A systematic review of cognitive effects of exercise in depression

Natascia Brondino[1*], Matteo Rocchetti[1], Laura Fusar-Poli[1], Erwan Codrons[2], Luca Correale[2], Matteo Vandoni[2], Corrado Barbui[3], Pierluigi Politi[1]

1. Department of Brain and Behavioral Science, University of Pavia, Pavia, Italy
2. Laboratory of Adapted Motor Activity, Department of Public Health, Experimental Medicine & Forensic Science, University of Pavia, Pavia, Italy.
3. WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, Section of Psychiatry, University of Verona, Verona, Italy

* corresponding author. Address correspondence to: Natascia Brondino, Department of Brain and Behavioral Science, University of Pavia, Via Bassi 21, 27100, Pavia, Italy. Telephone: +39 0382 987246; email: natascia.brondino@unipv.it

Running title: effect of exercise on cognition in depression

Abstract

Objective: The aim of the present systematic review and meta-analysis is to evaluate the impact of physical exercise on cognitive symptoms in depressed adult patients.

Methods: Systematic literature search was performed in Web of Science™ and CINAHL from inception to August 2016. Two reviewers independently selected randomized trials evaluating the effect of exercise on cognitive functions in patients with a validated diagnosis of depression. Outcome measures included global cognition and different cognitive domains (speed of processing, attention/vigilance, working memory, verbal and visual memory, reasoning).

Results: Eight trials met inclusion criteria (637 patients). A fixed-effects model showed absence of beneficial effect on global cognition (Hedges'g = 0.07, 95% CI -0.08 to 0.24, I^2=0%) as well as on specific cognitive domains. Sensitivity analyses did not show an impact of exercise in studies with shorter intervention duration compared to longer trials (between group heterogeneity Q = 3.564, df = 1, p = .059), single session per week compared to multiple sessions (Q = 2.691, df = 1, p = .101) and low exercise intensity compared with moderate/high intensity (Q = 2.952, df = 1, p = .086).

Conclusion: Our meta-analysis did not observe a substantial benefit of physical exercise on cognitive symptoms in depression.

PROSPERO registration number: CRD42016048131

Keywords

Exercise; depressive disorder; cognition; meta-analysis

Summations

1.	Physical exercise did not improve cognition in major depressive disorder
2.	Duration of the intervention, number of sessions per week and intensity of exercise did not impact the outcome

Considerations

1.	None of the selected studies acknowledged the presence of subjective complains of cognitive dysfunction in the included patients
2.	Cognition was frequently investigated as a secondary outcome, thus the included studies may suffer from lack of power

Introduction

Depression has become a major health concern worldwide. Recent estimates report that 350 millions of people in the world suffer from depression (1) and that this figure is going to increase even further in the next few decades. The presence of mood disorders determines a significant impairment in everyday living, particularly in social functioning, work productivity and rate of unemployment and absenteeism (2). As a result, depression was rated as the second cause of years lived with disability worldwide in 2010 (3).

Major Depressive Disorder (MDD) is frequently associated with cognitive deficits. Cognitive dysfunction in MDD may affect several domains, ranging from memory to executive functions, from vigilance to verbal abilities (4, 5). Cognitive impairment is present during the acute phase of the illness but may persist even during remission (6). In fact, cognitive dysfunction in MDD is particularly relevant for the long-term outcome and the functional adjustment of each patient (7). Additionally, antidepressant treatment is not highly effective in reducing cognitive symptomatology: a recent large randomized trial reported that antidepressants do not improve cognition in the acute phase of MDD, even if clinical depressive symptoms remitted (8). Previous studies have shown only a modest effect of antidepressants and in a few cognitive domains (such as verbal learning) (9).

Non-pharmacological interventions, such as psychotherapy or cognitive remediation therapy, have not been extensively studied as potential treatment for cognitive symptoms of MDD (9). Some evidence suggests a potential small cognitive effect for cognitive remediation therapy or cognitive behavioral therapy, but data are still sparse and controversial (10). Among non-pharmacological intervention, the use of physical exercise in fighting symptoms of depression has recently gained attention. A meta-analysis from Kvam, Kleppe (11) reported a significant effect of physical exercise in alleviating depressive symptoms with a moderate to large effect size. Of note, the positive effect of exercise was observed against different comparison conditions (no intervention or waiting-list or usual care) and exercise exerted a similar impact on affective symptoms compared to psychological or pharmacological treatment. In line with these findings, Schuch, Vancampfort (12) observed a larger beneficial effect of exercise in depression after accounting for the presence of publication bias. The most recent Cochrane Review reported a modest effect of exercise on symptoms of depression, as in the more methodologically robust trials exercise exerted only a smaller effect on depressive symptomatology (13).

One possible explanation for the efficacy of physical exercise in depression is linked to its biological correlates: in fact, in healthy adults, acute exercise determines an increase in serotonin serum levels (14) which are altered in depression (15). Additionally, as suggested by animal models, physical exercise may promote synaptic plasticity in the hippocampus through the brain derived neurotrophic factor (BDNF) (16). Furthermore, in MDD, BDNF levels are reduced in several brain areas (the hippocampus, the amygdala and the prefrontal cortex), leading to neuronal loss (17). Exercise promotes an increase in BDNF levels in healthy volunteers; this increase is in turn correlated with a positive impact on cognition (18).

Physical exercise has been associated with improved cognition in individuals suffering from mild cognitive impairment (19), in dementia (20) as well as in healthy subjects (21, 22). In fact, exercise, especially aerobic exercise, has been related to significant increase in grey matter in the frontal and the left superior temporal lobes as well as in white matter tracts within the anterior third of the corpus callosum (23). Additionally, functional imaging studies have detected an increased activation in the middle frontal gyrus and superior parietal cortex (which are involved in attention and inhibitory control) in older adults who underwent an aerobic exercise training (24).

A number of studies investigated the effect of exercise on cognitive dysfunction in depressed patients. However, study findings are controversial and partly inconsistent (25, 26). To the best of our knowledge, no quantitative synthesis has been conducted to evaluate cumulative effects of exercise on cognition.

Aims of the Study

Based on these premises, the aim of the present study is to assess whether physical exercise improves global cognition or specific cognitive domains in patients with depression. We conducted a systematic review and meta-analysis of randomised controlled trials in adult patients with depression.

Material and Methods

The present meta-analysis has been conducted according to the PRISMA statement (27). The review protocol was registered with PROSPERO (International database of prospectively registered systematic reviews in health and social care): CRD42016048131.

Search Strategy

Two authors (NB and LF) conducted a search from inception to August 2016 in Web of Science™ (including KCL Korean Journal Database, MEDLINE®, Russian Science Citation Index, and SciELO Citation Index) and CINAHL. We used the keywords ("exercise", "cognition", "randomized", "depression") and related MESH terms combined with Boolean operators. The details of the search strategy for each database are reported in Supplementary Material. All terms were searched individually in each database and then combined together. Additionally, reference lists from all the recovered papers were hand-searched for further relevant references. Furthermore, we performed a search of potential unpublished data on ClinicalTrials.gov.

Eligibility Criteria

We selected all randomized controlled trials yielding data on cognitive outcomes of physical exercise interventions for patient suffering from MDD. Inclusion criteria were as followed: randomized controlled studies; the effects of physical exercise on validated cognitive measures were investigated; physical exercise was compared with no physical exercise, a waiting list, treatment as usual, usual care, repeated assessment, or a minimal attention control group akin to psychological placebo; participants were adults (18 years or above) with a primary diagnosis of MDD according to DSM-III, DSM-IV, DSM-IV-TR or ICD-9, ICD-10 (both in acute phase or in remission). Considerable care was taken to exclude duplicate publications.

For the purpose of this review, exercise was defined according to the American College of Sports Medicine (28) as “a type of physical activity consisting of planned, structured, and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness”. This definition includes both aerobic (e.g. running, walking or cycling) and anaerobic activity (e.g. weight-lifting, climbing or isometric exercises). According to the ACSM definition, interventions using yoga or tai-chi were considered physical exercise and included in the analysis. To be more inclusive, we considered also studies in which physical exercise was used as an augmentation strategy for other conventional treatments (i.e. antidepressants or psychotherapy).

The control comparison group includes a broad range of cases, such as waiting list, relaxation, or treatment as usual.

Data Extraction

Two independent researchers (NB and MR) examined all titles and abstracts, and obtained full texts of potentially relevant papers. Working independently and in duplicate, NB and MR read the papers and determined whether they met inclusion criteria. Initial agreement between reviewer was high (k=.98). Any discrepancy was then solved by consensus. The risk of bias was assessed using the Cochrane risk of bias tool (29). The following items were considered: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other source of bias (e.g. potential conflict of interest). Initial agreement between the reviewers was high (k=.85); any disagreement was solved by discussion.

Outcomes

The primary outcome of interest was global cognition. Global cognition was defined as the average change in all cognitive measures employed in the included studies, according to Firth, Stubbs (30). When data from multiple single tasks for each cognitive domain were present, we calculated a mean score for each single domain. If studies reported only changes in individual cognitive domains or tasks, we calculated a global score using the mean changes in the cognitive domains reported.

Our secondary outcome was to study the effect of exercise on single cognitive domains. As for global cognition, when data from multiple single tasks for each cognitive domain were present, we calculated a mean score for each single domain.

Cognitive domains were categorized according to the criteria of the NIMH-MATRICS Neurocognition Committee and to the components of the MATRICS Consensus Cognitive Battery (MCCB) (31), as follows: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving (see Supplementary Material). The MCCB is considered valid and reliable in MDD (32). If a cognitive task reported in a study was not part of the MCCB, the task was inserted in the appropriate cognitive domains according to a previous review (33).

Statistical Analyses

For continuous outcomes, we pooled the standardised mean differences (SMDs) as different measurement scales were used. Because some studies had relatively small sample sizes we corrected the effect size for small sample bias, using Hedge's g.

In studies with multiple treatment groups the sample size of the comparison group was halved following standard Cochrane methodology (29). Heterogeneity between studies was determined using Cochrane's Q and I^2 values. Thresholds for the interpretation of heterogeneity were consistent with those of the Cochrane Collaboration (I^2 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to

100%: considerable heterogeneity) (34). A fixed-effects model was used if heterogeneity was moderate or less, otherwise a random effects model was applied. The overall effect in the fixed-effects model was calculated according to the DerSimonian-Laird method (35). According to Rosenthal (36), we adopted a pre-post correlation coefficient of 0.7, if not reported in the original article, to compute the SMD. The robustness of our findings was tested against publication bias by funnel plot visual inspection. Furthermore, we used the Trim and Fill method (37) to adjust the results according to unpublished studies. Furthermore, we conducted several sensitivity and subgroup analyses in order to evaluate the impact of moderators on pooled effect sizes and to test the strength of our assumptions (see below). All analyses were performed using Comprehensive Meta-Analysis 2.0 (38). The database used for calculation has been appended as Supplementary Material.

Sensitivity and subgroup analyses

Firstly, we performed an influence plot analysis by removing each study in order to identify possible outliers. Secondly, we performed a sensitivity analysis to find the level of pre-post data correlation needed to change the level of significance of the results (more or less than $p = .05$). Furthermore, we subdivided our sample according to median follow-up duration, level of physical exercise intensity according to American College of Sports Medicine (28), and number of sessions per week according to World Health Organization (1) and we calculated subgroup analyses for all the aforementioned variables.

Results

Search Results

The literature search identified 4734 publications (Web of Science® N = 3814; CINAHL N = 916; hand search N =4). After title/abstract screening, 114 publications were obtained for detailed evaluation and reasons for exclusion were reported in PRISMA diagram (Figure 1). Eight individual studies were deemed eligible for inclusion (25, 39-45). The main characteristics of the included studies are shown in Table 1.

@@@ Figure 1 about here @@@

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Characteristics of the included studies

In total 637 patients with depression were included in the selected studies and 365 were randomized to physical exercise. The mean age was 46.5 years (range = 18–72 years) and the samples were mostly composed by females (68.9%). Six out of eight studies used the Hamilton Depression Scale-17 item to evaluate symptom severity at baseline. The mean score at HAM-D was 16.35 in the overall dataset (ranging from 9.01 to 20.37 in the single studies). Median duration of follow-up was ten weeks. Number of sessions per week ranged from one to three. Four studies used aerobic exercise, three used mind-body interventions (such as tai-chi) and two anaerobic exercise. A comprehensive summary of the data is reported in Table 1.

Risk of bias assessment of the included studies

A summary report of the risk of bias is presented as Supplementary Material - Figure 1. According to the Cochrane Collaboration's tool (29), we defined a study as having an overall "high risk of bias", if it was judged as having a high risk in at least one out of six domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting). Low risk of bias was assigned if a study scored as low risk in all the domains. Six studies had adequate random sequence generation (25, 40-44), while the other two did not provide sufficient information and so they were rated as unclear (39, 45). Only four trials had adequate allocation concealment (25, 40-42). Given the nature of the intervention, all studies could not have achieved the blinding of participants and personnel. However, blinding of outcome assessors was reported in six studies (25, 39-42, 44). Attrition bias was observed in three of the included studies (39, 43, 44) while selective reporting was detected in two trials (25, 42). According to the Cochrane Collaboration's tool all the included studies should be considered at "high risk of bias".

Meta-Analysis of the effect of physical exercise on global cognition and single cognitive domains

The meta-analysis of the primary outcome (eight studies, 637 patients) revealed no significant effect of physical exercise on global cognition in patients suffering from MDD (*Hedges'g* = 0.07, 95% CI -0.08 to 0.24, p = .36; Q = 6.13, df = 8, p =.63, I^2=0%). The funnel plot inspection did not suggest publication bias and the Trim and Fill procedure did not change the results. No significant effect of physical exercise was detected in the speed of processing domain (g = 0.05, 95% CI -0.12 to 0.23, p = .53; Q = 6.55, df = 6, p = .36, I^2 = 8.43%), in the attention/vigilance domain (g = 0.06, 95% CI -0.11 to 0.23, p = .50; Q = 4.54, df = 6, p =.60, I^2 =0%), in the working memory domain (g = -0.02, 95% CI -0.09 to 0.25, p = .38; Q = 2.38, df = 5, p = .79, I^2 =0%), in the verbal learning and memory domain (g = 0.05, 95% CI -0.13 to 0.23, p = .60; Q = 7.01, df = 5, p = .22, I^2 = 28.71%), in the visual learning and memory domain (fixed effects model g = 0.24, 95% CI 0.01 to 0.48, p = .05; Q = 9.43, df = 3, p = .02, I^2 = 68.18%; random effects model g = 0.23, 95% CI -0.22 to 0.68, p = .32) and in the reasoning and problem solving domain (g = -0.07, 95% CI -0.26 to 0.12, p = .47; Q = 2.05, df = 4, p = .73, I^2 = 0%). Of note, exercise exerted a positive effect on visual learning and memory that disappeared using a random effects model to correct for the presence of substantial heterogeneity. The impact of physical exercise on global cognition and on individual cognitive domains is depicted in Figure 2.

@@@ Figure 2 about here @@@

Supplementary Analysis

By removing each study from the overall effect size, we did not find any significant difference in our results. We also tested the level of pre-post data correlation needed to reach a statistic significance on the overall global cognitive effect size. A nearly perfect correlation between pre and post data would have been needed to obtain a statistical significant result (r= .99).

As a priori stated, we decided to explore the effect of three moderators with three subgroup analyses. No significant difference was detected dividing the studies according to exercise intensity (low vs moderate-high intensity, between groups heterogeneity: Q = 2.95, df = 1, p = .09; see Supplementary Material - Figure 2), median duration of follow-up (≤10 weeks vs > 10 weeks duration, between groups heterogeneity: Q = 3.56, df = 1, p = .06; see Supplementary Material -Figure 3), or the number of weekly sessions (single vs multiple sessions per week, between groups heterogeneity: Q = 2.69, df = 1, p = .10, see Supplementary Material - Figure 4). However, a trend towards a more positive impact of low intensity exercise as well as short follow-up duration could be observed.

Discussion

The present meta-analysis was performed in order to evaluate the effect of physical exercise on cognitive symptoms in depression. Eight studies were included in the analysis: surprisingly, pooled effects sizes did not show an effect in favor of exercise. These results are in contrast with literature data showing positive effect of physical exercise on cognition in other psychiatric disorders such as schizophrenia (30). Influence plot analysis confirm the assumption that including different types of control comparison (such as waitlist, relaxation, treatment as usual, stretching) did not affect our results. Our subgroup analyses showed that the number of sessions per week, the duration of the follow-up and the intensity of the exercise did not change the null effect of exercise on cognition in patients diagnosed with MDD. However, the effect of low intensity exercise and shorter follow-up duration bordered significance. It could be hypothesized that a low number of exercise sessions per week as well as shorter follow-up might be more easily attended by patients with depressive symptomatology, thus resulting in a better outcome compared to a higher frequency of engagement (which could actually lead to high drop-out rate and reduced attendance with loss of beneficial effects). This is in line with the findings from Callaghan, Khalil (46): they observed that the possibility to choose the intensity of exercise was correlated with a reduction in depression severity. Additionally, selected studies with low intensity exercise included also tai-chi (42), yoga (45) and a mind-body intervention (39). These methods comprise not only physical exercise but also additional aspects such as meditation or breathing techniques which could exert additional benefits for the brain (47).

There are several aspects that should be taken into consideration before drawing definite conclusions on the efficacy of exercise on cognitive symptoms in depression. Firstly, some studies included in the analysis were part of larger randomized trials (25) or evaluated cognition as a secondary outcome measure (40, 41, 43, 48). As a consequence, these studies could be potentially underpowered to detect a significant difference in cognitive function between exercise and comparison group. Secondly, none of the included studies recruited patients complaining for subjective cognitive dysfunction at baseline. Furthermore, baseline severity of depressive symptoms as assessed by Hamilton Depression Rating Scale-17 items was low: in fact, a total score of 24 is generally used to differentiate moderate from severe depression (49). None of the selected studies exceeded this cut-off and patients were rated as having mild to moderate depression. As the severity of depressive symptomatology has been associated with worse cognitive impairment (50), it could be hypothesized that the patients included in the selected studies were only slightly impaired in their cognitive function and consequently may have displayed a small potential for improvement. For instance, in the studies from Lavretsky, Alstein (42)and Hoffman, Blumenthal (25) depressed patients had baseline scores on cognitive outcome similar to the general population according to normative values. Accordingly, a meta-analysis from Smith, Blumenthal (22) have shown that cognitive improvement was greater in patients suffering from Mild Cognitive Impairment than in non-cognitively compromised adults. Besides, a recent study from Greer, Grannemann (51) observed a possible cognitive effect of two different physical exercise intensities in MDD patients complaining cognitive symptoms at baseline. Even though this study did not include an inactive comparison group and this datum need to be considered with caution, we cannot exclude the relevance of a subjective perception of cognitive symptoms on the effect observed. This could question the sampling procedure of the studies included in the present meta-analysis and the generalizability of our results: the population of patients diagnosed with MDD complaining for cognitive symptomatology could be under-represented in the studies published so far.

In addition, our results may reflect heterogeneity of patients' response to exercise: a recent study (52) reported that only men with a specific polymorphism in the *BDNF* gene (Val66Met rs6265) showed a beneficial effect of physical exercise on somatic symptoms of depression. The presence of subgroups of patients responding positively to exercise may determine an important heterogeneity in response to physical activity and may involve also the cognitive domain.

Finally, some methodological aspects of physical exercise interventions of the selected studies should be discussed. Almost all studies complied with the WHO recommendations World Health Organization (1) which suggest at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or muscle-strengthening exercises on 2 or more days a week. However, it could be hypothesized that patients with depressive symptomatology may have difficulties in attending this prescribed schedule. In fact, drop-out rate for physical activity treatment in patients with depression are usually quite high, around 30% (53). Reasons for dropping-out are usually connected to lack of time (53) or unpleasant feelings connected with high imposed intensity exercise (54, 55). According to the ACSM guidelines, all studies having aerobic exercise as the active treatment used vigorous intensity. As a result, we observed a highly variable attrition rate in the included studies, ranging from 33% (39) to 11% (42, 43). Additionally, even in studies with low drop-out rate, mean attendance was one session per week instead of the required two or three per week (40, 41). Even though our subgroup analyses could only detect a not statistically significant trend towards more beneficial effect of exercise in low intensity exercise and shorter follow-up duration, it has been shown that the positive effect on specific cognitive domains in depressed patients could be related to the amount of physical exercise (51).

There are some limitations of our meta-analysis that should be taken into consideration. Firstly, even though our search was systematic and rigorous, we could have missed eligible studies inadvertently. Another potential limitation, inherent to the meta-analytic approach, is connected to the presence of clinical heterogeneity which could not be controlled as for statistical heterogeneity. Even if we tried to reduced clinical heterogeneity by selecting patients with a standardized diagnosis of MDD, we could not account for the presence of individual as well as genetic differences between patients. Additionally, we pooled together data from different cognitive measures belonging to specific cognitive domains. These cognitive tasks may vary in their ability to detect changes and in their reliability. Thus, our results could be partly attributed to the different psychometric characteristics of pooled cognitive tasks.

In conclusion, our meta-analysis was not capable of finding a substantial benefit of physical exercise on cognitive symptoms in depression. However, there are several methodological issues that could have hampered the possibility of finding an effect in this patient group. Above all, it is surprising that all the included studies did not consider to specifically investigate the present of subjective cognitive complains at baseline. Furthermore, none of the studies investigated patients with severe depression. Larger randomized studies focusing on the impact of physical exercise on cognition in depression should be designed in order to share more light on these issues. Nonetheless, the beneficial effect of exercise on affective symptoms as well as on general health status of depressed subjects is well known and physical activity is recommended as initial treatment in mild to moderate depression according to the NICE guidelines for depression (2009).

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Declaration of Interest

None of the authors reported any conflict of interest

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Table 1. Summary of the articles included in the meta-analysis

Author	Year	Sample size	Study design	Treatments	Outcome measure	Findings
Chan et al.	2012	75 MDD patients	Randomized, single blind, three arms (mind-body intervention, CBT, waiting list)	Waiting list, N = 16, age range: 31-62 years, 4M/12F; CBT, N = 17, age range: 34-57 years, 4M/13F; Mind-body, N = 17, age range:32-62 years, 2M/15F)	DVT, EEG, BDI-II	Positive effect of exercise
Hoffman et al.	2008	202 MDD (mean age 51.7 ± 7.6; 49M/153F, drop-out N = 42)	Randomized, parallel arm, partly single blind partly double blind	Aerobic exercise (N = 104, mean age:51 ± 7, 26M/78F), three sessions/week for 16 weeks, at 70-80% heart rate (HR) measured during a maximal test Sertraline (N = 49, mean age:51.8 ± 7.7, 12M/37F, drop-out = 7) minimum dose 50 mg titrated up to 200 mg Placebo (N = 49, mean age:51.2 ± 7.8, 11M/38F)	AN, COWAT, DS, DSF, DSB, R27T,ST-IC, TMT-A and -B, VPA from the Wechsler Memory Scale (WMS), LM from the WMS	Exercise was not superior to placebo, however beneficial effect of exercise on executive function compared to sertraline were observed
Krogh et al.	2009	165 MDD (mean age 38.9 ± 9.46; 43M/122F, drop-out N = 28)	Randomized, parallel arm, single blind	Aerobic exercise (N = 55, mean age:38.1 ± 9, 12M/43F, drop-out = 7), two 90 min sessions/week, treadmill, rowing, running or cycling till 89% heart rate (HR) measured during a maximal test Strength exercise (N = 55, mean age:41.9 ± 8.7, 10M/45F, drop-out = 8), two 90 min sessions/week, progressive increasing machine work till 75% of maximum strength Relaxation training (N = 55, mean age:36.7 ± 8.7, 21M/34F, drop-out = 13), two 90	DSB, DSF, SS7, TMT-A and -B, DS, AN, BT, RCFT	No effect on symptom severity Follow-up till 12 months

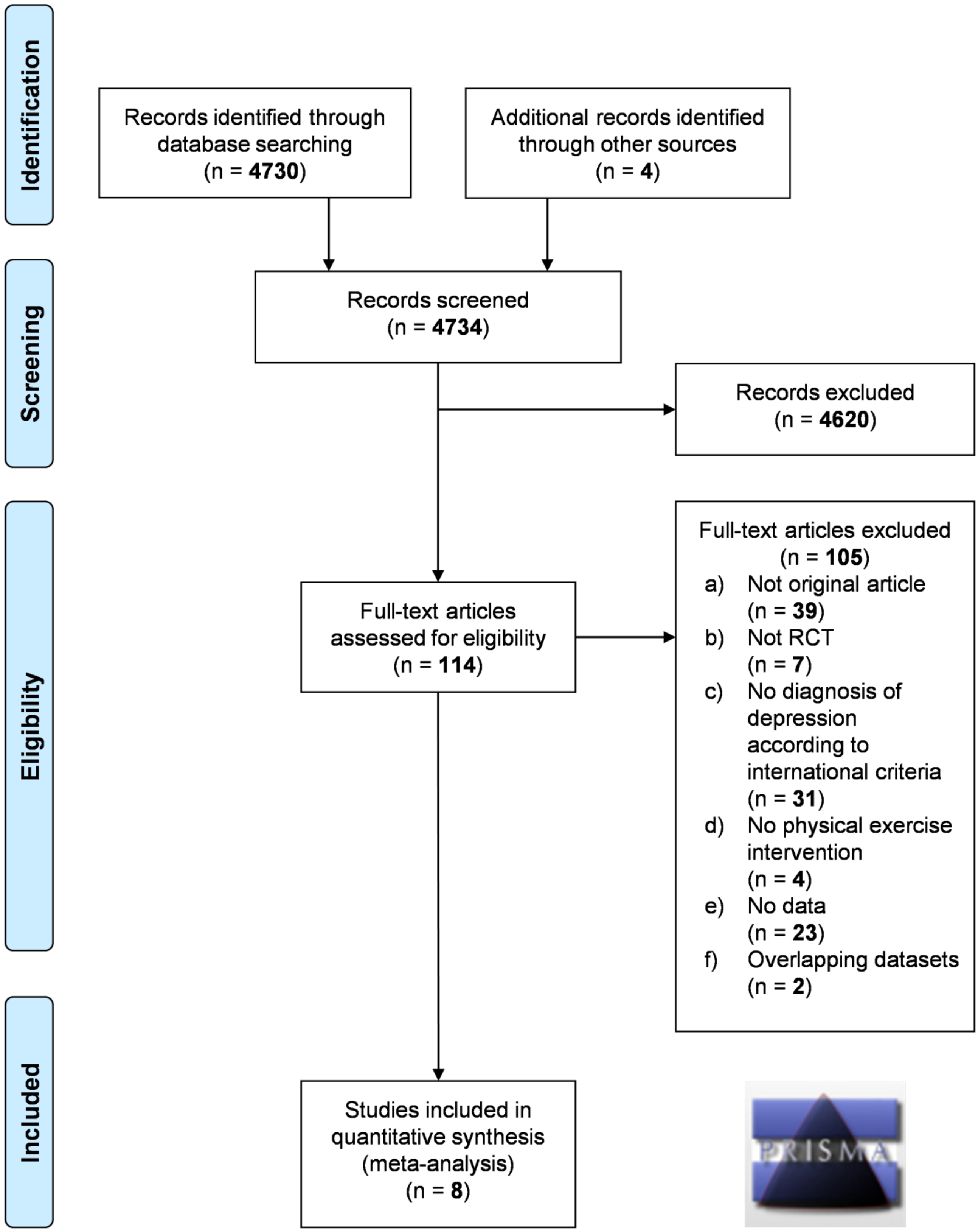
Author	Year	Sample size	Study design	Treatments	Outcome measure	Findings
				min sessions/week, muscle relaxation Duration of intervention 4 months		
Krogh et al.	2012	115 MDD (mean age 41.6; 38M/77F, drop-out N = 15)	Randomized, parallel arm, single blind	Aerobic exercise (N = 56, mean age:39.7 ± 11.3, 16M/40F, drop-out = 9), three 45 min sessions/week for 3 months, cycling till 80% heart rate (HR) measured during a maximal test Stretching (N = 59, mean age:43.4 ± 11.2, 22M/37F, drop-out = 6), three 45 min sessions/week for 3 months	DSB, DSF, SS7, ST-CC, ST-IC, TMT-A and -B, DS, AN, BT, RCFT	Aerobic exercise improved visual spatial memory compared to stretching, however no effect was found in any other cognitive domains
Lavretsky et al.	2011	73 MDD (18M/45F, drop-out N = 5)	Randomized, parallel arm, single blind, augmentation to escitalopram (10mg/die)	Tai chi (N = 36, mean age:69.1 ± 7.0, 13M/23F, drop-out = 3) Health Education (N = 37, mean age:72.0 ± 7.4, 15M/22F, drop-out = 2)	TMT-A, MMSE, CVLT, ST-IC, ST-CC	Tai-chi improved memory(CVLT long delay recall) compared to health education. No differences in other cognitive domains
Luttenberger et al.	2015	47 MDD (mean age: 43.91 ± 11.91; 20M/27F)	Randomized crossover design	Climbing (N = 22, mean age:42.71 ± 11.88, 10M/12F, drop-out = 3), one 3h session/week for 8 weeks Waitlist (N = 25, mean age:44.96 ± 12.08, 10M/15F, drop-out = 1), treatment as usual for 8 weeks	D2-R test	No improvement in attention and concentration in the climbing group
Oertel-Knochelet al.	2014	22 MDD (mean age: 40.00 ± 14.10 11M/11F)	Randomized, single blind, parallel arm	Aerobic exercise-cardiotraining (N = 8; mean age:36.63 ± 12.91; 4M/4F), three 45min sessions/week for 4 weeks Relaxation (N = 6, mean age: 41.37 ± 15.69, 2M/4F), three 45min sessions/week for 4 weeks	TMT-A, DS, AN, SS from the WMS-III, LNS, HVLT; BVMT, BDI, STAI	Aerobic exercise improved cognitive and symptoms severity more than relaxation, in particular in speed

Author	Year	Sample size	Study design	Treatments	Outcome measure	Findings
				Waiting list (N = 8, mean age: 42.21 ± 8.31, 5M/3F)		of processing, working memory and visual learning
Sharma et al.	2006	30 MDD (age range 18-45 years; 19M/11F)	Randomized, parallel arm, single blind	Yoga (N = 15, mean age:31.87 ± 8.78, 10M/5F), three 30 min sessions/week for 8 weeks Control group (same hand postures as yoga group but no meditation) (N = 15, mean age:31.67 ± 8.46, 9M/6F) three 30 min sessions/week for 8 weeks	LCT, TMT-A and -B, DSB, DSF, Ruff Figural Fluency test	Beneficial effect of yoga on LCT and DSB

Abbreviations: AN= Animal Naming; BDI=Beck Depression Inventory; BT= Buschke Test; BVMT= Brief Visuospatial Memory Test; COWAT= Controlled Oral Word Association Test; CVLT=California Verbal Learning Test; DS= Digit Symbol coding; DSB= Digit Span Backward; DSF= Digit Span Forward; DVT=Digit Vigilance Test; HVLT= Hopkins Verbal Learning Test; LCT= Letter Cancellation Test; LM= Logical Memory Subtest; LNS= Letter Number Span; MMSE=Mini Mental State Examination; RCFT=Rey-Osterrieth Complex Figure Test; R27T= Ruff 2 & 7 Selective Attention Test; SS7= Subtracting Serial 7s; STAI=State-Trait Anxiety Inventory; SS=Spatial Span; ST-CC= Stroop Task – congruent condition; ST-IC=Stroop Task – incongruent condition; TMT=Trail Making Test; VPA=Verbal Paired Associates Subtest of WMA-III

Figure 1. PRISMA flow diagram of the selection procedure

Figure 2. Forrest plot of the effect of physical activity on cognitive symptoms in depression



Study name	Intervention	Comparison	Hedge's g	Standard error	Lower limit	Upper limit	p-Value
Speed of Processing							
Hoffman et al. 2008	Aerobic Ex.	TAU or PCB	0.083	0.173	-0.255	0.422	0.629
Krogh et al. 2009	Aerobic Ex.	Relaxation	-0.018	0.233	-0.473	0.438	0.940
Krogh et al. 2009	Strenght Ex.	Relaxation	-0.042	0.232	-0.496	0.412	0.856
Krogh et al. 2012	Aerobic Ex.	Streching	-0.195	0.186	-0.560	0.169	0.293
Lavretsky et al. 2011	Tai-chi	TAU or PCB	0.525	0.244	0.047	1.004	0.031
Oertel-Knochel et al. 2014	Aerobic Ex.	Relaxation	0.493	0.514	-0.515	1.500	0.338
Sharma et al. 2014	Sahaj Yoga	Relaxation	0.041	0.355	-0.655	0.738	0.908
			0.055	**0.088**	**-0.118**	**0.228**	**0.533**
Attention / Vigilance							
Chan et al. 2013	Dejian Mind Body	Waiting List	0.740	0.352	0.050	1.429	0.036
Hoffman et al. 2008	Aerobic Ex.	TAU or PCB	0.009	0.172	-0.329	0.347	0.960
Krogh et al. 2009	Aerobic Ex.	Relaxation	0.077	0.231	-0.377	0.530	0.740
Krogh et al. 2009	Strenght Ex.	Relaxation	-0.120	0.232	-0.574	0.334	0.604
Krogh et al. 2012	Aerobic Ex.	Stretching	0.037	0.185	-0.326	0.401	0.840
Luttemberger et al. 2015	Rock Climbing	TAU or PCB	0.117	0.303	-0.478	0.711	0.701
Sharma et al. 2014	Sahaj Yoga	Relaxation	-0.028	0.355	-0.725	0.668	0.936
			0.060	**0.089**	**-0.114**	**0.234**	**0.501**
Working Memory							
Hoffman et al. 2008	Aerobic Ex.	TAU or PCB	0.012	0.172	-0.326	0.350	0.946
Krogh et al. 2009	Aerobic Ex.	Relaxation	-0.263	0.232	-0.718	0.192	0.257
Krogh et al. 2009	Strenght Ex.	Relaxation	0.132	0.232	-0.322	0.585	0.570
Krogh et al. 2012	Aerobic Ex.	Stretching	-0.097	0.185	-0.460	0.267	0.603
Oertel-Knochel et al. 2014	Aerobic Ex.	Relaxation	0.089	0.506	-0.903	1.080	0.861
Sharma et al. 2014	Sahaj Yoga	Relaxation	0.260	0.357	-0.441	0.960	0.468
			-0.022	**0.095**	**-0.208**	**0.163**	**0.816**
Verbal Learning and Memory							
Hoffman et al. 2008	Aerobic Ex.	TAU or PCB	0.002	0.173	-0.336	0.340	0.990
Krogh et al. 2009	Aerobic Ex.	Relaxation	-0.133	0.232	-0.587	0.320	0.564
Krogh et al. 2009	Strenght Ex.	Relaxation	-0.078	0.231	-0.531	0.376	0.737
Krogh et al. 2012	Aerobic Ex.	Stretching	-0.064	0.185	-0.428	0.299	0.728
Lavretsky et al. 2011	Tai-chi	TAU or PCB	0.518	0.244	0.039	0.996	0.034
Oertel-Knochel et al. 2014	Aerobic Ex.	Relaxation	0.786	0.527	-0.247	1.819	0.136
			0.048	**0.091**	**-0.131**	**0.227**	**0.598**
Visual Learning and Memory							
Krogh et al. 2009	Aerobic Ex.	Relaxation	0.084	0.231	-0.370	0.537	0.718
Krogh et al. 2009	Strenght Ex.	Relaxation	-0.246	0.232	-0.701	0.209	0.290
Krogh et al. 2012	Aerobic Ex.	Stretching	0.623	0.190	0.251	0.995	0.001
Oertel-Knochel et al. 2014	Aerobic Ex.	Relaxation	0.615	0.519	-0.402	1.632	0.236
			0.241	**0.121**	**0.005**	**0.478**	**0.045**
Reasoning and Problem Solving							
Hoffman et al. 2008	Aerobic Ex.	TAU or PCB	0.033	0.173	-0.305	0.372	0.847
Krogh et al. 2009	Aerobic Ex.	Relaxation	-0.058	0.231	-0.511	0.396	0.802
Krogh et al. 2009	Strenght Ex.	Relaxation	-0.111	0.232	-0.564	0.343	0.632
Krogh et al. 2012	Aerobic Ex.	Stretching	-0.253	0.187	-0.620	0.113	0.175
Sharma et al. 2014	Sahaj Yoga	Relaxation	0.217	0.356	-0.481	0.916	0.543
			-0.071	**0.096**	**-0.260**	**0.119**	**0.465**
Overall							
Chan et al. 2013	Dejian Mind Body	Waiting List	0.740	0.352	0.050	1.429	0.036
Hoffman et al. 2008	Aerobic Ex.	TAU or PCB	0.035	0.173	-0.303	0.373	0.838
Krogh et al. 2009	Aerobic Ex.	Relaxation	-0.043	0.232	-0.498	0.411	0.852
Krogh et al. 2009	Strenght Ex.	Relaxation	-0.069	0.232	-0.523	0.385	0.767
Krogh et al. 2012	Aerobic Ex.	Stetching	-0.081	0.186	-0.446	0.285	0.666
Lavretsky et al. 2011	Tai-chi	TAU or PCB	0.236	0.243	-0.240	0.713	0.331
Luttemberger et al. 2015	Rock Climbing	TAU or PCB	0.117	0.303	-0.478	0.711	0.701
Oertel-Knochel et al. 2014	Aerobic Ex.	Relaxation	0.495	0.516	-0.517	1.508	0.337
Sharma et al. 2006	Sahaj Yoga	Relaxation	0.150	0.356	-0.549	0.848	0.674
			0.075	**0.082**	**-0.086**	**0.237**	**0.362**