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A systematic review of trials investigating strength training in schizophrenia spectrum disorders

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Muscle strength is inversely associated with long-term mortality risk (Rantanen et al., 2000) and the incidence of metabolic syndrome in initially healthy men (Jurca et al., 2005). These effects appear contrary to the increased risk of cardiometabolic complications in schizophrenia (de Hert et al., 2011; Srihari et al., 2013). The benefits of strength training (ST) on psychopathology have not been investigated in sufficient detail, but some results indicate improvements of mood and anxiety (Cassilhas et al., 2010; Stanton et al., 2013) and thus positive effects on symptom severity in psychiatric disorders are to be expected.

The aim of this systematic review was to differentiate between the effects of ST and those of other types of training in schizophrenia patients. This report will serve as an addition to the published reviews on aerobic exercise and exercise in general and bridge the evidence gap regarding ST (Chalfoun et al., 2016; Dauwan et al., 2015; Firth et al., 2015; Gorczynski and Faulkner, 2010; Stanton and Happell, 2014; Vancampfort et al., 2014; Vancampfort et al., 2015b; Vancampfort et al., 2015a). To design effective add-on sports programs it is essential to know and understand the effects and mechanisms of each component, i.e., strength or endurance training.

This systematic review was performed in accordance with the PRISMA recommendations (Liberati et al., 2009; Moher et al., 2009). Methods were specified in advance in a protocol including eligibility criteria, definitions, search terms and data items (see Supplementary material). Two reviewers (K.K.-V., P.A.V.) performed a systematic search of the PubMed database (National Center for Biotechnology Information, NCBI, National Library of Medicine, NLM) and Cochrane Central Register of Controlled Trials (CENTRAL) The search was last updated on August 09, 2016. Additionally, we extracted data on risk of bias and conducted quality ratings for the analyzed trials with the Downs and Black Quality Index (Downs and Black, 1998). To investigate trials that had been registered but had not yet published we searched "clinicaltrials.gov" and the "WHO International Clinical Trials Registry Platform Search Portal".

The search identified 320 records (see Fig. 1, Supplementary material). Additional information on the excluded studies (Archie et al., 2003; Bredin et al., 2013; Fogarty et al., 2004; Nuechterlein et al., 2014; Pelham et al., 1993; Smith and Figetakis, 1970; Strassnig et al., 2015; Takeda et al., 2002) is also presented in the Supplementary material. Four of the nine finally selected reports covered the same study, so that a total of six studies were available for qualitative analysis.

Table 1 shows detailed characteristics and the results of the six studies. The results of the Cochrane Collaboration's tool for the assessment of the risk of bias are shown in Table 2 in the Supplementary material.

Only two studies examined the impact of isolated ST in patients with schizophrenia (Heggelund et al., 2012; Silva et al., 2015). An 8-week

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Table 1
Characteristics and results of individual studies.

Reference & design	Patients (sample)	Intervention incl. comparators	Outcomes in EG	Attendance and dropout rate
Heggelund et al. (2012) Controlled trial	n = 16, diagnosis of schizophrenia, schizotypal or delusional disorders (ICD 10: F20-F29); *mean age: 38 y; mean PANSS: 61; 5 male completers, 8 female completers;* in- and outpatients; department of psychiatry at a university hospital (monocentric); neuroleptics	8 weeks, 3 sessions/week Experimental group (EG): maximal strength training; n = 7; 5 min warm-up (treadmill, 70% intensity), leg press exercise ("54° incline leg press machine"(Heggelund et al., 2012, p. 3), controlled, 90° knee angle, rapid extension; 4 sets, 4 repetitions; 3 min rest between sets; 85–90% of 1RM; continuous increases; supervised) Control group (CG): computer game (Tetris); n = 9; 36 min/session; monitored	↑* (+19.7%) Efficiency of walking (percentage of the work input and work output in treadmill exercise test) ↓ (−5.6%) VO_{2peak} (incremental treadmill exercise test) ↑ (+38.1%) 1RM (leg press test) ↑ (+17.2%) Symptoms of schizophrenia (PANSS) ↑ (+13.3%) Physical and ↓ (−2.8%) mental health aspects of health-related quality of life (SF-36)	Adherence rate: 85 ± 9% in EG, 83 ± 6% in CG 86% completed EG 3 dropouts (1 in EG, 2 in CG); reasons: <80% adherence (1), disappeared (1), discharged (1)
Silva et al. (2015) RCT	n = 47, schizophrenia (DSM-IV); mean age: 33 y, *PANSS: 63;* all male; stable medication (6 weeks); 2 sites: Centro de Atenção Psicossocial and Faculdade de Ciências Médicas da Santa Casa de São Paulo (multicentric)	3 familiarization sessions, 20 weeks, 2 session/week, 60 min/session, 5 min warm-up (treadmill, 4 km/h) Experimental group I (EGI): "RESEX"; n = 14; "progressive resistance training program", (exercises for large muscle groups: leg press, leg curl, vertical traction, chest press, arm extension, arm curl, abdominal crunch; Technogym equipment; 40–85% of 1RM; 2–3 sets, 6–15 repetitions; 1–2 min interval) Experimental group II (EGII): "CONCEX"; n = 17; resistance training like RESEX (reduced sets: 1–2); endurance training (25 min/session, walking, running, treadmill, 40–75% of VO_{2max}); HR monitoring Control group (CG): "CTRL"; n = 16; same protocol; minimum load; 15 repetitions; 1 min rest; minimum speed (4 km/h)	↓* (−23.5%/−15.8%) Symptom severity (PANSS) ↓ (−74.6%/−67,1%) depressive symptoms (CDSS) ↑ (+22.4%/+11.4%) Health-related quality of life (SF-36) ↓ (−55.4%/−4.2%) Biomarkers (analyses of BDNF) ↓ (−1.1%/−0.02%) body mass ↑ (+22.9%/+10.9%) 1 RM leg press ↑ (* + 26.6%/+10.4%) 1 RM chest press	Adherence rate: >75% 86% completed in EGI 13 dropouts (2 in EGI, 8 in EGII, 3 in CG); reasons: protocol violation (8), disease (1), job (2), hospitalization (2)
"TOPFIT" (Scheewe et al., 2012b; Scheewe et al., 2012a; Scheewe et al., 2012c; Svatkova et al., 2015) RCT	n = 63, diagnosis of schizophrenia spectrum disorder (DSM-IV); *mean age: 30 y; mean PANSS: 63;* 46 male, 17 female; antipsychotics; IQ > 70;University Medical Center Utrecht, Netherlands; regional mental health care institutes (multicentric) MRI scans: n = 34 DTI scans: n = 33 CRF analysis: n = 33	6 months, 2 sessions/week, 60 min/session Experimental group (EG): n = 31; cardiovascular exercises; muscle strength exercises (6 exercises/session: biceps, triceps, abdominal, quadriceps, pectoral, and deltoid muscles, 3 sets, 10–15 repetitions; supervised; logbook; strict protocol; stepwise increase of intensity (week 1–3, 45%; week 4–12, 65%; week 13–26, 75% of HR reserve) Control group (CG): occupational therapy; n = 32; "creative and recreational activities such as painting, reading, and computer activities"	Cardio-respiratory fitness (CRF): ↑* (+0.9%) highest relative oxygen uptake ↑* (+9.7%)" peak work rate at the moment of exhaustion" (Scheewe et al., 2012b, p. 1835) ↓* (−10.7%) Symptom severity (PANSS) ↓ (−30.2%) depressive symptoms (MADRS) ↓ (−11%) BMI MRI data: ↓(−0.1%) intracranial volume, ↓ (−0.2%) total cerebrum, ↓ (−0.2%) grey matter, ↓ (−0.1%) white matter, ↑ (+0.2%) lateral ventricle, → (0%) third ventricle, ↓ (−1%) hippocampal volume, brain connectivity (↑* fractional anisotropy) Glucose and lipids (blood analyses): no sign. Changes Blood pressure and heart rate: no sign. Changes ↑ (+4.9%) Intelligence quotient	Attendance rate: 41 of 52 sessions; 72% >50% attendance! (n = 20 patients in EG and n = 19 patients in CG met minimal attendance [50%]); 93% completed exercise (attendance <50% not defined as dropout!) 9 dropouts (2 in EG, 7 in CG; significant difference); reasons: relapse (1), refuses to come (1), pregnancy (1), disinterest (3), personal reasons (1), lost contact (2)
Kim et al. (2014) Controlled trial	n = 40, paranoid schizophrenia (DSM-IV*); mean age: 49 y*; regular medication; hospitalized >3 y; Hyundae-Somang Psychiatry Unit, Eumseong-gun, Chungcheongbuk-do (monocentric)	12 weeks Experimental group (EG): n = 25; 3 sessions/week; 60 min/session: 10 min warm-up (stretching), 25 min strength training (8 exercises: "chest press, seated row, squat, shoulder press, biceps curl, triceps extension, calf raise, reverse crunch, "(Kim et al., 2014, p. 793) elastic band [thera], RPE 12–13), 25 min walking (60% of individual VO_{2max}, week 1–4: 50% of HRR, week 5–8: 60% of HR reserve, week 9–12: 70% of HR reserve); heart	Body composition: ↓* (−1.3%) weight, ↓* (−3.8%) waist circumference Physical function and muscle strength ↓* (−18%) YMCA step test, ↑* (+20.9%) Jump test, ↑ (+76.9%) sit-and-reach test, ↑* (+247.5%) standing on one leg with eyes closed test, ↑ (+5.5%) grip force, ↑* (+47.6%) isometric quadriceps force ↑* (+21.5%) BDNF serum levels ↓* (−7.1%) Systolic blood pressure, ↓* (−8.4%) Diastolic blood pressure, ↓*	4 dropouts (1 in EG, 3 in CG), reasons: personal reasons, health reasons not related to intervention

(continued on next page)

Table 1 (*continued*)

Reference & design	Patients (sample)	Intervention incl. comparators	Outcomes in EG	Attendance and dropout rate
		rate monitoring; RPE scale, nonconsecutive days, 1 week "adaptation period" Control group (CG): n = 15; 1 session/week; 60 min/session; stretching, dancing and recreational activity	(−6.7%) Resting heart rate Glucose and lipids (blood analyses): no sign. changes	
Marzolini et al. (2009) RCT	n = 13, schizophrenia/schizoaffective disorder (DSM-IV); mean age 45 y; 8 males, 5 females; medication; 1 participant with diabetes mellitus, 1 participant with coronary artery disease; Assertive Community Treatment (ACT) team (monocentric)	Experimental group (EG): n = 7; 12 weeks; 2 sessions/week; 90 min/session: 10 min warm-up (walking, flexibility), 20 min resistance training (half squat, heel raises, bicep curls, tricep extensions, dumbbells; 10 repetitions; week 1: 1 set, week 2–12: 2 sets; 30 s rest between sets; 60% of 1RM; RPE <15; slow movements; increase of repetitions and weight); up to 60 min/session aerobic training (walking, 1.6 to 6.4 km, 11–14 RPE, 60–80% of HR reserve, increase in distance and intensity), 5 min cool-down; heart rate monitoring; in group; supervised; in gym, weight room, 100 m indoor track or outside in a park + 1 session/week at home Control group (CG): n = 6; usual care	↑ (+5.2%) 6-min walking distance ↑* (+26.1%) 1RM biceps curl ↑ (+1.6%) body mass, ↓ (−0.1%) waist circumference ↑* (+16.3%) Mental Health Inventory (MHI, 18 items) ↓ (−2.7%) Resting systolic blood pressure	Mean attendance: 72 ± 4.4% for home exercises: 35% (sign. Lower) No dropouts Barriers: 47% unknown reasons, 27% medical issues, 8% supervised trip or family visit, 4% medical appointment
Leone et al. (2015) single group	n = 8, schizophrenia (DSM-IV); mean age: 34 y; outpatients; CSSS Hospital of Chicoutimi (monocentric)	Experimental group (EG): n = 8; 8 weeks; 2 sessions/week; 75 min/session; "mixed periodized training program"; strength training (7 exercises with Atlantis weight machines: biceps, triceps, pectorals, abdominals, gluteals, quadriceps, hamstrings[u]; week 1–4: maximal strength, 80% of 1RM, 3 sets, 6 repetitions; week 5–8: muscular endurance, 50% of 1RM, 25 repetitions, 2 min rest between sets[u]); 10–20 min endurance training (quick walking or running; week 1–4: 10 min, week 4–5: 15 min, week 6–7: 18 min, week 8: 20 min); intensity: as quickly as possible; laps with obstacles; 8 min circuit with activities of daily living (8 exercises; 1 min duration; 1 set; hand grip; load lifting and load transfer; moving forward-backward and left-right; circular motions with arms; stair climbing; turn a doorknob[u])	Physiological fitness Functional capacity: ↑* (+16%) estimated VO2 max, ml/min/kg ↑* (+25.1%) 1RM leg press ↑* (+26.1%) 1RM biceps curl Psychological outcomes: ↓* (−63%) Beck Depression Inventory, ↑* (+15.2%) Spiegel questionnaire for sleeping quality, ↓* (−18.7%) questionnaire for body dissatisfaction ↑ (+2.2%) body mass ↓* (−2.5%) waist circumference Glucose and lipids (blood analyses): no sign. changes	Minimum requirement of 75% sessions met by all participants, no dropouts

↑: increase; ↓: decrease; ↓* or ↑*: decrease or increase considered significant by authors; italics: values calculated by the authors from baseline group characteristics; [u]: unpublished information obtained from authors; BDNF: brain-derived neurotrophic factor; BMI: Body Mass Index; bpm: beats per minute; CDSS: calgary depression scale for schizophrenia; CG: control group; cm: centimeters; CRF: cardio-respiratory fitness; DSM-IV: diagnostic and statistical manual of mental disorders 4th Edition, Text Revision; DTI: diffusion tensor imaging; EG: experimental group; h: hour; HDL: high-density lipoprotein; HR: heart rate; ICD: international statistical classification of diseases and related health problems; IGF-1: insulin growth factor-1; IGFBP-3: IGF binding protein; IQ: intelligence quotient; kg: kilogram; km: kilometer; MADRS: Montgomery Åsberg Depression Rating Scale; MetS: metabolic syndrome; min: minute; ml: milliliters; MRI: magnetic resonance imaging; n: number of participants; nb: number; PANSS: positive and negative syndrome scale; RER: respiratory exchange ratio; RPE: rating of perceived exertion; s: seconds; SF-36: 36-item short form health survey; VAT: ventilatory anaerobic threshold; VO_2: oxygen uptake; W: watts; y: year; YMCA: Young Men's Christian association; 1RM: one repetition maximum.

intervention with a single exercise (leg press) did not improve psychopathology (PANSS) or quality of life measures, but it increased the net mechanical efficiency of walking and thus improve impaired walking performance (Heggelund et al., 2012). In contrast, in the RCT with machine-based ST for several large muscle groups (for details see Table 1, Silva et al., 2015) reported a significantly improved muscle strength and psychopathology (PANSS) but no statistically significant effect on depressive symptoms, general quality of life, or BDNF serum levels.

Five studies investigated ST combined with endurance training (Kim et al., 2014; Leone et al., 2015; Marzolini et al., 2009; Scheewe et al., 2012b; Scheewe et al., 2012a; Scheewe et al., 2012c; Silva et al., 2015; Svatkova et al., 2015). Silva et al. (2015) investigated a group with isolated ST and also a group with combined ST.

The findings are consistent to general recommendations (Johannsen et al., 2016; e.g. World Health Organization, 2010) that a balanced training including both strength and endurance components seems to generate the best health benefits. Our analyses of five studies that used interventions combining these contents showed improvements of muscle strength, physical fitness and symptom severity (Kim et al., 2014; Leone et al., 2015; Marzolini et al., 2009; Scheewe et al., 2012b; Silva et al., 2015). Only one study investigated the effects on brain structure and function (Scheewe et al., 2012c). No significant changes were detected in brain volumes, but an increase in structural connectivity and a correlation between cortical thickness and cardiorespiratory fitness. The direct comparison of ST alone and in combination with endurance training in the study by Silva et al. (2015) showed comparable effects

of both types of training except for finding significant improvements of negative symptoms (PANSS subscore) and physical role functioning (SF-36 subscore) in the isolated ST group. However, it cannot be ruled out that unspecific factors such as regular therapeutic contact, daily structure and social support drive some of the effects.

The evidence of two methodologically different studies is not sufficiently strong to give a recommendation for the therapeutic use of isolated ST. Nevertheless, based on the outcomes of five combined exercise groups from different studies, a training combining endurance and strength aspects can be recommended for patients with schizophrenia. Benefits in several important domains, such as psychopathology, can be expected. Different from other systematic reviews (Dauwan et al., 2015; Firth et al., 2015; Vancampfort et al., 2015b; Vancampfort et al., 2015a), we distinguished between different types of training.

The differences in methods (designs and interventions) and small sample sizes impair generalization of the results. The incomplete reporting of details of the interventions and usage of unspecific terms in some of the reviewed studies was a major limitation. The interventions are the starting points for every adaptation that researchers might later identify as a potential benefit. Especially the frequently used term "aerobic exercise" alone does not satisfactorily explain the training method, because it can be used for any activity that can be carried out with aerobic energy metabolism. As recommendation for future studies, we have compiled a checklist of methodological aspects to contribute to high quality exercise studies (see Fig. 2 in the Supplementary material).

Some limitations of the review process itself should be mentioned. The search was restricted to articles published in English, Spanish, French, or German. Three reports in Japanese or Chinese could not be retrieved in full text. No unpublished trials with negative results were identified through a search of the trial databases ("clinicaltrials.gov" and "WHO International Clinical Trials Registry Platform Search Portal").

In conclusion, the aspect of ST in schizophrenia has been underappreciated in research. Only one RCT (Silva et al., 2015) examined a whole-body ST program in patients with schizophrenia. This study indicated benefits in parameters of muscle strength and symptom severity. Isolated ST needs to be investigated in carefully designed RCTs and reported with correct nomenclature in future because it is relevant to differentiate between effects of different types of training.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.06.008.

Conflict of interest

K. Keller-Varady, P. A. Varady, A. Röh, B. Malchow have no conflict of interest. A. Schmitt was an honorary speaker for TAD Pharma and Roche and has been a member of advisory boards for Roche. P. Falkai has been an honorary speaker for Janssen-Cilag, GE Healthcare, Otsuka, Servier, Takeda, Astra-Zeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth and Essex. He was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. A. Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer has received a paid speakership from Desitin, Otsuka, and the Federal Union of German Associations of Pharmacists, and was member of the Roche Advisory Board.

Contributors

K. Keller-Varady prepared the protocol, search strategy, and the manuscript. K. Keller-Varady and P. A. Varady conducted the search and analyzed the results. A. Röh was available for solving disagreements between the two main reviewers regarding the inclusion of reports and reviewed the manuscript. A. Hasan and B. Malchow reviewed the protocol, search strategy, and the manuscript. A. Schmitt and P. Falkai reviewed the manuscript. All authors approved the final manuscript.

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