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Exercise Improves Clinical Symptoms, Quality of Life, Global Functioning, and Depression in Schizophrenia: A Systematic Review and Meta-analysis

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Background: **Physical exercise may be valuable for patients with schizophrenia spectrum disorders as it may have beneficial effect on clinical symptoms, quality of life and cognition.** ***Methods:*** **A systematic search was performed using PubMed (Medline), Embase, PsychInfo, and Cochrane Database of Systematic Reviews. Controlled and uncontrolled studies investigating the effect of any type of physical exercise interventions in schizophrenia spectrum disorders were included. Outcome measures were clinical symptoms, quality of life, global functioning, depression or cognition. Meta-analyses were performed using Comprehensive Meta-Analysis software. A random effects model was used to compute overall weighted effect sizes in Hedges' *g*.** ***Results:*** **Twenty-nine studies were included, examining 1109 patients. Exercise was superior to control conditions in improving total symptom severity ($k = 14$, $n = 719$: Hedges' $g = .39$, $P < .001$), positive ($k = 15$, $n = 715$: Hedges' $g = .32$, $P < .01$), negative ($k = 18$, $n = 854$: Hedges' $g = .49$, $P < .001$), and general ($k = 10$, $n = 475$: Hedges' $g = .27$, $P < .05$) symptoms, quality of life ($k = 11$, $n = 770$: Hedges' $g = .55$, $P < .001$), global functioning ($k = 5$, $n = 342$: Hedges' $g = .32$, $P < .01$), and depressive symptoms ($k = 7$, $n = 337$: Hedges' $g = .71$, $P < .001$). Yoga, specifically, improved the cognitive subdomain long-term memory ($k = 2$, $n = 184$: Hedges' $g = .32$, $P < .05$), while exercise in general or in any other form had no effect on cognition.** ***Conclusion:*** **Physical exercise is a robust add-on treatment for improving clinical symptoms, quality of life, global functioning, and depressive symptoms in patients with schizophrenia. The effect on cognition is not demonstrated, but may be present for yoga.**

Key words: psychopathology/functioning/cognition/yoga/aerobic exercise

Introduction

Schizophrenia, a severe psychiatric disorder, affects approximately 24 million people worldwide.[1] This disorder is characterized by (1) positive symptoms such as hallucinations and delusions, (2) negative symptoms including affective flattening, alogia and avolition, and (3) neurocognitive deficits including perception, memory, and attention, among others.[2] Negative and cognitive symptoms, emerging in the pre-psychotic stage, appear to be related.[3] Higher negative and cognitive symptoms are significantly associated with poorer functional outcome.[4,5] Treatment with antipsychotic drugs, applied as first line therapy, typically result in reduction in positive symptoms with minimal to no effects on negative and cognitive symptoms.[6] In addition, antipsychotics result in the side effects weight gain and metabolic syndrome.[7,8] Furthermore, reduced physical capacity in patients with schizophrenia is strongly related to negative and cognitive symptoms.[9,10] These risk factors are major contributors of cardiovascular diseases in schizophrenia which in turn is associated with 2- to 3-fold higher mortality rate compared to the general population.[11] Saha et al found an all-cause standardized mortality ratio of 2.58 showing an increase in mortality in these patients over the last decades.[12] Therefore, it is time to implement a therapy for patients with schizophrenia that decreases the negative symptoms and cognitive deficits, and also improves the functional and clinical outcome.

Physical inactivity has been described as the leading risk factor for global mortality.[13] The World Health Organization (WHO) 2009[14] reported that physical inactivity accounts for 27% of diabetes and 30% of ischemic heart diseases, whereas an active lifestyle reduces these risks, largely improving general health and wellness, and life expectancy.[14] Furthermore, physical activity in healthy aging populations is associated with improvement in cognitive functioning and depressive symptoms, delay in age-related cognitive decline and neurodegeneration.[15,16] On the brain level, exercise induces neurogenesis, modulates synaptic plasticity and increases several growth factors relevant for maintaining optimal brain function.[17] Animal studies have shown that exercise results in increased neurogenesis in the hippocampus and that this is associated with enhanced synaptic plasticity.[15,16,18] Basically, these effects are mediated via the exercise-related increase of several growth factors in the brain such as brain-derived neurotrophic factor (BDNF).[15,18,19] In schizophrenia, lower peripheral BDNF has been associated with poorer neurocognitive functioning and smaller hippocampal volumes.[19,20] Exercise has also been associated with changes in regional brain volume and integrity.[18] These exercise-induced effects on the brain have been replicated in healthy humans and clinical populations, such as dementia patients, showing increased brain volume in grey and white matter regions, increased white matter integrity in frontal and temporal lobes, increases in BDNF, reduction in depressive symptoms, and improvement in cognitive functioning in young and old.[21–31]

Thus, negative symptoms in schizophrenia are an important predictor of unfavorable disease course and outcome and are related to physical inactivity. Therefore, stimulating physical exercise in patients with schizophrenia might have beneficial effect on clinical symptoms. The aim of the present study was to quantitatively review the effects of physical exercise on clinical symptoms in patients with schizophrenia spectrum disorder. Secondarily, the impact of exercise on quality of life (QoL), global functioning, depression, and cognition was investigated.

Methods

Literature Search

This meta-analysis was performed according the Preferred Reporting for Systematic Reviews and Meta-analysis (PRISMA) Statement.[32] A systematic search was performed in the databases Pubmed (Medline), Embase, PsychInfo and Cochrane Database of Systematic Reviews (independently by M.D. and I.E.S.). Combinations of the following search terms were used: "schizophrenia," "schizoaffective," "schizophreniform," "psychosis," "psychotic," "exercise," "soccer," "physical," "training," "endurance," "aerobic," "sport," and "yoga" (supplementary table S1). The search cut-off date was July 31, 2015. Additionally, the reference lists of the retrieved articles were examined for cross-references. When necessary, corresponding authors were contacted to provide full text details of the study outcome measures. In case the full text of articles was not available and the corresponding information of the authors was not traceable, the abstract was used to retrieve the necessary information to avoid publication bias. There were no year or language limits.

Inclusion Criteria

By consensus (between M.D. and I.E.S.), studies meeting the following inclusion criteria were included:

1. Studies investigated the effect of any type of exercise as an intervention on psychiatric symptoms, QoL or global functioning, depressive symptoms or cognition. Both controlled and uncontrolled studies were included.
2. Studies including patients with a diagnosis of schizophrenia or schizophrenia spectrum disorder (schizophreniform, schizoaffective, delusional or psychotic disorder not otherwise specified) according to the diagnostic criteria of the *Diagnostic and Statistical Manual of mental Disorders*[2] (DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR), or the International Classification of Diseases-9 or 10.
3. Studies reported sufficient information to compute common effect size statistics (ie, mean and SD, exact *P*-, *t*-, or *z*-values) or corresponding authors provided these data upon request.

Studies using combined programs of weight reduction and exercise or using additional cognitive training besides exercise were included in order to obtain as much information as possible.

Exclusion Criteria

1. Studies investigating the effect of exercise on the outcome measures in an uncontrolled study or in a mixed population of patients with schizophrenia and any other psychiatric disorder were excluded from the meta-analyses.
2. Studies that only measured an outcome in the intervention group and not in a control group were excluded from the analysis of the specific outcome measure.

Studies that were excluded from the meta-analyses based on these criteria were, however, included in the descriptive (supplementary table S2) and methodological assessment of quality table of the study (supplementary table S3). The outcomes of these studies are reported separately (supplementary table S4).

Outcome Measures

The primary outcome measures were the standardized mean difference in clinical symptoms, measured by total scores on the Positive and Negative Syndrome Scale (PANSS)[33] or the Brief Psychiatric rating Scale (BPRS),[34] standardized mean difference in general, positive and negative symptom subscores of the PANSS or scores on the Scale for the Assessment of Positive Symptoms (SAPS),[35] or the Scale for the Assessment of Negative Symptoms (SANS).[36] Secondary outcome measures included QoL and depressive symptoms as assessed by various QoL and depression questionnaires, global, social and occupational functioning assessed by Global Assessment of Functioning scale (GAF)[37] and Social and occupational Functioning (Assessment) Scale (SOFAS/SOFS),[38] and mean change in cognitive domains.

Statistical Analysis

Data were pooled for all studies examining the effect of exercise on a specific outcome measure. Since the follow-up period of the included studies differed and some studies had more than 1 follow-up moment, the last follow-up moment of the study was used. For studies that added cognitive training to their program a few weeks after the start of the study, the last follow-up moment before the addition was used to investigate only the effect of exercise. In order to study the effect of the moderating variables type of exercise and type of control condition, studies were reclassified based on the type of exercise and type of control condition. Types of exercises were reclassified into 3 major domains: aerobic (eg, endurance training, cardiovascular exercises, treadmill walking), anaerobic (muscle strength training), and yoga. Studies using an aerobic exercise program but including anaerobic exercises to provide variation were classified as aerobic with an annotation of anaerobic training. Types of control conditions were reclassified into active (eg, schizophrenia patients playing table football, computer games or following occupational therapy) or passive (eg, healthy controls, schizophrenia patients included as waiting list or treatment as usual). See descriptive table for further details (supplementary table S2). When possible, moderator analyses for type of exercise and type of control condition were performed. For exercise, only aerobic and yoga exercise were compared because an insufficient number of studies examined the effect of only anaerobic exercise. Effect sizes were computed using Comprehensive Meta Analysis Version 2.0.[39] Per outcome measure, the magnitude and direction of effect was calculated for each individual study. Since most studies reported pre-exercise and post-exercise means and standard deviations, these values were used to compute the effect sizes. When possible, change scores were used instead of pre- and post-exercise scores in order to avoid overestimation of the true effect size because of pre-post intervention correlation. When means and standard deviations or change scores were not available, effect sizes were computed using exact *P*- or *t*-values. Hedges' g was used to quantify effect sizes of combined studies using a random effects model. A random effects model was used because of the variances in type and duration of applied exercise between studies, total duration of the study, and the limited number of studies for some outcome measures. Moreover, a random effects model allows generalization of the results on population level.[40] First, analyses were performed including all suitable studies per outcome measure. Subsequently, analyses were repeated by excluding outlier studies, defined as studies with an effect size that deviated more than 2 SDs from the mean weighted effect size.[41] Effect sizes with a *P*-value of <.05 were considered significant.

Furthermore, heterogeneity of results across studies was assessed by calculating the homogeneity statistic, I^2. I^2 describes the percentage of total variation across studies due to heterogeneity rather than chance. High heterogeneity (ie, $I^2 \geq 50\%$) makes interpretation of results unreliable.[42] Potential publication bias was first investigated by visual inspection of the funnel plots. An asymmetrical funnel plot indicates publication bias. Afterwards, the funnel plot asymmetry was tested with Egger's test with alpha of <.05 set as significance level (2-tailed).[43]

Results

The literature search yielded 61 quantitative studies (supplementary figure S1) that investigated the effect of any type of exercise on the outcome measures (supplementary table S2).[44–105] From these, 29 studies, investigating 1109 patients, were suitable to be included in the meta-analyses. The assessed methodological quality of all retrieved studies is shown in supplementary table S3.

Primary Outcome Measure: Clinical Symptoms

Fourteen studies, including 659 patients, examined the effect of exercise on total symptom severity (table 1).[56,61,62,64–66,75,76,85,90,94,96,99,101] Exercise showed a superior effect over active controls (8 studies, $N = 314$: Hedges' $g = .25$, $P < .05$), passive controls (8 studies, $N = 405$: Hedges' $g = .75$, $P < .001$), and an overall significant effect ($N = 719$: Hedges' $g = .39$, $P < .001$; figure 1) in reducing total symptom severity. Heterogeneity was high ($I^2 = 61\%$). The study by Visceglia et al[96] was considered an outlier (Hedges' $g = 2.08$) and excluded from the analysis. After exclusion, the overall (Hedges' $g = .37$, $P < .001$, table 1), and moderator based mean weighted effect sizes remained significant (active: Hedges' $g = .25$, $P < .05$; passive: Hedges' $g = .65$, $P < .001$). The effect size for comparison with passive and overall control group decreased slightly. The degree of heterogeneity among studies decreased, but remained high ($I^2 = 54\%$; table 1). Egger's test before and after excluding the outlier was nonsignificant indicating no publication bias.

The analysis of positive symptoms included 15 studies with a total of 641 patients (table 1).[45,50,56,61,65,66,74–76,79,85,90,94,96,101] Exercise was superior to active (9 studies, $N = 365$: Hedges' $g = .27$, $P < .05$), passive (9 studies, $N = 350$: Hedges' $g = .50$, $P < .05$), and overall controls in reducing positive symptoms ($N = 715$: Hedges' $g = .32$, $P < .01$; figure 2). Heterogeneity was high ($I^2 = 50\%$, table 1). No outliers were found. Egger's test was nonsignificant.

Regarding negative symptom scores, 18 studies could be retrieved, including a total of 765 patients (table 1).[45,50,56,59,61,65,66,74–76,79,85,90,92,94,96,101,102] Again, exercise turned out to be superior over active (10 studies, $N = 395$: Hedges' $g = .33$, $P < .01$), passive (12 studies, $N = 459$: Hedges' $g = .89$, $P < .001$), and overall controls in improving negative symptoms ($N = 854$: Hedges' $g = .49$, $P < .001$; figure 3). Heterogeneity among studies

Table 1. Overview Results for All Outcome Measures Showing Effect Size, 95% Confidence Interval, *P*-Value, and I^2

Outcome Measure	Studies (*N*)	Subjects/Patients (*N*)[a]	Hedges' *g*	95% CI	*P* Value	I^2 (%)
PANSS						
Total	14	659/659	.39	0.19–0.58	<.001	61
Total without outlier	13	641/641	.37	0.18–0.57	<.001	54
Positive	15	641/641	.32	0.14–0.50	<.01	50
Negative	18	765/765	**.49**	**0.31–0.67**	**<.001**	**60**
Negative without outlier	18	750/750	**.49**	**0.33–0.66**	**<.001**	**47**
General	10	436/436	**.27**	**0.04–0.50**	**<.05**	**58**
Quality of life						
Total	11	277/277	**.55**	**0.35–0.76**	**<.001**	**49**
Total without outlier	10	259/259	**.47**	**0.30–0.64**	**<.001**	**29**
QoL physical	9	238/238	**.50**	**0.11–0.89**	**<.05**	**63**
QoL physical without outlier	8	220/220	**.39**	**0.05–0.73**	**<.05**	**41**
QoL mental	9	197/197	.38	−0.06–0.82	.09	65
QoL mental without outlier	8	179/179	.33	−0.07–0.72	.10	47
QoL social	5	139/139	**.67**	**0.34–1.00**	**<.001**	**0**
QoL environmental	4	108/108	**.62**	**0.24–1.00**	**<.01**	**0**
Functioning	5	276/276	**.32**	**0.11–0.53**	**<.01**	**0**
Depression	7	316/296	**.71**	**0.33–1.09**	**<.001**	**79**
Depression without outlier	6	277/257	**.64**	**0.27–1.02**	**<.01**	**70**
Cognition						
Working memory	6	262/192	.23	−0.04–0.50	.09	49
Long-term memory	6	262/233	.14	−0.07–0.35	.19	14
Processing speed	4	201/180	.15	−0.10–0.40	.24	0
Attention and executive functioning	4	209/188	.07	−0.17–0.32	.55	59

Note: [a]Total number of subjects (patients in exercise group + control group with or without schizophrenia) / only number of schizophrenia patients (in exercise and control group). Bold values indicate significant effect sizes.

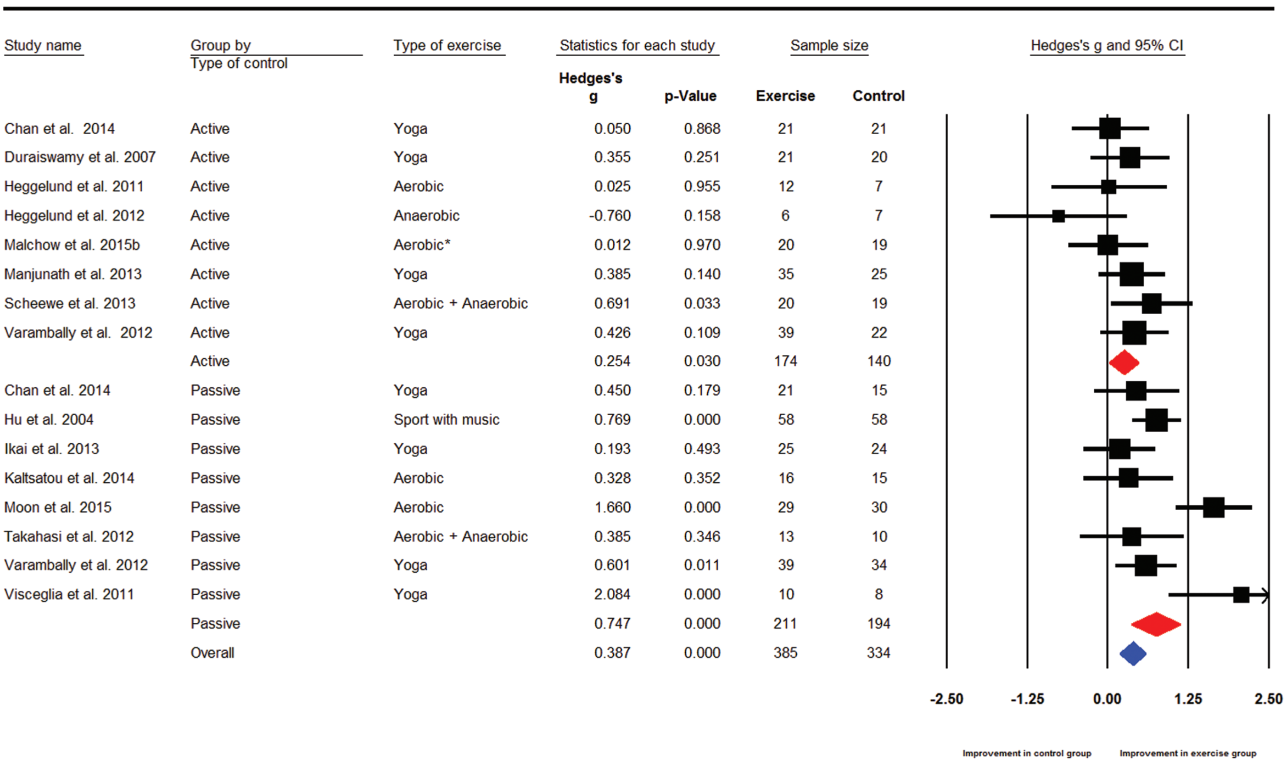

Fig. 1. Meta-analysis of the effect of exercise on total symptom severity. Effect sizes are grouped by the type of control patients as included in the individual studies. *With additional cognitive training.

Study name	Group by Type of control	Type of exercise	Statistics for each study Hedges's g	p-Value	Sample size Exercise	Control
Duraiswamy et al. 2007	Active	Yoga	0.249	0.418	21	20
Behere et al. 2011	Active	Yoga	0.400	0.193	27	17
Heggelund et al. 2011	Active	Aerobic	0.057	0.900	12	7
Varambally et al. 2012	Active	Yoga	0.315	0.235	39	22
Manjunath et al. 2013	Active	Yoga	0.423	0.106	35	25
Scheewe et al. 2013	Active	Aerobic + anaerobic	0.646	0.045	20	19
Oertel knochel et al. 2014	Active	Aerobic*	0.770	0.095	8	11
Malchow et al. 2015a	Active	Aerobic	-0.321	0.287	22	21
Malchow et al. 2015b	Active	Aerobic*	0.020	0.950	20	19
	Active		0.269	0.010	204	161
Acil et al. 2008	Passive	Aerobic	0.595	0.101	15	15
Behere et al. 2011	Passive	Yoga	0.018	0.949	27	22
Visceglia et al. 2011	Passive	Yoga	1.181	0.017	10	8
Varambally et al. 2012	Passive	Yoga	0.303	0.195	39	34
Takahasi et al. 2012	Passive	Aerobic + anaerobic	0.222	0.585	13	10
Ikai et al. 2013	Passive	Yoga	0.125	0.656	25	24
Kaltsatou et al. 2014	Passive	Aerobic	0.358	0.310	16	15
Oertel knochel et al. 2014	Passive	Aerobic*	0.129	0.775	8	10
Moon et al. 2015	Passive	Aerobic	1.693	0.000	29	30
	Passive		0.500	0.010	182	168
	Overall		0.321	0.001	386	329

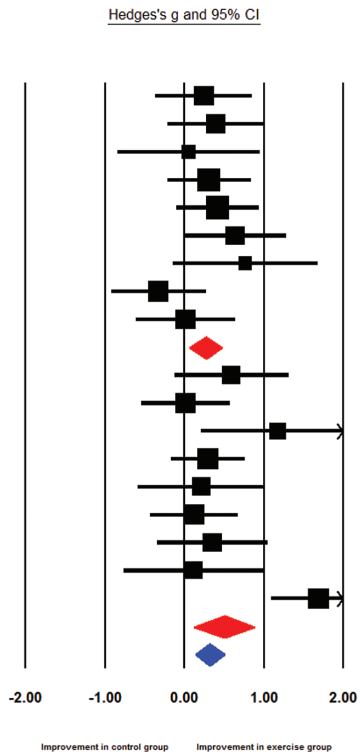

Fig. 2. Meta-analysis of the effect of exercise on positive symptoms. Effect sizes are grouped by the type of control patients as included in the individual studies. *With additional cognitive training

was high ($I^2 = 60\%$). The study by Gholipour et al[59] was considered an outlier (Hedges' $g = 2.40$). After removal, the effect size and significance level for the active control group and overall analysis remained unchanged. Effect size for the effect of exercise over passive control group decreased slightly with unchanged significance (Hedges' $g = .77$, $P < .001$). Heterogeneity among studies declined to moderate ($I^2 = 47\%$). Egger's test remained nonsignificant before and after exclusion of the outlier.

Concerning general symptom severity, the meta-analysis, including 10 studies with 436 patients studied,[61,65,66,74–76,90,94,96,101] showed an overall significant efficacy of exercise to controls in reducing general symptom severity. Heterogeneity was considered high ($N = 475$: Hedges' $g = .27$, $P < .05$, $I^2 = 58\%$; figure 4; table 1). The moderator analysis showed a superior effect of exercise compared to passive controls (6 studies, $N = 253$: Hedges' $g = .64$, $P < .01$), whereas no significant difference was found between exercise and active controls (5 studies, $N = 222$: Hedges' $g = .16$, $P = .24$). Egger's test showed no evidence for publication bias.

Additional moderator analyses for the type of exercise showed that both yoga and aerobic exercise were effective in reducing the total symptom severity (yoga: Hedges' $g = .44$, $P < .01$; aerobic: Hedges' $g = .59$, $P < .01$; supplementary figure S2; supplementary table S5), and positive symptoms (yoga: Hedges' $g = .31$, $P < .01$; aerobic: Hedges' $g = .43$, $P < .05$; supplementary figure S3; supplementary table S5). The significance of the effect sizes for total symptom severity remained unaffected after exclusion of the outlier study by Visceglia (supplementary table S5).[96] In addition, both yoga and aerobic exercise were comparable in reducing negative symptoms (yoga: Hedges' $g = .46$, $P < .001$; aerobic: Hedges' $g = .42$, $P < .05$; supplementary figure S4; supplementary table S5). Finally, yoga showed significant effect in reducing general symptoms, whereas aerobic exercise was nonsignificant (yoga: Hedges' $g = .44$, $P < .05$; aerobic: Hedges' $g = .39$, p=.14; supplementary figure S5; supplementary table S5).

Secondary Outcome Measures

Exercise turned out to be superior in improving QoL (Hedges' $g = .55$, $P < .001$; supplementary figure S6), global functioning (Hedges' $g = .32$, $P < .01$; supplementary figure S12), and reducing depression (Hedges' $g = .71$, $P = < .001$; supplementary figure S14). In the overall analysis, exercise was not superior to control conditions in improving any of the cognitive subdomains (Attention & executive functioning: Hedges' $g = .07$, $P = .55$; Processing speed: Hedges' $g = .15$, $P = .24$; Working memory: Hedges' $g = .23$, $P = .09$; Long-term memory: Hedges' $g = .14$, $P = .19$; supplementary figure S16–S19). However, moderator analyses for the type of exercise revealed a significant

Study name	Group by Type of control	Type of exercise	Statistics for each study: Hedges's g	p-Value	Sample size: Exercise	Control
Duraiswamy et al. 2007	Active	Yoga	0.533	0.087	21	20
Behere et al. 2011	Active	Yoga	0.438	0.155	27	17
Heggelund et al. 2011	Active	Aerobic	-0.327	0.475	12	7
Gholipour et al. 2012	Active	Exercise	1.206	0.002	15	15
Varambally et al. 2012	Active	Yoga	0.386	0.146	39	22
Manjunath et al. 2013	Active	Yoga	0.082	0.750	35	25
Scheewe et al. 2013	Active	Aerobic + anaerobic	0.475	0.135	20	19
Oertel knochel et al. 2014	Active	Aerobic*	0.014	0.974	8	11
Malchow et al. 2015a	Active	Aerobic	0.119	0.692	22	21
Malchow et al. 2015b	Active	Aerobic*	0.237	0.452	20	19
	Active		0.326	0.002	219	176
Acil et al. 2008	Passive	Aerobic	0.810	0.029	15	15
Behere et al. 2011	Passive	Yoga	0.663	0.023	27	22
Visceglia et al. 2011	Passive	Yoga	1.343	0.008	10	8
Gholipour et al. 2012	Passive	Exercise	2.395	0.000	15	15
Varambally et al. 2012	Passive	Yoga	0.498	0.035	39	34
Takahasi et al. 2012	Passive	Aerobic + anaerobic	0.233	0.567	13	10
Ikai et al. 2013	Passive	Yoga	0.393	0.166	25	24
Ulloa et al. 2013	Passive	Exercise	1.590	0.002	7	12
Kaltsatou et al. 2014	Passive	Aerobic	0.254	0.471	16	15
Oertel Knochel et al. 2014	Passive	Aerobic*	0.561	0.224	8	10
Moon et al. 2015	Passive	Aerobic	1.475	0.000	29	30
Nath et al. 2015	Passive	Exercise	1.071	0.000	30	30
	Passive		0.886	0.000	234	225
	Overall		0.491	0.000	453	401

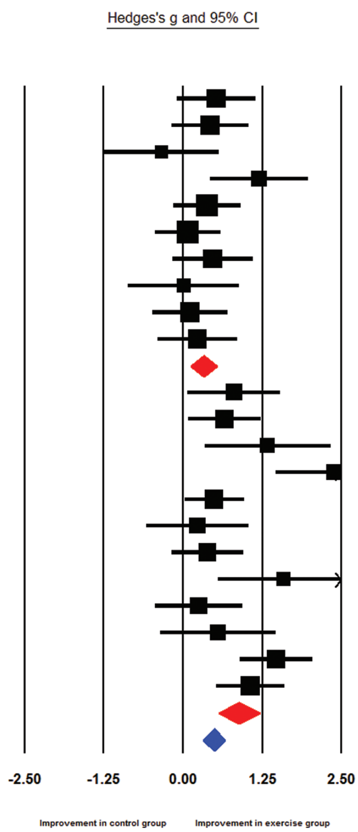

Fig. 3. Meta-analysis of the effect of exercise on negative symptoms. Effect sizes are grouped by the type of control patients as included in the individual studies. *With additional cognitive training.

Study name	Group by Type of control	Type of exercise	Statistics for each study: Hedges's g	p-Value	Sample size: Exercise	Control
Heggelund et al. 2011	Active	Aerobic	0.219	0.631	12	7
Varambally et al. 2012	Active	Yoga	0.226	0.391	39	22
Manjunath et al. 2013	Active	Yoga	0.386	0.139	35	25
Malchow et al. 2015a	Active	Aerobic	-0.194	0.517	22	21
Malchow et al. 2015b	Active	Aerobic*	0.098	0.754	20	19
	Active		0.160	0.235	128	94
Visceglia et al. 2011	Passive	Yoga	1.729	0.001	10	8
Varambally et al. 2012	Passive	Yoga	0.541	0.022	39	34
Takahasi et al. 2012	Passive	Aerobic + anaerobic	0.452	0.272	13	10
Ikai et al. 2013	Passive	Yoga	0.021	0.940	25	24
Kalsatou et al. 2014	Passive	Aerobic	0.137	0.697	16	15
Moon et al. 2015	Passive	Aerobic	1.272	0.000	29	30
	Passive		0.635	0.009	132	121
	Overall		0.272	0.021	260	215

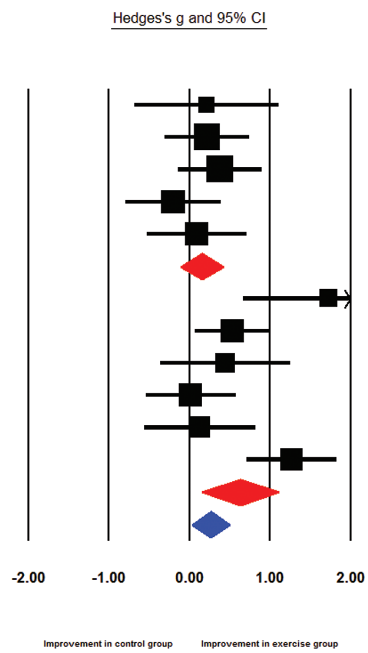

Fig. 4. Meta-analysis of the effect of exercise on general symptoms. Effect sizes are grouped by the type of control patients as included in the individual studies. * With additional cognitive training.

effect of yoga in improving the cognitive subdomain long-term memory (Hedges' $g = .32$, $P < .05$; supplementary figure S20; supplementary table S5).

Detailed results on the secondary outcome measures are shown in the supplementary materail.

Discussion

The aim of this study was to quantitatively review all available controlled trials on the efficacy of physical exercise in patients with a schizophrenia spectrum disorder. Twenty-nine studies, providing data on 1109 patients, were included in the analyses. Results showed an overall significant effect of exercise on clinical symptoms with medium effect sizes for total and negative symptoms, and small effect sizes for general and positive symptoms. Interestingly, only yoga showed significance in improving general symptoms, while both yoga and aerobic exercise were effective in reducing the total symptom severity, and positive and negative symptoms. In addition, both yoga and aerobic exercise showed a similar effect in improving QoL. Furthermore, exercise was beneficial in improving global functioning and depressive symptoms. Notably, evidence points more towards the beneficial effect of yoga in improving global functioning, and reducing depressive symptoms. Exercise in general showed a trend towards significance in improving the cognitive subdomain processing speed, while no effect on the other cognitive subdomains was demonstrated. However, a positive effect of yoga on the cognitive subdomain long-term memory and a trend towards significance for the subdomain attention and executive functioning were observed.

Previous work examining the contribution of psychiatric symptoms to functional outcome reveals that negative symptoms are significantly associated with functional outcome in schizophrenia,[3,5,106,107] while positive symptoms are less strongly correlated with functional impairment.[5,108] Moreover, negative symptoms are related to neurocognition and thereby also indirectly affect the outcome by mediating the relationship between neurocognition and outcome.[5,108] A reduction of negative symptoms in patients with schizophrenia can be achieved by participating in exercise, while antipsychotics have no effect on these symptoms.[109] A 2011 Cochrane review by Gorczynski and Faulkner[110] including 3 randomized controlled trials (RCT) found significant effect of exercise on negative symptoms, but not on positive symptoms.[110] However, since then many controlled studies have been conducted that provide evidence for beneficial effects of physical exercise on clinical symptoms in schizophrenia spectrum disorders.[50,59,61,62,65,66,74–76,79,85,90,92,94,96,99,101,102] These individual studies are included in the present meta-analyses. Therefore, the present quantitative review including 29 studies shows highly significant effect of physical exercise on both positive and negative symptoms when compared to the control situation.

Type of Exercise

The present meta-analyses show beneficial effects of both aerobic exercise and yoga on most outcomes measured, with better results for yoga in several occasions. Physical exercise in schizophrenia reduces psychological distress and state anxiety, while yoga, specifically, has been proposed to reduce positive and negative symptoms.[111] Eight studies included in the meta-analyses investigated yoga. All these studies applied the same type of yoga program consisting of *asanas* (ie, postures or exercise as standing, twisting, sun salutation, balance, joint rotations), pranayama (ie, breathing exercises), and relaxation exercises. None of the studies included meditation teachings in their yoga program.

Besides, exercise variables such as frequency, intensity, session duration, total intervention duration, and either or not supervision is present are nontrivial factors than can shape exercise in a way that is most effective for a specific patient group. In the present study, exercise sessions ranged from 16 minutes once[63] to 360–720 minutes per week.[90] The total intervention duration ranged from 3 weeks[51] to 8 months,[66] and were shortest for studies investigating yoga. The total intervention duration in most studies was around 12 weeks. For aerobic exercise, mostly 90–120 minutes of exercise per week were devoted, which is in line with the recommended amount of time patients with schizophrenia are advised to engage in physical exercise.[112] Although, the American College of Sports Medicine (ACSM) recommends a moderate-intensity cardiorespiratory exercise training of 150 minutes per week in adults.[113] This indicates that the current exercise interventions may not be sufficient in the present patient population. However, (normally inactive) persons (eg, schizophrenia patients) can also benefit from less amounts of exercise than recommended by the ACSM.[113] On the other hand, almost all studies in the meta-analyses made use of group exercise under supervision as is also recommended by the ACSM.[113] Group exercises are cost-effective and aid in the development of sense of relatedness.[112] Therefore, qualitative assessment of the present data recommends clinicians to implement supervised group exercise programs of at least 30min/day, 3 times per week for minimally 12 weeks, but to consider long-term continuation for more robust effects.

Strengths, Limitations, and Recommendations

The greatest strength of the present study is that it provides an up-to-date, and extensive quantitative and qualitative overview of the literature regarding the efficacy of different exercise interventions in schizophrenia. A previous meta-analysis by Firth and colleagues[114] on the same topic as the present study showed only beneficial effect of exercise in reducing positive and negative symptoms.[114] However, Firth et al investigated only English peer-reviewed RCTs, and excluded studies investigating yoga and/or combined weight reduction and exercise programs as intervention. The present study, however, included all the studies meeting these criteria and, therefore, was able to perform meta-analyses in several clinical outcome measures. Furthermore, the present study showed that the best results of exercise are seen in the yoga intervention groups. These results are one of the main differences with the study by Firth et al. Furthermore, the current study aimed to compare exercise with both active and passive types of control conditions and showed that exercise has greater efficacy in improving various outcome measures. The study by Firth et al[114] pooled data from studies with more than 2 non-exercise groups[114] and therefore couldn't compare exercise with different types of control conditions. Finally, the present study also included uncontrolled studies on exercise to provide a comprehensive qualitative overview of the results found in these studies, whereas Firth and colleagues excluded these type of studies.[114] These key differences with the study by Firth et al[114] emphasize the strength of the present results.

This study has also some limitations. First, only 6 studies could be included in the cognitive meta-analyses, so that the overall effect of exercise on cognition was underpowered and therefore not fully reliable. However, the results of the studies on cognition that could not be included also showed beneficial effect of exercise (supplementary table S4). Second, publication bias is an important possible drawback in meta-analytical studies. To take this into account, funnel plots were visually inspected and the funnel plots asymmetry was tested with Egger's test. However, none of the inspected and tested funnel plots showed asymmetry, increasing the validity of the found results. Third, an insufficient number of studies examined the effect of only anaerobic exercise, making a moderator analysis for this group not feasible. On the other hand, previous findings regarding the inefficacy of anaerobic exercise on brain functioning support its inferiority to other types of exercise.[114]

For future research into the efficacy of exercise in patients with schizophrenia spectrum disorders, a few methodological concerns should be taken into account. First, at least 2-arm studies should be performed instead of single-arm studies. Second, the use of an active control condition matched for time and personal contact is recommended. Blinded assessment of outcome measures, making use of standardized questionnaires and cognitive batteries are also recommendable,[108] applying supervised interventions to decrease drop-out rates,[115] and providing full data on type of exercise and associated program variables used. By this, homogeneity of studies will be increased and findings will be more robust and generalizable.

Conclusion

Exercise in patients with schizophrenia spectrum disorders has beneficial effects on clinical symptoms, QoL, global functioning, and depressive symptoms, with notably evidence for yoga in improving clinical symptoms, depression, and global functioning. In addition, yoga may have a positive effect on cognition, while no overall effect of exercise could be shown for cognition. Qualitative assessment of data recommends clinicians to implement supervised group exercise programs of at least 30min/day, 3 times per week for minimally 12 weeks, but to consider long-term continuation for more robust effects.

Supplementary Material

Supplementary material (references 116–152 are cited in the supplementary material) is available at http://schizophreniabulletin.oxfordjournals.org.

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