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Physical Exercise and Clinically Depressed Patients: A Systematic Review and Meta-Analysis

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Key Words
Exercise training · Physical exercise · Strength training · Weight lifting · Unipolar depression · Treatment of major depression

Abstract
Objective: The aim of this meta-analysis is to evaluate the effect of aerobic training and strength training as a treatment for depression in patients diagnosed with major depressive disorder. ***Methods:*** PubMed (Medline), ISI knowledge (Institute for Scientific Information), SciELO (Scientific Electronic Library) and Scopus databases were consulted from January 1970 to September 2011. Data were collected on variables as follows: total number of patients (pre- and postintervention), age, randomized (yes or no), diagnostic criteria, assessment instruments, and the percentage of remission and treatment response. Subsequently, we collected information on time intervention, intensity, duration, frequency, method of training (aerobic training and strength training) and type of supervision. Standardized mean differences were used for pooling continuous variables as endpoint scores. Binary outcomes, such as proportion of remission (no symptoms) and at least 50% reduction of initial scores (response), were pooled using relative risks. Random effects models were used that take into account the variance within and between studies. ***Results:*** Ten articles were selected and subdivided by their interventions, controlled training modality and levels of intensity. As there was no statistically significant difference between the two types of intervention (strength or aerobic training), we combined data which finally showed a 0.61 (95% CI: –0.88 to –0.33) standard deviation reduction in the intervention group compared to the control group. When the analysis was restricted only to those studies that used the Hamilton scale (n = 15), we observed a reduction of 3.49 points compared with the control group. ***Conclusion:*** Despite the heterogeneity of the studies, the present meta-analysis concluded that physical exercise improves the response to treatment, especially aerobic training. However, the efficacy of exercise in the treatment of depression was influenced by age and severity of symptoms.

Introduction

Projections from the World Health Organization (WHO) have estimated that major depressive disorder (MDD) will be the second leading cause of incapacitating

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disease by 2020 [1]. Nowadays, the most efficient treatment for MDD includes antidepressant medication and psychotherapy; however, less than 25% of the population has access to these treatments [2]. Physical exercise has been suggested as an efficient alternative treatment to reduce symptoms of depression since it reduces cost with drugs and hospitalizations, and may also improve health and physiological responses [3–8].

There are several hypotheses regarding the physiological and psychological mechanisms by which exercise impacts on mental health, such as enhancement of the synthesis and liberation of neurotrophic factors, as well as of cognitive functioning, angiogenesis, neurogenesis and plasticity [9]. Moreover, some studies have shown that physical exercise may improve social contact, quality of life and self-esteem. Furthermore, it may also contribute to increased independence in activities of daily living in older adults [10, 11]. Despite this wide range of possible positive effects of exercising observed in studies with humans and animals, evidence in clinical studies is still scarce [12–14].

In a recent meta-analysis, Conn [15] verified that physical exercise reduces depression symptoms in subjects without a clinical diagnosis of depression. However, systematic revision and meta-analysis studies that investigated only the clinically diagnosed depressed patients showed conflicting results [16, 17]. Divergence about training prescription draws attention to the importance of establishing a dose response relation between physical exercise and MDD. Generally, systematic reviews and meta-analyses on the topic indicate that few studies have good methodological quality, thus making it difficult to ascertain whether exercise is really efficient for treating depression [12, 13].

Among the several limitations in the studies, authors included the lack of randomization, the inclusion of subjects without clinical diagnosis, and the lack of blind analysis [13]. In a recent meta-analysis, Krogh et al. [16] selected only 3 out of the 13 existing studies which had achieved good quality criteria as randomized clinical studies. Authors showed weak evidence for the benefit of exercise in depression treatment in this study.

The goal of the present meta-analysis is to evaluate the effect of aerobic and strength training as a treatment for MDD, using various aspects such as remission and response to treatment, type of exercise, weekly frequency, duration of intervention, and duration and intensity of exercise.

Method

Information Sources

PubMed (Medline), ISI knowledge (Institute for Scientific Information), SciELO (Scientific Electronic Library) and Scopus databases were consulted from January 1970 to September 2011. The PRISMA statement was used in order to build and elaborate this systematic revision and meta-analysis [18].

Search

Search was conducted according to the strategies suggested by the Medline method, using combinations among the key words: *physical exercise* OR *aerobic exercise, nonaerobic exercise, physical activity, physical fitness, resistance, strength training, weight lifting* AND *major depression* OR *unipolar depression*. Search details were: *exercise* [MeSH terms] OR *exercise* [all fields] OR (*physical* [all fields] AND *exercise* [all fields]) OR *physical exercise* [all fields] AND *depressive disorder, major* [MeSH terms] OR (*depressive* [all fields] AND *disorder* [all fields] AND *major* [all fields]) OR *major depressive disorder* [all fields] OR (*major* [all fields] AND *depression* [all fields]) OR *major depression* [all fields] OR *depressive disorder* [MeSH terms] OR (*depressive* [all fields] AND *disorder* [all fields]) OR *depressive disorder* [all fields] OR (*major* [all fields] AND *depression* [all fields]). In addition, article references were screened and authors were contacted for additional information. The limits accepted were longitudinal studies, clinical trials, and randomized controlled trials in humans.

Study Selection

We included articles with longitudinal design and randomized and nonrandomized clinical trials which used physical exercise (aerobic training and strength training) as a single treatment for the group, which was defined as exercise monotherapy, or combined with pharmacological treatment. In this latter case, exercise was defined as secondary or adjuvant treatment. Moreover, we included only studies that described methodological parameters of exercise prescription. Articles which were not according to the purpose of this review or which did not present the detailed methods and results so as to be evaluated and used in the meta-analysis were also excluded.

The evaluators were blinded with regard to the data referring to the names of authors, journals and/or institutes. Titles and abstracts were independently assessed by two evaluators. Whenever there was disagreement on the evaluation, another reviewer was called to give his technical opinion.

Data Collection Process

Data were collected on variables as follows: total number of patients (pre- and post-intervention), age, randomized (yes or no), diagnostic criteria, assessment instruments, the percentage of remission and treatment response. Subsequently, we collected information on time intervention, intensity, duration, frequency, method of training and type of supervision.

Statistical Analysis

We estimated the pooled effect size by standardized mean differences (SMD), as the selected studies used different scales. According to Higgins and Green [19], I^2 statistics under 40% suggest that heterogeneity among studies might not be impor-

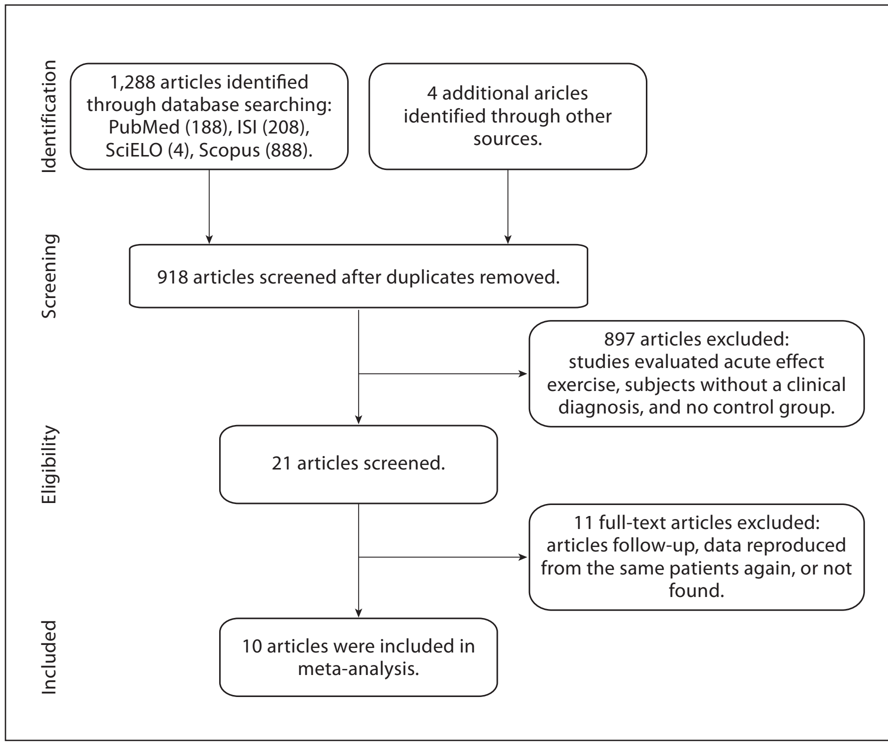

Fig. 1. Flow chart of search and selection for the articles included in the meta-analysis.

tant. On the other hand, values over 75% indicate considerable heterogeneity, which was the case for the SMD. Moreover, the test for homogeneity was highly significant ($\chi^2 = 63.1$; d.f. = 17; $p < 0.001$). For this reason we used random effects models that take into account the variance within and between studies. The same analysis was repeated using only the studies that have used the Hamilton scale for depression. Binary outcomes were also used for the proportion of remission (% reduction of MDD symptoms below the cutoff) and response (at least 50% reduction of initial scores), and the respective individual relative risks (RR) were pooled. Forest plots were used to present these findings. They were built in a way that the point estimates (SMD and RR) and 95% CI of individual studies were graphically displayed in each line and the pooled measure was shown at the bottom. Larger horizontal lines indicate less precise (smaller) studies. The columns to the right present the numerical findings and the relative weights received by each study in the process of combining them.

Estimates with p values ≤ 0.05 were considered statistically significant whilst values between 0.06 and 0.10 were suggestive (trend) of association.

Metaregression models were fitted to look into the role of the various study characteristics on the observed heterogeneity. Initially the variables were included into the model one at a time, and those with p values <20% were selected for the final model. The variables with p values <10% in the final model were considered statistically significant. All analyses were performed using Stata 10.0.

Results

We found 1,288 articles in the systematic search and 4 articles in the manual search. A total of 21 articles were selected, but specific cases were excluded. Two papers listed in other studies [16] located through a manual search were not found (Epstein, 1986, dissertation, and Mutrie, 1988, published in Annals of Congress), and articles that demonstrated no controlled intervention [20], or which did not show complete data [10, 21, 22] or were just follow-up from previous research [23–27], were removed from the analysis. Ten articles were included and classified by their interventions, controlled training modality or levels of intensity. Figure 1 describes the selection process of the studies included in this meta-analysis. The characteristics of these studies are described in table 1.

Figure 2 presents the standardized average differences in two subgroups of intervention. There was a reduction of 0.52 (95% CI: –0.79 to –0.25) and 0.96 (95% CI: –1.97 to 0.05) in standard deviations for aerobic activity and strength training, respectively. We found a statistically significant difference between aerobic training and control group (p = 0.001) and a trend for significance when strength training and control groups were compared (p =

Table 1. Characteristics of the selected studies

Author, year	Number of patients	Mean age	Training	Time weeks	Duration of session or number of exercises	Days per week	Intensity controlled	Supervised	Diagnostic criteria	Level of depression	Randomization	Type of treatment
Klein et al. [29], 1985	51	30.1	aerobic	12	45	–	no	yes	CIS	low/moderate	no	EM
Veale et al. [40], 1992	124	35.5	aerobic	12	–	3	no	yes	CIS	low/moderate	yes	CPT
Doyne et al. [41], 1987	40	25.83	aerobic	8	20	3	yes	yes	RDC	low	yes	EM
Singh et al. [33], 1997	32	71.3	strength	10	50	3	yes	yes	DSM-IV	low	yes	CPT
Dunn et al. [38], 2005a	72	35.9	aerobic	12	–	3	yes	yes	DSM-IV	low/moderate	yes	EM
Dunn et al. [38], 2005b	72	35.9	aerobic	12	–	3	yes	yes	DSM-IV	low/moderate	yes	EM
Dunn et al. [38], 2005c	72	35.9	aerobic	12	–	5	yes	yes	DSM-IV	low/moderate	yes	EM
Dunn et al. [38], 2005d	72	35.9	aerobic	12	–	5	yes	yes	DSM-IV	low/moderate	yes	EM
Singh et al. [32], 2005a	54	69	strength	8	60	3	yes	yes	DSM-IV	low/moderate	yes	CPT
Sing et al. [32], 2005b	54	70	strength	8	60	3	yes	yes	DSM-IV	low/moderate	yes	CPT
Blumenthal et al. [30], 2007a	202	53	aerobic	16	45	3	yes	yes	DSM-IV	low/moderate	yes	EM
Blumenthal et al. [30], 2007b	202	53	aerobic	16	45	3	yes	no	DSM-IV	low/moderate	yes	EM
Blumenthal et al. [30], 2007c	202	53	aerobic	16	45	3	yes	yes	DSM-IV	low/moderate	yes	EM
Blumenthal et al. [30], 2007d	202	53	aerobic	16	45	3	yes	no	DSM-IV	low/moderate	yes	EM
Knubben et al. [37], 2007	38	49.5	aerobic	2	30	5	yes	yes	DSM-IV	moderate	yes	CPT
Krogh et al. [31], 2009a	125	18–55	aerobic	16	40	2	yes	yes	ICD-10	low/moderate	no	CPT
Krogh et al. [31], 2009b	125	18–55	strength	16	40	2	yes	yes	ICD-10	low/moderate	no	CPT
Silveira et al. [34], 2010	20	71.6	aerobic	24	30	2	yes	yes	DSM-IV	low/moderate	no	CPT

Dunn, 2005a = Low intensity 3 days × control; Dunn, 2005b = moderate intensity 3 days × control; Dunn, 2005c = Low intensity 5 days × control; Dunn, 2005d = moderate intensity 5 days × control; Singh, 2005a = high intensity × control; Singh, 2005b = low intensity × control; Blumenthal, 2007a = supervised × sertraline; Blumenthal, 2007b = home × sertraline; Blumenthal, 2007c = supervised × control; Blumenthal, 2007d = home × control; Krogh, 2009a = aerobic × control; Krogh, 2009b = strength × control. RDC = Research Diagnostic Criteria; ICD-10 = International Classification of Disease 10; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders IV; CIS = Clinical Interview Schedule; EM = exercise monotherapy, treatment is defined as a single treatment for the group; CPT = combining with pharmacological treatment, is defined as secondary or adjuvant treatment for the group.

0.06). In both cases, the heterogeneity between the studies was high (I^2 = 69 and 88.5% for aerobic and strength, respectively). As there was no statistically significant difference between the two types of intervention, we combined the data which finally showed a 0.61 (95% CI: –0.88 to –0.33) standard deviation reduction in the intervention compared with the control group ($p < 0.001$).

When the analysis was restricted to those studies which used the Hamilton scale (n = 15), we observed a reduction of 3.49 points on the intervention compared with the control group. There was no difference between the types of intervention. Also, we found a significant heterogeneity between studies (I^2 = 73.4%). When studies were restricted to those using the Hamilton scale, only aerobic interventions could be evaluated.

Remission and outcome improvement were also defined using the Hamilton scale. Remission was 14% higher in the intervention compared to the control group (RR = 1.14; 95% CI: 0.97–1.35), but this difference was not statistically significant (p = 0.12; fig. 3). The heterogeneity for this set of studies was small (I^2 = 27.4%).

Figure 4 shows the combined RR for outcome improvement, defined as a 50% reduction in initial scores. There was a 49% increase in the probability of response to treatment with exercise training (RR = 1.49; 95% CI: 1.10–2.03; p = 0.01). No significant heterogeneity was observed in this case (I^2 = 22.9%).

According to data from the metaregression models presented in table 2, studies which were restricted to individuals over 60 years of age showed a higher efficacy than those found in studies with populations below 60 years, but not in studies with mixed age groups. The studies including patients with moderate/mild depressive symptoms showed a lower efficacy than that observed in studies restricted to patients with mild depressive symptoms.

Discussion

This meta-analysis investigated the effect of physical exercise in reducing depressive symptoms in MDD patients. We were able to confirm that physical exercise provides moderate benefits (SMD = 0.61) as a treatment for depression. An interesting result of the present study was to acknowledge that physical exercise is an efficient alter-

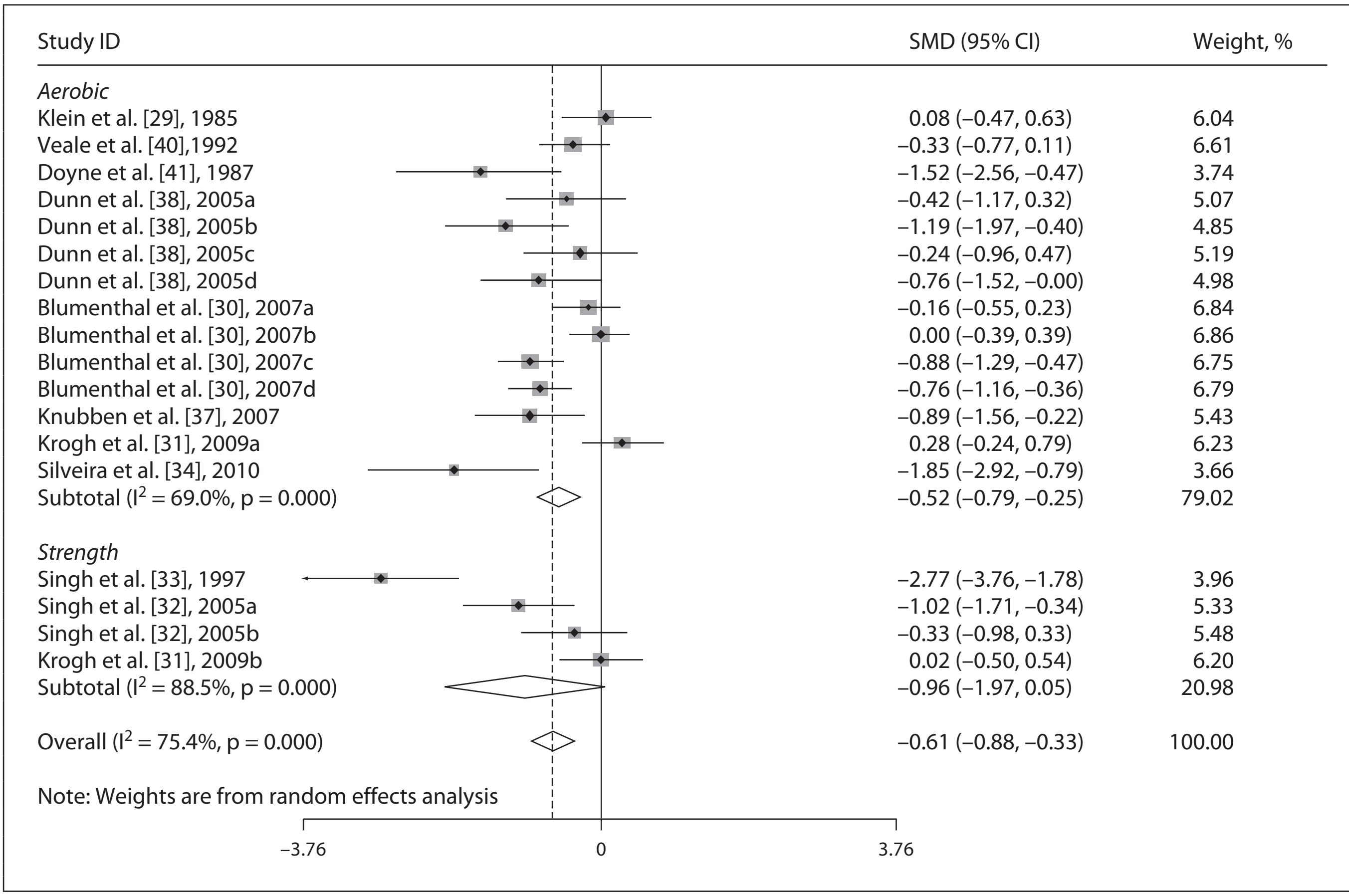

Fig. 2. Meta-analysis of studies assessing the effect of exercise in patients with clinically diagnosed depression by intervention.

native treatment for depression, promoting a 49% increase in the probability of response to treatment. Our results are in line with other meta-analysis studies, which have observed an improvement in the quality of publications in this area of research [12, 16, 28]. Seminal studies showed some methodological problems (e.g. nonrandomized controlled trials, no blinding of outcome assessment, and nonclinical populations) [20, 21] whilst recent clinical trials have shown stronger experimental designs [30–32].

In the present study, the efficacy of exercise in the treatment of depression was influenced by age and symptom severity. By using metaregression models, we were able to find that elderly subjects and patients with mild depressive symptoms presented a better treatment response with physical exercise than controls. Singh et al. [33] have demonstrated that strength training can reduce depressive symptoms and promote improvements in several aspects of quality of life, such as pain, vitality and social functioning. Moreover, Silveira et al. [34] have observed that depressive elderly patients showed increased brain cortical activity and significantly reduced depressive symptoms after 6 months of aerobic training. Blumenthal et al. [30, 35] have verified that aerobic training is as effective as antidepressant medication (sertraline) in reducing depressive symptoms. Therefore, it is reasonable to present the hypothesis that physical exercise may in some cases be considered an alternative to antidepressants for the treatment of MDD in older persons. This important finding might contribute to decreasing the use of medication and hospitalization and in promoting independence in activities of daily living in elderly patients, an outcome not usually observed in youths due to a 'ceiling effect'. It is important to highlight that the samples of all studies included in this meta-analysis consisted of patients with mild or moderate depression. This feature

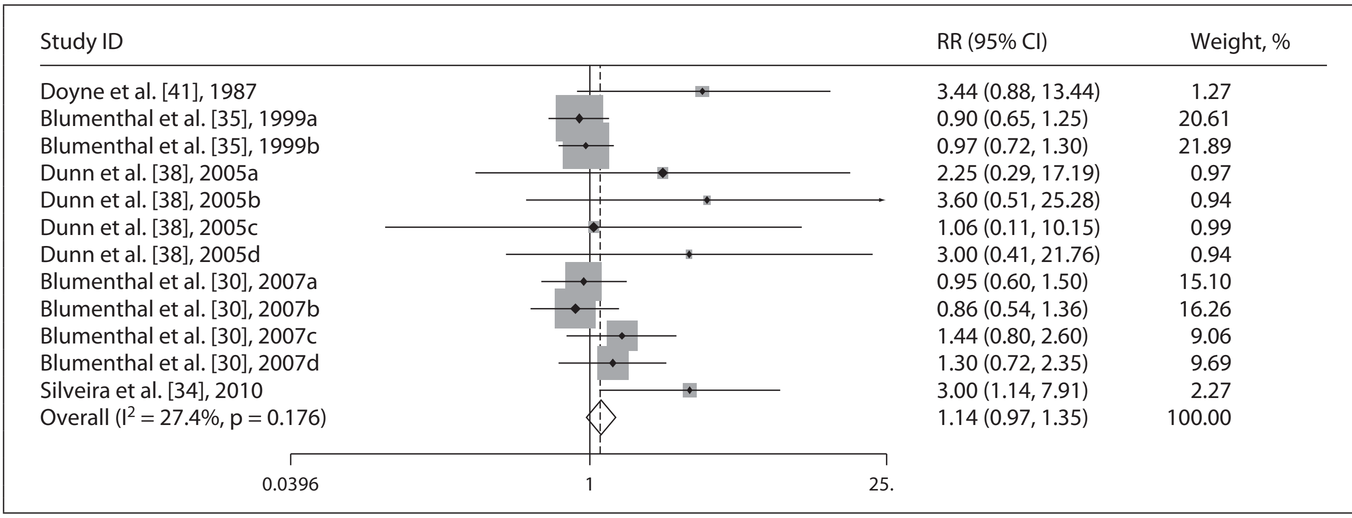

Fig. 3. Meta-analysis of studies assessing the remission of symptoms through the effect of exercise in patients with clinically diagnosed depression.

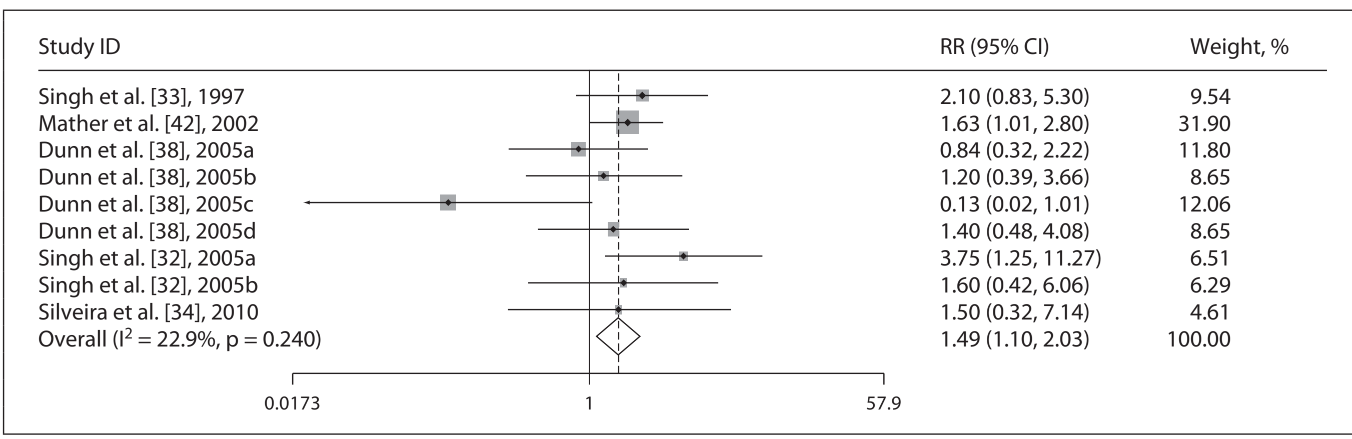

Fig. 4. Meta-analysis of studies assessing the combined RR for outcome improvement, defined as a 50% reduction in initial scores, of depression symptoms through the effect of exercise in patients with clinically diagnosed depression.

Table 2. Multivariate metaregression of the effect size of SMD according to age group and depression severity of patients

SMD	Coefficient	p	95% CI
Age >60 years	–0.74	0.041	–1.45, –0.03
Mixed age	–0.26	0.317	–0.81, 0.28
Severity	1.53	0.007	0.49, –2.57
Constant	–1.77	0.002	–2.81, –0.74

might also contribute to adherence due to a lower depressive symptom.

In an animal study, Russo-Neustadt et al. [36] have verified that both physical exercise and antidepressants promoted an increase in the synthesis of BDNF mRNA, a trophic factor which is a key in the establishment of neurogenesis and neuronal survival. Besides that, authors noted that exercise *plus* antidepressants provided an interaction response in both interventions, increasing the expression of BDNF mRNA. Considering that depression is associated with a decrease of BDNF synthesis whereas neurogenesis and antidepressant and physical exercise promotes an inverse response, it is conceivable to hypothesize that these neurobiological changes could contribute to explaining the effect of exercise as an additional treatment to depression. To the best of our knowledge, there are no randomized clinical trial studies which have so far investigated the effect of exercise on these parameters.

We showed that training parameters such as frequency, intervention period, intensity and duration of training, and the fact that it is supervised or not, do not exert any influence on the response to treatment. However, we should emphasize that the vast majority of studies have performed similar protocols, i.e. 30–60 min of moderate-intensity activities and low frequency (3 days·week^{-1}), whereas only 1 study evaluated the effect of physical exercise with higher frequency (5 days·week^{-1}) [37]. With respect to intensity, as no study has investigated vigorous intensities (above 90% VO_{2max}), we are not able to make any inference on the effects of these intensities in the treatment of depression. The latest results show that the best response on mood is obtained by moderate effort intensity. Regarding exercise duration, Dunn et al. [38] have verified that there is no difference between training 3 days·week^{-1} and training 5 days·week^{-1}. Authors concluded that an energy expenditure of 17 kcal·kg·week^{-1} is more efficient than spending 7 kcal·kg·week^{-1}, independent of frequency. This energy expenditure is equivalent to the recommendations from the American College of Sports Medicine which indicates at least 150 min·week^{-1} [5] as the best practice. Only 15 min·day^{-1} or 90 min·week^{-1} of moderate-intensity exercise is enough to provide significant benefits to physical health, especially to subjects with cardiovascular or metabolic diseases [39]. Despite the ideal recommendation, recent studies have demonstrated that exercising twice a week, with 30 min duration and moderate intensity can contribute to decreasing depressive symptoms in elderly subjects with MDD [23, 34].

After a 12-month investigation, results indicated that both training conditions (aerobic and strength training) reduced depressive symptoms. The utilization of one type of exercise (aerobic or strength) showed that it is efficient in the reduction of depression symptoms of clinically depressed patients [30, 32, 34]. Future studies that investigate other types of exercise (swimming, whole body vibration training, flexibility) and combine many modalities should be done.

Overall, our results point out that adding a routine of supervised physical exercise to pharmacological treatment would be the most suitable routine for elderly people with MDD so as to further improve the treatment response.

Some methodological problems still persist in the available studies, such as the absence of clinical diagnosis of MDD, the absence of supervised control group and exercises without intensity, and the methodological control of training parameters and exercise prescription (VO_{2max}, %RM). Future studies should include biomarker analyses and neuroimaging studies in order to better understand the neurophysiological effects and the role of the exercise in the treatment of depression.

Conclusion

The present meta-analysis concluded that physical exercise, mainly aerobic training, improves the response to depression treatment. However, the efficacy of exercise in the treatment of depression was influenced by age and severity of symptoms.

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Disclosure Statement

The authors have no conflicts of interest that are directly relevant to the content of this review.

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