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Resistance training in patients with schizophrenia: Concept and proof of principle trial

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1. Introduction

Among mental disorders, schizophrenia is one of the five leading causes of years lost to disability of adults (Whiteford et al., 2013). Even if positive symptoms can be sufficiently treated by antipsychotic medication and cognitive-behavioral therapy, negative symptoms (Fusar-Poli et al., 2015) and cognitive deficits (Nielsen et al., 2015) prevail very often. These symptoms, however, cause the most long-term disability and disease-associated burden in schizophrenia patients and impact every aspect of the individual's life (Vancampfort et al., 2012). Novel treatment strategies that promote functional recovery by decreasing negative symptoms and cognitive deficits are needed.

Additionally, there is a need for interventions fostering physical health. People with schizophrenia consistently have higher morbidity and mortality compared to the general population. The life expectancy of people with schizophrenia is shortened by up to 20 years (Vancampfort et al., 2018; Laursen et al., 2012) because of an increased risk for somatic comorbidities, such as cardiovascular diseases (Li et al., 2014), metabolic syndrome (Vancampfort et al., 2015) and diabetes (Firth et al., 2016). Unhealthy lifestyle habits such as a low level of physical activity contribute to the development of these conditions (Stubbs et al., 2016). This is why the World Health Organization (WHO) recommends in its guideline “Management of Physical Health Conditions in Adults with Severe Mental Disorders” behavioral lifestyle

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interventions in all people with severe mental disorder and cardiovascular risk factors or who are at risk of becoming overweight (WHO, 2018).

In the context of such lifestyle interventions, the importance of resistance exercise in promoting health and preventing disease has been previously discussed (Strasser et al., 2010). According to the WHO, resistance training is defined as physical activity, that increases skeletal muscle strength, power, endurance, and mass (WHO, 2010). In addition to improvements in skeletal muscle strength, resistance exercise has been shown to contribute to the prevention and management of atherosclerotic coronary heart disease (Braith and Stewart, 2006), hypertension (Pollock et al., 2000), diabetes (Colberg et al., 2010a) and obesity (Strasser and Schobersberger, 2010) in healthy individuals. Furthermore, cross-sectional studies have demonstrated that the muscle mass is inversely associated with the prevalence of the metabolic syndrome independent of cardiorespiratory fitness levels (Jurca et al., 2005) and results in a decreased all-cause mortality (FitzGerald et al., 2004; Rantanen et al., 2000). Thus, the inclusion of resistance training as an integral part of an exercise therapy and lifestyle modifying program has been endorsed by the American Heart Association and the American College of Sports Medicine (Nelson et al., 2007; Garber et al., 2011) as well as the American Diabetes Association (Colberg et al., 2010b).

Preliminary results regarding the effects of resistance training on psychopathology indicate possible positive effects on depressive symptoms. In particular, one randomized-controlled trial showed, that 24 weeks of resistance exercise led to an improved mood and reduced anxiety in 20 healthy elderly man (Cassilhas et al., 2010). Stanton et al. argued in their narrative review, that resistance training might be effective in alleviating symptom severity in depressive disorders (Stanton et al., 2013). Although resistance training has been shown to improve different aspects of physical and mental health, the way how it should be performed and possible clinical effects remain widely unknown among adults with schizophrenia. To date, research has focused on endurance formats of exercise, showing that add-on aerobic exercise treatment is effective in improving negative and general symptom severity, cognition, global functioning and quality of live in patients with schizophrenia (Dauwan et al., 2016). In contrast, resistance training is scarcely investigated in this population. In a systematic review by our group (Keller-Varady et al., 2018) only two studies could be identified examing the impact of isolated resistance training in patients with schizophrenia (Heggelund et al., 2012; Andrade e Silva et al., 2015). Among these, an 8-week non-randomized, not blinded intervention with 16 patients and only a single exercise (leg press) did not improve psychopathology or quality of life but the participants showed an improved walking performance (Heggelund et al., 2012). The other one was a randomized, single blind study which examined the efficacy of a 20 week-whole-body resistance training in 34 patients with schizophrenia (Andrade e Silva et al., 2015). The participants underwent a training consisting of two 60-min sessions per week which included exercises for each large muscle group (leg press, leg curl, vertical traction, chest press, arm extension, arm curl, abdominal crunch). The control condition involved the same training protocol but with minimal weight. The study could show a positive effect on psychopathology in comparison to the control group, however, regarding the outcomes quality of life and concentrations of neurotrophic factors (e.g. BDNF, IGF-1) no significant effects could be found. In a recently published non-randomized single-arm pilot study, 25 participants with first-episode psychosis recruited from community-based early intervention services underwent a 10 week-intervention with on the average 107min moderate-to-vigorous exercise per week. Thereby, the participants were offered gym training sessions twice per week containing aerobic as well as resistance exercise elements according to the participants' preference (Firth et al., 2018a). In comparison to a treatment-as-usual control group containing standard care in the community-based early intervention services, the participants of the intervention group achieved significant improvements regarding their psychosocial functioning measured by the SOFAS and the WHO-DAS their verbal short-term memory and scored lower on the Positive and Negative Syndrome Scale (Firth et al., 2018a).

In general, and not only for resistance training, study designs and outcome variables vary widely in previous exercise studies in mental disorders (Malchow et al., 2013). Unfortunately, this has hampered the design of efficient exercise programs intended to have the greatest possible benefits in schizophrenia patients. A specific resistance training for schizophrenia patients has not been developed and evaluated in more detail yet. Thus, it requires further investigation, whether the benefits of resistance exercise in schizophrenia patients contribute not only to fostering physical health but also help promoting functional recovery by decreasing negative symptoms and cognitive deficits. Remarkably, a cross-sectional analysis in 1162 individuals with schizophrenia reported that grip strength was strongly related to several cognitive domains (Firth et al., 2018b). Beneficial effects of resistance training on white matter connectivity and total cerebral matter volume have been proposed in a study combining resistance components with aerobic exercise (Svatkova et al., 2015; Scheewe et al., 2013). This could be related to growth hormone levels (such as BDNF and IGF-1) which were reported to be reduced in schizophrenia patients (Martinotti et al., 2012; Venkatasubramanian et al., 2007) but can be increased by resistance exercise as demonstrated in healthy subjects (Kraemer and Ratamess, 2005; Vega et al., 2010).

Based on this theoretical framework, the primary objective in this proof of concept trial was to evaluate the feasibility of a newly developed resistance program in schizophrenia patients according to current recommendations of the WHO and the American College of Sports Medicine for resistance training. The primary efficacy measure was functioning. In detail,we hypothesized that the resistance training compared to the balance and tone program would improve health-related difficulties assessed with the World Health Organization Disability Assessment Schedule (WHO-DAS) (Ustun et al., 2010) as a proxy for everyday functioning in schizophrenia patients.

2. Methods

2.1. Study design

We employed a single-blind, parallel assignment clinical trial design with participants randomized to attend either a newly developed resistance training or a balance and tone program (control condition). Thereby, we first aimed to evaluate the feasibility of the newly developed intervention and to test whether this intervention is superior to a balance and tone training regarding our primary outcome measure (WHO-DAS). The participants were examined before, during, immediately after and six weeks after the cessation of the intervention. As blinding of the intervention is not possible, all raters collected the data blinded and the statistician was blinded to the group membership. The study duration for each participant was 18 weeks (12 weeks intervention and 6 weeks follow-up).

2.2. Study participants

The study was conducted at the Department of Psychiatry and Psychotherapy of the University Hospital of the LMU Munich. The local ethics committee approved the protocol and all participants provided written informed consent. The data were collected between 06/2016 and 12/2017. The inclusion criteria were DSM-IV diagnosis of schizophrenia, PANSS total score before the beginning of the intervention $\leq$75, age between 18 and 60 years, contraception in women of childbearing age and German language skills.

The exclusion criteria were acute substance abuse other than tobacco use, acute suicidal ideations in the screening examination, other relevant psychiatric axis I diseases according to the Mini International

Neuropsychiatric Interview (MINI) German Version 5.0.0, other relevant neurological or physical diseases which could interfere with the planned investigations or have an influence on the parameters to be investigated, pregnancy and IQ < 80. The trial was registered at http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00010842.

2.3. Interventions: description and fidelity assessments

After giving consent, participants completed the diagnostic, clinical, performance and neurocognition baseline assessments, and were randomized in one of the intervention or the control group. The raters were all blind to the participants' intervention status. The study period was planned to be 18 weeks for each participant. It contained 5 examination times and a 12-week intervention. The examinations were undertaken in the screening phase (visit 0), before the start of the intervention (visit 1), after 4 weeks of intervention (visit 2) and after a further 8 weeks of intervention (visit 3). In visit 1 to 3, psychopathological and cardiovascular parameters were evaluated. Cognitive, laboratory and sports medicine parameters were measured only in visit 1 and 3. After 6 weeks, a naturalistic follow-up of clinical data and neurocognition was initially planned (visit 4).

2.3.1. Resistance training for schizophrenia patients (intervention)

The design of the intervention followed current recommendations for resistance training as detailed in the following paragraph. According to the WHO, training of the main muscle groups on 2 or more days per week should be performed (WHO, 2010). The "American College of Sports Medicine" also recommends resistance training of the main muscle groups 2 to 3 times a week (Garber et al., 2011). To increase muscle strength for beginners, training in the range of 60–70% of the maximum strength (one repetition maximum, 1-RM) should be executed. 2 to 4 sets per exercise should be performed with 1–12 repetitions per set. However, there is no total duration of training specified. The break time between training sessions for each individual muscle group is suggested to be at least 48 h (Garber et al., 2011). These recommendations had been realized in our trial in a newly developed resistance training as intervention, as detailed below. The training was designed to offer an intervention tailored to the needs of schizophrenia patients, who are often in a deconditioned physical state. The intensity of the training had been adjusted to the level of the participants. All large muscle groups were exercised adequately without the risk of overstraining.

The resistance training consisted of three units per week, of which two were carried out with a sling trainer and one with small equipment such as gym mat, gymnastic ball, elastic band and medicine ball. Since most clinics do not have a fitness room, the intervention was also designed to require only little space and equipment and could be implemented easily. A professional trainer (M.L. or C.M.) led the units and was present for guidance and support as well as for the collection of exercise related behavioral data. The training sessions were conducted not in a group but individually, in order to control for social interaction between the participants as possible confounding factor and to tailor the intervention to the needs of each individual. The exact training schedule is described in Fig. 1.

Each exercise unit had a duration of 40–50 min and included a warm-up and stretching period at the beginning (approx. 10 min), followed by resistance training as the main part (approx. 25–35 min) and a cool-down period at the end of each unit (approx. 5 min). In the first two weeks, the training had a duration of 40 min, which was extended to 50 min from the third week on. The training with small equipment consisted of the following seven exercises, which are also shown in Fig. 2: abdominal muscles: crunches with gymnastics ball; lower back: extension on gymnastics ball; upper back: rowing with elastic band; shoulder musculature: side lateral raises with elastic band; chest musculature: push-ups; leg muscles: squats with medicine ball, leg muscles: hip extension with gymnastics ball.

Equal to units with the sling trainer, a unit with the small equipment consisted of 3 sets with 8–10 repetitions per exercise (30s–40s each set) and a pause of approx. 60 s between each set. The training with the sling trainer aimed at strengthening the main muscle groups by selected exercises that can also performed by untrained persons. It included the following exercises (as illustrated in Fig. 3): squats (two-legged and one-legged), push-ups, rowing, wide rowing, back extension and leg bends. Each exercise consisted of 3 sets with 8–10 repetitions. The pause between each set was approx. 60 s. During the training in the interventional group as well as in the control group, the heart rate was measured. The subjective effort perception was assessed by the Ratings of perceived exertion (RPE) scale according to Borg and Noble (1974) for all training phases. In the first training unit and every 4 weeks, the lactate concentration was measured from the capillary blood of the earlobe after 25–30 min of training.

2.3.2. Balance and tone training (control group)

Participants randomized to the control group underwent a so-called "balance and tone training" as described by Liu-Ambrose et al. (2010). This is a combination of exercises from the areas of stretching, mobility, stability, balance and relaxation, which are compiled according to a standardized exercise catalogue. The control method had been chosen in order to minimize confounders (such as social interaction) which might influence the results. The intervention period, training duration and training frequency did not differ from the experimental group. The performance of a warm-up and cool-down period, the supervision by a sports scientist and the training documentation based on the measured heart rate, lactate concentration and effort perception were carried out similar to the experimental group as well. However, in contrast to the intervention group, the control group was not aimed at increasing the maximum force.

2.4. Outcome measurements

First, we aimed at investigating whether this new intervention can be implemented in patients with schizophrenia. Then we defined an improvement in the World Health Organization Disability Assessment Schedule (WHO-DAS) as primary outcome of our proof of principle trial to evaluate the efficacy of our new training program. The WHO-DAS was used in the 36-item interview version and represents an established instrument reflecting the patients' level of functioning in detail (Ustun et al., 2010; Federici et al., 2017). It examines the difficulties in six domains of life: cognition/perception, mobility, self-supply, interaction with other people, activities of everyday life and participation in social life. The scores of each domain are added and subsequently converted into a form where 0 stands for "no restriction" and 100 for "complete restriction".

The secondary outcome parameters included an assessment of psychopathology using the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia (PANSS) (Kay et al., 1987), of disease severity using the Clinical Global Impression Scale (CGI) (Guy, 1976), and of depressive symptoms using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993). The level of general functioning was evaluated with the Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976).

Neurocognition included the Verbal Learning and Memory Test (VLMT), assessing the verbal declarative memory (Helmstaedter, 2001), the Trail Making Test A and B (TMT) regarding complex visual scanning, motor speed, and the ability to shift strategies (Reitan and Wolfson, 1985) and the D2-Test with respect to the attention span (Brickenkamp et al., 2010). Further secondary outcome parameters were the participants' metabolic profile (waist circumference, pulse, body mass index). Strength of relevant muscle groups was assessed using a measuring system with a spring balance in the beginning and the end of the study. Additionally, the Physical Working Capacity (PWC130) was measured in an incremental exercise test, being the

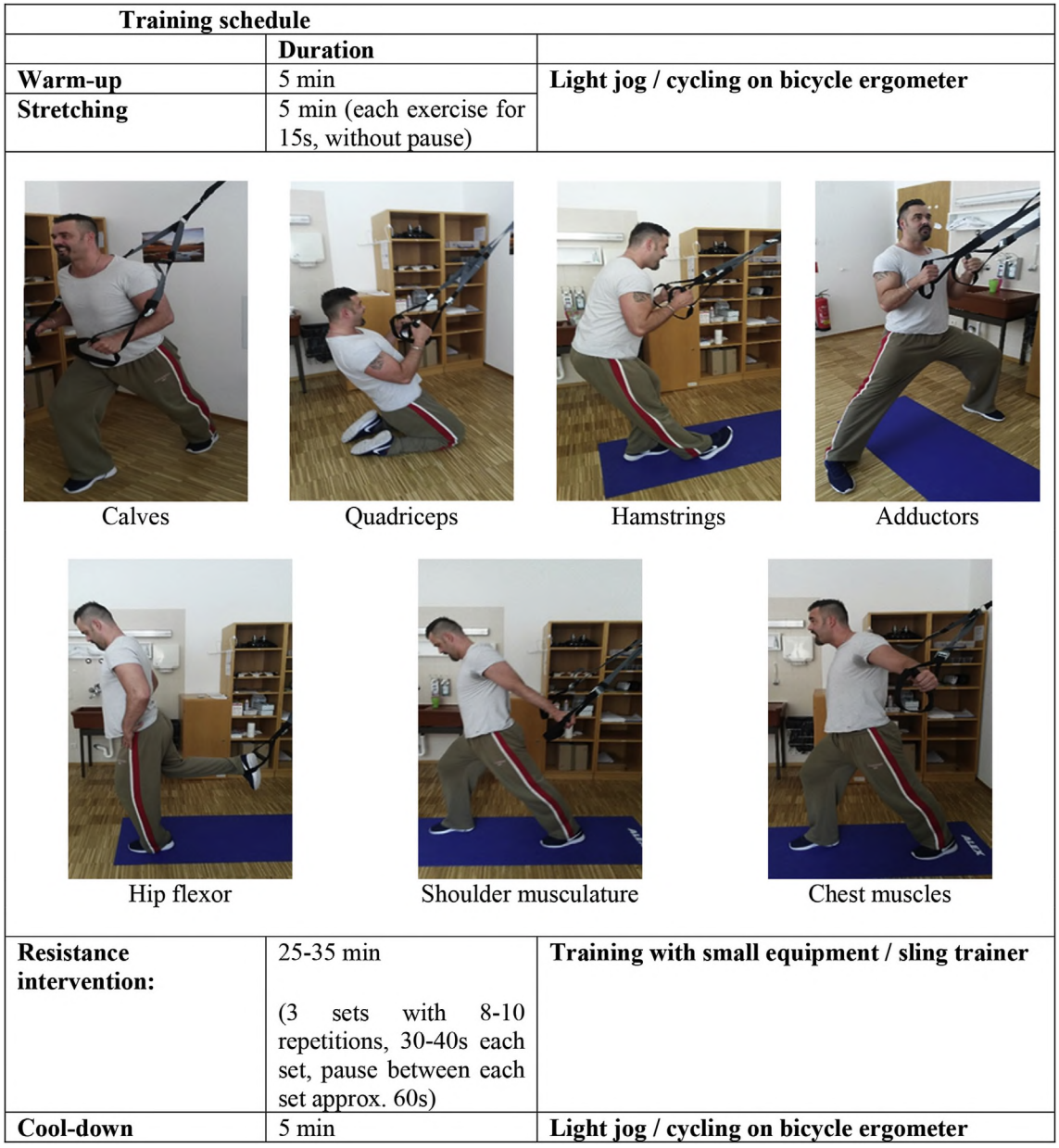

Fig. 1. Training schedule.

wattage, a person is capable to pedal at a heart rate of 130 bpm (Keller-Varady et al., 2016). The feasibility of the study was evaluated using the dropout rate, severe/adverse events and the mean attendance rate.

2.5. Statistical analyses

Data analyses were conducted using IBM SPSS Statistics, 25 (International Business Machines Corporation, Armonk, New York, USA). All tests were two-tailed and the significance level was $\alpha = 0.05$. At first, all variables were tested for normal distribution using the Kolmogorov-Smirnov test and for variance homogeneity between the groups with the Levene test.

The demographic and clinical variables were compared in order to determine continuous variables using One-way ANOVA or Mann-Whitney U tests and for categorical variables using Fisher's exact test. To identify time or group effects during the study, a linear mixed model (LMM) was used. For those variables where we found significant time × group interactions, we evaluated whether there were intervening variables (sex, age, education and medication) that had a significant influence on the respective target variables. If so, we included those variables in the linear models as covariates and reported them additionally. In cases of significant deviations from normality assumption or if inhomogeneous variances between the groups were detected, Friedman tests/Wilcoxon tests were applied. In the case of significant time effects from the main analyses, post-hoc analyses were carried out separately for the intervention and control group with adjustment for multiple comparisons according to the Sidak procedure (expressed as p_S).

3. Results

3.1. Study participants and feasibility

A total of 19 patients signed consent, four of them dropped out before the start of the study. 15 patients with schizophrenia (inpatients as well as outpatients) participated in this pilot study, of which 7 were randomized to the intervention group and 8 to the control group. Sociodemographic and clinical characteristics are presented in Table 1.

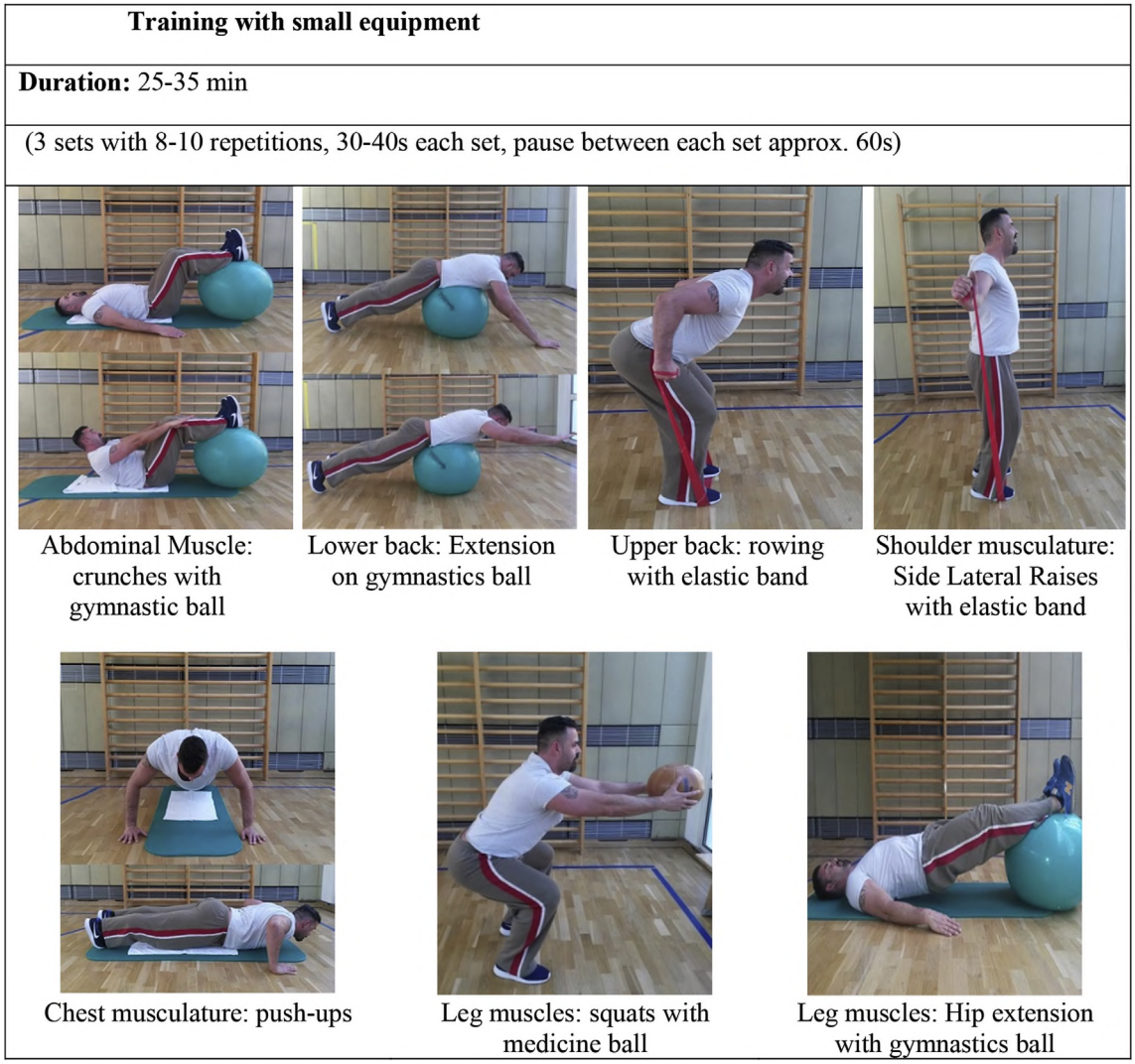

Fig. 2. Training with small equipment.

Except for their mean level of triglycerides and glucose, the groups did not differ significantly in any of the variables surveyed. 8 participants completed the study (4 of them in the intervention group, 4 in the control group). Despite much effort (e.g. making appointments at the end of V3, contacting patients via telephone) only two patients were available for the naturalistic follow-up examination, which is why the data of the last visit 4 could not be evaluated. Thus, this visit was excluded from all further analyses.

We were able to show that the new intervention can be offered to patients with schizophrenia and that those patients are able to participate in such a complex training. Of 15 participants 12 completed baseline measures, 6 both in the intervention and the control group. The 12-week intervention was completed by 8 participants (4 participants in the intervention and the control group respectively). The mean number of sessions attended was 17 out of 36 possible sessions (47%) and 21 out of 36 in the intervention group (58%).

3.2. Health related difficulties: WHO-DAS

The primary outcome parameter was a global improvement in the World Health Organization Disability Assessment Schedule (WHO-DAS). Over the course of the study, there were no significant time effects ($F_{(2,\ 7.969)} = 1.485$; $p = .283$), no significant group effects ($F_{(2,\ 7.969)} = 0.018$; $p = .982$) and no significant time × group interactions for the WHO-DAS (see Table 2 and Fig. 4).

3.3. Level of functioning assessed with the GAF

There were significant time effects ($F_{(2,\ 7.791)} = 32.638$; $p = .000$) with regard to the GAF, both groups showed improved scores over the course of time. However, these were more pronounced in the intervention group as indicated by a significant time × group interaction ($F_{(2,\ 7.791)} = 6.821$; $p = .019$, see Table 2 and Fig. 5). When GAF was adjusted for the intervening variable sex, there was still a significant time × group interaction ($F_{(2,\ 7.844)} = 6.835$; $p = .019$). The following post-hoc comparisons showed that after 4 weeks of resistance training, the mean GAF in the intervention group improved from 62.1 to 68.4 points (V1 vs V2: $p_S = .153$) and after a further 8 weeks of training to 74.5 points (V2 vs V3: $p_S = .051$; V1 vs V3: $p_S = .013$).

In the control condition after 4 weeks the mean GAF improved from 60.0 points to 63.8 points (V1 vs V2: $p = .206$) and to 66.8 (V2 vs V3: $p_S = .951$; V1 vs V3: $p_S = .001$) after a further 8 weeks of participating in the control group.

3.4. Schizophrenia symptoms and cognitive parameters

At baseline, there were no significant group differences between the control group and the intervention group regarding the PANSS score.

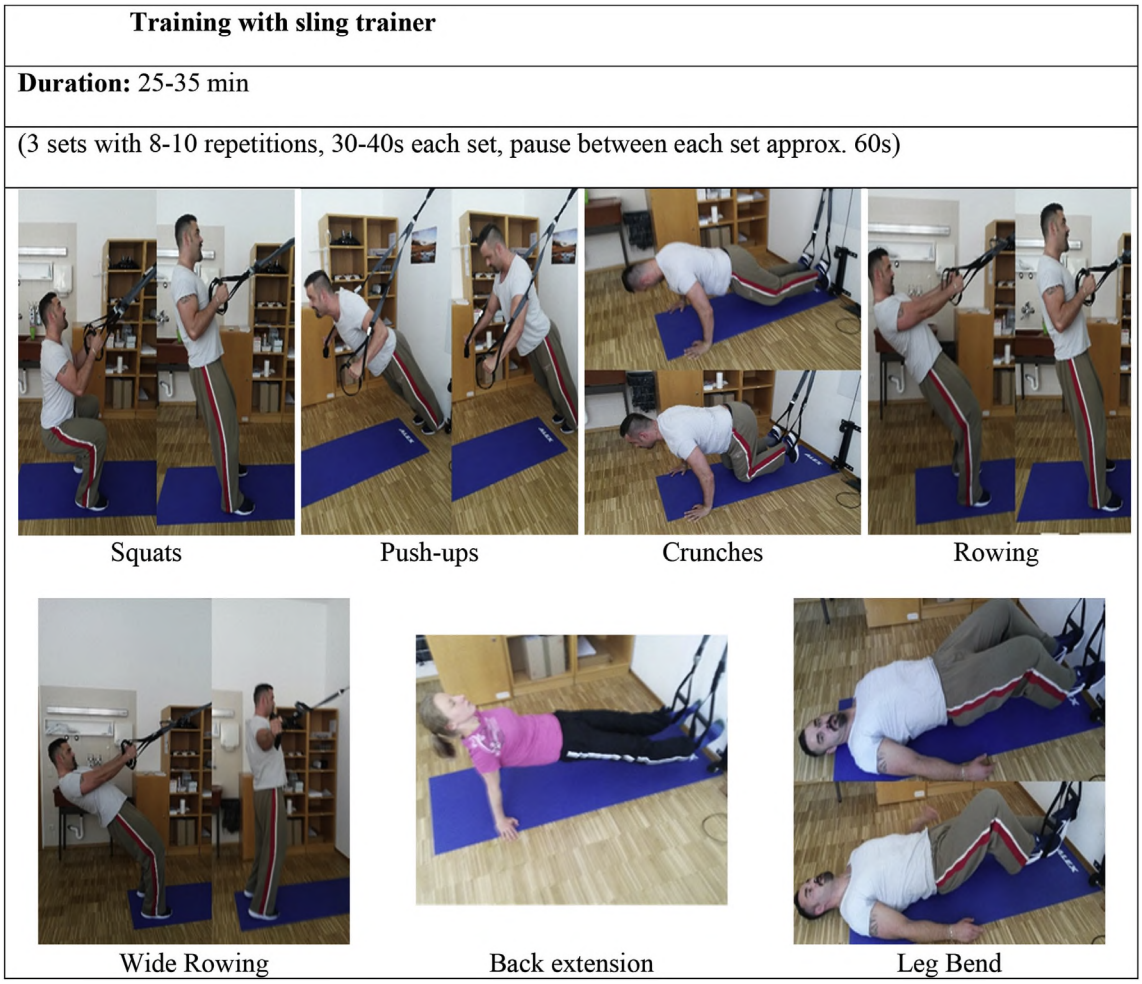

Fig. 3. Training with sling trainer.

After the intervention, a significant change in symptom severity was not observed in either the intervention group or the control group. Cognitive testing assessed with the trail-making-test A, B and the d2-test also showed no significant results (see Table 2).

3.5. Cardiovascular risk factors and physical performance

An analysis of the two groups separately found no significant time effects during the course of the study regarding cardiovascular risk factors (see Table 2). The addition of dietary interventions may be important to have an increased impact on metabolic outcomes for people with schizophrenia. Regarding the participants' physical performance including their muscle strength, there were significant time effects for the mean force values (z-transformed) and for the PWC130, but there were no significant effects for the values per kilogram body weight, which are more relevant as they are less prone to errors due to outliers. For PWC130 there was a significant time × group interaction ($p = .008$), as it was slightly improved only in the intervention group.

3.6. Adverse events

In the intervention group, two adverse events (AEs) were recorded, which included elbow pain and a tendosynovitis of the thumb after vocational physical exertion and were already known as pre-existing condition in a mild form. In the control group, three patients dropped out due to psychopathological aggravation with two of them being rehospitalized resulting in the documentation of a severe adverse event (SAEs) (see Fig. 6 flowchart). One additional participant of the control group complained about foot pain. None of the recorded SAEs or AEs were likely to be caused by the intervention or the control condition as they were not in a temporal context and occurred after other stress factors.

4. Discussion

This is a proof of concept study to evaluate the feasibility and efficacy of a novel resistance training intervention developed according to the WHO-recommendations and developed to address the needs of schizophrenia patients. While we were able to show that the training can be in principle be implemented in this population, the primary efficiency endpoint, defined as improvement in health-related difficulties according to the WHO-DAS, did not show a difference between study groups. However, patients randomized to the resistance training intervention showed a more pronounced improvement in general functioning according to the GAF. Moreover, for several outcome parameters an improvement over time in both groups could be established confirming that complex exercise interventions have the potential to improve various aspects of schizophrenia associated deficits.

The feasibility of the study was evaluated using the dropout rate, the mean attendance rate and severe/adverse events. The recorded adverse events were not likely to be related to the intervention or the control group as they were not in a temporal context and occurred after other stress factors. There were no withdrawals due to injuries which reflects the safety of our study design within the population of schizophrenia patients. In addition, the intervention was easy to implement, as neither a fitness room nor special equipment was required to conduct the

Table 1
Baseline characteristics.

Outcome measure	Intervention group			Control group			Group comparisons		
	N	Mean	SD	N	Mean	SD	Statistic	df	p
Demographics	7			8					
Gender (male: female)	5:2			4:4					.608[a]
							F		
Age (years)	7	36.3	9.9	8	30.4	8.0	1.63	1, 13	.224[b]
Education (years)	4	10.5	2.7	8	10.9	3.1	.04	1, 10	.840[b]
Cardiovascular parameters									
Waist (cm)	5	112.8	24.2	3	101.0	15.6	.55	1, 6	.485[b]
BMI (kg/m^2)	6	33.7	5.5	6	30.2	8.5	.71	1, 10	.421[b]
Pulse (bpm)	6	84.8	15.3	7	83.6	11.5	Z = −.07	1	.945[c]
Laboratory parameters									
Glucose (mmol/l)	6	94.3	16.3	7	82.1	12.4	Z = -2.37	1	.014[c]
Triglycerides (mmol/l)	6	200.8	111.5	7	95.7	43.9	5.33	1, 11	.041[b]
Psychopathology									
WHO-DAS	7	19.7	13.2	7	23.1	14.7	.22	1, 12	.646[b]
CGI	7	3.7	.8	8	3.6	.7	Z = −.25	1	.867[c]
CDSS	7	3.7	4.4	8	3.4	4.0	.03	1, 13	.878[b]
PANSS total	7	52.1	14.7	8	51.4	15.7	.01	1, 13	.924[b]
PANSS positive	7	12.3	3.9	8	10.1	4.8	.90	1, 13	.361[b]
PANSS negative	7	13.6	5.2	8	15.0	3.7	.38	1, 13	.546[b]
PANSS general	7	26.3	7.5	8	26.3	7.9	.00	1, 13	.993[b]
GAF	7	62.1	10.1	8	60.0	7.0	.26	1, 13	.621[b]
Cognitive Parameters									
Trail Making Test A (s)	7	32.6	15.9	8	23.4	4.1	Z = -.52	1	.613[c]
Trail Making Test B (s)	7	78.9	23.8	8	68.8	15.7	.97	1, 13	.343[b]
TMT B-A (s)	7	46.3	15.2	8	45.4	17.3	.01	1, 13	.916[b]
d2	7	169.7	57.2	8	161.8	25.4	Z = −.35	1	.779[c]
Performance diagnostics									
Strength per kg body weight[d]	6	2.66	.74	7	3.01	.91	.57	1, 11	.465[b]
Strength per kg body weight[e]	6	-.31	.75	7	.13	.96	.80	1, 11	.391[b]
PWC130 per kg	6	.79	.23	6	1.10	.42	2.67	1, 10	.134[b]
Medication									
CPZ	7	352.5	308.1	8	353.1	262.3	.00	1, 13	.997[b]

N: group size; SD: standard deviation; df: degrees of freedom; p: p-value; F: F-statistic; cm: centimeter; kg: kilogram; bpm: beats per minute; Z: Z-statistic; mmol/l: millimol per liter; s: seconds.
BMI: body mass index.
WHO-DAS: World Health Organization Disability Assessment Schedule ranges from 0 to 100, with lower scores indicating a lower grade of disability.
CGI: The Clinical Global Impressions score for severity ranges from 1(not mentally ill) to 7 (extremely ill).
CDSS: The Calgary Depression Scale for Schizophrenia ranges from 0 to 27, higher scores indicating more severe depression.
PANSS: The Positive and Negative Syndrome Scale ranges from 30 to 210, higher scores denoting more severe illness.
GAF: The Global Assessment of Functioning scale ranges from 1 to 100, with higher scores indicating better functioning.
TMT: Trail Making Test, used time (seconds) for versions A and B.
d2: d2 test of attention.
PWC130: Physical Working Capacity at 130 bpm heart rate.
CPZ: chlorpromazine equivalents.
[a] Comparison by Fisher's exact test.
[b] Comparison by One-way ANOVA.
[c] Comparison by Mann-Whitney *U* test.
[d] mean strength (N) divided by body weight (kg).
[e] Based on Z scores.

trainings. The relatively high costs of an individual training could in principle be reduced if the training would be carried out in groups in the future.

The drop-out rate in our study was 47% (see Fig. 6 for a flowchart). Three participants of the control group declined due to rehospitalisation. As further reasons for drop-outs, patients stated lack of motivation and lack of time. A high dropout rate in studies including physical activity in schizophrenia patients has been repeatedly reported, which is partly due to negative symptoms (Vancampfort et al., 2016). For instance, in a meta-analysis of prevalence and predictors of treatment dropout from physical activity interventions in schizophrenia patients, a mean dropout rate of 26.7% could be found (which is more than double than in nonactive control interventions) (Vancampfort et al., 2016). In another meta-analysis a total attrition of 32.5% was observed (Firth et al., 2015). Moreover, even studies with a dropout rate up to 50% are quite common (Romain et al., 2018). Lower drop-out rates were found in studies which were supervised by qualified professionals as it has already been provided for in our study design.

The mean number of sessions attended was 58% in the intervention group. In a meta-analysis of training interventions in schizophrenia patients, an adherence rate of 79% in supervised and 55% in solitary exercises was reported (Firth et al., 2015). As our intervention had professional supervision, the percentage in our study is lower than the expected one from previous studies. In the aforementioned study in patients with first-episode psychosis including resistance exercise elements a retention rate of 81% could be achieved. Possible reasons for the higher rate could be the younger, physical healthier sample (e.g. the participants BMI was higher in our study) with a shorter duration of illness and that the training sessions could be designed according to the participants preference (Firth et al., 2018a). This could be a useful measurement to reduce the attrition rate in future trials as well.

In our study we found no significant effects of resistance training on

Table 2
Primary and secondary outcome measures.

Outcome	Intervention Group									Control group									Statistics		
	V1			V2			V3			V1			V2			V3					
Psychopathology	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	F	df	p
WHO-DAS	7	19.7	13.2	5	18.7	16.4	4	17.2	11.4	7	23.2	14.7	4	12.2	9.9	4	18.1	12.2	.018	2, 7.97[a]	.982[b]
CGI	7	3.7	.8	5	3.6	.9	4	3.5	1.0	8	3.6	.7	4	3.3	0.5	4	3.3	.5	χ^2 = 2.00/.00	2/2	.368/1.00[c]
CDSS	7	3.7	4.4				4	3.8	3.6	8	3.4	4.0				4	.5	.6	.31	1. 10.35[a]	.587[b]
PANSS total	7	52.1	14.7				4	51.5	19.8	8	51.4	15.7				4	45.0	5.9	2.94	1, 6.32[a]	.135[b]
PANSS positive	7	12.3	3.9				4	12.3	6.1	8	10.1	4,8				4	7.8	1.0	0.50	1, 6.04	.508[b]
PANSS negative	7	13.6	5.2				4	12.8	4.1	8	15.0	3,7				4	15.8	3.0	1.88	1, 7.12	.212[b]
PANSS general	7	26.3	7.5				4	26.3	9.5	8	26.3	7.9				4	21.5	2.9	.01	1, 6.00	.925[b]
GAF	7	62.1	10.1	5	68.4	15.3	4	74.5	16.7	8	60.0	6.1	4	63.8	4.9	4	66.8	6.4	6.82	2, 7.791[a]	**.019**[b]
Cognitive Parameters																					
TMT A (s)	7	32.6	15.9				4	30.3	11.8	8	23.4	4.1				4	21.5	5.1	Z = .00/-.37	1/1	1.00/.713[d]
TMT B (s)	7	78.9	23.8				4	65.5	20.4	8	68.8	15.7				4	60.5	14.8	Z = −1.83/-1.10	1/1	.068/.273[d]
TMT B-A (s)	7	46.3	15.2				4	35.3	9.9	8	45.9	17.3				4	39.0	12.0	Z = −.37/-1.46	1/1	.715/.144[d]
d2	7	169.7	57.2				4	188.5	41.8	8	161.8	25.4				4	187.5	7.9	Z = −1.83/-1.84	1/1	.068/.066[d]
Cardiovascular parameters																					
BMI (kg/m^2)	6	33.7	5.5	4	34.3	6.2	4	35.7	6.4	6	30.3	8.5	3	35.4	8.9	4	34.7	8.7	χ^2 = .67/4.00	2/2	.717/.135[c]
Pulse (bpm)	6	84.8	15.3	5	89.8	10.4	4	80.5	12.3	7	83.6	11.5	5	82.8	8.6	4	85.5	11.4	χ^2 = 5.57/.13	2/2	.062/.936[c]
Laboratory parameters																					
Glucose (mmol/l)	6	94.3	16.3				3	89.0	9.5	7	82.1	12.4				3	97.3	13.2	Z = −.54/-1.60	1/1	.593/.109[d]
Triglycerides (mmol/l)	6	200.8	111.5				3	244.7	113.0	7	95.7	43.9				3	112.7	32.5	.50	1, 3.95[a]	.518[b]
Sports medicine Parameters																					
Strength per kg body weight[e]	6	2.66	0.73				3	3.07	1.33	7	3.01	0.91				4	3.52	1.95	1.32	1, 5.60[a]	.298[b]
Strength per kg body weight[f]	6	-.3	.8				3	.1	1.5	7	.1	1.0				4	.6	1.9	1.21	1, 5.75[a]	.315[b]
PWC130 per kg	6	.8	.2				2	.9	.02	6	1.1	.4				2	.7	.03	11.45	1, 8.76[a]	.008[b]

V1: visit 1; V2: visit 2 after 4 weeks; V3: visit 3 after 12 weeks; N: group size; SD: standard deviation; F: F-statistic; df: degrees of freedom; p: p-value; χ^2: Chi^2-statistic; Z: Z-statistic; s: seconds; kg: kilogram; bpm: beats per minute; mmol/l: millimol per liter.

WHO-DAS: World Health Organization Disability Assessment Schedule, CGI: Clinical Global Impression, CDSS: Calgary Depression Scale for Schizophrenia, PANSS: Positive and Negative Syndrome Scale, GAF: Global Assessment of Functioning, TMT: Trail Making Test, d2: d2 test, BMI: body mass index, PWC130: Physical Working Capacity at 130 bpm heart rate.

[a] Numerator df, denominator df.

[b] Comparison with linear mixed model, interaction time x group.

[c] Comparison of time effects with Friedman Test, χ^2, df, p: values for intervention group/control group.

[d] Comparison of time effects with Wilcoxon Test, χ^2, df, p: values for intervention group/control group.

[e] Mean strength (N) divided by body weight (kg).

[f] Based on Z scores.

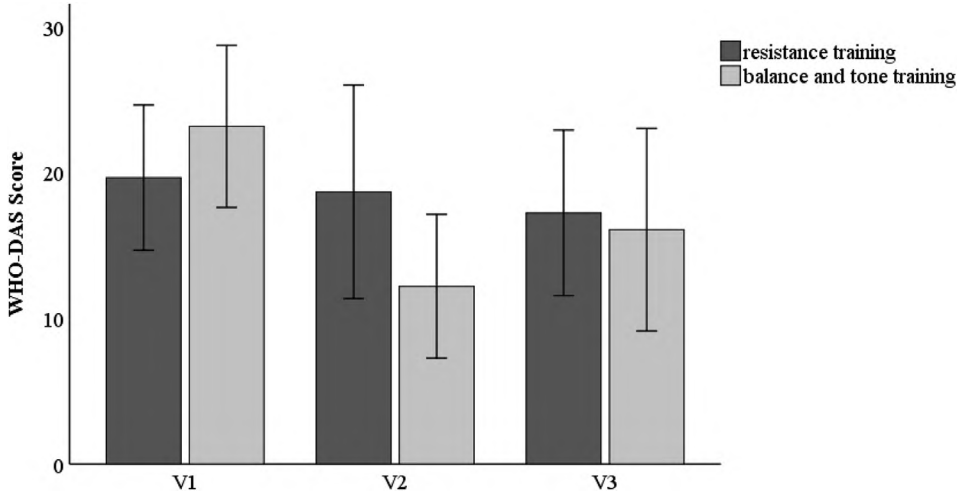

Fig. 4. Changes in WHO-DAS over the course of time in intervention and control group, error bars represent ± 1standard error of the mean (SE), lower scores indicating a lower grade of disability.

health-related difficulties assessed with the WHO-DAS as primary outcome parameter. Regarding the secondary outcome parameters, the GAF score improved in both groups after 12 weeks of training. However, the improvement after resistance training was more pronounced in the intervention than in the control group. In the past it could already be shown that GAF and WHO-DAS do not correlate and represent independent factors (Gspandl et al., 2018). A related effect in terms of a significant improvement regarding the GAF scores after 3 months of exercise in schizophrenia patients compared to a table soccer control group has been observed in former studies (Firth et al., 2018a; Malchow et al., 2015). A similar effect could also be demonstrated in a meta-analysis (Dauwan et al., 2016). This suggests that physical activity, regardless of the exact type of exercise, can lead to an improved level of functioning in schizophrenia patients. However, this issue needs further investigation in more detail in future studies.

The study had several limitations that need to be considered when interpreting the results. First, the study had only a small sample size. The number of participants was probably too small to show significant differences regarding the WHO-DAS and other outcome parameters compared to the active control condition. Previous studies consisting of resistance exercise elements that reported positive results regarding the PANSS and cognitive functioning displayed a larger sample size (Andrade e Silva et al., 2015; Firth et al., 2018a), a younger population (Firth et al., 2018a), and a higher retention rate (Firth et al., 2018a). However, the sample size of the presented trial is common for such a proof of principle trial, but the reader should be aware that all findings need to be confirmed in a larger trial.

No data could be analyzed for the follow-up visit as only one patient in each group was available. Possible reasons for this might be a lack of motivation or time, which had already caused the relatively high dropout rate. Since our study was a proof of principle trial, its primary objective was to investigate the feasibility and effectiveness of the newly developed resistance training. It will be up to future trials to investigate the long-term effects of resistance training.

Furthermore, the design of the control group could have been chosen too similar to show more significant effects between the groups. The participants randomized to the control group underwent a training, which included exercises aiming at improving stability and balance. These can represent a similar type of stress to the muscle than resistance training. Additionally, the frequency and duration of the training sessions or the attendance rate were possibly too low, the 12-week intervention might be a too short period of time for the patients to adapt to the intervention. However, it should be noted that the design of our newly developed intervention has been adapted to the

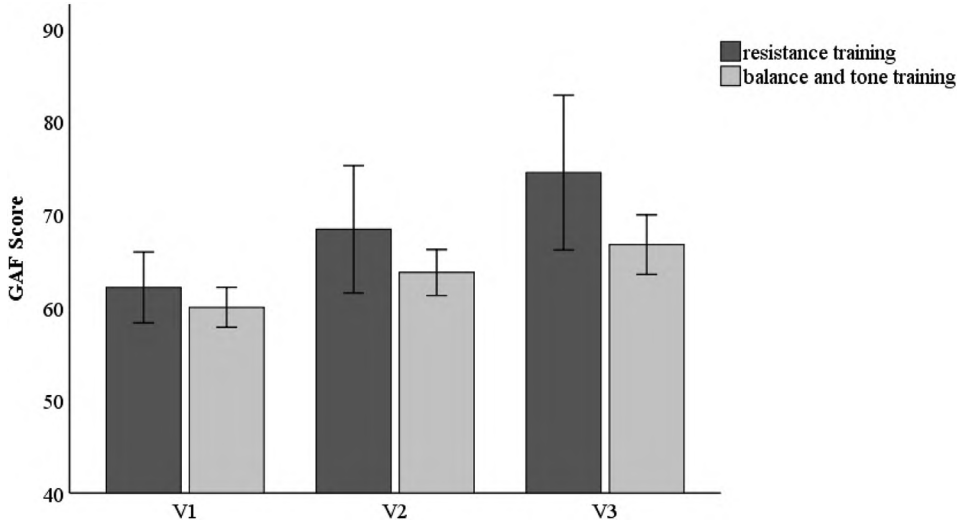

Fig. 5. Changes in the GAF score over the course of time in intervention and control group, with higher scores indicating better functioning, error bars represent ± 1standard error of the mean (SE).

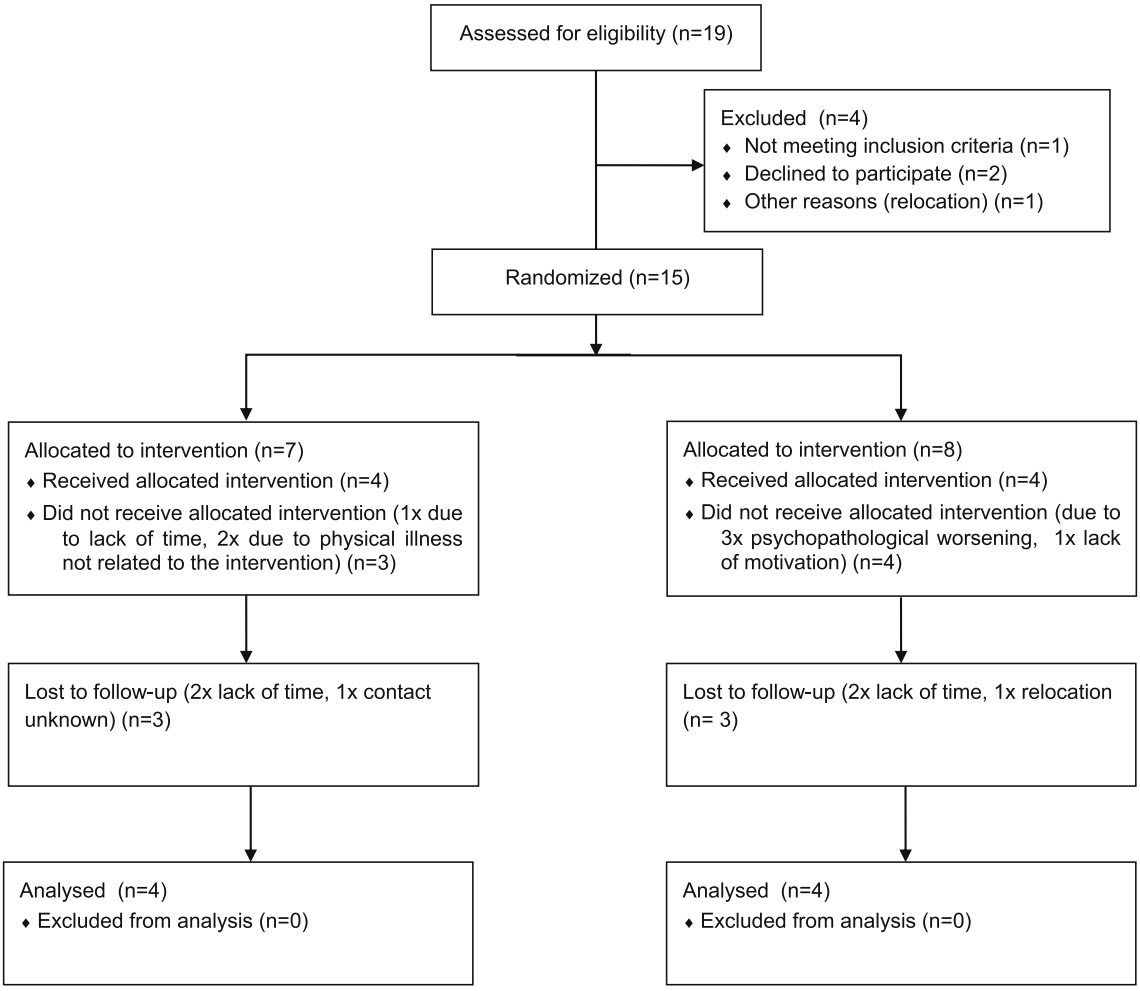

Fig. 6. Flowchart.

recommendations of the WHO and the American College of Sports Medicine. For future investigations, gym-based resistance training can be considered as an alternative to the here presented training. This could lead to an even greater increase of muscle strength, but carries a higher risk of injury in case of incorrect conduction and is associated with higher costs.

Proof of principle studies are necessary to assess effect size and possible superiority of an intervention before large randomized controlled trials can be made. Our study contributes to their conceptualization by having developed a resistance program according to current recommendations and a standardized evaluation of its effects.

In summary, our preliminary findings indicate that patients with schizophrenia can safely participate in resistance training with a relevant improvement in their level of functioning assessed with the GAF. Moreover, exercise interventions in general seem to improve general functioning. Larger multi-site studies are warranted to further evaluate the effects and possible mechanisms of resistance interventions in schizophrenia patients on a wider scale. In addition, longer intervention durations and follow-up examinations are needed to investigate the sustainability of those effects. In summary, even if the study proved to be safe, compliance and drop-out rate should be further improved. For this purpose, motivational components have been proven to be helpful (Vancampfort et al., 2016) and future studies should also add such components.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.09.015.

References

Addington, D., Addington, J., Maticka-Tyndale, E., 1993. Assessing depression in schizophrenia: the calgary depression scale. Br. J. Psychiatry 163 (S22), 39–44.
Andrade e Silva, B., et al., 2015. A 20-week program of resistance or concurrent exercise improves symptoms of schizophrenia: results of a blind, randomized controlled trial. Rev. Bras. Psiquiatr. 37 (4), 271–279.
Borg, G.A.V., Noble, B.J., 1974. Perceived exertion. Exerc. Sport Sci. Rev. 2, 131–153.
Braith, R.W., Stewart, K.J., 2006. Resistance exercise training: its role in the prevention of cardiovascular disease. Circulation 113 (22), 2642–2650.
Brickenkamp, R., Schmidt-Atzert, L., Liepmann, D., 2010. Test d2-Revision: Aufmerksamkeits-und Konzentrationstest. Hogrefe Göttingen.
Cassilhas, R.C., et al., 2010. Mood, anxiety, and serum IGF-1 in elderly men given 24 weeks of high resistance exercise. Percept. Mot. Skills 110 (1), 265–276.
Colberg, S.R., et al., 2010a. Exercise and type 2 diabetes: the American College of sports medicine and the American diabetes association: joint position statement. Diabetes Care 33 (12), e147–e167.
Colberg, S.R., et al., 2010b. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. Diabetes Care 33 (12), 2692–2696.
Dauwan, M., et al., 2016. Exercise improves clinical symptoms, quality of life, global

functioning, and depression in schizophrenia: a systematic review and meta-analysis. Schizophr. Bull. 42 (3), 588–599.
Endicott, J., et al., 1976. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatr. 33 (6), 766–771.
Federici, S., et al., 2017. World Health Organization disability assessment schedule 2.0: an international systematic review. Disabil. Rehabil. 39 (23), 2347–2380.
Firth, J., et al., 2015. A systematic review and meta-analysis of exercise interventions in schizophrenia patients. Psychol. Med. 45 (7), 1343–1361.
Firth, J., et al., 2016. Aerobic exercise improves cognitive functioning in people with schizophrenia: a systematic review and meta-analysis. Schizophr. Bull. 43 (3), 546–556.
Firth, J., et al., 2018a. Exercise as an intervention for first-episode psychosis: a feasibility study. Early intervention in psychiatry 12 (3), 307–315.
Firth, J., et al., 2018b. Grip strength is associated with cognitive performance in schizophrenia and the general population: a UK biobank study of 476559 participants. Schizophr. Bull. 44 (4), 728–736.
FitzGerald, S.J., et al., 2004. Muscular fitness and all-cause mortality: prospective observations. J. Phys. Act. Health 1 (1), 7–18.
Fusar-Poli, P., et al., 2015. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. Schizophr. Bull. 41 (4), 892–899.
Garber, C.E., et al., 2011. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med. Sci. Sport. Exerc. 43 (7), 1334–1359.
Gspandl, S., et al., 2018. Comparing global assessment of functioning (GAF) and World health organization disability assessment schedule (WHODAS) 2.0 in schizophrenia. Psychiatry Res. 259, 251–253.
Guy, W., 1976. ECDEU assessment manual for psychopharmacology—revised. 1976, rockville, MD: US department of health, education, and welfare. In: Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch. Division of Extramural Research Programs, pp. 218–222.
Heggelund, J., et al., 2012. Therapeutic effects of maximal strength training on walking efficiency in patients with schizophrenia–a pilot study. BMC Res. Notes 5 (1), 344.
Helmstaedter, C., 2001. VLMT Verbaler Lern-und Merkfähigkeitstest: Manual. Beltz-Test.
Jurca, R., et al., 2005. Association of muscular strength with incidence of metabolic syndrome in men. Med. Sci. Sport. Exerc. 37 (11), 1849.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Keller-Varady, K., et al., 2016. Endurance training in patients with schizophrenia and healthy controls: differences and similarities. Eur. Arch. Psychiatry Clin. Neurosci. 266 (5), 461–473.
Keller-Varady, K., et al., 2018. A systematic review of trials investigating strength training in schizophrenia spectrum disorders. Schizophr. Res. 192, 64–68.
Kraemer, W.J., Ratamess, N.A., 2005. Hormonal responses and adaptations to resistance exercise and training. Sport. Med. 35 (4), 339–361.
Laursen, T.M., Munk-Olsen, T., Vestergaard, M., 2012. Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr. Opin. Psychiatr. 25 (2), 83–88.
Li, M., et al., 2014. Schizophrenia and risk of stroke: a meta-analysis of cohort studies. Int. J. Cardiol. 173 (3), 588–590.
Liu-Ambrose, T., et al., 2010. Resistance training and executive functions: a 12-month randomized controlled trial. Arch. Intern. Med. 170 (2), 170–178.
Malchow, B., et al., 2013. The effects of physical exercise in schizophrenia and affective disorders. Eur. Arch. Psychiatry Clin. Neurosci. 263 (6), 451–467.
Malchow, B., et al., 2015. Effects of endurance training combined with cognitive remediation on everyday functioning, symptoms, and cognition in multiepisode schizophrenia patients. Schizophr. Bull. 41 (4), 847–858.
Martinotti, G., et al., 2012. Nerve growth factor and brain-derived neurotrophic factor concentrations in schizophrenia: a review. J. Biol. Regul. Homeost. Agents 26 (3), 347.
Nelson, M.E., et al., 2007. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Circulation 116 (9), 1094.
Nielsen, R.E., et al., 2015. Second-generation antipsychotic effect on cognition in patients with schizophrenia–a meta-analysis of randomized clinical trials. Acta Psychiatr. Scand. 131 (3), 185–196.
Pollock, M.L., et al., 2000. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription an advisory from the committee on exercise, rehabilitation, and prevention, council on clinical cardiology, American heart association. Circulation 101 (7), 828–833.
Rantanen, T., et al., 2000. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 55 (3), M168–M173.
Reitan, R.M., Wolfson, D., 1985. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation, vol. 4 Reitan Neuropsychology.
Romain, A.J., et al., 2018. Effects of high intensity interval training among overweight individuals with psychotic disorders: a randomized controlled trial. Schizophr. Res. 210, 278–286.
Scheewe, T.W., et al., 2013. Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: a randomised controlled trial in patients with schizophrenia and healthy controls. Eur. Neuropsychopharmacol. 23 (7), 675–685.
Stanton, R., Reaburn, P., Happell, B., 2013. Is cardiovascular or resistance exercise better to treat patients with depression? A narrative review. Issues Ment. Health Nurs. 34 (7), 531–538.
Strasser, B., Schobersberger, W., 2010. Evidence for resistance training as a treatment therapy in obesity. Journal of obesity 2011.
Strasser, B., Siebert, U., Schobersberger, W., 2010. Resistance training in the treatment of the metabolic syndrome. Sport. Med. 40 (5), 397–415.
Stubbs, B., et al., 2016. How much physical activity do people with schizophrenia engage in? A systematic review, comparative meta-analysis and meta-regression. Schizophr. Res. 176 (2–3), 431–440.
Svatkova, A., et al., 2015. Physical exercise keeps the brain connected: biking increases white matter integrity in patients with schizophrenia and healthy controls. Schizophr. Bull. 41 (4), 869–878.
Ustun, T.B., et al., 2010. Developing the World health organization disability assessment schedule 2.0. Bull. World Health Organ. 88 (11), 815–823.
Vancampfort, D., et al., 2012. The functional exercise capacity is correlated with global functioning in patients with schizophrenia. Acta Psychiatr. Scand. 125 (5), 382–387.
Vancampfort, D., et al., 2015. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 14 (3), 339–347.
Vancampfort, D., et al., 2016. Prevalence and predictors of treatment dropout from physical activity interventions in schizophrenia: a meta-analysis. Gen. Hosp. Psychiatry 39, 15–23.
Vancampfort, D., R, S., Probst, M., Stubbs, B., 2018. Aerobic exercise in people with schizophrenia. In: The Exercise Effect on Mental Health, Neurobiological Mechanisms. Routledge, New York.
Vega, S.R., et al., 2010. Effect of resistance exercise on serum levels of growth factors in humans. Horm. Metab. Res. 42 (13), 982–986.
Venkatasubramanian, G., et al., 2007. Insulin and insulin-like growth factor-1 abnormalities in antipsychotic-naive schizophrenia. Am. J. Psychiatry 164 (10), 1557–1560.
Whiteford, H.A., et al., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. The Lancet 382 (9904), 1575–1586.
WHO, 2010. Global Recommendations on Physical Activity for Health. World Health Organization.
WHO, 2018. WHO guidelines approved by the guidelines review committee. In: Management of Physical Health Conditions in Adults with Severe Mental Disorders. 2018. World Health Organization (c) World Health Organization, Geneva.