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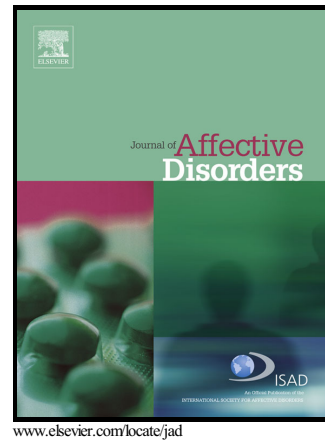
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Dropout from exercise randomized controlled trials among people with depression: A meta-analysis
and meta regression

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Running head: dropout in depression

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Abstract

Objective

Exercise has established efficacy in improving depressive symptoms. Dropouts from randomized controlled trials (RCT's) pose a threat to the validity of this evidence base, with dropout rates varying across studies. We conducted a systematic review and meta-analysis to investigate the prevalence and predictors of dropout rates among adults with depression participating in exercise RCT's.

Method

Three authors identified RCT's from a recent Cochrane review and conducted updated searches of major electronic databases from 01/2013 to 08/2015. We included RCT's of exercise interventions in people with depression (including major depressive disorder (MDD) and depressive symptoms) that reported dropout rates. A random effects meta-analysis and meta regression were conducted.

Results

Overall, 40 RCT's were included reporting dropout rates across 52 exercise interventions including 1,720 people with depression (49.1 years (range=19-76 years), 72% female (range=0-100)). The trim and fill adjusted prevalence of dropout across all studies was 18.1% (95%CI=15.0 to 21.8%) and 17.2% (95%CI 13.5 to 21.7, N=31) in MDD only. In MDD participants, higher baseline depressive symptoms (β 0.0409, 95%CI=0.0809 to 0.0009, $P=0.04$) predicted greater dropout, whilst supervised interventions delivered by physiotherapists (β -1.2029, 95%CI=-2.0967 to -0.3091, $p=0.008$) and exercise physiologists (β -1.3396, 95%CI=-2.4478 to -0.2313, $p=0.01$) predicted lower dropout. A comparative meta-analysis (N=29) established dropout was lower in exercise than control conditions (OR=0.642, 95%CI=0.43 to 0.95, $p=0.02$).

Conclusions

Exercise is well tolerated by people with depression and drop out in RCT's is lower than control conditions. Thus, exercise is a feasible treatment, in particular when delivered by healthcare professionals with specific training in exercise prescription.

Keywords: Depression; exercise; physical activity; dropout

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Introduction

Major depressive disorder (MDD) is a serious public health concern and consistently ranks in the top ten causes of disability worldwide (Murray et al 2015). In addition, sub-threshold depressive symptoms are also highly prevalent and together with MDD, 'depression' is pervasive and affects people of all ages, genders, countries and socioeconomic conditions (Ferrari et al., 2013). Treatment of depression is multifaceted, often including pharmacological treatment (e.g., antidepressants) and psychotherapies (e.g., cognitive behavioral therapy). Within the last decade, increased attention has focused on the benefits of exercise to improve depressive symptoms (Cooney et al., 2013; Knapen et al., 2015; Vancampfort et al., 2015c) and exercise is regarded as an effective therapeutic modality (Cleare et al., 2015).

Whilst the evidence for exercise to improve depressive symptoms is encouraging, the likely benefits of exercise extend beyond this paradigm (Knapen et al., 2015). For instance, previous research has demonstrated that exercise can improve quality of life (Schuch et al., 2015) and sleep quality (Rethorst et al., 2013). In addition, people with depression are at an increased risk of developing cardiovascular disease, diabetes and subsequent premature mortality (Holt et al., 2014; Vancampfort et al., 2015a). In the general population, there is strong evidence that exercise is essential in preventing and managing cardiovascular and metabolic disease (Naci and Ioannidis, 2013) (Hayashino et al., 2014).

Despite the benefits of exercise, people with depression experience a range of barriers to engaging in physical activity (Vancampfort et al., 2015b). A recent review of physical activity correlates established that higher depressive symptomatology, higher body mass index, presence of somatic co-morbidities and lower self-efficacy are particularly important barriers for people with depression to undertake regular physical activity (Vancampfort et al., 2015b). Unsurprisingly, dropouts from treatment represent a major barrier that preclude an individual benefitting from an intervention and appear to be a particular problem in people with depression (Cooper and Conklin,

2015). Previous research has demonstrated that patients who dropout from clinical trials often experience worse clinical outcomes, and strategies to improve adherence and ensure that patient benefit from interventions have been developed (Rutherford et al., 2013; Swift and Greenberg, 2014). Certain exercise program variables may pose particular challenges for people with depression (e.g. high intensity programs, or group sessions). However, very little information is known about dropouts in exercise trials among people with depression. One previous systematic review (Rethorst et al., 2009) with a last search date of over a decade ago, has considered dropout from exercise in people with depression. The authors calculated the numerical mean of dropouts at 14.6% across 18 studies. Another narrative review (Mura et al., 2014) reported that dropouts occur between 0 and 30% of people with MDD undertaking exercise across thirteen RCT and non RCT's. Whilst these reviews have been helpful, many important questions currently remain unanswered. For instance, it remains unclear how participant characteristics (e.g. age, gender), illness related factors (e.g. depressive symptom severity or antidepressant medication use), exercise characteristics (e.g. frequency, intensity, time and type of exercise) and the delivery of the intervention (e.g. supervised or not, professional background of the provider) influence dropout rates from exercise in people with depression. Moreover, it remains unclear if dropout is more common in exercise interventions than control arms of randomized control trials (RCT's). Clarifying these issues will assist the design of future RCT's, and increase adherence to exercise in clinical practice.

We conducted the first meta-analysis to investigate the prevalence of dropout and predictors in exercise RCT's in people with depression. Specifically, the current meta-analysis had the following aims: (i) to establish the prevalence of dropout in exercise RCT's among people with depression. (ii) To identify predictors that may influence dropout. (iii) Investigate predictors of dropout from exercise in people with MDD alone (iv) to compare the prevalence of dropout rates from exercise with the dropout in non-active control conditions.

Method

This systematic review adhered to the MOOSE guidelines (Stroup et al., 2000) and PRISMA statement (Moher et al., 2009), following a predetermined but unpublished protocol.

Inclusion criteria

Included in this meta-analysis were RCT's that: (a) Included adult participants with a primary diagnosis of MDD according to established criteria (e.g., DSM-IV, (American Psychiatric Association, 2000) or ICD-10, (World Health Organisation, 1993)) or those with depressive symptoms above clinical threshold determined by a validated screening measure (e.g., Hamilton Rating Scale for Depression, HMD-R), (Hamilton, 1967), Beck Depression Inventory (BDI or BDI-II (Beck A. T Ward, 1961)). We also included studies meeting our criteria where people with MDD were included in RCT's that also included patients with other affective disorder diagnoses such as bipolar disorder and dysthymia, (b) Investigated exercise interventions. Exercise interventions were defined as physical activity that is planned, structured, repetitive and purposive in the sense that improvement or maintenance of physical fitness or health was an objective (Caspersen et al., 1985). (c) Provided information on dropout rates. (d) Were published in an international peer-reviewed English language journal or publicly available thesis. We included multiple exercise arms (conditions) within a single RCT in the analyses but only when individuals exclusively participated in one active arm of the trial (e.g. did not participate in an aerobic exercise and strength exercise arms of a trial). We included trials that involved any type of exercise meeting the above criteria. For studies reporting follow-up assessments, data extraction focused on the active phase of the condition, as defined by the authors of each publication.

Information sources and searches

Articles were identified in a two-step strategy. First, three authors (BS, FS, SR) reviewed all articles identified (both included and excluded with reasons) by the recent Cochrane review on exercise for

depression (Cooney et al., 2013). Second, three independent reviewers (BS, FS, SR) searched Academic Search Premier, MEDLINE, Psychology and Behavioral Sciences Collection, PsycINFO, SPORTDiscus, CINAHL Plus and Pubmed without language restrictions from January 2013 until August 1st, 2015, using the key words: ((exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR "physical medicine" OR resistance OR lift*) AND (depression OR dysthymia)). In addition, reference lists of all eligible articles of recent reviews investigating the effectiveness of exercise versus control were screened to identify potentially eligible articles (Cooney et al., 2013; Josefsson et al., 2014; Silveira et al., 2013).

Study selection

In the first stage of the search strategy, three authors (BS, FS, SR) determined potentially eligible articles meeting criteria from the Cochrane review (Cooney et al., 2013). In the second stage, after removal of duplicates, two independent reviewers screened titles and abstracts of all potentially eligible articles. The same three authors applied the eligibility criteria, reviewed the full texts and a final list of included articles was reached through consensus.

Outcomes

The primary outcome was the dropout rate in exercise interventions in people with MDD/depressive symptoms. We adopted a definition of dropout consistent with its typical use in RCT's: unexpected participant attrition among individuals who were randomized to a treatment but failed to complete it (Cooper and Conklin, 2015). This definition included any participant who would be included in intention-to-treat (ITT) analyses, such as those who refused randomization, never attended a session, stopped attending sessions, or withdrew consent before completing the designated treatment. Patients who were lost to follow-up prior to randomization were not considered dropouts. Additionally, removal of study patients by investigators and instances of data

loss were not treated as dropouts. For comparison purposes, we also collected overall dropout rates in all non-active control conditions (e.g. wait list/ treatment as usual care (TAU)).

Data extraction

Two authors (BS, FS) extracted data using a predetermined data extraction form. We divided moderators of the extracted dropout rates broadly into three domains: participant variables, design/implementation variables and provider variables. Regarding participant variables we extracted information on mean age, % females, % taking antidepressants, presence of major comorbidities (defined as any major such as cardiovascular, metabolic, neurological conditions), baseline depressive symptoms and depression status (depressive symptoms v MDD). Design/implementation variables included whether the exercise intervention was conducted in a group setting, among inpatients or outpatients, study quality (see below), trial duration and type of exercise (aerobic exercise, strength training, mixed exercises or other). Finally, for provider variables we considered if the exercise intervention was supervised or not and the professional background of those who supervised and delivered the exercise intervention.

Risk of bias and quality assessment

Three authors (FS, JR, BS) assessed studies on the presence of high, low risk or unclear risk of bias according to the Cochrane Handbook definition (Higgins and Green 2008). The risk of bias was assessed on the following items: 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 presenting adequate allocation concealment and complete presentation of outcome data (intention-to-treat analysis) and blinding outcome assessors are considered studies with low risk of bias (high quality trials). The criteria selection was based on a previous Cochrane review (Cooney et al., 2013).

Meta-analysis

Due to the anticipated heterogeneity across studies, we conducted a random effects meta-analysis with Comprehensive Meta-Analysis software (CMA, Version 3). The meta-analysis was conducted in the following sequence. First, we calculated the prevalence of dropouts together with 95% CIs (effect size (ES), primary outcome) across all studies. Next, we conducted subgroup analyses for the dropout rates across all exercise studies comparing dropout rates according to study quality (high versus low), type of publication (peer review versus thesis), presence of comorbidities (comorbidities present versus no major comorbidities), depression categorization (MDD versus depressive symptoms), group exercises status (in group versus not in group), setting of study (inpatient versus outpatient), type of exercise intervention (aerobic exercise, strength training or mixed exercises), supervised exercise (supervised versus no supervision) and qualification of the person supervising (none, physical education personnel, physiotherapist, exercise physiologist, and other). Second, we conducted meta-regression analyses with potential moderators that may influence dropout rates across all studies. This included exerciser variables (mean age, % females, % taking antidepressants, presence of major comorbidities, baseline depressive symptoms and depression status (depressive symptoms v MDD)), design/ implementation variables (group setting or not, in inpatient/ outpatients, study quality, RCT duration, type of exercise (aerobic exercise, strength training, mixed exercises or other)) and provider variables (professional background of exercise supervisor). Third, we repeated the meta-regression analyses separately to investigate moderators for MDD studies only. Finally, we conducted a comparative meta-analysis of the dropout rates across all control conditions and secondly versus control groups that employed wait list/no active intervention or treatment as usual and compared this to dropout rates in exercise studies where possible. Heterogeneity was assessed with the Cochran Q and I^2 statistics for each analysis (Higgins et al., 2003). 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). Moreover, for the main dropout analysis 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.

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Results

Study selection

In the first stage of our search strategy, 37 RCT's were identified from a recent Cochrane review (Cooney et al., 2013). In the second stage, following the removal of duplicates, we identified 819 potentially relevant articles from our searches. At the full text review stage, we reviewed 78 articles (N=37 from stage 1 and 41 from our searches in stage 2) and excluded 38 with reasons. Details are summarized in figure 1. Overall, there were 40 unique RCT's that provided dropout data and were included in our review (Belvederi Murri et al., 2015; Blumenthal et al., 2007; Blumenthal et al., 1999; Blumenthal et al., 2012; Chu et al., 2009; Danielsson et al., 2014; Orth 1979; Dunn et al., 2005; Foley et al., 2008; Fremont and Craighead, 1987; Gary et al., 2010; Hallgren et al., 2015; Hemat-Far et al., 2012; Hess-Homeier, 1981; Hoffman et al., 2010; Huang et al., 2015; Kerling et al., 2015; Klein et al., 1984; Knubben et al., 2007; Krogh et al., 2009; Bonnet., 2005; Martinsen et al., 1985; Martiny et al., 2012; Mather et al., 2002; McNeil et al., 1991; Mota-Pereira et al., 2011; Mutrie, 1989; Nabkasorn et al., 2006; Pfaff et al., 2014; Pilu et al., 2007; Salehi et al., 2014; Schuch et al., 2015; Setaro, 1985; Shahidi et al., 2011; Sims et al., 2009; Singh et al., 1997; Singh et al., 2005; Veale et al., 1992; Verrusio et al., 2014; Williams and Tappen, 2008). Of these, 12 RCT's provided data comprising two or more dropout rates among people with depression that participated in exercise interventions in different arms within the RCT (Belvederi Murri et al., 2015; Blumenthal et al., 2007; Blumenthal et al., 1999; Chu et al., 2009; Dunn et al., 2005; Fremont and Craighead, 1987; Gary et al., 2010; Krogh et al., 2009; Salehi et al., 2014; Setaro, 1985; Singh et al., 2005; Williams and Tappen, 2008). Overall, dropout data were pooled from 52 unique exercise interventions (40 unique RCT's).

Insert Figure 1 about here

Study, participants and providers' characteristics

Across the 52 exercise interventions, 1,720 people with depression were enrolled in the exercise arms of the studies. The mean age of the exercise participants was 49.1 years (range=19 to 76 years), 72% were female (range=0-100%) and 40.1% were prescribed antidepressant medication (range=0-100%). The majority (N=44) of the exercise interventions were published in peer review journals, with 8 study estimates being obtained from theses (Bonnet 2005, Chu et al 2008 a and b, Hess-Homeier et al 1981, Mutrie 1988, Orth 1979, Setaro 1985 a and b). Most included adults with depression that were free from major comorbidities (N=44), without a known comorbid psychiatric diagnosis (N=48) and were conducted in outpatient settings (N=42). Most of the studies investigated aerobic exercise (N=41) with only four and three utilizing strength training and mixed strength and aerobic training respectively. When data were available, most of the exercise interventions were conducted in group settings (N=21) and most studies had some degree of supervision during the intervention (N=37). The most common providers of exercise were physical education personnel (N=15). The duration of the interventions were on average 11.7 weeks (range=1.3 to 32 weeks), and most studies adopted a frequency of 3 sessions per week (range=2-5).

Study quality and risk of bias

Twelve of the included RCT's (17 exercise arms) (Belvederi Murri et al., 2015; Blumenthal et al., 2007; Blumenthal et al., 1999; Blumenthal et al., 2012; Danielsson et al., 2014; Dunn et al., 2005; Hallgren et al., 2015; Krogh et al., 2009; Martiny et al., 2012; Mather et al., 2002; Pfaff et al., 2014; Schuch et al., 2015) were derived from studies deemed high quality whilst the remaining studies were deemed low quality.

Meta-analysis of dropout rates in exercise RCT's

Across the 52 exercise interventions, the pooled dropout rate was 15.4% (95%CI=12.7 to 18.5, $I^2=45\%$). There was evidence of publication bias (Egger=-1.5, $p<0.01$; Begg-0.36, $p<0.01$, funnel plots

in supplementary file 1) and the trim and fill adjusted dropout rate was 18.1% (95%CI=15.0 to 21.8%) with 17 adjusted studies.

Subgroup analyses

Full details of all of the subgroup analyses are presented in table 1. Key findings are highlighted below.

Study quality

Although higher quality studies with a lower risk of bias reported lower dropout rates (15%, 95% CI 9.11 to 17.8%) compared to lower quality studies (15.5%, 95%CI=11.5 to 20.0%) the between group difference was not significant ($p=0.9$). Higher dropout rates were seen among trials reported in theses (21.5%) compared to studies published in peer-reviewed journals (14.3%), with trend level significance ($p=0.053$).

Exerciser characteristics

Lower dropout was seen in exercisers among people with MDD (14.6%) than in people with other depressive disorders (17.7%) but this did not reach significance ($p=0.38$).

Design/ implementation characteristics

Significantly lower dropout from exercise was observed among people recruited from inpatient settings (7.85%, 95%CI=4.03 to 14.74%) compared to outpatient settings (16.23%, 95%CI=13.4 to 19.5%, $p=0.03$). There was also evidence of between group differences in dropout rates according to different exercise types, although this may reflect small study numbers (see table 1). Lower dropout rates were seen among supervised exercise studies (15.1%, 95%CI=11.9 to 19.04%) than unsupervised (19.63%, 95%CI=13.3 to 27.9%) although this was not statistically significant ($p=0.35$). There was no significant difference in the prevalence of dropout among exercisers according to the

professional group providing the supervision, although the highest rates of dropout were seen among studies in which participants received no professional supervision.

Table 1 here

Meta regression of dropout rates across all studies

Full details of all of the meta-regression results across all studies are presented in Table 2. No significant participant characteristics were identified, although studies with a higher proportion of female participants trended toward significantly higher dropout rates ($\beta=0.019$, 95%CI=-0.002 to 0.039, $p=0.07$). Illness related factors including antidepressant medication and baseline depressive symptoms did not moderate dropout rates. The setting of the study (inpatient versus outpatient) moderated lower dropout ($\beta=-1.407$, 95% CI -2.472 to -0.342, $p=0.009$, $R^2=0.28$). Only mixed exercise interventions (combination of strength and aerobic based protocols) moderated dropout rates ($\beta=1.78$, 95% CI 0.40 to 3.15, $p=0.01$).

Table 2 here

Meta regression of dropout among exercisers with major depressive disorder

Studies in which a higher proportion of participants were taking antidepressants were associated with lower dropout rates, although this effect was not statistically significant ($\beta=0.006$, 95%CI=-0.012 to 0.001, $p=0.09$, $R^2=0.40$). More pronounced depressive symptoms predicted a higher dropout rate among MDD participants ($\beta=0.041$, 95%CI=0.081 to 0.001, $p=0.04$, $R^2=0.34$). Studies conducted in inpatient settings had lower dropout versus outpatient settings ($\beta=-1.426$, 95%CI=-2.640 to -0.211, $p=0.02$, $R^2=0.28$). Exercise studies in which physiotherapists ($\beta=-1.203$, 95%CI=-2.097 to -0.309, $p=0.008$) and exercise physiologists ($\beta=-1.340$, 95%CI=-2.448 to -0.231, $p=0.01$) delivered the intervention also predicted lower dropouts. Exercise interventions delivered by physical education instructors also tended to be associated with lower dropout rates ($\beta=-0.673$, 95% CI -1.415 to 0.070,

p=0.07). Full details of the meta regression analyses of dropouts among exercisers with MDD are presented in Table 3.

Table 3 here

A comparative meta-analysis across 29 studies (Belvederi Murri et al., 2015; Blumenthal et al., 2007; Blumenthal et al., 1999; Blumenthal et al., 2012; Chu et al., 2009; Danielsson et al., 2014; Orth, 1979; Dunn et al., 2005; Foley et al., 2008; Fremont and Craighead, 1987; Gary et al., 2010; Hallgren et al., 2015; Hess-Homeier, 1981; Hoffman et al., 2010; Klein et al., 1984; Knubben et al., 2007; Krogh et al., 2009; Bonnet, 2005; Martiny et al., 2012; Mota-Pereira et al., 2011; Mutrie, 1989; Pfaff et al., 2014; Pihu et al., 2007; Schuch et al., 2015; Setaro, 1985; Shahidi et al., 2011; Singh et al., 2005; Veale et al., 1992; Williams and Tappen, 2008) established that people with depression were less likely to dropout from exercise interventions than those across all control conditions (OR=0.64, 95%CI=0.43 to 0.95, p=0.02, I²=49%). Dropout rates among exercise studies were not significantly different when compared to treatment as usual/ placebo/ wait list controls groups only (OR=0.70, 95%CI=0.39 to 1.24, p=0.22, I²=54%).

Discussion

The current meta-analysis is, to our knowledge, the first to investigate dropout rates and predictors in exercise RCT's among people with depression. Our results establish that the prevalence of dropout from exercise is relatively low among people with depression at 15.2% (corrected to 18.1% in trim and fill analysis) across 49 exercise arms, with comparable rates participants with MDD (14.5%). Our analyses also suggest that dropout rates are lower for inpatient settings, and meta regression analyses confirmed this finding ($\beta = -1.41$, 95% CI -2.472 to -0.342, $p = 0.009$). This relationship was also observed participants with MDD, where we also identified that higher baseline depressive symptoms ($\beta = 0.04$, 95% CI 0.081 to 0.001, $p = 0.04$) predicted greater dropout, whilst a higher proportion of participants taking antidepressant medication tended to lower dropout $\beta = (-0.01$, 95% CI 0.012 to 0.001, $p = 0.09$). Regarding the delivery of exercise interventions, those supervised by physiotherapists ($\beta = -1.2$, 95% CI -2.1 to -0.31, $p = 0.008$) and exercise physiologists ($\beta = -1.34$, 95% CI -2.45 to -0.23, $p = 0.01$) resulted in lower dropout rates. Finally, our comparative meta-analysis established that compared to control conditions, exercise results in significantly reduced dropout rates (OR=0.64, 95% CI 0.43 to 0.95).

The finding that exercise results in lower dropout rates compared to control conditions is important and suggests that exercise is feasible, well-accepted and tolerated by people with depression. Given the fact that the exercise is effective at reducing depressive symptoms (Cooney et al., 2013; Knapen et al., 2015; Vancampfort et al., 2015c) and that dropout can result in worse outcomes (Cooper and Conklin, 2015), our results add further evidence to justify the incorporation of exercise as medicine for people with depression (Vancampfort et al., 2015c). The prevalence of dropout among exercisers with depression is broadly similar to that reported in a recent meta-analyses investigating dropout from psychotherapy (19.9%; (Cooper and Conklin, 2015)) but lower than cognitive behavioral therapy (24.6%; (Hans and Hiller, 2013)). The prevalence of dropout from exercise trials in depression is lower than that observed in exercise trials among type 2 diabetes participants (20%;

(Umpierre et al., 2011)) and in exercise studies in schizophrenia (26.7%; (Vancampfort et al., Submitted)).

Our results confirm and extend a preliminary review (Rethorst et al., 2009), who found a mean dropout rate of 14.6% in 16 exercise RCT's in people with clinical depression. Specifically, for the first time, we identified moderators that influence dropout rates among people with depression participating in exercise RCT's. In particular, it appears that dropout rates are lowest for inpatient settings, similar to results in a recent meta-analysis of dropouts in schizophrenia exercise RCT's (Vancampfort et al., Submitted). This may reflect the added structure and social support that is available for exercise trials that are conducted in inpatient settings. Another factor that may contribute to the lower dropout for inpatient trials could be the additional burden for outpatients to travel to the treatment facility to participate in the intervention. Unlike a recent meta-analysis investigating self-guided web interventions for depression (Karyotaki et al., 2015) we did not find any evidence that gender moderated dropouts in exercise studies. Of interest, in MDD participants, we found that higher baseline depressive symptoms predict an increased dropout. In order to reduce the impact of dropouts in those with MDD, sessions supervised by physiotherapists and exercise physiologists should lead to lower dropout rates from future exercise studies. Thus, our findings extend calls to ensure that qualified personnel with expertise in exercise prescription implement exercise interventions in people with depression (Stanton and Reaburn, 2014). Given the marked and often complex physical comorbidity among those with diagnosed with MDD, including cardiometabolic diseases (Vancampfort et al., 2015; Vancampfort et al., 2013), physical therapists and exercise physiologists constitute a valuable resource to ensure that people with MDD acquire the potential benefits of exercise in this population. Moreover, mixed exercises increased the drop-out rate, possibly due to the fact that with either aerobic or strength programs specific stamina and strength objectives can be more readily achieved, empowering the perception of self-efficacy among patients compared to mixed exercise programs. We suggest programs with simple and specific objectives should be the goal in implementing exercise programs for people with depression which

may include walking or cycling. The analyses we have conducted further advance our understanding of the utility of exercise as a therapeutic tool in depression, addressing the call to address cardiovascular risk, metabolic and weight gain risk, linked to life-style factors, to some medications commonly administered in MDD, and also the depressive illness per se (Goldstein et al., 2015).

Limitations and future research

Several limitations should be considered when interpreting our findings, which largely reflect limitations in the primary studies included with our meta-analysis. First, some potentially important moderators of dropout, such as comorbid anxiety symptoms and socioeconomic variables (e.g. ethnicity, education) were not available in the dataset. Future research should therefore consider the impact of these important moderators. Second, we encountered heterogeneity in some of our analyses. However, our meta-regression analyses were able to explain large proportions of the between-study heterogeneity (see tables 2 and 3). Third, we encountered some publication bias, but conducted trim and fill analyses to adjust for this. Fourth, we encountered 16 studies that may have been eligible but did not report dropout rates and thus were excluded. It remains unclear and beyond the scope of the current paper, whether differences exist in participant, exercise intervention and study characteristics between those papers and the ones included in our manuscript. However, we urge future researchers to clearly report dropout rates and consider incorporating our moderators as a guide to minimize this phenomenon. Finally, few of the included studies provided sufficient detailed information on characteristics of dropouts versus completers, thus precluding direct comparative analyses of predictor variables. Thus, future research should explore important characteristics between completers and non-completers of exercise RCT's. Nevertheless, allowing for these caveats, our results provide important data that can guide clinicians, researchers and policy makers who are seeking to encourage people with depression to engage in exercise.

In summary, the current systematic review and meta-analysis has demonstrated that exercise is well accepted by participants with depression with significantly lower levels of dropouts compared to control conditions. Taken together, our results suggest that dropout rates in MDD are lower in inpatient settings and when delivered by professionals with qualifications to deliver exercise such as physiotherapists and exercise physiologists. Clinicians should be aware that people with MDD who exhibit higher depressive symptoms may be more inclined to dropout and additional support should be given to this group. Given that exercise is effective in reducing depressive symptoms, and has a wide range of other health benefits, our results will be of interest to those seeking to engage people with depression to exercise. Given the lower drop rates when physical therapists and exercise physiologists supervise exercises, these practitioners should be the first choice when considering increasing staff resources to facilitate people with depression engaging in regular exercise.

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Declaration of interests

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The other authors have nothing to declare.

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Highlights

- Across 37 RCTs, the dropout rate among exercisers with depression adjusted for publication bias was 18.1%.
- In people with MDD, higher baseline depressive symptoms predict greater dropout.
- Exercise interventions delivered by highly qualified personnel (physiotherapists and exercise physiologists) results in significantly lower dropout.
- In RCT's comparing exercise to control conditions, people randomised to exercise are significantly less likely to drop out than those allocated to control arms.

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The other authors have nothing to declare.

Conflict of interest

All authors report that they have no conflicts of interest in relation to this work.

Contributors

BS, FS, DV, PBW, SR and JR designed the study. BS, FS, SR, JR conducted searches, extracted data and conducted risk of bias assessments. BS analysed the data. BS wrote the manuscript and all authors provided critical revisions and comments. All authors have approved the final version of the manuscript.

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Analysis	Number of study estimates	Meta-analysis			Heterogeneity	
		Prevalence drop out	95% CI			Between group p value
					12	
Main analysis all depressed studies	52	15.4	12.75	18.50		45%
Study quality						
High quality	17	15.00	11.51	19.31		54%
Low quality	35	15.29	11.50	20.04	0.92	42%
Type of publication						
Peer review article	44	14.34	11.59	17.62		0%
Thesis	8	21.52	13.06	33.34	0.053	50%
Comorbidities						
No major comorbidities	44	16.75	13.14	19.58		40%
Comorbidities present	8	9.20	4.54	17.75	0.06	63%
Depression category						
Major depressive disorder	31	14.68	11.48	18.58		46%
Depressive symptoms	17	17.77	12.72	24.26	0.38	47%
Group exercise or not						
Not in group	19	14.83	9.26	22.88		60%
Group exercise	21	15.22	12.04	19.05	0.91	25%
Setting of study						
Outpatient	44	16.23	13.42	19.50		44%
Inpatient	6	7.85	4.03	14.74	0.03	0%
Type of exercise intervention						
Aerobic exercise	41	15.91	13.02	19.30		32%
Strength training	4	5.42	1.90	14.51		0%
Mixed exercises	4	22.54	13.85	34.38	0.02	68%
Supervised exercise sessions						
Supervised	37	15.17	11.97	19.04		49%
Unsupervised	9	19.63	13.31	27.99		35%
Mixture	5	10.92	5.62	20.16	0.35	0%
Person supervising exercise						
None	4	16.16	7.68	30.88		70%

Analysis	Number of study estimates	Meta-analysis				Heterogeneity
Physical education personnel	13	15.69	10.77	22.30		35%
Physiotherapist	3	13.39	6.29	26.25		0%
Exercise physiologist	1	11.76	3.27	34.45		0%
Other	11	14.54	7.32	26.83	0.80	69%

Table 1: meta-analysis results

Table 2 Meta regression of dropout rates across all studies

	Moderator	Number exercise groups	β	95% CI		P value	R ²
Main analysis all depression studies							
	Mean age	33	-0.0142	-0.0336	0.0052	0.151	0.09
	% females	31	0.0188	-0.0017	0.0393	0.072	0.07
	% taking antidepressants	38	-0.0032	-0.0091	0.0028	0.2938	0.10
	Baseline depressive symptoms	48	0.0029	-0.0208	0.0149	0.748	0.03
	Depressive symptoms v MDD	32	-0.2502	-0.7365	0.2361	0.3132	0.16
	Group exercise v not in group	48	-0.3062	-0.8348	0.2225	0.2563	0.19
	Inpatient v outpatient setting	48	-1.4073	-2.4724	-0.3422	0.0096	0.28
	Low v high quality study	48	0.2218	-0.2798	0.7235	0.3862	0.05
	Trial duration	48	0.0093	-0.0395	0.0581	0.7089	0.0
	Type of exercise	48					0.64
	Aerobic exercise		1.1674	-0.1546	2.4894	0.0835	
	Strength training		-0.084	-1.816	1.6479	0.9242	
	Mixed exercises		1.776	0.4001	3.1519	0.0114	
	Other		-1.6525	-4.7849	1.4799	0.3011	
	Not supervised v supervised	46	0.7011	-0.1212	1.5235	0.0947	0.26
	Who supervised	46					0.16
	Physical education personnel		-0.0562	-0.903	0.7905	0.8964	
	Physiotherapist		-0.286	-1.3534	0.7815	0.5995	
	Exercise physiologist		-0.4323	-1.8779	1.0133	0.5578	
	Nurse		-0.7989	-2.0198	0.422	0.1997	
	Other		-0.0927	-1.1296	0.9442	0.8609	

Key: MDD= major depressive disorder

Table 3- Meta regression of dropout rates among people with major depressive disorder

	Moderator	Number exercise groups	β	95% CI		P value	R ²
MDD only							
	Mean age	21	-0.0102	-0.0348	0.0145	0.419	0.11
	% females	21	0.0155	-0.0155	0.0465	0.3265	0.04
	% taking antidepressants	26	-0.0055	-0.0119	0.0009	0.0915	0.40
	Baseline depressive symptoms	29	0.0409	0.0809	0.0009	0.0453	0.34
	Group exercise v not in group	30	0.0773	-0.6939	0.8486	0.8442	0.0
	Inpatient v outpatient setting	30	-1.4257	-2.6403	-0.2111	0.0214	0.28
	Low v high quality study	28	0.3235	-0.3236	0.9705	0.3272	0.23
	Trial duration	30	0.0054	-0.0497	0.0604	0.8481	0.0
	Type of exercise	30					0.61
	Aerobic exercise		0.6733	-1.0997	2.4464	0.4567	
	Strength training		1.1958	-0.1415	2.533	0.0797	
	Mixed exercises		-0.7975	-3.9536	2.3586	0.6204	
	Other		1.5155	0.0518	2.9792	0.0424	
	Not supervised v supervised		-1.6525	-4.7896	1.4847	0.3019	
	Who supervised	30					1.0
	Physical education personnel		-0.6725	-1.4153	0.0704	0.076	
	Physiotherapist		-1.2029	-2.0967	-0.3091	0.0083	
	Exercise physiologist		-1.3396	-2.4478	-0.2313	0.0178	
	Other		-0.8935	-1.709	0.0781	0.15	

Key: MDD= major depressive disorder

Figure 1. Flowchart of studies selection

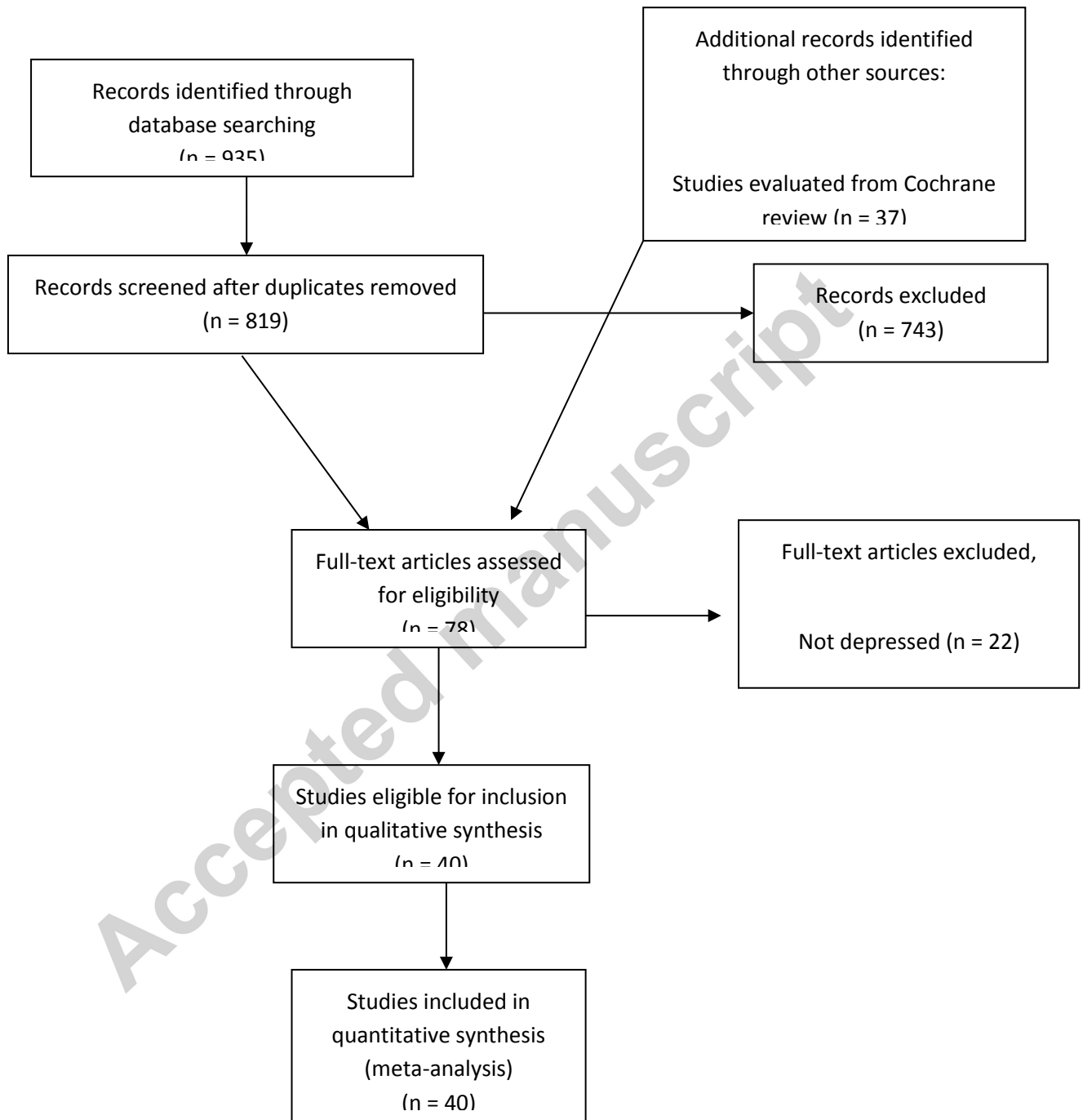


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