) as in the present study, or a control group that did not exercise. They reported a non-significant tendency of improvement in total PANSS score in the experimental group. Another study found that total PANSS improved somewhat in a cycling exercise group (−9%) and worsened in a non-exercise group (+13%) after 3 months (20). A significant reduction in depression has been found after an aerobic exercise intervention in a combined group of patients suffering from schizophrenia and bipolar disorder, which could possibly interfere with the result (14). Another study found a significant reduction in overall psychopathology using the Psychiatric Assessment Scale (PAS), Nurses Global Impressions Scale (NGI) and Symptom Checklist-90 (SCL-90) (16). The intervention included a combination of different types of sport activities, meditation and stress education. Thus, it was not possible to separate effects from aerobic exercise alone. Using qualitative measures, studies have reported mood-elevating effects and reduction in depression and anxiety (14, 34). In conclusion, both the type and duration of the intervention along with the type of instruments used to evaluate potential benefits might explain the diverging effects on symptoms of schizophrenia. In patients with chronic schizophrenia already receiving much psychosocial support, it might be difficult to demonstrate improvement in symptoms or in psychosocial function with an 8-week physical training intervention.

A limitation of the study is that we did not conduct a random allocation of subjects to the two groups, but included consecutive patients first to the HIT group and then to the CG group. Some patients with schizophrenia have distrust in randomization, and randomized controlled trials might exclude patients with a high level of symptoms from participating in studies evaluating this type of intervention in schizophrenia (21). To recruit patients, we had to explain very carefully and in detail what they were going to take part in. In this study, a randomized protocol would probably exclude the patients with severe hallucinations or delusions. All patients were able to participate in both interventions and none of them was selected because they fitted one of the groups more than the other. However, as they were specifically asked to participate in a either HIT or CG, their personal preference for that particular intervention might influence their decision. A selection bias cannot be ruled out and thus compromising the external validity.

This was an efficacy trial, and explored if HIT could work under ideal circumstances. The patients that adhere to less than 80% of the training sessions were excluded. The results can be generalized only to patients who adhere to the HIT. Additionally, the 8-week intervention period is a short period.

Conclusion

This study indicates that patients with schizophrenia have a level of VO_{2peak} that is associated with increased risk of CVD. The patients also seem to have poor net mechanical efficiency of walking and spend excessive energy during walking. HIT can effectively improve VO_{2peak} and net mechanical efficiency of walking during 8 weeks in patients that adhere to training. Treatment for schizophrenia should include efficient aerobic endurance training to contribute risk reduction of inactivity-related comorbidity and poor physical ability.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Paper III

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Paper IV

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Therapeutic effects of maximal strength training on walking efficiency in patients with schizophrenia – a pilot study

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Abstract

Background: Patients with schizophrenia frequently have disabling gait deficits. The net mechanical efficiency of walking (ϵ_{net}) is an accurate measure often used to evaluate walking performance. Patients with gait deficits have a reduced ϵ_{net} with excessive energy expenditure during sub-maximal walking. Maximal strength training (MST) improves ϵ_{net} in healthy individuals and is associated with reduced risk of mortality. The aim of this study was to investigate whether MST improves ϵ_{net} in patients with schizophrenia.

Methods: Patients (ICD-10 schizophrenia, schizotypal or delusional disorders (F20-F29)) were included in a non-randomized trial. Patients were assigned to one of two groups: 1) MST consisting of 4x4 repetitions at 85-90% one repetition maximum (1RM) performed in a leg press apparatus or 2) playing computer games (CG). Both groups carried out their activity three days per week for eight weeks. 1RM, ϵ_{net} at 60 watt walking, peak oxygen uptake (VO_{2peak}), the Positive and Negative Syndrome Scale (PANSS) and the 36-items short form (SF-36) were measured pre and post intervention.

Results: The baseline ϵ_{net} was 17.3 ± 1.2% and 19.4 ± 3.0% in the MST (n = 6) and CG groups (n = 7), respectively, which is categorized as mechanical inefficiency. The MST group improved 1RM by 79 kg ($p = 0.006$) and ϵ_{net} by 3.4% ($p = 0.046$) more than the CG group. The MST group improved 1RM and ϵ_{net}, by a mean of 83 kg ($p = 0.028$) and 3.4% ($p = 0.028$), respectively. VO_{2peak} at baseline was 34.2 ± 10.2 and 38.3 ± 9.8 ml·kg^{-1}·min^{-1} in the MST and CG groups, respectively, and did not change ($p > 0.05$). No change was observed in PANSS or SF-36 ($p > 0.05$).

Conclusions: MST improves 1RM and ϵ_{net} in patients with schizophrenia. MST could be used as a therapeutic intervention for patients with schizophrenia to normalize their reduced ϵ_{net}.

Keywords: Exercise, Gait disturbances, Walking efficiency, Schizophrenia

Background

Patients with schizophrenia frequently have disabling gait deficits. Often the patients have decreased walking speed, reduced stride length and balance deficits [1,2]. Gait deficits occur independently of the side effects of antipsychotic medication, but conventional antipsychotic treatment seems to worsen it [1]. Gait deficits influence the patients' well-being, quality of life and compliance to antipsychotic treatment [3,4].

Net mechanical efficiency of walking (ϵ_{net}) is a common physiological method used to evaluate walking and the metabolic consequences of gait deficits. This measure determines the magnitude of metabolic energy expenditure converted into mechanical work during walking. Gait deficits such as those in Parkinson's disease increase the metabolic cost of walking and reduce ϵ_{net} [5]. Consequently, patients with poor ϵ_{net} use excessive amounts of energy to sustain a given sub-maximal workload, which contributes to an elevated level of physical fatigue. Findings from our lab indicate that ϵ_{net} is reduced in

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patients with schizophrenia before entering an endurance training program [6].

Patients with poor ϵ_{net}, such as those with coronary artery disease and peripheral arterial disease, have derived benefit from lower limb maximal strength training (MST) [7-9]. MST aims to increase the ability to lift the highest possible weight in one repetition (1RM) and the ability to produce high forces at great speed. These adaptations have shown significant impacts in rehabilitation programs owing to their carry-over effects on walking performance measured as ϵ_{net} [8,10,11]. MST also has a number of beneficial effects, such as increased basal metabolic rate, improved glucose metabolism and improved cholesterol levels, that could reduce the high risk of cardiovascular disease and metabolic syndrome in patients with schizophrenia [12,13]. Strength training is scarcely investigated in patients with schizophrenia and no studies have investigated the effects of strength training on ϵ_{net} in patients with schizophrenia.

The objective in this pilot-study was to evaluate effects of 8 weeks MST on 1RM, ϵ_{net}, symptoms of schizophrenia and quality of life. We chose to compare the MST with inactivity in the form of playing a computer game (CG) over the same number of sessions. We hypothesized that MST would improve 1RM and ϵ_{net} more than inactivity (CG).

Methods

Study design

A controlled pilot study with pre-post intervention design was carried out. One group performed MST and one group spent the same amount of time playing computer games (CG). A non-randomized trial design was incorporated in this pilot study in order to prevent distrust of patients due to randomization and to avoid excluding the most severely ill patients [14]. The sample size estimate was based on the results of mechanical efficiency from a similar study showing a 3.4% mean difference in change between groups with a 95% CI (−0.01 to 6.8). The change was significant ($p < 0.05$) using a Mann–Whitney U test and 6 patients in each group [10]. The CG group also serves as a control group in another study [6]. All included patients were considered suitable for participation in both interventions. We first included patients to the CG group and then to the MST group. All patients performed pre and post tests and a supervised intervention three times per week in 8 weeks. The outcome assessment was not blinded. To avoid experimenter bias the planned test protocol was exactly adhered to in both groups.

Patients

Patients were in- and outpatients at the University Hospital psychiatric department. All patients lived under supervised conditions. To be included, patients had to have ICD-10 schizophrenia, schizotypal or delusional disorders (F20-F29). Patients were excluded if they had coronary heart disease, chronic obstructive pulmonary disease, any major changes in pharmacological treatment during the intervention period, were unable to perform testing, or adhered to less than 19 training sessions (80%). Included patients did not perform strength training or play computer games outside of the study. The patients' traditional therapy was unchanged during the intervention period. All patients took neuroleptics (Table 1). To clarify inclusion/exclusion criteria and somatic health a medical doctor performed a health examination at the beginning of the study. Diagnoses were confirmed by medical records. Sixteen patients were included, the first nine were assigned to CG and the next seven patients were assigned to MST. There were 5 in-patients included in the study, all of them in the CG group. Three patients did not complete the training period: in the CG group one patient was discharged from the hospital before completion and one

Table 1 Characteristics of the included patients [a]

	Maximal strength training (N = 6)	Computer game training (N = 7)	Between groups[b] *p*
Male/Female, N	1/5	4/3	0.266[c]
Age, year	37.5 ± 9.6	38.9 ± 11.4	1.000
Age at first contact with psychiatric services, year	23.5 ± 7.7	25.2 ± 6.3	0.836
Months of hospitalization	107.5 ± 58.6	70.0 ± 62.9	0.366
Height, cm	162 ± 10	175 ± 10	0.051
Body weight pre-intervention, kg	81.2 ± 32.2	85.3 ± 29.7	1.000
Body weight post-intervention, kg	82.5 ± 30.8	87.1 ± 29.9	0.945
Body mass index pre-intervention, $kg \cdot m^{-2}$	30.7 ± 11.2	27.6 ± 8.5	0.628
ICD-10 diagnosis, N			
Paranoid schizophrenia	2	4	0.592[c]
Disorganized schizophrenia	1		
Undifferentiated schizophrenia	2	2	
Unspecified schizophrenia	1		
Schizoaffective disorder		1	
Use of neuroleptics, N			
Clozapine	4	6	0.559[c]
Clozapine combined with neuroleptics	3	4	
Clozapine combined with risperidone	1		
Risperidone		1	
Zuclopenthixol	1		
Haloperidol	1		

[a]Data is presented as mean ± standard deviation.
[b]Man-Whitney U Test.
[c]Fisher's exact test.

patient disappeared; in the MST group, one patient was excluded because the patient completed less than 80% of the training sessions. No acute psychotic episodes were registered during the intervention. The study was approved by the National Committee for Medical and Health Research Ethics (REK Midt) and was conducted according to the Helsinki declaration. Written informed consent was obtained from all the included patients after the procedures were fully explained. Characteristics of the patients are presented in Table 1.

Interventions

All MST sessions started with a five minute warm-up on the treadmill at a workload corresponding to 70% of peak heart rate (HR_{peak}; the highest heart rate measured during the last minute of the peak oxygen uptake (VO_{2peak}) test). MST was then performed at a 54° incline leg press machine (Technogym, Italy). The weight was lowered in a controlled manner in the eccentric phase until the patient reached 90 degrees in the knee joint. Then the patients had a short stop (~0.5 second) before the weight was moved as rapidly as possible to complete extension. The training volume was four sets of four repetitions with a load corresponding to 85-90% 1RM. An exercise physiologist supervised the training sessions and ensured that the training load was increased with 2.5-5 kg each time patients managed to perform four sets with the determined load. Rest periods were three minutes between each set.

The CG group spent 36 minutes three times per week training to improve their ability in the computer game Tetris (THQ Inc. Calabasas Hills, CA), using an Xbox Video Game Systems (Microsoft Corporation, Redmond, USA). All sessions were monitored and patients were encouraged to improve performance.

Interventions were performed in the hospital's physical training facilities, with easy access for patients and staff. MST and CG was performed in separate rooms. Members of the staff were dedicated to implement the interventions as an integrated part of the treatment program.

Outcome measurements

Physical testing started with a ten minute warm-up at the treadmill at approximately 50-60% of VO_{2peak}. Patients then performed a six minute sub maximal walk on the DKCity treadmill (Tung Keng Enterprise CO., LTD. Taiwan) at a load corresponding to 60 watt (60 Newton meters per second, $60\ N \cdot m \cdot sec^{-1}$) and without holding onto the handrails. The speed and inclination at 60 watt was calculated from the bodymass (m_b) in kilo and elevation on the treadmill using Equation (1). The speed range used in the calculation was three to six kilometers per hour ($km \cdot h^{-1}$) and the elevation was adjusted accordingly. Sin θ is the sinus to the angle of elevation on the treadmill.

$$km \cdot h^{-1} = \frac{60N \cdot m \cdot \sec^{-1}}{(m_b \cdot 9.81N) \cdot \sin\theta^{\circ}} \cdot 3.6km \cdot h^{-1} \quad (1)$$

The measurements of pulmonary gas exchange were obtained between 5 and 5.5 minutes walking, using the Cortex Metamax II portable metabolic test system (Cortex Biophysik GmbH, Leipzig, Germany). Heart rate was assessed concurrently using a Polar S610i heart rate monitor (Polar Electro, Finland). ϵ_{net} was determined as the percentage of the work input (kilocalories) that is converted into work output, as presented in Equation (2). $\dot{W}$ is the steady power produced during walking, expressed as the Watt production converted into kilocalories per minute (Watt · 0.01433 $Kcal \cdot min^{-1}$). The net metabolic rate ($\dot{E}_{net}$) is kilocalories per minute estimated from the net oxygen consumption and the caloric value of the corresponding respiratory quotient (RQ). The net oxygen consumption is calculated by deducting the estimated resting oxygen consumption (3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) and the horizontal component of walking (0.1 $mL \cdot kg^{-1} \cdot min^{-1}$) [15] from the total oxygen consumption measured during walking.

$$\epsilon_{net} = \frac{\dot{W}}{\dot{E}_{net}} \cdot 100 \quad (2)$$

Immediately after testing ϵ_{net}, the patients proceeded with the VO_{2peak} testing protocol. The speed or the inclination was increased every minute until the patient was no longer able to continue, preferentially within 3–6 min. VO_{2peak} was accepted when VO_2 leveled off despite further increases in speed and when respiratory exchange ratio (RER) was above 1.10 [16]. The highest heart rate recorded during the last minute of the test was determined as HR_{peak}.

1RM was measured on the leg press machine using Olympic weights (Eleiko, Sweden). The lift was performed from complete extension to 90 degrees angle in the knee joint and back to complete extension. The load was increased successively until the patient was not able to lift the weight. Test procedures were carefully explained to the patients.

Symptoms of schizophrenia were assessed with the Positive and Negative Syndrome Scale (PANSS) [17]. The 36-item short form (SF-36) self-report instrument was used to assess the physical health and mental health aspect of health related quality of life [18]. SF-36 scales are found to be reliable for patients with schizophrenia [19].

Statistical methods

Data are expressed as mean and standard deviations (*SD*) unless otherwise noted. A related samples Wilcoxon test was used to determine changes from pre to post intervention. The Independent Sample Mann–Whitney U test was used to evaluate the changes and differences between groups. Categorical variables were tested using Fisher's exact test. The significance level was set at $p < 0.05$ (2-tailed). Statistical analyses were performed using the software program SPSS, version 17.0 (Statistical Package for Social Science, Chicago, IL).

Results

Patients in the MST (n = 6) and CG (n = 7) groups performed a mean of 85 ± 9% and 83 ± 6% of the scheduled training sessions, respectively. One patient in the CG group refused to execute maximal strength testing in the leg press machine. Apart from this missing test, the patients performed all of the planned tests.

The two groups did not differ pre-intervention with regard to 1RM ($p = 0.357$), ϵ_{net} ($p = 0.063$), VO_{2peak} ($p = 0.253$), total PANSS ($p = 0.517$) and SF-36 scores (physical health score: $p = 0.749$, mental health score: $p = 0.200$). During eight weeks of training, the MST group improved mean 1RM by 79 kg more than the CG group ($p = 0.006$). The MST group improved 1RM with 83 kg ($p = 0.028$), from mean 218 ± 45 kg to 301 ± 65 kg while the CG group did not change from pre- 214 ± 100 kg to post-intervention 218 ± 97 ($p = 0.465$). ϵ_{net} improved by 3.4% more in the MST group than in the CG group ($p = 0.046$; Table 2). The improvement in ϵ_{net} within the MST group was 3.4% ($p = 0.028$; Table 2). No change was observed in the CG group ($p > 0.999$). Changes in 1RM and ϵ_{net} from pre- to post-intervention are presented as percent changes in Figure 1. The VO_2 cost of walking at 60 watt was also reduced for the MST group after the intervention ($p = 0.028$), but not for the CG ($p = 0.0176$; Table 2). The VO_2 reduction in the MST group was not significantly larger than in the CG ($p = 0.063$), but was supported by a grater reduction in pulmonary ventilation ($p = 0.032$) and the respiratory exchange ratio ($p = 0.031$) in the MST group. No changes were observed from pre to post-intervention in VO_{2peak} in either group or between the groups ($p > 0.05$). Pre- and post-intervention VO_{2peak} was 34.2 ± 10.2 and 32.3 ± 8.5 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ in the MST and 38.3 ± 9.8 and 37.9 ± 9.9 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ in the CG group.

No significant changes were observed from pre- to post-intervention in the two groups in total PANSS (MST: $p = 0.115$, CG: $p = 0.753$), SF-36 physical health score (MST: $p = 0.173$, CG: $p = 0.116$) or mental health score (MST: $p = 0.463$, CG: $p = 0.345$). There were no differences in changes between groups (total PANSS: $p = 0.086$, physical health score: $p = 0.688$, mental health score: $p = 0.262$). The pre-intervention mean total PANSS score was 58 ± 12 and 63 ± 20 in the MST and CG groups respectively. The mean post-intervention PANSS scores was 68 ± 8 and 61 ± 19, in MST and CG groups respectively. The SF-36 mean physical health scores at pre- and post- intervention, were 45 ± 10 and 51 ± 11 in the MST group and 46 ± 8 and 48 ± 6 in the CG group, respectively. The mean mental health scores at pre- and post-intervention, were 36 ± 5 and 35 ± 8 in the MST group and 45 ± 11 and 48 ± 2 in the CG group, respectively.

Discussion

The findings indicate that patients with schizophrenia could safely participate in maximal strength training with a beneficial improvement in maximal strength and walking performance due to improved ϵ_{net}. These improvements occurred without affecting symptoms of schizophrenia.

The MST group improved their 1RM in incline leg press by 38%. This level of improvement is comparable with findings from studies investigating MST in patients with heart disease, chronic obstructive pulmonary disease, healthy subjects and distance runners. Improvements ranging from 27 to 44% have been reported after 8 weeks [8,10,11,20]. In line with the findings of Auchus

Table 2 Physiological variables measured during 60 Watt constant load sub-maximal treadmill walking [a]

	Maximal strength training (n = 6)		Computer game training (n = 7)		Difference pre-post between groups
	Pre	Post	Pre	Post	Mean (SE)
Net mechanical efficiency of walking (ϵ_{net}), %	17.3 ± 1.2	20.7 ± 2.9 [b]	19.4 ± 3.0	19.4 ± 2.5	3.4 (1.6) [c]
Oxygen uptake					
$L{\cdot}min^{-1}$	1.71 ± 0.38	1.60 ± 0.37 [b]	1.77 ± 0.49	1.77 ± 0.45	−0.12 (0.06)
$ml{\cdot}kg^{-1}{\cdot}min^{-1}$	22.0 ± 3.1	20.0 ± 2.9 [b]	21.5 ± 3.5	21.1 ± 3.2	−1.5 (0.7)
HR, $beats{\cdot}min^{-1}$	143 ± 9	137 ± 12	136 ± 17	133 ± 11	−4 (5)
V_E, $L{\cdot}min^{-1}$	44.9 ± 12.2	39.9 ± 12.2 [b]	45.5 ± 15.7	44.8 ± 12.8	−4.4 (1.7) [c]
RER	0.95 ± 0.06	0.90 ± 0.06 [b]	0.93 ± 0.04	0.92 ± 0.04	−0.04 (0.01) [c]

[a]Data is presented as mean ± standard deviation. HR: heart rate, V_E: total pulmonary ventilation, RER: respiratory exchange ratio, SE: standard error.
[b]differences within groups from pre to post intervention ($p < 0.05$).
[c]differences in change between groups ($p < 0.05$).

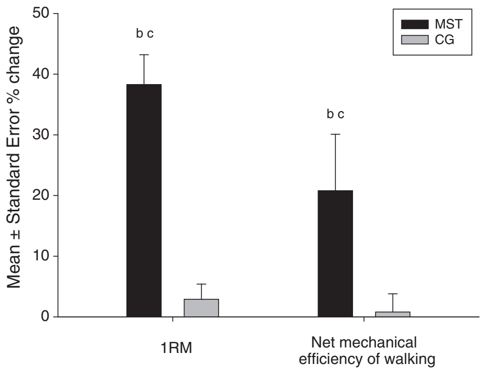

Figure 1 Percent changes in one repetition maximum (1RM) and net mechanical efficiency of walking. MST, maximal strength training; CG, playing computer games. [b]differences from pre to post intervention ($p < 0.05$). [c]differences in change between groups ($p < 0.05$).

et al. [21] this study suggests that patients with schizophrenia are able to participate in strength training and improve their 1RM. The improvement in 1RM occurred without changes in bodyweight.

The MST group improved ϵ_{net} significantly more than the CG group. This is in agreement with the strength training studies that have addressed effects on endurance performance. Although clinically significant, the 20% improvement in ϵ_{net} is somewhat smaller compared to 32-35% improvement found in other patient groups [8,10]. This might indicate that factors associated with the illness itself or side effects from antipsychotic medication may hamper the transfer effect from improved 1RM to improved ϵ_{net}. As expected, the VO_{2peak} did not change. Maximal strength training mainly results in neural system adaptations with improved maximal strength and ability to develop speed. MST does not result in cardiovascular system changes such as increased peak stroke volume and increased VO_{2peak} [7]. However, increased VO_{2peak} from endurance training is often followed by improved ϵ_{net} [6]. In this respect, the improved ϵ_{net} in this study is considered being a result of the MST intervention, not confounded by increased VO_{2peak}. On the contrary, the mean VO_{2peak} in the MST group worsened in absolute terms. The most plausible explanation is that patients could have reduced their endurance physical activities during the intervention. No outside intervention activity control were carried out.

The initial ϵ_{net} of 17.3% (MST) and 19.4% (CG) can be considered low and within the range of patients that walk with mechanical inefficiency [8,22]. The ϵ_{net} values in the present study are similar to values found in patients with coronary artery disease (19.2%) and lower than in healthy controls (24.7%) [22]. Gait deficits in schizophrenia have been reported, with the poorest gait patterns found in patients treated with conventional antipsychotics [1]. Patients with schizophrenia choose to walk slower (2.7 to 3.1 $km \cdot h^{-1}$), compared to healthy controls (3.4 $km \cdot h^{-1}$) [1]. From a metabolic point of view, it seems natural that the patients would walk slower if they had lower VO_{2peak} and poorer ϵ_{net}. Walking is usually undertaken at a speed that coincides with the lowest metabolic cost. Poor ϵ_{net} might be an obstacle in performing daily tasks and so might prevent patients from engaging in activities that require walking. Additionally, poor ϵ_{net} as well as other gait deficits might have implications for the patients' well-being [3]. Of interest, the MST improved ϵ_{net} to a level that is closer to healthy individuals [8,22].

Our study revealed no changes in the total PANSS score or SF-36. In absolute terms, there was an increase of 10 points in the MST group and a decrease of 2 points in the CG group on the total PANSS score. As there are no reasons to anticipate an adverse effect from MST, as would be reflected by an increase in PANSS score, we believe this tendency of a change is due to natural variations in the course of the illness and is probably valid for patients with schizophrenia. There is a small sample size in this study and other mediators or moderators such as depression, anxiety or fatigue due to the intervention were not measured. There are few reports of strength training on symptoms of schizophrenia. A single-group study found that patients reported improvement in a questionnaire that measured perceived psychological well being, but no improvement in the Zung Self Rating Depression Scale (SDS), after weight lifting therapy [21]. A case study described some improvements in Brief Psychiatric Rating Scale (BPRS) and the Nurses' Observational Scale for In-Patient Evaluation (NOSIE 30). The patient showed beneficial behavior changes in his daily activities. However, there is a need for larger scale and longitudinal intervention studies to determine whether strength training has the ability to decrease symptoms of schizophrenia. Considering the effect of MST on ϵ_{net} this seems to be sufficient reason to include MST in the treatment of schizophrenia. Furthermore, patients with schizophrenia have a high risk of dying from cardiovascular disease [23]. The 8-weeks training period performed in this study may not be sufficient to affect traditional measures of cardiovascular disease. Further studies should consider a longer period to investigate effects on common blood values. Patients who maintain a certain level of maximal strength through life may have a better chance of sustaining good health. A prospective cohort study of 8762 men aged from 20–80 years, found that maximal strength was independently and inversely associated with all-cause mortality [24]. The association persisted even after adjusting for cardiorespiratory fitness.

There are some limitations in this study. First, the allocation of patients was not randomized. Thus, a selection bias cannot be ruled out. To reduce the selection bias we ensured that all patients were eligible for both interventions. None of the patients were selected because they fitted one of the groups more than the other. Patients were not able to choose a particular group, but their personal preference for the intervention they were asked to participate in could have influenced their decision. A possible disadvantage of the non-randomized design is disclosed in the fact that the MST tend to be hospitalized longer, younger at first contact with psychiatric services and include more women. It could be hypothesized that both severity of illness and gender influenced baseline characteristics such as the SF-36, ϵ_{net} and VO_{2peak}. On the contrary, the effects of the interventions might not be very different between genders. However, the objective of this study was to evaluate the effects of the intervention those might not be different between genders. Although the outcome assessments were not blinded, all tests followed strict procedures and patients seemed to be motivated to perform their best regardless of the group. The effect of the intervention can only be generalized to patients that adhere to MST. The study also had a small sample size. This might be one reason for the tendency of a worsening of PANSS symptoms in the MST group. Furthermore, the 8-week intervention might be too short a period of time for patients suffering from schizophrenia to adapt to the intervention.

Conclusions

The current study found that the MST improved the patients 1RM to the same level as has been observed in other patient groups and in healthy controls. The MST did also improve the patients' ability to normalize the net mechanical efficiency of walking. MST is a safe and effective intervention to improve 1RM and net mechanical efficiency of walking in patients with schizophrenia.

Abbreviations

CG: Computer games; HR_{peak}: Peak heart rate; m_b: Bodymass; MST: Maximal strength training; $N \cdot m \cdot sec^{-1}$: Newton meters per second; PANSS: Positive and Negative Syndrome Scale; RER: Respiratory exchange ratio; SF-36: 36-item short form; Sin θ: Sinus to the angle of elevation on the treadmill; VO_{2peak}: Peak oxygen uptake; $\dot{W}$: Steady power production during walking in kilocalories per minute; ϵ_{net}: Net mechanical efficiency of walking; 1RM: One repetition maximum.

Author's contributions

GM, JH, JH and JH designed the study. JH and GEN recruited patients, performed testing and other data acquisition. GM and JH undertook the statistical analysis and JH wrote the first draft of the paper. All authors have contributed to and have approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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