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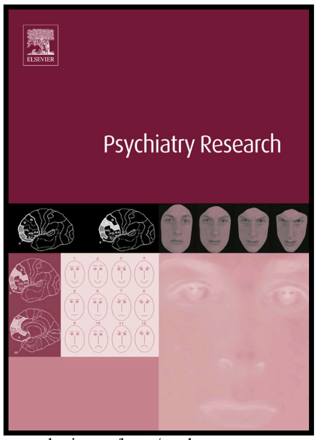

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An examination of the anxiolytic effects of exercise for people with anxiety and stress-related disorders: A meta-analysis

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Abstract

The literature regarding exercise for people with established anxiety disorders is equivocal. To address this issue, we conducted a systematic review and meta-analysis investigating the benefits of exercise compared to usual treatment or control conditions in people with an anxiety and/or stress-related disorders. Major electronic databases were searched from inception until December/2015 and a random effect meta-analysis conducted. Altogether, six randomized control trials (RCTs) including 262 adults (exercise n=132, 34.74[9.6] years; control n=130, 37.34[10.0] years) were included. Exercise significantly decreased anxiety symptoms more than control conditions, with a moderate effect size (Standardized Mean Difference=-0.582, 95%CI -1.0 to -0.76, p=0.02). Our data suggest that exercise is effective in improving anxiety symptoms in people with a current diagnosis of anxiety and/ or stress-related disorders. Taken together with the wider benefits of exercise on wellbeing and cardiovascular health, these findings reinforce exercise as an important treatment option in people with anxiety/stress disorders.

Keywords: exercise, physical activity, anxiety, stress,

1. Introduction

Anxiety disorders are pervasive mental health conditions and are currently the leading cause of global years lived with disability (Lopez et al., 2006; Baxter et al., 2014). Anxiety disorders (AD) such as generalized anxiety disorder (GAD), panic disorder (PD), and phobias, as well as closely related stress related disorders such as post-traumatic stress disorder (PTSD), are associated with a considerable range of deleterious impacts upon the individual, including lower quality of life (Mendlowicz and Stein, 2000), comorbid mental illness (Hofmeijer-Sevink et al., 2012) and elevated cardiovascular disease and associated premature mortality (Roest et al., 2012; Batelaan et al., 2016). Moreover, the societal and financial impacts are profound across the Western and Developing World (Chisholm et al., 2016).

Pharmacological agents such as selective serotonin reuptake inhibitors (SSRIs) and various forms of cognitive behavioral therapy (CBT) are the frontline treatments for people with anxiety/stress disorders (Hofmann and Smits, 2008; de Vries et al., 2016). Nevertheless, about a third of patients do not respond to SSRIs and CBT (Hofmann and Smits, 2008; de Vries et al., 2016). In addition, availability of those treatment options is scarce in developing world. In some stances, waiting times for psychotherapy can be lengthy (up to 12 months), resulting in a poor prognosis and more entrenched symptoms.

Exercise might be an alternative for subjects with AD unwilling to initiate medication or psychotherapy, or for subjects from regions where frontline resources are unavailable. There is evidence showing exercise can improve anxiety symptoms in people without established anxiety disorders (Conn, 2010; Herring et al., 2014; Rebar et al., 2015), including those with general chronic illness (Herring et al., 2010). However, the evidence for the anxiolytic effects of exercise in people with a diagnosis anxiety/stress disorders is equivocal and has considerable limitations. To date, one prior meta-analysis has investigated the potential benefits of exercise in people with a diagnosis of AD (Bartley et al., 2013) that concluded, that currently there is insufficient evidence to recommend aerobic exercise for their treatment. However, further investigation is now required due to more recent evidence (Gaudlitz et al., 2015; Powers et al., 2015; Rosenbaum et al., 2015) on the topic and methodological shortcomings with this prior analysis. First, exercise was compared to control conditions with established efficacy for anxiety such as mindfulness and non-aerobic physical activity, thus increasing the likelihood of a type II error. Second, no meta-regression investigated potential mediators despite the significant heterogeneity. Third, no trial with patients with anxiety/stress disorders such as PTSD was reviewed. Overall, the anxiolytic impact of exercise in comparison to usual treatment and the factors which may influence this impact, have yet to be examined. Given also the increased attention to the filed since the implementation of the above review, an update is essential.

We conducted a meta-analysis of exercise RCTs versus control conditions (including treatment as usual/ wait list/ TAU) among people with a diagnosis of an anxiety and/or a stress-related disorder. The specific aims of the current review were: (1) to evaluate the effects of exercise on anxiety symptoms in people with anxiety/stress disorders, (2) to identify moderators through meta-regression analyses, including sample characteristics (gender and age) and exercise intervention variables (length of the trial, frequency, dropout) that could impact the effects of exercise on anxiety symptoms; and (3) to evaluate the magnitude of the symptom reduction in control groups (control group response) of the included trials.

2. Methods

This systematic review is in line with the PRISMA statement (Moher et al., 2009) and the MOOSE guidelines (Stroup et al., 2000).

2.1 Inclusion criteria

Included in this meta-analysis were studies that fulfilled the following criteria. *First,* investigated adult participants with a primary diagnosis of any anxiety or stress disorder according to established criteria (e.g., Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Association, 2000)). The anxiety disorders eligible were: Generalized Anxiety Disorder (GAD), Panic Disorder (PD), Obsessive-Compulsive Disorder (OCD) and Social Phobia. We also included subjects suffering from Post-Traumatic Stress Disorder (PTSD). Despite not being currently classified as an anxiety disorder in the 5th edition of the DSM, PTSD was classified as anxiety disorder by the DSM-IV, it is highly comorbid with anxiety disorders and preserves several similarities regards the core symptoms with this specific group (Byllesby et al., 2016). *Second*, measured anxiety symptoms pre- and post-intervention (or mean change) using a validated measure (e.g., Hamilton scale for anxiety (Hamilton, 1959), PTSD checklist (Ruggiero et al., 2003)). *Third,* were Randomized Controlled Trials (RCTs) investigating exercise, as defined by Caspersen (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", in the active arm of the trial. Trials that used yoga, tai chi or qigong, were not included since previous studies found significant heterogeneity in these trials when compared with conventional aerobic or resistance exercise (Bridle et al., 2012). *Fourth*, included a non-active control group condition such as usual-care, wait-list control, placebo pills or other social activities (e.g.: classes of health education). Trials that compared other exercise intervention (e.g: Aerobic x anaerobic) for comparison or other structured active treatment comparison (such as pharmacotherapy, electroconvulsive therapy [ECT] or psychotherapy) were excluded. The inclusion of those control groups can often be expected to produce significant improvements over the course of a trial (Stubbs et al., 2016b). *Fifth,* were published in English language in a peer-reviewed journal.

2.2 Information sources and searches

Two independent reviewers (BS, FS) searched Academic Search Premier, MEDLINE, Psychology and Behavioral Sciences Collection, PsycINFO, SPORTDiscus, CINAHL Plus and Pubmed without language restrictions from database inception until 15/12/2015. The strategy search can be seen at the supplementary material. The reference lists of included articles were also considered for potentially eligible articles. Also, reference lists of previous systematic reviews evaluating the effects of exercise on anxiety were considered for potentially eligible articles (Bartley et al., 2013; Jayakody et al., 2013; Herring et al., 2014; Stonerock et al., 2015).

2.3 Study selection

Following the removal of duplicates, two independent reviewers (BS, FS) screened all potentially eligible articles using the titles and abstracts. Two authors then both applied the eligibility criteria, after obtaining the full texts, and generated a final list of included articles by consensus.

2.4 Outcomes

The primary outcome of interest was the mean change in anxiety symptoms in the exercise group versus the control group according to a validated outcome measure. The mean change effect size was calculated using the change from baseline to outcome for each group. The estimation of the effect size based on the mean change, instead the post-intervention outcome only, allow a more accurate assessment of the effect of the intervention since it accounts for potential differences between the groups at baseline. We calculated the standard mean difference (SMD) and 95% confidence intervals (CIs). Secondarily, we were interested in the mean change in anxiety symptoms in the control group along (expressed as SMD and 95% CI).

2.5 Data extraction

Two authors (FS, BS) independently extracted data using a data extraction form, including: sample (number of participants, age, % of women, % of participants taking antidepressants, and severity of baseline symptoms), exercise intervention (length of the trial, intensity of intervention [according the American College of Sports Medicine (ACSM) classification of intensity (Garber et al., 2011)], weekly frequency, and type of exercise and methodological factors (year of publication, instruments used in diagnosis and symptom severity assessment and drop-out rate of both groups). Finally, we extracted data on the mean and standard deviation (SD) pre- and post-test anxiety symptom rating scales for the exercise and the control group (primary outcome). In studies reporting more than one scale, we used data for the main outcome suggested by the authors. If this was not available, we used the mean change and SD from pre- and post-test, if reported within the study.

2.6 Risk of bias

Two authors (FS, BS) assessed studies on the presence of high, low risk or unclear risk of bias according to the Cochrane Handbook definition (Higgins and Green, 2011). The risk of bias was assessed by 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. To be considered of low risk of bias, studies had to 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 were based on previous studies (Cooney et al., 2013).

2.7 Meta-analysis

We used a random effects meta-analysis due to the expected heterogeneity. The SMD and 95% confidence intervals (CIs) were used as measures of effect size (ES). The meta-analysis was conducted in the following steps: first, we calculated the SMD statistic together with 95% CIs to establish the effects of exercise on anxiety across all studies using Comprehensive Meta-Analysis software (CMA; Version 3, Biostat, Englewood, New Jersey). Second, we conducted meta-regression analyses to investigate the potential moderators of the anxiolytic effects of exercise. Potential moderators were chosen a priori according to previous literature and included: sex, age, use of medication, the length of the trial, weekly frequency of the intervention and the rate of drop-out. Third, the mean control group response across trials was calculated. Heterogeneity was assessed with the Cochrane Q and I^2 statistics for each analysis (Higgins et al., 2003). Effects sizes can be interpreted as being considered small if > 0.2, moderate if > 0.5, or large if > 0.8 (Cohen, 1988). Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau (Begg and Mazumdar, 1994) and Egger bias test (Egger et al., 1997). In addition, we conducted a trim and fill adjusted analysis (Duval and Tweedie, 2000) to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric about the (new) effect size. Finally, the fail-safe number of negative studies that would be required to nullify (i.e. make $p>0.05$) the effect size was calculated (Rosenthal, 1979).

3. Results

3.1 Search results

Following the removal of duplicates from the searches, 3,999 entries were considered at the title and abstract level. From 62 full texts, six studies (Broocks et al., 1998; Herring et al., 2012; Gaudlitz et al., 2015; Powers et al., 2015; Rosenbaum et al., 2015) had met the inclusion criteria for the meta-analysis. A summary of the search results including reasons for exclusion are presented in figure 1.

Figure 1 here

3.2 Characteristics of included trials and participants

Across the 6 studies, 262 adults with anxiety/stress disorders were included, of whom 132 and 130 were randomised to exercise and control conditions, respectively. The anxiety disorders included were PD (Broocks et al., 1998; Gaudlitz et al., 2015), PTSD (Powers et al., 2015; Rosenbaum et al., 2015), GAD (Herring et al., 2012) whilst the other study included people with either GAD, PD or social phobia (Merom et al., 2008). The mean age was 34.74 (SD=9.6) years and 37.34 (SD=10.03) years for the exercise and control groups, respectively. All studies included in the analysis used aerobic exercise training, and all but one study (Rosenbaum et al., 2015) included outpatient samples, with a training frequency ranging from 1 (Powers et al., 2015) to 7 (Merom et al., 2008) times per week. The exercise intensity was 70% of VO2 max (Gaudlitz et al., 2015; Powers et al., 2015) and 12-17 in the RPE (Rosenbaum et al., 2015). The intensity of exercise is not clear in the other studies. Four studies used clinician rated (Broocks et al., 1998; Herring et al., 2012; Gaudlitz et al., 2015) and two used self-reported measures (Merom et al., 2008; Rosenbaum et al., 2015) to assess anxiety symptoms. In only one trial, the participants were performing exercise only (monotherapy) (Broocks et al., 1998). Three studies used in group format with an exercise session duration of 30 minutes. Participant details and symptom measures are presented in table 1. Only one trial was considered of high quality (low risk of bias) (Herring et al., 2012). Full details of the quality assessment can be found at supplementary table 2.

Table 1 here

3.3 Effect of exercise on anxiety symptoms

Across the six studies, exercise significantly reduced anxiety symptoms (SMD -0.581, 95%CI -1.0 to -0.76, p=0.02, I^2=66%) (Figure 2). The Egger (intercept = -3.37, p=0.08), and the Begg and Muzandar tests (Tau = -0.4, 0.25) did not indicated the presence of publication bias. The Duval and Tweedie trim and fill test did not adjusted the effect size.

3.4 Meta regression

Full details of the exploratory meta-regression are demonstrated in table 2. No potential variables were identified modifying the effects of exercise on anxiety and stress disorders.

Figure 2 here

3.5 Control group response of anxiety symptoms

A meta-analysis demonstrated that control groups had a non-significant improvement in anxiety symptoms over the course of the exercises RCTs (SMD -0.237, -0.764 to 0.271, p=0.37). The publication bias corrected value remained unchanged.

3.6 Meta-regression

A higher proportion of dropout in the control group (β = 0.044, 95% CI 0.019 to 0.069,p >0.001, R^2=1.00) and the lower quality of the study moderated a larger improvement in anxiety symptoms (β = -1.301, 95% CI -2.409 to -0.193, p=0.02, R^2=0.38).

Table 2 here

4. Discussion

Our data suggest that exercise should be considered an evidenced-based option for anxiety symptoms among people with anxiety/ stress related disorders. Specifically, when compared to control conditions, exercise has an effect size in the medium range. Whilst these findings suggest that exercise could be considered as an evidence-based treatment form for patients with anxiety disorders, one should note the limited number of reviewed trials (six). In addition, most of these trials were identified as being a high risk of bias. In our meta regression, it was not possible to identify significant moderators that explain heterogeneity in efficacy estimates.

Previous research (Bartley et al., 2013) suggesting that exercise is not effective for anxiety disorders due to the inclusion of active control groups, which might have reduced the effect size of exercise and a type II error. When considering the greatly increased risk of cardiovascular disease and associated mortality (Player and Peterson, 2011; Cohen et al., 2015) in anxiety disorders, along with the evidence of exercise in the prevention and management of cardiovascular disease in other mental disorders and non-clinical populations (Naci and Ioannidis, 2013; Rosenbaum et al., 2014), it is clear that the benefits of exercise for people with anxiety could extend considerably beyond treating mental health symptoms (unlike other treatments such as antidepressants and CBT). However, there is currently limited data looking at the impact of exercise on these important outcomes and therefore future research is required to examine this.

Previous research in antidepressants has found that baseline severity of anxiety symptoms does not influence antidepressant response (de Vries et al., 2016). Within our meta-regression, we did not find any significant effect on baseline anxiety symptoms and treatment outcome from exercise. Importantly, we have found a moderate effect (SMD = -0.58) on anxiety symptoms reductions, which is of similar magnitude of the anxiolotyc effects from common pharmacotherapy such as paroxetine (SMD = -0.56), flouxetine (SMD = -0.56), quetiapine (SMD = -0.56), fluvoxamine (SMD = -0.60) and venlafaxine (SMD = -0.50) in people with anxiety disorders (Bandelow et al., 2015). Despite the evidence of efficacy, we detected moderate levels of heterogeneity between studies, which were not explained by potential moderators assessed in the study in our meta regression. Nonetheless, this is perhaps unsurprising given the relatively small number of studies included. Given this, the investigation of potential moderators of the benefits of exercise in anxiety/ stress related disorders should be an area of priority.

Unlike in the control groups within depression in a recent meta-analysis (Stubbs et al., 2016b), we did not find evidence of control groups significantly improving in anxiety symptoms. However, meta-regression of the control group response indicates that a higher drop out in the control group influenced a more considerable improvement in anxiety symptoms, indicating a survival bias within the literature that researchers of future RCTs should consider when undertaking exercise studies. This also demonstrates the great importance of conducting intention-to-treat analysis in exercise RCTs. According to the Consort statement (Moher et al., 2001), intention-to-treat analysis should be used to evaluate the outcomes of RCTs. Research in people with depression (Stubbs et al., 2016a) and schizophrenia (Vancampfort et al., 2016), has demonstrated that supervision by suitably qualified exercise professionals is associated with lower dropout rates. Given this, in practice, clinicians with expertise in the delivery of exercise might assist in maximizing participation and the benefits gained from exercise in people with anxiety disorders. This can be done assisting patients to identify the exercise characteristics that are more suitable in terms of type, intensity and volume. Also, in order to improve adherence, exercise professionals should assist patients to improve their: (a) sense of autonomy (i.e., experiencing a sense of psychological freedom when engaging in exercise), (b) individual competence (i.e., ability to attain desired outcomes following the exercise program), and (c) need for relatedness (i.e., being socially connected when being physically active) (Vancampfort et al., 2015).

There is a set of potential neurobiological and psychological mechanism explaining the anxiolytic effects of exercise however, the exact reasons are yet to be elucidated. Exercise-related increases in BDNF is one potential mechanism (Asmundson et al., 2013). Studies have found an increase in BDNF serum levels following an acute exercise bout in people with anxiety disorders (Strohle et al., 2010). To the best of our knowledge, however, no study evaluated the BDNF response to long-term interventions in people with anxiety disorders. Exercise seems to regulate the autonomic system (AS) functioning. Heart rate variability (HRV), a marker of AN functioning, or more specifically, of parasympathetic system activity, is reduced in people with anxiety disorders, and may play a role in anxiety symptoms regulation (Alvares et al., 2016). Exercise, in turn, may improve AN functioning, increasing the HRV (Hsu et al., 2015), that may mediate the anxiety symptoms reduction in some, but not all people with increased anxiety symptoms (Gaul-Alacova et al., 2005). Other potential biological mechanisms refers to the reduction of arousal at neuronal level due susceptive exercise exposition, mediated by increases on B-endorphins, serotonin, and other endogenous opioid neuropeptide transmitters (Asmundson et al., 2013; Herring et al., 2014). The potential psychological mechanisms refer to decreases of anxiety sensitivity, occasioned to the frequent exposure to the anxiety symptoms in the exercise context (Smits et al., 2008), an increase of the self-efficacy (Petruzzello et al., 1991) and a improvement on negative affect via changes in self-esteem (Petruzzello et al., 1991). However, future research is required to fully elucidate the potential anxiolytic mechanisms of exercise.

Due to low variability in the data, it was not possible to investigate the influence of the frequency, intensity and type of exercise on outcomes observed. Therefore, clinical recommendations should remain in line with general health recommendations (ACSM) or the International Organization of Physical Therapists in Mental Health (Vancampfort, 2012) : Perform at least 150 minutes of moderate intensity physical activity or 75 of moderate to vigorous aerobic activity per week. It can be achieved in bouts of 10 minutes, spread across the day.

It is important to note some limitations with our meta-analysis. First, we only included six RCTs with a modest number of participants and which were mostly rated as low quality. Second, the RCTs included within this review included various different types of anxiety disorder and it was not possible to conduct subgroup analyses to investigate the benefits of exercise on different anxiety disorder types. Studies in PTSD were included in our review since PTSD was considered an anxiety disorder until the DSM-IV, being classified as a stress-related disorder in DMS-5. Considering the exclusion of the two trials in people with PTSD, the SMD is reduced to -0.48, and is no longer significant p=0.11 (data available on request). Inversely, we did not identify any RCT in people with obsessive compulsive disorder that meet our criteria. Therefore, more high quality research is needed within each specific anxiety disorder.

We suggest that further high quality RCTS could investigate the role of intensity, volume, frequency and type of exercise on anxiety symptoms in people with anxiety disorders. Also, the putative mechanisms of the effects of exercise on anxiety symptoms are not elucidated, and deserve some attention.

5. Conclusion

In conclusion, our data suggests that exercise is seen as an effective intervention in improving anxiety symptoms in people with anxiety and stress-related disorders. However, the small number of trials should be considering in the interpretation of these results, and more high quality trials are required. Given the wider benefits of exercise on wellbeing and cardiovascular markers, we suggest that exercise should be considered an important treatment option among this population.

Declaration of interest

None to declare from any author.

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Table 1 Summary of included studies

Study	*Sample size*		*Age*		*Gender*		*Antidepressant use*		*Outcome*	*Diagnosis*	*Length of the trial weeks*	*Weekly frequency*
	Exercise (n=)	Control (n=)	Exercise (mean or range)	Control (mean or range)	Exercise (% females)	Control (% females)	Exercise (% taking)	Control (% taking)				
Broocks et al., 1998	16	15	31.8	34.8	62.5	60	0	0	HAM-A**	PD	10	3 to 4
Gaudlitz et al., 2015	24	23	35.4	36.2	50	55	?	?	HAM-A**	PD	8	3
Herring et al.,2011	10	10	20.7	24.2	100	100	20	20	PSWQ**	GAD	6	2
Merom et al., 2008	38	36	38.7	39.4	71	86	?	?	DASS21[a]*	GAD, PD, or SP	8 - 10	7
Powers et al., 2015	5	4	?	?	?	?	?	?	PSSI**	PTSD	12	1
Rosenbaum et al., 2015	39	42	47.1	52.1	8	24	?	?	PCL-C *	PTSD	12	3

DASS21[a] = Depression anxiety stress scale, GAD = generalized anxiety disorder, HAM-A = Hamilton scale for anxiety, PCL-C = PTSD checklist–civilian version, PD = panic disorder, PSSI = PTSD symptom scale - interview, PSWQ = Penn state worry questionnaire, SP = social phobia. * = Self-rated, ** = clinician rated.

Table 2: Meta-regression of moderators/correlates of effects of exercise on anxiety

	Moderator	Number RCTs	β	95% CI		P value	R^2
Main exercise response							
	Year publication	6	0.048	-0.028	0.126	0.212	0.21
	Length of the trial	5	-0.141	-0.483	0.200	0.412	0.00
	Weekly frequency	5	0.136	-0.116	-0.389	0.283	0.00
	Age control	5	0.013	0.068	-0.041	0.637	0.00
	Age exercise	5	0.019	0.075	-0.036	0.508	0.00
	%females control	5	-0.000	0.018	-0.019	0.924	0.00
	%females exercise	5	-0.003	0.013	-0.019	0.704	0.00
	%dropout control	4	0.060	0.126	-0.006	0.072	0.60
	%dropout exercise	4	0.025	0.237	-0.186	0.813	0.00
	Symptom severity	4	-0.649	-1.531	0.232	0.146	0.00
	Study quality	6	-0.533	-1.573	0.670	0.359	0.00
CGR							
	Year publication	6	-0.052	-0.140	0.034	0.233	0.07
	Length of the trial	5	-0.436	-0.988	0.115	0.123	0.00
	Weekly frequency	5	0.008	-0.375	0.392	0.562	0.66
	Age control	5	-0.027	0.016	-0.071	0.223	0.00
	%females control	5	0.002	0.019	-0.015	0.824	0.00
	%dropout control	4	0.044	-0.019	-0.069	**>0.001**	1.00
	Symptom severity	4	-0.023	-0.450	0.403	0.913	0.59
	Study quality	6	-1.301	-2.409	-0.193	**0.022**	0.38

CGR = Control group response, CI = Confidence Interval, RCTs = Randomized clinical trials.

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Highlights

- Previous literature regarding the benefits of exercise for anxiety/ stress disorders is equivocal.
- Our data suggest that exercise is more effective than control at reducing anxiety symptoms.
- Given its wider health benefits, exercise should be considered a strategy to improve the health of this population.

Figure 1. Flowchart of study selection

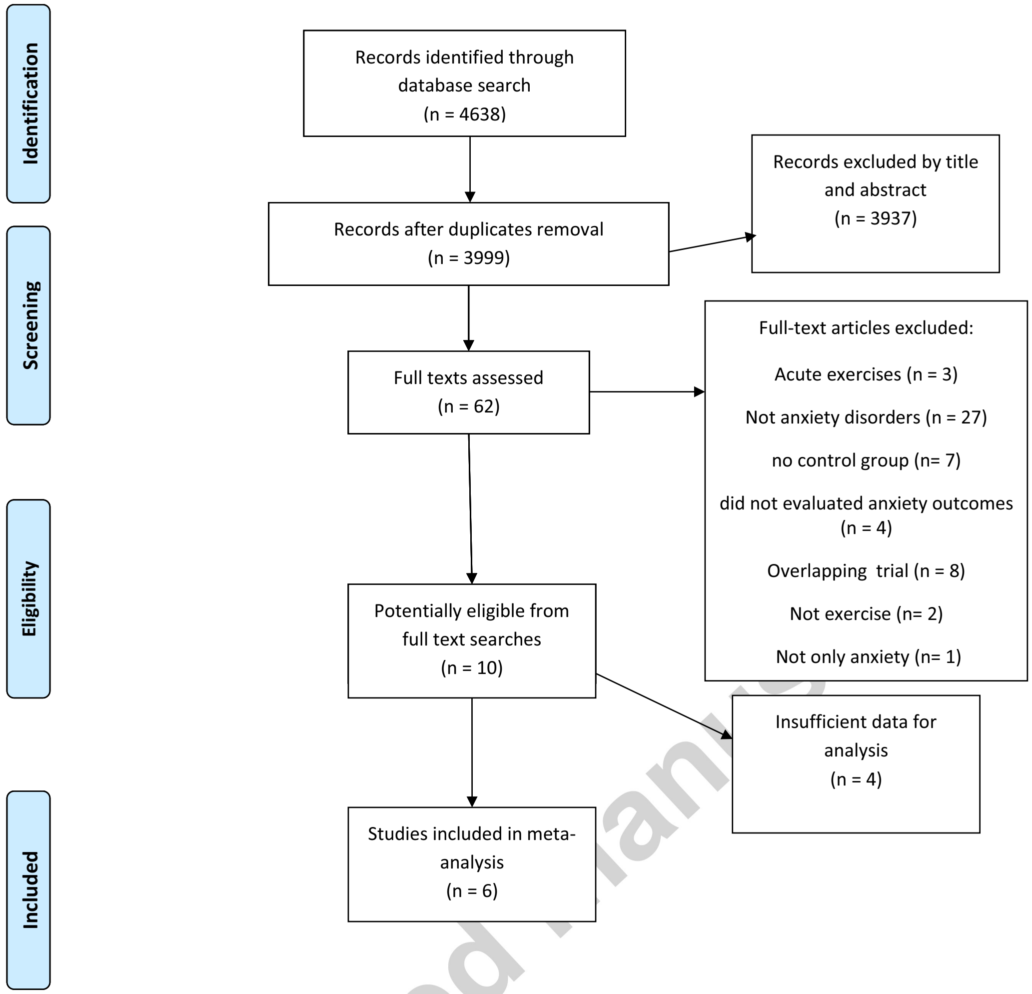

Figure 2 effect of exercise on anxiety symptoms

Study name	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Broocks et al,. 1998	-1.418	0.402	-2.206	-0.630	0.001
Glauditz et al,. 2015	-0.012	0.292	-0.584	0.560	0.967
Herring et al,. 2011	-0.533	0.455	-1.425	0.359	0.241
Merom et al,. 2008	-0.166	0.313	-0.779	0.448	0.596
Powers et al,. 2015	-2.648	0.916	-4.443	-0.852	0.004
Rosenbaum et al,. 2015	-0.316	0.224	-0.754	0.123	0.158
Overall	-0.582	0.258	-1.087	-0.076	0.024

Statistics for each study

$I^2 = 66.6\%$