Effects of Exercise Therapy on Cardiorespiratory Fitness in Patients with Schizophrenia

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ABSTRACT

SCHEEWE, T. W., T. TAKKEN, R. S. KAHN, W. CAHN, and F. J. BACKX. Effects of Exercise Therapy on Cardiorespiratory Fitness in Patients with Schizophrenia *Med. Sci. Sports Exerc.*, Vol. 44, No. 10, pp. 00–00, 2012. **Background**: Increased mortality in schizophrenia is caused largely by 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 patients with schizophrenia and in controls. **Methods**: Sixty-three patients with schizophrenia and 55 controls, matched for gender, age, and socioeconomic status, were randomized 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 ($\dot{V}O_{2peak}$) and peak work rate (W_{peak}). Minimal compliance was 50% of sessions ($n = 52$). **Results**: Male and female patients with schizophrenia had a relative $\dot{V}O_{2peak}$ of 34.3 ± 9.9 and 24.0 ± 4.5 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively. Patients had higher resting HR ($P < 0.01$) and lower peak HR ($P < 0.001$), peak systolic blood pressure ($P = 0.02$), relative $\dot{V}O_{2peak}$ ($P < 0.01$), W_{peak} ($P < 0.001$), RER ($P < 0.001$), minute ventilation ($P = 0.02$), and HR recovery ($P < 0.001$) than controls. Relative $\dot{V}O_{2peak}$ was 90.5% ± 19.7% ($P < 0.01$) of predicted relative $\dot{V}O_{2peak}$ in male and 95.9% ± 14.9% ($P = 0.18$) in female patients. In patients, exercise therapy increased relative $\dot{V}O_{2peak}$ compared with decreased relative $\dot{V}O_{2peak}$ after occupational therapy. In controls, relative $\dot{V}O_{2peak}$ increased after exercise therapy and to a lesser extent after life as usual (group, $P < 0.01$; randomization, $P = 0.03$). Exercise therapy increased W_{peak} in patients and controls compared with decreased W_{peak} in nonexercising patients and controls ($P < 0.001$). **Conclusion**: Patients had lower CRF levels compared with controls and reference values. Exercise therapy increased $\dot{V}O_{2peak}$ and W_{peak} in patients and controls. $\dot{V}O_{2peak}$ and W_{peak} decreased in nonexercising patients. **Key Words:** CARDIORESPIRATORY FITNESS, PHYSICAL HEALTH, CARDIOVASCULAR EXERCISE, MORTALITY

Schizophrenia is a severe and chronic psychiatric illness characterized 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 comorbidities (20). Patients with schizophrenia have a two- to threefold increased mortality rate compared with the general population (41), resulting in a 20% reduction in life expectancy (36). Up to 40% of excess mortality can be attributed to suicide and unnatural deaths (12). In schizophrenia, standardized mortality ratios of most major natural death categories are increased compared with the general population (i.e., digestive, endocrine, infectious, and nervous diseases) (36). The single largest cause of death in patients with schizophrenia is CHD. Patients with schizophrenia are two times more likely to die of CHD than the general population (11).

Several lifestyle factors influence the physical health status of patients with schizophrenia and negatively affect their risk for CHD. Patients with schizophrenia are much more likely to smoke, and 70% to 75% of patients with schizophrenia can be classified as being physically inactive and do not meet minimal physical activity recommendations (15,30). In addition, patients with schizophrenia are more likely to have a reduced nutritional status because of an unhealthy diet (31). Moreover, many atypical antipsychotics induce significant weight gain, increasing the risk of diabetes mellitus Type II, the metabolic syndrome, and ultimately CHD (33,35).

Besides the abovementioned factors, low cardiorespiratory fitness (CRF) has been recognized as an independent risk factor for all-cause mortality in adults and a key risk factor for CHD-related mortality (5,26). A recent meta-analysis in

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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 (26). In schizophrenia, high-quality studies investigating CRF are scarce (42). A cross-sectional study reported obese patients with schizophrenia had low CRF levels compared with population standards. Strikingly, only two participants in the entire sample (n = 117) fit the categorization of "moderate fitness level." All other participants scored below population standards. This indicates poor CRF is a key modifiable risk factor (37). Interestingly, a recent trial showed that 8 wk of high-intensity, anaerobic exercise training increased CRF in patients with schizophrenia (22). A large Finnish cohort sample showed adolescents who later developed psychosis, at the age of 15–16 yr, had a relatively low level of CRF (odds ratio, 2.2; 95% confidence interval, 0.6–7.8), as measured using a submaximal cycle ergometer test (27).

To the best of our knowledge, no prior randomized 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 with matched physically inactive but otherwise healthy controls as well as compared with reference values. Furthermore, we investigated whether a 6-month exercise program improves CRF in patients with schizophrenia and controls.

METHODS

Sample and setting. This multicenter 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, and GGZ Friesland) (n = 37). Participants were enrolled in the study between May 2007 and May 2010, written informed consent was obtained after the procedures, and possible adverse effects were explained. This trial was part of the TOPFIT project (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 randomization 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 6 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*) (2). Diagnosis was confirmed by a psychiatrist (WC, NV, or JS) using the Comprehensive Assessment of Schizophrenia and History (4). Patients were stable on antipsychotic medication, i.e., using the same dosage for at least 4 wk before inclusion. They showed no evidence for significant cardiovascular, neuromuscular, endocrine, or other somatic disorders that prevented safe participation in the study (10). Patients had no primary diagnosis of alcohol or substance abuse and had an intelligence quotient (IQ) ≥70, as measured with the Wechsler Adult Intelligence Scale Short Form (WAIS-III SF) (13).

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 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 centers.

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 conforms criteria as mentioned by the American Thoracic Society/American College of Chest Physicians recommendations (3). CRF, the primary outcome measure, was defined as the highest relative (mL·min^{-1}·kg^{-1}) mean oxygen uptake at any 30-s interval during the test ($\dot{V}O_{2peak}$) and the peak work rate at the moment of exhaustion (W_{peak}) (6). HR (12-led ECG) 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}, $\dot{V}CO_2/\dot{V}O_2$) equaled or exceeded 1.1 (17).

The following exercise parameters were reported, in accordance to the American Thoracic Society/American College of Chest Physicians (3): resting HR (HR_{rest}, in bpm), peak exercise HR (HR_{peak}, in bpm), peak systolic and diastolic blood pressure (mm Hg), relative peak oxygen uptake level ($\dot{V}O_{2peak}$, in mL·min^{-1}·kg^{-1}), absolute peak oxygen uptake level ($\dot{V}O_{2peak}$, in mL·min^{-1}), peak minute ventilation ($\dot{V}_{Epeak}$, in mL·min^{-1}), peak work rate (W_{peak}, in W), RER_{peak}, oxygen pulse (O_{2pulse}, $\dot{V}O_{2peak}/HR_{peak}$ in mL·beat^{-1}) as well as ventilatory anaerobic threshold (VAT, $\dot{V}O_2$ in mL·min^{-1}), and difference between HR_{peak} and recovery HR (HR after 5 min of recovery (biking at 50 W)) (HR_{diff}, in bpm). CPET data among patients with schizophrenia and healthy controls were compared with reference values calculated according to Jones et al. (25) for absolute $\dot{V}O_{2peak}$ (mL·min^{-1}), HR_{peak} (bpm), O_{2pulse}, and VAT ($\dot{V}O_2$; in

$mL \cdot min^{-1}$). For relative $\dot{V}O_{2peak}$ ($mL \cdot min^{-1} \cdot kg^{-1}$), reference values according to Cooper and Storer (14) were used.

Intervention. The exercise intervention was designed to improve CRF and primarily incorporated cardiovascular exercises. Muscle strength exercises (six exercises weekly; three times 10 to 15 repetitions maximum for biceps, triceps, abdominal, quadriceps, pectoral, and deltoid muscles) were included to provide variation. The program followed the recommendations of the American College of Sports Medicine (ACSM) (1,28). 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 6 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 HR reserve based on baseline CPET data (1).

Patients not randomized to exercise therapy were offered occupational therapy 1 h twice weekly for 6 months. Occupational therapy comprised creative and recreational activities. Compared with exercise therapy, occupational therapy provided a similar amount of structure and attention, but no physical activation. Controls not randomized to exercise were assigned to life as usual and were not allowed to incorporate in moderate physical activity more than 1 h weekly.

Statistical analyses. SPSS 18.0.1 (SPSS, Chicago, IL) was used to analyze 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. If of nonnormal distribution, logarithmic transformation was applied or nonparametric testing was performed.

Baseline comparisons. Multiple ANOVAs for noncategorical variables and χ^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}, HR_{peak}, systolic and diastolic blood pressure, relative and absolute $\dot{V}O_{2peak}$, $\dot{V}_{Epeak}$, 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 relation between age, BMI, and $\dot{V}O_{2peak}$ in both patients and controls. In patients, correlations were calculated as well between $\dot{V}O_{2peak}$ and illness duration, severity of psychosis, and antipsychotic medication used (in haloperidol equivalent). Pearson product–moment correlations were also calculated to examine the relation between smoking (average number of cigarettes per day) and percentage of reference relative and absolute CRF.

Comparison with reference data. Paired sample t-tests were performed to assess differences in individual baseline and reference relative and absolute $\dot{V}O_{2peak}$, 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 equaled 100%.

Effects of exercise therapy. For CRF change analyses, minimal compliance was set at 50% of 52 sessions because a minimum workload is needed to be able to expect an effect in untrained subjects (1). 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 $\dot{V}O_{2peak}$, $\dot{V}_{Epeak}$, W_{peak}, RER_{peak}, O_{2pulse}, VAT, and HR_{diff} as dependent variables and group (patient or control) and randomization (exercise or occupational therapy/life as usual) as independent variables. For relative and absolute $\dot{V}O_{2peak}$ analyses, baseline $\dot{V}O_{2peak}$ was added as a possible confounder.

RESULTS

Baseline characteristics. Patients were randomized to exercise (n = 31) or occupational therapy (n = 32), whereas controls were randomized to exercise (n = 27) or life as usual (n = 28). As shown in Table 1, controls were T1 matched to patients for gender, age, and socioeconomic status (40), but as expected, controls had lower BMI (P = 0.01) and higher IQ ($P \leq 0.001$). Furthermore, on average, patients smoked significantly more cigarettes per day than controls ($P < 0.001$).

Dropout of patients was significantly higher in occupational therapy (n = 7) compared with exercise therapy patients (n = 2, $\chi^2(2) = 8.33$, P = 0.02). One healthy control (randomized to life as usual) dropped out because of serious physical illness. Although 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 because of 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 significance, 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 comedication (Table 2). T2

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 $\dot{V}O_{2peak}$ ($P < 0.01$), W_{peak} ($P < 0.001$), RER_{peak} ($P < 0.001$), $\dot{V}_{Epeak}$ (P = 0.02), HR_{diff} ($P < 0.001$), and, at trend-level significance, lower absolute $\dot{V}O_{2peak}$ (P = 0.09) than controls. No significant baseline differences between patients and controls

TABLE 1. Baseline characteristics of all patients with schizophrenia and healthy controls.

	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	0.80
Height (cm)	179.1 ± 11.0	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[2]	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	26.0 ± 5.5	0.13	0.72	23.9 ± 3.5	24.0 ± 3.2	0.02	0.90	6.60	**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	.1 ± .4	1.6 ± 5.9	1.70	0.20	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 (40).
[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.

in peak diastolic blood pressure ($P = 0.68$), O_{2pulse} ($P = 0.76$), and VAT ($P = 0.20$) were found between patients and controls (Table 3). Except higher HR_{rest} in exercise therapy (78.3 ± 16.3) compared with 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 $\dot{V}O_{2peak}$ was not different in compliant (≥50%) versus noncompliant (<50%) patients ($P = 0.65$) and controls ($P = 0.86$). Age was inversely correlated to relative $\dot{V}O_{2peak}$ in male ($r = -0.34$, $P = 0.01$) but not in female ($r = -0.39$, $P = 0.13$) patients with schizophrenia and in male ($r = -0.27$, $P = 0.12$) and female ($r = -0.20$, $P = 0.42$) controls. BMI was inversely correlated to relative $\dot{V}O_{2peak}$ in male ($r = -0.67$, $P < 0.001$) and female ($r = -0.54$, $P = 0.03$) patients with schizophrenia and in 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 $\dot{V}O_{2peak}$ and severity of psychosis in male patients ($r = -0.252$, $P = 0.091$) but not in female patients ($r = -0.234$, $P = 0.383$). Both in male and female patients, illness duration (males, $r = -0.229$, $P = 0.125$; females, $r = -0.181$, $P = 0.503$) or antipsychotic medication use (males, $r = -0.173$, $P = 0.263$; females, $r = -0.201$, $P = 0.473$) was not significantly correlated with $\dot{V}O_{2peak}$. Smoking was inversely correlated to the percentage of reference relative ($r = -0.21$, $P = 0.02$) and absolute ($r = -0.24$, $P < 0.01$) $\dot{V}O_{2peak}$.

Comparison with reference data. Individual baseline relative and absolute $\dot{V}O_{2peak}$ values for male and female patients and controls are set out against reference values in Table 4. Relative $\dot{V}O_{2peak}$ was 90.5% ± 19.7% ($P < 0.01$) of predicted relative $\dot{V}O_{2peak}$ in male patients with schizophrenia compared with 99.6% ± 13.5% ($P = 0.46$)

TABLE 2. Clinical characteristics of included patients for exercise therapy and occupational therapy.

	Treatment			
	EX (n = 31)	OT (n = 32)	Analyses[a]	
Characteristic	Mean ± SD	Mean ± SD	F	P
Diagnosis assessed with CASH (schizophrenia/schizoaffective disorder/schizophreniform disorder) (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	0.80
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 stabilizer (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
CAN sum[c]	8.4 ± 2.9	8.3 ± 3.4	0.03	0.86

Results are presented as mean ± SD 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 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.

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

	Group		Analyses	
	Patients (n = 63)	Controls (n = 55)		
Characteristic	**Mean ± SD**	**Mean ± SD**	***F***	***P***
HR_{rest} (bpm)[a]	73.8 ± 15.0	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 $\dot{V}O_{2peak}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)[a]	31.6 ± 9.9	35.9 ± 5.5	7.92	<**0.01**
W_{peak} (W)[a]	218.5 ± 51.5	255.0 ± 54.1	14.06	<**0.001**
Absolute $\dot{V}O_{2peak}$ ($mL \cdot min^{-1}$)[a]	2532.2 ± 668.2	2736.0 ± 627.0	2.87	0.09
$\dot{V}_{Epeak}$ ($mL \cdot min^{-1}$)[a]	95.7 ± 26.0	106.6 ± 25.2	5.30	**0.02**
RER_{peak} ($\dot{V}CO_{2peak}/\dot{V}O_{2peak}$[a]	1.27 ± .15	1.37 ± .09	21.16	<**0.001**
O_{2pulse} ($\dot{V}O_{2peak}/HR_{peak}$)[a]	14.6 ± 3.4	14.4 ± 3.2	0.09	0.76
VAT ($\dot{V}O_2$ in $mL \cdot min^{-1}$)[a]	1577.4 ± 451.2	1690.5 ± 496.1	1.669	0.20
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.

in male controls. In female patients with schizophrenia, relative $\dot{V}O_{2peak}$ was 95.9% ± 14.9% (P = 0.18) of predicted relative $\dot{V}O_{2peak}$ versus 110.3% ± 19.0% (P = 0.06) in female control subjects. Absolute $\dot{V}O_{2peak}$ in male patients with schizophrenia was 95.5% ± 20.7% (P = 0.12) of predicted absolute $\dot{V}O_{2peak}$ compared with 103.4% ± 13.3% (P = 0.17) in male controls. In female patients with schizophrenia, absolute $\dot{V}O_{2peak}$ was 96.8% ± 15.3% (P = 0.42) of predicted values compared with 112.3% ± 17.0% (P < 0.01) in female controls.

CRF 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), because of anxiety, no breath analyses were assessed. For most subjects, peripheral muscle fatigue (>50%) was the main reason for cessation of the test. Other reasons for cessation mentioned were dyspnea (±10%) and general fatigue (<10%).

In patients, exercise therapy increased relative $\dot{V}O_{2peak}$, whereas relative $\dot{V}O_{2peak}$ decreased after occupational therapy. In controls, increased relative $\dot{V}O_{2peak}$ was seen after exercise therapy and, although to a lesser extent, after life as usual (group, P < 0.01; randomization, P = 0.03). Exercise therapy increased W_{peak} in patients and controls compared with decreased W_{peak} in occupational therapy patients and life-as-usual controls (randomization, P < 0.001). The change over time in W_{peak} differed, at trend-level significance, between patients and controls (group × randomization, P = 0.09). Increased absolute $\dot{V}O_{2peak}$ levels were seen in controls compared with patients (group, P = 0.03). Also, absolute $\dot{V}O_{2peak}$ increased, at trend-level significance, after exercise therapy (randomization, P = 0.07). After exclusion of one outlier, the exercise effect was no longer significant (randomization, P = 0.11). Increases in absolute $\dot{V}O_{2peak}$ did not differ between groups (group × randomization, P = 0.95). Reduced O_{2pulse} was seen in patients compared with controls (group, P = 0.03). A trend-level significant exercise effect was seen for O_{2pulse} (randomization, P = 0.08). Effects in O_{2pulse} did not differ between groups (group × randomization, P = 0.90). VAT increased significantly after exercise subjects compared with non-exercise subjects (randomization, P < 0.01). VAT effects did not differ between groups (group × randomization, P = 0.37).

TABLE 4. Actual baseline versus reference absolute and relative $\dot{V}O_{2peak}$, 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).

	Male Patients (n = 46)				Male Controls (n = 36)			
	Actual	**Reference**	***t***	***P***	**Actual**	**Reference**	***t***	***P***
Relative $\dot{V}O_{2peak}$ ($mL \cdot min^{-1} \cdot kg^{-1}$[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 $\dot{V}O_{2peak}$ ($mL \cdot min^{-1}$)[a]	2762.4 ± 596.8	2900.9 ± 243.9	−1.57	0.12	3085 ± 437	2994.3 ± 293.1	1.40	0.17
HR_{peak} (bpm)[a]	176.2 ± 16.1	191.6 ± 4.3	−7.04	<0.001	193.8 ± 10.0	191.7 ± 4.8	1.26	0.22
O_{2pulse} ($\dot{V}O_{2peak}/HR_{peak}$)[a]	15.6 ± 2.9	15.1 ± 1.2	1.20	0.24	16.0 ± 2.6	15.6 ± 1.3	1.10	0.28
VAT ($\dot{V}O_2$ 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 $\dot{V}O_{2peak}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)[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 $\dot{V}O_{2peak}$ ($mL \cdot min^{-1}$)[a]	1870.3 ± 342.9	1928.9 ± 168.0	−0.83	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} ($\dot{V}O_{2peak}/HR_{peak}$)[a]	11.4 ± 2.6	10.2 ± 0.7	2.04	0.06	11.3 ± 1.8	9.8 ± 0.7	4.14	0.001
VAT ($\dot{V}O_2$ in $mL \cdot min^{-1}$)[a,b]	1187.3 ± 309.0	16/0	—	—	1363.3 ± 334.6	19/0	—	—

Results are 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% $\dot{V}O_2$ predicted.
AQ2 [c] Lower score indicates superior fitness.

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

	Patients (n = 33)				Controls (n = 53)				P^a		
	EX (n = 17)		OT (n = 16)		EX (n = 26)		LaU (n = 27)				
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Group	Randomization	Group × Randomization
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	0.20	0.25
HR_{peak} (bpm)[d]	178.2 ± 14.0	173.9 ± 20.0	171.1 ± 22.8	168.2 ± 19.7	188.3 ± 11.1	184.2 ± 13.8	193.0 ± 12.0	188.9 ± 14.4	0.81	0.71	0.71
Peak systolic blood pressure (mm Hg)[d]	124.9 ± 14.3	121.3 ± 13.2	125.9 ± 7.6	129.4 ± 10.0	123.1 ± 10.1	119.3 ± 15.1	121.1 ± 13.2	120.2 ± 12.1	0.49	0.13	0.52
Peak diastolic blood pressure (mm Hg)[d]	76.1 ± 9.3	74.7 ± 7.6	76.9 ± 10.8	78.0 ± 9.1	75.2 ± 10.4	71.3 ± 7.6	73.9 ± 7.7	71.7 ± 7.1	0.20	0.36	0.87
$\dot{V}O_{2peak}$ (mL·min^{-1}·kg^{-1})[b]	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	<0.01	0.03	0.80
W_{peak} (W)[b]	226.4 ± 39.8	248.4 ± 42.2	246.1 ± 55.3	237.8 ± 51.3	263.8 ± 54.0	272.4 ± 68.4	247.4 ± 54.9	243.7 ± 57.9	0.40	<0.001	0.09
$\dot{V}O_{2peak}$ (mL·min^{-1})[b]	2629 ± 479	2654 ± 534	2764 ± 741	2661 ± 624	2833 ± 657	3026 ± 850	2665 ± 625	2718 ± 729	0.03	0.07	0.95
$\dot{V}_{Epeak}$ (mL·min^{-1})[b]	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}[b]	1.27 ± .11	1.28 ± .09	1.26 ± .10	1.26 ± .10	1.36 ± .09	1.32 ± .11	1.39 ± .08	1.36 ± .13	0.17	0.83	0.78
O_{2pulse} (mL·beat^{-1})[b]	14.8 ± 2.9	14.9 ± 3.0	16.0 ± 3.3	15.5 ± 2.7	15.0 ± 3.4	16.1 ± 4.4	13.8 ± 3.2	14.1 ± 3.8	0.03	0.08	0.90
VAT ($\dot{V}O_2$ in mL·min^{-1})[b]	1546.4 ± 294	1633.4 ± 370	1693.1 ± 495	1619 ± 445	1697 ± 495	1943.5 ± 681	1691.3 ± 525	1627.8 ± 660	0.30	<0.01	0.37
HR_{diff} (bpm)[b]	40.5 ± 13.3	40.7 ± 12.2	40.7 ± 17.9	39.8 ± 17.0	55.4 ± 11.5	57.3 ± 12.5	56.3 ± 13.2	57.6 ± 12.9	0.44	0.73	0.93

Results are presented as mean ± SD. Significant results are presented in bold.

[a] All analyses were performed with general linear model, repeated-measures design.

[b] Higher scores indicate superior fitness.

[c] For resting HR, 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.

[d] Lower scores indicate superior fitness.

EX, exercise patients and controls; OT, occupational therapy patients; LaU, life-as-usual controls.

No other group, randomization, or group × randomization effects were seen (Table 5). Except for absolute $\dot{V}O_{2peak}$, exclusion of outliers had no influence on results.

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 $\dot{V}O_{2peak}$ of 34.3 ± 9.9 and 24.0 ± 4.5 mL·kg^{-1}·min^{-1}, respectively. Our results demonstrate that patients with schizophrenia, on average, age 29 yr old, have reduced relative $\dot{V}O_{2peak}$ and peak workload (W_{peak}) compared with matched and physically inactive healthy controls. In addition, comparison of individual and reference values for relative $\dot{V}O_{2peak}$ shows 10%–15% reductions in CRF levels, especially in male patients with schizophrenia. In our study, the difference in relative $\dot{V}O_{2peak}$ between patients and matched controls (4.3 mL·kg^{-1}·min^{-1}) corresponds to a more than 13% increased mortality risk in patients with schizophrenia (26,34).

This randomized 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 $\dot{V}O_{2peak}$ and markedly improved W_{peak} in patients with schizophrenia compared with decreased relative $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ by, on average, 2.2 mL·kg^{-1}·min^{-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 (16) concluded that 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 (19,38) and two "gold standard" cardiopulmonary exercise testing (21,37). Opposite to Deimel and Lohmann (16), recent studies show CRF can be reliably assessed in patients with schizophrenia, which is congruent with data from our study (21,37). At baseline, all controls and all but four patients with schizophrenia met maximal effort demand ($RER_{peak} \geq 1.1$), 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 $\dot{V}O_{2peak}$ values in patients with schizophrenia compared with age, gender, and socioeconomic status matched controls (Tables 3 and 4). Compared with the present study, Heggelund et al. (21) found higher $\dot{V}O_{2peak}$ values in male (37.1 ± 9.2 $mL \cdot kg^{-1} \cdot min^{-1}$) and female (35.6 ± 10.7 $mL \cdot kg^{-1} \cdot min^{-1}$) 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 $\dot{V}O_{2peak}$ values are achieved in cycle ergometer protocols (present study) compared with treadmill protocols (21) could explain these differences (23). Another explanation might be that people from Nordic countries have higher fitness levels (7).

As in our study, Strassnig et al. (37) incorporated cycle ergometer tests. Yet, their participants had extremely low relative $\dot{V}O_{2peak}$ values compared with 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 with the present study. In our data, as in Strassnig et al. (37), age was inversely correlated to $\dot{V}O_{2peak}$. The study by Strassnig et al. (37) 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, generalizability 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 $\dot{V}O_{2peak}$ and W_{peak} in patients with schizophrenia and inactive controls compared with nonexercising patients and controls. Moreover, contrary to nonexercising controls, relative $\dot{V}O_{2peak}$ and W_{peak} reduced in nonexercising patients. The improvement in $\dot{V}O_{2peak}$ in exercising controls was larger than that in exercising patients. The difference in relative $\dot{V}O_{2peak}$ improvement may in part be due to higher exercise compliance in controls compared with patients. In addition, there is evidence that patients with schizophrenia experience mitochondrial dysfunction, which may also affect their ability to improve $\dot{V}O_{2peak}$ (39). However, Heggelund et al. (22), although not using a randomized controlled trial, showed that high intensity training (4 × 4-min bouts at 85%–95% of HR_{peak}) did increase relative $\dot{V}O_{2peak}$ by 12% in patients with schizophrenia. Possibly, relative $\dot{V}O_{2peak}$ 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 randomized controlled design that $\dot{V}O_{2peak}$ and W_{peak}, both CRF measures, decreased progressively in nonexercising patients with schizophrenia. In addition, age was inversely associated with relative $\dot{V}O_{2peak}$, more so than that in controls. Research has unequivocally shown decreased $\dot{V}O_2$ is associated to increased mortality in healthy males and females (5,26). Evidence is growing that poor CRF is a key risk factor for the development of CHD in patients with schizophrenia also (16,19,21,37,38,42). 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 (9,29,32,43). Moreover, long-term exercise adherence rates average 40% to 65% in healthy populations as well (24). 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 (8). Second, higher exercise frequency, longer session duration, and possibly individualized 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 (1). 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 with inactive matched controls. Exercise therapy, 1 to 2 h a week for 6 months, was able to increase relative $\dot{V}O_{2peak}$ and W_{peak} in exercising patients and controls compared with nonexercising participants. Furthermore, in nonexercising patients, CRF decreased over the 6-month study period. Future studies should enroll 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 individualized exercise intensity could lead to more pronounced CRF benefits in patients with schizophrenia (18,22).

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The results of the present study do not constitute endorsement by ACSM.

REFERENCES

1. American College of Sports Medicine. American College of Sports Medicine Position Stand: the recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc*. 1998;30(6):975–91.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., text revision. Washington (DC): Author; 2000. p. 426.
3. American Thoracic Society/American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167(2):211–77.
4. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry*. 1992;49(8):615–23.
5. Aspenes ST, Nilsen TI, Skaug EA, et al. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. *Med Sci Sports Exerc*. 2011;43(8):1465–73.
6. Astorino TA. Alterations in VOmax and the VO plateau with manipulation of sampling interval. *Clin Physiol Funct Imaging*. 2009;29(1):60–7.
7. Åstrand PO, Rodahl K, Dahl H, Strømme SB. *Textbook of Work Physiology: Physiological Bases of Exercise*. 4th ed. Champaign (IL): Human Kinetics; 2003. p. 656.
8. Beebe LH, Smith K, Burk R, et al. Effect of a motivational intervention on exercise behavior in persons with schizophrenia spectrum disorders. *Community Ment Health J*. 2011;47(6):628–36.
9. Beebe LH, Tian L, Morris N, Goodwin A, Allen SS, Kuldau J. Effects of exercise on mental and physical health parameters of persons with schizophrenia. *Issues Ment Health Nurs*. 2005; 26(6):661–76.
10. Bille K, Figueiras D, Schamasch P, et al. Sudden cardiac death in athletes: the Lausanne Recommendations. *Eur J Cardiovasc Prev Rehabil*. 2006;13(6):859–75.
11. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. *Br J Psychiatry*. 2000;177:212–7.
12. Bushe CJ, Taylor M, Haukka J. Mortality in schizophrenia: a measurable clinical endpoint. *J Psychopharmacol*. 2010;24(Suppl 4):17–25.
13. Christensen BK, Girard TA, Bagby RM. Wechsler Adult Intelligence Scale—Third Edition short form for index and IQ scores in a psychiatric population. *Psychol Assess*. 2007;19(2):236–40.
14. Cooper CB, Storer TW. *Exercise Testing and Interpretation; A Practical Approach*. Cambridge: Cambridge University Press; 2001. p. 278.
15. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res*. 2005;76(2–3):135–57.
16. Deimel H, Lohmann S. Physical capacity of schizophrenic patients. *Rehabilitation*. 1983;22(2):81–5.
17. Doherty M, Nobbs L, Noakes TD. Low frequency of the "plateau phenomenon" during maximal exercise in elite British athletes. *Eur J Appl Physiol*. 2003;89(6):619–23.
18. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine Position Stand: quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43(7):1334–59.
19. Gretchen-Doorly D, Kite RE, Subotnik KL, et al. Cardiorespiratory endurance, muscular flexibility and strength in first-episode schizophrenia patients: use of a standardized fitness assessment. *Early Interv Psychiatry*. 2011; doi: 10.1111/j.1751-7893.2011.00313.x. AQ3
20. Harvey PD, Green MF, Keefe RS, Velligan DI. Cognitive functioning in schizophrenia: a consensus statement on its role in the definition and evaluation of effective treatments for the illness. *J Clin Psychiatry*. 2004;65(3):361–72.
21. Heggelund J, Hoff J, Helgerud J, Nilsberg GE, Morken G. Reduced peak oxygen uptake and implications for cardiovascular health and quality of life in patients with schizophrenia. *BMC Psychiatry*. 2011;11(1):188.
22. Heggelund J, Nilsberg GE, Hoff J, Morken G, Helgerud J. Effects of high aerobic intensity training in patients with schizophrenia: a controlled trial. *Nord J Psychiatry*. 2011;65(4):269–75.
23. Hermansen L, Saltin B. Oxygen uptake during maximal treadmill and bicycle exercise. *J Appl Physiol*. 1969;26(1):31–7.
24. Ice R. Long-term compliance. *Phys Ther*. 1985;65(12):1832–9.
25. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis*. 1985;131(5):700–8.
26. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009; 301(19):2024–35.
27. Koivukangas J, Tammelin T, Kaakinen M, et al. Physical activity and fitness in adolescents at risk for psychosis within the Northern Finland 1986 Birth Cohort. *Schizophr Res*. 2010;116(2–3):152–8.
28. Kraemer WJ, Adams K, Cafarelli E, et al. American College of Sports Medicine Position Stand: progression models in resistance training for healthy adults. *Med Sci Sports Exerc*. 2002;34(2): 364–80.
29. Kwon JS, Choi JS, Bahk WM, et al. Weight management program for treatment-emergent weight gain in olanzapine-treated patients with schizophrenia or schizoaffective disorder: a 12-week randomized controlled clinical trial. *J Clin Psychiatry*. 2006;67(4): 547–53.
30. Lindamer LA, McKibbin C, Norman GJ, et al. Assessment of physical activity in middle-aged and older adults with schizophrenia. *Schizophr Res*. 2008;104(1–3):294–301.
31. McCreadie RG. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. *Br J Psychiatry*. 2003;183: 534–9.
32. Menza M, Vreeland B, Minsky S, Gara M, Radler DR, Sakowitz M. Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. *J Clin Psychiatry*. 2004;65(4):471–7.
33. Meyer JM, Davis VG, McEvoy JP, et al. Impact of antipsychotic treatment on nonfasting triglycerides in the CATIE Schizophrenia Trial phase 1. *Schizophr Res*. 2008;103(1–3):104–9.
34. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346(11):793–801.
35. Newcomer JW, Ratner RE, Eriksson JW, et al. A 24-week, multicenter, open-label, randomized study to compare changes in glucose metabolism in patients with schizophrenia receiving treatment with olanzapine, quetiapine, or risperidone. *J Clin Psychiatry*. 2009;70(4):487–99.
36. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry*. 2007;64(10):1123–31.
37. Strassnig M, Brar JS, Ganguli R. Low cardiorespiratory fitness and physical functional capacity in obese patients with schizophrenia. *Schizophr Res*. 2011;126(1–3):103–9.

38. Vancampfort D, Probst M, Sweers K, et al. Eurofit test battery in patients with schizophrenia or schizoaffective disorder: reliability and clinical correlates. *Eur Psychiatry*. 2011. doi.org/10.1016/j.eurpsy.2011.01.009.
39. Verge B, Alonso Y, Valero J, Miralles C, Vilella E, Martorell L. Mitochondrial DNA (mtDNA) and schizophrenia. *Eur Psychiatry*. 2011;26(1):45–56.
40. Verhage F. *Revised Scoring Method for Educational Level*. Groningen (The Netherlands): Department of Neuropsychology, University Hospital Groningen; 1983. p. 169.
41. von Hausswolff-Juhlin Y, Bjartveit M, Lindstrom E, Jones P. Schizophrenia and physical health problems. *Acta Psychiatr Scand Suppl*. 2009;(438):15–21.
42. Wildgust HJ, Beary M. Are there modifiable risk factors which will reduce the excess mortality in schizophrenia? *J Psychopharmacol*. 2010;24(Suppl 4):37–50.
43. Wu MK, Wang CK, Bai YM, Huang CY, Lee SD. Outcomes of obese, clozapine-treated inpatients with schizophrenia placed on a six-month diet and physical activity program. *Psychiatr Serv*. 2007;58(4):544–50.

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