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

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Scheewe TW, Backx FJG, Takken T, Jörg F, van Strater ACP, Kroes AG, Kahn RS, Cahn W. Exercise therapy improves mental and physical health in schizophrenia: a randomised controlled trial.

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 (MetS).
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 with 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 with occupational therapy. No effect for MetS (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.

Key words: mental health; physical health; need of care; cardiovascular fitness; metabolic syndrome

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Significant outcomes

- Exercise therapy, when performed once to twice a week for 1 h, decreases symptoms of schizophrenia and depression in schizophrenia patients compared with occupational therapy.
- Exercise therapy improves cardiovascular fitness in patients with schizophrenia compared with occupational therapy.

Limitations

- Given limited effects in the intention-to-treat analyses, treatment non-adherence in schizophrenia is an important factor that could threaten the implementation of exercise therapy in daily practice.
- Due to drop-out and non-compliance, per protocol analyses were performed on only 39 subjects.
- Due to limited exercise frequency, intensity and session duration, apart from trend improvement in triglycerides, metabolic syndrome did not improve significantly.

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 comorbid psychiatric disorders. Depression in particular is highly prevalent among patients with schizophrenia (4). Thus, antipsychotics fall short in treating the core symptoms and the comorbid 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 comorbid 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 comorbid 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.

Material 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 $\geq$ 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 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; pipamperone, 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 with exercise therapy, occupational therapy provided a similar amount of structure and attention, thus minimizing the possibility that the hypothesised exercise effect is the result of non-specific 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 (SPSS, Chicago, IL, USA). 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 χ^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 (χ^2 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 χ^2-tests, $\alpha = 0.15$). 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).

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

	Treatment				
	EX (n = 31)		OT (n = 32)		Analysis*
Characteristics	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))†	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)	3/11/2016		6/9/2017		0.56
Employment (welfare/ working/unemployed/ student)	24/5/1/1		26/3/3/0		0.49
Marital status married/ (single/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	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)‡	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	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§	14.4	1.8	11.2	2	0.11
CAN sum¶	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)	26.6	6.6	26	5.5	0.72
BFP (%)	24.5	9.1	25.7	8.5	0.58
MetS (% yes)	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 (mM)	1.5	1.1	1.5	1	0.99
HDL cholesterol (mM)	0.97	0.3	1.1	0.3	0.11
Glucose (mM)	5.4	0.6	5.2	0.5	0.17

*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.
†Psychosocial status, expressed as highest level of education of one of both parents according to Verhage (41).
‡Baseline antipsychotic doses in haloperidol equivalent in mg/day.
§MADRS are EXP-values of the logarithmic transformed data due to non-normal distribution (all other outcome data were normally distributed).
¶CAN sum of met and unmet needs. Clinical data: 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.

Results

Participants

Included subjects were randomised to exercise therapy (49%; $n = 31$) or occupational therapy (51%; $n = 32$) (42). 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 with patients randomised to exercise therapy (7%; $n = 2$; $\chi^2 = 8.33$; $P = 0.02$). Though a higher percentage of women (53%) dropped-out or were non-compliant compared with men (35%), this difference did not reach statistical significance ($\chi^2 = 0.79$; $P = 0.37$). Thirty-nine patients (exercise therapy: 65% ($n = 20$); occupational therapy: 59% ($n = 19$)) met compliance demands (study diagram see Fig. 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 6 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; $P = 0.07$).

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 with occupational therapy was found for PANSS total score ($P = 0.37$). Per protocol, exercise therapy significantly decreased PANSS total score (−20.7%) compared with 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 with occupational therapy. When site was added to the analyses, this did not change the results.

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 with 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 with occupational therapy ($P = 0.76$). Per protocol, a significant effect for CAN was found. Need of care decreased after exercise therapy (−22.0%) as

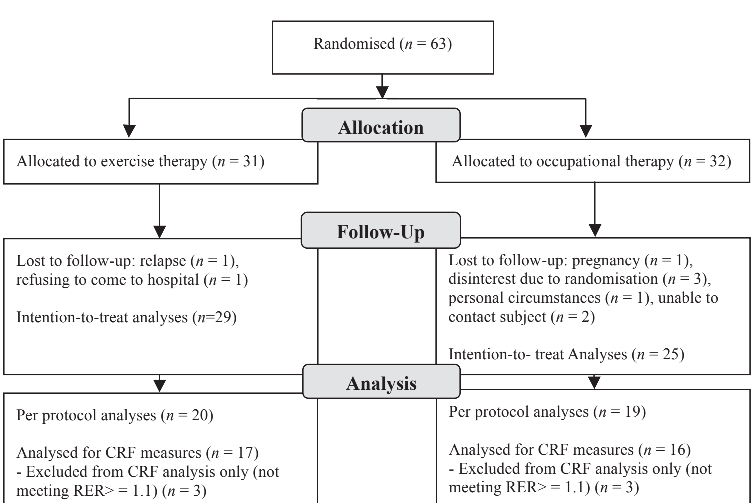

Fig. 1. Flow diagram of the study.

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

	Treatment									
	EX (n = 29)				OT (n = 25)					
	Baseline		Follow-up		Baseline		Follow-up			
Outcome variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P*	η_p^2†
Primary‡										
PANSS total	63.4	11.6	59.1	11.8	62.3	10.1	60.8	11.2	0.371	0.02
Secondary‡										
MADRS§	13.9	1.8	9.7	2	11.7	2	10.7	1.9	0.065	0.06
CAN sum¶	8.3	3	7	2.8	8.2	3.1	7.4	2.8	0.757	0
Primary**										
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‡										
BMI (kg/m^2)	26.8	6.9	26.6	5.8	26.8	6	27.2	6.2	0.36	0.02
BFP (%)	24.9	9.3	24.4	9.6	27.1	9.1	28	8.6	0.39	0.02
MetS (% yes)	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)	127.9	15.8	125.3	15.8	124.8	9.9	127.5	12.7	0.249	0.03
Diast BP (mm/hg)	75.7	9.2	75.5	7.6	76.5	9.8	78.6	8.7	0.242	0.03
Triglyc (mM)	1.6	1.1	1.5	1	1.5	1.1	1.6	1	0.19	0.04
HDL (mM)**	0.9	0.2	1.1	0.2	1	0.3	1	0.2	0.115	0.07
Glucose (mM)	5.4	0.7	5.5	0.7	5.3	0.6	5.5	0.6	0.721	0

*Except for MetS where chi-square test was performed, all analysis were performed with general linear model, repeated measures design.
†Effect sizes given as Partial eta square (η_p^2).
‡Lower follow-up scores indicate improvement.
§MADRS are EXP-values of the logarithmic transformed data due to non-normal distribution of data.
¶CAN sum of met and unmet needs.
**Higher follow-up scores indicate improvement, Clinical data: 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.

compared to occupational therapy (−4.0%) (P = 0.05). When site was added to the analyses, this did not change the 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 with occupational therapy (−2.9%) led to a significant W_{peak} increase ($P < 0.01$). No significant change after exercise therapy (0%) compared with 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 with 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 with 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 with 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 schizo-

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)

	Treatment											
	EX (n = 20)					OT (n = 19)						
	Baseline		Follow-up			Baseline		Follow-up				
Outcome variables	Mean	SD	Mean	SD	%†	Mean	SD	Mean	SD	%†	P	η_p^{2}*
Primary‡												
PANSS total	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‡												
MADRS§	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¶	8.2	3	6.4	2.9	−22	7.6	2.7	7.3	2.7	−4	0.05	0.1
Primary**												
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‡												
BMI (kg/m^2)	27.3	7.1	27	6	−1.1	27.9	6	28.4	6.3	4.8	0.27	0.04
BFP (%)	24.9	9.3	24.4	9.6	−2	27.1	9.1	28	8.6	3.3	0.183	0.05
MetS (% yes)	50	–	40	–	−10	36.8		42.1		5.3	0.493	
Waist circ (cm)	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 (mM)	1.6	1.1	1.4	1	−13.5	1.7	1.2	1.6	0.9	−2.4	0.075	0.1
HDL (mM) **	0.9	0.2	1.1	0.2	11.7	1	0.3	1	0.2	−2	0.115	0.07
Glucose (mM)	5.4	0.7	5.6	0.7	−2.6	5.3	0.7	5.5	0.7	−2	0.717	0

*Effect sizes given as Partial eta square (η_p^2).
†Percentage change in mean score from baseline to follow-up.
‡Lower follow-up scores indicate improvement.
§MADRS are EXP-values of the logarithmic transformed data due to non-normal distribution of data.
¶CAN sum of met and unmet needs.
**Higher follow-up scores indicate improvement, 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.

phrenia 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 because 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 exer-cise 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 non-specific 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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