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Collaborative care of outpatients with schizophrenia: the role of physical health and aerobic interval training

Thesis for the Degree of Philosophiae Doctor

Trondheim, 2019

Norwegian University of Science and Technology

Faculty of Medicine and Health Sciences

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21st of June 2016: Patient NN increased treadmill velocity and incline on his own accord and responded positively to adding more weight on the leg press device.

Me: *"NN, you've become strong recently."*

NN flexed his arms above his head with his biggest grin and took a piece of fruit on his way out of the clinic, while completely ignoring the cake on the table (which of course another patient had brought).

20th of January 2017: *«Can I join the training session today too? »*

Patient in the training group who had undergone treadmill and leg press testing the day before, texted Bente (municipal health care professional) for an unscheduled training session at the clinic.

Content

Acknowledgements

I sincerely thank my supervisors for all their time and support. Einar Vedul-Kjelsås, you have always been supportive, and your supervision has been invaluable. Jørn Heggelund, you introduced me to the world of physiology in psychiatry and our project would surely not exist without you. Eivind Wang, I am in awe of your expertise in exercise physiology. You have been tremendously helpful, substantially enhancing my physiology/research expertise. I am forever grateful to you all.

My thesis was funded by the Norwegian ExtraFoundation for Health and Rehabilitation in cooperation with the national association for heart and lung disease (LHL), and St. Olavs Hospital, and received grants from The Norwegian Directorate of Health and The Liaison Committee for education, research and innovation in Central Norway. I thank Gunnar Morken, Ismail Cüneyt Güzey, and Solveig K. Reitan (AFFU) for their vital contributions to the project. Pål Sandvik, head of Østmarka, thank you for the opportunity to combine working as a researcher at the clinic with this thesis for the past years.

Mona Nygård, although working on this project the last 4 years has been rewarding, it has certainly been challenging. Working together has been utterly invaluable for the completion of this thesis. Joshua Taylor, your contribution in the lab was extremely helpful. Fellow PhD candidates/researchers at the department, thank you for both academic discussions and not-so-very-academic-yet-hilarious stories by the coffee table(s) at NTNU/St. Olavs Hospital.

Aksel H. Skjelbred, Kari K. Herre and Bente S. Svendsen, your work with the patients has not only been vital to the completion of our project, but also my knowledge of working with this patient group. Further, I thank all the patients who participated. Your time and effort will surely contribute to improved treatment of future patients.

Cathrine Johansen, evolving from girlfriend to wife during my work with this thesis is testament to your patience. I cherish you more than anything. Last, my family and friends, you have always showed interest and encouragement these years. Thank you for your support.

Mathias Forsberg Brobakken

Trondheim, 2019

Abbreviations

ADL	Activities of daily living
AIT	Aerobic interval training
a-vO_{2diff}	Arterio-venous oxygen difference
BMI	Body mass index
CG	Control group
CVD	Cardiovascular disease
FGC	Force-generating capacity
HDL	High-density lipoprotein
HR_{peak}	Peak heart rate
ICD-10	International statistical classification of diseases 10^{th} revision
LDL	Low-density lipoprotein
MET	Metabolic equivalent of task
PANSS	Positive and negative syndrome scale
REC	Regional committee for medical and health research ethics
RER	Respiratory exchange ratio
SV_{peak}	Peak stroke volume
TG	Collaborative care training group
V_E	Total pulmonary ventilation
$\dot{V}O_{2peak}$	Peak oxygen uptake
$\dot{Q}$	Cardiac output
1RM	One repetition maximum
30sSTS	30-second sit-to-stand test
6MWT	6-minute walk test

List of papers

Paper I

Brobakken MF, Nygård M, Taylor JL, Güzey IC, Morken G, Reitan SK, Heggelund J, Vedul-Kjelsaas E, Wang E. A comprehensive cardiovascular disease risk profile in patients with schizophrenia. Scandinavian Journal of Medicine & Science in Sports. 2019; 29(4): 575-585.

Paper II

Nygård M, **Brobakken MF**, Roel RB, Taylor JL, Reitan SK, Güzey IC, Morken G, Vedul-Kjelsaas E, Wang E, Heggelund J. Patients with schizophrenia have impaired muscle force-generating capacity and functional performance. Scandinavian Journal of Medicine & Science in Sports. 2019; 29(12): 1968-1979.

Paper III

Brobakken MF, Nygård M, Güzey IC, Morken G, Reitan SK, Heggelund J, Wang E, Vedul-Kjelsaas E. Aerobic interval training in standard treatment of outpatients with schizophrenia: a randomised controlled trial. Acta Psychiatrica Scandinavica. 2019; 140: 498-507.

Paper IV

Brobakken MF, Nygård M, Güzey IC, Morken G, Reitan SK, Heggelund J, Vedul-Kjelsaas E, Wang E. One-year aerobic interval training in outpatients with schizophrenia. Under review 2019.

Summary

Patients with schizophrenia are inactive, have high rates of cardiovascular diseases (CVD) and reduced life expectancy compared to the general population. However, few studies have included directly measured aerobic capacity ($\dot{V}O_{2peak}$), recognised as a strong predictor of CVD and premature mortality, in CVD risk assessment in patients with schizophrenia. Skeletal muscle force-generating capacity (FGC) in the lower extremities, and how it relates to functional performance, is also inadequately described in this patient group. Further, integrating aerobic interval training (AIT), specifically structured to target the heart and thus $\dot{V}O_{2peak}$, in a collaborative outpatient treatment model involving both specialised (exercise supervision) and municipal health services (transportation and social support) is unexplored.

The aims of this thesis were:

1) To compare $\dot{V}O_{2peak}$, body composition, blood pressure, blood glucose/lipids and smoking status with healthy reference values and explore the relationship between $\dot{V}O_{2peak}$ and physical activity in patients with schizophrenia.
2) To compare leg press maximal muscle strength (1RM) and rapid force development and functional performance in patients with schizophrenia with age- and sex-matched healthy references.
3) To investigate the short-term (12 weeks) feasibility and effects of the collaborative outpatient treatment model on $\dot{V}O_{2peak}$, body composition and blood glucose/lipids in outpatients with schizophrenia.
4) To investigate the long-term (1-year) feasibility and effects of the collaborative outpatient treatment model on $\dot{V}O_{2peak}$, body composition and blood glucose/lipids in outpatients with schizophrenia.

In paper I, we assessed $\dot{V}O_{2peak}$ and a wide range of CVD risk factors in 48 patients with schizophrenia spectrum disorders and 48 age- and sex-matched healthy references. We revealed that men and women with schizophrenia have reduced $\dot{V}O_{2peak}$ (men, 27%; women, 30%), and that physical activity was weakly and inconsistently associated with $\dot{V}O_{2peak}$, suggesting that increasing physical activity may not translate to reduced CVD risk. Although the patient group was likely high at risk of developing CVD through low $\dot{V}O_{2peak}$, categorised

as overweight (body mass index, 26.0 ± 6.1 kg · m^2; waist circumference, 103 ± 17 cm) and many were current smokers, this was not reflected in abnormal blood pressure, lipids or glucose. In paper II, we assessed lower extremity force-generating capacity and functional performance in the same patients and healthy references. We documented that while the men with schizophrenia displayed reduced allometrically scaled 1RM (19%) and rapid force development (30%), the women with schizophrenia had reduced rapid force development (25%) and tended to have lower 1RM (13%) compared to the healthy references. We also documented that the patients with schizophrenia had poorer functional performance measured as walking efficiency (14%), 6-minute walking (22%), chair-raising (48%), unipedal balance with eyes open (20%) and closed (73%) and stair climbing (63%) compared to the healthy references. This systematically poorer functional performance was associated with 1RM and rapid force development. For paper III and IV, we randomised 48 outpatients with schizophrenia to either a collaborative care training group (TG) performing AIT twice a week at the clinic or a control group (CG) receiving an introduction to training and advice to continue training. In paper III, we documented that AIT was feasible when integrated in collaborative care, as 64% of the patients completed this intervention. After 12 weeks, the TG improved $\dot{V}O_{2peak}$ by 10%, reducing risk of CVD and early death substantially. In the CG, $\dot{V}O_{2peak}$ did not change while body weight increased (1.9 kg). Interestingly, after categorising patients in the TG based on whether they had completed 70% of the AIT sessions per protocol, $\dot{V}O_{2peak}$ was found to increase both in patients with high and low adherence to the training. In paper IV, $\dot{V}O_{2peak}$ was maintained from 12-weeks to 1-year in the TG, while decreased (6%) in the CG from 6-months to 1-year. Adherence to AIT remained high throughout the study in the TG yielding a completion rate of 60%, while no CG patients conducted AIT on their own after 1-year. In conclusion, these papers showed systematically reduced physical health in patients with schizophrenia. To improve physical health and life expectancy, $\dot{V}O_{2peak}$ assessment should be included in routine clinical care, and AIT delivered through a long-lasting collaborative outpatient treatment involving both specialised and municipal health services. An introduction to AIT and recommendation to continue training without support does not, however, improve physical health in outpatients with schizophrenia spectrum disorders.

Introduction

Schizophrenia

Schizophrenia spectrum disorders are characterised by a range of signs and symptoms, commonly classified into positive, negative, cognitive, disorganisation, mood and motor symptoms. The clinical expression may be different between patients and may change during the course of illness (77). Prevalent features include hallucinations, delusions, thought insertion, avolition (lack of initiative), anhedonia (inability to feel pleasure), alogia (speech deprivation), apathy (lack of interest), disorganised thinking and behaviour, impaired insight and cognitive deficits related to memory, processing speed, and executive functions (77). There are two acknowledged and widely used systems for disease classification, namely the International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders. The former is maintained by the World Health Organization and globally accepted and utilised, and the latter is developed by the American Psychiatric Association and commonly used in the United States, Canada and Australia. While some differences between the two classification systems still exist, such as the required minimum illness duration and presence of social/occupational dysfunction for schizophrenia classification (78), the concordance between the systems have improved recent years along with the utilisation in clinics and research (78).

Although prevalence rates have shown to vary across sites and depending on diagnostic criteria, median lifetime schizophrenia risk has been reported at ~7 per 1’000 persons (0.7%) on a world-wide basis, with ~60% of patients diagnosed being men (47). Onset of schizophrenia usually occurs from adolescence to early adulthood (48), and remains an illness with high societal costs (35). In fact, in 2012 the total cost of schizophrenia over 12 months in Norway was estimated at ~7.9 billion NOK (890 million USD) mainly due to hospital admission and other treatment costs, community care services, social security and loss of productivity (15), underpinning the importance of developing appropriate strategies to counter the poor physical health and disability accompanying the schizophrenia illness.

Life expectancy and physical health

Patients with schizophrenia spectrum disorders have 10-20 years shorter life expectancy (33, 40). The primary cause of the elevated mortality in patients with schizophrenia is cardiovascular diseases (CVD) (56, 62). This may have multifactorial causes, as patients with schizophrenia are more often physically inactive, overweight/obese, smoke, abuse illicit substances, and have higher consumption of alcohol and poor diet quality than the general population (11, 59, 75, 90). Furthermore, patients with schizophrenia often undergo antipsychotic treatment that commonly have adverse side-effects. Antipsychotics are dichotomised into typical (first-generation) and atypical (second-generation). Both are usually efficacious for eliminating psychotic symptoms in most patients with schizophrenia; however, particularly typical antipsychotics have shown to increase the risk of extrapyramidal side-effects. Side-effects occur either within hours/days of treatment (acute) or after prolonged treatment (tardive). They include dystonia (spasms and muscle contractions), akathisia (motor restlessness), parkinsonism, bradykinesia (slow movement) and tardive dyskinesia (irregular movement), potentially impacting both a patient's physical functioning and his/her ability to tolerate the medical treatment (61). Although the introduction of atypical antipsychotics decreased this risk (albeit not fully eliminated), these have shown to affect weight gain and sedation even more than typical antipsychotics (42). Side-effects such as adiposity, abnormal lipid profiles and elevated blood glucose are commonly observed following second-generation antipsychotic treatment (51), increasing risk of developing CVD in patients.

The health improvements in the general population over the last decades have not been observed in patients with schizophrenia, consequently increasing the mortality gap (52). Although the exact causes of the increasing mortality gap are unclear, it has been suggested that the benefits of improved health care may not be received to the same degree by this patient group (52). In fact, a study conducted in the United States showed that non-treatment rates among patients with schizophrenia for diabetes, hypertension and dyslipidaemia were 30%, 62% and 88%, respectively, suggesting that these patients may be underserved in terms of monitoring and treatment of CVD (50). Systemic barriers to treatment through access to medical care and quality of primary medical care have been shown in outpatients with severe mental illness (43), along with an inclination not to utilise medical services even if available (9). Taken together, this highlights that treatment targeting physical health, specifically CVD,

and tailored to the needs of patients with schizophrenia may be crucial to eliminate the health inequality and improve longevity in this patient group.

Aerobic endurance performance

Pate and Kriska (58) described a model for evaluating interindividual differences in aerobic endurance performance consisting of three factors: aerobic capacity (commonly measured as peak oxygen uptake, $\dot{V}O_{2peak}$), lactate threshold and work efficiency. This model has been supported by other studies (10, 29). Work efficiency, determined from the ratio of work output to oxygen cost, has shown to differ considerably among subjects (58). It may be particularly low in untrained patient groups (27, 36), implying that submaximal whole body work will tax an unnecessarily large portion of $\dot{V}O_{2peak}$. Lactate threshold, the point where lactate accumulation supersedes elimination, remains unaltered following exercise when expressed at a % of $\dot{V}O_{2peak}$ (30). Thus, of the three factors, $\dot{V}O_{2peak}$ is recognised as the single most important factor explaining the variance in aerobic endurance performance (92).

Aerobic capacity

Definition and limitations

$\dot{V}O_{2peak}$ is defined as the highest rate the body is able to consume oxygen during exhaustive exercise with large muscle mass (58). $\dot{V}O_{2peak}$, a product of cardiac output ($\dot{Q}$ = heart rate [HR] · stroke volume [SV]) and arterio-venous oxygen difference (a-vO_{2diff}), is derived from the Fick equation:

(1) $\dot{V}O_{2peak} = \dot{Q} \cdot a - vO_{2diff}$

Among the most important factors constituting the O_2 pathway from the atmosphere to the muscle are ventilation, pulmonary diffusing capacity, $\dot{Q}$, oxygen-carrying capacity of the blood and skeletal muscle oxidative capacity, all of which are essential to maintain a constant O_2 flow (7). The bottleneck in this O_2 pathway will determine aerobic capacity and, if one or more of the O_2 pathway factors are inhibited e.g. through illness, aerobic capacity will be

affected (68, 86). Limitations to $\dot{V}O_{2peak}$ may be different between subjects of unequal training status. Whereas $\dot{Q}$ seems to be the main factor limiting $\dot{V}O_{2peak}$ in moderately active and healthy subjects, subjects considered inactive and untrained will potentially be limited by skeletal muscle's respiratory capacity during sustained work, even in the presence of excess oxygen supply (22).

Aerobic capacity and physical health

$\dot{V}O_{2peak}$ has shown to be a strong and independent predictor of mortality risk, even more so than other established risk factors such as diabetes, smoking and hypertension (49). An improvement of 1 metabolic equivalent of task (MET; 3.5 mL $\cdot$ kg^{-1} $\cdot$ min^{-1}) is associated with decreased risk of all-cause mortality by 12-13% and cardiovascular events (coronary heart disease/CVD) by 15% in men and women (38, 49). Importantly, aerobic capacity has shown to protect against all-cause mortality even in the presence of conventional CVD risk factors such as obesity, diabetes, high cholesterol, hypertension and smoking (49). Similar all-cause mortality risk has also been observed among obese and nonobese subjects with high aerobic capacity (41, 46). This is likely because $\dot{V}O_{2peak}$ integrates numerous physiological systems such as the pulmonary, cardiovascular and muscular systems, and differences in aerobic capacity are largely attributed differences in $\dot{Q}$ (24, 30). Furthermore, all human locomotion requires a certain amount of oxygen to be consumed for energy transfer. Hence, $\dot{V}O_{2peak}$ is essential not only for elite level aerobic endurance performance, but also for the ability to conduct activities of daily living (ADLs) and functional performance tasks successfully. This underlines aerobic capacity's cardioprotective and rehabilitative role in physical health.

Aerobic capacity in patients with schizophrenia

Relatively few studies have previously examined aerobic capacity directly in a relatively large group of patients with schizophrenia. There are, however, observations that $\dot{V}O_{2peak}$ may be low in this patient group (25, 34). In fact, values as low as 19 and 14 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} in obese men and women with schizophrenia, respectively, have been observed (73). Although aerobic capacity is essential for health promotion in this patient group, direct $\dot{V}O_{2peak}$ assessment as part of routine clinical care and CVD risk assessment is scarce. This may be due to the resource demanding nature of conducting such tests. Ergospirometers

commonly used to assess $\dot{V}O_{2peak}$ directly are expensive while undertaking tests requires time, experienced personnel and motivated patients. Furthermore, different protocols have previously been utilised, such as application of cycle ergometers, known to yield lower values (32), and indirect aerobic capacity estimation models (83), increasing the difficulty of comparing results across studies. In addition, how $\dot{V}O_{2peak}$ relates to other conventional and more frequently measured CVD risk factors in this patient group is unclear.

Skeletal muscle force-generating capacity

Definition and implications

Skeletal muscle force-generating capacity (FGC) is commonly assessed through the two following properties: maximal muscle strength and rapid force development. While maximal muscle strength is usually determined from the highest weight a subject can lift in a given movement (one repetition maximum, 1RM), rapid force development is calculated from the force production during a submaximal lift. Maximal muscle strength has shown to associate with mortality risk from all-causes, CVD and suicide (55, 66). Both properties are recognised as highly influential regarding the successful completion of ADLs (3, 76). However, functional performance tasks, such as regaining balance for fall prevention, seems to be more related to the ability to generate force rapidly (2), as reaching maximal muscle strength requires more time (> 200 ms) to be fulfilled (5). Increased FGC following maximal strength training has shown to improve work efficiency (57), consequently impacting aerobic endurance performance as well. Thus FGC, particularly in the functionally relevant lower extremities, is an important contributor towards independent living and disability prevention in humans.

Force-generating capacity in patients with schizophrenia

To the author's knowledge, no study has previously compared lower extremity 1RM and rapid force development in a relatively large group of patients with schizophrenia with age- and sex-matched healthy references. Attenuated standing broad jump distance (82) has been demonstrated in patients with schizophrenia previously, indicating reduced FGC. Associations between handgrip strength and cognitive function such as working memory and processing speed have also been observed in this patient group (19). Furthermore,

neuromuscular alterations such as atrophy of type I and II muscle fibres, reduced number of motor units and increased motor unit action potential have been reported in patients with schizophrenia (8, 21, 23), likely attenuating FGC. These observations have been made in both medicated and medication-naïve patients with schizophrenia; however, antipsychotics may also affect the neuromuscular system (42). Although FGC is essential for disability prevention and longevity in humans, lower extremity FGC, and its potential association with functional performance in ADLs such as walking, stair climbing, and balance, remains unexplored in this patient group.

Training to improve aerobic capacity

Since $\dot{V}O_{2peak}$ is widely acknowledged to be an essential part of endurance performance, functional performance and physical health, the most efficient way to improve $\dot{V}O_{2peak}$ has been a source of constant debate. During recent decades, however, research has shown that interval training with high aerobic intensity is far superior to endurance training with moderate intensity for improving $\dot{V}O_{2peak}$ both in health (30) and a wide range of patient groups such as heart failure (91), coronary artery disease (63) and metabolic syndrome patients (79). Aerobic interval training (AIT) has also shown to be both feasible and yield similar improvements in $\dot{V}O_{2peak}$ in peripheral arterial disease (31), substance use disorder patients (20) and inpatients with schizophrenia (26). It is thus utilised as a countermeasure for poor physical health in various patient populations. The hallmark of AIT is endurance exercise training with large muscle groups, e.g. uphill walking/running, conducted at an intensity corresponding with 85-95% of HR_{peak} and usually lasting between 3-8 minutes. Both intensity and duration of intervals are tailored to tax oxygen transport organs, particularly the heart, while discontinuing the interval before too much lactate is accumulated through anaerobic energy transfer (53, 89). Improvements in $\dot{V}O_{2peak}$ following AIT have shown to associate strongly with increased SV of the heart and $\dot{Q}$ (30).

Physical activity and exercise as treatment

A meta-analysis of 35 studies representing 3’453 patients diagnosed with schizophrenia spectrum disorders showed that while this patient group may be less physically active than the general population, more than half of the included patients met the 150 minutes of

moderate physical activity per week commonly recommended by health authorities (75). Nevertheless, previous studies have revealed that risk of CVD and premature mortality remains high in this patient group with indications of low $\dot{V}O_{2peak}$ and FGC. While objectively measured physical activity has been associated with an increased risk of poor cardiometabolic health in healthy references (16), its relationship with $\dot{V}O_{2peak}$ may be weak (12). This relationship has not been explored in patients with schizophrenia but may be an important topic to explore given the high prevalence and importance of screening for CVD in this patient group. Although patients with schizophrenia are in need of effective $\dot{V}O_{2peak}$-improving endurance exercise training to counter the poor cardiovascular health, and the likely accompanying accelerated aging process, physical activity and exercise interventions for this patient group seem somewhat random (17). To the best of our knowledge, only one study from our research group has previously conducted an AIT intervention in patients with schizophrenia (26). Heggelund and colleagues (26) conducted an 8-week AIT non-randomised controlled trial of inpatients with schizophrenia undergoing treatment at a psychiatric ward, yielding a 12% improvement in $\dot{V}O_{2peak}$. Thus, short-term AIT seems to be both feasible and effective for inpatients with schizophrenia. However, the application of AIT in an outpatient clinic in this patient group, both in the short and long term, and the potential effects remain elusive.

Adherence and support for exercise training

As interest in the promotion of physical health in patients with schizophrenia has increased immensely recent decades, this has led to questions regarding how treatment should be tailored to improve compliance. In fact, drop-out rates of > 50% are often reported in antipsychotic clinical studies in patients with schizophrenia (45), suggesting study compliance may be an issue in general in this patient group. Regarding exercise interventions, a meta-analysis showed that exercise delivered to groups of patients with schizophrenia spectrum disorders resulted in lower patient attrition (22 vs. 43%) and higher adherence (79 vs. 55%) to the training compared to solitary exercise conducted after a brief introductory period (17). Furthermore, supervision has also been highlighted as a critical issue promoting patient attendance (77 vs. 30%) compared to non-supervision with introduction to training, advice and free gym membership (17).

The importance of training supervision has been demonstrated in a meta-analysis of qualitative studies exploring motivating factors and barriers to exercise in patients with severe mental illness (18). Limited know-how and availability of transportation have also been suggested as contributing factors to lack of exercise adherence (74). Another study applying AIT over 6 months in overweight individuals with psychotic disorders displayed 50% drop-out before study completion (64), underlining the difficulty in maintaining training adherence over long periods and the need to tailor strategies for delivering training to this patient group. The low aerobic capacity previously observed, taken together with the clinical features and symptomology often expressed, suggests that patients with schizophrenia may require collaborative assistance from both specialised and municipal health care services to be able to adhere to both short- and long-term AIT in an outpatient setting.

Thesis perspectives

To promote longevity in patients with schizophrenia spectrum disorders, the starting point should be an adequate description of the patient populations' physical health that also includes exercise capacity. Directly measured aerobic capacity in combination with other CVD risk factors and physical activity is inadequately described in patients with schizophrenia. FGC in the lower extremities and functional performance are important for healthy living and disability prevention in all humans and warrants a better understanding in patients with schizophrenia, and exactly how functional performance relates to FGC in the lower extremities in this patient group remains a topic of investigation.

Previous evidence suggests that aerobic capacity may be particularly low in patients with schizophrenia, and that the patients may require extra support to adhere to treatment. Although AIT is feasible and effective in inpatients with schizophrenia in the short term, it is still unclear if this knowledge holds true also in an outpatient clinic with adherence support and a longer training period. Therefore, it is imperative to explore if AIT, delivered through a newly developed collaborative treatment model involving both specialised and municipal health care services, is feasible and may improve the physical health of outpatients with schizophrenia.

Aims and hypotheses

The main objective of this thesis was to examine the need for - and the treatment effect of - a collaborative outpatient treatment model for exercise training therapy in patients with schizophrenia spectrum disorders.

In paper I, the aim was to examine CVD risk in patients with schizophrenia by comparing directly measured $\dot{V}O_{2peak}$ and conventional risk factors to healthy reference values and explore the relationship between $\dot{V}O_{2peak}$ and physical activity. We hypothesised that a) patients with schizophrenia have reduced $\dot{V}O_{2peak}$ compared to age- and sex-matched healthy references, b) $\dot{V}O_{2peak}$ is associated with daily physical activity, and c) patients with schizophrenia are overweight and have blood lipids and glucose outside reference limits.

In paper II, the aim was to compare lower extremity muscle FGC, measured as 1RM and rapid force development, and functional performance in patients with schizophrenia with age- and sex-matched healthy references. We hypothesised that a) patients with schizophrenia have reduced FGC and functional performance compared to healthy references, and b) functional performance and defined daily dose of antipsychotic medication are associated with reduced FGC.

In paper III and IV, the aim was to assess the feasibility and effects of AIT delivered through a collaborative outpatient treatment model and compare it with a control group (CG) receiving a short introduction to AIT and advice to train on their own. We measured $\dot{V}O_{2peak}$ and conventional risk factors, along with assessment of patient retention, attendance and adherence to the training protocol. In paper III, we hypothesised that a) outpatients with schizophrenia randomised to the collaborative care training group (TG) are able to participate in a structured AIT program twice a week for 12 weeks with adherence support (feasibility success criterion set at 60% patient retention), and b) will improve $\dot{V}O_{2peak}$ more than patients in the CG. In paper IV, we hypothesised that after 1-year a) outpatients randomised to the TG will improve $\dot{V}O_{2peak}$ more than patients in the CG, and b) have higher adherence to the training protocol compared to the CG.

Methods

Design

All four papers in this thesis were based on data collected for the Long-term Exercise Training Therapy versus Usual Care in Patients with Schizophrenia (LEXUS) project, a two-group randomised controlled trial which aimed at assessing the feasibility and effects of AIT and maximal strength training as part of a collaborative treatment model (described below) of outpatients diagnosed with schizophrenia spectrum disorders. Paper I and II were based on data collected at inclusion. In paper III, data collected 3 months post-inclusion were used, while paper IV was based on 1-year outcomes. Training sessions and tests were done between January 2016 and January 2019. The regional committee for medical and health research ethics (REC South East: 2015/1611) accepted this project, which was done in accordance with the Helsinki declaration (ClinicalTrials.gov identifier: NCT02743143).

Collaborative outpatient treatment model

This collaborative treatment model involved both specialised and municipal health care services in a coordinated attempt to integrate exercise training in care of outpatients with schizophrenia spectrum disorders.

Specialised health care service

All tests and training sessions were conducted at the Exercise Training Clinic, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. Patients arrived at the clinic in groups two times per week between 12:00 and 14:00, and for each training session 4-6 patients typically exercised at the same time. Two experienced health care professionals at the clinic delivered and supervised each training session. A standardised exercise diary was used to deliver the training protocol to patients. Two exercise physiologists conducted physiological tests.

Municipal health care service

Outpatients living in Trondheim municipality (total area: 342 km^2) were provided with the service, which was conducted by 1-2 municipal health care workers. This service consisted of transportation by minibus to and from all training and test sessions at the clinic and, when necessary, patients received a text message or phone call in the morning before appointments. Patients were picked up from their homes at either 11:30, 12:30 or 13:30 before training sessions. Considering one trip with the minibus took ~20 minutes, one exercise appointment took ~2 hours in total per group to complete. Patients were also given running shoes and a gift certificate at the local sports apparel store at inclusion to ensure that patients had the necessary equipment to attend training sessions.

Subjects

Sixty-eight patients' study eligibility were assessed prior to inclusion. After excluding 20 patients for not meeting inclusion criteria (n = 8), declining to participate due to lack of motivation (n = 10) and other reasons (n = 2), 48 outpatients (28 men, 35 ± 10 years; 20 women, 35 ± 12 years) aged 18-65 years old and diagnosed with schizophrenia spectrum disorders (schizophrenia, schizotypal or delusional disorders; ICD-10; F20-29) were included in paper I-IV. In paper I and II, we compared our outpatient group with 48 age- (± 2 years) and sex-matched healthy references recruited among employees and students at the University Hospital. Exclusion criteria were observation of contraindications to exercise testing (6) (terminal or life-threatening medical conditions, current pregnancy, mothers < 6 months post-partum, inability to carry out test procedures) and treatment at an acute psychiatric ward. The same exclusion criteria were used for the reference group, but also included diagnosis of severe mental illness. A physician assessed patients' study eligibility, and an experienced senior psychiatrist examined patients' diagnoses through medical records prior to inclusion.

Interventions

After inclusion, all 48 outpatients were randomised to one of the two following groups:

1) TG: Training sessions started and ended with 5 minutes warm-up and cool-down at ~70% of HR_{peak}. Patients performed 4 x 4 minutes of treadmill walking/running at 85-95% of HR_{peak} with 3 minutes active rest at 70% of HR_{peak} in between. Inclination

was set at ≥ 5% for the whole session. Treadmill sessions lasted 35 minutes and were done twice a week. This equalled 24 training sessions prior to 12-weeks testing in paper III. Excluding 4 weeks of testing, 96 sessions were done prior to 1-year testing in paper IV.

2) CG: Patients received two introductory training sessions (as described above) to learn the protocol and were advised to continue training on their own. These sessions were done at the clinic 1 and 4 weeks after inclusion.

Outcomes

Patients' psychiatric service utilisation prior to inclusion and medication status before and during this 1-year study were extracted from medical records. To assess patients' symptom severity, the positive and negative syndrome scale (PANSS) (37) was examined at inclusion by two PANSS-certified psychiatric nurses at the department.

Treadmill test: Peak oxygen uptake and walking efficiency

$\dot{V}O_{2peak}$ was assessed in paper I, III and IV while walking efficiency was assessed in paper II. All tests were conducted in our laboratory with the same equipment and procedures for all included subjects. Patients were familiarised with the treadmill (PPS Med, Woodway Gmbh, Germany) procedures before testing. A metabolic test device (MetaMax II, Cortex Biophysik Gmbh, Germany) was used to evaluate $\dot{V}O_2$ and respiratory parameters (total pulmonary ventilation, V_E; respiratory exchange ratio, RER) throughout the treadmill tests. An individualised protocol (26, 27, 30) was used, and subjects were instructed to start the test with 5 minutes warm-up at a velocity of 4.5 km · h^{-1} and 4% inclination. If unable to complete this workload, velocity was decreased by 1 km · h^{-1}. The mean $\dot{V}O_2$ over the last minute was used to calculate energy expenditure. External work accomplished and energy expenditure ($\dot{V}O_2$) were converted into kcal for the following calculation of walking efficiency (88):

$$(2)\ \text{Walking efficiency} = \frac{\text{External work accomplished } (\text{kcal} \cdot \text{min}^{-1})}{\text{Energy expenditure } (\text{kcal} \cdot \text{min}^{-1})} \cdot 100$$

After completing warm-up and walking efficiency measurements, the test progressed by increasing velocity by 0.5-1 km · h^{-1} or 2-3% inclination every 2-3 minutes until subjects reached exhaustion. $\dot{V}O_{2peak}$ was determined as the mean of the three highest measurements over 30 seconds, with V_E/RER calculated from the corresponding period. HR_{peak} (V800, Polar Electro, Finland) was determined as the highest heart rate observed at peak workload. Subjects were encouraged to maximise their effort throughout the test, and $\dot{V}O_{2peak}$ was accepted with an RER value ≥ 1.05 and/or the observation of a plateau in $\dot{V}O_2$ measurements at peak workload. To confirm maximisation of effort, patients repeated the test after 2-5 days if RER values were < 1.05. In paper IV, SV_{peak} was calculated from oxygen pulse ([$\dot{V}O_{2peak}$ / HR_{peak}] · 100) at peak workload.

Physical activity assessment

In paper I, triaxial accelerometers (wGT3X-BT, ActiGraph LLC, USA) were used to assess physical activity in patients with schizophrenia spectrum disorders. Software was device-specific (ActiLife v. 6.13.2) and used for all analyses. The device used was a light-weight hip-worn accelerometer able to detect movement in three axes (vertical, horizontal right-left and horizontal front-back) and record these accelerations at user-specified bouts (time intervals). Human locomotion is recorded through activity counts, thus by increasing physical activity and intensity, higher activity counts are recorded. Uniaxial and triaxial activity counts are commonly used in physical activity research, with the latter alternative detecting additional complexity to human locomotion specifically through measuring steps per day and counts per minute (85).

Patients were instructed to wear the accelerometer for a minimum of 1 week up to 4 weeks and only allowed to take the device off during showering or swimming. All patients who used the device for ≥ 4 days were included in analyses (80). Minimum wear time for a valid day was set at ≥ 10 hours per day. Sixty consecutive minutes with spike tolerance of 0-100 counts per 1-2 minutes was used to define non-wear. Twenty-four hours minus non-wear was used to determine wear time and bouts were set at 60 seconds (80). Uniaxial activity counts with predetermined cut-points were used to examine sedentary behaviour and physical activity

intensities and set at: sedentary, 0-99 counts; light intensity, 100-2019 counts; moderate intensity, 2020-5998 counts; vigorous intensity, ≥ 5999 counts.

Conventional CVD risk factor assessment

In paper I, body mass, body mass index (BMI), waist and hip circumference, blood pressure and smoking status were assessed in both patients with schizophrenia spectrum disorders and healthy references. In paper I, III and IV these risk factors were assessed in the patients along with fasting blood samples (glucose, triglycerides, high-density lipoprotein-(HDL), low-density lipoprotein-(LDL) and total cholesterol). BMI was calculated as body weight divided by height squared. Waist circumference measurements were taken between the cresta iliaca anterior superior and the margin of the lower rib, while hip circumference was measured around the widest part of the buttocks, both to the nearest cm (60). Blood pressure was examined using an auscultation device (ProBP 2400, Welch Allyn, USA) after 15 minutes rest while seated. Patients were only allowed to drink water the last 8 hours before blood samples were taken. A clinical chemistry system (ADVIA Chemistry XPT system, Siemens Medical Solutions Diagnostics Inc., Germany) was used to examine blood samples.

For definition of the presence of conventional CVD risk factors, the following criteria were used: obesity, BMI ≥ 30 kg · m^2; abdominal obesity, waist circumference ≥ 102 cm (men) and 88 cm (women); hypertension, systolic and/or diastolic blood pressure ≥ 140/90 mmHg; increased triglycerides, > 2.6 mmol · L^{-1}; elevated total cholesterol, > 6.1 mmol · L^{-1}, > 6.9 mmol · L^{-1} and > 7.8 mmol · L^{-1} in patients < 30, 30-49 and ≥ 50 years old, respectively; decreased HDL-cholesterol, < 0.8 mmol · L^{-1} (men) and < 1.0 mmol · L^{-1} (women); increased LDL-cholesterol, > 4.3 mmol · L^{-1}, > 4.7 mmol · L^{-1}, 5.3 mmol · L^{-1} in patients < 30, 30-49 and ≥ 50 years old, respectively; increased glucose, > 6.0 mmol · L^{-1} (60, 67).

Force-generating capacity: maximal muscle strength and rapid force development

In paper II, skeletal muscle FGC in the lower extremities was assessed through 1RM and rapid force development in both patients with schizophrenia spectrum disorders and healthy references. A 40º incline leg press apparatus (Hammer Strength HSLLP, Life Fitness, USA)

was used and subjects were familiarised with the procedures before testing. Each lift started from a position where the knees were extended, slow movement down to 90º angle in the knee joint with a short stop (< 1 s) before pressing to the starting position. Subjects' 1RM was obtained after 4-8 lifts. Subjects were given 3-minute rest periods between each lift. Load was increased by 5-20 kg for each attempt until unable to complete the lift. Maximal load completed was used as 1RM.

After completing the 1RM test, subjects proceeded to rapid force development assessment. Load during the rapid force development assessment was set at 70% of 1RM. With up to 3 minutes rest between each attempt, subjects were instructed to perform the leg press with a slow eccentric movement, a short stop (< 1 s) and maximal mobilisation in the concentric phase, emphasising reaching maximal intended velocity. The MuscleLab system (Ergotest Innovation AS, Norway) was used to examine time spent in the concentric phase, using the best attempt to calculate rapid force development. External force of each lift, work distance and lifting time were used to calculate rapid force development in $Nm \cdot s^{-1}$ (71).

$$(3)\ \text{Rapid force development} = \frac{(\text{Force} \cdot \sin(40)) \cdot \text{work distance (m)}}{\text{Lifting time (s)}}$$

in which force (N) = weight lifted (kg) $\cdot$ 9.81 m $\cdot$ s^2

Recommended procedures for allometric scaling was applied to compare subjects with different body mass (m_b) (96). Maximal muscle strength is proportional to muscle cross-sectional area (L^2) and body mass proportional to body volume (L^3); thus, 1RM was reported as scaled to m_b and $m_b^{2/3}/m_b^{0.67}$. Rapid force development was calculated from force (L^2) multiplied by distance (L) over time (L); thus, scaled to m_b and $m_b^{2/3}/m_b^{0.67}$.

Functional performance

In paper II, four different functional performance tests were conducted in both patients with schizophrenia spectrum disorders and healthy references. All functional performance tests

were done on the same day and in the following order: for the 6-minute walk test (6MWT) (81), subjects were instructed to walk as fast as possible for 6 minutes, without running, around two cones set 15 meters apart. Distance was measured in meters.

Subjects proceeded to the 30-second sit-to-stand test (30sSTS) (81). Starting from a seated position with arms folded across the shoulders, subjects were instructed to complete as many full stands as possible in 30 seconds. Number of completed full stands was documented and used for analyses.

The unipedal stance test was done without shoes (70). Subjects were instructed to keep their arms folded across the shoulders and balance on one foot for as long as possible up to 60 seconds. Each subject performed 3 attempts on each foot, alternating between each foot. The procedure was also done with eyes closed. The test with the longest stance with eyes open and closed was used for analyses. The following criteria to regain balance were used to stop a test: moving the standing foot, moving the inactive foot towards or away from the standing foot, using the arms, managing 60 seconds of stance or opening eyes during eyes-closed test.

For the stair climbing test, subjects were instructed to walk/run 18 steps as fast as possible up and down 3 times. The attempt was recorded in seconds. The staircase included a platform requiring an additional step to be completed. Subjects were required to use all steps, allowed to run and use the bannister to prevent falls.

Feasibility/adherence

In paper III and IV, patient retention/attrition throughout the studies was assessed. Attendance to the training sessions at the clinic were documented. Adherence to the AIT protocol was examined by documenting workload (velocity and inclination) and HR after 3 minutes during each treadmill interval. Patients randomised to the CG were asked to document the amount of exercise they had self-administered in a journal they were provided with at inclusion and asked if they had undertaken AIT on their own before 3 months, 6 months and 1-year testing.

Randomisation procedure

After inclusion, the Unit of Applied Clinical Research at the Norwegian University of Science and Technology provided the computer-based method for randomisation to ensure blinded allocation of patients. Patients were randomised to either the TG or CG interventions in a 1:1 ratio.

Statistical analyses

Data in tables are mean ± standard deviation if normally distributed, median and range if found to deviate from normality, and mean ± standard error in figures. Q-Q plots and Kolmogorov-Smirnov test of normality were used to examine data distribution while statistical significance was set at 0.05 (two-tailed) for analyses.

Paper I-II: Independent samples t-tests (continuous variables) and chi-square tests (categorical variables) were used to assess intergroup differences. Association between variables were assessed with Pearson correlation coefficient.

Paper III-IV: To reduce likelihood of type I error and due to equal and random allocation of patients, no assessment of intergroup differences at baseline was done. Inter- and intragroup differences were examined following the intention to treat principle using repeated measures linear mixed models for primary analyses. The estimation method of restricted maximum likelihood was used with outcome measures the dependent variables, time and group as fixed effects and patients as random effects. Least significant difference correction method was used. To assess if data were missing at random, Little's MCAR test was applied. In paper III, success criterion for feasibility assessment was set at 60% patient retention, and further per protocol analyses on treadmill test variables were conducted with ANCOVA, categorising patients in the TG as high or low adherers to the training protocol if they had completed ≥ or < 70% of the AIT sessions as described in the protocol. In paper IV, to compare the number of patients in each group (TG and CG) who exercised regularly in accordance with the AIT protocol, Fisher's exact test was used.

Power calculations were done prior to paper I, III and IV using a statistical power of 0.8. In paper I, to observe a difference in $\dot{V}O_{2peak}$ of 0.375 L · min^{-1} compared to the healthy references, expecting a similar-sized standard deviation, including a minimum of 17 men and 17 women with schizophrenia spectrum disorders was required. In paper III and IV, to observe a difference in $\dot{V}O_{2peak}$ between the TG and CG of 0.350 L · min^{-1} at post-tests (30), assuming a standard deviation of 0.220 L · min^{-1}, we needed 8 patients in each group to complete the interventions. To strengthen the foundation of interpretation by improving generalisability, and to counter the relatively high number of expected drop-out (drop-out rates of > 30% are commonly observed in exercise interventions in patients with schizophrenia (17)), we included 28 men and 20 women with schizophrenia (TG, 25; CG, 23).

For analyses across papers, Pearson correlation coefficient was used to examine association between daily physical activity (steps per day, counts per minute and physical activity intensity) and allometrically scaled 1RM and rapid force development.

Summary of results

Paper I. A comprehensive cardiovascular disease risk profile in patients with schizophrenia.

1. Absolute and relative $\dot{V}O_{2peak}$ were lower in men (absolute: 1.06 L · min^{-1}, 25%; relative: 12.9 mL · kg^{-1} · min^{-1}, 27%; both $p < 0.01$) and women (absolute: 0.32 L · min^{-1}, 13%, $p < 0.05$; relative: 11.5 mL · kg^{-1} · min^{-1}, 30%, $p < 0.01$) with schizophrenia compared to healthy references.
2. Men (16 b · min^{-1}, 9%, $p < 0.01$) and women (18 b · min^{-1}, 10%, $p < 0.01$) with schizophrenia displayed reduced HR_{peak} compared to healthy references.
3. In all patients, vigorous physical activity was associated with $\dot{V}O_{2peak}$ ($r^2 = 0.21$, $p < 0.05$), while daily physical activity (steps per day and counts per minute) was not.
4. The same relationships were present in men with schizophrenia, where only vigorous physical activity associated with $\dot{V}O_{2peak}$ ($r^2 = 0.24$, $p < 0.05$).
5. The opposite was observed in women with schizophrenia, where daily physical activity was associated with $\dot{V}O_{2peak}$ (steps per day, $r^2 = 0.26$; counts per minute, $r^2 = 0.25$; both $p < 0.05$), while vigorous physical activity was not.
6. Our patient group was categorised as overweight (BMI, 26.0 ± 6.1 kg · m^2; waist circumference, 103 ± 17 cm).
7. More men with schizophrenia were current smokers ($\chi^2 = 5.6$, $p < 0.05$) compared to healthy references, while this was not observed in the women with schizophrenia.
8. Mean blood pressure was below hypertension levels, and cholesterol, triglycerides and glucose were within healthy reference limits for our patient group.

Paper II. Patients with schizophrenia have impaired muscle force-generating capacity and functional performance.

1. In men, 1RM allometrically scaled ($m_b^{0.67}$: 19%, $p < 0.01$) and expressed relative to body mass (m_b: 19%, $p < 0.01$) was lower in patients with schizophrenia compared to

healthy references, as was rapid force development ($m_b^{0.67}$: 30%; m_b: 30%, both $p < 0.01$).

2. In women, 1RM allometrically scaled tended ($m_b^{0.67}$: 13%, $p = 0.067$) to be lower in patients compared to healthy references, while was lower expressed relative to body mass (m_b: 19%, $p < 0.01$), as was rapid force development ($m_b^{0.67}$: 25%; m_b: 30%, both $p < 0.01$).
3. Patients with schizophrenia displayed systematically poorer functional performance scores (walking efficiency, 14%; 6MWT, 22%; 30sSTS, 48%; unipedal stance eyes open, 20%; eyes closed, 73%; stair climbing, 63%; all $p < 0.01$) compared to healthy references.
4. Both allometrically scaled 1RM and rapid force development were associated with all functional performance tests (all $p < 0.01$) and defined daily dose of antipsychotic medication (both $r = -0.36$, $p < 0.05$).

Paper III. Aerobic interval training in standard treatment of outpatients with schizophrenia: a randomised controlled trial.

1. Sixty-four percent of patients randomised to the TG completed this 12-week intervention.
2. TG patients improved both their absolute (0.27 ± 0.33 L · min^{-1}) and relative (3.1 ± 3.7 mL · kg^{-1} · min^{-1}) $\dot{V}O_{2peak}$ by 10% (both $p < 0.01$) after 12 weeks, accompanied by a 14% increase in peak treadmill workload (17 ± 21 watts, $p < 0.05$), while no change in controls was observed.
3. At post-test, patients categorised as high adherers displayed higher absolute (0.25 ± 0.32 L · min^{-1}, $p < 0.05$) and relative (3.0 ± 3.6 mL · kg^{-1} · min^{-1}, $p < 0.05$) $\dot{V}O_{2peak}$ compared to controls.
4. Patients categorised as low adherers also displayed higher relative (2.4 ± 3.8 mL · kg^{-1} · min^{-1}, $p < 0.05$) $\dot{V}O_{2peak}$ and absolute $\dot{V}O_{2peak}$ tended (0.15 ± 0.33 L · min^{-1}, $p = 0.17$) to be higher compared to controls after 12 weeks.
5. After 12 weeks, no difference between the TG and controls in conventional CVD risk factors was observed; however, body weight (1.9 ± 4.0 kg, $p < 0.05$) and BMI (0.5 ± 1.1 kg · m^{-2}, $p < 0.05$) increased in the controls, with no change in the TG present.

Paper IV. One-year aerobic interval training in outpatients with schizophrenia.

1. In the TG, both absolute (12-weeks: 0.24 ± 0.25 L · min^{-1}, 9%; 6-months: 0.27 ± 0.24 L · min^{-1}, 10%; 1-year: 0.22 ± 0.25 L · min^{-1}, 8%; all $p < 0.01$) and relative (12-weeks: 2.7 ± 3.1 mL · kg^{-1} · min^{-1}, 9%; 6-months: 3.2 ± 3.0 mL · kg^{-1} · min^{-1}, 10%; 1-year: 3.3 ± 3.1 mL · kg^{-1} · min^{-1}, 11%; all $p < 0.001$) $\dot{V}O_{2peak}$ increased from baseline.
2. In contrast, in the CG only relative $\dot{V}O_{2peak}$ decreased from 6-months to 1-year (-1.8 ± 3.8 mL · kg^{-1} · min^{-1}, 6%, $p < 0.05$).
3. One-year heart effects revealed that HR_{peak} increased (3 ± 7 b · min^{-1}, $p < 0.05$) and decreased (-3 ± 7 b · min^{-1}, $p < 0.05$) in the TG and controls, respectively, while SV_{peak} tended (0.87 ± 2.15 mL · b^{-1}, $p = 0.12$) to be higher in the TG than controls.
4. Conventional CVD risk factors did not change in either group.
5. One-year rates regarding regular AIT were 15/25 in the TG (difference compared to controls: $p < 0.0001$), returning a 60% completion rate, and 0/23 in the controls.

Results across papers

1. In all patients, vigorous physical activity was associated with allometrically scaled 1RM ($r^2 = 0.12$, $p < 0.05$). This association was not present when analysing sexes separately, and no other association between daily physical activity and 1RM or rapid force development was observed.

Discussion across papers

The papers in this thesis examined factors key to physical health, and the effects of AIT delivered through a collaborative treatment model specifically tailored to target aerobic capacity and adherence to training in outpatients with schizophrenia spectrum disorders. The main findings were that men and women with schizophrenia displayed systematically reduced $\dot{V}O_{2peak}$ values and lower leg press FGC compared to healthy references, indicating accelerated aging. Furthermore, the poor functional performance observed in the patients, measured as walking efficiency, 6MWT, 30sSTS, balance tests and stair climbing were associated with 1RM and rapid force development. Daily physical activity was weakly and inconsistently associated with $\dot{V}O_{2peak}$ and FGC, and while the patient group was classified as overweight (BMI, 26.0 ± 6.1 kg · m^2; waist circumference, 103 ± 17 cm) with high number of smokers, mean blood pressure and lipids/glucose were within healthy limits. AIT, delivered through the collaborative outpatient treatment model, improved $\dot{V}O_{2peak}$ by 10% in 12 weeks and maintained it throughout the 1-year study. In contrast, control group patients receiving an introduction to AIT and advice to comply with the training increased their body weight after 12 weeks and decreased their $\dot{V}O_{2peak}$ (6%) from 6-months to 1-year. Patient retention in the TG after 1-year was only marginally lower than after 12 weeks (60 vs. 64%), and while 15 out of 25 TG patients regularly performed AIT throughout the year, not one patient (0/23) in the CG performed AIT on their own. Taken together, our studies suggest that not only are patients with schizophrenia high at risk of CVD and premature mortality, but also that AIT, delivered through collaborative care, is feasible and effective for attenuating this risk in the short and long term.

Physical health in patients with schizophrenia

Aerobic capacity

In paper I, we revealed that $\dot{V}O_{2peak}$ was 27% and 30% (~3 METs) lower in men and women with schizophrenia spectrum disorders, respectively, compared to our age- and sex-matched healthy reference group, and that 87% of our patient group displayed reduced $\dot{V}O_{2peak}$ by 1 MET (3.5 mL · kg^{-1} · min^{-1}) compared to the level commonly observed in the general population (13), in line with our hypothesis. Directly measured treadmill $\dot{V}O_{2peak}$ in our patients was similar to a previous and somewhat smaller study from our group, utilising the

same protocol (25). Although the degree to which $\dot{V}O_{2peak}$ is reduced in patients with schizophrenia has been of debate, our results are similar to other studies, documenting reduced $\dot{V}O_{2peak}$ through direct testing using treadmill and ergometer cycle protocols (34, 73). Our results are strengthened by the inclusion of direct treadmill testing in a relatively large group of outpatients diagnosed with schizophrenia. However, notably, values as low as 19 and 14 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} in obese men and women, respectively, with schizophrenia have been observed (73). This difference may be caused by some patient populations being even more untrained compared to our cohort. It may also be impacted by application of cycle ergometers during testing, known to underestimate $\dot{V}O_{2peak}$ by 5-20% (32). Given that low $\dot{V}O_{2peak}$ has been documented previously, and the fact that patients with schizophrenia have 15-20 years reduced life expectancy mainly through CVD, the poor aerobic capacity observed in our patient cohort is unsurprising. It is also noteworthy that the ~3 METs lower $\dot{V}O_{2peak}$ puts our patient group both high at risk of developing CVD and early death and on par with what is typically expected from 60-65-year-old men and women (13).

The low $\dot{V}O_{2peak}$ in our patients confirmed that the cohort should be regarded as untrained. Interestingly, ~10% lower HR_{peak} was observed in both men and women with schizophrenia compared to the healthy references. Referring to the Fick equation, the low HR_{peak} observed likely impacted $\dot{Q}$, and thus $\dot{V}O_{2peak}$. Since different limitations to sustained whole-body exercise between trained and untrained subjects exist, namely central haemodynamic and local muscle oxidative capacity respectively (22), it is possible that the low HR_{peak} was caused by physiological impairment often seen with aging (72). Another potential mechanism may be psychological factors and the difficulty in reaching exhaustion during the treadmill test, even though patients were encouraged to provide maximal effort and no difference in RER was observed between groups. It should also be noted that some patients included in this study underwent clozapine treatment, previously shown to increase resting adrenergic stimulation and heart rate, which in turn may cause autonomic dysregulation (94). Although 20 out of 48 patients were current smokers, $\dot{V}O_{2peak}$ was not different between smokers and non-smokers, and was thus unlikely to have been influenced to any large extent by this factor. Nevertheless, the close link between heart function and $\dot{V}O_{2peak}$ suggests that the poor aerobic capacity is a central component driving the high risk of CVD development in this patient group.

Force-generating capacity

In paper II, we documented for the first time that lower extremity FGC was reduced compared to healthy references. We observed reduced allometrically scaled 1RM (19%) and rapid force development (30%) in men with schizophrenia, while in the women rapid force development was reduced (25%) and 1RM tended (13%) to be lower compared to the reference group. Maximal muscle strength and rapid force development are previously undocumented in this patient group, and our results are strengthened by the inclusion of a relatively large group of patients who undertook direct measurements of FGC in the functionally relevant lower extremities utilising a leg press device. Approximately 10% reduced muscle strength has previously been demonstrated per decade of aging (44). The ~15% lower muscle strength observed in our patient group is associated with 15 years of aging and, taken along with the low aerobic capacity from paper I, this supports the suggestion of accelerated aging in patients with schizophrenia. Our findings are in line with a previous study indicating reduced FGC through attenuated standing broad jump distance in this patient group (82). The attenuated FGC observed in the patients may be partly due to both neuromuscular alterations such as muscular atrophy, elevated action potential and lower number of motor units previously documented in patients with schizophrenia (8, 21, 23). Interestingly, in paper II an association between defined daily dose of antipsychotic medication and allometrically scaled maximal muscle strength and rapid force development was observed. Although antipsychotic medical treatment has previously shown to impact the neuromuscular system (42), the association between dose of antipsychotics and FGC has not been documented before, and this observation suggests that patients more heavily medicated than others are more likely to experience reduced FGC in the functionally relevant lower extremities and its potentially debilitating consequences.

Implications for functional performance

The patients' reduced $\dot{V}O_{2peak}$ and muscle FGC observed in paper I and II suggests that ADLs are likely to either be experienced as more strenuous and less manageable than by their healthy counterparts, since ADLs will require a larger portion of the available capacity, or patients will be unable to successfully conduct these ADLs at all. In line with this notion, we observed a systematically attenuated functional performance compared to the healthy

references in paper II. In fact, some of the patients were, somewhat alarmingly, unable to conduct all functional performance tests on the same day as they were experienced as highly vigorous. In paper II, an association was also observed between all functional performance tasks and both allometrically scaled 1RM and rapid force development, in accordance with our hypothesis. As FGC is well recognised to influence the ability to conduct ADLs in humans (3, 76), this association was as expected. Furthermore, increased FGC following maximal strength training has shown to improve work efficiency in healthy adults (57) and patients with schizophrenia (28), consequently affecting aerobic endurance performance as well. This in turn underlines that both aerobic capacity and FGC, particularly in the functionally relevant lower extremities, are both important contributing factors for disability prevention in patients with schizophrenia.

Aerobic capacity, force-generating capacity and physical activity

In paper I, and results across papers utilising measures of FGC produced for paper II, daily physical activity was weakly and inconsistently associated with $\dot{V}O_{2peak}$ and allometrically scaled maximal muscle strength, but not rapid force development. Associations were observed between daily physical activity, measured as steps per day and counts per minute, and $\dot{V}O_{2peak}$ in women with schizophrenia. However, these associations were relatively weak (r^2 = ~0.25) and not observed in men with schizophrenia. Further, vigorous physical activity was associated with $\dot{V}O_{2peak}$ in men. Again, this association was relatively weak (r^2 = ~0.25) and not observed in the women. Our results are similar with previous studies reporting similar observations in both healthy adults and older subjects (12, 85). This may be due to daily physical activity not necessarily being conducted at an appropriate format, intensity or duration required to realise high aerobic intensity and thus elicit adaptations in oxygen transport organs (30, 53, 72).

The only association between daily physical activity and muscle FGC observed was between vigorous physical activity and allometrically scaled 1RM (r^2 = 0.12) in all patients, albeit this relationship was not present when analysing sexes separately. Considering both the specificity and overload principles, in order to improve skeletal muscle FGC exercise must be of an appropriate format and load sufficient to stress the neuromuscular system (69). Since the patient group was categorised as both overweight and untrained, it is possible that some

compensatory response in maximal muscle strength from vigorous physical activity may have occurred. However, as the directionality of this association cannot be established, the weak association observed and its disappearance when analysing sexes separately, the contribution of physical activity for FGC improvements is questionable at best. Thus, it is unlikely that the physical activity undertaken by the patients at the time of measurement was of a format or intensity sufficient to elicit adaptations in either $\dot{V}O_{2peak}$ or lower extremity FGC.

Conventional cardiovascular disease risk factors

Our patient group was categorised as overweight by BMI and waist circumference assessment, and more men with schizophrenia than healthy references were current smokers in our study. In contrast to our hypothesis, this was not mirrored in other conventional risk factors commonly measured such as blood pressure, cholesterol, triglyceride and glucose levels outside healthy reference limits. Given that physical health and exercise as treatment has been part of clinical care in psychiatry for some time (20, 25, 54), it is possible that the Scandinavian health care system is more aware of the excess health risks in these patient groups. Although the high risk of CVD and premature mortality is well established in patients with schizophrenia, this does not seem to be well reflected in the current blood pressure measurements or blood samples. Thus, it is possible that routine clinical care considering these factors in isolation may not necessarily assess this risk accurately when screening for the potential development of CVD in this patient group.

Effects of aerobic interval training in the short and long term

In accordance with our hypotheses, the TG receiving collaborative care improved $\dot{V}O_{2peak}$ by 9% after 12-weeks and maintained it throughout the study intervention (6-months: 10%; 1-year: 11%). The improvement from inclusion up to 12-weeks was calculated as 0.5% (12 mL $\cdot$ min^{-1}) per session or 0.7% (18.5 mL $\cdot$ min^{-1}) per session in accordance with the protocol. Our group's previous study in inpatients with schizophrenia observed an increase of similar size (0.6% per session; 19.1 mL $\cdot$ min^{-1}) after 8-weeks (26). Recognising that facilitating high compliance to training may be particularly difficult in this patient group, as evident by the decreased $\dot{V}O_{2peak}$ observed from 6-months to 1-year in the CG, it is very encouraging that patients diagnosed with schizophrenia are able to maintain their aerobic capacity above the

baseline level over such a long period of time. However, since our TG's $\dot{V}O_{2peak}$ was still below the level commonly observed in healthy adults (13), increasing the training frequency from 2 to 3 times per week to elicit further improvements could have been an interesting and actionable strategy, especially given the relatively low risk of drop-out demonstrated by low patient attrition from 12-weeks to 1-year.

The ~1 MET increase in $\dot{V}O_{2peak}$ following 1-year of AIT has previously shown to decrease risk of developing CVD by 15% and all-cause mortality by 12-13% (38, 49). Given that aerobic capacity declines with aging, the improvement observed also implies that the outpatients in the TG may be compared to 50-55-year-old healthy references (13), a reduction of 10 years after 1-year of AIT. This will likely have implications for physical health, aerobic endurance performance and disability prevention, as evident through the increased peak workload in paper III, since patients will consequently use a smaller portion of their aerobic capacity to perform ADLs.

After 1-year, HR_{peak} increased and decreased (2%) in the TG and CG, respectively, while SV_{peak} tended to be higher (5%) in the TG. The improvement observed in $\dot{V}O_{2peak}$ for the TG was likely due to higher $\dot{Q}$, as demonstrated previously (14). However, the increase in HR_{peak} is in contrast to the decline often observed following endurance training in healthy adults (95). This may be due to different limitations to aerobic capacity observed in subjects with different training status (22). Our patients' low baseline $\dot{V}O_{2peak}$, taken together with the increased HR_{peak}, suggests that the TG patients were less limited by these peripheral factors after 1-year of AIT and subsequently more capable of taxing the oxygen transport system.

In paper III, patients randomised to the CG increased their body weight (1.9 kg) and BMI (0.5 kg $\cdot$ m^{-2}) after 12-weeks, while no change in the TG was observed throughout this 1-year study. Mortality rates seem to be similar in obese and non-obese subjects with high $\dot{V}O_{2peak}$ (46), suggesting that weight status may not necessarily be as important as other risk factors to the development of CVD. However, other aspects such as experiencing reduced health-related quality of life, physical and social function, vitality, self-esteem and increased pain and public distress have been reported with weight gain in patients with schizophrenia (4,

39). It is thus possible that adherence-supported AIT may protect against both body composition alterations and unfavourable changes in experienced physical and mental health.

Feasibility and adherence

After 12-weeks and 1-year, respectively, patient retention rates were 64% and 60% in the collaborative care TG and 78% and 74% in the CG. Further, while all remaining patients in the TG regularly performed AIT at the clinic after 1-year, not one single patient in the CG continued to exercise on their own between 6-months and 1-year. In line with our hypotheses, our results indicate that the collaborative treatment model involving specialised and municipal health care services, specifically developed for this outpatient group, was feasible both in the short and long term, and yielded higher adherence to training than an introduction to AIT coupled with advice to continue training. Notably, although most of our patients experienced a range of positive, cognitive and negative symptoms, patient retention was preserved from 12-weeks to 1-year but for one patient in each group unwilling to continue participating in the study. The drop-out rates were marginally higher than the mean 33% drop-out reported from a meta-analysis of training studies lasting from 1.5 to 6-months in patients with schizophrenia (17), suggesting that adherence to training may remain high throughout long-lasting studies if interventions are adequately tailored to the patients' needs.

Patient retention and adherence to training remained relatively high throughout this 1-year intervention even though the treadmill intervals were done at a high aerobic intensity. Higher adherence to training has been reported in exercise interventions with high intensities compared with low-to-moderate intensities in patients with schizophrenia (84), possibly due to AIT being highly effective for improving aerobic capacity (30). In accordance with our study aim, providing transportation and supervision likely facilitated adherence, factors previously proposed as key to ensure compliance to training interventions in patients with schizophrenia (74, 84). It is thus unlikely that the efficacy of AIT alone is sufficient for maintaining training adherence, underpinned by the decreased $\dot{V}O_{2peak}$ observed from 6-months to 1-year in the CG. This may not only be unsurprising, but also an important observation. While patients with schizophrenia are less physically active compared to the general population, > 50% of the patients have been shown to comply with the recommendation of 150 minutes moderate physical activity per week (75). However, as

observed in study I and IV in this thesis, $\dot{V}O_{2peak}$ was low at inclusion and decreased from 6-months to 1-year in the CG, and daily physical activity was weakly and inconsistently associated with $\dot{V}O_{2peak}$. This suggests that the increasing number of advices and information regarding the importance of physical activity and exercise alone may not be enough (1, 75, 93), and that AIT should be delivered via a collaborative effort with adherence support in the long term to improve this factor key to physical health.

Of note, although adherence to AIT remained relatively high throughout the study, if a strict categorisation based on the completion of all four intervals and reaching targeted training intensity during all intervals is applied, only 41% of the sessions were conducted according to protocol. This may be due to both the long duration of our intervention and its implementation in an outpatient setting, both previously suggested to influence training adherence in patients with schizophrenia (64, 84). However, in paper III, $\dot{V}O_{2peak}$ increased both in patients with high and low adherence to the training protocol, with little difference observed between these subgroups. It is possible that both the untrained status in our patients, the effectiveness of the AIT protocol and statistical power influenced this lack of difference (30, 87). Importantly, it should be noted that the training supervisors at the clinic always sought to encourage patients to maximise their effort during the intervals and to do their best to comply with the number and intensity of intervals, likely an important factor yielding increased $\dot{V}O_{2peak}$ even in the presence of imperfect AIT adherence.

Practical considerations

Some patients had difficulty completing the treadmill test. The test required patients to walk or run to exhaustion with a mask tightly wrapped around their face. Exercising at such an intensity was unfamiliar to most patients, and produced a sense of anxiety in some, which may be because symptoms of anxiety and vigorous exercise may be experienced as rather similar. Quite a few patients thought the mask would limit their oxygen availability and, taken together with pre-existing anxiety in some cases, this required extra flexibility in the manner the tests were conducted to complete them. For instance, four of the patients required a cognitive behavioural therapy-like approach to the treadmill test (which one of the physiologists had experience with), starting with only wearing the mask off the treadmill ramp and, after a while, increasing gradually from warm-up to vigorous treadmill walking.

This approach was not only necessary for including these patients in the study, but arguably also strengthened our cohort's representability and, in turn, our study generalisability.

In our experience, using the diary and a small piece of paper describing the protocol taped to every treadmill were important to streamline the process of delivering the training in the clinic. Even though a couple patients expressed that the training could be somewhat tedious at times during this 1-year study, the majority seemed to like the fact that the training was rather uncomplicated and similar from session to session. Only minor adjustments were done from one session to another by increasing velocity (0.1 km $\cdot$ h^{-1}) and/or inclination (1%) to facilitate progression and control intensity with improving fitness. Of note, in some cases the health care professional supervising the training took the liberty of standing beside patients who might require extra encouragement to continue their effort, while at the same time documenting heart rate and treadmill workload. This was possible due to this relatively resource-effective way of instructing patients during training.

Although the support, through supervision at the clinic and transportation and phone communication from municipal health service, certainly was comprehensive, it was arguably also quite necessary, as evident by the lack of self-administered training in the CG. The municipal health care professional taking part in this project was essential for facilitating compliance both with training and testing at the clinic. This person not only transported patients to the clinic, but also tailored her approach to the needs of the patients, such as sending text messages and calling to remind patients of their appointments or motivating them when necessary. This close and rather vigilant approach to meeting patients where they were, physically and psychologically, was likely important for this collaborative care approach to work properly. We certainly recognise that these are not documented or systematic observations from any of the publications, but more practical considerations based on experiences in the clinic for the past 3 years while conducting this project, which may be valuable information if such a protocol is implemented in future studies.

Thesis limitations

This was a single-centre study; thus, including multiple clinics and municipalities would potentially improve generalisability and external validity of our results. Further, the potential for selection bias towards exercise intervention studies is impossible to eliminate. However, all patients that were eligible were asked to participate and the randomised design would ensure that any disparities are equally distributed among the groups. To further examine the mechanisms for the improvements in aerobic capacity, directly measuring SV and local muscle oxidative capacity in vivo or in vitro would certainly have been of interest. However, including these measures would likely have been very ambitious, as they require expensive equipment, expertise, and motivated patients familiarised with an even greater range of procedures in addition to the test battery already included in the project. In paper IV, we included data on adherence to AIT in the CG. This was done through assessment of training diaries and by asking patients if they had conducted AIT on their own since the last test period, although it may be difficult for patients with schizophrenia spectrum disorders to accurately recall and document regular exercise training.

Implications and future perspectives

In paper I and II, we revealed reduced $\dot{V}O_{2peak}$ and lower extremity skeletal muscle FGC in the patients compared to the healthy references. As both are key elements in prevention of disability, CVD and premature mortality, assessing these factors should be part of routine clinical care. Directly measuring $\dot{V}O_{2peak}$, the gold standard for aerobic capacity examination, is resource demanding, hence conducting such tests is not always feasible in the clinic. This has led to the development of less resource-demanding indirect methods of estimating $\dot{V}O_{2peak}$ through maximal, submaximal and non-exercise test procedures (65). Maximal test protocols seem to provide the most valid and reliable alternatives to direct measures for estimating $\dot{V}O_{2peak}$ (65). Submaximal test procedures require less exertion from subjects and may be easier to conduct, and non-exercise estimations require subjects only to answer questionnaires. Although both may provide information beneficial for clinicians when used to assess risk of developing CVD, these measures are less robust and results should be interpreted with caution (65). In turn, results may be contrasted to what is commonly observed in healthy references (13).

In future studies, developing less resource-demanding methods of estimating aerobic capacity for CVD risk assessment is warranted. Furthermore, assessing the effects of increasing training frequency from 2 to 3 sessions per week on aerobic capacity and other established CVD risk factors would be of interest, particularly due to the low risk of further drop-outs. However, some issues regarding AIT adherence remains, as 41% of sessions were done per protocol, and 90% of the drop-out from the TG occurred between randomisation and the 12-weeks follow-up. Additional motivational aspects seeking to improve adherence during this period should be considered and exploring the feasibility and potential effects of including motivational interviewing, for instance, would certainly be of interest. Improving motivational aspects may also have implications for more cost-effective exercise training delivery with less adherence support, which would be beneficial for the application of AIT at more clinics across health care systems.

It would also be interesting to evaluate patients' physical health 1-year after study completion to explore if patients were able to maintain training on their own after participating in a treatment model with such comprehensive adherence support as in our study. Furthermore, while we examined patients' use of psychiatric services prior to study inclusion, we did not assess this during this 1-year study. Therefore, assessment of the potential effects on psychiatric service utilisation and hospitalisation both throughout the intervention and 1-year after study completion may certainly be a topic of further research. Additionally, as aerobic capacity has previously shown to be the strongest predictor of CVD and early death, the potential implications of improved long-term $\dot{V}O_{2peak}$ on incidence of CVD, mortality and disability, and subsequently a financial burden assessment, may be of great importance.

Conclusions

$\dot{V}O_{2peak}$ was 27% and 30% lower in men and women diagnosed with schizophrenia spectrum disorders, respectively, compared to healthy references. We also found FGC, measured as 1RM and rapid force development, in the functionally relevant lower extremities to be attenuated in the patients by 19% and 30% in the men and 13% and 25% in the women, respectively. Performance in functional tasks developed to reflect ADLs was also systematically reduced in the patients, measured as walking efficiency (14%), 6MWT (22%), 30sSTS (48%), unipedal balance with eyes open (20%) and closed (73%) and stair climbing (63%), and these performance levels were found to associate with 1RM and an rapid force development. Interestingly, although measuring daily physical activity is generally fronted as a simple and logical indication of health-related outcomes, it was weakly and inconsistently associated with both $\dot{V}O_{2peak}$ and FGC, suggesting its application in CVD risk and physical health assessment may be questioned. Furthermore, many of the included patients were overweight and current smokers. However, in contrast to our hypothesis, blood pressure, blood lipids or glucose levels were within healthy reference limits.

Our study revealed that 12 weeks of AIT, delivered through the collaborative care model, was feasible as 64% of outpatients randomised to this group completed the study. Outpatients in the TG improved $\dot{V}O_{2peak}$ by 10% after 12 weeks, and the improvement was present in patients with both high and low adherence to the training protocol. $\dot{V}O_{2peak}$ was maintained from 12 weeks to 1-year in the TG, returning a 60% completion rate and high training adherence. In contrast, the CG, where patients received an introduction to AIT and advice to continue training on their own, displayed increased body weight (1.9 kg) and BMI (0.5 kg $\cdot$ m^{-2}) after 12 weeks, and reduced $\dot{V}O_{2peak}$ (6%) from 6-months to 1-year. All outpatients in the CG stopped training from 6-months to 1-year. Our studies showed that AIT delivered through a collaborative outpatient treatment model involving specialised and municipal health services is feasible and yields important improvements in aerobic capacity that potentially may reduce the high risk of disability, CVD and premature mortality. Introducing patients to AIT and advising them to comply with the protocol and act on their own initiative is, however, insufficient to combat this risk in outpatients with schizophrenia.

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