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Morres, Ioannis; Hatzigeorgiadis, Antonis ; Stathi, Afroditi; Comoutos, Nikos ; Arpin-Cribbie, Chantal ; Charalampos Krommidas, Charalampos ; Theodorakis, Yannis

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1   **Aerobic exercise for adult patients with major depressive disorder in mental health**

2   **services. A systematic review and meta-analysis**

3

4   Short title: Exercise and Major Depression

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6   Ioannis D. Morres[1*], Antonis Hatzigeorgiadis[1], Afroditi Stathi[2], Nikos Comoutos[1], Chantal

7   Arpin-Cribbie[3], Charalampos Krommidas[1], Yannis Theodorakis[1]

8

9   [1]School of Physical Education and Sport Science, University of Thessaly, Trikala, Greece

10   [2]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham,

11   Birmingham, UK

12   [3]Department of Psychology, Laurentian University, Ontario, Canada

13

14   *Corresponding author:

15   Ioannis D. Morres, Ph.D.

16   Postdoctoral Fellow

17   University of Thessaly, School of Physical Education & Sport Science

18   Trikala, Karyes, 42100,

19   Greece

20   Tel: +30 24310 47009

21   Email: iomorres@pe.uth.gr

22

1   **Abstract**

2   Although exercise is associated with depression relief, the effects of aerobic exercise

3   (AE) interventions on clinically depressed adult patients have not been clearly supported. The

4   purpose of this meta-analysis was to examine the antidepressant effects of AE vs. non-

5   exercise comparators exclusively for depressed adults (18-65 years) recruited through mental

6   health services with a referral or clinical diagnosis of major depression. Eleven e-databases

7   and bibliographies of nineteen systematic reviews were searched for relevant randomized

8   controlled trials. A random effects meta-analysis (Hedges' g criterion) was employed for

9   pooling post-intervention scores of depression. Heterogeneity and publication bias were

10   examined. Studies were coded considering characteristics of participants and interventions,

11   outcomes and comparisons made, and study design; accordingly, sensitivity and subgroup

12   analyses were calculated. Across 11 eligible trials (13 comparisons) involving 455 patients,

13   AE was delivered on average for 45minutes, at moderate intensity, three times/week, for 9.2

14   weeks and showed a significantly large overall antidepressant effect ($g = -0.79$, 95% CI = -

15   1.00, -0.57, $p < .00$) with low and non-statistically significant heterogeneity ($I^2 = 21\%$). No

16   publication bias was found. Sensitivity analyses revealed large or moderate to large

17   antidepressant effects for AE ($I^2 < 33\%$) among trials with lower risk of bias, trials with short-

18   term interventions (up to 4 weeks), and trials involving individual preferences for exercise.

19   Subgroup analyses revealed comparable effects for AE across various settings and delivery

20   formats, and in both outpatients and inpatients regardless symptom severity. Notwithstanding

21   the small number of trials reviewed, AE emerged as an effective antidepressant intervention.

Introduction

Depression is a life threatening and disabling mental illness affecting increasingly large proportions of the society at an alarming rate worldwide (Global Burden of Disease Study 2013 Collaborators, 2015; Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). Major depressive disorder (also referred to as clinical depression) is the most common type of depression seriously challenging health systems especially since it is often recurrent and treatment resistant.

Physical exercise is widely recommended in depression treatment (NICE, 2009; CANMAT, 2016; Stanton & Reaburn, 2014). It has been associated with depression relief in various meta-analytic reviews (Craft & Landers, 1998; Rethorst, Wipfli, & Landers, 2009; Robertson, Robertson, Jepson, & Maxwell, 2012; Schuch et al., 2016; Silveira et al., 2013; Stanton & Reaburn, 2014), even after risk of bias was considered (e.g., Rethorst et al., 2009; Schuch et al., 2016). In contrast, other meta-analyses set this association into question after coding for lower risk of bias (Cooney et al., 2013; Krogh, Hjorthøj, Speyer, Gluud, & Nordentoft, 2017; Krogh, Nordentoft, Sterne, & Lawlor, 2011).

Considering carefully the attributes of these meta-analytic studies, however, we identified methodological aspects that could potentially justify these equivocal conclusions. Particularly, in a number of trials reported in these meta-analyses the samples included participants who were recruited through mental health services but also through media advertisements. Also, in a number of trials the diagnosis of depression was not based on valid diagnostic criteria. Three meta-analytic studies, Krogh et al. (2011), Krogh et al. (2017) and Kvam, Kleppe, Nordhus, and Hovland (2016) have exclusively focused on exercise trials for patients with a diagnosis of major depression based on valid diagnostic criteria including the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) or the International Classification of Disease (World Health Organization, 1992).

1 However, some of the trials in these three studies included media respondents. Media

2 respondents may have strong outcome expectations or motivation to lifestyle changes;

3 Blumenthal and Ong (2009) reported that community volunteers of exercise trials for

4 depression are typically motivated to exercise. Instead, depressed patients recruited through

5 health services do not seem to be comparably motivated, as they show high dropout rates

6 from exercise on referral schemes (Crone, Johnston, Gidlow, Henley, & James, 2008; James

7 et al., 2008; Tobi, Kemp, & Schmidt, 2017). In addition, a number of trials reviewed by these

8 three meta-analyses included samples with other mood disorders (e.g., dysthymia), or samples

9 with older adult (+65 years) or both adult (18-65 years) and older adult depressed patients.

10 Older depressed adults show distinct differences in depression (Fiske, Wetherell, & Gatz,

11 2009), demonstrate higher depression relief through exercise (Silveira et al., 2013), and are

12 more likely to complete exercise on prescription programs than adult peers (James et al.,

13 2008). Finally, these three meta-analyses included trials comparing exercise to other exercise

14 activities (e.g., stretching). Such exercise activities, however, have been also shown to

15 improve depression, thus confounding the true antidepressant effect of exercise intervention

16 and misleading relevant conclusions (Schuch, Morres, Ekkekakis, Rosenbaum, & Stubbs,

17 2017).

18 In addition to the issues identified above, the quality of the relevant meta-analysis

19 could improve through a more appropriate assessment for the risk of bias. While exercise

20 reviews for depression are typically coding trials for risk of bias, attributable to the

21 association of systematic errors with overestimation of treatment efficacy (Moher et al., 1998;

22 Schulz, 2001; Schulz, Chalmers, Hayes, & Altman, 1995), this coding has not been based on

23 tools designed for physical therapy interventions, such as physical exercise. This seems

24 essential as intervention-specific design aspects including dropouts may remain undetected

25 and continue to influence conclusions, especially because exercise is perceived as requiring

1 higher time- and effort-demands than other health behaviors (Turk, Rudy, & Salovey, 1984).

2 Relevant coding has been recently addressed by meta-analytic studies in the exercise-anxiety

3 area (Ensari, Greenlee, Motl, & Petruzzello, 2015; Stonerock, Hoffman, Smith, & Blumenthal,

4 2015). Finally, we identified in the literature that the antidepressant effects of aerobic exercise

5 (AE) in particular remain unexplored by meta-analyses, although AE (e.g., walking) is the

6 most pursued type of physical activity in mental health services (Sørensen, 2006).

7   Taking into account all the issues identified above, the purpose of our study was to

8 explore the antidepressant effects of AE intervention, when compared to non-exercise

9 comparators in adult patients, 18-65 years of age, recruited through mental health services

10 with a referral or a clinical diagnosis of major depressive disorder. Towards this goal, coding

11 for risk of bias was addressed based on a tool structured for physical therapy interventions.

12   **Method**

13   This review was conducted in accordance to the Preferred Items for Systematic

14 Reviews and Meta-Analyses (PRISMA) statement that ensures quality through a standard list

15 of 27 items (Moher, Liberati, Tetzlaff, & Altman, 2009).

16 *Literature search*

17   Eligibility criteria of study characteristics included; (1) participants 18-65 years old,

18 recruited via mental health services with a referral or with a previous diagnosis of major

19 depression (without psychotic features) as a primary disorder and not as a result of a mental or

20 medical disorder/condition; (2) AE interventions as defined by the American College of

21 Sports Medicine (ACSM) (Pollock et al., 1998); (3) comparison of AE interventions to any

22 treatment form (e.g., psychotherapy, medication) or condition (e.g., waiting list) excluding

23 exercise activities; (4) outcome measures of depression as a primary outcome; (5) studies with

24 a design of a randomized controlled trial (RCT). Given, however, the limited number of

25 exercise trials for clinically depressed adults seen in literature, it was an a priori decision of

1 this meta-analysis to (i) include comparative efficacy trials and (ii) compare AE to a second

2 intervention (excluding exercise activities) should three-arm RCTs were allocated. Previous

3 meta-analyses for exercise on depression are seen to typically include comparative efficacy

4 trials (e.g., Krogh et al., 2017; Kvam et al., 2016). Finally, the search covered the period from

5 1980 to March 2017 for trials written in English.

6   Two authors independently conducted the literature search. A total of ten electronic

7 databases were searched: SCOPUS, PubMed, PEDro, and the PsyINFO, SPORTDiscus,

8 Academic Search Complete, Education Resource Information Centre via EBSCO. Also, the

9 Proquest Dissertations and Theses database was searched for unpublished studies. In addition,

10 we searched the Trials Register of Promoting Health Interventions (TRoPHI; EPPI Centre),

11 ClinicalTrials.Gov, and the World Health Organization (WHO) International Clinical Trials

12 Registry Platform (ICTRP). We used medical subject headings (e.g., MESH) when possible

13 or text word terms including: depressive disorder, depression, diagnosis, patients, adult

14 (limiters 18-65years), and exercise, aerobic, running, swimming, jogging, walking or

15 bicycling. The full search strategy for the PubMed is given in supplementary material 1.

16   Trials were initially screened through titles and abstracts. Full text versions were

17 obtained subject to positive initial screening. Hand searching was also conducted; we

18 screened the bibliographies of all major systematic reviews including Cochrane reviews in the

19 exercise-depression area in the last 20 years. This led to the revision of 19 systematic reviews

20 (supplementary material 2).

21 *Data extraction*

22   Data were extracted and checked for accuracy and for duplicates onto prepared forms

23 by the first and the fourth author. Subsequently, the two authors reached a consensus on the

24 eligible trials. Researchers of eligible trials were contacted by e-mail to provide additional

25 information on clinical/methodological aspects to their studies. Two reminders were sent

1   within a period of two months. All but one author provided clinical clarifications involving

2   delivery formats of exercise interventions (supervision, location, individually or group) and

3   status of participants (outpatients or inpatients). Also, three authors were contacted to provide

4   methodological clarifications. Relevant information was obtained and included number of

5   dropouts, concealed allocation, blind assessment or baseline balance.

6   *Coding*

7   Coding of eligible trials was based on the PICOS criteria that refer to Participants,

8   Interventions, Comparisons, Outcome measures and Study design (PICOS) (Moher et al.,

9   2009). Hence, coding included the following study characteristics: (1) participants:

10   hospitalized or non-hospitalized (inpatients or outpatients); severity of depression (mild,

11   moderate or severe); (2) intervention: duration ($\leq$ 4weeks), frequency (< 3 days/week, 3

12   days/week or > 3 days/week), intensity (lower, moderate or vigorous), setting (outdoors or

13   indoors), social format (in groups or individually), delivery format (supervised or non-

14   supervised); (3) comparisons: AE vs. non-exercise comparators; (4) outcome measures: rating

15   (self- or clinician-rated); (5) study design: RCTs or comparative efficacy trials with higher or

16   lower risk of bias scores of methodological qualities (score of < 6 or $\geq$ 6) on the

17   Physiotherapy Evidence Database scale (PEDro) (de Morton, 2009).

18   *Risk of bias*

19   The PEDro scale is a well-established comprehensive measure of methodological

20   quality in the literature of physical therapy (Bhogal, Teasell, Foley, & Speechley, 2005),

21   which has shown good psychometric properties (de Morton, 2009; Macedo et al., 2010;

22   Maher, Sherrington, Herbert, Moseley, & Elkins, 2003). Also, the PEDro scale is increasingly

23   used in various research areas (e.g., Knols, de Bruin, Shirato, Uebelhart, & Aaronson, 2010;

24   Pan, Wang, Xie, Du, & Guo, 2014; Pinto et al., 2012), including the area of exercise and

25   anxiety (e.g., Ensari et al., 2015). In the area of exercise for depression, two systematic

1 reviews have employed the PEDro scale (Perraton, Kumar, & Machotka, 2010; Stanton &

2 Reaburn, 2014), but neither was a meta-analysis. Internal validity on the PEDro scale is

3 assessed on a point system favoring between-groups comparisons and point

4 estimates/variability measures; blinding patients, therapists and assessors; baseline balance,

5 intention-to-treat, and drop-outs. The maximum score for the internal validity criteria is 10; in

6 our study the maximum score was 8, as it is difficult, if not impossible, to blind

7 patients/therapists in exercise trials for depression. A cut-off score of 6 was employed for

8 classification of higher quality RCTs (lower risk of bias). This score represents the point of

9 reference for high quality trials when using the PEDro scale (Maher et al., 2003). The first

10 and the third authors independently assessed the methodological quality of each trial, and

11 sought consensus on the relevant evaluations. Cohen's Kappa statistic was computed, and

12 interpreted based on the Landis and Koch reference to estimating the inter-rater agreement

13 (Landis & Koch, 1977).

14 *Statistical analysis*

15   The software Comprehensive Meta-Analysis (Version 2.0, Biostat, Englewood, New

16 Jersey) was used to calculate intervention effects. A random effects model using the Hedges'

17 g criterion was employed to estimate standardized mean differences in depression scores from

18 pre- to post-intervention between exercise and non-exercise comparators (Borenstein, Hedges,

19 Higgins, & Rothstein, 2010). The selection of a random effects model lies upon the

20 assumption that there is a sampling error (within-study error) and between-study variance.

21 Also, the Hedges' g criterion was selected because it prevents overestimation of an effect-size

22 when the retrieved studies are less than 20. Hedge's g algorithms were interpreted with the

23 Cohen's d standards (Cohen, 1992) where values of .20, .50 and .80 point a small, moderate

24 and large intervention effect, respectively.

1   Statistical heterogeneity was assessed with the Cochran's Q and I^2 statistics for each

2   trial (Higgins, Thompson, Deeks, & Altman, 2003) taking into account that I^2 values up to

3   40% are unlikely to be important (Higgins & Green, 2011). Publication bias was assessed by

4   means of visual inspection of the funnel plots and the Begg-Mazumbar Kendall's tau (Begg &

5   Mazumdar, 1994) and Egger bias test (Egger, Smith, Schneider, & Minder, 1997) for the

6   main composite analysis. In case of significant publication bias, the trim and fill statistical

7   procedure was considered on the right and left side of the plot (Duval & Tweedie, 2000). This

8   procedure adds or removes studies to balance an asymmetrical funnel plot and adjusts the

9   effect-size accordingly. In this manner, an unbiased estimate of the effect is provided. Further,

10   the fail and safe criterion (Rosenthal, 1979) was employed to calculate the number of studies

11   needed to nullify significant effects (e.g., >.05) for the main composite analysis. A fail-safe

12   number of five times the number of reviewed comparisons plus 10 (5K+10) is seen as the

13   cutoff score for considering the results robust (Rosenthal, 1979).

14   Also, three sensitivity analyses were performed to explore the robustness of our main

15   finding (overall effect-size). First, we coded lower risk of bias trials (PEDro score ≥ 6)

16   because meta-analytic reviews have reported equivocal conclusions on the association of

17   exercise with antidepressant effects in high quality trials (e.g., Cooney et al., 2013; Krogh et

18   al., 2017; Krogh et al., 2011; Rethorst et al., 2009; Schuch et al., 2016). In the second and

19   third sensitivity analyses we coded trials with short-term (up to four weeks) or preference-

20   oriented exercise interventions, respectively, because both interventional aspects comprised a

21   promising strategy in the only currently available pragmatic RCT for exercise in adult

22   depressed women who were living in the community and recruited though health services

23   (Callaghan, Khalil, Morres, & Carter, 2011); both analyses would potentially contribute to the

24   clarification of the translational value of our main finding for pragmatic settings (routine

25   practice).

1   In addition, eight subgroup analyses were computed based on the PICOS criteria in

2   order to explore in detail the effect of AE on depression across various delivery formats,

3   comparisons and settings, in both out- and in-patients with various depressive symptom

4   severities, and outcome measures used. Differences in effects-sizes for subgroup comparisons

5   were considered significant if non-overlapping 95% confidence intervals for the different

6   subgroup was found (Higgins & Green, 2011). Subgroup analyses involved consideration that

7   less than five comparisons as estimates of effect may reveal imprecise results (Borenstein,

8   Hedges, Higgins, & Rothstein, 2009).

9   Publication bias tests including the Begg-Mazumbar Kendall's tau and Egger bias test

10   were also performed, taking into account, however, that ten or more comparisons are needed

11   to provide more accurate results (Sterne et al., 2011). Also, risk difference (RD) investigated

12   potential differences in the number of dropouts between the AE and non-exercise comparators.

13   Finally, a p-value of 0.05 was considered for significance in all computations.

14   **Results**

15   The PRISMA flow diagram for study selection is presented in Figure 1. Eleven trials

16   involving 455 patients recruited via mental health services were eligible for inclusion. These

17   studies are presented in Table 1 and 2 and are marked (*) in the reference list. One study

18   (Veale et al., 1992) reported two trials, but only the first compared AE to a non-exercise

19   condition and was allocated as Veale et al. (1992-a). Also, Salehi et al. (2016) was a three-

20   arm comparative efficacy trial that employed AE, electroconvulsive therapy (ECT), and AE +

21   ECT. In line to our a priori decision to review comparative efficacy trials and exclude trials

22   with exercise controls, we reviewed only the comparisons of AE vs. ECT and AE + ECT vs.

23   ECT and allocated as Salehi et al. (2016-a) and Salehi et al. (2016-b), respectively. Also, in

24   the three-arm trial of Sadeghi et al. (2016), AE was compared to the non-exercise comparator

25   of "group discussions". This trial, however, compared also cognitive therapy as a second

1   intervention to the same non-exercise comparator. Due to small number of exercise trials for

2   depression, we compared AE to "group discussion" and allocated it as Sadeghi et al. (2016-a),

3   whereas the comparison of AE to cognitive therapy was allocated as Sadeghi et al. (2016-b).

4   The eleven eligible trials yield 13 comparisons and used continuous outcomes at pre/post-

5   intervention with higher scores indicating more severe depression. Based on available

6   evidence from six of the reviewed trials (see Table 1), an average of 65% of eligible patients

7   entered into studies. Finally, trials were implemented in North and South America, Europe

8   and Asia (Table 1).

9   *Study characteristics*

10   Only one eligible trial did not employ fully supervised-based AE (Mota-Pereira et al.,

11   2011); it included one supervised session (in a hospital gymnasium) and four non-supervised

12   home-based sessions per week. Also, AE was delivered on average three times/week, at

13   moderate intensity, with a session length of 45minutes, and total program duration of 9.2

14   weeks. A comparable number of trials recruited outpatients or inpatients, used equipment-

15   based or -free modalities, administrated clinician- or self-rated outcomes, employed group or

16   individual formats, and were delivered inside or outside a hospital. Also, a comparable

17   number of trials compared AE to treatment as usual (TAU), antidepressant medication or

18   psychological therapies. In two trials, AE was compared to non-exercise comparators of

19   waiting list (Oertel-Knöchel et al., 2014) and self-administrative group discussion (Sadeghi et

20   al., 2016). Seven trials were conducted indoors, and seven recruited patients with moderate-

21   severe or severe depression. The average dropout rate for the intervention and non-exercise

22   comparators was 14.8% and 14.5%, respectively.

23   *Risk of bias*

24   Seven trials (64%) received a score of ≥ 6 on the PEDro scale that indicates lower risk

25   of bias. In contrast, four trials showed higher risk of bias, as they received a score of < 6 on

1 the PEDro scale (see Table 2). Cohen's Kappa statistic was .77, portraying a substantial inter-

2 rater reliability on the PEDro scoring (Landis & Koch, 1977).

Meta-analysis

4 Pooled results showed that AE revealed a significantly large overall antidepressant

5 effect compared to non-exercise comparators (g = -0.79, 95% CI -1.00, -0.57, p < .00) with

6 low and non-significant heterogeneity (Q = 15.20, p = 0.23, I^2 = 21%). The Begg-Mazundar

7 Kendall's tau (tau -0.21, p = 0.29) and Egger bias test (intercept -2.48, p = 0.12) indicated no

8 publication bias (see Table 3 and Figure 2). Also, the funnel plot did not show evidence of

9 asymmetry (Figure 3). In addition, the fail-safe algorithm indicated that 218 studies with no

10 antidepressant effect for AE would be required to nullify the significance of the main result.

11 This indicates no publication bias, given that the relevant fail-safe standard (5k+10) for this

12 review is 75 studies (5 X 13 comparisons +10). Therefore, computation of trim and fill

13 analysis did not appear to be essential.

Sensitivity analyses

15 The sensitivity analysis for lower risk of bias trials displayed a moderate to large

16 effect for AE on depression (g = -0.70, 95% CI -0.94, -0.45, p < .00) with negligible

17 heterogeneity (I^2 = 2%). The sensitivity analysis for trials involving individual exercise

18 preferences displayed a large effect for AE (g = -0.84, 95% CI -1.17, -0.51, p < .00) with very

19 low and non-significant heterogeneity (I^2 = 7%). The sensitivity analysis for trials with short-

20 term interventions displayed a moderate to large effect for AE (g = -0.71, 95% CI -1.09, -0.34,

21 p < .00) with low and non-significant heterogeneity (I^2 = 30%). Details are presented in Table

22 3.

Subgroup Analyses

24 Eight subgroup analyses were conducted on the basis of the PICOS criteria (Moher et

25 al., 2009) excluding the study design criterion (S) that was coded by our first sensitivity

1   analysis. All the analyses revealed statistically significant effects for AE. Furthermore, none

2   of the analyses provided evidence for significant differences for effect-sizes between the

3   different groups; no publication bias was recorded; and levels of heterogeneity were non-

4   significant. The analyses are described below and the full statistics are presented in Table 4.

5   *Participants*

6   Aerobic exercise showed large and moderate to large effects for outpatients and

7   inpatients, and for patients with any severity classification in depression (g range = -.71 to -

8   .97). In these samples heterogeneity was low and non-significant (I^2 from 2% to 41%).

9   *Intervention*

10   Large effects were found in trials where AE included equipment-free modalities, and

11   was conducted in individual or group formats, and in indoor, outdoor or non-hospital settings

12   (g range = -0.77 to -1.07). In addition, moderate to large or moderate effects were seen in

13   equipment-based AE (g = -0.67, 95% CI -.98, -0.35, p < .00) or in hospital settings (g = -0.61,

14   95% CI -0.96, -0.27, p < .00). In all computations, levels of heterogeneity were non-

15   significant and ranged from 0% to 53%. Finally, no dropout differences were found between

16   the aerobic and the non-exercise comparators (RD = 0.01, 95% CI -0.03, 0.05, p = 0.59, I^2 =

17   0%).

18   *Comparisons*

19   Compared to antidepressants/TAU, AE showed large antidepressant effect (g = -0.75,

20   95% CI -1.01, -0.48, p < .00). Similar effects were seen in the comparison of AE to

21   psychological treatments when these treatments were performed as mono-therapy/part of

22   multi-therapeutic program (g = -0.85, 95% CI -1.21, -0.48, p < .00). Heterogeneity was low

23   (I^2 0% and 42%, respectively) and non-significant.

24   *Outcome measures*

1   Large and moderate to large, respectively, antidepressant effects for AE were found in

2   trials with self-rated (g = -0.97, 95% CI -1.35, -0.59, p < .00) or clinician-rated (g = -0.69,

3   95% CI -0.94, -0.44, p < .00) outcome measures. Heterogeneity was low (I^2 26% and 9%,

4   respectively) and non-significant. Also, a reduction of depression score by 4.5 points was seen

5   in trials employing the clinician-rated outcome of the Hamilton Rating Scale for Depression

6   (HAMD) (-4.48, 95% CI = -7.69, -1.25, standard error = 1.64, p < .00), and by 7 points in

7   trials employing the self-rated outcome of the Beck Depression Inventory-I or II (-6.96, 95%

8   CI = -12.49, -1.42, standard error = 2.83, p = 0.01).

9   **Discussion**

10   In this review, AE showed a significant large overall antidepressant effect (g = -0.79)

11   on adult patients recruited via mental health services with a referral or a clinical diagnosis of

12   major depression. Heterogeneity was low and non-significant (I^2 = 21%), and no signs of

13   publication bias were found.

14   Our study included only trials with depressed patients recruited via mental health

15   services; this could be considered a step forward in the literature. Previous meta-analyses

16   included a number of trials with depressed persons recruited via media advertisements.

17   However, media respondents may have a non-clinical depression, despite a high score in

18   depression checklists, or a possible diagnosis given before/at study entry. Moreover, they may

19   have strong outcome expectations and determination for lifestyle change; Blumenthal and

20   Ong (2009) report that community volunteers for exercise trials for depression are typically

21   motivated to exercise. Depressed patients instead, may have a more challenging clinical

22   profile given that they have suffered tenacious symptoms, including psychosocial impairment

23   that led to a mental health service, and they may often experience failure or disappointment

24   because the service use uncovers the disease severity/complexity and the need for systematic

25   care (Bursztajn & Barsky, 1985; Maguire, Cullen, O'Sullivan, & O'Grady-Walshe, 1995;

1   Morgan, 1989). To this extent, depressed patients referred to exercise on referral schemes are,

2   unsurprisingly, showing high dropout rates, often the highest among all health referrals

3   (Crone et al., 2008; James et al., 2008; Tobi et al., 2017). Therefore, our findings that stem

4   from trials with patients with a referral or clinical diagnosis of depression are representative to

5   routine practice and, thus, of additional value.

6   Another positive aspect of our study dealt with the inclusion of trials with only adult

7   depressed patients of 18-65 years old. This separation appeared to be essential because older

8   adult (+65years) depressed patients manifest distinct clinical differences in depression (Fiske

9   et al., 2009) and higher depression relief through exercise (Silveira et al., 2013), and are more

10   likely to complete exercise on prescription programs (James et al., 2008).

11   Importantly, 64% of our trials mirrored lower risk of bias (PEDro score $\geq$ 6). To the

12   best of our knowledge, only two systematic (but not meta-analytic) reviews for exercise and

13   depression have previously employed the PEDro scale (Perraton et al., 2010; Stanton &

14   Reaburn, 2014). These studies reported a score of $\geq$ 6 on the PEDro scale for 43% (Perraton et

15   al., 2010) and 100% (Stanton & Reaburn, 2014) of their reviewed trials. Exercise and anxiety

16   meta-analyses (Ensari et al., 2015; Stonerock et al., 2015) that employed the PEDro scale

17   have reported substantially fewer trials with lower risk of bias (33%) compared to our review.

18   Also, three sensitivity analyses were performed. The first recorded a significant

19   moderate to large antidepressant effect for AE among lower risk of bias trials. This is in line

20   to Rethorst et al. (2009) or Schuch et al. (2016) who found similar effects for exercise on

21   depression after coding for lower risk of bias, but in contrast to reviews that reported no

22   antidepressant effect for exercise after relevant coding (Krogh et al., 2017; Krogh et al., 2011).

23   The present finding is of key-importance given that high risk of bias is linked with

24   overestimation of treatment efficacy (Moher et al., 1998; Schulz, 2001; Schulz et al., 1995).

25   Further, the use of the PEDro scale, which was developed to evaluate risk of bias for physical

1 therapy interventions such as physical exercise, suggests that when intervention-specific

2 design aspects (e.g., dropouts) are included in the relevant evaluation do not confound results.

3 In the second sensitivity analysis, short-term AE (up to 4 weeks) showed a moderate

4 to large effect on depression highlighting its vital role at the early stage of care, as the most

5 frequent treatment of pharmacotherapy is typically requiring a period of 4 weeks before

6 providing any benefit (Gartlehner et al., 2011; John M. Eisenberg Center for Clinical

7 Decisions Communications Science, 2011; Seehusen & Sheridan, 2013). In further support of

8 its vital role at the early stage of mental health care, AE has been also shown to improve well-

9 being of major depressed patients after a single session (Bartholomew, Morrison, & Ciccolo,

10 2005), and to decrease depression after ten consecutive daily sessions in a sample comprising

11 both bipolar and major depressed patients (Knubben et al., 2007). In the third sensitivity

12 analysis AE involving individual preferences revealed large antidepressant effects.

13 Preference-based exercise appears to be a promising strategy in adolescent and adult general

14 population segments (e.g., Hamlyn-Williams, Freeman, & Parfitt, 2014; Rose & Parfitt, 2007),

15 in patients with various health disorders (Morton, Biddle, & Beauchamp, 2008) and in

16 depressed patients participating in pragmatic RCTs (Callaghan et al., 2011; Carter et al.,

17 2015; Morres, Stathi, Martinsen, & Sørensen, 2014). Therefore, this strategy warrants further

18 attention by researchers and practitioners.

19 The findings of the second and third sensitivity analyses (up to four-week exercise and

20 involvement of individual preferences) provide potentially important translational evidence

21 for routine practice as they concur with the only currently available AE trial with a pragmatic

22 design for adult depressed women ($\leq$ 65years) recruited through health services (Callaghan et

23 al., 2011). This RCT reported antidepressant effects for a four-week and preference-based AE

24 program implemented in public gyms for depressed women living in the community

25 (Callaghan et al., 2011).

1   Based on the subgroup analyses, AE brought about a large or moderate to large

2   improvement in depression in a wide range of delivery formats; through equipment-based or

3   equipment-free modalities, inside or outside a hospital, outdoors or indoors, in groups or

4   individually, and in cohorts with outpatients or inpatients, and with different depressive

5   symptom severity. In the two remaining subgroup analyses, AE favored over psychological

6   treatments or antidepressants/TAU, demonstrating large effects on depression. Overall, AE

7   was found to be comparably effective across all eight subgroup analyses. Noteworthy, three

8   of our reviewed trials consisted of treatment-resistant depressed samples (Mota-Pereira et al.,

9   2011; Oertel-Knöchel et al., 2014; Pilu et al., 2007). Another notable finding was that

10   supervised AE had clinically meaningful antidepressant effects; in trials using the clinician-

11   rated HAMD or the self-rated BDI outcomes, we found a reduction in depression score by 4.5

12   and 7 points, respectively. Both reductions are considered clinically meaningful, as the

13   relevant cutoff score is 3 points (NICE, 2009). Finally, AE showed similar dropout rates to

14   non-exercise comparators. Given that exercise is perceived as requiring higher time- and

15   effort-demands than other health behaviors (Turk et al., 1984), the lack of differences in

16   dropout rates between AE and non-exercise treatment modalities for depression is of major

17   importance.

18   Several limitations of the study require consideration. First, a small number of trials

19   were allocated. However, this is widely seen as a limitation of the field. Also, we tried to run

20   a robust analysis to offset threats caused by publication bias. In addition, most of our

21   sensitivity and subgroup analyses (89%) computed at least five arms, which is considered an

22   essential number to avoid imprecise results (Borenstein et al., 2009). Second, we did not code

23   for side-effects of exercise because only Legrand and Neff (2016) explored side-effects, with

24   37% of the sample reporting transient joint/muscular soreness, diarrhea or fatigue. Although

25   these effects did not preclude patients from completing the interventions (Legrand & Neff,

2016), exploration of side-effects of exercise via standardized tests is an important priority.

Based on limited data, almost 12% of mental health patients experience a side-effect by exercise (side-effects and patients' diagnoses were not clarified) (Sørensen, 2006). Also, only 6% of depressed patients (including older adults) assigned to physical activity programs describe the potential of a side-effect (Searle et al., 2011).

Third, our reviewed trials did not fully describe design criteria or clinical characteristics. Although all but one author provided comprehensive feedback to our inquiries, future trials need to detail intervention and non-exercise comparators. Of particular importance, the contact time of exercisers with supervisors and/or peers may have a confounding impact on the favourable comparison of exercise to non-exercise comparators. Such confounding bias, however, did not seem to occur in our study; in our subgroup analyses AE was more effective than non-exercise comparators of either increased or decreased contact time with service providers/users (e.g., psychological treatments or antidepressant medication). Nevertheless, future trials should equalize groups in contact time and present relevant information in order to allow researchers draw even firmer conclusions on whether AE per se favours non-exercise comparators in depressed patients.

A final issue that needs to be discussed concerns the representativeness of our findings to routine practice. Specifically, 35% of the patients identified as eligible for participation by our reviewed trials appeared to be reluctant to entering into studies. However, considering the pessimistic profile of depression and the high time and effort demands of exercise, this percentage appears rather low. Nevertheless, barriers to entering into studies with AE programs need to be identified by future trials. Only two of our reviewed trials provided such information, reporting lack of interest as a predominant barrier (Legrand & Neff, 2016; Schuch et al., 2015). Since lack of interest is a key symptom of depression, recruiters may find it difficult to trigger interest to exercise these patients. However, a study conducted in

1 routine practice for mental health patients from both hospital and day-care centers has

2 provided promising evidence (Sørensen, 2006). Particularly, exercise participation was

3 predicted solely by intrinsic regulation, reflecting inherent pleasure and participation for its

4 own shake (Sørensen, 2006). To this extent, autonomy supportive environments, providing

5 options for the type and intensity of exercise, which promote intrinsically regulated exercise

6 behavior (Ryan & Deci, 2000), might trigger interest in eligible but reluctant to exercise

7 depressed patients.

Conclusion

9   This is the first meta-analytic study to compare the antidepressant effects of AE to

10 treatments for depression excluding exercise activities, in adult patients (18-65) with a referral

11 or clinical diagnosis of major depression, who were recruited through mental health services

12 and not through media advertisements. Supervised AE compared favorably to treatments for

13 depression across various delivery formats, comparisons or settings, and regardless symptom

14 severity and type of outcome measure. Importantly, the antidepressant effect of AE was not

15 affected among trials with lower risk of bias, trials with short-term (up to four weeks) exercise

16 interventions, or trials with interventions involving individual preferences for exercise.

17 Notwithstanding the limited number of trials reviewed, AE was found to be an effective

18 antidepressant intervention.

<div style="text-align:center">References</div>

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Table 1. Description of reviewed trials

Trial, Country, Sample	Interventions	N/ ♀ %	age m/sd	attend. dropouts %	physiolog. gains	concurr. psychiatr. therap. %	depression pre/post
Mota-Pereira et al., (2011) Portugal outpatients	Eligible patients entered into study: 73% A. Aerobic Exercise (more depressed) Walking for 30-45min/5times/week/12weeks. One weekly session was individual/supervised by a sport scientist at hospital on treadmill, 5.0km/h/0° grade equal to 3.7-4 METs (moderate intensity). Home-based walking 4times/week, intensity prescription via accelerometers (>1952 counts) or perceived exertion (e.g., no shortness of breath). Compliance support: reminders, staff emphasized the exercise benefits, consulted family members on social support for exercise.	22/ 57.9	48.6/ 2.3	91 14	--- ---	100 [A]	HAMD-17 severe/ improved to mild [§, †]
	B. Usual pharmacotherapy (control group) Non-sedating antidepressants.	11/ 80	45.3/ 3.1	--- 9	--- ---	---	mild/ not improved
	Major Inclusion Criteria : treatment resistance after 9-15 months of combined pharmacotherapy, no regular exercising, no psychotherapeutic treatment, no change in medication in the last 6weeks						
Martinsen et al., (1985) Norway inpatients	A. Aerobic Exercise Group-based/supervised outdoor jogging & walking for 60min, 3times/week/9weeks at 50-70% VO$_{2}$max, supplemented by bicycling and/or swimming sessions at the patient's preference.	28/ ---	--- ---	--- 14.2	VO$_{2max}$ [§, †]	32 [A] 100 [P,OT]	BDI moderate/ improved to mild [§, †]
	B. Occupational therapy (control group) Occupational therapy 60min, 3 times/week/9weeks.	21/ ---	--- ---	--- 10.5	not improved	66 [A] 100 [P]	moderate/ improved [§]
	Major Inclusion Criteria: both males and females						

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Table 1 continued

Trial, Country, Sample	Interventions	N/ ♀ %	age m/sd	attend. dropouts %	physiolog. gains	concurr. psychiatr. therap. %	depression pre/post
Schuch et al., (2015) Brazil inpatients	Eligible patients entered into study: 47% A. Aerobic Exercise Exercise for 45min, 3times/week/3weeks at self-selected type (stationary bicycle, treadmill, or stepper) and intensity exercise, provided that 16kcal/kg/week are completed. Individual/supervised at hospital.	25/ 72	38.8/ 11.5	--- 8	--- ---	80 [A] 8 [ECT]	HAMD-17 severe/ improved to normal [§, †]
	B. Treatment as usual (control group) All patients were prescribed antidepressants. ECT was prescribed to 8% of the patients.	25/ 76	41.7/ 10.4	--- 4	--- ---	--- ---	severe/ improved to mild [§]
	Major Inclusion Criteria: a score of ≥25 on HAMD-17						
Rueter, (1980) USA outpatients	A. Aerobic Exercise Individual/supervised (co-running) running for at least 20min, 3times/week/10weeks (public indoors sport track). Pace allowed talking, non-competitive, no distance/speed criteria.	11/ ---	--- ---	--- 18	--- ---	100 [A]	BDI moderate/ improved to minimal [§, †]
	B. Counseling Therapy (control group) Group & individual counseling for 10weeks, at least 30min/week. Also, on waiting list for participating in the aerobic exercise program.	11/ ---	--- ---	--- 18	--- ---	---	moderate/ not improved
	Major Inclusion Criteria: both males and females, a score of >15 on BDI						

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Table 1 continued

Trial, Country, Sample	Interventions	N/ ♀ %	age m/sd	attend. dropouts %	physiolog. gains	concurr. psychiatr. therap. %	depression pre/post
Sadeghi et al., (2016) Iran outpatients	A. Aerobic exercise Supervised, 50-60min/8weeks. Warm up: 10min stretching, breathing, exercises of upper/lower limbs, running in place at low intensity. The same exercises 60-80%MHR, 30-35min. Cooling down: same exercises at low intensity, 10-15min.	16/ 81	20.9/ 1.0	--- ---	--- ---	---	BDI moderate/ improved to mild [§, †]
	B. Cognitive Therapy Cognitive therapy for 8 weeks, 2 times/week/4weeks, and 1 time/week in the remaining 4 weeks.	16/ 75	21.1/ 1.2	--- ---	--- ---	---	moderate/ improved to mild [§, †]
	C. Group meetings (control group) Self-administrative group meetings of 45-60min to discuss issues raised by the group members.	14/ 79	20.9/ 1.2	--- ---	--- ---	---	moderate/not improved
	Major Inclusion Criteria: BDI score 13-28, no medication						
Salehi et al., (2016) Iran inpatients	Eligible patients entered into study: 86% A. Aerobic exercise Individual/supervised cycling/treadmill for 40-45min, 3times/ week/4weeks at 60-75% VO2max.	20/ 25	29/ 5.1	100 0	--- ---	100 [A]	HAMD-17 severe/improved to mild [§]
	B. Electroconvulsive Therapy ECT 3times/week/4weeks.	20/ 35	29.7/ 6.28	100 0	--- ---	100 [A]	severe/ improved to mild [§]
	C. Aerobic Exercise + Electroconvulsive Therapy Aerobic exercise + ECT as described above.	20/ 35	30.2/ 6.2	100 0	--- ---	100 [A]	severe/ improved to mild [§]
	Major Inclusion Criteria: age 25 to 40, HAMD score of >2						

Table 1 continued

Trial, Country, Sample	Interventions	N/ ♀ %	age m/sd	attend. dropouts %	physiolog. gains	concurr. psychiatr. therap. %	depression pre/post
Pilu et al., (2007) Italy outpatients	Eligible patients entered into study: 71% A. Aerobic Exercise Group/supervised for 60min/2times/week/32weeks, 5min warm up, 50min on a self-selected cardio-fitness machine, change every 4min (20 options), 5min cooling down. Community-based gym.	10/ 100	--- ---	--- 0	--- ---	100 [A]	HAMD-17 severe/ improved to normal-mild [§, †]
	B. Pharmacotherapy (control group) 70% on SSRIs, 10% on SNRIs, and 5% of the patients on SSRI + SNRI + Tricyclic antidepressants.	20/ 100	--- ---	--- 0	--- ---	---	severe/not improved
	Major Inclusion Criteria: female, 2month persistence of score of >13 on HAMD-17 despite medication						
Legrand et al., (2016) France inpatients	Eligible patients entered into study: 73% A. Aerobic exercise Supervised/individual daily brisk walking or jogging for 30min/10days at 65-75% of MHR, park outside hospital, 92% individual sessions.	14/ 64	45.3/ 10.0	--- 7.1	--- ---	100 [A]	BDI severe/improved to mild- moderate [§, †]
	B. Stretching exercise Supervised daily stretching 30min/10days on thighs, calves, gluteal, back, shoulders 60secs (60secs break), hospital.	11/ 72	41.0/ 13.2	--- 18	--- ---	100 [A]	severe/ improved [§]
	C. Pharmacotherapy (control group) All patients were treated with antidepressants; 70% on SSRI's, 20% on SSNRI's, 10% on dopamine agonist.	10/ 70	49.1/ 16.5	--- 10.5	--- ---		severe/not improved
	Major Inclusion Criteria: BDI score of >28, antidepressant drug therapy initiated < 2 weeks before participation in the trial						

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Table 1 continued

Trial, Country, Sample	Interventions	N/ ♀ %	age m/sd	attend. dropouts %	physiolog. gains	concurr. psychiatr. therap. %	depression pre/post
Veale et al., (1992)	Eligible patients entered into study: 71%						
	A. Aerobic Exercise	48/	---	---	VO_{2max} [§, †]	45 [A]	CIS
UK	Group/supervised running 3imes/week/12 weeks in a public park just outside hospital. Warm-up/stretching before running.	---	---	25		100 [P]	moderate-severe/ improved [§, †]
outpatients							
	B. Treatment as usual (control group)	35/	---	---	not	34 [A]	moderate-severe/
	Supportive psychotherapy.	--	---	17.2	improved		improved [§]
	Major Inclusion Criteria: >17 total weighted score and >2 depression severity score on the CIS						
Oertel-Knöchel et al., (2014)	A. Aerobic exercise	8/	36.6/		---	100 [CT]	BDI
	Group-based, supervised, for 45min, 3 times/week/4weeks at 60-70%MHR. Warm-up for 10min, 25min cardio training (aerobic exercise, aerobic with boxing exercises and circuit training) and 10min cool-down.	50	12.9		---		moderate/ improved to mild moderate [§]
Germany				drop outs:			
inpatients	B. Relaxation	6/	41.3/	32%	---	100 [CT]	moderate/
	Group-based, supervised, for 45min, 3times/week/4weeks. Breathing exercises, "enjoy exercises", "imaginary journey", relaxation or acceptance and awareness training. No yoga, no muscle progressive relaxation.	66	15.6	across all groups	---		improved [§]
	C. Waiting (control)	8/	42.2		---	---	moderate/
	No intervention.	38	8.3		---		not improved [§]
	Major Inclusion Criteria: stable medication 1 month before and during the trial, disease duration at least 5years						

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Table 1 continued

Trial, Country, Sample	Interventions	N/ ♀ %	age m/sd	attend. dropouts %	physiolog. gains	concurr. psychiatr. therap. %	depression pre/post
Kerling et al., (2015) Germany inpatients	A. Aerobic exercise Group-based, supervised by study nurses, for 51min, 3times/week/6 weeks at moderate intensity and at 13max at the Borg scale. Warm up for 6min, 25min on a bicycle ergometer, and for 20min on arm ergometer, cross trainer, stepper, treadmill, and recumbent or rowing ergometer at personal preference.	22/ 45	44.2/ 8.5	>90 0	RHR[§] VO_{2peak}[§] LMax[§] VAT[§]	77 [A] 100 [CBT]	MADRS moderate-severe/ improved to mild-moderate [§]
	B. Treatment as usual (control group) Antidepressant drugs and CBT were prescribed to 75% and 100% of the patients, respectively. As part of their routine treatment, all patients attended a daily supervised-based physical activity program of ball games, walking, and stretching at moderate intensity for 20min.	20/ 30	40.9/ 11.9	--- 0	not improved	100 [PA]	moderate-severe/ improved to mild-moderate [§]

Major Inclusion Criteria: no acute/chronic infectious disease, no acute/lifetime immunological disease

A: Antidepressants, BDI: Beck Depression Inventory, C: Counseling, CBT: Cognitive behavioral therapy, CIS: Clinical Interview Schedule, CT: Cognitive training, ECT: Electroconvulsive therapy, HAMD-17: Hamilton Rating Scale Depression, LMax: Maximum lactate concentration, MADRS: Montgomery-Åsberg Depression Rating Scale, Max: Maximum, M: Mean, METs: Metabolic Equivalents, MHR: Maximum heart rate, MIC: Major inclusion criteria, OT: Occupational therapy, P: Psychotherapy, PA: Physical activity, RHR: Resting heart rate, SD: Standard deviation, SNRI: Serotonin-norepinephrine reuptake inhibitor, SSRI: Selective serotonin reuptake inhibitor, VO_{2peak}: Peak oxygen uptake, VAT: Ventilatory anaerobic threshold, §: Statistically significant difference within group, †: Statistically significant difference in comparison to control group.

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Table 2. Consensus scores of design quality for reviewed trials

PEDro Criteria	Random Allocation	Concealed Allocation	Baseline Balance	Blinding Patient/Therapist/Assessor	Dropout (<15%)	ITT	Statistical Comparison Between Groups	Point and Variability Measures	PEDro Total Score
Trials									
Schuch et al. (2015)	1	1	1	0/0/1	1	1	1	1	8
Kerling et al. (2015)	1	1	1	0/0/1	1	1	1	1	8
Legrand and Neff (2016)	1	1	1	0/0/0	1	1	1	1	7
Salehi et al. (2016)	1	1	1	0/0/1	1	1	1	1	7
Pilu et al. (2007)	1	0	1	0/0/0	1	1	1	1	6
Mota-Pereira et al. (2011)	1	1	0	0/0/1	1	0	1	1	6
Oertel-Knöchel et al. (2014)	1	0	1	0/0/1	0	1	1	1	6
Martinsen et al. (1985)	1	0	1	0/0/0	1	1	1	0	5
Sadeghi et al. (2016)	1	0	1	0/0/1	0	0	1	1	5
Veale et al. (1992-a)	1	0	1	0/0/0	0	0	1	1	4
Rueter (1980)	1	0	1	0/0/0	0	0	1	1	4

PEDro: Physiotherapy Evidence Database scale; ITT: Intention to Treat

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Table 3. Meta-analytic findings of the effect of aerobic exercise on depression; overall effect and sensitivity analyses

	Trials/Arms	Treatment Effectiveness			Publication Bias		Heterogeneity	
		g	CI 95%	p value	Egger intercept	Begg-Mazumbar Kendall's tau	Cochrane Q	I^2
Overall effect	11/13	-0.79	-1.00, -0.57	0.00	-2.48, p=0.12	-0.22, p=0.29	15.20, p=0.23	21%
PEDro score of ≥6 [1,2,4-6,9,10]	7/8	-0.70	-0.94, -0.45	0.00	-1.87, p=0.42	-0.03, p=0.90	7.16, p=0.41	2%
Up to 4 weeks [2,5,9,10]	4/5	-0.71	-1.09, -0.34	0.00	-1.18, p=0.74	-0.00, p=1.00	5.79, p=0.22	30%
Exercise preferences [1,3,6,10]	4/4	-0.84	-1.17, -0.51	0.00	-3.73, p=0.52	-0.17, p=0.73	3.23, p=0.36	7%

CI 95%: Confidence Intervals; g: Hedge's g; PEDro: Physiotherapy of Evidence Database Scale.
[1]Kerling et al. 2015; [2]Legrand and Neff, 2016; [3]Martinsen et al. 1985; [4]Mota-Pereira et al. 2011; [5]Oertel-Knöchel et al. 2014; [6]Pilu et al. 2007; [9]Salehi et al. 2016; [10]Schuch et al. 2015.

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Table 4. Meta-analytic findings of the effects of aerobic exercise on depression; subgroup analyses

	Trials/Arms	Treatment Effectiveness			Publication Bias		Heterogeneity	
		g	CI 95%	p value	Egger intercept	Begg-Mazumbar Kendall's tau	Cochrane Q	I^2
Participants								
Outpatients [4,6-8,11]	5/6	-0.84	-1.16, -0.51	0.00	-3.14, p=0.13	-0.53, p=0.13	6.12, p=0.29	18%
Inpatients [1-3,5,9,10]	6/7	-0.75	-1.06, -0.44	0.00	-1.36, p=0.67	-0.00, p=1.00	8.89, p=0.18	32%
Mild-moderate/moderate [3,5,7,8]	4/5	-0.97	-1.43, -0.51	0.00	-2.58, p=0.48	-0.10, p=0.81	6.79, p=0.15	41%
Moderate-severe/severe [1,2,4,6,9-11]	7/8	-0.71	-0.94, -0.48	0.00	-1.92, p=0.42	-0.18, p=0.54	7.16, p=0.41	2%
Intervention								
Equipment-based [1,5,6,9,10]	5/6	-0.67	-0.98, -0.35	0.00	-1.59, p=0.63	-0.00, p=1.00	6.59, p=0.25	24%
Equipment-free [2,3,7,8,11]	5/6	-0.94	-1.28, -0.60	0.00	-3.00, p=0.17	-0.40, p=0.26	6.96, p=0.22	28%
Group exercise [1,3,5,6,11]	5/5	-0.80	-1.09, -0.51	0.00	-0.62, p=0.80	-0.00, p=1.00	3.48, p=0.48	0%
Individual exercise [2,4,7,9,10]	5/6	-0.87	-1.30, -0.43	0.00	-4.39, p=0.14	-0.40, p=0.26	10.78, p=0.06	53%
Indoors [1,4-7,9,10]	7/8	-0.77	-1.10, -0.44	0.00	-3.54, p=0.13	-0.25, p=0.39	12.05, p=0.09	41%
Outdoors [2,3,11]	3/3	-0.94	-1.30, -0.58	0.00	-1.95, p=0.59	-0.00, p=1.00	1.37, p=0.50	0%
Hospital [1,5,9,10]	4/5	-0.61	-0.96, -0.27	0.00	-0.64, p=0.88	-0.00, p=1.00	5.62, p=0.23	28%
Non-hospital [2,3,6,7,11]	5/5	-1.07	-1.41, -0.72	0.00	-3.08, p=0.09	-0.30, p=0.46	4.65, p=0.33	14%
Comparisons								
Antidepressants or TAU [1,2,4,6,10,11]	6/6	-0.75	-1.01, -0.48	0.00	-1.38, p=0.35	-0.27, p=0.45	1.87, p=0.87	0%
Psychological treatments [1,3,7,8,11]	5/6	-0.85	-1.21, -0.48	0.00	-3.69, p=0.16	-0.40, p=0.26	8.64, p=0.12	42%
Outcomes								
Self-rated [2,3,5,7,8]	5/6	-0.97	-1.35, -0.59	0.00	-2.50, p=0.41	-0.13, p=0.71	6.81, p=0.24	26%
Clinician-rated [1,4,6,9-11]	6/7	-0.69	-0.94, -0.44	0.00	-1.56, p=0.62	-0.09, p=0.76	6.65, p=0.35	9%

CI 95%: Confidence Intervals; g: Hedge's g; TAU: Treatment as usual
[1]Kerling et al. 2015; [2]Legrand and Neff, 2016; [3]Martinsen et al. 1985; [4]Mota-Pereira et al. 2011; [5]Oertel-Knöchel et al. 2014; [6]Pilu et al. 2007; [7]Rueter, 1980; [8]Sadeghi et al. 2016; [9]Salehi et al. 2016; [10]Schuch et al. 2015; [11]Veale et al. 1992.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.
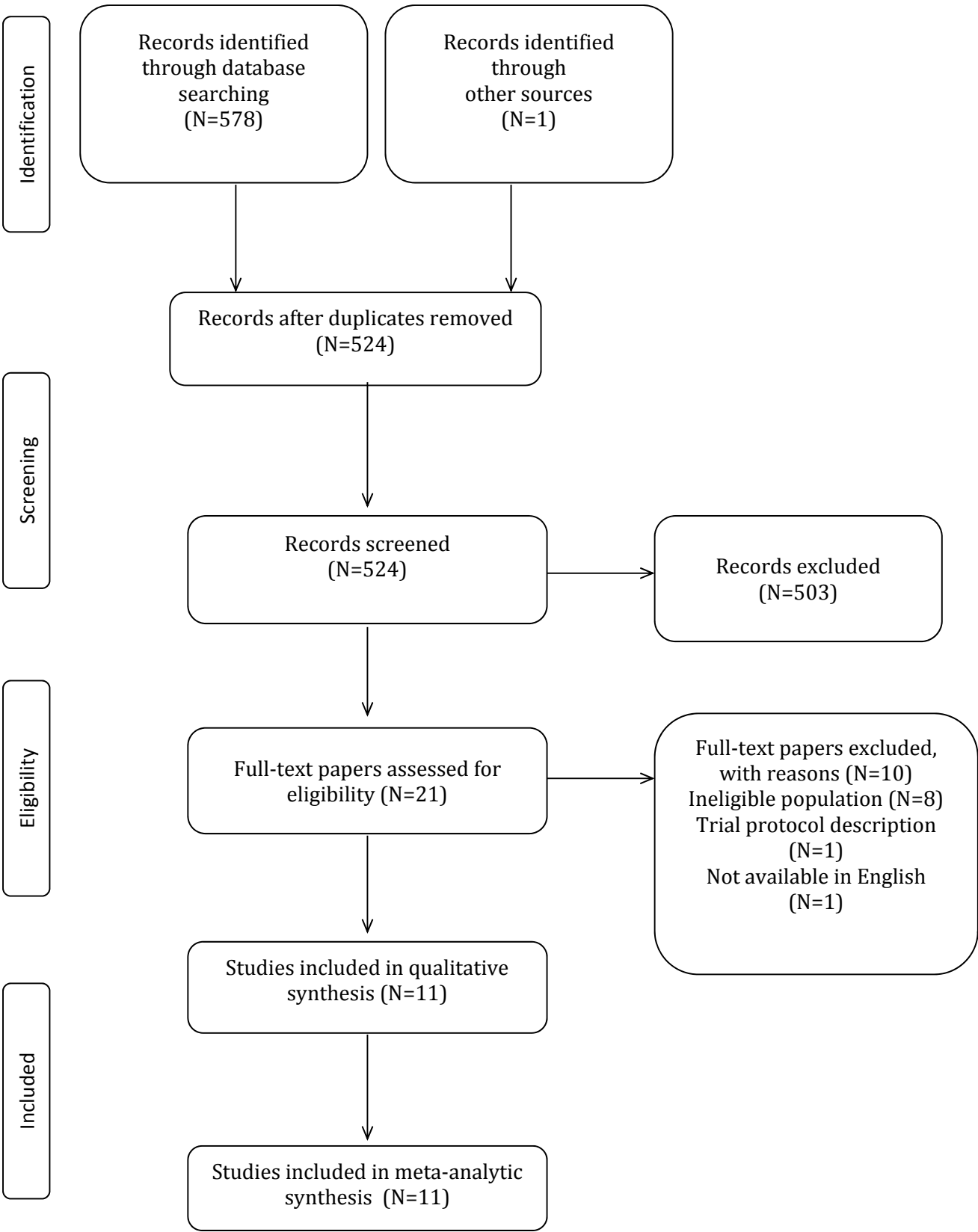
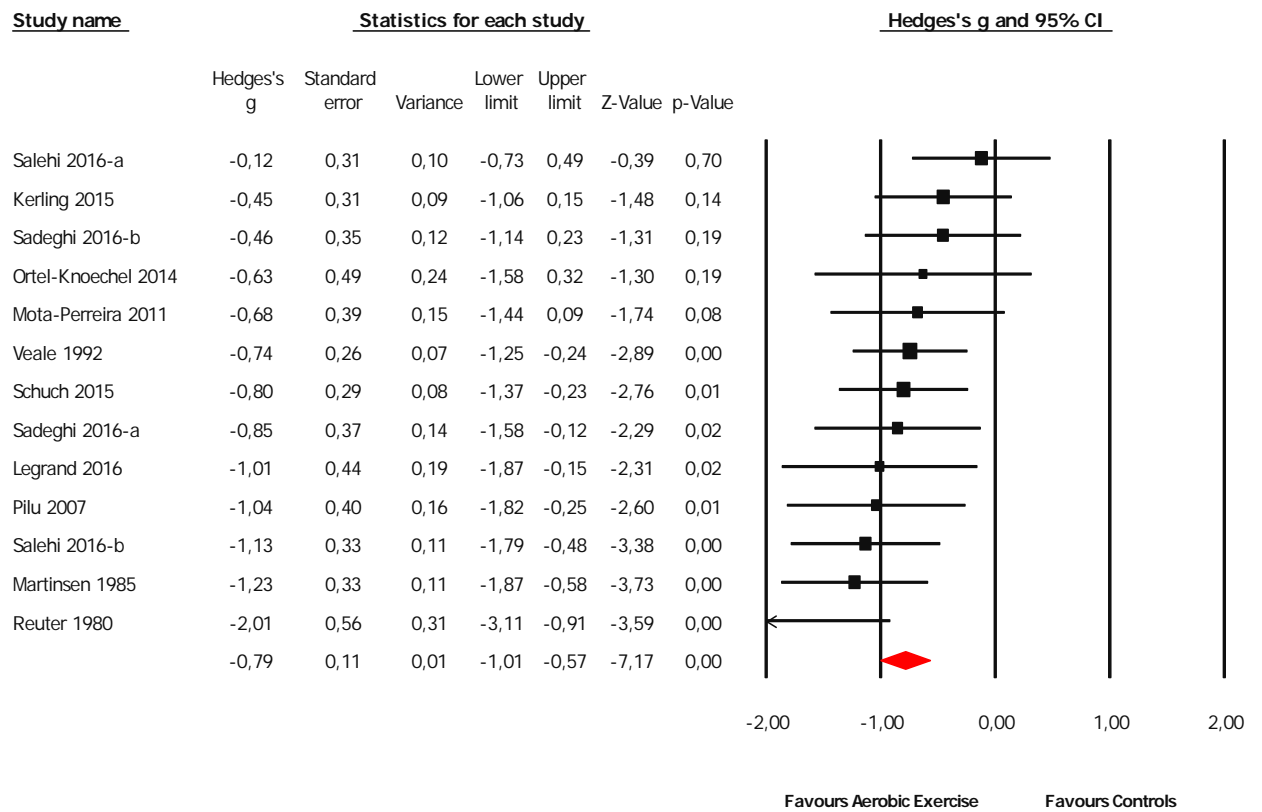Figure 2. Meta-analysis of depressive symptom score.

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Salehi 2016-a	-0,12	0,31	0,10	-0,73	0,49	-0,39	0,70
Kerling 2015	-0,45	0,31	0,09	-1,06	0,15	-1,48	0,14
Sadeghi 2016-b	-0,46	0,35	0,12	-1,14	0,23	-1,31	0,19
Ortel-Knoechel 2014	-0,63	0,49	0,24	-1,58	0,32	-1,30	0,19
Mota-Perreira 2011	-0,68	0,39	0,15	-1,44	0,09	-1,74	0,08
Veale 1992	-0,74	0,26	0,07	-1,25	-0,24	-2,89	0,00
Schuch 2015	-0,80	0,29	0,08	-1,37	-0,23	-2,76	0,01
Sadeghi 2016-a	-0,85	0,37	0,14	-1,58	-0,12	-2,29	0,02
Legrand 2016	-1,01	0,44	0,19	-1,87	-0,15	-2,31	0,02
Pilu 2007	-1,04	0,40	0,16	-1,82	-0,25	-2,60	0,01
Salehi 2016-b	-1,13	0,33	0,11	-1,79	-0,48	-3,38	0,00
Martinsen 1985	-1,23	0,33	0,11	-1,87	-0,58	-3,73	0,00
Reuter 1980	-2,01	0,56	0,31	-3,11	-0,91	-3,59	0,00
	-0,79	0,11	0,01	-1,01	-0,57	-7,17	0,00

Hedges's g and 95% CI

Favours Aerobic Exercise   Favours Controls

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Figure 3. Funnel Plot.

Funnel Plot of Standard Error by Hedges's g