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

Submission date
28/07/2011

Recruitment status
No longer recruiting

Registration date
21/09/2011

Overall study status
Completed

Last Edited
30/10/2015

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] 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 schizophreniform 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

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
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 progam 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

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Patient information can be found at www.umcutrecht.nl/topfit (in Dutch)

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 excercise (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 Vo2-reserve (Vo2-R)) (ACSM, 1998). Individual workload of each participant was determined according patients hear rate reserve as determined by the baseline Maximal Exercise Tolerance Test (METT) (Godfrey, 1974).

Intervention Type
Behavioural

Primary outcome measure
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 (VO2max) 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 (CO2) 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).

Secondary outcome measures

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).

Overall study start date
01/04/2007

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

Age group
Adult

Lower age limit
18 Years

Upper age limit
48 Years

Sex
Both

Target number of participants

Aim is to include 80 patients and 80 healthy subjects, randomized to either exercise (40 patients, 40 controls) or occupational therapy (40 patients)/life as usual (40 controls)

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)

Sponsor details
Heidelberglaan 100
Utrecht
Netherlands
3508GA

Sponsor type

Hospital/treatment centre

Website
http://www.umcutrecht.nl

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

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
Janssen Cilag

Funder Name
Dutch Assiociation for Psychomotor Therapy (Netherlands)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration