The TOPFIT study

‘The Outcome of Psychosis and Fitness Therapy’

The studies described in this thesis were performed at the Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, the Netherlands.

The TOPFIT study was financially supported by the Dutch Diabetes Research Foundation, (2007.00.040), Lilly Pharmaceuticals, Houten, the Netherlands (Ho01- TOPFIT), Janssen Pharmaceuticals, Tilburg, the Netherlands, and the Dutch Psychomotor Therapy Foundation, Utrecht, the Netherlands.

Publication of this thesis was financially supported by the Rudolf Magnus Institute of Neuroscience and the Federatie Vaktherapeutische Beroepen, Utrecht, the Netherlands.

Cover design:	Krista van der Horst, Thomas Scheewe & Logo Huis
Design:	Marlene Marlet (M Tekst & Beeld, Bunnik)
Printed by:	Ipskamp Drukkers, Enschede, the Netherlands

ISBN 978-94-6191-477-4

The TOPFIT study

‘The Outcome of Psychosis and Fitness Therapy’

De TOPFIT studie

‘Het beloop van psychose in relatie tot fitnesstherapie’

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op donderdag 13 december 2012 des ochtends te 10.30 uur

door

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geboren op 22 december 1976
te IJsselstein

Promotoren: Prof. dr. R.S. Kahn
Prof. dr. F.J.G. Backx

Co-promotoren: Dr. W. Cahn
Dr. T. Takken

‘..Il y a du bon en tout mouvement’

[‘..there’s some good in all movement’]

Vincent van Gogh, Brieven aan zijn broeder. Deel 1 (ed. J. van Gogh-Bonger). Mij. voor goede en goedkoope lectuur, Amsterdam 1914.

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General introduction

Introduction

The studies conducted in this thesis are the result of the TOPFIT study, an acronym for 'The Outcome of Psychosis and Fitness Therapy' study. In style, the acronym was thought of while biking home from the University Medical Center Utrecht with a colleague psychomotor therapist. The aim of the studies presented in this thesis is threefold. First, to explore differences in physical activity, cardiorespiratory fitness, and energy intake between patients with schizophrenia and matched, healthy control subjects. Second, to examine whether exercise therapy can improve mental and physical health of patients with schizophrenia. Third, to investigate whether exercise therapy is able to attenuate the progressive brain volume loss found in patients with schizophrenia.

Schizophrenia

Schizophrenia is a heterogeneous illness with varying manifestations across patients but the effect of the illness is often severe and it is therefore generally considered the most devastating, chronic psychiatric illness.[1] In general, schizophrenia is characterised by a disruption of thought processes, emotion, perception, reality testing, and behaviour. Schizophrenia symptoms manifest themselves along two symptom dimensions: positive (psychotic) symptoms and negative symptoms. Positive symptoms refer to an excess of normal functioning and consist of hallucinations (false perceptions), delusions (false believes), and disorganised thinking. These symptoms are commonly present during (recurrent) psychotic episodes. The negative symptoms, such as blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation) are often present before, during, and after psychotic episodes. Lastly, patients with schizophrenia often suffer from cognitive symptoms, in example (working) memory, attention, concentration, and executive functioning (planning and organisation of behaviour) deficits. In clinic and research, the "Diagnostic and Statistical manual of Mental Disorders-IV-TR" (DSM-IV) criteria for schizophrenia are most widely used.[2] For a diagnosis of schizophrenia, DSM-IV requires a disturbance in one or more major areas of functioning (i.e. work, interpersonal relations or self-care), markedly below the level achieved prior to the onset (criteria for schizophrenia: see **Table 1**).

Table 1. Diagnostic criteria for schizophrenia, according to DSM-IV.[2]

A. **Characteristic symptoms:** Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. delusions
2. hallucinations
3. disorganised speech (e.g., frequent derailment or incoherence)
4. grossly disorganised or catatonic behaviour
5. negative symptoms, i.e., affective flattening, alogia, or avolition

B. **Social/occupational dysfunction:** For a significant portion of time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. **Duration:** Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. **Schizoaffective and mood disorder exclusion:** schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive episode, manic episode, or mixed episode have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. **Substance/general medical condition exclusion:** The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. **Relationship to a pervasive developmental disorder:** If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

(Adapted from Diagnostic and Statistical Manual of Mental Disorders, 4th ed.)[2]

Epidemiology

The lifetime risk of developing schizophrenia varies between studies but has been estimated around 0.7%.[3] Whereas the first disease symptoms in males generally manifest themselves around the age of 15 to 30 years old, with a peak between the age of 20 to 25 years old, the average age of onset in females is around 30 years old.[4] Men have a 1.4 increased relative risk to develop the illness compared to women.[3,5]

Etiology

Although the etiology of schizophrenia remains largely unknown it is generally accepted that schizophrenia is determined for a large part by genetic factors, but environmental factors such as obstetric complications,[6] cannabis use,[7] high degree of prenatal infection or malnutrition, a history of winter birth (for a review see[8]), and low (parental) socioeconomic status[9] also play a negative role in the etiology of the illness. Currently, it is not fully understood how genetic and environmental factors influence pathophysiological mechanisms leading to the disease.[10] Nevertheless, several hypotheses have been proposed. First, the neurodevelopmental hypothesis suggests schizophrenia is a disorder of brain development. Premorbid abnormalities later in life lead to occurrence of psychosis. A finding consistent with this hypothesis is the before mentioned association of schizophrenia with obstetric complications.[6] Second, the neurodegenerative hypothesis of schizophrenia proposes schizophrenia is a disorder caused by brain degeneration during the course of life. Third, the progressive neurodevelopmental hypothesis views schizophrenia as a lifetime disorder of development, plasticity, and ageing. In this hypothesis elements of the neurodevelopmental and neurodegenerative hypotheses are brought together (for a review see[11]).

Evidence for these hypotheses one can find through Magnetic Resonance Imaging (MRI) studies. MRI has enabled in vivo visualisation of brain structures in patients with schizophrenia. Results unequivocally show small and subtle brain abnormalities are involved in the pathophysiology of schizophrenia. In schizophrenia patients, structural brain abnormalities, in particular smaller cortical grey matter, enlargement of lateral and third ventricles, and decreased hippocampal volume have consistently

been demonstrated.[12,13] Longitudinal studies have shown these brain abnormalities are progressive in nature[14] and occur in the early[15] as well as chronic phase of the illness.[15,16] All studies[16-19] but one[20] have indicated these changes are related to outcome such that schizophrenia patients with poorer outcome show more severe brain abnormalities.

More recently, MRI-techniques have enabled measurement of cortical thickness, in other words the thickness of the grey matter of the human cerebral cortex.[21-24] Van Haren and colleagues,[25] in a longitudinal 5-year follow-up study, showed that excessive and progressive thinning of the cortex over time exists in widespread areas of the brain, most clearly in the frontal and temporal areas in patients with schizophrenia. As with regional structural brain abnormalities, more severe cortical thinning appeared to be related to poorer outcome.

Currently, the origin of these progressive brain volume abnormalities in schizophrenia is not fully understood. Researchers have suggested that these reductions are core to the illness and could be due to the so-called "toxic" effects of the psychotic state of the brain.[17,26-28] It has been shown that genetic factors play a role in the progressive brain volume reductions in schizophrenia patients.[29,30] Nevertheless, several (unhealthy) environmental factors such as alcohol abuse,[31] cannabis use,[32,33] and antipsychotic treatment[25,34,35] have also been found to influence brain changes over time in schizophrenia. Investigating the causes of progressive brain changes in schizophrenia is relevant as it can lead to the development of treatment strategies to attenuate or even reverse the progressive changes.

Treatment

The treatment of schizophrenia consists of a combination of interventions typically offered by a multi-disciplinary team. Since the first antipsychotic medication was introduced in the 1960s, antipsychotic medication has become the cornerstone of treatment.[36] A meta-analysis showed that pharmacotherapy is effective in the treatment of psychosis.[37] Two types of antipsychotic medicine are distinguished namely first- and second-generation antipsychotics. First generation antipsychotics

are characterised by their antagonistic effect and high affinity for dopamine receptors, in particular D2 receptors, which is thought to give these agents the ability to reduce the positive symptoms. Second generation antipsychotics are antagonists, not only for dopamine D2 receptors but also serotonin (5-Hydroxytrypitamine) and other neurotransmitters. Second generation antipsychotics have a lower risk of causing extrapyramidal symptoms or tardive dyskinesia. Three large double-blind randomised trials showed that no difference in effectiveness between first- and second-generation antipsychotics exists when looking at positive symptoms.[38-40] Only Clozapine has superior efficacy and effectiveness as compared to first-generation antipsychotics.[41] Antipsychotics are less successful in treating negative and cognitive symptoms.[1,42,43]

Psychosocial treatment

The fact that antipsychotic medication is unable to successfully treat all symptoms of the illness[1,42,43] underlines the need for multi-disciplinary treatment of patients with schizophrenia including psychosocial treatments as add-on therapies to improve treatment of symptoms and promote functional recovery.[44] Previous research on psychosocial approaches to treatment of schizophrenia has yielded incremental evidence of efficacy of cognitive behavioural therapy, social skills training, family psycho-education, assertive community treatment and supported employment. Other psychotherapeutic approaches such as peer support services, personal therapy, and motivational interviewing to improve adherence are promising but are yet to yield systematic evidence in support.

Psychomotor therapy

In the Netherlands, psychomotor therapy is widely used in the treatment of patients with schizophrenia. Reviews have suggested that psychomotor therapy may positively effect mental and physical health but as studies so far have had several methodological limitations, additional studies are needed.[45-49] In total, approximately 600 psychomotor therapists are working in the Netherlands. Psychomotor therapy (or body and movement psychotherapy) is a professional treatment, characterised by methodological and purposeful utilisation of movement, physical exercise or bodily experiences for people with psychosocial or psychiatric illnesses. The aim

of psychomotor therapy is to bring about or contribute to a change in behaviour and thereby take away or reduce psychosocial or psychiatric problems or help people how to better cope with these problems. Psychomotor therapy incorporates movement and bodily oriented methods. Movement oriented methods are derived from physical activity, sports, and physical education whereas bodily oriented methods aim at peoples own bodily experiences, in example relaxation, breathing, sensory-awareness, mindfulness based stress reduction or yoga.[50]

Outcome

It has been well established that patients with schizophrenia benefit from maintenance treatment with antipsychotic medication.[51] Still a substantial proportion of patients either relapse despite taking medication or become non-adherent with antipsychotic medication, estimates of treatment discontinuation ranging from 25-75%.[52,53] In addition, patients with schizophrenia frequently suffer co-morbid psychiatric disorders, depression in particular being highly prevalent with a lifetime risk of 60-80% compared to 8-26% risk in the general population.[54] Schizophrenia has a variable course of illness, some patients never recover from their first psychotic episode, others recover completely and may or may not experience one or more psychotic episodes after.[55] It is estimated that about 75% of patients with schizophrenia have relapses and continued disability.[56] The severity of this illness is underlined by reduced competitive employment rates compared to the general population. It is estimated that fewer than 20% of patients with schizophrenia are involved in (part-time) competitive employment.[57,58]

Life-expectancy

The mortality risk in patients with schizophrenia is two to three times higher compared to the general population leading to a 20% reduction in life expectancy.[59-63] Up to 40% of excess mortality can be attributed to suicide and unnatural deaths.[64] Yet natural (somatic) causes of death are the major contributor of premature mortality in schizophrenia patients.[59,60,63] In schizophrenia standardised mortality ratios of most natural death categories are increased compared to the general population (i.e. digestive, endocrine, infectious, and nervous diseases).[63] The single largest cause

of death in patients with schizophrenia is coronary heart disease. Patients with schizophrenia are two times more likely to die of coronary heart disease than the general population.[65]

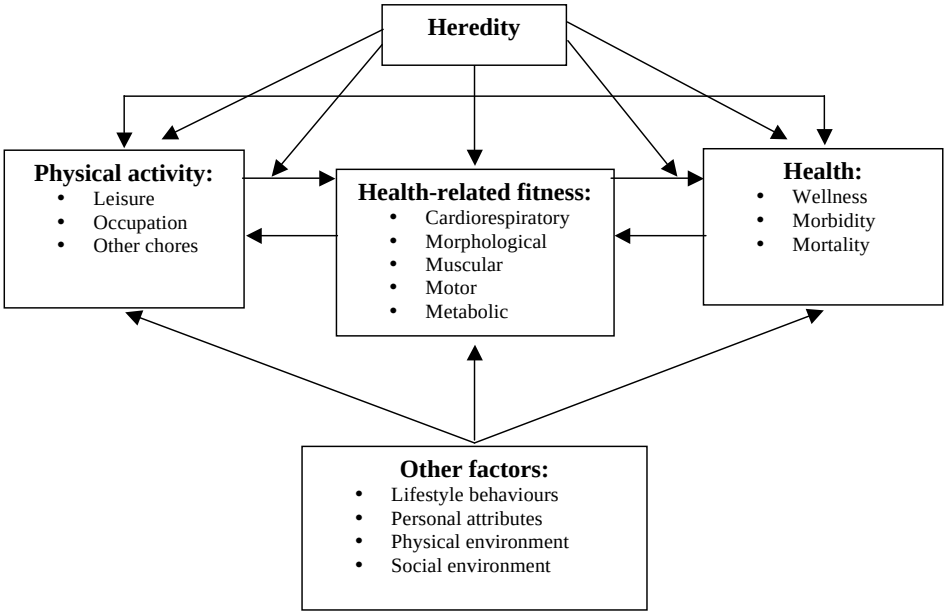
Obesity

The increased cardiometabolic risk is partly attributable to antipsychotic medication use since a number of agents lead to considerable weight gain and dyslipidaemia.[66,67] Overweight and obesity are key risk factors for a number of physical illnesses such as diabetes mellitus, coronary heart disease, hypertension, and certain cancers.[68,69] Obesity is three- to fourfold more prevalent in schizophrenia patients than in the general population.[70,71] The ethiopathogenesis of weight gain in schizophrenia patients is not entirely understood but besides psychotropic treatment side effects, individual lifestyle choices also clearly play a role.[69] Patients with schizophrenia are more likely to smoke,[72] be physically inactive,[73] have poor cardiorespiratory fitness,[74,75] and make poor dietary choices.[76-79]

Physical activity and cardiorespiratory fitness and energy intake

The study of physical activity, cardiorespiratory fitness and both mental and physical health parameters is preferably done within a conceptual model, proposed by Bouchard and Shephard.[80] This model describes the possible associations and identifies influencing factors between physical activity, physical fitness (of which cardiorespiratory fitness is an essential aspect), and health. In their model of health related fitness (see **Figure 1**), Bouchard and Shephard[80] state that physical activity, physical fitness and health are dependent on each other and that simultaneously, genetic and environmental factors play an important role in the interaction. People suffering a chronic illness, for example patients with schizophrenia, are limited in their ability to be physically active and as a consequence have poor physical (or cardiorespiratory) fitness levels. Improvement of physical activity and cardiorespiratory fitness will lead to improvement of health.

Figure 1. Relationships between physical activity, health-related fitness and health.[80]



Physical activity

Physical inactivity has been identified as the fourth leading risk factor for global mortality and is thus responsible for 6% of deaths globally.[81] Accurate quantification of physical activity is essential when comparing physical activity levels in a certain patient population to that in healthy comparison subjects. In the literature, three types of physical activity assessments are distinguished: criterion, objective, and subjective methods. Criterion methods are the most reliable and valid measurements and include doubly labelled water, indirect calorimetry, and direct observation.[82] To date, one study with schizophrenia patients reported using a criterion method, namely doubly labelled water, and found energy expenditure was 21% lower in male schizophrenia patients, treated with clozapine (n=8), compared to World Health Organization recommendations.[83] Criterion methods are invasive and/or expensive and require a laboratory setting making application of criterion methods on a larger scale difficult. Objective physical activity assessment methods include activity monitors such as pedometers and accelerometers.[82] Using accelerometry, no differences were found

in the amount of physical activity undertaken between patients with schizophrenia (*n*=16) and healthy control subjects (*n*=6).[73] Subjective methods for assessment of physical activity include questionnaires and activity diaries. Self-report assessments have limited validity due to recall errors and social desirability bias.[84,85] Since a majority of patients with schizophrenia suffer from memory impairments[86] this further endangers validity of subjective methods for physical activity assessment in schizophrenia patients. In schizophrenia patients, four studies have reported physical activity, using subjective assessment methods, and these studies found schizophrenia patients spend less time on physical activity and are less likely to participate in sports compared to non-psychiatric comparison subjects or the general population.[73,76,87,88] Thirty percent of schizophrenia patients versus 62% of the comparison group were classified as being regularly physically active[73] and one out of four patients met the minimum health recommendation of 150 minutes of exercise per week.[89] To conclude, studies to date have several limitations such as the use of subjective assessment methods, small sample sizes, and often lack a well-matched and locally recruited healthy control group.

Cardiorespiratory fitness

Low cardiorespiratory fitness has been recognised as an independent risk factor for all-cause mortality in adults and a key risk factor for coronary heart disease related mortality.[90,91] A recent meta-analysis in the healthy population has shown an inverse association between cardiorespiratory fitness and coronary heart disease.[91] In men, low cardiorespiratory fitness was found to predict mortality due to coronary heart disease even better than smoking, hypertension or diabetes.[91] In schizophrenia, high quality studies investigating cardiorespiratory fitness are scarce.[92]

The criterion method for assessment of cardiorespiratory fitness is the 'gold-standard' incremental cardiopulmonary exercise test with respiratory gas-exchange analysis.[93] (For a test set-up see **Figure 2**, appendix 1.) The first study to assess and report cardiorespiratory fitness in patients with schizophrenia and untrained healthy controls, using this criterion method, found patients obtained fitness values one-third below standard for untrained healthy controls. In addition, it was concluded that incremental cardiopulmonary exercise testing had limited feasibility in patients

with schizophrenia since many patients terminated at sub-maximal loads.[94] Two recently published cross-sectional studies showed that the incremental exercise test was, however, well received and tolerated with good protocol adherence.[74,75] Strassnig and co-workers[74] found in a cross-sectional study that obese patients with schizophrenia, on average aged 45 years old, had exceedingly low cardiorespiratory fitness levels compared to population standards. Only two patients in the entire sample (*n*=117) fit the categorisation of 'moderate fitness level'. They concluded poor cardiorespiratory fitness is an eminent modifiable cardiovascular risk factor in schizophrenia.[74] A Norwegian study found lower cardiorespiratory fitness levels, especially in male patients with schizophrenia compared to normative fitness levels of healthy individuals.[75] Interestingly, using sub-maximal exercise testing, a large Finish cohort sample showed adolescents who later developed psychosis, at the age of 15 to 16 had poorer cardiorespiratory fitness levels compared to controls (odds ratio: 2.2; 95% confidence interval: 0.6-7.8).[95]

Energy intake (and energy expenditure)

Frequently mentioned causal lifestyle factors for weight gain are poor dietary habits (high energy intake) and high levels of physical inactivity (low energy expenditure). In schizophrenia however, empirical studies into these factors are scarce and results are inconsistent. Most studies found patients with schizophrenia have poor dietary habits with higher energy intake compared to healthy control subjects or general population data.[76,78,88,96] Still, two studies found lower total energy intake in patients with schizophrenia compared to healthy controls but patients did make unhealthy food choices (for example consuming fewer fruit servings).[97,98]

Exercise therapy

One of the movement oriented methods incorporated in psychomotor therapy is exercise therapy. A number of reviews have reported the positive effects of exercise therapy in patients with schizophrenia.[45-49] Unfortunately, these reviews all have methodological limitations as they were based primarily on studies that lacked randomisation and one review used broad diagnostic inclusion criteria.[45]

Mental health outcomes

As for mental health effects, interestingly, lower physical activity participation has been associated with greater negative symptoms and reduced functional exercise capacity has been associated with poorer functional outcome and more severe negative, depressive, and cognitive symptoms.[99] Randomised intervention studies examining the effect of exercise on positive and negative symptoms have been inconclusive. Some studies[100-102] report a beneficial effect on these symptoms while others do not.[103-105] Inconsistencies in results are possibly due to methodological limitations such as not reporting exercise intensity, limited duration of training,[105] and small sample sizes, totalling 10 to 19 subjects only.[101,102,104,105] Exercise therapy is an established treatment for mild to moderate depression[106,107] and also in schizophrenia there is some evidence that exercise decreases co-morbid depressive symptoms.[108,109]

Physical health outcomes

Both physical inactivity and poor cardiorespiratory fitness have been recognised as independent risk factors for all-cause mortality.[81,90,91] Several randomised controlled studies have combined physical activity with diet counselling in patients with schizophrenia and most investigations found reductions in weight and body mass index,[103,110] body fat percentage[103,104] but not all.[101] In addition, improvement of waist and hip circumference, and triglycerides were reported.[111] Marzolini and co-workers,[101] in a small, randomised controlled trial in which muscle strength training plus walking versus no intervention was offered, reported improved muscular strength. A non-randomised controlled trial, showed that 8 weeks of high intensity cardiovascular exercise training increased cardiorespiratory fitness by 12% in patients with schizophrenia.[105] Since this study is the first to report cardiorespiratory fitness improvement in patients with schizophrenia this particular study is of importance. However, generalisability is limited due to the lack of randomisation, small sample size (19 subjects completed the trial), and the fact that only inpatients were included in the trial.[105]

Outcomes on brain plasticity

Animal studies have unequivocally shown that physical exercise positively affects brain morphology, especially in the hippocampus, and brain functioning.[112,113] In healthy elderly, studies have shown that exercise increases cerebral grey and white matter[114] and hippocampal volumes.[115] To date, one neuro-imaging study examined the effects of exercise therapy in male patients with schizophrenia[102] and found hippocampus volume enlargement after three months exercise (*n*=8) compared to table football (*n*=8). Moreover, this increase in hippocampus volume was related to cardiorespiratory fitness improvement.[102] Effects of exercise therapy and improvement of cardiorespiratory fitness on global brain volumes and cortical thickness in patients with schizophrenia have not been examined previously.

Outline of the thesis

This chapter (**chapter 1**) introduced the rationale for the TOPFIT study. The TOPFIT study comprises a multicentre randomised controlled trial, including patients with schizophrenia as well as physically inactive but otherwise healthy controls, matched to patients for gender, age, and socioeconomic status. In the TOPFIT study, patients with schizophrenia are randomised to a 6-month cardiovascular exercise therapy or occupational therapy. Healthy controls are randomised to the same 6-month cardiovascular exercise program versus life-as-usual.

In **chapter 2** we objectively assessed physical activity, total and active energy expenditure, steps, lying down and sleeping time in patients with schizophrenia and healthy controls. Moreover, associations of physical activity and cardiorespiratory fitness to mental and physical health parameters in patients with schizophrenia are evaluated.

In **chapter 3** energy intake and energy expenditure is studied in a cross-sectional design. Dietary intake, in particular energy and nutrient intake, in patients with schizophrenia is compared to that of locally recruited, healthy controls. In addition, the dietary intake of patients with schizophrenia is compared to that of gender, age,

and body mass index matched, general population data. Lastly, in **chapter 3** we investigate whether energy intake or energy expenditure is associated with obesity.

In **chapter 4**, cardiorespiratory fitness of patients with schizophrenia compared to that of matched, healthy controls is studied. This chapter also describes the longitudinal results of the randomised controlled trial, examining effects of a 6-month cardiovascular bi-weekly exercise therapy on cardiorespiratory fitness in both patients and inactive healthy controls.

In **chapter 5** the effects of the 6-month cardiovascular bi-weekly exercise therapy on mental and physical health parameters in patients with schizophrenia are evaluated.

Chapter 6 comprises of the effect of exercise therapy on change in global brain volume, hippocampal volume, and cortical thickness in schizophrenia patients and inactive healthy controls. Irrespective of diagnosis and intervention, associations between cardiorespiratory fitness improvement and structural brain changes are described.

In **chapter 7** a brief summary and discussion of the main findings of abovementioned studies is presented with special attention for methodological considerations, implications for clinical practice, and suggestions for future studies.

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2

Physical (in)activity in schizophrenia patients and matched healthy controls; associations to mental and physical health parameters

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Abstract

Background: The objective of this study was to assess physical activity (PA) and inactivity in schizophrenia patients compared to healthy controls. Associations between both PA and cardiorespiratory fitness (CRF) and mental and physical health parameters in patients were also examined.

Methods: PA was assessed with SenseWear Pro-2 body monitoring system (SWA) for three 24-hour bouts in schizophrenia patients (n=63) and matched healthy controls (n=55) with an average age of 29 years. Moderate and vigorous PA (MVPA), moderate PA, vigorous PA, total and active energy expenditure (TEE and AEE), steps, lying down and sleeping time were estimated from SWA. Severity of symptoms (Positive and Negative Syndrome Scale and Montgomery and Åsberg Depression Rating Scale), CRF, and metabolic syndrome were assessed.

Results: Schizophrenia patients performed less MVPA (P=0.005) and moderate activity (P<0.001), had lower TEE (P=0.001) and AEE (P=0.002), and more lying down (P<0.0001) and sleeping time (P<0.0001) per day compared to healthy controls. Participants were less physically active during the weekend compared to weekdays. The amount of MVPA, but especially CRF was negatively associated with severity of negative symptoms in schizophrenia patients. Only CRF was negatively associated with BMI.

Conclusion: Schizophrenia patients undertake less PA, expend less TEE and AEE, and spend more time lying down and sleeping compared to healthy controls. Interventions should be tailored to the activity pattern of patients and focus on increasing PA and decreasing sedentary behaviour. We found strong associations of CRF with both negative symptoms and BMI, thus treatment aimed at CRF-improvement should be developed.

Introduction

The mortality risk in schizophrenia patients is two to three times higher compared to the general population leading to a 20% reduction in life expectancy.[1-5] Natural causes of death, mainly cardiovascular diseases, are the major contributor of premature mortality in schizophrenia patients.[1,2,5]

The increased cardiometabolic risk is partly attributable to antipsychotic medication use since numerous agents lead to weight gain.[6,7] A poor lifestyle adds to the risk since patients are likely to smoke,[8] be physically inactive,[9] and have poor fitness.[10-12] Lower physical activity (PA) as well as poor cardiorespiratory fitness (CRF) were seen in teenagers who later developed psychosis.[13] Regular PA has evidently proven to be a key component in the prevention of weight gain.[14] A review of literature suggests PA reduces the risk of over 25 chronic conditions, in particular coronary heart disease.[15,16] Both physical inactivity and poor CRF have been recognised as independent risk factors for all-cause mortality.[17-19]

Surprisingly, only few studies have focused on the amount of PA in schizophrenia patients as compared to healthy controls.[9,20-22] Using self-report, schizophrenia patients reported spending less than half the time on PA compared to a non-psychiatric comparison group. 30% of schizophrenia patients versus 62% of the comparison group were classified as being regularly physically active. Using accelerometry, no difference in PA between patients (n=16) and the comparison group (n=6) was found, possibly due to the small sample size.[9] By means of questionnaire assessment, schizophrenia patients reported taking less leisure exercise,[20] spending less time on moderate physical activity (MPA),[22] and were less likely to participate in sports.[21] Only one out of four patients met the minimum health recommendation of 150 minutes exercise per week.[23] Compared to World Health Organization recommendations, the energy expended on PA was estimated to be 21% lower in schizophrenia patients using clozapine.[24]

Available studies have several limitations such as use of subjective measurement of physical activity and absence of well-matched and locally recruited controls. Three studies relied solely[20-22] and one[9] predominantly on questionnaires to quantify PA which have limited validity.[25,26] As schizophrenia patients suffer from memory impairments[27] the validity of self-report is further endangered. A pilot study showed

pedometers, but not logbooks were feasible in schizophrenia[28] and two studies found no or poor associations between self-report and accelerometry assessed PA.[9,23] Sedentary behaviour was shown to have an important influence on the metabolic rate.[29] Contrary to pedometers and accelerometers, the SenseWear Pro-2 body monitoring system (SWA) (BodyMedia Inc.®, Pittsburgh, PA, USA) is able to detect sedentary behaviour, increasing energy expenditure associated with cycling, upper body movement, walking on an incline, and carrying static loads.[30,31] Thus, there is a need for objective assessment of PA in schizophrenia patients.[32,33]

For the development of successful interventions it is important to better understand PA among schizophrenia patients. CRF should be investigated in addition to PA, since correlates of the latter may have a larger influence on cardiometabolic risk.[34] While positive symptoms in schizophrenia patients were positively correlated to CRF,[10] Vancampfort and co-workers[35] suggest PA and CRF should be taken into account in relation to mental and physical health.

To the best of our knowledge this is the first study to objectively monitor PA during three 24-hour bouts using the SWA in schizophrenia patients and matched healthy controls. The aim of this study was to describe PA in schizophrenia patients in comparison to physically inactive but otherwise healthy controls. To investigate PA patterns, variation in PA throughout the week was examined. The second aim was to determine whether both PA and CRF were associated to mental and physical health parameters in schizophrenia patients.

Methods

Participants

This study included data of 63 patients with a schizophrenia spectrum disorder and 55 healthy comparisons, matched for gender, age, and socioeconomic status (expressed as the highest educational level of one of the parents). Patients were recruited at the University Medical Center Utrecht (the Netherlands) (*n*=26) and regional mental health care institutes (Altrecht; GGZ Duin- en Bollenstreek; GGZ Friesland) (*n*=37). Participants were enrolled in the study between May 2007 and May 2010 and written informed consent was obtained after the procedures and possible side effects were explained. This study was part of a randomised controlled trial, named the TOPFIT study ('The Outcome of Psychosis and Fitness Therapy') and registered in the ISRCTN register (http://www.controlled-trials.com/ISRCTN46241817/). Patients had a diagnosis of schizophrenia (*n*=45), schizoaffective (*n*=15) or schizophreniform disorder (*n*=3) according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), confirmed using Comprehensive Assessment of Schizophrenia and History (CASH).[36] Patients were stable on antipsychotic medication, i.e. using the same dosage for at least four weeks prior to inclusion, showed no evidence of significant somatic disorders that prevented safe participation in the study,[37] had no primary diagnosis of alcohol or substance abuse, and an IQ≥70, as measured with the Wechsler Adult Intelligence Scale Short Form (WAIS-III SF).[38] Healthy participants (*n*=55) were recruited locally through advertisements. Inclusion criteria for the healthy controls were no diagnosis of psychiatric disorders according to DSM-IV lifetime, no first-degree relative with a psychotic or depressive disorder, and being physically inactive before inclusion (i.e., less than one hour of MPA weekly). The study was approved by the Human Ethics Committee of the University Medical Center Utrecht and research committees of participating centres.

Measures

All measurements were assessed by a qualified research assistant and a sports physician. Participants wore the SenseWear Pro-2 body monitoring system (SWA) (BodyMedia Inc.®, Pittsburgh, PA, USA) during three 24-hour time bouts (two weekdays and one weekend day) except during water-based activities. The SWA is

worn over the right arm triceps muscle and assesses minute to minute data through multiple sensors, namely a two-axis accelerometer and sensors measuring heat flux, galvanic skin and near body-temperature. Data are combined with gender, age, body weight and height, to estimate PA and energy expenditure using algorithms developed by the manufacturer (SenseWear Professional software, version 5.1.0.1289). SWA objectively records PA and energy expenditure.[31,39,40]

Several variables were calculated from the SWA data. PA is expressed in average metabolic equivalents (MET; in kcal/hour/kg), an indicator of daily energy expenditure. The unit MET is used to estimate the amount of oxygen used by the body during PA. Daily average time spend in total moderate and vigorous physical activity (MVPA) (≥3MET), moderate (MPA) (3-6 MET), vigorous (VPA) (≥6 MET) were calculated from all minutes with a MET-value. Total energy expenditure (TEE; in kcals), active energy expenditure (AEE; in kcals: ≥3 MET), steps, lying down and sleeping time were also estimated. Data was accepted when the average on-body measuring time was at least 1368 minutes (95% of a 24-hour bout).

Cardiorespiratory fitness (CRF) was assessed with a cardiopulmonary exercise test, performed using a 20-$W \cdot min^{-1}$ stepwise incremental protocol to exhaustion on a cycle ergometer (Lode Excalibur, Lode BV, Groningen, the Netherlands)[41] and defined as the highest oxygen uptake of any 30-second interval during the test (VO_{2peak} in $ml \times min^{-1} \times kg^{-1}$).[42] Waist circumference (in cm's) and anthropometric measurements (height in cm's and weight in kg's), using the same calibrated equipment in all participants, and metabolic syndrome (MetS), assessed according to the International Diabetes Foundation criteria,[43] were obtained.

To evaluate severity of schizophrenia symptoms, the Positive and Negative Syndrome Scale (PANSS) total, positive, negative, and general (sub)scores were assessed.[44] The Montgomery Åsberg Depression Rating Scale (MADRS) assessed co-morbid depressive symptoms.[45] Information on amount and type of prescribed antipsychotic and other medication was gathered. Current antipsychotic medication prescribed was described in cumulative dosage and converted into haloperidol equivalents (conformable to a table from the Dutch National Health Service.[46]

Data analysis

SPSS 18.0.1 (SPSS, Chicago, IL) was used to analyse the data. All statistical tests were performed two-tailed and a *P*-value of <0.05 was considered significant. Data were examined for outliers. All analyses were performed with and without extreme outliers to examine their influence on results. In case of non-normal distribution logarithmic transformation was applied.

Group comparisons

Multiple analyses of variance for non-categorical variables and χ^2 analyses for categorical variables were used to examine differences between schizophrenia patients and matched healthy controls in demographic and clinical variables. Univariate analyses (ANCOVA) were used to examine differences in MVPA, MPA, VPA, TEE and AEE, steps, lying down and sleeping time between patients and healthy controls. Gender, age, and Body Mass Index (BMI) were included in analyses as possible confounding factors. To investigate if differences exist between day of measurement (weekdays versus weekend) within and between groups (patients versus controls), repeated measures analysis of variance were performed comparing the average weekday versus weekend day MVPA, MPA, VPA, TEE and AEE, steps, lying down, and sleeping time. Correction for multiple testing was applied according to the Bonferroni-correction procedure.

Associations of MVPA and CRF with health

In patients backward linear regression analysis (criterion: probability of *F*-to-remove >=0.10) was used to assess whether the independent variables gender, age, PANSS positive, PANSS negative, PANSS general, and MADRS-score were associated with both MVPA and CRF. Similarly, we examined the association between physical health parameters (gender, age, BMI, haloperidol equivalent of antipsychotic medication prescribed, and number met criteria for the MetS) and both MVPA and CRF.

Results

Group characteristics

Demographic and clinical characteristics are shown in **Table 1**. Healthy controls had lower BMI (P=0.01), higher CRF (P<0.01), higher IQ (P=<0.001), and smoked less cigarettes per day (P=<0.001). Male patients were younger (mean age: 28 vs. 33 years old; P=0.02) than female patients, but no differences in other demographic or clinical variables were found. There were no differences in type ($\chi^2(9)=5.68$; P=0.77) and dose ($F(1,58)=1.24$; P=0.27) of antipsychotic medication used between genders.[47]

Group differences in physical (in)activity

All variables, except MPA, VPA, and AEE, complied with normality and homogeneity of variance demands. After logarithmic transformation of these variables all data were analysed parametrically. Average on-body percentage was below 95% in one patient and three controls thus 62 patients and 52 healthy controls, with an average on-body time of 98.3% (SD: 1.4) and 98.0% (SD: 1.2) respectively, were included in further analyses. Results are presented in **Table 2**. Compared to healthy controls, patients performed significantly less MVPA (P=0.005) and MPA (P=<0.001), but the difference in VPA did not reach significance (P=0.15). Schizophrenia patients had significantly lower TEE (P=0.001) and AEE (P=0.002) compared to controls. Though average steps taken was lower in schizophrenia patients (mean: 8040) than in controls (mean: 8884) this difference did not reach significance (P=0.16). Patients had significantly more lying down (P=<0.001) and sleeping (P<0.001) minutes per day than controls. Bonferroni-correction for multiple testing had no influence on the conclusions.

Table 1. Demographic and clinical characteristics for schizophrenia patients and matched healthy controls.

	Group					
	Patients		**Controls**			
Characteristic	**(*n* = 63)**		**(*n* = 55)**			
	n		***n***		***F***	***P***
Gender (male/ female) [b]	46 / 17		36 / 19		0.79	0.37
CASH (schizophrenia/ schizoaffective disorder/ schizophreniform disorder) [b,c]	45 / 15/ 3					
Parental education level (n(education level: 1,2,3,4,5,6,7, unknown)) [b,d]	1,2,2,10,25,13,8,2		0,1,0,6,18,18,12,0		6.79	0.34
	Mean	**SD**	**Mean**	**SD**		
Age (year) [a]	29.6	7.4	29.3	7.7	0.07	0.80
Height (cm) [a]	177.9	9.2	178.2	10.1	0.03	0.86
Weight (kg) [a]	83	19.2	76.3	14.3	4.51	**0.04**
BMI (kg/m^2) [a,e]	26.3	6	23.9	3.3	6.6	**0.01**
VO_{2peak} ($mL \cdot min^{-1} \cdot kg^{-1}$) [a,f]	31.6	9.9	35.9	5.5	7.92	**<0.01**
WAIS Total IQ [a,g]	87.2	15.6	108.1	13.8	58.13	**<0.001**
Smoking (cigarettes/day) [a]	11.8	10.5	0.9	4.3	52.03	**<0.001**
Alcohol usage (glasses/week) [a]	3.6	6.9	5	5.2	1.5	0.23
PANSS total score [h]	62.6	10.7				
PANSS positive factor score	15.52	4				
PANSS negative factor score	17.46	5.8				
MADRS score [i]						
Duration of illness (years)	6.6	5.8				
Hospitalisation until measurement (days)	193.7	265.3				
HEQ dose (mg/day) [j]	8.1	5.2				

Significant differences at p<.05 level are presented in bold.
[a] ANOVA was used.
[b] χ^2 was used.
[c] CASH: Comprehensive Assessment of Schizophrenia and History.
[d] Psychosocial status, expressed as highest level of education of one of both parents according to Verhage.[47]
[e] BMI: Body mass index.
[f] VO_{2peak}: highest oxygen uptake of any 30-second interval during the test.
[g] WAIS: Wechsler Adult Intelligence Scale Short Form.
[h] PANSS total score: Positive and Negative Syndrome Scale assesses severity of psychosis.
[i] MADRS score: Montgomery and Åsberg Depression Rating Scale assessing severity of depression.
[j] HEQ dose: baseline antipsychotic medication used in haloperidol equivalent in milligrams per day.

Table 2. Physical activity (PA) in patients with schizophrenia and matched healthy controls, controlled for gender, age, and BMI influences.

Characteristic	Group			
	Patients (*n* = 62)	**Controls (*n* = 52)**	**Analyses**	
	Mean ± SD	**Mean ± SD**	***F***	***P***
MVPA (≥3 MET; min/day) [a,d]	136.4 ± 70.2	185.2 ± 68.6	8.39	**0.005***
Moderate (3-6 MET; min/day) [a, c]	105.3 ± 72.1	152.1 ± 63.3	12.98	**<0.001***
Vigorous (>6 MET; min/day) [a, c]	10.5 ± 20.3	16.1 ± 26.6	2.1	0.15
Total energy expenditure (kcal/day) [a]	2897 ± 582	3036 ± 455	10.74	**0.001***
Active energy expenditure (kcal/day) [a, c]	718 ± 595	965 ± 421	9.62	**0.002***
Steps (steps/day) [a]	8040 ± 3072	8884 ± 2837	1.97	0.16
Lying down (hours/day) [b]	11.4 ± 2.1	8.6 ± 1.2	65.95	**<0.0001***
Sleeping time (hours/day) [b]	9.2 ± 1.9	6.5 ± 1	68.63	**<0.0001***

Results presented as mean ± standard deviation.
Significant results are presented in bold.
*Significant after Bonferroni correction for multiple testing.
[a] Higher score indicates superior physical activity.
[b] Lower score indicates superior physical activity.
[c] EXP-values of logarithmically transformed and analysed data are presented.
[d] MVPA: Moderate and Vigorous Physical Activity.

Physical activity throughout the week

Except for VPA, participants performed significantly less time on MVPA and MPA, had lower TEE and AEE, less steps, and more time lying down and sleeping during the weekend compared to weekdays (see **Table 3**). After Bonferroni-correction for multiple testing participants still had significantly less steps and more time lying down and sleeping. No significant differences between the two 24-hour weekday assessments were found in either patients or controls for any of the PA variables (all *P*-values >.20). Whereas no differences in PA or energy expenditure were found between Saturdays or Sundays in healthy controls, patients had less MVPA (P=0.04) and lower TEE (P=0.005) and AEE (P=0.009) on Saturdays compared to Sundays.

Table 3. Differences between day of measurement (weekdays versus weekend) within (day) and between groups (day × group; patients versus controls) for schizophrenia patients and healthy controls.

Characteristic	Group							
	Patients (*n* = 62)		Controls (*n* = 52)		Statistics			
	Weekday	Weekend	Weekday	Weekend	Day		Day × Group	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	*F*	*P*	*F*	*P*
MVPA (≥3 MET; min/day) [a,c]	144.8 ± 82.2	121.6 ± 74.7	190.6 ± 84	174.6 ± 74.7	5.8	**0.02**	0.2	0.7
MPA (3-6 MET; min/day) [a,d]	126.4 ± 75.7	106.5 ± 61.9	165.7 ± 71.2	152.6 ± 60.4	5.3	**0.02**	0.2	0.63
VPA (>6 MET; min/day) [a,e]	17.5 ± 16.6	15.2 ± 26.4	24.9 ± 23.5	21.9 ± 27.7	1.1	0.29	0.02	0.89
TEE (kcal/day) [a,f]	2943 ± 634	2805 ± 621	3069 ± 522	2970 ± 475	6.5	**0.01**	0.2	0.67
AEE (kcal/day) [a,g]	896 ± 546	745 ± 525	1055 ± 471	979 ± 432	4.8	**0.03**	0.5	0.47
Steps (steps/day) [a]	8565 ± 3522	6990 ± 3522	9104 ± 3251	8443 ± 3669	9.8	**0.002***	1.6	0.2
Lying down (hours/day) [b]	11.1 ± 2.2	11.9 ± 3.3	8.1 ± 1.3	9.6 ± 2.3	17	**<0.0001***	1.7	0.19
Sleeping time (hours/day) [b]	8.8 ± 2.1	9.8 ± 2.7	6.1 ± 0.9	7.3 ± 1.9	25.1	**<0.0001***	0.2	0.62

Results presented as mean ± standard deviation.
Significant results are presented in bold.
*significant after Bonferroni correction for multiple testing.
Statistics for weekday and weekend day are shown under 'day'.
Statistics for day × group (patient/healthy control) interactions are shown under 'group'.
[a] Higher score indicates superior physical activity.
[b] Lower score indicates superior physical activity.
[c] MVPA: Moderate and Vigorous Physical Activity.
[d] MPA: Moderate Physical Activity.
[e] VPA: Vigorous Physical Activity.
[f] TEE: Total energy expenditure.
[g] AEE: Active energy expenditure.

Associations of MVPA and CRF with mental and physical health

For mental health, a significant final model for MVPA emerged ($F_{1,,59}$=4.46; *P*=0.039; R^2=0.069) in which increasing severity of negative symptoms (PANSS negative: beta=-0.263; *P*=0.039) was significantly associated with less MVPA. For mental health, a significant model for CRF emerged also ($F_{4,56}$=16.944; *P*<0.00000001; R^2=0.548) in which female gender (female versus male; beta=-0.359; *P*<0.0001), higher age (beta=-0.383; *P*<0.00001), more general (PANSS general: beta=-0.200;

P=0.052) and in particular negative symptoms (PANSS negative: beta=-0.542; *P*<0.000001) were significantly associated with poorer CRF.

For physical health, no significant final model for MVPA emerged since none of the physical health variables were significantly associated with MVPA. For physical health, a significant model for CRF did emerge ($F_{3,54}$=20.360; *P*<0.00000001; R^2=0.531) in which female gender (female versus male; beta=-0.303; *P*=0.003), higher age (beta=-0.200; *P*=0.052), and higher BMI (beta=-0.493; *P*<0.00001) were significantly associated with poorer CRF.

When negative symptoms and BMI were combined in one regression model with CRF, both factors were equally related.

Discussion

This study examined objectively measured PA in schizophrenia patients compared to inactive healthy controls. Schizophrenia patients performed significantly less MVPA, MPA, had lower TEE and AEE, and more lying down and sleeping time per day. Both schizophrenia patients and healthy controls were less physically active during the weekend, but only schizophrenia patients were less active on Saturdays compared to Sundays. The amount of MVPA, but especially cardiorespiratory fitness level was associated with severity of negative symptoms in schizophrenia patients. Only cardiorespiratory fitness, but not MVPA, was associated with BMI.

The present study is novel for it included objectively measured 24-hour assessments providing additional knowledge on TEE and AEE, lying down and sleeping time. Previous studies used self-report[9,20-22] which, especially in schizophrenia patients, has limited validity.[25] Some (feasibility) studies in schizophrenia patients used accelerometers or pedometers to assess PA, but were hampered by their small sample sizes and/or lack of a healthy control group.[9,23,28,48,49]

Our results are consistent with previous studies which reported less PA in schizophrenia patients compared to healthy subjects.[9,20-22] In line with previous findings, we found schizophrenia patients spend less time on MPA but not on VPA.[22] In contrast, using self-report schizophrenia patients reported less VPA compared to healthy controls yet the same study reported no difference in MPA or VPA.[9] In accordance with the only previous study that used doubly labelled water, the established criterion standard method for free-living energy expenditure assessment, we found reduced TEE and AEE in schizophrenia patients.[24]

One of the inclusion criteria for controls in the present study was being physically inactive. Compared to a study assessing PA by means of SWA in healthy volunteers[50] our controls, as expected, were less physically active (i.e. <9.000 versus >12.000 steps day^{-1}). In general, lower socioeconomic status has been related to a more sedentary lifestyle,[51] also in schizophrenia patients.[32] Controls were matched to schizophrenia patients for socioeconomic status in this study. Compared to the general population schizophrenia patients are likely to be even less physically active than reported in the present study.

In line with a recent review, we found the amount of MVPA and especially CRF was associated with severity of negative symptoms in schizophrenia patients.[32] A previous study found CRF was only associated with severity of positive symptoms.[10] Negative symptoms evidently impact an individual's functional capacity in daily activities.[52] Since some intervention studies showed exercise decreased severity of negative symptoms but others did not, more research is warranted.

Weight gain interventions for people taking antipsychotic medication have primarily focused on reducing caloric intake.[53] Yet, given current and previous results, treatment should focus both on an increase of PA and a reduction of inactivity.[24,54,55] Given the strong association of CRF with BMI, PA interventions aimed at reduction of the cardiometabolic risk should focus on CRF improvement.[34] Two recent intervention studies showed this was feasible in schizophrenia patients.[11,12]

Contrary to accelerometry, SWA is able to detect increasing energy expenditure associated according to the type of PA.[30,31] In addition, SWA can identify periods of removal directly.[56] The present study accepted data only if average on-body time was at least 1368 minutes compared to 600 - 720 minutes daily in previous studies.[9,23,48] A systematic review of accelerometry studies showed that 3 - 5 measurement days were required to reliably estimate habitual PA.[57] Still, a recent SWA-study showed at least 3 monitoring weekdays plus Saturday and Sunday were needed.[50] Indeed, our results show both patients and controls were less physically active on weekends compared to weekdays. Whereas in a previous SWA-study, healthy controls were more physically active on Saturday and less on Sunday compared to weekdays,[50] no indication of this was found in our study. Schizophrenia patients were even less physically active on Saturdays compared to Sundays, perhaps due to a lack of initiative or avoidance of crowded places. This information is useful since treatments can target specifically those days where patients are most lethargic. A 12-week randomised controlled trial in which pedometers were combined with motivational interviewing in schizophrenia patients found significant body weight loss (mean difference: 2.21 kg; P=0.03) compared to the control group.[54]

Some limitations should be considered when interpreting present findings. First, SWA reliably assesses PA and energy expenditure in normal and overweight healthy adults,[31,39,40,58] yet has not been validated in schizophrenia patients. SWA

overestimated energy expenditure in obese subjects and the current study included 17 obese participants.[58] Papazoglou and co-workers[31] used an older software version than the present study which was later shown to have inferior accuracy. Second, as this is a cross-sectional study relationships but not causality between MVPA, CRF and mental and physical health parameters could be examined. Third, participants volunteered to engage in the study which may have led to some selection bias because subjects motivated for PA and health improvement might have had greater interest in this study.

In conclusion, our study shows schizophrenia patients undertake less PA, expend less TEE and AEE, and spend more time lying down and sleeping compared to physically inactive matched, healthy controls. Whereas both patients and controls were less physically active during the weekend, only patients had less physical activity on Saturdays compared to Sundays. Interventions should be tailored to the activity pattern of patients and focus on increasing PA and decreasing sedentary behaviour. Given associations of PA with negative symptoms and remarkably strong associations of CRF with both negative symptoms and BMI, the latter should be a primary treatment aim in schizophrenia patients.

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3

Energy expenditure and energy intake in schizophrenia: A cross-sectional study

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Abstract

Introduction: Some studies have examined energy intake in patients with schizophrenia and no previous study included objective energy expenditure and cardiorespiratory fitness measures. We investigated whether energy intake and expenditure of schizophrenia patients was different from healthy controls and BMI-matched general population data. Predictors of (abdominal) obesity were also investigated.

Method: A cross-sectional study included 30 schizophrenia patients and 48 healthy controls, matched for gender, age, and parental education level. Dietary intake (energy/nutrient and food groups) over the previous 12 months was assessed by a validated food frequency questionnaire. To control for BMI, energy and nutrient intake of schizophrenia patients was also compared to BMI-matched general population data from the Dutch National Food Consumption Survey. Daily physical activity was determined by the SenseWear and cardiorespiratory fitness (VO_{2peak} in $ml \cdot min^{-1}$) by a graded exercise test. ANCOVA and Mann-Whitney U Tests examined group differences in intake and regression analyses examined predictors of obesity.

Results: No significant differences in energy or nutrient intake were found between schizophrenia patients (mean±sd energy intake=2338±676kcal) and healthy controls (2077±453) (P=0.15) or between schizophrenia patients and BMI-matched general population data (2477±798) (P=0.34). When controlling for BMI, physical activity or fitness, energy and carbohydrate intake were higher in patients compared to healthy controls (P<0.05). (Abdominal) obesity was associated with schizophrenia, female gender, socioeconomic status, physical inactivity and poor cardiorespiratory fitness, not with energy intake.

Conclusion: Energy and nutrient intake of schizophrenia patients were similar to healthy controls and BMI-matched general population data. When controlling for BMI, physical activity and fitness, energy and carbohydrate intake was higher in patients compared to controls. (Abdominal) obesity in schizophrenia was best predicted by lower energy expenditure, not by higher energy intake suggesting patients with schizophrenia have greater energy intake, yet one should especially focus on increasing daily activity and improving fitness to reduce weight.

Introduction

Life expectancy of schizophrenia patients is on average reduced by 25 years compared to the general population, largely due to additional prevalence of physical illnesses.[1] Overweight and obesity are key risk factors of a number of physical illnesses such as diabetes mellitus, coronary heart disease, dyslipidemia, hypertension, and certain cancers.[1,2] Body mass index (BMI; kg/m^2) is often calculated to assess overweight (BMI≥25) and obesity (BMI≥30). Obesity is three- to fourfold more prevalent in schizophrenia patients than in the general population.[3,4] In schizophrenia abdominal obesity is often seen and should be taken into consideration when assessing mortality risk in schizophrenia patients.[5]

The ethiopathogenesis of weight gain in schizophrenia patients is not entirely understood. Both psychotropic treatment side effects as well as individual lifestyle choices clearly play a role.[1] The association of atypical antipsychotic medication and weight gain has been thoroughly investigated and confirmed,[6] however weight gain in schizophrenia patients was reported long before the introduction of antipsychotics.[7]

Frequently documented causal lifestyle factors for weight gain are poor dietary habits and physical inactivity. However, empirical studies into these factors are scarce and results are inconsistent. Although most studies found patients with schizophrenia have poor dietary habits with higher energy intake compared to healthy control subjects or general population data,[8-11] two studies found that even though schizophrenia patients made more unhealthy food choices (i.e. consuming fewer fruit servings), their total energy intake was lower compared to healthy controls.[12,13]

In addition to dietary intake, several studies have investigated the amount of daily physical activity in schizophrenia. These studies found that patients were less physically active than the general population[8-10,14] even though they relied on self-reported physical activity, which tends to be higher than the actual observation, especially among obese persons.[15] Furthermore, cardiorespiratory fitness might play a role in the occurrence of obesity in schizophrenia. Compared to the general population, patients with schizophrenia have very poor cardiorespiratory fitness, and this lack of fitness has not only been found in the older age group but in a younger age group as well.[16] To our knowledge, no study has included all relevant putative risk factors for obesity in their design.

The present study compares energy and nutrient intake in schizophrenia patients (*n*=30) with healthy controls (*n*=48), being locally recruited, physically inactive, and matched for gender, age, and socioeconomic status. To control for BMI, energy and nutrient intake of schizophrenia patients will also be compared to a gender, age, and BMI matched sample (*n*=605) randomly extracted from the Dutch National Food Consumption Survey (DNFCS).[17] Furthermore, we examine (abdominal) obesity in relation to various lifestyle factors (e.g. dietary intake, smoking, alcohol use and physical activity, cardiorespiratory fitness) to assess which factors might contribute most to (abdominal) obesity.

Materials and methods

Study population

This trial was part of the TOPFIT study ('The Outcome of Psychosis and Fitness Therapy') and registered in the ISRCTN register (http://www.controlled-trials.com/ISRCTN46241817/). Diet was assessed in a subsample of 30 patients with a schizophrenia spectrum disorder and 48 healthy controls, matched for gender, age, and socioeconomic status (operationalised as parental educational level). In total, 63 patients and 55 healthy controls were included in the TOPFIT study between May 2007 and May 2010. Diagnosis in patients was confirmed by a psychiatrist using the Comprehensive Assessment of Schizophrenia and History (CASH).[18] Patients were stable on (antipsychotic) medication, i.e. using the same dosage for at least four weeks prior to inclusion, showed no evidence for significant cardiovascular, neuromuscular, endocrine or other somatic disorders. Risk of cardiovascular disorders was assessed extensively following Lausanne recommendations (personal and family history, physical examination, laboratory testing, electrocardiogram).[19] Schizophrenia patients had no primary diagnosis of alcohol or substance abuse and had an IQ≥70, as measured with the Wechsler Adult Intelligence Scale Short Form (WAIS-III SF).[20] Healthy participants, recruited via advertisements in newspapers, had no diagnosis of psychiatric disorders according to DSM-IV lifetime, no first-degree relative with a psychotic or depressive disorder, and were physically inactive before inclusion (i.e., undertaking less than one hour of moderate physical activity weekly).

The study was approved by the Human Ethics Committee of the University Medical Center Utrecht and research committees of participating centres. Written informed consent was obtained after the procedures and possible side effects were explained.

Measures

In schizophrenia patients and healthy controls, dietary intake was assessed by a validated food frequency questionnaire (FFQ).[21,22] The FFQ contained questions about the amount and mean consumption of 178 food items during the past year. Further information was sought on consumption frequency for different sub-items, preparation methods and additions. Coloured photographs were used to estimate portion sizes for 28 food items. The questionnaire allows estimation of the daily

consumption of different food groups (i.e. potatoes, vegetables, fruit). The 2006 Dutch food composition table was used to calculate energy and nutrient intakes.[23] The FFQ was validated for food groups with 12 monthly 24-hour recalls and biomarkers in 24-h urine and serum samples. The median relative validity was 0.61 for men with a range from 0.21 for cooked vegetables to 0.78 for sugar and sweets, and 0.53 for women with a minimum of 0.31 for vegetables and a maximum of 0.87 for alcoholic beverages.[21,22] For the present analyses, 18 food groups were used. The FFQ was administered in a face-to-face interview in patients, in the controls the FFQ was self-administered.[24]

To enable comparison of energy and nutrient intake of schizophrenia patients with gender, age, and BMI-matched healthy subjects, data from the Dutch National Food Consumption Survey (DNFCS)[17] were used. A randomly extracted gender, age, and BMI matched sample (*n*=605) was extracted from the complete DNFCS-dataset (*n*=3819). Dieticians assessed energy and nutrient intake in DNFCS by means of two non-consecutive 24-hour dietary telephone recalls per participant. Each person was interviewed twice with an interval of about 4 weeks. In order to gain insight into the habitual food consumption, recalls were spread equally over all days of the week and the 4 seasons. For DNFCS subjects, gender, age, height, weight, and BMI were reported.

In all schizophrenia patients and matched healthy controls, sociodemographic information, BMI, waist circumference, and metabolic syndrome (MetS), according to the International Diabetes Foundation criteria,[25] were assessed. Daily physical activity was measured objectively using the SenseWear Pro2 body monitoring system (BodyMedia Inc., Pittsburgh, PA, USA).[26-28] Using SenseWear, physical activity was assessed during three 24-hour bouts (two weekdays and one weekend day) and defined as the average number of minutes of physical activity equal to or above 3 metabolic equivalents (METs; $kcal \cdot kg^{-1} \cdot hour^{-1}$) daily. The highest absolute oxygen uptake (VO_{2peak} in $ml \cdot min^{-1}$) and relative oxygen uptake (VO_{2peak} in $ml \cdot kg^{-1} \cdot min^{-1}$) were measured with an incremental cardiopulmonary ergometer exercise test (CPET).[29]

In patients, Positive and Negative Syndrome Scale (PANSS)[30] and the Montgomery and Åsberg Depression Rating Scale (MADRS)[31] assessed severity of symptoms. The

Camberwell Assessment of Needs (CAN)[32] assessed patients' level of functioning. Detailed information on amount and type of prescribed antipsychotic and other medication was gathered.

Statistical analyses

SPSS 18.0.1 was used to analyse the data. All statistical tests were performed two-tailed and a *P*-value of <0.05 was considered significant. Multiple analyses of variance for non-categorical variables and χ^2 analyses for categorical variables were used to examine differences between patients, matched healthy controls, and when applicable general population data, in socio demographic and clinical characteristics. For normally distributed data, means (95% confidence interval) were calculated and multiple analyses of covariance (ANCOVA) were used to examine differences between groups in energy, nutrient and/or food group intake. Significant findings in demographic and clinical characteristics were added to the analyses one-by-one to assess their effect on the results. For non-normal distributed energy, nutrient and/or food group intake data, median (inter quartile range) was calculated, and non-parametric testing (Mann-Whitney U Test) was performed. Given the small total sample size, ratios of mean/median intake of schizophrenia patients (*n*=30), matched healthy controls (*n*=48), as well as matched general population (*n*=605) values were also calculated. For schizophrenia patients, the influence of differences in cumulative dosage of antipsychotic medication used (converted into haloperidol equivalents) and type of antipsychotic medication used (olanzapine/clozapine versus other antipsychotics) on energy intake were examined (using Pearson's correlation and t-tests). As nicotine using schizophrenia patients have been found to have more unhealthy diets compared to non-nicotine users,[9] an independent samples t-test assessed whether patients who smoked had higher total energy intake compared to non-smoking patients. To assess which factors predicted (abdominal) obesity, backward linear regression analyses (criterion: probability of *F*-to-remove >=0.10) were performed with group (patient or control), gender, dietary intake (in kcal), physical activity, cardiorespiratory fitness (VO_{2peak} in $ml \cdot min^{-1}$), amount of cigarettes, number of alcohol consumptions daily and level of parental education. BMI and waist circumference were chosen as dependent variables since they are highly predictive

for somatic co-morbidity.[33] To account for possible unknown confounders for obesity in schizophrenia, similar backward linear regression analyses were performed for factors significantly associated with BMI and waist circumference in patients only.

Results

Demographic and clinical characteristics for patients, healthy controls, and (if available) general population data, are shown in **Table 1**.

Somatic health parameters

Schizophrenia patients had higher weight (P=0.003), BMI (P=0.002), and waist circumference (P<0.00001) compared to healthy controls. Also, patients compared to controls suffered from the metabolic syndrome more frequently (P=0.001), were less physically active (P=0.007), and had lower $VO_{2\ peak}$ (P<0.001), were more likely to smoke (P<0.001), smoked more cigarettes a day (P=0.001), and were more likely to use drugs (P=0.004) compared to healthy controls.

Energy and nutrient intake

Energy and nutrient intake data were normally distributed, and are presented in **Table 2**.

Schizophrenia patients had similar energy intake compared to healthy controls. The ratio indicates patients tended to have higher energy intake (mean kcal for patients divided by mean kcal for healthy controls (ratio I): 1.13), but this difference did not reach statistical significance (P=0.15). However, when BMI, physical activity or VO_{2peak} were entered in the analyses as covariates, energy intake was significantly higher in schizophrenia patients compared to healthy controls (P<0.05). Compared to BMI-matched general population data, patients were not different in the amount of daily energy intake. Ratio differences between patients and BMI-matched healthy controls indicate, though not reaching statistical significance (P=0.35), somewhat lower total energy intake in patients (mean kcal for patients divided by mean kcal for healthy controls (ratio II): 0.94). The relative percentage of calories derived from major nutrients (carbohydrates, fat, saturated fat, mono- and polyunsaturated fat, and proteins) was not statistically different between schizophrenia patients and healthy controls (see ratio I in **Table 2**) or between schizophrenia patients and BMI matched general population data (see ratio II in **Table 2**). When either waist circumference, metabolic syndrome, smoking or drugs usage (yes/no) was added to the analyses as a covariate, patients were found to consume a significantly higher percentage

of carbohydrates compared to healthy controls ($P<0.05$). For the intake of other nutrients, addition of covariates had no influence on results. No differences between patients and controls (ratio I) or general population data (ratio II) were found in dietary fibre intake (gram/1000kcal/day). Schizophrenia patients who smoked cigarettes had higher energy intake (mean calories: 2535; SD: 595) versus non-smoking patients (mean calories: 1876; SD: 655) ($P<0.05$).

Food group intake

Food group intake data were not normally distributed. Patients consumed more dairy products ($P=0.01$), but less wine ($P<0.001$), beer ($P=0.02$), and strong alcohol beverages ($P=0.01$) compared to healthy controls. For other food groups, no significant differences between patients and controls were found. Ratios, though non-significant, were higher in patients compared to controls for all other food groups except fruit (ratio: 0.91) with highest intake ratio-differences found for juice (ratio: 1.25) and soft drinks (ratio: 1.30). Results are shown in **Table 3**.

Table 1. Demographic and clinical (physical and mental health) characteristics for schizophrenia patients, matched healthy controls, and m matched general population data.

Characteristic	Schizophrenia patients (*n*=30)	Healthy Controls (*n*=48)	General population (*n*=605)		Analyses
Physical health	**Mean± SD/%**	**Mean± SD/%**	**Mean± SD/%**		***P***
Age (years)	31.2± 8.1	30.1± 7.9	31.5± 7.8		0.46
Gender (% men) [a]	73.3	64.6	75		0.28
Height (cm)	178.5 ± 9.8	177.5± 10.3	179.6± 9.4		0.28
Weight (kg)	88.4± 19.7	75.5± 13.7	86.7± 14.6	I,III	**<0.00001**
BMI (kg/m²)	27.9± 6	23.9± 3	26.8± 4	I,III	**<0.00001**
Waist circumference (cm)	99 ± 14.7	84.3 ± 9.9			**<0.00001**
MetS (% yes) [a]	46.7	12.5			**0.001**
PA (>3MET; minutes/day)	142.8 ± 79	206.1 ± 105.7			**0.007**
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	30 ± 8.7	37.3 ± 7.5			**<0.001**
Smoked during last six months (% yes) [a]	70	14.6			**<0.00001**
Cigarettes in current smokers (cigarettes/day)	18.1± 7.3	5.8± 7.2			**0.001**
Alcohol usage during last six months (% yes) [a]	73.3	87.5			0.11
Alcohol in alcohol users (glasses/week)	5.1± 9.3	6.7± 5.6			0.40
Any drug use during past 6 months (% yes) [a]	26.7	4.2			**0.004**
Mental health					
Parental education (level (%)) [a,b]	3(3), 4(23), 5(33), 6(20), 7(20)	2(2), 4(13), 5(33), 6(31), 7(21)			0.49
IQ (0-155)	92.5± 18	108.5± 13.6			**<0.001**
Diagnosis (schizophrenia/schizo-affective/ schizophreniform) (in %)[c]	83/10/7				
Illness duration (years)	7.6± 6.6				
HEQ dosage (mg/ day) [d]	8.2± 4.2				
(Antipsychotic) medication:					
Atypical (% yes)	90				
Second (% yes)	20				
Antidepressant (% yes)	26.7				
Mood stabilizer (% yes)	10				
Benzodiazepines (% yes)	16.7				
PANSS total *(measures severity of psychosis)*	57 ± 10.1				
MADRS *(measures severity of depression)*	10.2± 6				
CAN sum	6.3± 2.3				

Results presented as mean ± standard deviation or percentage, significant results are presented in bold.
Note I: patients sig. diff. from controls, Note II: patients sig. diff. from the general population, Note III: controls sig. diff. from the general population, [a] Pearson χ^2 test was used, [b] Socioeconomic status was assessed by means of parental education level (according to Verhage)[24].
[c] Comprehensive Assessment of Schizophrenia and History (CASH) [18], [d] HEQ dose: baseline antipsychotic medication used in haloperidol equivalent in milligrams per day, Abbreviations: BMI=body mass index, MetS= metabolic syndrome, PA=physical activity, VO_{2peak}= peak oxygen uptake level , IQ= intelligence quotient, Wechsler Adult Intelligence Scale (WAIS) was used to estimate total intelligence quotient (IQ) at baseline, PANSS=Positive and Negative Syndrome Scale, MADRS= Montgomery and Åsberg Depression Rating Scale, CAN sum of met and unmet needs.

Table 2. Energy and nutrient intake of schizophrenia patients versus matched healthy controls (Ratio 1) and of patients versus matched general population (Ratio II).

Nutrient [a]	Group				
	Schizophrenia patients (*n*=30)	Healthy controls (*n*=48)	General population (*n*=605)		
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Ratio I	Ratio II
Energy (kcal/day)	2338 (2052;2624)	2077 (1851;2303)	2477 (2415;2539)	1.13	0.94
Carbohydrates (% energy)	48.6 (46;51.2)	46.2 (44.2;48.3)	46.3 (45.8;46.9)	1.05	1.05
Fat (% energy)	34.5 (32.3;36.8)	35.1 (33.3;36.9)	35 (34.5;35.6)	0.98	0.99
Saturated fat (% energy)	12.9 (11.8;13.9)	12.8 (12;13.7)	13 (12.7;13.2)	1.01	0.99
Monunsaturated fat (% energy)	12.8 (11.8;13.9)	13.4 (12.6;14.2)	12.3 (12;12.5)	0.96	1.04
Polyunsaturated fat (% energy)	6.3 (5.5;7.1)	6.3 (5.6;6.9)	6.8 (6.7;7)	1	0.93
Protein (% energy)	15.6 (14.5;16.8)	15.6 (14.7;16.5)	15.3 (15;15.5)	1	1.02
Dietary fibre (g/1000 kcal/day)	9.9 (8.9;11)	10.6 (9.8;11.4)	9.1 (8.9;9.3)	0.93	1.09

Results presented as mean (lower and upper 95% confidence interval (CI)).
[a] Nutrient intakes are predicted after regression calibration.
Significant results are presented as follows: **p*<0.05, ***p*<0.01, ****p*<0.001.

Table 3. Food intake of schizophrenia patients and matched healthy controls.

Food [a]	Group		
	Schizophrenia patients (*n*=30)	Healthy controls (*n*=48)	Ratio I
	Median (P25;P75)	Median (P25;P75)	
Potatoes	76.1 (46.6;147.5)	69.5 (50.2;108.5)	1.09
Vegetables	102.2 (62.6;159.1)	96.3 (76.7;137.1)	1.06
Fruit	115.6 (32.9;244.9)	126.6 (79.2;220.5)	0.91
Dairy	667.8 (334.5;1033.1)	440 (260;596.1)	1.52*
Grains	85.6 (48;152.5)	81.2 (55.9;127.9)	1.05
Meat	113.6 (71.1;141.8)	99.9 (75.3;135.8)	1.14
Fish	11.2 (4.5;15.3)	11 (7.2;18)	1.02
Fat	58 (35.7;81.7)	54.5 (38.5;70.2)	1.06
Sweets	26.8 (15.4;49.1)	26 (16.4;40.7)	1.03
Pastry and Cookies	11.4 (2.4;24.7)	12.6 (7.5;24.7)	0.90
Juice	97 (39.3;284.2)	77.5 (24.9;115.3)	1.25
Soft drinks	146.4 (20.5;387.4)	111.8 (36.7;291.5)	1.30
Coffee/ tea	570.8 (262.5;906.3)	500 (251;750)	1.14
Wine	0 (0;0.68)	13.3 (1.1;41)	-***
Beer	2.2 (.0;66.7)	44.3 (.0;221.4)	0.05*
Strong alcoholic drinks	.0 (.0;.0)	.0 (.0;3.3)	-*

[a] Food (g per day) intakes are predicted after regression calibration.
Ratio I: ratio between schizophrenia patients and matched healthy subject.
Significant results are presented as: *p<0.05, **p<0.01, ***p<0.001.

Associations with antipsychotic medication

Total cumulative dosage of antipsychotic medication used was not associated with energy intake (r=0.006, *P*=0.975) nor did the type of antipsychotic medication influence energy intake in schizophrenia patients (t=0.442, *P*=0.662).

Predictors of BMI and waist circumference

Using the backward method, a significant model emerged for BMI ($F_{2,69}$=6.964, *P*<0.001, R^2=0.288). BMI was significantly associated to group (patient vs. control; beta=0.394; *P*=0.001), gender (female vs. male; beta=0.340; *P*=0.012), the amount of physical activity undertaken (beta=-0.268; *P*=0.016), and cardiorespiratory fitness level (beta=0.363; *P*=0.008). Smoking, alcohol usage, energy intake, and parental level of education were not associated with BMI.

Using a backward method, a significant model for waist circumference emerged ($F_{3,69}$=13.381; *P*<0.0000001; R^2=0.437) in which group (patient vs. control; beta=0.437; *P*<0.0001), the amount of physical activity undertaken (beta=-0.317; *P*=0.002), parental education level (beta=-0.215; *P*=0.025), and cardiorespiratory fitness level (beta=0.335; *P*=0.001) were significantly associated to waist circumference. In this model, gender, alcohol usage, smoking, and energy intake were not significant.

Including schizophrenia patients only, the findings for factors influencing BMI and waist circumference remained the same.

Discussion

In the current study energy and nutrient intake in schizophrenia patients and healthy controls matched for age, gender and level of parental education or between schizophrenia patients and a sample of BMI-matched general population were similar. After controlling BMI, physical activity and fitness, total energy and carbohydrate intake were higher in schizophrenia patients compared to healthy controls. Schizophrenia patients consumed more dairy products and drank less alcoholic beverages compared to healthy controls. Furthermore, schizophrenia patients had a higher prevalence of metabolic syndrome, higher BMI and waist circumference, were more physically inactive, had lower cardiorespiratory fitness, and smoked more cigarettes compared to controls. Increased BMI values were associated with schizophrenia, female gender, physical inactivity, and lower cardiorespiratory fitness, and not with energy intake. High waist circumference was related to schizophrenia, lower socioeconomic status, physical inactivity, and lower cardiorespiratory fitness level.

To the best of our knowledge this is the first study that included objectively measured physical activity and cardiorespiratory fitness measurements when investigating the energy balance in schizophrenia patients. Previous studies that have included physical activity measurements used self-recall[8-10,14,34] which correlates only low-to-moderately with direct measures of physical activity.[35] Another strength of our study is that locally recruited, healthy controls were included ensuring all (activity) variables were administered uniformly. All previous studies[8,9,11,13] but one[12] compared diet of schizophrenia patients to general population data, usually not BMI-matched. In addition, results of schizophrenia patients were compared to age, gender, and BMI matched general population data assessed during the same time period.

The present study showed that schizophrenia patients had higher average BMI than healthy controls matched for age, gender, and socioeconomic status, but total energy or nutrient intake was similar. However, schizophrenia patients had 13% higher energy intake compared to healthy controls and, after controlling for BMI, physical activity or VO_{2peak}, the difference in energy intake was found to be significant. After one year, a daily extra 13% calorie-intake could add up to considerable weight gain. Previous studies show inconsistent results in this respect; some studies show reduced

energy and nutrient intake (-26%,[13]; -17%,[12]) whereas another study found 39% higher energy intake among schizophrenia patients.[36] These studies compared schizophrenia patients to a non-BMI-matched control group from the general population. In a large study with BMI-matched controls, Ratliff and colleagues[37] found 8% higher energy intake in the schizophrenia patient group, but this was not statistically significant. Our results are comparable to Ratliff and colleagues[37] and suggest that inconsistent results from previous studies may be due to lack of matching for BMI. Compared to the BMI-matched control group, we found that schizophrenia patients had a 6% lower total energy intake. As far as we know, besides the current study, only Ratliff and co-workers[37] used a BMI-matched control population. Future studies, sufficiently powered, should use BMI-matched controls to provide more definitive answers regarding the total energy intake of schizophrenia patients compared to the general population.

Several general issues may account for different results between our study and previous studies. First, large country-to-country BMI-differences are known to exist.[38,39] Patients and healthy controls in our sample had lower average BMI compared to previously published Western society samples.[8-13] Second, lower average age of participants in our study (13 - 23 years younger) compared to other studies[8-11,13] could reflect progressive worsening of somatic health over the course of the illness.[40] Third, in our study food frequency questionnaires assessed habitual food intake over the past year while other studies, except Roick and co-workers,[10] used (repeated) 24-hourt recalls[11,13]. A FFQ generally overestimates dietary intake compared to other methods like 24-hour recalls. However, because the FFQ was also used to assess dietary intake in healthy controls, these different methods will not influence the difference observed between patients and controls to a large extent.[21,22] In addition, the FFQ relies on memory to report habitual food intake over the past year. We made an effort to overcome this by administering the FFQ face-to-face in patients, but cannot exclude that this may have influenced results. Fourth, inclusion of healthy controls who were matched for socioeconomic status may, at least partly, explain the limited or absent differences in energy and nutrient intake between groups.[38]

In the Netherlands, compared to other European countries, large quantities of dairy products are consumed.[41] Our results show schizophrenia patients consumed even

larger quantities of dairy products compared to locally recruited healthy controls. Despite relatively high saturated fat content of dairy products,[42] higher intake is not associated with an increased risk of cardiovascular diseases or diabetes mellitus in healthy subjects and total and low-fat dairy may even be associated with lower risk of coronary heart disease.[43-45] Higher ratios indicate schizophrenia patients possibly consumed less fruit and more juice and soft drinks, though this did not reach significance. This would be in line with results from previous studies and indicate schizophrenia patients make poorer food choices.[8-10,13] The lower mean consumption of alcohol in schizophrenia patients compared to healthy controls was consistently found in previous nutrition studies.[8-10,14,34] In schizophrenia patients, a U-shaped pattern of alcohol consumption indicates higher proportions of non- and of hazardous drinkers.[10] Consistent with previous studies,[8-10,14,34] our study found schizophrenia patients were more likely to smoke (and more heavily). Consistent with McCreadie and colleagues,[9] who found nicotine users made poorer dietary choices, we found nicotine using schizophrenia patients had significantly higher energy intake. Cigarette smoking leads to excess mortality risk and this risk increases with the number of cigarettes smoked.[46] Smoking cessation and reduction appears feasible and should actively be offered to schizophrenia patients.[47,48]

Our results show that obesity indices, both BMI and waist circumference, were best predicted by schizophrenia, physical inactivity, and lower cardiorespiratory fitness level, and not by energy intake. In line with these results, Roick and co-workers[10] reported that 17% of variance in obesity was explained by reduced physical activity. Wang and colleagues[49] also showed that in schizophrenia patients, decreased physical activity and reduced intake of monounsaturated fatty acids were responsible for metabolic risks (assessed as elevated C-reactive protein), not increased energy intake per se. In addition, for waist circumference the current study found lower socioeconomic status to be a significant predictor. In countries with high socioeconomic development lower socioeconomic status is associated to an increased body weight.[50]

There are some study limitations that need to be considered. First, this cross-sectional study included only a limited number of subjects and results may thus not be representative of the whole general schizophrenia population. Second, except for

dairy products and alcohol usage this study found limited or no differences in energy, nutrient and food group intake between schizophrenia patients and healthy controls or BMI-matched general population data. Possibly the cohort was too small to detect significant differences for certain variables. Higher total energy and food group ratios (>1) indicate schizophrenia patients tended to eat more of all foods except fruits, pastry and cookies, and alcoholic beverages which they tended to consume less (ratios <1). Third, due to the sample size we were not able to examine gender differences or the exact influence of type and dose of antipsychotic medication used on energy intake or expenditure. Fourth, healthy controls did not match to schizophrenia patients for BMI. After controlling for BMI, energy intake was found to be higher in patients compared to healthy controls. Still, general population data did match to schizophrenia patients for BMI, and no significant difference in energy intake was found between groups. Fifth, we relied on self-report to assess dietary intake, which may be subject to misclassification. However, the FFQ was validated against 12 24-hour recalls, showing sufficient validity for most food groups. Despite this, our FFQ was not validated specifically for schizophrenia patients and one should note that a FFQ is not designed to assess absolute nutrient intakes but rather to rank participants according to nutrient intake. Because we used the same method to assess dietary intake in both patients and healthy controls, we do not think this influenced the comparison with healthy controls. However, one should keep this in mind when interpreting the absolute intakes among schizophrenia patients.

In conclusion, we found similar energy and nutrient intake of schizophrenia patients as compared to matched healthy controls or a BMI-matched sample of the general population. When controlling for BMI, physical activity and fitness, total energy and carbohydrate intake was higher in schizophrenia patients compared to healthy controls. Obesity indices were the best predicted by physical inactivity and poor cardiorespiratory fitness, not by energy intake. This suggests that patients with schizophrenia have greater energy intake, but to reduce weight one should particularly focus on increasing daily activity and improving cardiovascular fitness. Future studies are warranted to further investigate the relation between physical health, including obesity indices, and lifestyle factors. Furthermore, studies are needed focusing on improving physical health in larger groups of schizophrenia patients.

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4

Effects of exercise therapy on cardiorespiratory fitness in patients with schizophrenia

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Medicine & Science in Sports & Exercise 2012;44:1834-42

Abstract

Background: Increased mortality in schizophrenia is caused largely by coronary heart disease (CHD). Low cardiorespiratory fitness (CRF) is a key factor for CHD mortality. We compared CRF in patients with schizophrenia to CRF of matched, healthy controls and reference values. Also, we examined the effects of exercise therapy on CRF in schizophrenia patients and controls.

Methods: Sixty-three schizophrenia patients and 55 controls, matched for gender, age, and socioeconomic status, were randomised to exercise (n=31) or occupational therapy (n=32) and controls to exercise (n=27) or life-as-usual (n=28). CRF was assessed with an incremental cardiopulmonary exercise test and defined as the highest relative oxygen uptake (VO_{2peak} in $ml \cdot kg^{-1} \cdot min^{-1}$) and peak work rate ($W_{peak}$ in Watt). Minimal compliance was 50% of sessions (n=52).

Results: Male and female schizophrenia patients had a relative VO_{2peak} of 34.3 (±9.9) $ml \cdot kg^{-1} \cdot min^{-1}$ and 24.0 (±4.5) $ml \cdot kg^{-1} \cdot min^{-1}$, respectively. Patients had higher resting heart rate (HR) (P<0.01) and lower peak HR (P<0.001), peak systolic blood pressure (P=0.02), relative VO_{2peak} (P<0.01), W_{peak} (P<0.001), respiratory exchange rate (P<0.001), minute ventilation (P=0.02), and HR recovery (P<0.001) than controls. Relative VO_{2peak} was 90.5% ± 19.7% (P<0.01) of predicted relative VO_{2peak} in male and 95.9% ± 14.9% (P=0.18) in female patients. In patients, exercise therapy increased relative VO_{2peak} compared to decreased relative VO_{2peak} after occupational therapy. In controls, relative VO_{2peak} increased after exercise therapy and to a lesser extend after life-as-usual (group: P<0.01; randomisation: P=0.03). Exercise therapy increased W_{peak} in patients and controls compared to decreased W_{peak} in non-exercising patients and controls (P<0.001).

Conclusion: Patients had lower CRF-levels compared to controls and reference values. Exercise therapy increased VO_{2peak} and W_{peak} in patients and controls. VO_{2peak} and W_{peak} decreased in non-exercising patients.

Introduction

Schizophrenia is a severe and chronic psychiatric illness, characterised by a marked decline in functioning. Even after treatment with antipsychotic medication, patients with schizophrenia typically are at high risk for relapse and manifest multiple somatic co-morbidities.[1] Patients with schizophrenia have a two- to threefold increased mortality rate compared to the general population,[2] resulting in a 20% reduction in life expectancy.[3] Up to 40% of excess mortality can be attributed to suicide and unnatural deaths.[4] In schizophrenia standardised mortality ratios of most major natural death categories are increased compared to the general population (i.e. digestive, endocrine, infectious, and nervous diseases).[3] The single largest cause of death in schizophrenia patients is coronary heart disease (CHD). Patients with schizophrenia are two times more likely to die of CHD than the general population.[5]

Several lifestyle factors influence the physical health status of patients with schizophrenia and negatively impact their risk for CHD. Patients with schizophrenia are much more likely to smoke, and 70-75% of patients with schizophrenia can be classified as being physically inactive and do not meet minimal physical activity recommendations.[6,7] In addition, patients with schizophrenia are more likely to have a reduced nutritional status due to an unhealthy diet.[8] Moreover, many atypical antipsychotics induce significant weight gain, increasing the risk of diabetes mellitus type II, the metabolic syndrome and ultimately CHD.[9,10]

Besides the above-mentioned factors, low cardiorespiratory fitness (CRF) has been recognised as an independent risk factor for all-cause mortality in adults and a key risk factor for CHD-related mortality.[11,12] A recent meta-analysis in the healthy population has shown an inverse association between CRF and CHD. In men, low CRF was found to predict mortality due to CHD even better than smoking, hypertension or diabetes.[12] In schizophrenia, high quality studies investigating CRF are scarce.[13] A cross-sectional study reported obese patients with schizophrenia had low CRF levels compared to population standards. Strikingly, only two participants in the entire sample (n=117) fit the categorisation of 'moderate fitness level'. All other participants scored below population standards. This indicates poor CRF is a key modifiable risk factor.[14] Interestingly a recent trial showed that eight weeks of high intensity, anaerobic exercise training increased CRF in patients with schizophrenia.[15] A large

Finish cohort sample showed adolescents who later developed psychosis, at the age of 15-16 had a relatively low level of CRF (OR 2.2; 95% CI 0.6-7.8), as measured by means of a submaximal cycle ergometer test.[16]

To the best of our knowledge, no prior randomised controlled trial has examined the effects of an exercise intervention on CRF in patients with schizophrenia and matched healthy controls. Thus, we studied whether CRF in patients with schizophrenia is lower compared to matched, physically inactive, but otherwise healthy controls as well as compared to reference values. Furthermore, we investigated whether a six-month exercise program improves CRF in patients with schizophrenia and controls.

Methods

Sample and setting

This multi-centre study included 63 patients with a schizophrenia spectrum disorder and 55 healthy comparisons, matched for gender, age, and socioeconomic status (expressed as the highest educational level of one of the parents). Patients were recruited at the University Medical Center Utrecht (the Netherlands) (*n*=26) and regional mental health care institutes (Altrecht; GGZ Duin- en Bollenstreek; GGZ Friesland) (*n*=37). Participants were enrolled in the study between May 2007 and May 2010 and written informed consent was obtained after the procedures and possible side effects were explained. This trial was part of the TOPFIT study ('The Outcome of Psychosis and Fitness Therapy') and registered in the ISRCTN register (http://www.controlled-trials.com/ISRCTN46241817/). After baseline measurements, a computer-generated randomisation procedure, incorporating concealed allocation (ratio 1:1), was performed with stratification for gender, recruitment site and body mass index (BMI; below or above 25). Patients were assigned to exercise or occupational therapy whereas controls were assigned to exercise or life-as-usual for six months. In specific, schizophrenia spectrum disorder patients had the following diagnoses: schizophrenia (*n*=45), schizoaffective (*n*=15) or schizophreniform disorder (*n*=3) according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).[17] Diagnosis was confirmed by a psychiatrist using the Comprehensive Assessment of Schizophrenia and History (CASH).[18] Patients were stable on antipsychotic medication, i.e. using the same dosage for at least four weeks prior to inclusion. They showed no evidence for significant cardiovascular, neuromuscular, endocrine or other somatic disorders that prevented safe participation in the study.[19] Patients had no primary diagnosis of alcohol or substance abuse and had an IQ≥70, as measured with the Wechsler Adult Intelligence Scale Short Form (WAIS-III SF).[20]

Healthy participants (*n*=55) were recruited from the local population via advertisements. The inclusion criteria for the healthy controls were no diagnosis of psychiatric disorders according to DSM-IV lifetime, no first-degree relative with a psychotic or depressive disorder, and being physically inactive before inclusion (i.e., undertaking less than one hour of moderate physical activity weekly). The study was approved by the Human Ethics Committee of the University Medical Center Utrecht and research committees of participating centres.

Assessments

CRF was assessed with a cardiopulmonary exercise test (CPET), performed using a 20-W·min^{-1} stepwise incremental protocol to exhaustion on an upright cycle ergometer (Lode Excalibur, Lode BV, Groningen, The Netherlands). The test was terminated at voluntary exhaustion or conform criteria as mentioned by the American Thoracic Society/ American College of Chest Physicians recommendations (ATS/ ACCP).[21] CRF, the primary outcome measure, was defined as the highest relative (mL·min^{-1}·kg^{-1}) mean oxygen uptake any 30-s interval during the test (VO_{2peak}) and the peak work rate at the moment of exhaustion (W_{peak}).[22] HR (12-led electrocardiogram) and oxygen uptake were measured continuously during the CPET (MetaLyzer® 3B; Cortex Medical GmbH, Leipzig, Germany). Before each individual test, ergometer equipment was calibrated according to the manufacturer's instructions. Blood pressure was monitored in a lying down position before commencement of CPET and on the bike just before cessation of the test. Maximal efforts at exhaustion were assumed when the peak RER (RER_{peak}, VCO_2/VO_2) equalled or exceeded 1.1.[23]

The following exercise parameters were reported, in accordance to ATS/ACCP:[24] resting HR (HR_{rest}, in bpm), peak exercise HR (HR_{peak}, in bpm), peak systolic and diastolic blood pressure (in mm Hg), relative peak oxygen uptake level (VO_{2peak}, in mL·min^{-1}·kg^{-1}), absolute peak oxygen uptake level (VO_{2peak}, in mL·min^{-1}), peak minute ventilation (V_{Epeak}, in mL·min^{-1}), peak work rate (W_{peak}, in W), RER_{peak}, oxygen pulse (O_{2pulse}, VO_{2peak}/HR_{peak} in mL·beat^{-1}) as well as ventilatory anaerobic threshold (VAT, VO_2 in mL·min^{-1}), and difference between HR_{peak} and recovery HR (HR after 5 minutes of recovery (biking at 50 W)) (HR_{diff}, in bpm). CPET data among patients with schizophrenia and healthy controls were compared to reference values calculated according to Jones et al.[25] for absolute $VO_{2\ peak}$ (mL·min^{-1}), HR_{peak} (bpm), $O_{2\ pulse}$, and VAT (VO_2, in mL·min^{-1}). For relative $VO_{2\ peak}$ (in ml·min^{-1}·kg^{-1}), reference values according to Cooper and Storer were used.[26]

Intervention

The exercise intervention was designed to improve CRF and primarily incorporated cardiovascular exercises. Muscle strength exercises (six exercises weekly; three times 10-15 repetitions maximum for biceps, triceps, abdominal, quadriceps,

pectoral, deltoid muscles) were included to provide variation. The program followed the recommendations of the American College of Sports Medicine (ACSM).[27,28] Exercise therapy was supervised by a psychomotor therapist. Information on amount of training and compliance was registered in a logbook. Exercise subjects were prescribed an hour of exercise twice weekly for six months. To prevent dropout of subjects due to injury and exhaustion, exercise intensity was increased stepwise (week 1-3: 45%; week 4-12: 65%; week 13-26: 75% of heart rate reserve based on baseline CPET data).[27]

Patients not randomised to exercise therapy were offered occupational therapy one hour twice weekly for six months. Occupational therapy comprised creative and recreational activities. Compared to exercise therapy, occupational therapy provided a similar amount of structure and attention, but no physical activation. Controls not randomised to exercise were assigned to life-as-usual and were not allowed to incorporate in moderate physical activity more than one hour weekly.

Statistical analyses

SPSS 18.0.1 (SPSS, Chicago, IL) was used to analyse the data. All statistical tests were performed two-tailed and a P value of <0.05 was considered significant. Data were examined for outliers. All analyses were performed with and without extreme outliers to examine their influence on results. In case of non-normal distribution logarithmic transformation was applied or non-parametric testing was performed.

Baseline comparisons

Multiple ANOVAs for non-categorical variables and $\chi 2$ analyses for categorical variables were used to examine differences between groups in demographics and clinical characteristics. Univariate analyses were used to examine baseline differences in HR_{rest}, HR_{peak}, systolic and diastolic blood pressure, relative and absolute VO_{2peak}, V_{Epeak}, W_{peak}, RER_{peak}, O_{2pulse}, VAT as well as HR_{diff} between patients and controls and between exercise and occupational therapy/life-as-usual. Pearson product-moment correlations were calculated to examine the relationship between age, BMI, and VO_{2peak} in both patients and controls. In patients, correlations were calculated as well between VO_{2peak} and illness duration, severity of psychosis, and antipsychotic

medication used (in haloperidol equivalent). Pearson product-moment correlations were also calculated to examine the relationship between smoking (average number of cigarettes per day) and percentage of reference relative and absolute CRF.

Comparison with reference data

Paired samples *t*-tests were performed to assess differences in individual baseline and reference relative and absolute VO_{2peak}, HR_{peak}, O_{2pulse}, and VAT within subjects, stratified for gender and group (patients vs. controls). Also, differences between reference values and CRF results of patients and controls were calculated and expressed in percentages such that the reference value equalled 100%.

Effects of Exercise Therapy

For CRF change analyses, minimal compliance was set at 50% of 52 sessions since a minimum workload is needed to be able to expect an effect in untrained subjects.[27] To assess time-by-time effects for CRF parameters, repeated measures ANOVAs were performed with HR_{rest}, HR_{peak}, peak systolic and diastolic blood pressure, relative and absolute VO_{2peak}, V_{Epeak}, W_{peak}, RER_{peak}, O_{2pulse}, VAT, and HR_{diff} as dependent variables and group (patient or control) and randomisation (exercise or occupational therapy/ life as usual) as independent variables. For relative and absolute VO_{2peak} analyses, baseline VO_{2peak}, was added as a possible confounder.

Results

Baseline characteristics

Patients were randomised to exercise (*n*=31) or occupational therapy (*n*=32) whereas controls were randomised to exercise (*n*=27) or life-as-usual (*n*=28). As shown in **Table 1**, controls were matched to patients for gender, age, and socioeconomic status,[29] but as expected, controls had lower BMI (*P*=0.01) and higher IQ (*P*=<0.001). Furthermore, on average, patients smoked significantly more cigarettes per day than controls (*P*<0.001). [29]

Dropout of patients was significantly higher in occupational therapy (*n*=7) compared to exercise therapy patients (*n*=2; $\chi^2(2)=8.33$; *P*=0.02). One healthy control (randomised to life-as-usual) dropped out due to serious physical illness. Though, at that time undiscovered, this physical illness was present before inclusion and was unrelated to the study. It was the only (serious) adverse event to take place during this trial. Baseline CPET was performed in all included patients and controls. In one patient no oxygen measurements were acquired due to anxiety.

Thirty-nine patients (62%; exercise: *n*=20; occupational therapy: *n*=19) and 53 controls (96%; exercise: *n*=26; life-as-usual: *n*=27) met minimal compliance demands of 50% of 52 offered sessions. Mean number of sessions in the final group was not statistically different between exercise (41 ± 8) and occupational therapy patients (42 ± 7; F(1,38)=1.00; *P*=0.32). However, compliance in the final patient group was, albeit at trend-level significant, different from exercise controls (45 ± 7; F(1,63)=2.95; *P*=0.09). There were no significant differences between exercise and occupational therapy patients in clinical variables or dose and type of antipsychotic or co-medication (see **Table 2**).

Table 1. Baseline characteristics of all patients with schizophrenia (EX=exercise therapy; OT=occupational therapy) and healthy controls (EX=exercise therapy; LaU= life-as-usual).

Characteristic	**Patients (*n* = 63)**				**Controls (*n* = 55)**				**Group Analyses**	
	EX (*n* = 31)	**OT (*n* = 32)**	***F***	***P***	**EX (*n* = 27)**	**LaU (*n* = 28)**	***F***	***P***	***F***	***P***
Age, (yr)	29.2 ± 7.2	30.1 ± 7.7	0.23	0.63	29.8 ± 8.3	28.8 ± 7.3	0.21	0.65	0.07	0.8
Height (cm)	179.1 ± 11	176.8 ± 7.1	0.99	0.32	179.9 ± 10.5	176.5 ± 9.6	1.56	0.22	0.03	0.86
Weight (kg)	84.6 ± 19.5	81.5 ± 19.1	0.41	0.53	77.8 ± 16.2	74.9 ± 12.3	0.54	0.47	4.51	**0.04**
Gender (M/F)	23:8	23:9	0.04 [b]	0.84	18:9	18:10	0.03 [b]	0.85	0.79 [b]	0.37
BMI ($kg \cdot m^{-2}$)	26.6 ± 6.6	26 ± 5.5	0.13	0.72	23.9 ± 3.5	24 ± 3.2	0.02	0.9	6.6	**0.01**
Parental education [a] (level (count))	1(1), 3(1), 4(7), 5(14), 6(4), 7(4)	2(2), 3(1), 4(3), 5(11), 6(11), 7(4)	6.87 [b]	0.33	4(2), 5(9), 6(8), 7(8)	2(1), 4(4), 5(9), 6(10), 7(4)	3.21 [b]	0.52	6.79 [b]	0.34
Smoking (cigarettes per day)	11.9 ± 11.4	11.7 ± 9.7	0.01	0.93	0.1 ± 0.4	1.6 ± 5.9	1.7	0.2	52.03	**<0.001**
IQ (0-155) [c]	85.5 ± 11.4	88.9 ± 18.8	0.77	0.38	110.3 ± 13.8	105.9 ± 13.7	1.39	0.25	58.13	**<0.001**

Results are presented as mean ± SD unless indicated otherwise. Significant results are presented in bold.
[a] Socioeconomic status was assessed by parental education level according to Verhage.[29]
[b] Pearson χ^2 test was used.
[c] Wechsler Adult Intelligence Scale was used to estimate total IQ at baseline.
EX, exercise therapy; OT, occupational therapy; LaU, life as usual.

Table 2. Clinical characteristics of included patients for exercise therapy (EX) and occupational therapy (OT).

Characteristic	Treatment		Analyses [a]	
	EX (*n* = 31)	OT (*n* = 32)		
	Mean ± SD	Mean ± SD	*F*	*P*
Diagnosis assessed with CASH (schizophrenia/ schizoaffective/ schizophreniform) (*n* patients)	24 / 6/ 1	21 / 9/ 2	1.12	0.57
Duration of illness (d)	2302.5 ± 2056.5	2540.1 ± 2233.2	0.19	0.66
Antipsychotic dosage ($mg \cdot d^{-1}$) [b]	8.1 ± 5.8	8.2 ± 4.6	0.01	0.93
Antipsychotic medicine (*n* (dose)):			5.35	0.8
Aripiprazole	4 (19)	4 (21)		
Clozapine	8 (338)	8 (359)		
Haloperidol	0	1 (7)		
Olanzapine	8 (14)	10 (16)		
Penfluridol	2 (18)	0		
Pimozide	1 (8)	0		
Quetiapine	2 (500)	2 (800)		
Risperidone	4 (5)	3 (5)		
Zuclopentixol	1 (12)	1 (20)		
Second antipsychotic (*n* patients)	4	7	4.40	0.62
Antidepressant (*n* patients)	11	7	1.43	0.23
Mood stabiliser (*n* patients)	0	3	5.26	0.07
Benzodiazepines (*n* patients)	8	5	1.12	0.57
PANSS total *(measures severity of psychosis)*	63.6 ± 11.2	61.7 ± 10.1	0.51	0.48
MADRS *(measures severity of depression)*	16.6 ± 8.3	13.8 ± 8.5	1.84	0.18
Camberwell Assessment of Needs (CAN sum) [c]	8.4 ± 2.9	8.3 ± 3.4	0.03	0.86

Results presented as mean ± standard deviation unless stated otherwise.
[a] EX and OT were compared at baseline on relevant clinical characteristics, depending on data, ANOVA, χ^2, or Mann-Whitney *U*-tests were used.
[b] Baseline antipsychotic doses in haloperidol equivalent in milligrams per day.
[c] CAN sum of met and unmet needs.
PANSS, Positive and Negative Syndrome Scale; MADRS, Montgomery and Åsberg Depression Rating Scale; CAN, Camberwell Assessment of Needs; EX, exercise therapy; OT, occupational therapy; CASH, Comprehensive Assessment of Schizophrenia and History.

Baseline comparisons

At baseline, patients had higher HR_{rest} ($P<0.01$) and lower HR_{peak} ($P<0.001$), peak systolic blood pressure ($P=0.02$), relative VO_{2peak} ($P<0.01$), W_{peak} ($P<0.001$), RER_{peak} ($P<0.001$), V_{Epeak} ($P=0.02$), HR_{diff} ($P<0.001$), and at trend-level significance lower absolute VO_{2peak} ($P=0.09$) than controls. No significant baseline differences between patients and controls in peak diastolic blood pressure ($P=0.68$), O_{2pulse} ($P=0.76$), and VAT ($P=0.20$) were found between patients and controls (see **Table 3**). Except higher HR_{rest} in exercise therapy (78.3 ± 16.3) compared to occupational therapy patients (69.5 ± 12.5; $F(1,62)=5.86$, $P=0.02$), no baseline differences in fitness scores were found between exercise versus occupational therapy patients or exercise versus life-as-usual controls. Relative VO_{2peak} was not different in compliant (≥50%) versus non-compliant (<50%) patients ($P=0.65$) and controls ($P=0.86$). Age was inversely correlated to relative VO_{2peak} in male (r=-0.34; $P=0.01$) but not in female (r=-0.39; $P=0.13$) patients with schizophrenia, male (r=-0.27; $P=0.12$) and female (r=-0.20; $P=0.42$) controls. BMI was inversely correlated to relative VO_{2peak} in male (r=-0.67; $P<0.001$) and female (r=-0.54; $P=0.03$) patients with schizophrenia, male (r=-0.61; $P<0.001$) and, at trend-level significance in female (r=-0.42; $P=0.08$) controls. There was a trend-level significant negative correlation between VO_{2peak} and severity of psychosis in male patients (r=-0.25; $P=0.09$) but not in female patients (r=-0.23; $P=0.38$). Both in male and female patients, illness duration (males: r=-0.23; $P=0.13$; females: r=-0.18; $P=0.50$) or antipsychotic medication use (males: r=-0.17; $P=0.26$; females: r=-0.20; $P=0.47$) were not significantly correlated with VO_{2peak}. Smoking was inversely correlated to the percentage of reference relative (r=-0.21; $P=0.02$) and absolute (r=-0.24; $P<0.01$) VO_{2peak}.

Table 3. Baseline fitness scores for patients with schizophrenia and matched healthy controls.

Characteristic	Group		Analyses	
	Patients (*n* = 63)	Controls (*n* = 55)		
	Mean ± SD	Mean ± SD	*F*	*P*
HR_{rest} (bpm) [b]	73.8 ± 15	67.3 ± 9.8	7.52	**<0.01**
HR_{peak} (bpm) [a]	172.8 ± 17.7	190.4 ± 11.6	39.39	**<0.001**
Peak systolic blood pressure (mm Hg) [b]	169.3 ± 19.6	178.8 ± 22.1	5.94	**0.02**
Peak diastolic blood pressure (mm Hg) [b]	73.8 ± 12.5	72.8 ± 11.8	0.17	0.68
Relative VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) [a]	31.6 ± 9.9	35.9 ± 5.5	7.92	**<0.01**
W_{peak} (W) [a]	218.5 ± 51.5	255 ± 54.1	14.06	**<0.001**
Absolute VO_{2peak} ($mL \cdot min^{-1}$) [a]	2532.2 ± 668.2	2736 ± 627	2.87	0.09
V_{Epeak} ($mL \cdot min^{-1}$) [a]	95.7 ± 26	106.6 ± 25.2	5.3	**0.02**
RER_{peak} (VCO_{2peak}/VO_{2peak}) [a]	1.27 ± .15	1.37 ± 0.09	21.16	**<0.001**
O_{2pulse} (VO_{2peak}/HR_{peak}) [a]	14.6 ± 3.4	14.4 ± 3.2	0.09	0.76
VAT (VO_2 in $mL \cdot min^{-1}$) [a]	1577.4 ± 451.2	1690.5 ± 496.1	1.669	0.2
HR_{diff} (bpm) [a]	39.4 ± 14.6	55.3 ± 12.6	38.83	**<0.001**

Significant results are presented in bold.
[a] Higher score indicates superior fitness.
[b] Lower score indicates superior fitness.

Comparison with reference data

Individual baseline relative and absolute VO_{2peak} values for male and female patients and controls are set out against reference values in **Table 4**. Relative VO_{2peak} was 90.5% ± 19.7% (*P*<0.01) of predicted relative VO_{2peak} in male patients with schizophrenia compared to 99.6% ± 13.5% (*P*=0.46) in male controls. In female patients with schizophrenia, relative VO_{2peak} was 95.9% ± 14.9% (*P*=0.18) of predicted relative VO_{2peak} versus 110.3% ± 19.0% (*P*=0.06) in female control subjects. Absolute VO_{2peak} in male patients with schizophrenia was 95.5% ± 20.7% (*P*=0.12) of predicted absolute VO_{2peak} compared to 103.4% ± 13.3% (*P*=0.17) in male controls. In female patients with schizophrenia, absolute VO_{2peak} was 96.8% ± 15.3% (*P*=0.42) of predicted values compared to 112.3% ± 17.0% (*P*<0.01) in female controls**.**

Table 4. Actual baseline versus reference absolute and relative VO_{2peak}, HR_{peak}, and O_{2pulse} of all subjects plus the actual VAT and number of subjects who comply with VAT reference demand, stratified for gender and group (patients vs. controls).

Characteristic	Male patients (*n* = 46)				Male controls (*n* = 36)			
	Actual	Reference	*t*	*P*	Actual	Reference	*t*	*P*
Relative VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) [a]	34.3 ± 9.9	38.0 ± 7.6	-3.26	**<0.01**	37.9 ± 4.9	38.5 ± 5.8	-0.74	0.46
Absolute VO_{2peak} ($mL \cdot min^{-1}$) [a]	2762.4 ± 596.8	2900.9 ± 243.9	-1.57	0.12	3085 ± 437	2994.3 ± 293.1	1.4	0.17
HR_{peak} (bpm) [a]	176.2 ± 16.1	191.6 ± 4.3	-7.04	**<0.001**	193.8 ± 10	191.7 ± 4.8	1.26	0.22
O_{2pulse} (VO_{2peak}/HR_{peak}) [a]	15.6 ± 2.9	15.1 ± 1.2	1.2	0.24	16 ± 2.6	15.6 ± 1.3	1.1	0.28
VAT (VO_2 in $mL \cdot min^{-1}$) [a,b]	1713.1 ± 413.8	40/6	—	—	1863.2 ± 483.1	35/1	—	—
	Female patients (*n* = 16)				**Female controls (*n* = 19)**			
Relative VO_{2peak} ($mL \cdot min^{-1} \cdot kg^{-1}$) [a]	24.0 ± 4.5	25.3 ± 4.9	-1.40	0.18	32.1 ± 4.5	29.6 ± 4.9	2.02	0.06
Absolute VO_{2peak} ($mL \cdot min^{-1}$) [a]	1870.3 ± 342.9	1928.9 ± 168	-.83	0.42	2074 ± 317.9	1853.2 ± 174.4	3.12	**<0.01**
HR_{peak} (bpm) [a]	163.8 ± 18.9	188.4 ± 5.5	-6.61	**<0.001**	183.9 ± 11.8	189.6 ± 5.3	-2.23	**0.04**
O_{2pulse} (VO_{2peak}/HR_{peak}) [a]	11.4 ± 2.6	10.2 ± .7	2.04	0.06	11.3 ± 1.8	9.8 ± .7	4.14	**0.001**
VAT (VO_2 in $mL \cdot min^{-1}$) [a,b]	1187.3 ± 309	16/0	—	—	1363.3 ± 334.6	19/0	—	—

Results presented as mean ± SD unless stated otherwise. Significant results are presented in bold.
[a] Higher score indicates superior fitness.
[b] VAT is presented as the number of subjects who comply versus the number of subjects who do not comply with VAT reference demand: VAT>40% VO_2 predicted.
[c] Lower score indicates superior fitness.

Cardiorespiratory fitness change

Six patients (exercise: *n*=3; occupational therapy: *n*=3) did not meet the maximal effort criterion ($RER_{peak} \geq 1.1$) and were therefore excluded from the peak exercise data analyses. In one patient (occupational therapy: *n*=1), due to anxiety, no breath analyses were assessed. For a majority of subjects, peripheral muscle fatigue (>50%) was the main reason for cessation of the test. Other reasons for cessation mentioned were dyspnoea (±10%) and general fatigue (<10%).

In patients, exercise therapy increased relative VO_{2peak} while relative VO_{2peak} decreased after occupational therapy. In controls, increased relative VO_{2peak} was seen after exercise therapy and, though to a lesser extent, after life-as-usual (group: $P<0.01$; randomisation: $P=0.03$). Exercise therapy increased W_{peak} in patients and controls compared to decreased W_{peak} in occupational therapy patients and life-as-usual controls (randomisation: $P<0.001$). The change over time in W_{peak} differed, at trend-level significance, between patients and controls (group × randomisation: $P=0.09$). Increased absolute VO_{2peak} levels were seen in controls compared to patients (group: $P=0.03$). Also, absolute VO_{2peak} increased, at trend-level significance, after exercise therapy (randomisation: $P=0.07$). After exclusion of one outlier, the exercise effect was no longer significant (randomisation: $P=0.11$). Increases in absolute VO_{2peak} did not differ between groups (group × randomisation: $P=0.95$). Reduced O_{2pulse} was seen in patients compared to controls (group: $P=0.03$). A trend-level significant exercise effect was seen for O_{2pulse} (randomisation: $P=0.08$). Effects in O_{2pulse} did not differ between groups (group × randomisation: $P=0.90$). VAT increased significantly after exercise subjects compared to non-exercise subjects (randomisation: $P<0.01$). VAT effects did not differ between groups (group × randomisation: $P=0.37$). No other group, randomisation or group × randomisation effects were seen (see **Table 5**). Except for absolute VO_{2peak}, exclusion of outliers had no influence on results.

Table 5. Baseline and follow-up CRF data for exercise patients and controls, occupational therapy patients, and life-as-usual controls.

Characteristic	Patients (*n* = 33)				Controls (*n* = 53)				*P* [a]		
	EX (*n* = 17)		OT (*n* = 16)		EX (*n* = 26)		LaU (*n* = 27)		I [a]	II [a]	III [a]
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up			
HR_{rest} (bpm) [b,c]	77.9 ± 18.2	75.4 ± 15.1	70.4 ± 14.1	74.3 ± 15.1	67.6 ± 10.9	65.7 ± 12.3	66.2 ± 7.9	64.6 ± 12.2	0.35	0.2	0.25
HR_{peak} (bpm) [d]	178.2 ± 14	173.9 ± 20	171.1 ± 22.8	168.2 ± 19.7	188.3 ± 11.1	184.2 ± 13.8	193 ± 12	188.9 ± 14.4	0.81	0.71	0.71
Peak syst. bp. (mm Hg) [c]	124.9 ± 14.3	121.3 ± 13.2	125.9 ± 7.6	129.4 ± 10	123.1 ± 10.1	119.3 ± 15.1	121.1 ± 13.2	120.2 ± 12.1	0.49	0.13	0.52
Peak diast. bp. (mm Hg) [c]	76.1 ± 9.3	74.7 ± 7.6	76.9 ± 10.8	78 ± 9.1	75.2 ± 10.4	71.3 ± 7.6	73.9 ± 7.7	71.7 ± 7.1	0.2	0.36	0.87
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) [d]	32.6 ± 8.9	32.9 ± 9.7	33.3 ± 12.3	31.1 ± 9.3	36.4 ± 5.8	38.8 ± 7.8	35.6 ± 5.5	36.2 ± 7	**<0.01**	**0.03**	0.8
W_{peak} (W) [d]	226.4 ± 39.8	248.4 ± 42.2	246.1 ± 55.3	237.8 ± 51.3	263.8 ± 54	272.4 ± 68.4	247.4 ± 54.9	243.7 ± 57.9	0.4	**<0.001**	0.09
VO_{2peak} ($ml \cdot min^{-1}$) [d]	2629 ± 479	2654 ± 534	2764 ± 741	2661 ± 624	2833 ± 657	3026 ± 850	2665 ± 625	2718 ± 729	**0.03**	0.07	0.95
V_{Epeak} ($mL \cdot min^{-1}$) [d]	101.3 ± 24.2	104.5 ± 26.8	106.3 ± 26.9	100.6 ± 24.1	107.7 ± 24.5	112.5 ± 26.8	105.7 ± 27.4	109.0 ± 30.9	0.17	0.17	0.34
RER_{peak} (VCO_{2peak}/VO_{2peak}) [d]	1.27 ± 0.11	1.28 ± 0.09	1.26 ± 0.1	1.26 ± 0.1	1.36 ± 0.09	1.32 ± 0.11	1.39 ± 0.08	1.36 ± 0.13	0.17	0.83	0.78
O_{2pulse} ($mL \cdot beat^{-1}$) [d]	14.8 ± 2.9	14.9 ± 3	16 ± 3.3	15.5 ± 2.7	15 ± 3.4	16.1 ± 4.4	13.8 ± 3.2	14.1 ± 3.8	**0.03**	0.08	0.9
VAT (VO_2 in $mL \cdot min^{-1}$) [d]	1546.4 ± 294	1633.4 ± 370	1693.1 ± 495	1619 ± 445	1697 ± 495	1943.5 ± 681	1691.3 ± 525	1627.8 ± 660	0.3	**<0.01**	0.37
HR_{diff} (bpm) [d]	40.5 ± 13.3	40.7 ± 12.2	40.7 ± 17.9	39.8 ± 17	55.4 ± 11.5	57.3 ± 12.5	56.3 ± 13.2	57.6 ± 12.9	0.44	0.73	0.93

Results presented as mean ± SD. Significant results are presented in bold.
[a] All analyses were performed with general linear model, repeated measures design (I=Group; II=Randomisation; III=Group x Randomisation).
[b] For resting heart rate, all eligible subjects were included in the analysis (EX=20; OT=19). For all other analyses, only subjects who complied with the maximal exercise testing demand ($RER_{peak} \geq 1.1$) were included.
[c] Lower scores indicate superior fitness.
[d] Higher scores indicate superior fitness.
EX, exercise patients and controls; OT, occupational therapy patients; LaU, life-as-usual controls; Peak syst. bp., Peak systolic blood pressure; Peak diast. bp., Peak diastolic blood pressure.

Discussion

The current study examined CRF of patients with schizophrenia as well as matched controls. Furthermore, the effect of a 6-month biweekly exercise therapy on CRF was studied. Male and female patients with schizophrenia had a relative VO_{2peak} of 34.3 ± 9.9 and 24.0 ± 4.5 $mL \cdot min^{-1} \cdot kg^{-1}$, respectively. Our results demonstrate that patients with schizophrenia, on average, age 29 yr old, have reduced relative VO_{2peak} and peak work load (W_{peak}) compared to matched and physically inactive healthy controls. In addition, comparison of individual and reference values for relative VO_{2peak}, shows 10-15% reductions in CRF levels, especially in male patients with schizophrenia. In our study, the difference in relative VO_{2peak} between patients and matched controls (4.3 $mL \cdot min^{-1} \cdot kg^{-1}$) corresponds to a more than 13% increased mortality risk in patients with schizophrenia.[12,30]

This randomised clinical trial is the first to examine the influence of exercise therapy on CRF in patients with schizophrenia. Moreover CRF was assessed by "the gold standard" graded-exercise test with respiratory gas-exchange analysis. Results show exercise, once to twice a week for 6 months, slightly increased relative VO_{2peak} and markedly improved W_{peak} in patients with schizophrenia compared to decreased relative VO_{2peak} and W_{peak} in nonexercising patients with schizophrenia. Exercise therapy completely ameliorated this progressive CRF decrease seen in nonexercising patients with schizophrenia. In controls, exercise improved relative VO_{2peak} by, on average, 2.2 $mL \cdot min^{-1} \cdot kg^{-1}$ and W_{peak} by 9.6 W, indicating that the intervention was effective in increasing CRF in healthy subjects.

Before 2011, only one cross-sectional study investigated CRF through graded exercise testing in patients with schizophrenia. Deimel and Lohmann[31] concluded patients with schizophrenia demonstrate lower aerobic-anaerobic threshold but terminated the test at submaximal workloads, indicating that maximal ergometer testing is unreliable in these subjects. In the past year, four cross-sectional studies were published examining CRF in schizophrenia. Two of which incorporated submaximal exercise testing[32,33] and two "gold standard" cardiopulmonary exercise testing.[14,34] Opposite to Deimel and Lohmann,[31] recent studies show CRF can be reliably assessed in patients with schizophrenia, which is congruent with data from our study.[14,34] At baseline, all controls and all but four patients with schizophrenia met maximal effort demand

(RER_{peak} ≥1.1), although patients with schizophrenia did reach significantly lower average RER_{peak} values than controls. This could in part be due to poorer CRF and the fact that they are not accustomed to perform high-intensity exercise.

In accordance with previous CPET studies, our results show decreased relative VO_{2peak} values in patients with schizophrenia compared to age, gender, and socioeconomic status matched controls (**Tables 3** and **4**). Compared to the present study, Heggelund et al.[34] found higher VO_{2peak} values in male (37.1 ± 9.2 $mL \cdot min^{-1} \cdot kg^{-1}$) and female (35.6 ± 10.7 $mL \cdot min^{-1} \cdot kg^{-1}$) patients. Given higher average age (males 5.4 yr and females 2.6 yr older) with comparable HR_{peak}, this is opposite to expectation. Possibly the fact that somewhat lower VO_{2peak} values are achieved in cycle ergometer protocols (present study) compared to treadmill protocols,[34] could explain these differences.[35] Another explanation might be that people from Nordic countries have higher fitness levels.[36]

As in our study, Strassnig et al.[14] incorporated cycle ergometer tests. Yet, their participants had extremely low relative VO_{2peak} values compared to the present study. This is, at least in part, explained by a higher average age (45 vs. 29 yr old) and BMI (37 vs. 26) compared to the present study. In our data, as in Strassnig et al.,[14] age was inversely correlated to VO_{2peak}. The study by Strassnig et al.[14] provides relevant information on increased cardiovascular risk of obese patients with schizophrenia and possibly describes a later stage of the illness. Given more heterogenic patient characteristics, generalisability of results obtained in this study, appears to be better.

Our results demonstrate that exercise, only once to twice a week for 6 months, increased relative VO_{2peak} and W_{peak} in patients with schizophrenia and inactive controls compared to nonexercising patients and controls. Moreover, contrary to nonexercising controls, relative VO_{2peak} and W_{peak} reduced in nonexercising patients. The improvement in VO_{2peak} in exercising controls was larger than that in exercising patients. The difference in relative VO_{2peak} improvement may in part be due to higher exercise compliance in controls compared to patients. In addition, there is evidence that patients with schizophrenia experience mitochondrial dysfunction, which may also affect their ability to improve VO_{2peak}.[37] However, Heggelund et al.,[15] although not using a randomised controlled trial, showed that high intensity training (4 x 4 min bouts at 85%-95% of HR_{peak}) did increase relative VO_{2peak} by 12% in patients with

schizophrenia. Possibly, relative VO_{2peak} improvement in exercising subjects (patients and controls) could have been more pronounced if training intensity had been higher than 75% of HR reserve.

Our study is the first to show in a robust experimental randomised controlled design that VO_{2peak} and W_{peak}, both CRF measures, decreased progressively in nonexercising patients with schizophrenia. In addition, age was inversely associated with relative VO_{2peak}, more so than in controls. Research has unequivocally shown decreased VO_2 is associated to increased mortality in healthy males and females.[11,12] Evidence is growing that poor CRF is a key risk factor for the development of CHD in patients with schizophrenia also.[13,14,31-34] Importantly, our results indicate that, with only 1 to 2 h of exercise therapy per week, this progressive decrease of CRF can be prevented, which should lead to reduced mortality in schizophrenia. We therefore recommend including exercise therapy in the usual care of patients with schizophrenia.

There are some limitations to this study. First, because of dropout and noncompliance, the longitudinal analyses were performed on a relatively small number of patients. Nevertheless, the compliance rate of this study is comparable with previously published exercise trials in patients with schizophrenia and seems a normal feature in patients with schizophrenia.[38-41] Moreover, long-term exercise adherence rates average 40% to 65% in healthy populations as well.[42] Still, especially in this patient group, therapy adherence is problematic and should be improved. A recent study demonstrated increased adherence to exercise regiments in schizophrenia by incorporation of motivational techniques.[43] Second, higher exercise frequency, longer session duration, and possibly individualised exercise intensity may have improved patients' CRF further. For improvement of CRF in healthy subjects, the ACSM suggests at least three exercise sessions a week.[27] It is noteworthy that our trial shows that only one to two exercise sessions of moderate intensity lead to improved CRF. Third, because no follow-up period was assessed after study cessation, it is not known whether CRF improvements sustained, nor whether patients have continued exercise regularly.

In conclusion, patients with schizophrenia had lower CRF-levels compared to matched, inactive controls. Exercise therapy, 1 to 2 h a week for 6 months, was able to increase relative VO_{2peak} and W_{peak} in exercising patients and controls compared to

nonexercising participants. Furthermore, in nonexercising patients, CRF decreased over the 6-month study period. Future studies should enrol more patients and use longer follow-up periods to validate our findings. Priority should be given to exercise adherence improvement in patients with schizophrenia, for example, by incorporating motivational techniques. Increased exercise frequency, session duration, and individualised exercise intensity could lead to more pronounced CRF benefits in patients with schizophrenia.[15,44]

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Exercise therapy improves mental and physical health in schizophrenia: A randomised controlled trial

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Acta Psychiatrica Scandinavica 2012; in press

This is the pre-peer reviewed version of the above mentioned article which has been published in final form at http://www.ncbi.nlm.nih.gov/pubmed/23106093

Abstract

Objective: The objective of this multicenter randomised clinical trial was to examine the effect of exercise versus occupational therapy on mental and physical health in schizophrenia patients.

Method: Sixty-three patients with schizophrenia were randomly assigned to 2 h of structured exercise (n=31) or occupational therapy (n=32) weekly for 6 months. Symptoms (Positive and Negative Syndrome Scale) and cardiovascular fitness levels (W_{peak} and VO_{2peak}), as assessed with a cardiopulmonary exercise test, were the primary outcome measures. Secondary outcome measures were the Montgomery and Åsberg Depression Rating Scale, Camberwell Assessment of Needs, body mass index, body fat percentage, and metabolic syndrome.

Results: Intention-to-treat analyses showed exercise therapy had a trend-level effect on depressive symptoms (P=0.07) and a significant effect on cardiovascular fitness, measured by W_{peak} (P<0.01), compared to occupational therapy. Per protocol analyses showed that exercise therapy reduced symptoms of schizophrenia (P=0.001), depression (P=0.012), need of care (P=0.050), and increased cardiovascular fitness (P<0.001) compared to occupational therapy. No effect for metabolic syndrome (factors) was found except a trend reduction in triglycerides (P=0.08).

Conclusion: Exercise therapy, when performed once to twice a week, improved mental health and cardiovascular fitness and reduced need of care in patients with schizophrenia.

Introduction

Schizophrenia, which is characterised by positive, negative, and cognitive symptoms, is one of the leading causes of disability among persons aged twenty to forty.[1] Although the main treatment of schizophrenia is antipsychotic medication,[2] patients often continue to experience positive, and negative symptoms[3] and patients with schizophrenia frequently suffer from co-morbid psychiatric disorders. Depression in particular is highly prevalent among patients with schizophrenia.[4] Thus, antipsychotics fall short in treating the core symptoms and the co-morbid depressive symptoms in schizophrenia.

Furthermore, 70-75 % of patients with schizophrenia can be classified as being physically inactive and do not meet minimal physical activity recommendations.[5] Interestingly, lower physical activity participation has been associated with greater negative symptoms and reduced functional exercise capacity has been associated with poorer functional outcome and more severe negative, depressive, and cognitive symptoms.[6,7]

Exercise therapy is an established treatment for mild to moderate depression,[8] and also in schizophrenia there is some evidence that exercise decreases depressive symptoms.[9,10] Randomised intervention studies examining the effect of exercise on positive and negative symptoms have been inconclusive. Some studies[11-14] report a beneficial effect on these symptoms while others do not.[15,16] Inconsistencies in results may be due to methodological limitations of published studies (i.e. not reporting exercise intensity), duration of training,[16] and small sample sizes, totalling 10-19 subjects only.[11,13,14,16]

In addition to a possible beneficial effect on the core symptoms and the co-morbid depressive symptoms, exercise therapy is also expected to improve physical health of patients with schizophrenia.[17] Patients with schizophrenia have a two to three-fold increased morbidity and mortality rate,[18] resulting in a 20% reduction in life expectancy.[19] Several lifestyle factors negatively influence physical health as patients with schizophrenia are likely to smoke,[20] are physically inactive,[5,21] suffer from malnutrition due to an unhealthy diet,[20] and have reduced cardiorespiratory fitness.[22,23] Moreover, many antipsychotics, particularly olanzapine and clozapine,

induce significant weight gain, increasing the risk of diabetes mellitus (type II) and metabolic syndrome (MetS).[24,25]

Aims of the study

We undertook a single blind, randomised controlled trial to examine the effects of a 6-month exercise therapy program as compared to an active control condition namely occupational therapy, on positive, negative and co-morbid depressive symptoms, need of care, and physical health in patients with schizophrenia. We hypothesise exercise therapy will improve positive, negative and depressive symptoms as well as physical health more than occupational therapy.

Materials and methods

Participants and setting

This multicenter study included 63 patients of the University Medical Center Utrecht, The Netherlands (*n*=26) and three regional mental health care institutes (Altrecht; GGZ Duin- en Bollenstreek; GGZ Friesland) (*n*=37). Participants were enrolled in the study between May 2007 and May 2010. This randomised controlled trial was registered in the ISRCTN register (http://www.controlled-trials.com/ISRCTN46241817/). Treating psychiatrists asked whether eligible patients were interested in the study. After having given permission, patients were contacted and fully informed both verbally and in writing by the research team. Written informed consent was obtained before inclusion. After baseline measurements a computer-generated randomisation procedure, incorporating concealed allocation (ratio 1:1), was followed with stratification for gender, location and body mass index (BMI; below or above health related upper limit of 25). Patients were either assigned to exercise therapy or occupational therapy for 6 months.

All patients were diagnosed with schizophrenia (*n*=45), schizoaffective (*n*=15) or schizophreniform disorder (*n*=3) according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Diagnosis was confirmed using the Comprehensive Assessment of Schizophrenia and History (CASH).[26] Patients were stable on antipsychotic medication, that is, taking the same dosage for at least 4 weeks prior to inclusion, and displayed no evidence of significant cardiovascular, neuromuscular, endocrine, or other somatic disorders that prevented safe participation in the study. Risk of cardiovascular disorders was assessed extensively following Lausanne recommendations (personal and family history, physical examination, laboratory testing, electrocardiogram).[27] Patients did not have a primary diagnosis of alcohol or substance abuse and had an IQ≥70, as measured with the Wechsler Adult Intelligence Scale Short Form (WAIS-III SF).[28] Patients received no remuneration for participation except expense allowances for travel costs. The study was approved by the Human Ethics Committee of the University Medical Center Utrecht and research committees of participating centers.

Measures

All baseline and follow-up measurements (after 6 months of intervention) were assessed by a research assistant and sports physician, blinded to randomisation.

Primary outcome measure for mental health change were psychiatric symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) total score.[29] Additionally, five-factor scores were calculated: positive, negative, and disorganisation symptoms, excitement and emotional distress.[30] For secondary outcome measures of mental health, the Montgomery Åsberg Depression Rating Scale (MADRS) assessed comorbid depressive symptoms.[31] The Camberwell Assessment of Need (CAN) rating scale investigated need of care by means of the sum of met and unmet clinical and social needs.[32]

Primary outcome for physical health was cardiorespiratory fitness (CRF) as assessed with a cycle ergo meter cardiopulmonary exercise test (CPET; Lode Excalibur, Lode BV, Groningen, The Netherlands).[33] CRF was defined as peak work rate at the moment of exhaustion (W_{peak} in Watts) and highest oxygen uptake during the last 30 s of the test (VO_{2peak} in ml/kg/min).[34] Maximal efforts were assumed when the respiratory exchange rate equalled or exceeded 1.1. The following were the secondary physical health parameters: BMI (kg/m^2), body fat percentage (BFP) determined via sum of four skin folds method using a Holtain skinfold calliper,[35] and metabolic syndrome (MetS), assessed according to the International Diabetes Foundation criteria[36] which included abdominal obesity and at least two of the following indicators: hypertension, elevated triglycerides, low high lipoprotein (HDL) cholesterol and raised fasting plasma glucose.

Information on amount and type of prescribed antipsychotic and other medication was gathered by the research assistant at baseline and monthly between baseline and 6 months. Antipsychotics were described in cumulative dosage and converted into haloperidol equivalents (clozapine, 40:1; olanzapine, 2.5:1; risperidone, 1:1; aripiprazole, 3.75:1; quetiapine, 50:1; pimozide, 0.85:1; pipamperon, 50:1; penfluridol, 1:1; broomperidol, 1:1; zuclopentixol, 5:1; haloperidol, 1:1 conformable to a table from the Dutch National Health Service).[37]

Intervention

The exercise therapy intervention was designed to improve CRF and primarily incorporated cardiovascular exercises. Muscle strength exercises (six exercises per week; three times 10-15 repetitions maximum for biceps, triceps, abdominal, quadriceps, pectoral, deltoid muscles) were included to provide variation. The program followed the recommendations of the American College of Sports Medicine.[38,39] Exercise therapy was delivered uniformly according to a strict protocol and supervised by a psychomotor therapist specialised in psychiatry. Information on amount of training and compliance were registered in a logbook. Exercise therapy patients were prescribed an hour of exercise twice weekly for 6 months. To prevent dropout of patients due to injury and exhaustion, exercise intensity was increased gradually (week 1-3: 45%; week 4-12: 65%; week 13-26: 75% of heart rate reserve based on baseline CPET).[38]

Patients randomised to the control group were offered occupational therapy by an occupational therapist 1 h twice weekly for 6 months. Occupational therapy comprised creative and recreational activities such as painting, reading, and computer activities. Compared to exercise therapy, occupational therapy provided a similar amount of structure and attention, thus minimising the possibility that the hypothesised exercise effect is the result of nonspecific mechanisms of action. Information on the amount of moderate to vigorous physical activity outside the intervention was obtained monthly. Participants who were randomised to occupational therapy were allowed a maximum of 60 min of moderate physical activity weekly. Participants randomised to occupational therapy were offered exercise therapy at the end of the study.

Data Analysis

The data were analysed using SPSS 18.0.1. All statistical tests were performed two-tailed and a *P*-value of <0.05 was considered significant. Multiple analysis of variance for non-categorical variables and $\chi 2$ analysis for categorical variables were used to examine differences between exercise and occupational therapy group in baseline demographic and clinical characteristics. Data were examined for outliers and normal distribution of dependent variables. All analyses were performed with and without outliers to examine their impact on results. In case of non-normal distribution

logarithmic transformation was applied, and if necessary, non-parametric testing was performed.

Analyses were performed on intention-to-treat basis as well as per protocol. Intention-to-treat analyses included all subjects that were randomised, making efforts to obtain outcome data for all participating subjects, and analysing data for those patients with follow-up outcome data, disregarding missing data.[40] Per protocol analyses were performed with those patients who had a minimum compliance of 50% of offered sessions (n=52), since a minimum workload of an hour a week is needed to be able to expect an effect in untrained subjects.[38] To adjust for non-specific mechanisms of action, a 50% compliance rate was demanded from occupational therapy subjects as well.

To assess time-by-time effects for mental and physical health parameters, repeated measures analysis of variance were performed with PANSS total, MADRS, CAN, VO_{2peak}, and W_{peak}, BMI, BFP, MetS (χ2 test), and separate MetS factors as dependent variables and randomisation (exercise or occupational therapy) as independent variable. In case of a significant PANSS total score result, additional tests were performed on the five-factor scales of the PANSS. Possible confounders (gender, age, IQ, duration of illness, BMI, medication, alcohol use, drug use, and smoking) were determined by testing differences between exercise and occupational therapy (t-tests and χ2-tests, α=0.15). Confounders were included in the model if the univariate point estimate of the effect under consideration (e.g. delta PANSS total score) changed with at least 10%. To examine whether the effect differed between subjects included at the University Medical Center and those at the regional mental health institutes site was added as a confounder in the analyses. In addition, partial eta squared (η_p^2) effect sizes were presented where respectively 0.01<0.06, 0.06<0.14, and 0.14 or higher corresponded to a small, medium, and large effect size.[41]

Results

Participants

Included subjects were randomised to exercise therapy (49%; *n*=31) or occupational therapy (51%; *n*=32). No significant differences between exercise and occupational therapy patients in baseline characteristics (**Table 1**) and type or dose of (antipsychotic) medication at baseline were found. Male participants were younger (mean age: 28 vs. 33 years old; *P*=0.02) than female participants, but no differences in other baseline demographic or clinical variables were found. Despite efforts to minimise the attrition rate such as use of telephone reminders, more patients randomised to occupational therapy (22%; *n*=7) were lost to follow-up compared to patients randomised to exercise therapy (7%; *n*=2; χ^2=8.33; *P*=0.02). Though a higher percentage of women (53%) dropped-out or were non-compliant compared to men (35%), this difference did not reach statistical significance (χ^2=0.79; *P*=0.37). Thirty-nine patients (exercise therapy: 65% (*n*=20); occupational therapy: 59% (*n*=19)) met compliance demands (study diagram see **Figure 1**). At baseline, non-compliant exercise therapy and occupational therapy patients had higher PANSS positive (*F*=4.98, *P*=0.03) and PANSS excitement (*F*=5.29, *P*=0.03) factor scores than compliant patients, other baseline demographic and clinical characteristics were similar. There were no significant differences between compliant exercise and occupational therapy subjects in baseline demographic and clinical characteristics. Mean number of attended 1 h sessions in the compliant group was equal for exercise therapy (41 ± 8) and occupational therapy subjects (42 ± 7; *P*=0.32).

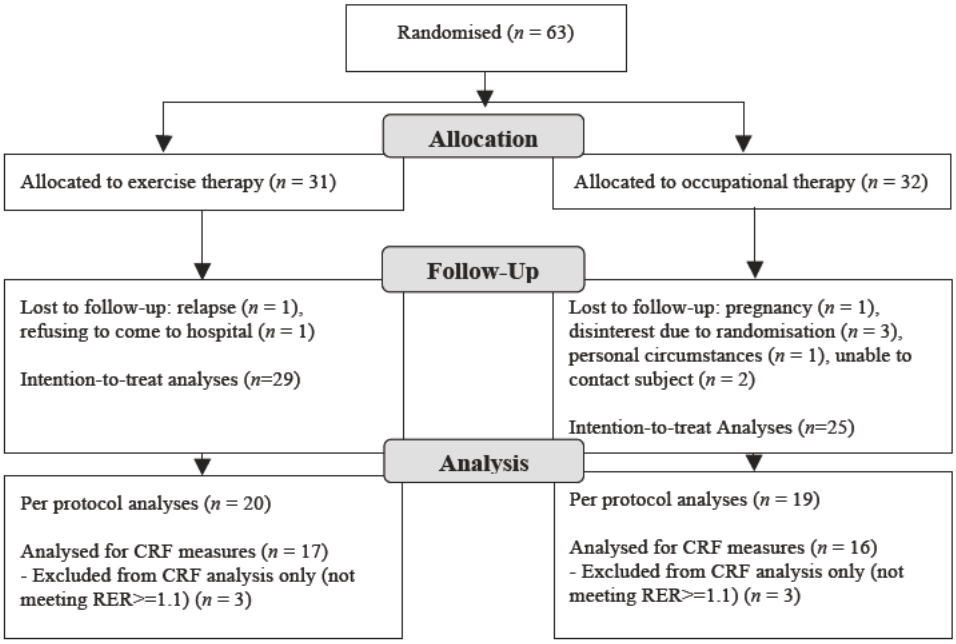
There was no difference in antipsychotic medication used (in haloperidol equivalent total: 1553±1276 mg) during the six months of exercise therapy versus occupational therapy patients (1714±1069; *P*=0.67). There was trend-level difference in number of hospitalisations (exercise therapy: 0.05±0.22; occupational therapy: 0.26±0.45; *P*=0.07).

Table 1. Baseline demographic and clinical characteristics of included patients for exercise (EX) and occupational therapy (OT).

Characteristic	Treatment				
	EX (*n* = 31)		OT (*n* = 32)		Analysis [a]
	n		*n*		*P*
Gender (male/ female)	23 / 8		23 / 9		0.84
Diagnosis (schizophrenia/ schizoaffective disorder/ schizophreniform disorder)	24 / 6/ 1		21 / 9 / 2		0.8
Parental education level (number of subjects (level 1-7)) [b]	1(1), 2(3), 6(4), 13(5), 5(6), 4(7)		2(2), 1(3), 3(4), 11(5), 9(6), 4(7)		0.33
Treatment (inpatients/dayhospital/out-patients)	3/11/16		6/9/17		0.56
Employment (welfare/working/ unemployed/student)	24/5/ 1/1		26/3/3/0		0.49
Marital status (single/married/divorced)	30 / 0 / 1		26 / 4 / 2		0.1
Ethnicity (Caucasian/other)	21 / 10		26 / 6		0.22
	Mean	**SD**	**Mean**	**SD**	***P***
Age (years)	29.2	7.2	30.1	7.7	0.63
WAIS Total IQ [e]	85.2	11.4	81.5	19.1	0.53
Duration of illness (days)	2302.5	2056.5	2540.1	2233.2	0.66
Antipsychotic dosage (mg/day)[c]	8.1	5.8	8.2	4.6	0.93
Hospitalisation until baseline (days)	130.1	125.8	257.2	345	0.4
PANSS Total [e]	63.6	11.2	61.7	10.1	0.48
Positive factor	15.5	3.8	15.6	4.2	0.89
Negative factor	18.9	6.5	16.1	4.8	0.05
Disorganisation factor	18.9	4.5	19.4	3.9	0.61
Excitement factor	13.3	3	13.4	2.6	0.84
Emotional distress factor	17.7	4.7	17.6	4.8	0.34
MADRS [d,e]	14.4	1.8	11.2	2	0.11
CAN sum [e]	8.4	2.9	8.3	3.4	0.86
Height (cm)	179.1	11	176.8	7.1	0.32
Weight (kg)	84.6	19.5	81.5	19.1	0.53
W_{peak} (W)	218	47.9	219	55.4	0.95
VO_{2max} (ml/kg/min)	31.9	10	31.7	10.1	0.94
BMI (kg/m^2) [e]	26.6	6.6	26	5.5	0.72
BFP (%) [e]	24.5	9.1	25.7	8.5	0.58
MetS (% yes) [e]	45.2	-	25	-	0.09
Waist circumference (cm)	93.4	15.6	93.3	16.5	0.98
Systolic blood pressure (mm/hg)	127.5	15	123.4	9.5	0.2
Diastolic blood pressure (mm/hg)	76.3	8.6	76.2	9.6	0.97
Triglycerides (mmol/L)	1.5	1.1	1.5	1	0.99
HDL cholesterol (mmol/L) [e]	0.97	0.3	1.1	0.3	0.11
Glucose (mmol/L)	5.4	0.6	5.2	0.5	0.17

[a] EX and OT were compared at baseline on relevant baseline demographic and clinical characteristics, depending on data, ANOVA, chi-square or Mann-Whitney *U*-tests were used.
[b] Psychosocial status, expressed as highest level of education of one of both parents according to Verhage.[42]
[c] baseline antipsychotic doses in haloperidol equivalent in mg/day.
[d] MADRS are EXP-values of the logarithmic transformed data due to non-normal distribution (all other outcome data was normally distributed).
[e] Clinical data abbreviations; WAIS, Wechsler Adult Intelligence Scale; PANSS, Positive and Negative Syndrome Scale; MADRS, Montgomery and Åsberg Depression Scale; CAN, Camberwell Assessment of Needs; BMI, Body Mass Index; BFP, Body fat percentage; MetS, Metabolic Syndrome; HDL cholesterol, high density lipoprotein cholesterol.

Figure 1. Flow diagram of the study.



Primary outcome mental health

Tables 2 and **3** show the main effects of the intervention for all primary and secondary outcome variables in the intention-to-treat analyses and per protocol analyses, respectively.

No significant intention-to-treat effect of exercise therapy compared to occupational therapy was found for PANSS total score (P=0.37). Per protocol, exercise therapy significantly decreased PANSS total score (-20.7%) compared to occupational therapy (+3.3%) (P<0.01). Given this significant effect for PANSS total score, additional analyses for the five PANSS factors were performed. Exercise therapy significantly decreased PANSS positive (P<0.01), disorganisation (P=0.02), excitement (P<0.01), emotional distress (P=0.05), and led to a trend-level significant decrease for PANSS negative (P=0.07) in comparison to occupational therapy. When site was added to the analyses, this did not change the results.

Table 2. Intention-to-treat effects of intervention (exercise therapy (EX) vs. occupational therapy (OT)) on primary and secondary outcome variables for mental and physical health.

Outcome variables	Treatment									
	EX (n = 29)				OT (n = 25)					
	Baseline		Follow-up		Baseline		Follow-up			
Primary: [c]	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	P^a	η_p^{2b}
PANSS Total [g]	63.4	11.6	59.1	11.8	62.3	10.1	60.8	11.2	0.371	0.02
Secondary: [c]										
MADRS [d,g]	13.9	1.8	9.7	2	11.7	2	10.7	1.9	0.065	0.06
CAN sum [e,g]	8.3	3	7	2.8	8.2	3.1	7.4	2.8	0.757	0
Primary: [f]										
W_{peak} (W)	223.7	44.3	240.7	41.7	230.2	56.5	223.6	50.7	**0.004**	0.16
VO_{2max} (ml/kg/min)	32.3	10.1	31.9	10	32.5	11.1	29.8	7.7	0.132	0.05
Secondary: [c]										
BMI (kg/m^2) [g]	26.8	6.9	26.6	5.8	26.8	6	27.2	6.2	0.36	0.02
BFP (%) [g]	24.9	9.3	24.4	9.6	27.1	9.1	28	8.6	0.39	0.02
MetS (% yes) [g]	48.3		34.5		28		32		0.284	
Waist circ (cm)	94.3	16	95.1	14.3	97.4	15.9	98.9	16	0.591	0.01
Syst BP (mm/hg) [g]	127.9	15.8	125.3	15.8	124.8	9.9	127.5	12.7	0.249	0.03
Diast BP (mm/hg) [g]	75.7	9.2	75.5	7.6	76.5	9.8	78.6	8.7	0.242	0.03
Triglyc (mmol/L) [g]	1.6	1.1	1.5	1	1.5	1.1	1.6	1	0.19	0.04
HDL (mmol/L) [f,g]	0.9	0.2	1.1	0.2	1	0.3	1	0.2	0.115	0.07
Glucose (mmol/L)	5.4	0.7	5.5	0.7	5.3	0.6	5.5	0.6	0.721	0

Results presented as mean ± standard deviation, significant results are presented in bold.
[a] Except for MetS where Chi-square test was performed, all analysis were performed with general linear model, repeated measures design.
[b] Effect sizes given as Partial eta square (η_p^2).
[c] Lower follow-up scores indicate improvement.
[d] MADRS are EXP-values of the logarithmic transformed data due to non-normal distribution of data.
[e] CAN sum of met and unmet needs.
[f] Higher follow-up scores indicate improvement.
[g] Clinical data abbreviations; PANSS, Positive and Negative Syndrome Scale; MADRS, Montgomery and Åsberg Depression Scale; CAN, Camberwell Assessment of Needs; BMI, Body mass index; BFP, Body fat percentage; MetS, Metabolic Syndrome; Waist circ, waist circumference; Syst BP, systolic blood pressure; Diast BP, diastolic blood pressure; Triglyc, triglycerides; HDL, high density lipoprotein cholesterol.

Table 3. Per protocol effects of intervention (exercise therapy (EX) vs. occupational therapy (OT)) on primary and secondary outcome variables for mental and physical health (compliance at least 50% of offered sessions).

Outcome variables	Treatment											
	EX (n = 20)					OT (n = 19)						
	Baseline		Follow-up			Baseline		Follow-up				
Primary: [c]	**Mean**	**SD**	**Mean**	**SD**	**%** [a]	**Mean**	**SD**	**Mean**	**SD**	**%** [a]	***P***	η_p^2 [b]
PANSS Total [g]	62.4	12.5	55.7	11.8	-20.7	60	9.6	61.1	10.2	3.3	0.001	0.27
Positive	14.6	3.5	12.5	4.5		14.8	3.8	15.7	4.6		0.003	0.22
Negative	19.3	6.1	17.8	4.9		16.1	5.2	17.2	5.8		0.069	0.09
Disorganisation	18.8	4.9	17.1	5		18.7	4.3	19.6	4.1		0.017	0.14
Excitement	12.5	2.1	11.3	1.9		13	2.2	14	1.8		0.002	0.23
Emotional distr.	17.9	4.1	15	5		17.8	4.9	17.4	4.8		0.049	0.1
Secondary: [c]												
MADRS [d,g]	13.1	1.8	8.3	2.1	-36.6	11.4	2.1	10.9	1.9	-4.4	0.012	0.16
CAN sum [e,g]	8.2	3	6.4	2.9	-22	7.6	2.7	7.3	2.7	-4	0.05	0.1
Primary: [f]												
W_{peak} (W)	226.4	39.8	248.4	42.2	9.7	246.1	55.3	237.8	51.3	-3.3	<0.001	0.34
VO_{2max} (ml/kg/min)	32.3	9.4	32.2	9.5	-0.3	33.6	12.6	30.5	8.9	-9.2	0.066	0.11
Secondary: [c]												
BMI (kg/m^2) [g]	27.3	7.1	27	6	-1.1	27.9	6	28.4	6.3	4.8	0.27	0.04
BFP (%) [g]	24.9	9.3	24.4	9.6	-2	27.1	9.1	28	8.6	3.3	0.183	0.05
MetS (% yes) [g]	50	-	40	-	-10	36.8		42.1		5.3	0.493	
Waist circ (cm) [g]	95.2	15.4	95.1	13.4	-0.1	100.6	15.8	101.5	16.2	0.9	0.573	0.01
Syst BP (mm/hg)	125.7	14.5	123.3	14.8	-1.9	125.8	7.3	127.8	10.6	1.6	0.387	0.02
Diast BP (mm/hg)	76.7	9.1	75.7	7.6	-1.3	77.6	10.4	78.2	8.5	0.8	0.35	0.03
Triglyc (mmol/L)	1.6	1.1	1.4	1	-13.5	1.7	1.2	1.6	0.9	-2.4	0.075	0.1
HDL (mmol/L) [f]	0.9	0.2	1.1	0.2	11.7	1	0.3	1	0.2	-2	0.115	0.07
Glucose (mmol/L)	5.4	0.7	5.6	0.7	-2.6	5.3	0.7	5.5	0.7	-2	0.717	0

[a] Percentage change in mean score from baseline to follow-up.
[b] Effect sizes given as Partial eta square (η_p^2).
[c] Lower follow-up scores indicate improvement.
[d] MADRS are EXP-values of the logarithmic transformed data due to non-normal distribution of data.
[e] CAN sum of met and unmet needs.
[f] Higher follow-up scores indicate improvement.
[g] Clinical data: PANSS, Positive and Negative Syndrome Scale; Emotional distr., Emotional distress; MADRS, Montgomery and Åsberg Depression Scale; CAN, Camberwell Assessment of Needs; BMI, Body mass index; BFP, Body fat percentage; MetS, Metabolic Syndrome; Waist circ, waist circumference; Syst BP, systolic blood pressure; Diast BP, diastolic blood pressure; Triglyc, triglycerides; HDL, high density lipoprotein cholesterol.

Secondary outcome mental health

As MADRS scores were positively skewed data were logarithmically transformed. There was a trend-level intention-to-treat effect of exercise therapy (-30.2%) compared to occupational therapy (-8.5%) in depression score (MADRS) (P=0.07). Per protocol, MADRS score improved significantly more after exercise therapy (-36.6%) than after occupational therapy (-4.4%) (P=0.01). No significant intention-to-treat effect of exercise therapy was found for CAN compared to occupational therapy (P=0.76). Per protocol, a significant effect for CAN was found. Need of care decreased after exercise therapy (-22.0%) as compared to occupational therapy (-4.0%) (P=0.05). When site was added to the analyses, this did not change results.

Primary outcome physical health

For the intention-to-treat analyses all subjects with two measurements were included in the W_{peak} and VO_{2peak} analyses. Exercise therapy (+7.6%) compared to occupational therapy (-2.9%) led to a significant W_{peak} increase (P<0.01). No significant change after exercise therapy (0%) compared to occupational therapy (-8.8%) in VO_{2peak} was found (P=0.13). For per protocol analyses 6 patients (3 exercise therapy; 3 occupational therapy) were excluded from the W_{peak} and VO_{2peak} analyses since they did not meet maximal effort criteria. From baseline to follow-up, exercise therapy significantly increased W_{peak} (P<0.001) by 9.7% compared to a decreased W_{peak} of 3.3% after occupational therapy. There was a trend-level change in VO_{2peak} after exercise therapy (-0.3%) compared to occupational therapy subjects (-9.2%) (P=0.07). When site was added to the analyses, this did not change the results.

Secondary outcome physical health

No significant intention-to-treat effect of exercise therapy compared to occupational therapy was found for MetS (P=0.28), BMI (P=0.36), BFP (P=0.39), waist circumference (P=0.59), systolic blood pressure (P=0.25), diastolic blood pressure (P=0.24), triglycerides (P=0.19), HDL cholesterol (P=0.12), and glucose (P=0.72). Per protocol, a trend-level improvement of triglycerides after exercise therapy (-13.5%) as compared to occupational therapy (-2.4%) was found (P=0.08). When site was added to the analyses, this did not change the results.

Discussion

In this randomised controlled trial, the largest so far, we examined the effects of a 6-month exercise program on mental and physical health in patients with schizophrenia, on average aged 30 years old who were stable on antipsychotic medication. Although the intention-to-treat analyses revealed no difference between exercise therapy versus occupational therapy, in those patients with schizophrenia who were compliant to exercise therapy (one to 2 h a week), positive symptoms and comorbid depressive symptoms, need of care substantially diminished with even a trend reduction in negative symptoms and number of hospitalisations. Furthermore, cardiovascular fitness increased during exercise therapy as compared to occupational therapy.

To the best of our knowledge, no previous randomised clinical trial has examined the influence of exercise therapy on need of care and only a few studies have examined the effects on schizophrenia symptoms and depression. Moreover, interpretation of earlier studies was hampered by their small total sample sizes of 10-19 subjects.[11,13,14,16] Nevertheless, our findings are in line with these previous studies suggesting that exercise therapy could be beneficial in reducing the core symptoms[11,13,14] as well as depression[9,10] in schizophrenia.

The mechanisms by which exercise therapy decreases schizophrenia symptoms and depression are not fully understood. In depression, exercise leads to physiological changes such as increased levels of neurotransmitters (e.g. endorphins).[43] Other suggested mechanisms for exercise effects on mental health are psychological changes such as social support, improved perceptions of competence, self-efficacy, and distraction.[44] Interestingly exercise therapy has been shown to increase hippocampal volumes in schizophrenia[14] suggesting exercise-induced brain plasticity might instigate the mental health improvement in schizophrenia patients.

In schizophrenia, poor cardiovascular fitness is a key risk factor for the development of cardiovascular disease.[45] A recent physical activity consensus statement states that in schizophrenia patients, a small increase in the amount of physical activity is useful since it could already improve the somatic risk profile.[46] This randomised controlled trial is the first to examine the influence of exercise therapy on cardiovascular fitness in patients with schizophrenia utilizing ‘the gold standard’ graded-exercise test with

respiratory gas-exchange analysis. Our results show that exercise therapy significantly increased W_{peak} and at trend-level improved VO_{2peak}, as compared to occupational therapy. Finding a trend improvement in VO_{2peak} only can be explained by (i) a relatively low training intensity,[16] (ii) mitochondrial dysfunction in schizophrenia, which may also affect their ability to improve mitochondrial oxygen utilisation and hence VO_{2peak}.[47]

Furthermore, there was a trend reduction of fasting triglycerides over the 6 months of exercise therapy. A meta-analysis has shown elevated triglycerides to be associated with an increased risk of cardiovascular disease, even when adjusting for HDL cholesterol level and other risk factors.[48] Although changes in BMI, BFP, waist circumference, blood pressure, HDL cholesterol, and fasting glucose were not significantly different between the two groups in our study, results consistently favoured the exercise therapy group. Possibly, frequency, intensity, and session duration of exercise were too limited to induce more substantial effects in these physical parameters.[16,49] The lack of a significant weight change in patients who received exercise therapy is consistent with findings of a meta-analysis showing that isolated exercise therapy, not offered in conjunction with diet, is ineffective in obese subjects.[50]

This study has some limitations. First, due to a high drop-out rate and low compliance not all subjects were included in the analyses. Still, a majority of participants, namely 65% of exercise therapy patients, met minimal compliance demands and in these patients exercise had robust effects on psychosis and depression. This percentage is comparable to previously published exercise studies in schizophrenia patients.[11,15] Although exercise appears to improve mental and physical health in schizophrenia, non-adherence threatens the implementation of exercise therapy in daily practice. Indeed, we found that non-compliant patients were more severely ill than compliant patients with schizophrenia. Also, for patients with worse functioning, namely those with an IQ lower than 70 (exclusion criterion), this intervention might be less doable. Some studies have shown that motivational techniques improve exercise adherence in schizophrenia patients[51,52] and others suggested involving family members, friend or caretakers, in example by having them exercise together with patients, could improve treatment adherence.[53] This may especially improve adherence in low functioning patients. Furthermore, in example body-oriented psychotherapy[54] and

yoga therapy[55] have also shown to decrease symptoms severity in schizophrenia patients. Tailoring the intervention to personal preference may improve effectiveness and generalisability. Furthermore, given the limited intention-to-treat effects specific subjects' characteristics complying with either exercise or occupational therapy could explain our results. Nevertheless, no evidence for this hypothesis was found as no baseline differences between compliant exercise and occupational therapy patients were found. Second, participants randomised to their non-preferred intervention may have been less likely to experience psychological benefits.[56] Third, the absence of a 'treatment as usual' group may be considered a limitation as it is now unknown what happens to patients' health if no intervention is given. However, if we had included a treatment as usual control group, improvements could have resulted from nonspecific effects such as attention or physical activity undertaken for travelling to the training facilities. For future studies three arms would be preferable (treatment as usual, active control group and exercise therapy group). Fourth, a selection bias could have occurred by attracting particularly those patients with interest in exercise and health improvement. Finally, as we did not follow-up patients after study cessation, it is undetermined whether patients continued to exercise and whether the overall health improvement would have lasted.

In conclusion, exercise therapy one to 2 h weekly evidently improved mental health, improved cardiovascular fitness and reduced need of care in patients with schizophrenia. Future studies should enrol larger number of patients with longer follow-up periods to validate our findings. Furthermore, given limited effects in intention-to-treat analyses, methods should be investigated to improve exercise therapy compliance. Exercise therapy appears to be an effective add-on treatment in schizophrenia.

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6

Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: A randomised controlled trial in patients with schizophrenia and healthy controls

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European Neuropsychopharmacology 2012; in press

Abstract

The objective of this study was to examine exercise effects on global brain volume, hippocampal volume, and cortical thickness in schizophrenia patients and healthy controls. Irrespective of diagnosis and intervention, associations between brain changes and cardiorespiratory fitness improvement were examined. Sixty-three schizophrenia patients and fifty-five healthy controls participated in this randomised controlled trial. Global brain volumes, hippocampal volume, and cortical thickness were estimated from 3-Tesla MRI scans. Cardiorespiratory fitness was assessed with a cardiopulmonary ergometer test. Subjects were assigned exercise therapy or occupational therapy (patients) and exercise therapy or life-as-usual (healthy controls) for six months 2 h weekly. Exercise therapy effects were analysed for subjects who were compliant at least 50% of sessions offered. Significantly smaller baseline cerebral (grey) matter, and larger third ventricle volumes, and thinner cortex in most areas of the brain were found in patients versus controls. Exercise therapy did not affect global brain and hippocampal volume or cortical thickness in patients and controls. Cardiorespiratory fitness improvement was related to increased cerebral matter volume and lateral and third ventricle volume decrease in patients and to thickening in the left hemisphere in large areas of the frontal, temporal and cingulate cortex irrespective of diagnosis. One to 2 h of exercise therapy did not elicit significant brain volume changes in patients or controls. However, cardiorespiratory fitness improvement attenuated brain volume changes in schizophrenia patients and increased thickness in large areas of the left cortex in both schizophrenia patients and healthy controls.

Introduction

In schizophrenia, structural brain abnormalities, in particular smaller grey matter volume, enlargement of lateral and third ventricles, decreased hippocampal volume, and cortical thinning have consistently been demonstrated.[1-3] Longitudinal studies have shown that these brain volume abnormalities are progressive in nature,[4] not only in the early phases of the illness[5] but also in chronic stages.[6,7] These changes are related to the clinical course as several studies have shown that patients with poorest outcome have most pronounced brain loss over time.[5,6,8,9] To explain these progressive brain volume reductions in schizophrenia, researchers have suggested that these reductions are core to the illness and could be due to the so-called "toxic" effects of the psychotic state of the brain.[10-12] Some evidence has been provided by the findings of a five year follow-up MRI study which found longer duration of psychosis during follow-up was associated with more pronounced grey matter volume reductions and increases of ventricular volume.[8] In addition, it has been shown that genetic factors play a role in the progressive brain volume reductions in schizophrenia patients.[13,14] Nevertheless, others have argued that volume decrease over time originates from (unhealthy) environmental factors patients with schizophrenia are frequently exposed to.[15-20]

Indeed, alcohol abuse,[20] cannabis use,[15,16] and antipsychotic treatment[17-19] have been found to influence brain changes over time in schizophrenia. Furthermore, physical inactivity[21] and poor cardiorespiratory fitness[22] could also explain brain volume reductions seen in schizophrenia. If physical inactivity and poor cardiorespiratory fitness explain the brain volume reductions in schizophrenia, one would expect that the brain volume decreases will diminish when cardiorespiratory fitness increases. Interestingly, animal studies have unequivocally shown that physical exercise positively affects brain morphology, especially in the hippocampus, and brain functioning.[23,24] In healthy elderly, studies have shown that exercise increases cerebral grey and white matter[25] and hippocampal volumes.[26] As far as we know only one neuroimaging study has been performed examining the effects of exercise in schizophrenia.[27] They examined the hippocampal volume and found hippocampus volume enlargement after three months of exercise in male patients (*n*=8). Moreover,

this increase was related to cardiorespiratory fitness improvement.[27] They did not examine the effects on global brain volume nor on cortical thickness.

This study examines the effect of exercise therapy on global brain volume, hippocampus, and cortical thickness in schizophrenia patients and healthy controls. Since we recently showed that exercise therapy in schizophrenia improves cardiorespiratory fitness, in particular peak workload (measured as W_{peak}),[28] we also investigated the association between changes in global brain volumes, hippocampus and cortical thickness and change in cardiorespiratory fitness.

Experimental procedures

Sample and setting

This multicentre study included 63 patients with a schizophrenia spectrum disorder and 55 healthy controls, matched for gender, age, and socioeconomic status of their parents (expressed as highest educational level of one of the parents). Patients were recruited at the University Medical Center Utrecht (The Netherlands), the Institute for Mental Health Care Altrecht (Utrecht, The Netherlands), GGZ Duin- en Bollenstreek (Voorhout, The Netherlands), and GGZ Friesland (Heerenveen, The Netherlands). Participants were enrolled in the study between May 2007 and May 2010 and written informed consent was obtained after the procedures and possible side effects were explained. After baseline measurement, a computer-generated randomisation procedure, incorporating concealed allocation (ratio 1:1), was performed with stratification for gender, recruitment site and Body Mass Index (BMI; below or above critical 25). Patients were assigned to exercise therapy or occupational therapy whereas controls were assigned to exercise therapy or life as usual for six months. Patients had a diagnosis of schizophrenia (n=45), schizoaffective (n=15) or schizophreniform disorder (n=3) according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).[29] Diagnosis was confirmed by psychiatrists using the Comprehensive Assessment of Schizophrenia and History (CASH).[30] Patients were stable on antipsychotic medication, i.e. using the same dosage for at least four weeks prior to inclusion. They showed no evidence for significant cardiovascular, neuromuscular, endocrine or other somatic disorders that prevented safe participation in the study.[31] Patients did not have a primary diagnosis of alcohol or substance abuse and had an IQ≥70, as measured with the Wechsler Adult Intelligence Scale Short Form (WAIS-III SF).[32]

Healthy participants were recruited via advertisements from the local population. The inclusion criteria for the healthy controls were an age between 18 and 48 years, no diagnosis of psychiatric disorders according to DSM-IV lifetime,[29] no first-degree relative with a psychotic or depressive disorder, and being physically inactive before inclusion (i.e., undertaking less than 1 h of moderate physical activity weekly).

The study was approved by the Human Ethics Committee of the University Medical Center Utrecht and research committees of participating centres.

Assessments

All subjects underwent a six months intervention. Demographic and clinical baseline and follow-up measurements were assessed by a research assistant and sports physician blind to randomisation. All assessments at baseline and follow-up were acquired within a time frame of 14 days.

Cardiorespiratory fitness testing

Cardiorespiratory fitness (CRF) was assessed with a cardiopulmonary exercise test (CPET), performed using a 20 watt per minute (W/min) stepwise incremental protocol to exhaustion on a cycle ergometer (Lode Excalibur, Lode BV, Groningen, the Netherlands).[33] CRF was defined as the peak work rate at the moment of exhaustion (W_{peak} in wattage (W)).[34] Heart rate (twelve led ECG) and oxygen uptake were measured continuously during the CPET (MetaLyzer® 3B, Cortex Medical GmbH, Leipzig, Germany). Maximal efforts were assumed when the respiratory exchange rate (RER) equalled or exceeded 1.1.[35]

Symptom severity and medication

To evaluate severity of symptoms, the Positive and Negative Syndrome Scale (PANSS) total score was assessed in patients.[36] Information on amount, type and compliance of prescribed antipsychotic and other medication was gathered for lifetime, at baseline and monthly between baseline and six months. Antipsychotics are described in cumulative dosage (up to baseline and baseline to follow-up) and converted into haloperidol equivalents (clozapine, 40:1; olanzapine, 2.5:1; risperidone, 1:1; aripiprazole, 3.75:1; quetiapine, 50:1; pimozide, 0.85:1; pipamperon, 50:1; penfluridol, 1:1; broomperidol, 1:1; zuclopentixol, 5:1; haloperidol, 1:1 in conformance with a table from the Dutch National Health Service).[37] Detailed information on medication prescription and compliance was assessed monthly by the research assistant.

Imaging and preprocessing

Structural MRI scans of the whole brain were acquired on a single 3 Tesla Achieva medical scanner (Philips, Best, The Netherlands). A three dimensional (3D)

anatomical T_1-weighted image of the whole head was acquired (Fast Field Echo (FFE) using parallel imaging; 180 0.8-mm contiguous sagittal slices, echo time [TE] = 4.6 ms, repetition time [TR] = 10 ms, flip angle = 90°, Field of View (FOV) = 240 mm/100%, in-plane voxel size 0.75 × 0.75 mm^2, reconstruction matrix = 200 × 320 × 320). Volumetric processing was performed on the computer network of the Department of Psychiatry of the Brain Division, University Medical Center Utrecht, The Netherlands. All brain images were coded to ensure investigator blindness to subject identification.

Volumetric processing

The T1-weighted images were automatically placed in Talairach orientation[38] without scaling, by registering them to a model brain. Intracranial masks were created by registration from the T1-weighted image to a model brain using an iterative process of non-linear transformations with increasing precision up to voxel resolution. This model brain was created from an independent group of schizophrenia patients, their siblings and healthy controls[39] following a similar procedure as described previously.[40] Intracranial masks were manually edited, where necessary. The intracranial segment served as a mask for all further segmentation steps. The T1-weighted images were corrected for field inhomogeneities using the N3 algorithm.[41] An automatic image-processing pipeline was used to define the volume of the cerebrum, cerebral grey matter and white matter.[42] In short, pure grey and white matter intensities were directly estimated from the image. The amounts of pure and partial volume voxels were modelled in a non-uniform partial volume density, which is fitted to the intensity histogram. Expected tissue fractions, based on the pure intensities and the partial volume density, were subsequently computed in each voxel within the cerebrum. Total brain volume was calculated by adding the grey and white matter volumes. Lateral and third ventricle volumes were also assessed. The software included histogram analysis, mathematical morphology operations, and anatomical knowledge-based rule to connect all voxels of interest, as was validated before.[43] The segments for lateral and third ventricles were visually checked and edited to ensure an accurate segmentation.

Hippocampus volume

Measurement of hippocampal volume was done using automated hippocampal volume methodology (FMRIB software library, FSL 4.1). Hippocampi were automatically labelled using the subcortical segmentation routines "FIRST," provided as part of the FSL software distribution (version 4.1.2, http://www.fmrib.ox.ac.uk/fsl/). Before starting the FSL-FIRST-based segmentation the T1-weighted images were automatically placed in Talairach orientation as described earlier. The initial step for FSL-FIRST was an affine registration of each brain to MNI-152 space.[44] The correct affine registration was visually confirmed in all cases. The number of modes of variation for the hippocampal template to be warped to fit the individual hippocampi was set to 300. Each automatically segmented hippocampus was saved as an inclusive binary mask in the same space as the original image. The volumes of right and left hippocampi were extracted. See also ENIGMA Consortium protocols, http://enigma.loni.ucla.edu/protocols/.

Cortical thickness

To estimate cortical thickness, we used the CLASP (Constrained Laplacian Anatomic Segmentation Using Proximity) algorithm designed at the McConnell Brain Imaging Centre of the Montreal Neurological Institute.[45-47] A 3-dimensional surface consisting of 81,920 polygons was fitted to the white matter-grey matter interface. This defined the inner surface of the cortex, which was then expanded to fit the grey matter-cerebrospinal fluid interface, thereby creating the outer cortical surface.[46,47] Cortical thickness was estimated by taking the distance between the two surfaces; thus, each polygon vertex on the outer surface had a counterpart vertex on the inner surface. The surfaces of both measurements for each participant were registered to an average surface created from 152 individuals,[48] allowing comparison of cortical thickness locally between participants at baseline and the follow-up measurement. Region-of-Interests (ROIs) were automatically segmented using the automated anatomical labelling (AAL) atlas,[49] resulting in 78 ROIs (39 for both left and right hemispheres). For each person, the change in cortical thickness was calculated for each of the AAL areas.

Intervention

The exercise therapy intervention was designed to improve CRF and primarily incorporated cardiorespiratory exercises. Cardiorespiratory exercises were performed using the following exercise equipment: upright bicycle ergometer, recumbent bicycle ergometer, rowing machine, cross-trainer, and treadmill. In addition, muscle strength exercises (six exercises per week; three times 10 - 15 repetitions maximum for biceps, triceps, abdominal, quadriceps, pectoral, deltoid muscles) were included to provide variation. The programme followed the recommendations of the American College of Sports Medicine.[50,51] Exercise therapy was supervised by a psychomotor therapist specialised in psychiatry. Information on amount of training and compliance was registered in a logbook. Exercise therapy subjects were prescribed an hour of exercise, consisting of both cardiovascular exercises (40 min) and muscle strength exercises (20 min) twice weekly for six months. To prevent dropout of patients due to injury and exhaustion, exercise intensity was increased stepwise (week 1-3: 45%; week 4-12: 65%; week 13-26: 75% of heart rate reserve based on baseline CPET).[50] Patients not randomised to physical therapy were offered occupational therapy by an occupational therapist 1 h twice weekly for six months. Occupational therapy comprised creative and recreational activities. Compared to exercise therapy, occupational therapy provided a similar amount of structure and attention, but no physical activation.

Statistical analysis

SPSS 18.0.1 was used to analyse the demographic and brain volume data. All statistical tests were performed two-tailed and a *P*-value of <0.05 was considered significant. Data were examined for outliers. Analyses were performed with and without outliers to examine their impact on the results. In case of non-normal distribution logarithmic transformation was applied, or non-parametric testing was performed.

Previously, exercise therapy was found to reduce symptom severity[52] and increase hippocampal volume in schizophrenia patients[27]. Moreover, parahippocampal gyrus growth was only seen in schizophrenia patients with a higher intelligence.[53] In case of significant brain volume change results, PANSS total change, antipsychotic medication used between baseline and follow-up (in haloperidol equivalent), and

intelligence were added to analyses to investigate whether these factors explain results.

All analyses were performed in those subjects who were compliant at least 50% of 52 sessions, unless stated otherwise. The minimal compliance demand is chosen since a minimal workload of at least one hour weekly is needed to be able to expect any effect in untrained subjects.[51]

Baseline comparisons

Multiple analyses of variance for non-categorical variables and $\chi 2$ analyses for categorical variables were used to examine differences between groups in demographics and clinical characteristics. Univariate analyses were used to examine baseline brain volume differences between patients and controls and between exercise therapy and occupational therapy/life-as-usual. For measures of cortical thickness, regression analyses were used, with gender, age and handedness as covariates to investigate main effects for group, intervention and the interaction between group and intervention.

Brain volume change

Brain volume change was calculated by subtracting baseline volume from follow-up volume. To assess the differential effect of intervention (exercise therapy versus occupational therapy/life-as-usual) on brain volume (change) between the groups multiple linear regression analyses were performed. For cerebrum, cerebral grey and white matter, lateral and third ventricles, and hippocampal volume, change was added as the dependent variable in analyses. Group (patient or control), intervention (exercise therapy or occupational therapy/life-as-usual), and the group × intervention interaction were the independent variables. Intracranial volume, gender, and age were included as covariates.

For cortical thickness, regression analyses were used with age, gender, and handedness as covariates, to examine change in thickness per AAL region. This produced *F* statistics at each AAL region for the effect of group (patient versus controls), intervention (exercise therapy versus occupational therapy/life-as-usual), and group × intervention. We adjusted for multiple comparisons using a False Discovery

Rate (FDR=0.05, two-tailed).[54] In addition, mean cortical thickness change in each hemisphere was investigated using regression analyses, using the same covariates.

Effect CRF change on brain volume

Previously, we showed that W_{peak} improved after exercise therapy compared to occupational therapy in patients with schizophrenia.[28] We therefore performed further analyses to examine whether an increased CRF ameliorated brain volume deterioration in patients with schizophrenia and investigated whether this effect is seen in healthy controls, independent of intervention. To assess the effect of CRF change on brain volume (change) multiple linear regression analyses were performed on all included subjects with two successful scans (so not using the 50% compliance criterion). For cerebrum, cerebral grey and white matter, lateral and third ventricles, hippocampal volume, and cortical thickness, change was the dependent variable in analyses. Group (patient or control), CRF-change, measured as W_{peak}-change, and an interaction group × W_{peak}-change were the independent variables. Intracranial volume, gender and age were included as covariates when investigating brain volume change. Handedness, gender and age were included as covariates when investigating cortical thickness change.

Results

In total, 31 patients were randomised to exercise therapy and 32 patients to occupational therapy, whereas 27 healthy controls were randomised to exercise therapy and 28 to life-as-usual (see study diagram in **Figure 1**). Diagnostic subgroups were equally distributed between exercise therapy (schizophrenia: *n*=24; schizoaffective disorder: *n*=6; schizophreniform disorder: *n*=1) and occupational therapy patients (schizophrenia: *n*=21; schizoaffective disorder: *n*=9; schizophreniform disorder: *n*=2; $\chi^2(4)=1.67$, *P*=0.80). Drop-out of patients was significantly higher in the occupational therapy (*n*=7) compared to the exercise therapy group (*n*=2, $\chi^2(2)=8.33$, *P*=0.02). Mean number of attended sessions did not differ significantly between exercise therapy patients (mean ± SD; 41 ± 8), exercise therapy controls (44 ± 7), and occupational therapy patients (43 ± 7; $F(2,58)=1,37$, *P*=0.26). Detailed baseline demographic and clinical data are depicted in **Table 1**.

Figure 1. Flow diagram for exercise therapy (EX) and occupational therapy (OT) patients, EX and life as usual (LaU) controls.

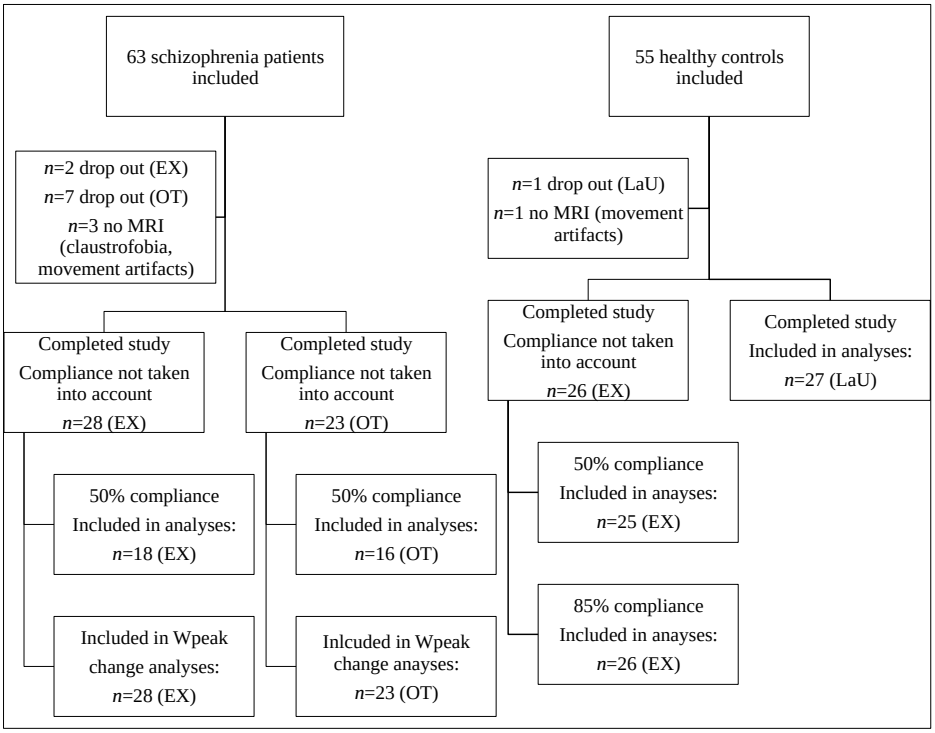


Table 1. Demographic and clinical characteristics of all exercise therapy (EX) and occupational therapy (OT) patients, EX and life as usual (LaU) controls with baseline and follow-up MRI and compliance of at least 50% of 52 sessions.

	Treatment									
	Patients (*n*=32)				**Controls (*n*=52)**					
Characteristic	**EX (*n*=18)**		**OT (*n*=14)**		**EX (*n*=25)**		**LaU (*n*=27)**			
	N		***N***		***N***		***N***		**Statistic**	***P***
Gender (male/ female)[a]	14 / 4		12 / 2		18 / 7		18 / 9		1.93	0.59
CASH (schizophrenia/ 295.7/ 295.4)[a]	14 / 3/ 1		10/ 4/ 0						1.33	0.51
Parental education level (number of subjects (educational level: 2,3,4,5,6,7)) [a, b]	0,1,5,6,4,2		0,0,2,5,4,3		0,0,1,8,8,8		1,0,4, 8,10,4		13.7	0.55
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age (year) [c]	28.5	7.3	31.1	8	29.5	8.3	28.4	7	0.44	0.72
Length (cm) [c]	178.9	10.9	178.6	5.6	180.5	10.6	176.6	9.8	0.71	0.55
Baseline weight (kg) [c]	85.8	18.8	85.2	20.1	78.2	16.6	74.6	12.4	2.28	0.09
Follow-up weight (kg) [c]	84.6	16.2	87.6	21.6	78	16	74.7	12.6	2.61	0.06
Baseline BMI (kg/m^2) [c]	27.2	7.5	26.6	5.7	23.8	3.4	23.9	3.1	2.67	0.05
Follow-up BMI (kg/m^2) [c]	26.7	6.2	27.4	6.3	23.8	3.3	23.9	3	3.23	**0.03**
Baseline VO_{2peak} (ml/kg/min) [c]	32	9.1	34.8	12.5	36.7	5.7	35.6	5.4	1.33	0.27
Follow-up VO_{2peak} (ml/kg/min) [c]	32.6	9.4	31.5	9.6	39.2	7.8	36.2	7	3.5	**0.02**
Baseline *W*peak (W) [c]	221.6	43.5	247.9	57.9	265.6	54.3	247.4	54.9	2.41	0.07
Follow-up *W*peak (W) [c]	247.6	40.9	236.1	52.6	275.2	68.3	243.7	57.9	1.94	0.13
Baseline WAIS Total IQ [c]	84.8	12	99.1	22.1	111.8	13.2	105.8	14	12.1	**<0.001**
Baseline PANSS total score [c, d]	61.4	11.2	59	10.2					0.35	0.56
Follow-up PANSS total score [c, d]	54.8	12.1	58.9	9.8					1.05	0.31
Duration of illness (years) [a]	6	5.7	7.9	5					0.93	0.34
Hospitalisation until baseline (days) [e]	109.9	107	268	398.4					105.000	0.43
Baseline HEQ dose (mg/day) [c, f]	7.3	6.2	9.2	4.5					.847	0.37
HEQ baseline to follow-up (mg) [c, g]	1489.1	1331.7	1821.2	975.9					0.61	0.44

Significant differences at <0.05 level are presented in bold.
EX, OT, and LaU were compared (at baseline) on relevant demographic and clinical characteristics.
[a] Chi-square were used.
[b] Psychosocial status, expressed as highest level of education of one of both parents according to Verhage.[55]
[c] ANOVA was used.
[d] PANSS total score: Positive and Negative Syndrome Scale assesses severity of psychosis.
[e] Mann-Whitney *U*- tests was used.
[f] baseline antipsychotic medication used in haloperidol equivalent in milligrams per day.
[g] antipsychotic medication used between baseline and follow-up MRI-scans in haloperidol equivalent in milligrams.

Table 2. Raw baseline and follow-up brain volumes in subjects with a minimal compliance of 50% of 52 sessions. In column I, unstandardised regression coefficients b indicate the brain volume change in patients relative to controls (i.e. main effect of group). Columns II and III provide the results from the interaction between group and intervention. Column II shows the effect of exercise in controls only, and column III shows the additive effect of exercise in patients, corrected for sex, age and intracranial volume, in which b represents the corrected volume difference in millilitres.

Outcome variables	**Patients (*n*=32)**				**Controls (*n*=52)**				**I**			**II**			**III**		
	EX (*n*=18)		**OT (*n*=14)**		**EX (*n*=25)**		**LaU (*n*=27)**		**Changes in patients compared to controls**			**Effect of exercise in controls only**			**Additive effect of exercise in patients**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**b**	**t**	***P***	**b**	**t**	***P***	**b**	**t**	***P***
Intracranial volume																	
Baseline	1520.8	139.4	1526.1	130.4	1506.8	135.6	1535.8	132.5									
Follow-up	1519.4	139.8	1524.6	131.2	1507.4	135.9	1535.1	132.1	-1.51	-1.28	0.21	1.36	1.3	0.2	-0.55	-0.33	0.74
Total cerebrum																	
Baseline	1100.4	111.5	1104.7	96.9	1113.5	103	1134.8	99.4									
Follow-up	1098.3	110.6	1102.1	100.1	1110.2	102	1134.3	97.1	-1.18	-0.33	0.74	-2.72	-0.89	0.37	2.62	0.53	0.6
Grey matter																	
Baseline	590.5	54.8	601	53.4	606.9	55.9	623.8	51.4									
Follow-up	589.2	52.3	596.6	58.4	602.1	56.8	622.3	50	-1.19	-0.34	0.74	-2.36	-0.8	0.43	4.68	0.98	0.33
White matter																	
Baseline	509.8	66.5	503.8	60	506.6	52.7	511	56									
Follow-up	509.1	67.3	505.6	59.1	508.1	52.2	512	55.9	0.01	.004	1	-0.36	-0.2	0.84	-2.07	-0.71	0.48
Lateral ventricle																	
Baseline	16.89	7.92	17.88	9.9	14.39	8.1	14.64	9.04									
Follow-up	17.09	7.96	18.21	10.42	14.77	8.32	14.43	8.91	0.47	1.25	0.22	0.57	1.79	0.08	-0.68	-1.30	0.2
Third ventricle																	
Baseline	0.84	0.42	0.93	0.49	0.58	0.28	0.7	0.28									
Follow-up	0.84	0.39	0.96	0.56	0.59	0.29	0.67	0.27	0.05	1.47	0.15	0.03	1.05	0.3	-0.05	-1.16	0.25
Hippocampal volume																	
Baseline	8.01	0.8	7.99	0.7	8.07	0.66	8.13	0.87									
Follow-up	7.93	0.82	8	0.64	8.06	0.64	8.06	0.85	0.07	1.28	0.2	0.06	1.26	0.21	-0.14	-2	0.05

All global brain volume measurements are expressed in mean and SD millilitres (ml). The real effect of exercise in patients (in ml) is calculated by adding b in column II (effect in controls) to b in column III (additive effect in patients), significant differences at <0.05 level are presented in bold.

Baseline volumes

After controlling for age, gender, and intracranial volume, patients had significantly lower baseline volumes of the cerebrum ($F(1,77)=0.763$, $P=0.007$), cerebral grey matter ($F(1,77)=10.95$, $P=0.001$), and higher baseline volumes of the third ventricle ($F(1,77)=8.14$, $P=0.006$). In addition, the mean cortical thickness in each hemisphere was significantly smaller in patients as compared to controls (left: $F(1,77)=17.69$, $P<0.001$; right: $F(1,77)=12.64$, $P=0.001$) (see **Table 2**). Locally, the cortex was thinner in almost all parts of the brain in patients relative to controls, reaching significance (FDR corrected: right $P<0.030$ and left $P<0.036$) in 26 out of 39 ROIs in the right hemisphere and 33 out of 39 ROIs in the left hemisphere. No significant difference in volumes of cerebral white matter ($F(1,77)=0.11$, $P=0.74$), hippocampus ($F(1,76)=0.67$, $P=0.42$), and lateral ventricles ($F(1,77)=1.97$, $P=0.17$) were found (see **Table 2**). No differences were found in brain volumes and cortical thickness at baseline between those patients assigned to exercise versus occupational therapy or in controls assigned to exercise therapy versus life-as-usual.

Brain volume change

No significant main effect for group or intervention nor interaction effects between the two were found for change in cerebral, cerebral grey and white matter, lateral and third ventricle volume (see **Table 2**). For change in hippocampal volume, group or intervention effects were not significant, the interaction effect reached trend level significance ($P=0.05$). In schizophrenia patients, hippocampal volume decreased slightly after exercise therapy with no change after occupational therapy; the opposite effect was observed in the healthy controls. No significant main effect for group or intervention nor an interaction effect was found for change in cortical thickness. Thus, exercise therapy, once to twice a week for 1 h during six months did not increase global brain volume, hippocampal volume, or cortical thickness in schizophrenia patients or healthy controls.

Table 3. The association between global brain volume change and CRF change (W_{peak}), expressed as the unstandardised b (in ml change/W change in W_{peak}) for healthy controls, and the additive effects in patients.

Outcome variables	All subject with two MRI-scans					
	W_{peak} Change In healthy controls only			W_{peak} Change Additive in patients		
	b	**t**	***P***	**b**	**t**	***P***
Cerebral volume change	-0.001	-0.012	0.99	0.164	2.03	**0.045**
Grey matter change	-0.019	-0.302	0.763	0.159	1.911	0.059
White matter change	0.018	0.346	0.73	0.005	0.077	0.939
Lateral ventricle change	0.002	0.327	0.745	-0.018	-2.138	**0.035**
Third ventricle change	0.0003	0.661	0.51	-0.0018	-2.539	**0.013**
Hippocampal volume	0.0004	0.473	0.637	0.0005	0.443	0.659

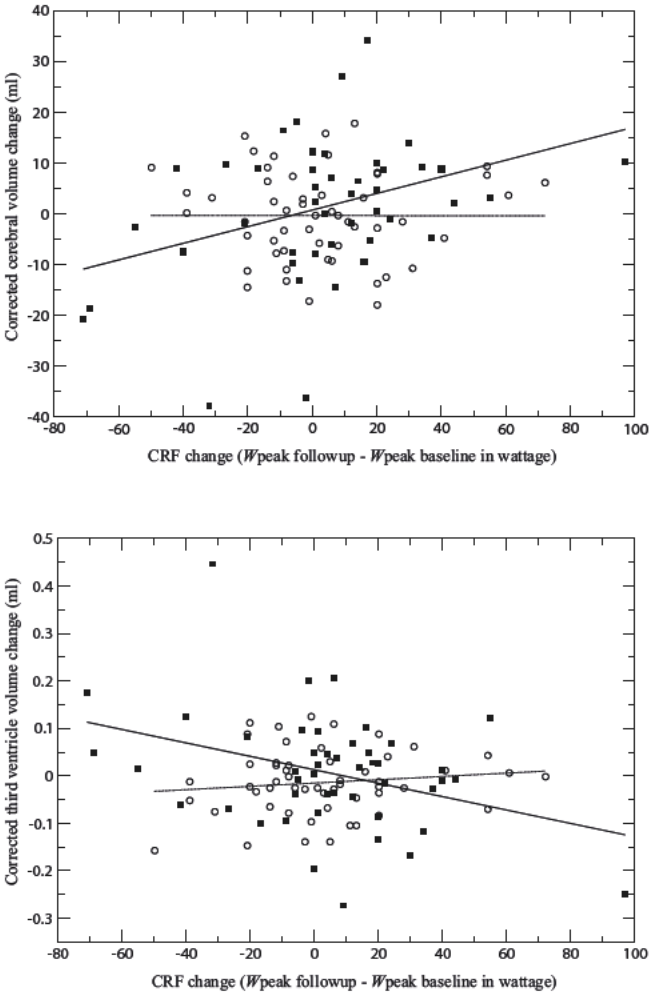
Results expressed as b which represents the corrected brain volume difference in millilitres, corrected for gender, age, and intracranial volume, significant differences at <0.05 level are presented in bold.

Effect CRF change on brain volume

For this analysis all individuals who had two MRI scans and two CRF measures were included. Interaction effects between CRF improvement and group were found. CRF improvement was significantly related to cerebral matter volume increase (0.164 ml/W; *P*=0.045), lateral ventricle (-0.018ml/W; *P*=0.035) and third ventricle volume decrease (-0.0018 ml/W; *P*=0.013) in patients but not in healthy controls (cerebral matter: -0.001ml/W; *P*=0.990; lateral ventricle volume: 0.002ml/W; *P*=0.745; third ventricle volume: 0.0003 ml/W; *P*=0.510; see **Table 3** and **Figure 2**). CRF improvement was, at trend-level significance, related to increase in cerebral grey matter (0.159ml/W; *P*=0.059) in patients but not in healthy controls (cerebral grey matter: -0.019 ml/W; *P*=0.763; see **Table 3**). Exclusion of outliers did not change findings except for lateral ventricle volume where exclusion of one outlier led to a trend-level significant effect of CRF improvement (-0.013ml/W; *P*=0.078). Addition of symptom severity (PANSS total) change, antipsychotic medication use, and intelligence as covariates in the analyses had no influence on these results. In addition, CRF improvement was significantly associated with thickening (or less thinning) in the left hemisphere only (t> 2.29, P<0.024 after FDR correction), in large parts of the frontal, temporal and cingulate cortex (see **Figure 3**, appendix 2). In the right hemisphere all but four *t*-values were positive as well, indicating a thickening of

the cortex (or less thinning) being associated with an increase in CRF, but none of the areas reached significance. For cortical thickness change, no significant interaction between Group and CRF change was found.

Figure 2. Scatterplot of relationship between cerebral (a) change (grey matter change looks similar) and third (b) ventricle volume change (lateral ventricle volume change looks similar) (in ml, corrected for gender, age, IC-volume) and CRF change in W_{peak} for patients (squares) and healthy controls (circles) with successful MRI-scans at baseline and follow-up.



Discussion

This six-month randomised controlled trial investigated the effect of exercise therapy on global brain volumes, hippocampal volume and cortical thickness in patients with schizophrenia and healthy volunteers. In addition, cardiorespiratory fitness improvement achieved after six-months of exercise was related to the brain changes. At baseline, in line with a large body of evidence,[1-3] we found smaller cerebral and grey matter volumes, larger third ventricle volume and thinning of most areas of the cortex in patients with schizophrenia as compared to healthy controls. There was no global brain volume, hippocampal volume and cortical thickness change over time in patients and healthy controls, who were randomised to the exercise therapy group, as compared to those subjects who were randomised to the occupational therapy or/ life as usual groups. Nevertheless, overall improvement in cardiorespiratory fitness in the patients was associated with an increase in total cerebral matter volume (or less volume decrease) and attenuated increase (or even decrease) in lateral and third ventricle volumes.

In addition, improvement in cardiorespiratory fitness was associated with cortical thickening (or less thinning) in the left hemisphere in patients with schizophrenia as well as in healthy controls. This suggests that moderate exercise induces subtle changes in cerebral (grey matter) volume most clearly (at least measurably) expressed in changes in cortical thickness. The underlying mechanisms of brain volume increases as a result of improved fitness are still unknown, but increased production of neurotrophic growth factors, improved vascularisation, and improved energy metabolism, all of which are of central importance in neurogenesis[23,24,56] seem to play a role. Given the crucial role exercise plays in neuronal plasticity, exercise therapy may ameliorate brain abnormalities in schizophrenia.

Failing to find an association between global brain volumes and cardiorespiratory fitness in healthy controls could be related to the young mean age of the subjects since not many brain changes occur in this age span.[57] In line with this explanation, a randomised trial showed exercise to increase both cerebral grey and white matter in sedentary older adults[25] whereas exercise was only found to attenuate the grey matter insula volume loss in young and mid-aged adults.[58]

Exercise therapy did not cause hippocampal volume to increase in patients with schizophrenia nor in healthy controls. Furthermore, hippocampal volume change was not related to cardiorespiratory fitness improvement. As far as we know, only one MRI study examined the effects of exercise on brain volumes in schizophrenia. Pajonk and co-workers[27] found hippocampal volume increased in schizophrenia patients randomised to 30 minutes of exercise three times weekly for three months (12%) as well as in exercising healthy controls (16% increase). In healthy elderly, after one year of exercise, the anterior hippocampal volume was increased but the posterior hippocampal volume was not affected by exercise.[26] Thus, failing to find an effect of exercise on hippocampal volume in our study is unexpected, as there is also robust evidence from animal studies that hippocampal neurogenesis occurs as a result of exercise.[23] The failure to find a relationship between exercise/ cardiorespiratory fitness improvement and hippocampal volume possibly resulted from a low average weekly exercise frequency performed by patients in our study compared to Pajonk and colleagues[27] (1.5 versus 2.6 exercise sessions weekly). Differences in results may also have resulted from the segmentation procedure which was used. Incorporation of manual segmentation of hippocampal volumes, as used by Pajonk and co-workers,[27] has shown to have higher reliability compared to automated segmentation[59] as used in the present study whereas automated procedures are less time consuming, less costly, and have no inter-rater and possibly lower intersession variability in a longitudinal design.[60]

Some limitations should be considered when interpreting the present results. First, due to drop out, poor quality MRI-scans, and limited compliance, the final sample size for exercise therapy analyses was relatively small. The longitudinal exercise therapy analyses were performed on 62% of the initial number of included patients. Therapy adherence in schizophrenia patients is problematic and needs to be improved. As shown by two recent studies adherence to exercise regiments in schizophrenia can be increased by incorporation of motivational techniques.[61,62] Second, exercise frequency in the present study was limited namely one to two 1 h sessions weekly. This is lower than was previously incorporated by Pajonk and colleagues[27]. We suggest future studies incorporate a higher, for example three sessions weekly, exercise frequency. Third, this trial did not include a 'treatment as usual' and therefore

we were unable to examine the differential effect of exercise therapy, occupational therapy versus treatment as usual. No follow-up measurements were performed in our study. Therefore, it remains unknown whether patients continued to exercise after trial cessation and whether improvement of cardiorespiratory fitness and associated global brain volumes and cortical thickness changes lasted.

In summary, our study shows that improvement in cardiorespiratory fitness is associated with cortical thickening in most areas of the left frontal, temporal, and cingulate cortices in schizophrenia patients and healthy controls. Fitness improvement is also associated with an increase in total cerebral matter volume increase (or attenuated volume decrease) and a decrease in lateral and third ventricle volume (or less increase) in the patients (not in the healthy controls). However, exercise therapy, at least when limited to 1 – 2 h weekly for six months as was the case in our study, did not elicit significant brain volume changes. Further research is warranted to examine whether exercise therapy can ameliorate brain abnormalities in schizophrenia patients.

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7

Summary and general discussion

Summary and general discussion

Schizophrenia, a severe and devastating chronic psychiatric illness, is characterised by positive (psychotic) symptoms, negative symptoms, and cognitive symptoms.[1] Despite current treatment, of which antipsychotic medication is a key element, about 75% of patients with schizophrenia have relapses and continued disability.[2] Also, a majority of patients are diagnosed with co-morbid psychiatric disorders, in particular depression is highly prevalent among patients with schizophrenia.[3] Furthermore, life expectancy of schizophrenia patients is reduced by 20% compared to the general population,[4-8] largely due to additional prevalence of physical illnesses.[4,5,8] There is a need for the development of successful add-on therapies to further improve mental and physical health of patients with schizophrenia.

The importance of physical activity and cardiorespiratory fitness for the improvement of health in the general population is well studied and widely accepted.[9,10] However, systematic reviews indicate there is a paucity of and need for more rigorous scientific studies that focus on (increasing) physical activity and cardiorespiratory fitness and their effect on mental and physical health in patients with schizophrenia.[11-15] Empirical studies into the association of energy balance, in specific energy expenditure versus energy intake, and mental and physical health parameters in patients with schizophrenia are also scarce and results somewhat inconsistent.[16-21]

When focusing on the pathophysiological mechanisms which lead to schizophrenia, genetic as well as environmental factors play a role,[22,23] yet currently these factors are not fully understood.[24] Results from magnetic resonance imaging (MRI) studies have consistently demonstrated that structural brain abnormalities, in particular reduced grey matter and hippocampal volumes and increased ventricle volumes, play a role in the pathophysiology of schizophrenia.[25,26] The origin of these brain abnormalities is not fully understood yet but it has been proposed that also here genetic[27,28] as well as environmental factors[29,30,31] play a role. Antipsychotic medication has also been found to (positively) influence brain volume changes in schizophrenia.[32-34] All longitudinal studies[35-38] but one[39] indicate that the severity of brain abnormalities is worse in those patients with poorer outcome. A better understanding of brain abnormalities in

schizophrenia is of importance not only for the understanding of the illness but also because it may lead to the development of interventions which (partly) prevent or ameliorate brain abnormalities and hopefully improve outcome.

The studies described in this doctoral thesis, all part of the TOPFIT study, tried to address the before mentioned gaps in current literature. The aims of the TOPFIT study were to examine whether (**I**) differences in physical activity (**chapter 2**), energy intake (**chapter 3**), and cardiorespiratory fitness (**chapter 4**) exist between patients with schizophrenia and healthy control subjects, and whether these factors are associated to health parameters in patients, (**II**) exercise therapy effects mental and physical health parameters in patients with schizophrenia (**chapter 4** and **chapter 5**), and lastly whether (**III**) exercise therapy and improvement of cardiorespiratory fitness have a protective influence on brain volume changes in patients with schizophrenia and healthy controls (**chapter 6**).

This final **chapter** summarises and discusses the main findings of this thesis. In addition, methodological considerations, implications for clinical practice, and directions for future research will be made.

Main findings

In **Chapter 2** we examined physical activity and energy expenditure in a cross-sectional design in 62 schizophrenia patients and 52 physically inactive but otherwise healthy controls. Physical activity was assessed objectively with the SenseWear Pro-2 body monitoring system for three 24-hour bouts. SenseWear assesses minute-to-minute data through multiple sensors and reliably estimates physical activity and energy expenditure.[40-42]

We demonstrated that, on average, schizophrenia patients were a third less physically active and as a consequence had lower total and active energy expenditure compared to healthy controls. On average, patients spent an additional three hours per day lying down and sleeping compared to the healthy controls. Since one of the inclusion

criteria for healthy controls in this study was being physically inactive, it is likely that, as compared to the general population, patients with schizophrenia are even less physically active than was reported in this study.

In line with a recent review, we found the amount of physical activity and especially cardiorespiratory fitness was associated with severity of negative symptoms in schizophrenia patients.[43] Negative symptoms evidently impact an individual's functional capacity in daily activities.[44] Also, we showed cardiorespiratory fitness, but not the amount of physical activity undertaken, was associated with the level of (abdominal) obesity, an important mortality risk factor.[45,46] The associations between physical activity and cardiorespiratory fitness and key variables for mental and physical health that were reported in our study, are consistent with the conceptual model presented by Bouchard and Shephard[10] as their model of healthy related fitness states that physical activity and physical fitness are interrelated with health. It needs to be noted that the conceptual model of Bouchard and Shephard[10] describes several factors which have not been taken into account in the present study, for example heredity and social environment.

In addition to energy expenditure, which we studied in **chapter 2**, we investigated whether patients with schizophrenia ate more and/ or a more unhealthy diet compared to healthy controls. Therefore, in a cross-sectional study (**chapter 3)**, we examined energy expenditure and energy intake and predictors of obesity in 30 patients with schizophrenia and 48 healthy controls. Dietary intake over the past 12 months was assessed by a validated food frequency questionnaire.[47] Energy and nutrient intake of patients with schizophrenia was also compared to body mass index (BMI) matched general population data from the National Food Consumption Survey.[48] Physical activity and cardiorespiratory fitness were assessed respectively with the SenseWear armband and an incremental cardiopulmonary exercise test.

We could report that energy and nutrient intake in schizophrenia patients and healthy controls matched for age, gender and level of parental education or between schizophrenia patients and a sample of BMI-matched general population were

similar. After controlling for BMI, physical activity and fitness level, total energy and carbohydrate intake were higher in schizophrenia patients compared to healthy controls. Schizophrenia patients consumed significantly more dairy products (i.e. milk), of which the Dutch already consume relatively large proportions,[49] and less alcoholic beverages compared to healthy controls. Finally, no association between energy intake and obesity was found, but a relationship between obesity and both physical inactivity and poor cardiorespiratory fitness was reported. Partly consistent with our results, Wang and colleagues[50] showed decreased physical activity but also reduced intake of monounsaturated fatty acids was responsible for metabolic risk, not increased energy intake per se.

In the discussion of **chapter 3**, we stated that schizophrenia patients had higher average BMI than healthy controls matched for age, gender, and socioeconomic status, but total energy or nutrient intake was similar. However, schizophrenia patients had 13% higher energy intake compared to healthy controls and, after controlling for BMI, physical activity or VO_{2peak}, the difference in energy intake was found to be significant. After one year, a daily extra 13% calorie-intake could add up to considerable weight gain. Also, food group ratios (median intake for patients divided by the median intake for healthy controls) higher than 1 indicated that schizophrenia patients tended to eat more of all foods except fruits, pastry and cookies of which they tended to consume less (ratios lower than 1). This is in line with results from previous studies and indicates schizophrenia patients make poorer food choices.[16,18-20]

In **chapter 4**, a cross-sectional comparison of cardiorespiratory fitness of patients with schizophrenia to that of matched, healthy controls was performed. Also, the longitudinal effect of the six-month biweekly cardiovascular exercise therapy on cardiorespiratory fitness was examined, both in patients as well as in healthy controls. Sixty-three schizophrenia patients and 55 controls, matched for gender, age, and socioeconomic status, were randomised to six-month exercise therapy (n=31) or occupational therapy (n=32) biweekly for one hour and controls were randomised to either exercise (n=27) or life-as-usual (n=28). Cardiorespiratory fitness was assessed with 'the gold standard' graded-exercise test with respiratory gas-exchange analysis

and defined as the highest relative oxygen uptake (VO_{2peak} in $ml \cdot kg^{-1} \cdot min^{-1}$) and peak work rate ($W_{peak}$ in Watt).[51] Analyses were performed on longitudinal results of participants who complied with the minimal compliance demand (50% of sessions (*n*=52)).

We demonstrated that patients with schizophrenia, on average aged 29 years old, had reduced relative VO_{2peak} and W_{peak} compared to physically inactive healthy controls. In addition, 10-15% reductions in fitness levels between individual and reference values were seen, especially in male patients. We stressed that the difference in relative VO_{2peak} between patients and matched controls alone (4.3 $ml \cdot kg^{-1} \cdot min^{-1}$), according to previously published studies, corresponded to a more than 13% increased mortality risk in schizophrenia patients.[52,53]

Longitudinal results showed exercise therapy performed one to two hours weekly for six-months, slightly increased relative VO_{2peak} and markedly improved W_{peak} in patients with schizophrenia versus decreased relative VO_{2peak} and W_{peak} in non-exercising patients. Thus, in non-exercising patients a progressive fitness decrease was seen which was ameliorated by exercise therapy. In controls, exercise improved relative VO_{2peak} by on average 2.2 $ml \cdot kg^{-1} \cdot min^{-1}$ and W_{peak} by 9.6 Watts indicating that the intervention was effective in increasing fitness levels in healthy subjects. Evidence is growing that poor cardiorespiratory fitness is a key mortality risk factor in patients with schizophrenia also.[54-59] Our results suggested that, with only one to two hours of exercise therapy per week, a progressive decrease of fitness could be prevented and thereby the mortality risk in schizophrenia possibly decreased. Therefore we proposed that improvement of cardiorespiratory fitness should be a treatment aim in interventions, for example in psychomotor therapy, for patients with schizophrenia.

In **chapter 5**, we further examined the effects of a six-month exercise therapy program as compared to an active control condition on mental and physical health parameters in patients with schizophrenia. For this purpose, 63 patients with schizophrenia were randomly assigned to an hour of structured exercise (*n*=31) or occupational therapy (*n*=32) biweekly for six months. Outcome measures for mental health change were

severity of primary disease symptoms (Positive and Negative Syndrome Scale),[60] severity of depression (Montgomery and Åsberg Depression Rating Scale),[61] and need for care (Camberwell Assessment of Needs).[62] Cardiovascular fitness (VO_{2peak} and W_{peak}), body mass index, body fat percentage, and metabolic syndrome assessed change in physical health. Analyses were performed on intention-to-treat basis (all subjects that were randomised and for whom follow-up outcome data were present)[63] as well as per-protocol with those patients who met minimum compliance demands of 50% of offered sessions (*n*=52).

Except a trend-level improvement in the severity of depression, the intention-to-treat analyses revealed no difference between exercise versus occupational therapy. In contrast, we reported that psychotic symptoms, co-morbid depressive symptoms, and need for care improved significantly in compliant patients after exercise therapy compared to occupational therapy, thus with one to two hours of therapy weekly. Both intention-to-treat as well as per-protocol analyses showed a significant improvement of W_{peak} and per protocol analyses showed a trend-level improvement in relative VO_{2peak}. Changes in body mass index, body fat percentage, and metabolic syndrome were not significantly different between the two groups. Change percentages consistently favoured the exercise therapy group so perhaps higher frequency, intensity, and session duration could lead to more significant improvement in these physical parameters.[64,65] Since non-compliant exercise and occupational therapy patients had worse symptom severity than compliant patients, we suggested that exercise therapy was an effective add-on treatment in schizophrenia, particularly in somewhat higher functioning patients.

In **chapter 6** we addressed a more fundamental research question, namely whether exercise therapy and fitness improvement could, at least in part, attenuate brain volume loss that is found in patients with schizophrenia. By means of a randomised controlled trial exercise effects on global brain volume, hippocampal volume, and cortical thickness in schizophrenia patients (exercise therapy: *n*=18; occupational therapy: *n*=16) and healthy controls (exercise therapy: *n*=25; life-as-usual: *n*=27) were examined. Secondly, associations between brain changes and cardiorespiratory

fitness changes were investigated irrespective of the intervention condition in patients (*n*=51) and controls (*n*=53). For this purpose, as described previously, patients were assigned exercise therapy or occupational therapy whereas controls were assigned exercise therapy or life-as-usual for six-months two hours weekly. Before and immediately after the intervention structural MRI scans of the whole brain were acquired on a 3 Tesla scanner and from these scans global brain volumes, hippocampal volume, and cortical thickness were estimated.

First, consistent with previous findings,[25,26,66] we reported significantly smaller baseline cerebral (grey) matter, and larger third ventricle volumes, and thinner cortex in most areas of the brain in patients with schizophrenia versus healthy controls. Second, we showed that, when performed once to twice weekly for one hour during six months, no exercise therapy effect existed on global brain volume, hippocampal volume or cortical thickness in patients or controls. Third, we found that fitness improvement was related with an increase in total cerebral matter volume increase (or attenuated volume decrease) and a decrease in lateral and third ventricle volume (or less increase) in patients with schizophrenia, but not in healthy controls. These effects remained significant even after controlling for antipsychotic medication used or changes in psychotic symptom severity. Fourth, we reported that overall improvement in cardiorespiratory fitness was associated with cortical thickening (or less thinning) in most areas of the left frontal, temporal, and cingulate cortices in schizophrenia patients and healthy controls.

Not finding an effect of exercise therapy on hippocampal volume or an association of the latter with cardiorespiratory fitness improvement is in contradiction to a previous 1.5 Tesla MRI-study in schizophrenia patients,[67] a 3 Tesla MRI-study in healthy elderly,[68] and numerous animal studies (for a review see[69]) which have reported exercise to positively affect hippocampal volume. Possibly, a lower exercise frequency and/or intensity in our study led to this negative finding. In the conclusion of this study, we emphasised that further research is warranted to elucidate whether exercise therapy can attenuate brain volume loss that is found in patients with schizophrenia.

Methodological considerations

The TOPFIT study had several methodological strengths. First, incorporation of a randomised controlled trial design in **chapters 4**, **5**, and **6** enabled us to set apart cause-and-effect. Second, validated and reliable methods were used to assess outcome variables. In particular inclusion of (I) objectively assessed physical activity, (II) criterion method assessment of cardiorespiratory fitness, and (III) estimations of global brain volume, hippocampal volume, and especially cortical thickness using 3 Tesla MRI scans in an exercise trial are novel in schizophrenia research.

The studies presented in this doctoral thesis also have some methodological limitations. First, the studies presented in **chapter 2** and **chapter 3** had a cross-sectional design. In other words, all measurements were assessed at the same moment in time in participants. This type of research is useful when comparing different populations, in the TOPFIT study patients with schizophrenia to matched healthy controls, at a single point in time. However, cross-sectional studies cannot provide definite information about cause-and-effect relationships. Thus causality cannot be inferred from the associations between physical activity, cardiorespiratory fitness and health parameters, reported in **chapters 2** and **3**.

Second, as was previously pointed out in a review by Faulkner and Biddle,[12] the heterogeneity of schizophrenia and its (pharmacological) treatment, make generalisability difficult. Patients with schizophrenia included in the TOPFIT study were prescribed a variety of antipsychotic and other medications in different doses. In the longitudinal studies we corrected for this by including medication (haloperidol) equivalents in the analyses. Distortion of results due to medication differences however, cannot be completely excluded. Also, generalisability is difficult since patients in the TOPFIT study came from a wide variety of clinical settings. Still, no difference between patients randomised to exercise versus occupational therapy in treatment setting (inpatient, day hospital or outpatient) was found. As non-compliant patients were found to be more severely ill than compliant patients and patients with an IQ lower than 70 (exclusion criterion) were excluded from the studies, the

intervention offered in the TOPFIT study might be less doable for patients with lower functioning.

Third, a selection bias may have occurred as the TOPFIT study may have attracted especially those patients and healthy controls with interest in exercise and healthy improvement. Indeed we know that there was a selection bias as fewer women were included into this trial. This could however, in part result from the slightly decreased relative risk of developing schizophrenia for women.[70,71] It could also result from on average better outcome in female patients as they may come into contact with psychiatric centres less frequent than male patients.[72]

Lastly, a limited number of patients and controls were included in the TOPFIT study and this should be taken into account when interpreting its results. At the same time, to the best of our knowledge, the TOPFIT study is the largest randomised controlled trial that has investigated structured exercise therapy to date. In addition, due to a high dropout rate and low compliance not all subjects were included in the analyses. Still, drop-out and non-compliance, namely 35% of included exercise therapy patients, are comparable to previously published exercise studies in schizophrenia patients.[73,74]

Implications for clinical practice

Some practical implications can be formulated based on the findings of the studies reported in this thesis. We described that patients with schizophrenia were much less physically active, expended less energy, and spent an additional three hours daily on sedentary behaviour (lying down and sleeping) compared to healthy inactive subjects **(chapter 2).** Given these and previous results, treatment should focus both on increasing physical activity and on reducing sedentary behaviour.[75-77]

In line with a large body of research,[78] patients included in our study had reduced physical health, already at an average age of 30 years old as we found patients with schizophrenia to have a higher prevalence of metabolic syndrome and higher body mass index compared to controls (**chapter 3**). Furthermore, in **chapter 4**, we

showed that patients with schizophrenia had poorer cardiorespiratory fitness levels compared healthy inactive controls. Also, in **chapter 2 and chapter 3** we found that physical activity but more strikingly cardiorespiratory fitness and not energy intake, was strongly associated with (abdominal) obesity in patients with schizophrenia. Overweight and obesity are key risk factors for a number of physical illnesses such as diabetes mellitus, coronary heart disease, hypertension, and certain cancers.[78,79] Lastly, cardiorespiratory fitness was strongly related to severity of negative symptoms. Taken together, we suggest inclusion of cardiorespiratory fitness improvement as a primary treatment aim in patients with schizophrenia.

In the current study, exercise therapy consisted of two one hour sessions predominantly containing cardiovascular exercises but also muscle strength exercises. We believe the current study, when combined with previous knowledge, indicates that an increase in exercise frequency and session duration as well as individualised exercise intensity could lead to pronounced cardiorespiratory benefits in schizophrenia patients.[64,65] Since Heggelund and co-workers[65] showed that high intensity training (4x4 minute bouts at a 85-90% of maximum heart rate intensity) increased relative VO_{2peak} by 12% in patients with schizophrenia, we suggest to include high intensity training in treatment programs.

Chapter 4 and chapter 5 showed drop-out and non-compliance endanger successful implementation of exercise therapy in clinical practice. We suggest to incorporate motivational techniques in order to improve exercise adherence in patient with schizophrenia.[80,81] We also suggest to involve family members, friends or caretakers, in example by having them exercise together with patients. This may improve treatment adherence,[82] especially in low functioning patients. We suggest tailoring the intervention to personal preference since this may improve effectiveness and generalisability. In example other psychomotor therapy treatments such as body-oriented psychotherapy[83] and yoga therapy[84] should be offered additionally since they have been shown to decrease symptom severity in patients with schizophrenia.

Directions for future research

This study gives rise to a number of research questions that need to be addressed in future studies. First, the associations that were reported in the cross-sectional studies (**chapter 2** and **chapter 3**) should be investigated in prospective studies to tease apart cause and effect. Second, the intervention studied in this trial appeared to be more suitable for the somewhat higher functioning patients. Future studies should develop treatment strategies, for example implementation of motivational techniques,[80,81] in particular for lower functioning patients. Also, as fewer females were included into the present trial, future exercise therapy studies should particularly put effort into inclusion of female patients with schizophrenia. Third, future studies should elucidate what exercise intensity, frequency, type and duration leads to mental health improvements in patients with schizophrenia. Since we reported change percentages for physical health parameters consistently favoured exercise therapy but did not reach statistical significance, future studies should especially clarify how better effectiveness can be accomplished and also how many participants need to be included to be able to detect statistically significant differences. Fourth, as no follow-up period was assessed after study cessation, it is unknown whether patients have continued exercise regularly nor whether improvements have sustained and for how long. Fifth, future studies should incorporate factors of the conceptual model by Bouchard and Shephard[10], describing relations between health, physical activity, and health-related fitness. Especially heredity and social environment should be taken into account in future studies. Sixth, as only an active control group (occupational therapy) was included in the studies described in this thesis, it is unknown what occurs with patients' health if no intervention (treatment-as-usual) is given. Seventh, we report an association between aerobic fitness improvement and global brain abnormalities in schizophrenia and cortical thickening in patients and controls. Future studies should examine the effect of exercise therapy in high-risk subjects and first-episode patients with schizophrenia, as they are known to show the greatest reduction in brain volumes.[85] In particular it would be interesting whether progression of the disease, and the decrease in brain volumes, could be diminished by regular physical exercise.

Concluding remarks

In sum, this doctoral thesis described:

- patients with schizophrenia were less physically active and had decreased cardiorespiratory fitness levels compared to physically inactive but otherwise healthy control subjects;
- energy and nutrient intake of schizophrenia patients was similar as compared to matched healthy controls or a BMI-matched sample of the general population. When controlling for BMI, physical activity and fitness, total energy and carbohydrate intake was higher in schizophrenia patients compared to healthy controls;
- physical activity and especially cardiorespiratory fitness, not energy intake, were associated with negative symptomatology and (abdominal) obesity in patients with schizophrenia;
- six months of biweekly exercise therapy improved cardiorespiratory fitness of patients with schizophrenia and healthy controls;
- exercise therapy, when performed an hour once to twice weekly, improved mental health, reduced need for care, and improved cardiorespiratory fitness in patients with schizophrenia, but had no significant effects on other physical health parameters;
- one to two hours of exercise therapy weekly for six months did not significantly effect brain volume changes in patients with schizophrenia or healthy controls.
- cardiorespiratory fitness improvement was associated with attenuated global brain volume changes in schizophrenia patients and cortical thickening (or less cortical thinning) in large areas of the left hemisphere, not only in patients with schizophrenia but also in healthy controls.

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Nederlandse samenvatting

Samenvatting

Schizofrenie is een ernstige en chronische psychiatrische aandoening. Schizofrenie wordt gekenmerkt door de aanwezigheid van positieve (psychotische) symptomen, negatieve symptomen en cognitieve symptomen. Zelfs wanneer patiënten optimaal behandeld worden, waarbij behandeling met antipsychotische medicatie van groot belang is, valt ongeveer 75% van de patiënten één of meer keer terug. Bij een meerderheid van de patiënten is dan ook sprake van blijvend verminderd functioneren. Ook andere psychiatrische aandoeningen, met name depressies, komen bij patiënten met schizofrenie vaak voor. Bovendien is de levensverwachting van patiënten met schizofrenie 20% lager dan de algemene bevolking wat vooral veroorzaakt wordt door het vaker voorkomen van lichamelijke aandoeningen. Er is dan ook behoefte aan werkzame aanvullende behandelvormen die de mentale en lichamelijke gezondheid van patiënten met schizofrenie verder kan verbeteren.

Het belang van lichamelijke activiteit en (cardiorespiratoire) fitheid voor het verbeteren van gezondheid is in de algemene bevolking goed onderzocht en wordt algemeen erkend. Systematische reviews laten echter zien dat er een gebrek is aan kwalitatief hoogstaande onderzoeken die zich richten op de invloed van (verbetering van) lichamelijke activiteit en fitheid op de mentale en lichamelijke gezondheid van patiënten met schizofrenie. Ook zijn er weinig empirische onderzoeken verschenen waarin de energiebalans, oftewel energie-inname aan de ene kant en energieverbruik aan de andere kant, in relatie tot mentale en lichamelijke gezondheid bij patiënten met schizofrenie is onderzocht. Bovendien zijn de uitkomsten van deze onderzoeken tegenstrijdig.

In de pathofysiologie van de ziekte schizofrenie spelen zowel genetische alsook omgevingsfactoren een rol, waarbij de precieze rol van en relatie tussen deze factoren nog niet helemaal begrepen wordt. Onderzoeken die gebruik maken van magnetic resonance imaging (MRI) technieken laten overtuigend zien dat bij patiënten met schizofrenie structurele hersenafwijkingen voorkomen. Met name een vermindering van grijze stof en hippocampusvolumes en een toename van ventrikelvolumes (hersenholtes) spelen dan ook een rol in de pathofysiologie van de ziekte schizofrenie. De oorzaak van deze structurele hersenvolumeveranderingen wordt niet geheel begrepen,

maar zowel genetische alsook omgevingsfactoren spelen een rol. Ook antipsychotische medicatie blijkt een (positieve) invloed op hersenvolumeveranderingen bij schizofrenie te hebben. Uit longitudinaal onderzoek blijkt dat patiënten bij wie het breinvolume sneller vermindert, ook het functioneren meer verstoord is. Er zijn aanwijzingen dat beweging en verbetering van fitheid een positieve invloed op de hersenen hebben. Mogelijk dat door fitnesstherapie de afname van hersenvolume bij patiënten met schizofrenie kan worden tegengegaan.

De onderzoeken die staan beschreven in dit proefschrift maken allen deel uit van de TOPFIT studie. Het doel van de TOPFIT studie is om te onderzoeken in hoeverre:

I. er verschillen in lichamelijke activiteit (**hoofdstuk 2**), energie-inname (**hoofdstuk 3**) en fitheid (**hoofdstuk 4**) bestaan tussen patiënten met schizofrenie en gezonde vrijwilligers, waarbij ook de relatie tussen deze factoren en gezondheidsparameters bij patiënten onderzocht is;
II. fitnesstherapie een positief effect heeft op de mentale en lichamelijke gezondheid van patiënten met schizofrenie (**hoofdstuk 4 en 5**);
III. fitnesstherapie en verbetering van fitheid een beschermende werking hebben op hersenvolumeveranderingen bij patiënten met schizofrenie alsook bij gezonde vrijwilligers (**hoofdstuk 6**).

In **hoofdstuk 7** worden de belangrijkste resultaten van de TOPFIT studie samengevat. Hierbij worden achtereenvolgens ook de methodologische aspecten, gevolgen voor de klinische praktijk en suggesties voor toekomstig onderzoek besproken.

Samenvatting van de hoofdstukken 2 t/m 6

In **hoofdstuk 2** onderzochten wij de lichamelijke activiteit en het energieverbruik in een dwarsdoorsnede-onderzoek bij 62 patiënten met schizofrenie en 52 lichamelijk inactieve, maar voor het overige gezonde vrijwilligers. Lichamelijke activiteit werd drie keer 24 uur objectief gemeten met de SenseWear. De SenseWear bepaalt, van minuut tot minuut betrouwbaar, de mate van lichamelijke activiteit en het energieverbruik. Hierbij maakt SenseWear gebruik van 5 verschillende sensoren.

De resultaten lieten zien dat patiënten met schizofrenie gemiddeld een derde minder lichamelijk actief waren en dat zij hierdoor ook minder energie verbruikten dan gezonde vrijwilligers. Gemiddeld brachten patiënten per dag 3 uur meer liggend en slapend door dan gezonde vrijwilligers. Omdat één van de voorwaarden voor gezonde vrijwilligers om aan het onderzoek mee te mogen doen lichamelijke inactiviteit was, oftewel minder dan 1 uur per week matig intensief bewegen, is het waarschijnlijk dat patiënten vergeleken met de algemene bevolking nog minder lichamelijk actief zijn dan uit dit onderzoek naar voren komt.

In overeenstemming met de uitkomsten van een recent overzichtsartikel (review), bleek de hoeveelheid lichamelijke activiteit en met name de cardiorespiratoire fitheid in ons onderzoek gerelateerd te zijn aan de ernst van negatieve symptomen bij patiënten met schizofrenie. Negatieve symptomen duiden op de afwezigheid of het verminderd aanwezig zijn van bepaald gedrag, bijvoorbeeld energieverlies, geen plezier meer in dingen kunnen hebben of lusteloosheid. Dit is belangrijk omdat negatieve symptomen een grote invloed hebben op de mate waarin iemand zijn of haar dagelijkse activiteiten kan uitvoeren. In ons onderzoek bleek cardiorespiratoire fitheid, maar niet de hoeveelheid lichamelijke activiteit, gerelateerd te zijn aan de mate van overgewicht. Overgewicht is een belangrijke risicofactor voor vervroegd overlijden.

In **hoofdstuk 3** onderzochten wij in hoeverre patiënten met schizofrenie vergeleken met gezonde vrijwilligers meer voedsel en/of meer ongezond voedsel tot zich nemen. Hiervoor werden in een dwarsdoorsnede-onderzoek bij 30 patiënten met schizofrenie en 48 gezonde vrijwilligers het energieverbruik. de energie-inname en voorspellers voor overgewicht onderzocht. De voedselinname over de afgelopen 12 maanden werd in kaart gebracht met een gevalideerde voedingfrequentie-vragenlijst. De energie- en nutriënteninname van patiënten met schizofrenie werden ook vergeleken met gegevens van de, voor wat betreft de mate van overgewicht (Body Mass Index (BMI)) vergelijkbare, algemene bevolking (National Food Consumption Survey). Lichamelijke activiteit en fitheid werden respectievelijk gemeten door gebruik te maken van de SenseWear en een maximale inspanningstest met ademgasanalyse op een fietsergometer.

De resultaten van dit onderzoek lieten zien dat de inname van energie en nutriënten bij patiënten met schizofrenie ten opzichte van gezonde vrijwilligers, die gematcht waren voor wat betreft leeftijd, geslacht en het opleidingsniveau van ouders, vergelijkbaar was. De energie-inname en nutriënteninname van patiënten met schizofrenie was ook vergelijkbaar met gegevens van de, voor wat betreft BMI-gematchte, algemene bevolking. Echter, wanneer rekening gehouden werd met verschillen in BMI, lichamelijke activiteit of fitheid, bleek dat de totale inname van energie en koolhydraten wel hoger was bij patiënten met schizofrenie dan bij gezonde vrijwilligers. Ook nuttigden patiënten met schizofrenie vergeleken met gezonde vrijwilligers significant meer melkproducten, waarvan Nederlanders in zijn algemeenheid al relatief veel nuttigen, en juist minder alcoholische dranken. Tot slot werd er geen verband gevonden tussen energie-inname en overgewicht, maar was de hoeveelheid lichamelijke activiteit en de mate van fit zijn wel negatief gerelateerd aan de mate van overgewicht. Met andere woorden, hoe minder patiënten bewogen en hoe minder fit iemand was, hoe meer sprake er was van overgewicht.

In **hoofdstuk 4** is de cardiorespiratoire fitheid van patiënten met schizofrenie vergeleken met die van gematchte, gezonde vrijwilligers. Daarnaast is het effect van een 6 maanden durende cardiovasculaire fitnesstherapie op de cardiorespiratoire fitheid onderzocht bij patiënten met schizofrenie en bij gezonde vrijwilligers. 63 patiënten met schizofrenie en 55 gezonde vrijwilligers, vergelijkbaar voor wat betreft leeftijd, geslacht en socio-economische status, werden via loting verdeeld over een interventie- dan wel controlegroep. 31 patiënten lootten 2 keer per week een uur fitnesstherapie gedurende 6 maanden en 32 patiënten lootten eenzelfde aantal keer activiteitentherapie. 27 gezonde vrijwilligers lootten dezelfde fitnesstherapie en 28 gezonde vrijwilligers lootten life-as-usual, hen werd niet actief iets aangeboden maar ze mochten niet méér gaan bewegen. Cardiorespiratoire fitheid werd bepaald door middel van een ‘gouden standaard’ stapsgewijze maximale inspanningstest met ademgasanalyse op een fiets. Cardiorespiratoire fitheid werd omschreven als de maximale relatieve zuurstofopnamecapaciteit (VO_{2peak} in ml/kg/min) en de maximale belasting (W_{peak} in Watt). De analyses om het effect van de interventie versus controleactiviteit te bepalen

werd uitgevoerd bij deelnemers die voldeden aan de minimale eis voor wat betreft aanwezigheid (50% van het totaal aantal therapiesessies (*n*=52).

Patiënten met schizofrenie, met een gemiddelde leeftijd van 29 jaar oud, hadden vergeleken met gezonde vrijwilligers een verminderde relatieve zuurstofopnamecapaciteit en hielden de test veel minder lang vol. Ze bereikten daardoor een lagere maximale belasting. Met name bij mannelijke patiënten werd, in vergelijking met normscores, een 10-15% lagere fitheid gevonden. In de discussie van **hoofdstuk 4** wordt benadrukt dat deze verminderde fitheid (relatieve VO_{2peak}) bij patiënten met schizofrenie alleen, dus los van andere risicofactoren, overeenkomt met een 13% verhoogd overlijdensrisico.

Uit de longitudinale resultaten van dit onderzoek bleek dat fitnesstherapie, mits 1 tot 2 uur per week uitgevoerd gedurende 6 maanden, tot een beperkte toename van fitheid (relatieve VO_{2peak}) en een robuuste verbetering van het maximale vermogen (W_{peak} in Watt) leidt bij patiënten met schizofrenie ten opzichte van de patiënten die activiteitentherapie volgden. Ook bleek dat fitnesstherapie de toenemende verslechtering van fitheid, zoals te zien was bij de patiënten die zes maanden lang niet aan fitnesstherapie deelnamen, voorkomen werd. Feit dat bij de gezonde vrijwilligers fitnesstherapie de fitheid met gemiddeld 2.2 ml/kg/min en de maximale belasting met gemiddeld 9.6 Watt verbeterde, geeft aan dat de aangeboden fitnesstherapie in staat was de fitheid van deelnemers te verbeteren. Zoals gesteld, een verminderde fitheid is een belangrijke risicofactor voor vervroegd overlijden. Onze resultaten lijken erop te wijzen dat, met slechts 1 tot 2 uur fitnesstherapie per week, de progressieve verslechtering van fitheid tegengegaan werd en hiermee het risico op vervroegd overlijden mogelijk verminderd werd. Wij stellen voor dat verbetering van cardiorespiratoire fitheid een standaard behandeldoel wordt in de behandeling van patiënten met schizofrenie, bijvoorbeeld in het kader van psychomotorische therapie.

In **hoofdstuk 5** werd het effect van een 6 maanden durende cardiovasculaire fitnesstherapie ten opzichte van een actieve controle-activiteit, namelijk activiteiten-therapie, op de mentale en lichamelijke gezondheid van patiënten met

schizofrenie onderzocht. Hiervoor werd 63 patiënten na loting 6 maanden lang wekelijks 2 uur fitnesstherapie (*n*=31) of activiteitentherapie (*n*=32) aangeboden. De mentale gezondheid werd bepaald door de ernst van psychotische klachten, depressieve klachten en de behoefte aan zorg te meten. Hiervoor werden respectievelijk de volgende meetinstrumenten gebruikt: Positive and Negative Syndrome Scale, Montgomery and Åsberg Depression Rating Scale en de Camberwell Assessment of Needs. Om het effect van fitnesstherapie op de lichamelijke gezondheid te bepalen, werden fitheid, overgewicht, lichaamsvetpercentage en metabool syndroom gemeten.

Bij dit soort onderzoek kunnen resultaten op verschillende manieren worden bekeken. Wanneer alle mensen die geloot waren, dus ongeacht of ze de therapie werkelijk hadden gevolgd, meegenomen werden, leek fitnesstherapie de ernst van depressieve klachten in vergelijking met activiteitentherapie te verminderen. Wanneer patiënten bekeken werden die gedurende 6 maanden 1 tot 2 uur per week fitnesstherapie daadwerkelijk volgden, werd een duidelijke vermindering van psychotische klachten, depressieve klachten en zorgbehoefte gevonden.

Fitnesstherapie verbeterde verder de maximale belasting (W_{peak} in Watt). Fitnesstherapie verbeterde de maximale zuurstofopnamecapaciteit (VO_{2peak} in ml/kg/min) bij patiënten met schizofrenie daar waar deze na activiteitentherapie verslechterde. Voor wat betreft overgewicht, lichaamsvetpercentage en metabool-syndroom waren verbeteringen als gevolg van fitnesstherapie zo klein dat geen significante resultaten gevonden werden. Alleen de hoeveelheid triglyceriden in het bloed leek als gevolg van 1 tot 2 uur fitnesstherapie per week te verbeteren.

Wanneer de intensiteit van training verhoogd wordt, bijvoorbeeld 2 tot 3 keer per week 90 minuten fitnesstherapie, zouden patiënten met schizofrenie waarschijnlijk meer vooruitgang boeken ten aanzien van hun lichamelijke gezondheid. Patiënten die niet voldeden aan de minimale aanwezigheidseis (50% van totaal aantal therapiesessies) hadden ernstiger psychotische klachten. Fitnesstherapie zoals deze nu aangeboden werd is, in ieder geval bij iets beter functionerende patiënten met schizofrenie, een effectieve behandelmethode.

In **hoofdstuk 6** werd een onderzoeksvraag met een meer fundamenteel wetenschappelijk karakter beantwoord, namelijk of fitnesstherapie en verbetering van fitheid het hersenvolumeverlies, zoals gevonden bij patiënten met schizofrenie, kan tegengaan. In een gerandomiseerde interventiestudie is het effect van fitnesstherapie op globaal hersenvolume, hippocampusvolume en dikte van de hersenschors (ofwel corticale dikte) bij patiënten met schizofrenie (fitnesstherapie, *n*=18; activiteitentherapie, *n*=16) en gezonde vrijwilligers (fitnesstherapie, *n*=25; life-as-usual, *n*=27) onderzocht. Daarnaast is bij patiënten (*n*=51) en gezonde vrijwilligers (*n*=53) onderzocht of veranderingen in breinvolume gerelateerd waren aan veranderingen in fitheid, ongeacht wat deelnemers geloot of aan therapie gevolgd hadden. Om deze onderzoeksvragen te beantwoorden werden patiënten via loting toegewezen aan 2 uur per week fitnesstherapie of activiteitentherapie gedurende 6 maanden. Gezonde vrijwilligers lootten 2 uur per week fitnesstherapie of life-as-usual, ook gedurende 6 maanden. Voorafgaand aan en direct na afloop van de interventie werd bij iedere deelnemer een structurele hersenscan verkregen via een 3-Tesla MRI-scanner. Van deze MRI-scans werden het globaal hersenvolume, hippocampus-volume en de dikte van de hersenschors afgeleid.

Ten eerste werd, overeenkomstig bevindingen van eerdere studies, een significante afname van cerebraal (grijze)stofvolume, een toename van derde ventrikelvolume en een dunnere hersenschors in de meeste gebieden van de hersenen gevonden bij patiënten met schizofrenie vergeleken met gezonde vrijwilligers. Ten tweede lieten resultaten zien dat 1 tot 2 uur fitnesstherapie per week gedurende 6 maanden geen effect had op globaal hersenvolume, hippocampusvolume of dikte van de hersenschors bij patiënten met schizofrenie of gezonde vrijwilligers. Ten derde bleek, alleen bij patiënten met schizofrenie, verbetering van fitheid gerelateerd aan toename (of aan minder afname) van totaal hersenvolume en afname (of minder toename) van lateraal en derde ventrikelvolume. Antipsychotica en veranderingen in ernst van psychotische klachten hadden op deze resultaten geen invloed. Tot slot lieten resultaten zien dat verbetering van fitheid bij patiënten met schizofrenie en ook bij gezonde vrijwilligers, geassocieerd was aan verdikking (of minder verdunning) van de hersenschors in de meeste gebieden van de linker frontale, temporale en cingulate cortex.

D

Dankwoord

Dankwoord

De bergtop op de omslag zal, door hen die het Annapurna massief in Nepal kennen, wellicht herkend zijn. De berg met dubbele top, luisterend naar de naam Machhapuchhre (Fishtail mountain), wordt door boeddhisten en hindoes gezien als heilig. Eén van de meest karakteristieke bergtoppen ter wereld met een hoogte van 6997 meter is dan ook nimmer beklommen. De TOPFIT beklimming was bij momenten ook steil en ogenschijnlijk eindeloos. De TOP is echter bereikt en het eindresultaat, in de vorm van dit proefschrift, ligt voor u. En ik? Ik sta op de TOP te juichen en geniet!

Ten eerste bedank ik graag alle patiënten die hebben deelgenomen aan TOPFIT. Ik heb diep respect voor de bergen die jullie, vaak dagelijks, moeten beklimmen. Voor dit onderzoek hebben jullie vrijwillig zes maanden lang tal van extra toppen beklommen. Ik denk aan het reizen van en naar het UMC Utrecht (soms van heinde en ver), de fietstesten, MRI scans, interviews, testjes en deelname aan de fitness- en activiteitentherapie zelf: een absolute TOP-prestatie waarvoor ik een diepe buiging maak! Ook de gezonde controles die zich een half jaar lang hebben ingezet voor het TOPFIT onderzoek ben ik veel dank verschuldigd. Het was mij een groot plezier met jullie samen te werken.

Veel dank ben ik verschuldigd aan mijn promotoren, Professor dr. René S. Kahn en Professor dr. Frank J.G. Backx. Beste René, ik vind het indrukwekkend hoe jij alle bergbeklimmers van jouw expeditieteam(s) begeleidt. Je ziet als geen ander de optimale route naar de TOP en bent daarbij in staat deze kraakhelder en zonder omweg te communiceren. Bedankt voor de kans die je mij gaf, de ondersteuning en het vertrouwen. Beste Frank, jij hebt veel inzet geleverd voor een ‘vreemde bergeend in jouw bijt’. Dankzij jouw bijdrage hebben we mooie dingen meegemaakt en bereikt. Ik denk aan de last-minute handtekeningen die jij voor de, later toegewezen, subsidieaanvraag zette in de snijzaal van het ziekenhuis en de Efteling alwaar jij tijdens het Sportmedisch Jaarcongres 3 prijzen mocht uitreiken aan evenveel afwezige gelukkigen (waarvan ik er één was). Prachtig om deze prijs bij jou thuis alsnog in ontvangst te mogen nemen; tekenend voor jouw stijl.

Mijn co-promotoren, Dr. Wiepke Cahn en Dr. Tim Takken, dank ik tevens zeer. Beste Wiepke, zonder jou was de TOPFIT-expeditie nooit en te nimmer van de grond gekomen, laat staan voltooid. Je enthousiasme en creativiteit zijn grenzeloos en eerlijk gezegd, jij bij tijd en wijlen ook. Ik zie ons nog, na het schrijven van weer een subsidieaanvraag, midden in de nacht een lege parkeergarage van het UMC Utrecht inlopen. Natuurlijk bracht jij mij wel even thuis. Ik waardeer je beschikbaarheid en positivisme en je had gelijk: 'het komt allemaal goed'. Ik ga onze gesprekken en jouw lach missen. Beste Tim, wat ben jij, in ogenschijnlijke ontspanning, bizar productief. Jij hebt op je (werk)racefiets de TOP 5 keer bereikt eer ieder ander halverwege is. Onze samenwerking werd de laatste periode intensiever en het verwerken, analyseren en beschrijven van de data met jou was een feestje. Ik ben heel blij ook jou mijn co-promotor te kunnen noemen.

De co-auteurs van de diverse artikelen wil ik hartelijk bedanken voor het meedenken en meeschrijven. Graag bedank ik de leden van de beoordelingscommissie, Prof. dr. Lieuwe de Haan, Prof. dr. Marc De Hert, Prof. dr. Hilleke Hulshoff Pol, Prof. dr. Iris Sommer en in het bijzonder voorzitter Prof. dr. Robert Wagenaar voor het lezen en beoordelen van het manuscript.

In het kader van het multi-centrum onderzoek TOPFIT heb ik kunnen samenwerken met tal van professionals. Bij Altrecht is mijn dank groot voor allen die betrokken waren. Met name bedank ik Ronald van de Kamp, Floor Massier, casemanagers en psychiaters van het ABC-huis, Ellen ten Napel, Hans den Houdijker en George Hak voor hun inzet. Bij GGZ Duin- en Bollenstreek bedank ik graag Annelies van Strater, Andrea Landman, Marion Scholten, activiteiten begeleiders, casemanagers en PMT-ers van Fit Your Body. Jammer genoeg heeft maar een beperkt aantal patiënten bij GGZ DenB deelgenomen; aan jullie heeft dit zeker niet gelegen. Het laatste deelnemende centrum dat betrokken raakte bij TOPFIT was GGZ Friesland en onze samenwerking was productief, stimulerend en plezierig, waarvoor dank. In het bijzonder bedank ik graag mijn twee heldinnen uit het 'hoge Noorden', Frederike Jörg en ElseInge Schaafsma! Dank ook aan DeMIX Fitness Nieuwegein, Sportcentrum Olympos

Utrecht, Gymplaza St. Nyk en Tigra Heerenveen voor de verleende medewerking aan TOPFIT.

Mijn paranimfen, Anna Kroes en Maria de Glint, ook jullie nemen een bijzondere plaats in. Als onderzoeksassistenten van TOPFIT zijn jullie mijn absolute steun en toeverlaat geweest, mijn 'klimmaatjes'. Lief en leed hebben we gedeeld en met mijn ogen dicht zou ik op elke berghelling ter wereld blind op jullie vertrouwen. Ik zie zomaar een 'berg' voor mij, zegge bij Vezelay of Bibracte, en begin enorm te glimlachen. Jullie inzet voor de expeditie TOPFIT was grandioos en ongeëvenaard. Nu zijn jullie beiden, sterker dan ooit, andere bergen aan het beklimmen en ik ben zeer trots op jullie. Ook trots ben ik dat jullie mij ter zijde willen staan bij de verdediging van mijn proefschrift. Ik kan mij geen andere of betere paranimfen wensen.

Super-Paula Ywema en natuurlijk mega-Joyce van Baaren, wat fijn dat jullie altijd voor mij klaar stonden voor praktische en mentale ondersteuning. Wat hebben we samen veel gelachen, bijvoorbeeld met het bedenken en organiseren van een afdelingsuitje. Neeltje van Haren, voor mij was de TOP die wij moesten bedwingen één van de lastigste (MRI-artikel). Zozeer als ik er vooraf als een berg tegenop zag, zo fijn verliep onze samenwerking. Met jou zou ik gerust nog vele wetenschappelijke bergen beklimmen. Dat jij die Vidi hebt binnengehaald is zó terecht, wat ben jij vet goed en super cool! Aan het rijtje supervrouwen moet minimaal nog één iemand worden toegevoegd: Lena Donk, in het expeditieteam Afdeling Psychiatrie ben jij degene die, voor de groep uitlopend, het volgende kamp bereikt en de boel ook heeft georganiseerd voordat de rest het kamp überhaupt bereikt heeft. Ik mis je nu al enorm als leidinggevende en vertrouwenspersoon. Een organisator als jij, daar kan een bergbeklimmer enkel van dromen. Afscheid nemen, dat doen wij op onze manier, in bergwandeltempo, rustig aan en stap voor stap.

De (oud-)collega's van de psychomotorische therapie (PMT) & bewegingsagogie van de Afdeling Psychiatrie. Bij jullie heb ik mij al die jaren op mijn gemak gevoeld. Met name jullie waren het die mijn drukte, afwezigheid en chaos moesten 'verdragen'. Allen maakten wij deel uit van een eigen expeditieteam (lees zorglijn),

maar tegelijkertijd zaten wij letterlijk en soms figuurlijk op afstand en vormden we een hecht team. Jasper van Duuren, jouw eigenheid, eerlijkheid en vakinhoudelijke kennis waren in die eerste jaren van groot belang voor mij. Cindy van de Bogert, een prettige samenwerking die van relatief korte duur was. José Bonekamp, met sommige mensen zit je binnen één minuut op dezelfde frequentie en jij en ik hebben dat. Wij bedachten samen het TOPFIT acroniem. Michiel Koenen, jij kwam, zag en overwon; de master PMT, een vliegerongeluk met gevolgen op Texel, een passende nieuwe baan en natuurlijk TOP PMT-ster Eliane Leydens. Ik zie jullie nog naast elkaar zitten op kantoor: 'we willen je wat vertellen…'. Kijk waar we nu staan met ons werk, onze vriendschap (al is de frequentie beperkt) en bovenal onze gezinnen. Vivian van Schijndel, wij werden echte (bergklim)buddies. Het voelt goed zo op elkaar te kunnen bouwen en het voelt gek niet meer je collega te zijn! Bernou Molenbeek-Bonsma, jij kwam als bewegingsagoog toen ik aan de TOPFIT-beklimming begon. Het lijkt alweer een eeuwigheid geleden, njet? Doe mij een pondje van die Fryske nuchterheid van jou en doe er ook een onsje van jouw energie bij ;-). Albertine de Haan, wij gaan 'way back', tot aan ons eerste jaar aan de Calo (1996) en wie had toen kunnen bedenken dat wij later als collega's naast elkaar zouden zitten. Ik bewonder je intelligentie, sensitiviteit, oprechtheid en scherpe inzichten. Ook jullie, Aafke Strikwerda en Joke Hellinga, wil ik bedanken voor het invallen tijdens mijn schrijftijd. Speciale dank gaat uit naar Davy Vancampfort, je bent een begaafd PMT-onderzoeker met een geweldige passie voor ons vak. Amber de Herdt, zet hem op met jouw studie!

Alle stagiaires, betrokken bij TOPFIT, jullie waren geweldig, bedankt! In willekeurige volgorde bedank ik Esther Klinckenberg, Kristel Baris & Henrike Klok-van Laar, Tom Niessen & Femke Zuidhoek, Carolien van Geertsom & Sofie Zonneveld, Merle Bredero & Marinke de Sonnaville, Alwin Cuperus & Jorien ter Mors, Arianne Scholten, Jamila Abou, Rho von Liebenstein, Michiel Koenen (ook nog gedaan samen idd ☺), Martijn Koevoets, Jiska Sietsma & Annabeth Groenman. Wat hebben jullie veel in huis en wat ben ik nieuwsgierig te horen hoe het jullie vergaat en waar jullie terecht zijn gekomen! Heel graag hoor ik het op 13 en 14 december 2012.

Voor wat betreft MRI, ICT, dataverwerking en (statistiek) ondersteuning bedank ik alle uiterst kundige, uitermate intelligente en gezellige (oud-)collega's van de Afdeling Psychiatrie en daarbuiten, in het bijzonder Caroline van Baal, Rachel Brouwer, Eske Derks, Martijn van den Heuvel, René Mandl, Piet Meindertsma en Hugo Schnack. Voor het scannen wil ik alle laboranten en de 'flows' Florian Bootsman (speciale dank voor je opzet in mijn opleiding tot scanbevoegde) & Mirjam Bloemendaal bedanken. Op menig typisch te noemen tijdstip hebben we gescand, gepraat, gegeten en onbedaarlijk gelachen. Voor het verwerken van de scans dank ik Gayane Sarkisyan. Gayane, met jouw intelligentie en doorzettingsvermogen kom jij er zeker! Speciale dank ook aan Jeanette Sopacua, Emmy Drost en Elly Schreurs! Mariken de Krom en Krista Poel van het RMI, beiden bedankt. Van 'Research Online' dank ik Frank Leus en Joost Schotsman (TOPPER), het was een flinke klimwand waar we, door omstandigheden, met vertraging aan begonnen, maar de TOP is bereikt. Peter Deschamps, mijn spss-promotie-maatje, het doet mij veel deugd dat wij elkaar blijven zien.

De (oud-)collega onderzoekers van Afdeling Psychiatrie dank ik in voor de gezelligheid bij congres, koffieapparaat en tennistoernooi plus het feit dat ik altijd binnen kon lopen voor advies: Steven Bakker, Maria Boersma, Marc Bohlken, Geartsje Boonstra, Heleen Boos, Elemi Breetvelt, Mariët van Buuren, Guusje Collin, Thalia van der Doef, Renate Floor-Siebelink, Sander Haijma, Anna Hedman, Janna Marie Hoogendam, Cédric Koolschijn, Jurjen Luykx, Arija Maat, Monica Rais, Miriam Salden, Afke Terwisscha van Scheltinga, Christiaan Vinkers, Antoin de Weijer, Jurriaan Witteman, Bram Zandbelt en vele anderen. Professor dr. Magriet Sitskoorn, veel dank voor de begeleiding, ik heb het zeer gewaardeerd. Marieke Langen, wat heerlijk, ineens waren we kamergenoten. Super bedankt voor de momenten van weerspiegeling (de parallellen zijn niet te missen), de koffie en lunches. Roomy voor even, ook wij houden contact!

De (oud-)collega's van zorglijn A2 en A3 wil ik in het bijzonder bedanken voor de jarenlange, plezierige samenwerking. Ien de Jong en Michel Alexander, jullie bereidheid actief betrokken te raken bij TOPFIT en de inzet waarmee jullie dit deden,

getuigt van liefde voor de patiënten. Carry van de Kappelle, bij jou begon het in maart 2003. Wie zet nu het tennistoernooi voort (anders kun jij het niet meer winnen)? Alle (oud-)collega's van A3, in het bijzonder Krissie Aerts, Rina Aslander, Jenny Beauveser, Angela 'Bennett', Marit Bierman, Carla Braam, Esther Caspers, Liesbeth Garrels, Bep Geurtsen, Margit Jongerius, Peter Knipmeijer, Laura Kouwenberg, Anneke Kuipers, Annick van 't Land, Jiska Peper, Marieke Putter, Marion Scholten, Jean-Paul Selten, Nicoletta van Veelen, Dineke van de Velde, Martin Voerman, Elisabeth Vonk, Attie Voorsluijs, Jacob Vorstman en Yvonne Wildbret, jullie zijn stuk voor stuk kanjers, ik ga jullie missen, bedankt voor alles! Saskia Palmen, maar goed dat het beklimmen van de Mount Everest niet óók nog op jouw lijstje stond! Samen zouden we kletsend aan de klim beginnen (en ik zou spoedig mijlenver achter je aan lopen ;-).

Van de Afdeling Revalidatie, Verplegingswetenschap & Sport wil ik alle sportartsen bedanken die testen hebben uitgevoerd, in het bijzonder Wout van der Meulen (jij zou zo bij de psychiatrie kunnen werken, fantastische human skills), Anne Hindriks (goede dokter, trotse mama) en David van der Sluijs. Verder kunnen niet onvermeld blijven: Liesbeth Barelds (nog een testje tussendoor inplannen, geen brug te ver), Janneke Sterk (Vredenburg met tennishelden van weleer was super) en Marrette Broekman, Sandor Schmikli (onnavolgbaar v.w.b. kennis), Wouter de Vries en Anne-Marie Beijsterveldt (voor de wandelingen, de steun en de kritische bespiegelingen). Tot slot dank ik cardioloog Dr. Rienk Rienks voor het beoordelen van afwijkende ECG's.

Dat ik zo'n gelukkig mens ben komt grotendeels door de goede vriendschappen waarmee ik gezegend ben. Jullie geven mij het gevoel dat we met elkaar elke beklimming aankunnen! Tennis en vriendschap gaan optimaal samen, Vechtlust(ers), bedankt! En heren, de wintercompetitie kan weer beginnen, kan niet wachten. Kootsj Sabine de Greeff, zonder jouw service was mijn wedstrijd niet zo soepel verlopen! Krista van der Horst, onze vriendschap gaat ver terug en jouw creativiteit komt bij alle life-events van pas, trouwen, kind krijgen en promoveren, jij weet er grafisch raad mee. Veel dank!

Lieve mama & Piet, papa & Christine, Thedo & Diny, bedankt voor de altijd aanwezige steun. Jullie zijn mijn berggidsen in het leven. Altijd stimuleren jullie mij op expeditie te gaan en mij te ontwikkelen. Jullie gaven mij de ruimte om hierbij, soms verstandig en soms onverstandig, vooral mijn eigen route te bepalen, te zijn wie ik ben. Het gaat om de wandeling, niet alleen om de TOP zelf. Ischa, Bart, zwagers, schoonzussen, neefjes en nichtjes, ik heb jullie allen zo lief.

Liefste Janneke en Pietertje, jullie zijn mijn alles. Het uitzicht vanaf de TOP is zoals hij is, onbeschrijflijk mooi, dankzij jullie. En staand op de TOP kijken wij uit op de vergezichten van onze toekomst, wat een fijn vooruitzicht.

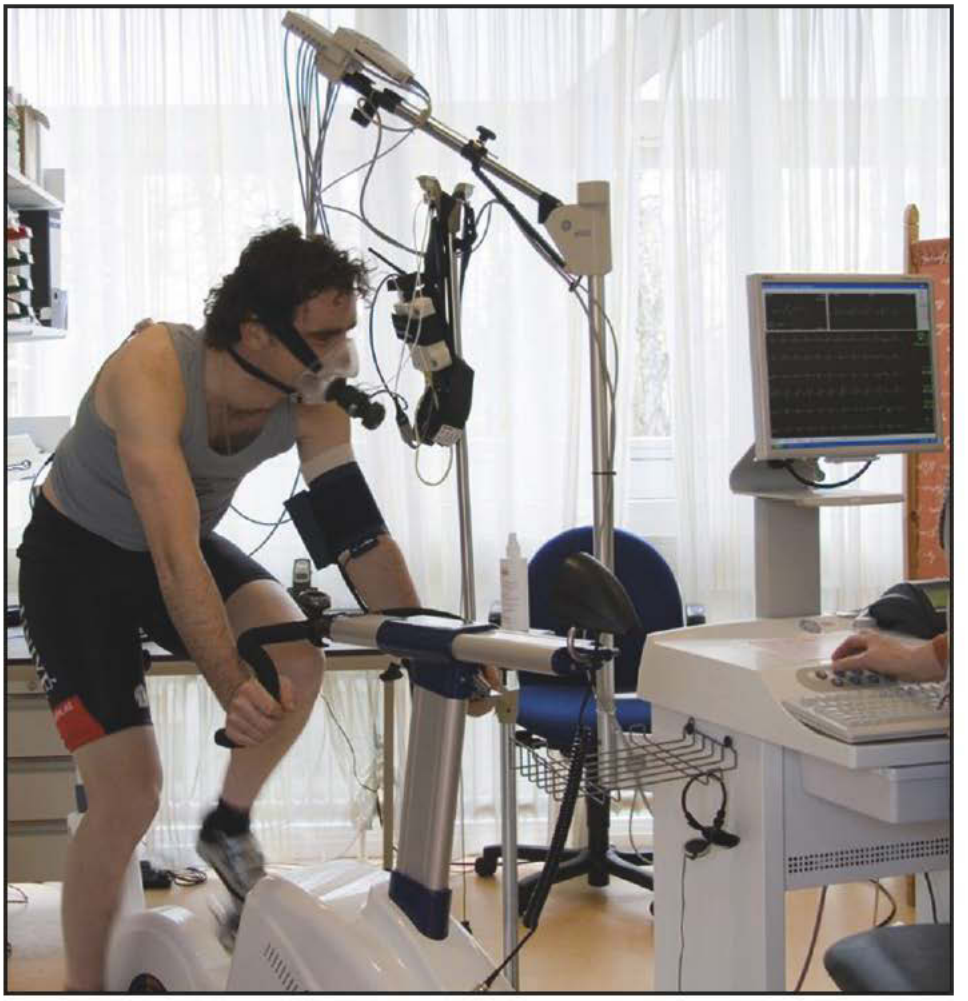
Machhapuchhare Mountain, Nepal

A

Appendix

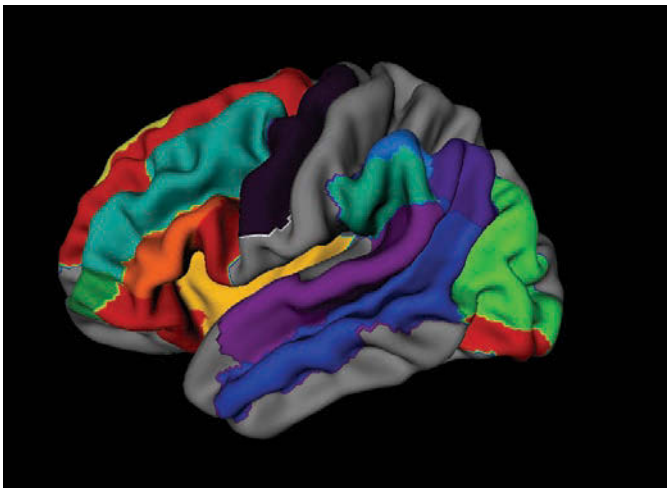
Appendix 1 (bij hoofdstuk 1)

Figure 2. Test set-up of an incremental cardiopulmonary exercise test with respiratory gas-exchange analysis.

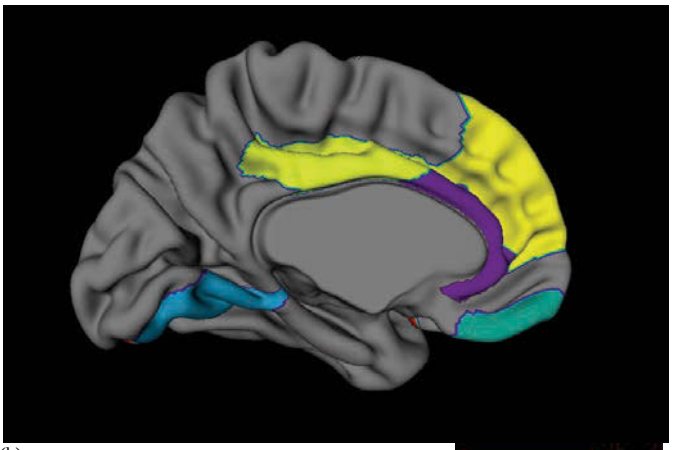


Appendix 2 (bij hoofstuk 6)

Figure 3. Lateral (a) and medial (b) view depicting significant associations between CRF improvement (W_{peak} change in W) and thickening (or less thinning) in the left hemisphere, in large parts of the frontal, temporal and cingulate cortex.

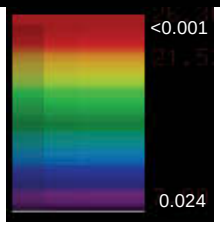


(a)



(b)

Legend:



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