

# The effects of a 6-month exercise program on mental and physical health and brain volumes in patients with schizophrenia and matched healthy controls

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<b>Registration date</b> 21/09/2011	<b>Overall study status</b> Completed	<input type="checkbox"/> Protocol
<b>Last Edited</b> 30/10/2015	<b>Condition category</b> Mental and Behavioural Disorders	<input type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
		<input type="checkbox"/> Individual participant data
		<input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

About one percent of the population is affected with schizophrenia during their lifetime. Patients with schizophrenia suffer from one or more psychotic episodes in which they have symptoms such as hallucinations and delusions. An example is that a psychotic person hears voices. These symptoms are often called positive symptoms. Besides these, patients with schizophrenia often suffer from negative symptoms. They are, for example, less physically active and take less initiative compared to healthy people. In addition, they often suffer from cognitive issues such as poor short-term memory and difficulties in executive functions (i.e. planning activities). Also, it is more difficult for patients with schizophrenia to work and maintain social contacts. The positive effects of physical activity on general health is well accepted. Also, research has shown exercise to be a successful treatment for mild to moderate depression. Exercise might also be an effective add-on therapy in the treatment of patients with schizophrenia. However, until today, little scientific research has examined this. The aim of this study is to investigate whether exercise improves mental and physical health in patients diagnosed with schizophrenia, schizoaffective disorder and schizofreniform disorder, compared with patients receiving occupational therapy. Since schizophrenia is considered a brain disease, investigators also examine whether exercise improves brain health in patients with schizophrenia, when compared to occupational therapy. Lastly, to better interpret the effect of exercise, matched healthy subjects will also be asked to participate in this study.

### Who can participate?

1. Patients aged 18 to 48 diagnosed with schizophrenia, schizoaffective disorder or schizofreniform disorder
2. Healthy volunteers aged 18 to 48

### What does the study involve?

Participants are randomly allocated to either the intervention group or the control group. The intervention group exercise for one hour twice weekly for six months, including cardiovascular

and muscle strength exercise. The control group are offered occupational therapy twice weekly for six months, which includes creative, recreational and social activities such as painting and computer activities, and a maximum of one hour a week of sports activities.

What are the possible benefits and risks of participating?

Participants may benefit from improved mental and physical health. There is little risk involved. However, even though the exercise program is adjusted to every participant's personal fitness, one can get a muscle injury. In case of injury, a sports physician will examine and if necessary treat the injury, free of charge.

Where is the study run from?

This study is organized by the UMC Utrecht, in collaboration with three other mental health institutes in The Netherlands. The study takes place at different locations in the Netherlands (UMC Utrecht, Altrecht Mental Health Nieuwegein, Mental health care Duin- en Bollenstreek and Mental health care Friesland) but most measurements will take place at the UMC Utrecht, The Netherlands.

When is the study starting and how long is it expected to run for?

April 2007 to December 2010.

Who is funding the study?

The study is funded primarily by the Psychiatry Department of the UMC Utrecht. In addition, grants were received from the Dutch Diabetes Foundation, Eli Lilly Pharmaceuticals and Janssen Cilag Pharmaceuticals.

Who is the main contact?

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## Contact information

### Type(s)

Scientific

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## Additional identifiers

### Protocol serial number

05/286

# Study information

## Scientific Title

Effects of a 6-month cardiovascular exercise program on symptomatology, cardiovascular fitness and brain volumes in patients with schizophrenia: a multicentre randomised controlled trial

## Acronym

TOPFIT

## Study objectives

TOPFIT: The Outcome of Psychosis and Fitness Therapy

1. A six month cardiovascular exercise program improves symptomatology, co-morbid depressive symptoms and outcome in patients with schizophrenia more than occupational therapy
2. A six month cardiovascular exercise program improves cardiovascular fitness and physical health parameters in patients with schizophrenia more than occupational therapy.
3. A six month cardiovascular exercise program improves the reported progressive brain volume decreases in patients with schizophrenia more than occupational therapy as measured by magnetic resonance imaging (MRI).

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

1. Medical Research Ethics Committee (Medisch Ethische Toetsingscommissie) of the UMC Utrecht, the Central Committee for Human Related Research (Centrale Commissie Mensgebonden Onderzoek), 22/06/2006
2. The local medical ethics board of the participating mental health institutes:
  - 2.1. Altrecht Mental Health, 05/01/2007
  - 2.2. GGZ Duin en Bollenstreek, 10/03/2008
  - 2.3. GGZ Friesland, 06/08/2009

## Study design

Multicentre randomised controlled trial

## Primary study design

Interventional

## Study type(s)

Treatment

## Health condition(s) or problem(s) studied

Schizophrenia

## Interventions

Patients randomized to the control group were offered occupational therapy (OT) biweekly for six months. OT comprised creative, recreational and social activities such as painting and computer activities. OT provides a similar amount of daily structure, activation, and given attention from the therapist. The main factor of difference between randomized groups was the amount of exercise undertaken. Patients in the OT group were allowed to do sports activities at a low intensity level, for a maximum of one hour a week.

The exercise (EX) intervention was designed to improve cardiovascular health and primarily incorporated cardiovascular exercises. Muscle strength exercises (6 exercises per week; main muscle groups; 3 times 10 to 15 repetitions maximum) were included to provide variation in the physical exercise program. The program followed recommendations of the American College of Sports Medicine (ACSM; American College of Sports Medicine, 1998; Kraemer et al., 2002). The exercise program was registered in the subjects logbook, providing information on amount of training and compliance. Ex subjects, both patients and controls, exercised one hour twice weekly for six months. To prevent dropout of patients due to injury, exhaustion and overload, workload was increased stepwise (week 1-3: 45%; week 4-12: 65%; week 13-26: 75% of  $Vo_2$ -reserve ( $Vo_2$ -R)) (ACSM, 1998). Individual workload of each participant was determined according patients heart rate reserve as determined by the baseline Maximal Exercise Tolerance Test (METT) (Godfrey, 1974).

## **Intervention Type**

Behavioural

## **Primary outcome(s)**

To investigate whether a 6-month cardiovascular exercise program will provide greater improvement on the following symptomatology and cardiovascular fitness than occupational therapy measurements in patients with schizophrenia. Another primary objective is to examine whether the reported progressive brain volume decreases in schizophrenia will diminish more through a 6-month cardiovascular exercise program than occupational therapy as measured by MRI.

### **1. Symptomatology measurements:**

1.1. Positive and Negative Syndrome Scale (PANSS): This test is a 30-item rating scale designed to measure severity of psychopathology in adult patients with schizophrenia. Five components have been reported: positive, negative, depression, agitation-excitement, and disorganisation (Wolthaus et al., 2000; Bell et al., 1994).

1.2. Clinical Global Impression Scale (CGI): measure the clinical global impression by means of two scales, one for present state and one for change

### **2. Physical measurements:**

Maximal Exercise Tolerance Test (METT): Each subject will undergo an exercise test according to the Godfrey-protocol bicycle ergometer test. The maximum oxygen uptake capacity ( $VO_2$ max) can be determined validly and reliably with this protocol. After two minutes of biking at 50 watt the workload is increased by 20 watts every minute until exhaustion is reached. Ventilation, oxygen consumption and expired carbon dioxide ( $CO_2$ ) are measured.

### **3. MRI measures:**

Volume measurements: Quantitative assessments of intracranial, total brain, gray and white matter of the cerebrum (total brain excluding cerebellum and stem), lateral and third ventricles, and peripheral cerebrospinal fluid (CSF) volumes will be performed

All measurements are performed at baseline (before randomisation) and immediately after the six month intervention period. All measurements are assessed by a rater, blinded for randomisation, within 14 days, and all measurements are assessed within 7 days prior or after assessment of the Positive and Negative Syndrome Scale (PANSS).

## **Key secondary outcome(s)**

To examine whether a 6-month cardiovascular exercise program will provide greater improvement on psychiatric and somatic co-morbidity than occupational therapy in patients with schizophrenia. Also, a secondary objective of this study is to examine whether changes are found

in binary masks of gray and white matter and in intensities of white-matter nervous paths between regions of interest as measured by MRI. The following assessments will be done as secondary objectives:

1. Psychiatric co-morbidity measurements:

1.1. Montgomery and Asberg Depression Rating Scale (MADRS): degree of severity of depressive symptoms, sensitive measure of change in symptom severity during treatment

1.2. Cumulative antipsychotic medication: cumulative life-time antipsychotic medication in haloperidol (mg) equivalent

1.3. Number of hospitalisations: number and duration of hospitalisations (days) between T0 and T6

1.4. Camberwell Assessment of Need (CAN): assesses the community services requirements of patients with severe mental illness. Has the ability to aid routine care and treatment and highlights likely areas for further assessment

1.5. Quality of Life-Short version (QLS): measures general physical condition, important human activities, and general quality of life

1.6. Continuous Performance Test, Identical Pairs Version (CPT-IP): assesses more complex attention-dependent task requiring formation and transient maintenance of a representation of task relevant information for correct task performance

1.7. Auditory Verbal Learning Test (AVLT): multiple measures of immediate and delayed ability to recall presented visual information (words) and recognition of formerly presented information

1.8. Digit-Symbol Task (DST): is regarded as a measure primarily of speed of information processing, although it also reflects psychomotor speed and short-term memory

2. Somatic co-morbidity measurements:

2.1. Body Mass Index

2.2. Amount of daily physical activity (measured with SenseWear PRO2 Body Monitor System)

2.3. Factors of the metabolic syndrome: Blood pressure, abdominal obesity, triglycerides, cholesterol and glucose, measured sober (prior to food intake) at the same time (for example 10:00 a.m.) at T0 and T6

2.4. Body Fat percentage

3. MRI procedures:

3.1. Voxel Based Morphometry (VBM): Binary masks of grey and white matter will be made based on histogram analyses and series of mathematical morphological operators. The binary grey matter masks will be analysed using voxel-based morphometry

3.2. Diffusion Tensor Imaging (DTI): DTI relates image intensities to the relative mobility of endogenous tissue water molecules. The resulting diffusion tensor field of the brain is used to track white-matter nervous paths between regions of interest

All measurements are performed at baseline (before randomisation) and immediately after the six month intervention period. All measurements are assessed by a rater, blinded for randomisation, within 14 days, and all measurements are assessed within 7 days prior or after assessment of the Positive and Negative Syndrome Scale (PANSS).

**Completion date**

31/12/2010

## **Eligibility**

**Key inclusion criteria**

Patients must meet the following criteria to be eligible for enrolment:

1. Diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder according to

Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) and assessed with the Comprehensive Assessment of Schizophrenia and History (CASH) (Andreasen et al., 1992).

2. 18 - 48 years old
3. Stable on antipsychotic medication
4. Written informed consent

Healthy control subjects must meet the following criteria to be eligible for enrolment:

1. No diagnosis of a psychiatric disorder according to DSM-IV ever
2. 18 - 48 years old
3. Matching amount of physical activity compared to included patients, as measured before intervention by the SenseWear PRO2 Body Monitoring System
4. Matching level of parental education compared to included patients, as measured before intervention by means of the verhage method
5. Matching body mass index (BMI) compared to included patients, as measured before intervention
6. No first degree relative with a psychotic or depressive disorder
7. Written informed consent

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

18 years

### **Upper age limit**

48 years

### **Sex**

All

### **Key exclusion criteria**

1. Evidence of significant cardiovascular disorders that might prevent safe participation in the study. Risk of cardiovascular disorders will be assessed following Lausanne recommendations
2. Evidence of significant neuromuscular or endocrine, or other disorders (for example joint disease) that might prevent safe participation in this study
3. A primary diagnosis of alcohol or substance abuse
4. intelligence quotient (IQ) < 70, as measured with Wechsler Adult Intelligence Scale Short Form (WAIS-III SF): short version of the WAIS-III, gives an estimate of an individuals intellectual functioning.
5. Organic brain disorder or other clinically significant concurrent medical illness
6. Severe head trauma
7. With occurrence of certain medical diseases (for example fever) a subject can be temporarily be excluded from the intervention

### **Date of first enrolment**

01/04/2007

**Date of final enrolment**

31/12/2010

## Locations

**Countries of recruitment**

Netherlands

**Study participating centre**

Heidelberglaan 100

Utrecht

Netherlands

3508GA

## Sponsor information

**Organisation**

University Medical Center Utrecht (Netherlands)

**ROR**

<https://ror.org/0575yy874>

## Funder(s)

**Funder type**

Hospital/treatment centre

**Funder Name**

University Medical Centre Utrecht (Netherlands)

**Funder Name**

Dutch Diabetes Foundation (Netherlands) (ref: 2007-00-040)

**Funder Name**

Eli Lilly and Company (ref: 001-TOPFIT)

**Alternative Name(s)**

Lilly, Eli Lilly & Company, Eli Lilly & Co., Eli Lilly And Co, Eli Lilly & Co

**Funding Body Type**

Government organisation

**Funding Body Subtype**

For-profit companies (industry)

**Location**

United States of America

**Funder Name**

Janssen Cilag

**Funder Name**

Dutch Association for Psychomotor Therapy (Netherlands)

## Results and Publications

**Individual participant data (IPD) sharing plan****IPD sharing plan summary****Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes