

Review article

Moderators of response in exercise treatment for depression: A systematic review

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ABSTRACT

Introduction: Exercise have antidepressant effects in people with Major Depressive Disorder (MDD). However, about to half of patients do not respond to exercise. The identification of factors that moderates the antidepressant effects of exercise in people with MDD may help researchers and health professionals to identify sub-groups of patients that would benefit more from exercise.

Methods: A systematic review was carried out using Medline(PubMed), EMBASE and psycINFO up to April 2015. Individual and composite moderators were summarized and the strength of the evidence was assessed.

Results: Eleven studies were included for review resulting in the identification of potential individual (two biological, three clinical, two psychological and two social individual) and two potential composite moderators (the interaction between BDNF and Body Mass Index (BMI) and between family history of mental illness and gender). Only the two biological features and the BDNF x BMI interaction provided confirmatory evidence.

Limitations: Due the different statistical approaches used in the studies, it was not possible to perform meta-analyses. The small number of studies and the exploratory nature of the evidence limits a wider generalization of the findings.

Conclusion: Potential clinical, psychological, social or biological moderators were identified. However, the small number of studies and the limited strength of the evidence requires further studies before drawn definitive results. Further trials should consider the inclusion of moderators analysis using an a-priori, theoretical/evidence based hypothesis in order to provide high quality evidence for the use of personalized medicine in exercise for depression.

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1. Introduction

The use of Personalized Medicine is one of the strategic plans of the National Institute for Mental Health to improve treatment outcomes in the mental health (Insel et al., 2010). Personalized treatments in medicine and health area imply identification of the individual factors that predicts response or remission, resulting in better care outcomes and reduced costs (Kraemer et al., 2002; Wallace et al., 2013).

In Major Depressive Disorder (MDD), personalized medicine is particularly relevant because, at best, half of patients presents a acute clinical response (a decrease of 50% or more of the symptoms) to an initial pharmacological antidepressant treatment, and only one third presents remission (no longer meet criteria for depression diagnosis) (Sinyor et al., 2010). In this line, the identification of those subgroups of patients with increased, or decreased, likelihood of success in different treatments may play a key role in choosing the “best treatment” for each patient, and for improved treatment outcomes (Gvozdic et al., 2012; Kraemer et al., 2002; Malhi et al., 2013; Papakostas and Fava, 2008).

Recent guidelines suggested that exercise can be considered a therapeutic option for depression (Malhi et al., 2015) with consistent benefits to physical health, being a cornerstone to improve cardiorespiratory capacity (Stubbs et al., 2016) and decrease the risk of metabolic disorders (Stubbs et al., 2015a). On mental health, there are some discussion on the efficacy of exercise in depressive symptoms improvement. For example, a recent review found that clinical trials with good methodological quality does not support significant reductions on depressive symptoms (Cooney et al., 2013). It should be noted, however, that control groups used in clinical trials presents large and significant antidepressant effects (Stubbs et al., 2015b), decreasing the ability of detection of effects in exercise groups.

Despite the effect on symptom reduction remission rates in clinical trials are not optimal, ranging from 11% to 41%, for low and high doses of exercise, respectively (Dunn et al., 2005). In other words, about to half of people with depression will not experience significant improvements from exercise. One potential explanation to the heterogeneity in response rates can be due the heterogeneity of depression itself (Schuch and de Almeida Fleck, 2013). In this regard, the use of personalized medicine in exercise treatment for depression, identifying potential moderators (pre-treatment factors that modifies the magnitude or the direction of the effect of an intervention in an outcome (Kraemer et al., 2002)) can be of great interest for clinicians and researchers.

There is a wide range of factors that can potentially moderate response or remission of people with MDD to pharmacological

treatment or psychotherapies, including clinical (e.g.: depression severity), demographical (e.g.: age, sex), psychological (e.g.: personal traits or characteristics), biological (e.g.: biomarkers), social and environmental factors (Button et al., 2015; Donker et al., 2013; MacPherson et al., 2014; Ozomaro et al., 2013; Papakostas and Fava, 2008). However, the potential moderators of the antidepressant effects of exercise remains poorly understood.

A previous study found initial evidence of the potential use of personalized medicine in physical activity and depression, identifying potential subgroups that are less likely to be engaged in physical activity (Vancampfort et al., 2015). In clinical trials, some studies have shown that neurogenesis and inflammation biomarkers, family history of depression, and severity of physical symptoms can moderate the effects of exercise on depression (Herman et al., 2002; Rethorst et al., 2013; Toups et al., 2011). However, to the best of our knowledge, no systematic review aimed to identify potential moderators of the antidepressant effects of exercise in people with MDD. The present review can be a hallmark for the creation and discussion of a body of evidence in the field, suggesting potential directions for investigation in further clinical trials.

The identification of potential moderators can suffer seriously from some issues such as the lack of an a-priori, evidence/theoretical based hypothesis, and the use of non-reliable or valid measures of moderators (Pincus et al., 2011). In this regard, the assessment of the strength of the evidence is required to provide an adequate comprehension of the generalization of the findings.

The objectives of the present study were to: (1) perform a systematic review of the potential moderators associated with treatment outcomes in randomized clinical trials evaluating the antidepressant effects of exercise in people with MDD; and (2) evaluate the strength of the evidence of the potential moderators of response.

2. Methods

The systematic review was carried out in three steps: literature search, study selection and data extraction, following the PRISMA guidelines (Moher et al., 2009).

2.1. Literature search

A comprehensive search of papers published up to April 2015 was carried out on Medline (PubMed), EMBASE and PsycINFO, using the following strategy: ((exercise OR physical activity) AND depress* AND (moderator OR predictor OR clinical trial OR

randomized controlled trial) NOT (yoga OR cesarean OR review OR pregnancy OR menopau* OR natal* OR multiple sclerosis OR work* OR COPD OR mice OR rat OR hamster OR stroke OR fibromyalgia OR diabete* OR heart failure OR cancer OR kidney OR coronary artery disease OR parkins* OR HIV OR student* OR Low back pain OR urinary OR angina)). The strategy was created to be used in Medline and was adapted to EMBASE and PsycINFO. Additional hand-searches were carried out on the references of selected studies, as well as, in the clinical trials analyzed by the last version of the “exercise for depression” meta-analysis and their authors (Cooney et al., 2013).

2.2. Study selection

The articles were selected by three independent reviewers (FBS), (ACK) and (RSD) and their relevance was judged by their title and abstract. The inclusion criteria were: (1) evaluate adult (> 18 years) patients with the diagnosis of MDD according the DSM-IV, DSM-5 or ICD-10 criteria; (2) use an exercise-based intervention, as defined by Caspersen et al. (1985) as a planned, structured, repetitive and purposive, in the sense that improvement or maintenance of one or more components of physical fitness is an objective; (3) evaluate the relationship of any clinical, psychological, demographical social, or biological characteristics at baseline with response or remission rates or depressive symptoms improvement, according to standardized treatment outcomes; (4) be written in English and (5) present original data.

The articles included were read, and the studies excluded where those that (1) included patients with clinical comorbidities; (2) included patients whose psychiatric diagnosis was other than MDD or minor depression (e.g.: Bipolar Disorder, Schizophrenia, abuse or dependence of alcohol or other drugs), according the DSM-IV, DSM-5 or ICD-10 criteria and (3) used Tai-chi, Yoga or similar activity.

2.3. Data extraction

Three independent reviewers (FBS), (ACK) and (RSD) extracted the data concerning the sample, intervention, intervention length, response/remission rate and the predictive variables. Different papers presenting redundant data of the same study were included only once in the review. In that case, the paper presenting the moderator as the main outcome was selected for review. Case an study include more than one exercise group (e.g.: different modalities, different intensities) and present the analysis of each different group separately, each group will be extracted separately. Only the moderators of the acute phase of the treatment were included. Different papers presenting different variables of the same study protocol were included in the review.

2.4. Outcome measures

The outcomes evaluated in the present study were any biological, clinical, demographical, psychological or social baseline characteristic, trait or factor that presents a direct or inverse association with treatment outcomes. Treatment outcomes were defined as a significantly increased response or remission rates (according the criteria defined by each study author) or a greater decrease of depressive symptoms when compared to the control group.

The factors were grouped in six categories: biological (e.g.: neurogenesis biomarkers, oxidative stress, inflammatory biomarkers, any hormone or enzyme, genetic), clinical (e.g., depression severity, family history of mental illness recurrence of episode, anxiety symptoms), demographical (e.g.: employment status, gender, weight), psychological (e.g.: self-esteem, self-efficacy,

locus of control, personality), social (e.g.: attention, social activities, social support) or composite moderators (e.g.: the interaction between two or more moderators of any above cited groups).

2.5. Analysis

We adapted the Sallis et al. (2000) coding model was adapted to provide a summary of the strength of association for each potential individual moderator. This approach was used since the authors use different statistical tests to present the results (e.g.: Spearman and Pearson correlations, ANOVA, ANCOVA, mixed-effects repeated measures analysis and logistic regression models), and it would be would be impractical use a meta-analytical approach of different tests.

2.6. Coding

The results were shown in percentages and total number of studies showing a significant association/total number of studies that tested the association. Each study that identified a significant direct association was computed with an “+”, studies that identified inverse associations were computed as “–”, and studies that found no significant association were computed as “0”. Case most studies support an association for any direction (e.g.: direct association), and a lesser number of studies support an association for the other direction (e.g.: inverse), the studies in lesser number will be computed as founding no association. The final summary represents the sum of the number of studies supporting the association. Analysis can be interpreted as the following: the existence of a direct “+” or inverse “–” association case 60–100% of studies support an significant direct “+” or inverse “–” association, respectively; as “?”, if only 34–59% of studies support an significant association for the same direction, indicating an inconsistent association or “0”, if 0–33% of studies support an significant association for the same direction, indicating no association. To be considered consistent, it is required that a minimum of 4 studies or arm trials evaluate a single moderator. This method was previously used on correlates of physical activity in bipolar disorder and schizophrenic patients (Vancampfort et al., 2013, 2012).

2.7. Strength of moderator assessment

The strength of the analysis of was assessed according the Pincus et al. (2011) methodological assessment of moderators in clinical trials. The scoring in composed by 5 criteria: (1) use of an a-priori hypothesis, if the study mention that the moderator analysis was planned a-priori; (2) use of an theoretical or evidence based selection of moderators, if the description of theoretical background, or the reference to other published evidence leading to the hypothesis is provided; (3) assessed the moderator prior to randomization, if the study states that baseline measurement occurred prior to randomization; (4) use of an adequate moderator measure, if there is published evidence to support good measurement properties of the assessment/instrument used the for target population and; (5) provide an adequate presentation of statistical values, ideally, when the study report a pooled effect size with 95% confidence intervals. Other acceptable analysis includes regression. Each of the five items is classified as Yes/No and each. The “Yes” for all five items suggests that the study provides a confirmatory evidence. Four or less “Yes” are indicative of exploratory evidence.

2.8. Quality of the trial

The quality of the trial was evaluated by two independent reviewers: (FBS) and (RSD) for each study. Case the moderator

analysis is a secondary outcome published separated of the trial reporting the main outcome and does not report enough information for quality of the trial assessment, the quality was assessed in studies that reported the main outcomes. The risk of bias of the studies were classified as being high, low or unclear considering the following factors: random sequence generation, allocation concealment, blinding of participants, blinding of those delivering the intervention, blinding of outcome assessors, incomplete data outcome, selective reporting or others. Studies were considered as being of low risk of bias if present adequate allocation concealment AND presentation of outcomes data according to intention-to-treat principles AND blinding outcome assessors. The criteria used for risk of bias assessment was based on the Cochrane Handbook definition (Higgins and Green, 2011).

3. Results

Initially, 2089 papers were identified as potentially relevant. At the end of study selection, ten studies were selected. In addition, one study was (Blumenthal et al., 2007) included through manual searches on previous reviews (Cooney et al., 2013). After the initial eligibility, 11 papers were selected. The flow chart indicating reasons for exclusion is shown in Fig. 1.

Of the 11 selected studies, five were conducted in US (Blumenthal et al., 2007; Herman et al., 2002; Rethorst et al., 2013; Toups et al., 2011; Trivedi et al., 2011), two in Denmark (Krogh et al., 2009, 2012), two in Australia (Singh et al., 1997, 2005), one in Portugal (Mota-Pereira et al., 2011) and one in Brazil (Schuch et al.,

2015). One study (Herman et al., 2002) has analyzed the moderators of response from previously published data (Blumenthal et al., 1999), thus, only the study with the analysis of moderators as main outcomes was included for review. Three studies (Rethorst et al., 2013; Toups et al., 2011; Trivedi et al., 2011) of the same protocol (Trivedi et al., 2006) were included due the fact that they present different outcomes. Each one was analyzed individually. Four studies have more than one group and each group was analyzed separately when presents analysis of each moderator for each group separately (Rethorst et al., 2013; Singh et al., 2005; Toups et al., 2011; Trivedi et al., 2011).

Studies that evaluated moderators of response or remission in populations without diagnosis of depression were not included in the review due the fact that the findings may not be generalized to the whole group of major depressed patients. A detailed description of the studies was provided in Table 1.

3.1. Features associated with response or remission

Twenty four individual and two composite moderators were identified across the studies. The summary scores of individual moderators were presented in the Table 2.

3.2. Individual moderators

3.2.1. Biological biomarkers

Five individual biological moderators were tested and two were identified as potential moderators. Tumor necrosis factor alpha (TNF- α) and Brain derived neurotrophic factor (BDNF) levels at

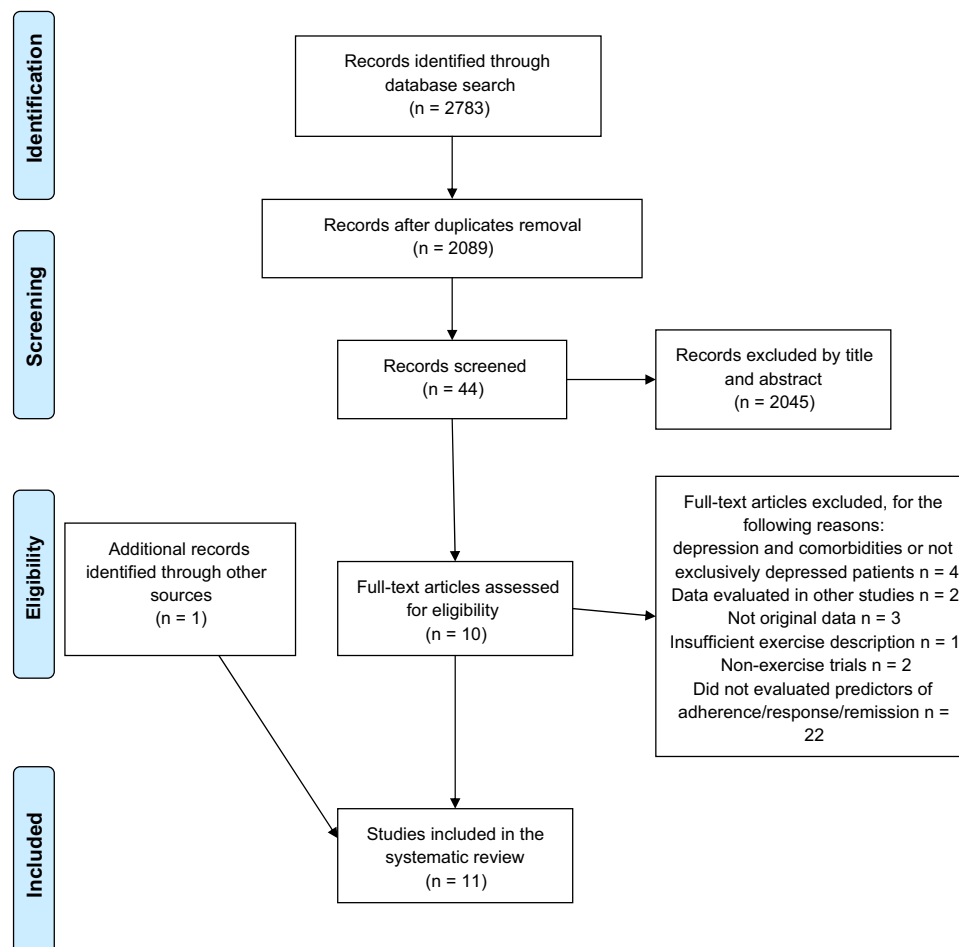


Fig. 1. Flowchart of study selection.

Table 1
Description of the studies.

Study	Sample			Methods					Results	
	Size	Age	Depression severity	Groups	Instruments	Response/remission criteria	Analysis	Moderators tested	Response/remission	Test value (r , r^2 , F , X^2)
Singh et al. (1997)	$n=32$	Older	Dysthymia, minor depression, mild to moderate MDD	Strength $\times$ "Attention"	BDI	Remission: no longer meet criteria (not specified); Response: $> 50\%$ reduction on BDI;	Correlation (not specified)	Depression severity	Response: Strength=59% $\times$ Attention=26%; Remission: Strength=82% $\times$ Attention=40%	Depression severity ($r=0.5$)*
Herman et al. (2002)	$n=156$	Middle age and older	Mild to severe	Aero $\times$ Sertraline $\times$ Aero+Sertraline	BDI, HAMD	Remission: no longer met MDD criteria (DSM-IV) and 8 or $>$ In HAMD	ANOVA	Anger, Depression severity (BDI and HAMD), Dysfunctional attitudes, Employment, Life satisfaction, Physical symptoms, Social Support, State anxiety	Remission: Total=53%; exercise group=47% $\times$ M=60% $\times$ combined=53%.	Anger ($F=7.37$), Depression severity (BDI, $F=1.08$; HAMD*, $F=10.21$), Dysfunctional attitudes ($F=7.98$), Employment ($X^2=3.68$), Life satisfaction ($F=43.59$), Physical symptoms ($X^2=11.21$)*, Social support ($F=9.24$)*, Self-esteem, ($F=20.16$)*, State anxiety ($F=68.60$)*
Singh et al. (2005)	$n=60$	Older	Dysthymia, minor depression mild to moderate MDD	HIGH Strength $\times$ LOW Strength $\times$ GP care	HAMD	Remission: no longer meet criteria (not specified) Response: $> 50\%$ of reduction on HAMD scores;	Correlation (not specified)	Belief in efficacy of exercise	Response: HIGH PRT=61%; LOW PRT=29%; GP care=21%	Belief in efficacy of exercise (High $r=0.24$; Low $r=0.54$ *)
Blumenthal et al. (2007)	$n=202$	Middle age and older	Mild to moderate	HB (Aero) $\times$ S (Aero) $\times$ Sertra $\times$ Placebo	HAMD	Remission: no longer meet MDD criteria (DSM-IV) and a HAM-D score of 8 $<$	Generalized Linear Model	Depression severity	Remission: HB=30%; S=44%; M=39%; and Placebo=27%	Depression severity (?)
Krogh et al. (2009)	$n=165$	Adults	Mild to moderate	Strength $\times$ Aero $\times$ Relaxation	HAMD	Remission: No longer meet ICD-10 criteria for MDD and a HAMD score of 8 $<$	Mixed Effect Models	Sex	Remission: Strength=40.4%; Aero=29.2%; Control=31.7%	Sex (?)
Mota-Pereira et al. (2011)	$n=33$	Adults	Mild to moderate	S and HB Aero+usual T $\times$ Usual T	HAMD	Remission: HAMD=7 or $<$ Response: $> 50\%$ reduction on HAMD scores	ANOVA	Depression severity, Global functioning,	Usual T: Remission=0%; response=0%; Aero+usual T: Remission=26%; Response=21%	Depression severity (?)*, Global functioning (?)*
Trivedi et al. (2011)	$n=122$	Adults	Mild to moderate	Aero (4 KKW) $\times$ Aero (16 KKW)	IDS-C	Remission: IDS-C 12 or $<$	Generalized Linear Model	Sex and Sex $\times$ Family history of mental illness interaction ^a	Remission: 4 KKW=15.5%; 16 KKW=28.3%	Sex: Men ($\tau=5.4$)* Women ($\tau=2.1$) Sex $\times$ Family history of mental illness Men ($\tau=2.9$)* Women ($\tau=2.0$)*
Toups et al. (2011)	$n=104$	Adults	Mild to moderate	Aero (4 KKW) $\times$ Aero (16 KKW)	IDS-C	Remission: IDS-C 12 or $<$	Mixed Effect Models	BDNF, BMI, Marital status, Quality of life and BDNF $\times$ BMI interaction ^a	Remission: 4 KKW=15.5%; 16 KKW=28.3%	BDNF ($\tau=-0.25$)*, BMI ($\tau=0.05$), Marital status ($\tau=2.83$)*, Quality of life ($\tau=-0.15$)* and BDNF $\times$ BMI interaction

Krogh et al. (2012)	n = 115	Adults	Mild to moderate	Aero × Stretching	HAMD	Remission: no longer meet DSM-IV criteria for MDD and a HAMD = 8 or < 12 or < 12	Mixed Effect Models	Depression severity, recurrent depression, sex	Remission: Aero: 28.6%; Control Group: 30.5%	($r = -0.04$)*
Rethorst et al. (2013)	n = 105	Adults	Mild to moderate	Aero (4 KKW) × Aero (16 KKW)	IDS-C	Response: 50% of reduction on HAMD scores; Remission: 7 or < 12	Mixed Effect Models	IL 1b, IL-6, INF- γ , TNF- α	Remission: 4 KKW = 15.5%; 16 KKW = 28.3%	IL 1b (?), IL-6 (?), INF- γ (?), TNF- α ($r = -0.61$)*
Schuch et al. (2015)	n = 50	Adults	Severe	Aero + Usual T × Usual T	HAMD	Response: 50% of reduction on HAMD scores; Remission: 7 or < 12	Pearson correlation	Age, BMI, Depression severity, recurrent depression, sex, weight	Remission: Aero + Usual T = 48%; Usual T = 32%	Age (?), BMI (?), Depression severity (?), recurrent depression (?), sex (?), weight (?)

Aero = Aerobic exercise; BDNF = Brain-derived neurotrophic factor; BMI = Body mass index; GP care = General practitioner care; HAMD = Hamilton scale for depression; HB = Home-based; HR = Heart rate; INF- γ = Interferon; IDS-C = Inventory for depressive symptomatology-clinician; IL-1b = Interleukin 1 beta; IL-6 = Interleukin 6; KKW = Kilocalories per week; M = Medication; METS = Metabolic equivalents; PRT = Progressive resistance training; TNF- α = Tumor necrosis factor alpha; QoL = Quality of life; S = Supervised, Usual T = Usual treatment.

* Composite moderator.

* $p < 0.05$.

baseline were directly [both, “+”, 1/1 (100%)] associated with greater or a more rapid decrease of depressive symptoms, respectively.

3.2.2. Clinical features

The most commonly evaluated clinical feature was baseline depression severity. The baseline depression severity was inconsistently associated [“?”, 3/7 (42.8%)] with treatment outcomes. Global functioning [“+”, 1/1 (100%)] and the frequency of physical symptoms (somatic symptoms) [“+”, 1/1 (100%)] were directly and trait anxiety was inversely associated [“–”, 1/1 (100%)] with treatment outcomes. No other individual clinical feature was identified.

3.2.3. Demographical features

No individual demographical feature moderates the antidepressant effects of exercise.

3.2.4. Psychological features

Belief in exercise efficacy as a treatment for depression [“?”, 1/2 (50%)] and QoL [“?”, 2/4 (50%)] were inconsistently associated with treatment outcomes. Life satisfaction [“+”, 1/1 (100%)] and self-esteem [“+”, 1/1 (100%)] were directly associated with response/remission. No other psychological moderator was identified.

3.2.5. Social features

Social support [“+”, 3/3 (100%)] and marital status [“+”, 2/2 (100%)] at baseline were directly associated with better outcomes.

3.3. Composite moderators

Toups et al. (2011) found that higher serum BDNF at baseline was associated with more rapidly improvement of depressive symptoms. In addition, BDNF and Body Mass Index (BMI) interaction predicts the response to exercise, where subjects with higher BDNF and higher BMI presents greater response rates and subjects with lower BDNF and higher BMI presents the lower response rates.

Trivedi et al. (2011) found gender and family history of mental illness moderates the antidepressant effects of exercise. Men, regardless the family history of mental illness and women without family history of mental illness presents greater remission rates for higher doses of exercise.

3.4. Strength of moderator assessment

Only two studies (Rethorst et al., 2013; Toups et al., 2011) meet the criteria for confirmatory evidence. The other nine studies were classified as exploratory evidence. The strength of evidence assessment studies can be seen in detail in Table 3.

3.5. Quality of the trials

Three studies present the results of the secondary outcomes (Herman et al., 2002; Rethorst et al., 2013; Toups et al., 2011) and the quality of the trial was assessed in the study that reported the main outcomes. The quality of the Herman et al. (2002) study was assessed at the Blumenthal et al. (1999) study, the quality of the other two studies (Rethorst et al., 2013; Toups et al., 2011) were both assessed at the Trivedi et al. (2011) study.

Eight studies (Blumenthal et al., 2007; Herman et al., 2002; Krogh et al., 2009, 2012; Rethorst et al., 2013; Schuch et al., 2015; Toups et al., 2011; Trivedi et al., 2011) presenting moderators of response are based on trials with low risk of bias and the other three are based on trials with high risk of bias (Mota-Pereira et al., 2011; Singh et al., 1997, 2005).

Table 2

Summary of studies of individual moderators of response or remission to exercise treatment for depression.

Variable	Significantly associated		Not significantly associated		Association (+ / -)	Summary
	Reference	Association (+ / -)	Reference			
<i>Biological</i>						
BDNF	Toups et al. (2011)	+			+	1/1 (100%)
IFN- γ			Rethorst et al. (2013)		0	0/1 (0%)
IL-1 β			Rethorst et al. (2013)		0	0/1 (0%)
IL-6			Rethorst et al. (2013)		0	0/1 (0%)
TNF- α	Rethorst et al. (2013)	+			+	1/1 (100%)
<i>Clinical</i>						
Depression Severity	Singh et al. (1997), Mota-Pereira et al. (2011) and Herman et al. (2002)	—	Blumenthal et al. (2007), Krogh et al. (2012), Schuch et al. (2015) and Herman et al. (2002)		0	3/7 (33.3%)
Dysfunctional Attitudes			Herman et al. (2002)		0	0/1 (0%)
Global Functioning	Mota-Pereira et al. (2011)	+			+	1/1 (100%)
Physical Symptoms	Herman et al. (2002)	+			+	1/1 (100%)
Recurrence of Depression			Krogh et al. (2012) and Schuch et al. (2015)		0	0/2 (0%)
State Anxiety	Herman et al. (2002)	—			—	1/1 (100%)
<i>Demographical</i>						
Age			Schuch et al. (2015)		0	0/1 (0%)
BMI			Schuch et al. (2015)		0	0/1 (0%)
Employment			Herman et al. (2002)		0	0/1 (0%)
Gender (male)	Trivedi et al. (2011)	+	Krogh et al. (2009, 2012) and Schuch et al. (2015)		0	1/4 (25%)
Weight			Schuch et al. (2015)		0	0/1 (0%)
<i>Psychological</i>						
Anger			Herman et al. (2002)		0	0/1 (0%)
Belief in efficacy of exercise	Singh et al. (2005) ^a	+	Singh et al. (2005) ^b		+	1/2 (50%)
Belief in GP Ability to treat depression			Singh et al. (2005) ^{a,b}		0	0/1 (100%)
Life satisfaction	Herman et al. (2002)	+			+	1/1 (100%)
Locus of control			Singh et al. (2005) ^{a,b}		0	0/2 (0%)
Personality type			Singh et al. (2005) ^{a,b}		0	0/2 (0%)
Quality of Life			Singh et al. (2005) ^{a,b}		0	0/2 (0%)
Self-efficacy			Singh et al. (2005) ^{a,b}		0	0/2 (0%)
Self-esteem	Herman et al. (2002)	+			+	1/1 (100%)
<i>Social</i>						
Social Support	Herman et al. (2002) and Singh et al. (2005) ^{a,b}	+			+	3/3 (100%)

+ = Direct association, - = Inverse association, 0 = No association, GP = General Practice, IFN- γ = Interferon gamma, IL-1 β = Interleukin one Beta, IL-6 = Interleukin six, TNF- α = Tumor Necrosis Factor Alpha.

^a Low intensity exercise.

^b High intensity exercise.

Table 3

Strength of the evidence assessment.

Study	Was the subgroup analysis specified a-priori	Was the selection of subgroup factors for analysis theory/evidence driven	Were subgroup factors measured prior to randomization	Was measurement of subgroup factors measured by adequate (reliable and valid) measurements, appropriate for the target population	Does the analysis contain an explicit test of the interaction between moderator and treatment	Strength of evidence
Singh et al. (1997)	No	No	Yes	Yes	No	Exploratory evidence
Herman et al. (2002)	No	No	Yes	Yes	Yes	Exploratory evidence
Singh et al. (2005)	Yes	Yes	Yes	Yes	No	Exploratory evidence
Blumenthal et al. (2007)	No	No	Yes	Yes	No	Exploratory evidence
Krogh et al. (2009)	No	No	Yes	Yes	No	Exploratory evidence
Mota-pereira et al. (2011)	No	No	Yes	Yes	No	Exploratory evidence
Trivedi et al. (2011)	Yes	No	Yes	Yes	Yes	Exploratory evidence
Toups et al. (2011)	Yes	Yes	Yes	Yes	Yes	Confirmatory evidence
Krogh et al. (2012)	No	No	Yes	Yes	Yes	Exploratory evidence
Rethorst et al. (2013)	Yes	Yes	Yes	Yes	Yes	Confirmatory evidence
Schuch et al. (2015)	No	No	Yes	Yes	No	Exploratory evidence

4. Discussion

The review identified several potential individual biological, clinical, psychological, and social and two potential composite moderators of the antidepressant effects of exercise on depression. However, none was consistently associated with better outcomes in analysis including 4 or more groups. Also, only two individual biological moderators (BDNF and TNF- α serum levels) and one composite moderator (the interaction between BDNF and BMI) provided confirmatory evidence according.

Clinical moderators were the most evaluated moderators. Baseline severity of depression was evaluated in six unique trials (seven subgroups), presenting an inconsistent moderating role. Although some evidence suggesting that exercise is also efficacious for more severe forms of MDD (Knubben et al., 2007; Schuch et al., 2015), the present review does not support baseline severity of depressive symptoms as moderator. Importantly, a major limitation of this analysis is that the studies evaluated different ages and exercise modalities. Also, most of studies enrolled mildly to moderately depressed participants or presented the baseline mean of severity classified into the mild to moderate range. Only one study evaluated a sample composed by inpatients with severe depression (Schuch et al., 2015); thus, it is possible that the severely depressed group of patients was underrepresented. Global functioning, frequency of physical symptoms and state anxiety were identified as moderators in individual studies (Herman et al., 2002; Mota-Pereira et al., 2011). However, these findings needs further replication. No other clinical feature was identified as a potential moderator.

Psychological features were the second most evaluated features. Belief in efficacy of exercise as a treatment for depression was inconsistently identified as a potential moderator of the antidepressant effects of low intensity strength exercise, but not for high intensity (Singh et al., 2005). This finding is based, however, in a single study in older. Further studies are required to evaluate the role of belief in efficacy of exercise in younger samples, as well as, in aerobic interventions.

Social support moderates the effects of exercise on depression in older adults (Herman et al., 2002; Singh et al., 2005), while marital status moderates the effects of aerobic exercise, regardless the dose of exercise in adults (> 18 years) (Toups et al., 2011). Interestingly, social support appears to moderate not only the antidepressants of exercise, but also of other treatments as pharmacological antidepressants (Bosworth et al., 2002), and psychotherapies (Lindfors et al., 2014). Of note, the moderating role of social support was identified in older and further studies are needed evaluating the moderating role of social support in younger adults. In this regard, people with a poorer social support may require additional attention from mental health workers in order to promote better treatment outcomes.

Only study one found that men present greater remission rates compared to women (Trivedi et al., 2011). The other studies did not found any association. A major limitation with regard to this finding is that two of the three studies (Krogh et al., 2009, 2012) did not found significant differences on the remission rates between intervention and control groups, showing the lack of specific effects of exercise. The lack of exercise specific effects in the studies may decreased the ability to detect a significant role of gender predicting the antidepressant effect of exercise.

Two individual biological moderators were identified in single studies, BDNF and TNF- α . The findings, however, are of limited generalization. The studies evaluated the effects of aerobic exercise in a sample composed of partial responders to Selective Serotonin Reuptake Inhibitors (SSRI) (Rethorst et al., 2013; Toups et al., 2011). Thus, it is possible that the SSRI's have raised the serum levels of BDNF to a level higher than found in non-medicated patients, or patients that are using other antidepressants.

Also, the higher levels of TNF- α found in the patients of the TREAD study may be representative of a subgroup of patients that are non-responsive to previous pharmacological treatment and again, some caution is needed before the generalization of these findings to non-medicated patients or patients that are taking other class of antidepressants or other medications. At this moment, it is not possible to determine the biological mechanisms (mediators) that underlies the antidepressant effects of exercise in people with MDD (Schuch et al., 2016), however, the present review suggests that BDNF and TNF- α are targets that deserves further investigation regards its use as potential moderators.

Four of the psychological moderators evaluated have some potential conceptual overlap or are close constructs. However, they were analyzed separately. It was the case for life satisfaction and Quality of Life (QoL) and for Self-efficacy and Self-esteem. Life satisfaction (Herman et al., 2002) and self-esteem (Singh et al., 2005) were identified as potential moderators of response to aerobic exercise interventions in older adults, while QoL was an inconsistent moderator, moderating the response to aerobic exercise in adults, but not to strength exercise in older adults (Singh et al., 2005; Toups et al., 2011). These findings suggests that the research on moderators can be a challenge since different moderators can be found in different subgroups of patients (QoL was a significant moderator in younger adults but not in older adults), and related to different exercise characteristics (strength $\times$ aerobic). In this regard, individual moderators can be useful predicting the effects of exercise on depression, however, combined moderators can be more reliable and with a greater clinical significance identifying subgroups with greater chance of successful response (Kraemer et al., 2002; Wallace et al., 2013).

In the present review, two studies identified two composite moderators: Higher BDNF levels interacts with BMI, and participants presenting the higher values of BDNF and BMI presents a higher decrease of depressive symptoms compared to those with higher BDNF but lower BMI (Toups et al., 2011). Also, gender and family history of mental illness interacts moderating the antidepressant effects of exercise, showing that exercise may be more efficacious for women without family history of mental illness when compared to women with family history of mental illness (Trivedi et al., 2011). It should be noted, however, that these results are from the same sample of partial responders to previous pharmacological treatment, using the same aerobic intervention. Thus, further trials investing the role of composite moderators in other samples of older patients, as well as, using other modalities of exercise are required.

Some studies included in this review present some limitations. Only two (Rethorst et al., 2013; Toups et al., 2011) studies provided confirmatory evidence according the Pincus et al. (2011) criteria of the strength of the evidence. In fact, four trials clearly stated that aimed to evaluated the potential moderators (Rethorst et al., 2013; Singh et al., 2005; Toups et al., 2011; Trivedi et al., 2011) and only three provide a brief rationale for the selection of this moderators (Rethorst et al., 2013; Singh et al., 2005; Toups et al., 2011). These limitations can result in the identification of spurious findings found due the use multiple testing ("fishing" effect) (Bender and Lange, 2001). Accordingly, it is recommended the use of a-priori hypothesis, driven by theoretical or evidence based background, using valid and reliable measures, and with a clear presentation of the statistical values to improve the strength of the evidence and avoid the potential issue of the "fishing" effects due multiple testing.

4.1. Limitations and strengths

The major limitation in the present study is the lack of an meta-analytical approach. There was significant heterogeneity regards

the statistical tests (Correlations, analysis of variances, analysis of covariance), sample (older $\times$ young adults) and methods (aerobic $\times$ strength exercises) used in the studies. Also most of moderators were evaluated in only one study. Due that reasons, a qualitative analysis with summarized scores would provide an easier and more meaningful interpretation of the results. It should be noted, however, that the Sallis (2000) methods requires a minimum of four groups/studies for each moderator to be considered consistent and only depression severity at baseline, gender and quality of life analysis have four or more groups.

Other limitation is that three (Mota-Pereira et al., 2011; Singh et al., 1997, 2005) of the eleven trials included were considered of being of high risk of bias. This studies provided data for clinical (Depression severity and global functioning) and psychological (Belief in efficacy of exercise, belief in GP ability to treat depression, locus of control, personality type, quality of life, self-efficacy, self-esteem, social support) moderators and some caution should be taken in the interpretation of this results.

The study used a well conducted, pre-specified protocol, according to the PRISMA recommendations (Moher et al., 2009) to select, evaluate, report and synthesize the studies. In the present study, any clinical trial that evaluated the effects of exercise on depression was kept until the read of full text step. This strategy was used since several trials do not state in the title or abstract that evaluated potential moderators and we carefully considered this issue to avoid the miss of potential relevant articles. In addition, the present review may potentially suffer from publication bias, which is a common limitation of systematic reviews.

5. Conclusion

There are several clinical (somatic symptoms, state anxiety, and global functioning), psychological (Life-satisfaction and self-esteem), social (social support and marital status) and biological features (BDNF and TNF- α) that potentially predict or moderate the antidepressant effects of exercise. However, the small number of studies and the methodological limitations in the analysis of moderators requires a greater number of studies before definitive conclusions. Further studies evaluating the moderating role of clinical, psychological, social and biological features, as well as composite features supported by an a priori hypothesis, driven by theoretical or evidence based background, using valid and reliable measures, and with a clear presentation of the statistical values are required studies in order to provide confirmatory evidence of moderators of successful use of exercise as a treatment for depression.

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Conflict of interest

None.

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