Psychiatry Research 244 (2016) 202–209

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Exercise improves depressive symptoms in older adults: An umbrella review of systematic reviews and meta-analyses

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ARTICLE INFO

Article history:
Received 31 January 2016
Received in revised form
1 July 2016
Accepted 17 July 2016
Available online 22 July 2016

Keywords:
Physical activity
Depression
Elderly
Review

ABSTRACT

Late-life depression is a growing public health concern. Exercise may be of added value but the literature remains equivocal. We conducted a systematic overview of meta-analyses and an exploratory pooled analysis of previous meta-analyses to determine the effect of exercise on depression in older adults. Two independent researchers searched Pubmed, CINAHL, Cochrane Plus, PsycArticles, and PsycInfo for meta-analyses on exercise in late-life depression. Methodological quality was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) Instrument. We pooled effect sizes from previous meta-analyses of randomized controlled trials to determine the effect of exercise on depression in older adults. The systematic review yielded 3 meta-analyses. In total, 16 unique cohorts of 1487 participants were included. The quality of the three included meta-analyses was considered as "moderate" according to AMSTAR scores. No serious adverse events were reported. Compared to controls (n=583), those exercising (n=541) significantly reduced depressive symptoms. Our umbrella review indicates that exercise is safe and efficacious in reducing depressive symptoms in older people. Since exercise has many other known health benefits, it should be considered as a core intervention in the multidisciplinary treatment of older adults experiencing depression.

Contents

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http://dx.doi.org/10.1016/j.psychres.2016.07.028
0165-1781/

1. Introduction

Depression is a major public health problem throughout the world affecting more than 350 million people worldwide (World Health Organisation, 2012). It is the most common mental illness among older adults (Alexopoulos, 2005; Strawbridge et al., 2002). Depression is a debilitating condition associated with increased somatic morbidity (Vancampfort et al., 2013), premature mortality (Sutcliffe et al., 2007), lower levels of well-being, poorer physical, social, and cognitive functioning, greater risk of suicide (Conwell et al., 2000), and increased use of health care facilities (Katon et al., 2003). Moreover, in the older population, loneliness and social isolation are potential risk factors for depression (Adams et al., 2004). The prevalence of depressive disorders apparently decreases with age (Scott et al., 2008), with prevalence of major depressive disorder in community samples of adults aged 65 and older ranging from 1 to 10%. Clinically significant depressive symptoms are present in approximately 15% of community-dwelling older adults (Fiske et al., 2009). Compared to younger populations, the prevalence of depression is higher in those with type 2 diabetes (Freitas et al., 2016), chronic pain (de Waal et al., 2016), and those with specific clinical conditions (Hasin et al., 2005; Park et al., 2012; Blazer, 2003) The onset and maintenance of depressive disorder in late life is due to a range of factors including genetic vulnerability, age-associated neurobiological and cognitive changes, and a variety of stressful life events that occur more frequently in late life such as bereavement, reduction in financial incomes, providing care for an ill relative and occurrence of illness reducing autonomy in daily life (Carta et al., 2008; Fiske et al., 2009).

Unfortunately, treatment of depression is inappropriate for most older adults (Karlsson et al., in press) with a limited number of evidence-based treatments. The current treatments for depression in older age include antidepressants, electroconvulsive therapy, cognitive behaviour therapy, and exercise (Frazer et al., 2005). Although medication for depression might be effective for some, they may also have undesirable cardio-metabolic side-effects (Vancampfort et al., 2013), high costs (Meekums et al., 2015) and can be associated with risk of falls (Richards et al., 2007; Stubbs et al., 2015). The value of exercise to improve health (Warburton et al., 2006) particularly among those with depression have been explored in the general population (Knapen et al., 2009).

Considerable progress has been made in understanding the effect of exercise in late-life depression and numerous systematic reviews and meta-analyses have been published (Forsman, et al., 2011; Patel et al., 2012). Conclusions based on systematic reviews of randomized controlled trials (RCTs) are considered the top of the hierarchy of evidence (Moe et al., 2007). Despite the fact that meta-analyses are the cornerstone of evidence based medicine and considered the “gold standard”, there is an increasing realisation that even a perfect meta-analysis with perfect data can only provide a partial overview of an intervention available to clinicians (Stubbs et al., 2015). When one considers the complex nature of depression in older adults and the multitude of ways to deliver aerobic exercise and resistance training interventions available, this notion becomes evidently clear. In addition, there is a rising challenge for busy clinicians to keep on top of the evidence base of any given topic and it is not feasible for clinicians to read multiple individual systematic reviews. Moreover, differences in scope, methods of analysis, results, and quality of systematic reviews can cause great confusion and make it difficult for policy makers to access the review-level evidence, and for researchers to know where gaps in the evidence exist. They serve as a useful starting point for decision makers to unpack the evidence towards finding solutions to improve practice and identify areas where new research is needed. Therefore the popularity of umbrella reviews, or systematic reviews of systematic reviews has increased. With these regards, overviews of systematic reviews are an efficient way to gather and summarize in a single source the best available evidence on the effectiveness of interventions (Ioannidis, 2009). They serve as a useful starting point for decision makers to unpack the evidence towards finding solutions to improve practice and identify areas where new research is needed.

Given the aforementioned, we performed a systematic review of the literature to identify meta-analyses investigating the effects of exercise interventions on depression in older adults. Specifically our purpose was: (1) to appraise past meta-analyses on exercise in late life depression; and (2) to synthesize past meta-analytical findings to inform future related policy and research.

2. Methods

2.1. Literature search

Two independent reviewers (DC and DV) conducted a systematic review of Pubmed, CINAHL, Cochrane Plus, PsycArticles, and PsycInfo from inception to August 2015. The search terms and strategy were: (elderly or older or aged) and (depression or depressive) and (exercise and physical activity) and (meta-analysis). In addition manual searches of reference lists from peer-reviewed journals were conducted.

2.2. Inclusion criteria

Meta-analyses of RCTs that investigated exercise effects on depression in older adults were included. More specifically, meta-analyses had to meet the following criteria: (a) inclusion of people with a formal diagnosis using standardized Diagnostic and

Statistical Manual (DSM) (American Psychiatric Association, 2000) or the International Classification of Disease (ICD) (World Health Organisation, 1993) criteria and/or individuals with elevated levels of depressive symptoms diagnosed by clinician-based or self-report depression symptom questionnaires using a recognized threshold, (b) limited to people with a minimum age of >60 years, irrespective of the treatment setting; (c) investigating the effects of exercise interventions on depression or depressive symptoms with either a comparison or control group. All types of exercise regardless the type and intensity were included. Exercise is defined in this review as any bodily movement produced by skeletal muscles that results in energy expenditure (Kriskaa and Caspersen, 1997); (e) published in either a peer-reviewed journal or academic book; and (f) written in the English language.

2.3. Data extraction

Two independent reviewers systematically extracted information following a predefined format. The extracted study characteristics included qualitative summaries of (1) aims of the meta-analysis, (2) search strategies, (3) inclusion criteria, and (4) characteristics of the exercise interventions researched. The extracted quantitative variables included (1) year of publication, (2) number of included studies (*k*), (3) sample size (N summed across included studies), (4) average age, (5) percent male, and (6) effect size results, e.g. standard mean differences (SMD) for the exercise interventions in comparison with the control interventions; (7) main conclusions.

2.4. Methodological quality

The Assessment of Multiple Systematic Reviews (AMSTAR) instrument was used to empirically assess the quality of the included meta-analyses. Scores range from 0 to 11 with higher scores indicating greater quality (Shea et al., 2009). The AMSTAR scale involves dichotomous scoring (i.e., 0 or 1) of 11 items related to the methodological rigor of systematic reviews and meta-analyses (e.g., comprehensive search strategy, publication bias assessment). AMSTAR scores are graded as high (8–11), medium (4–7) and low quality (0–3) (Shea et al., 2009, 2007). All extracted review information and quality rankings were compared to ensure inter-rater reliability. The independent reviewers reached 100% consensus between effect size data points. Initial consensus was 89%. However, discussion over discrepancies ultimately yielded

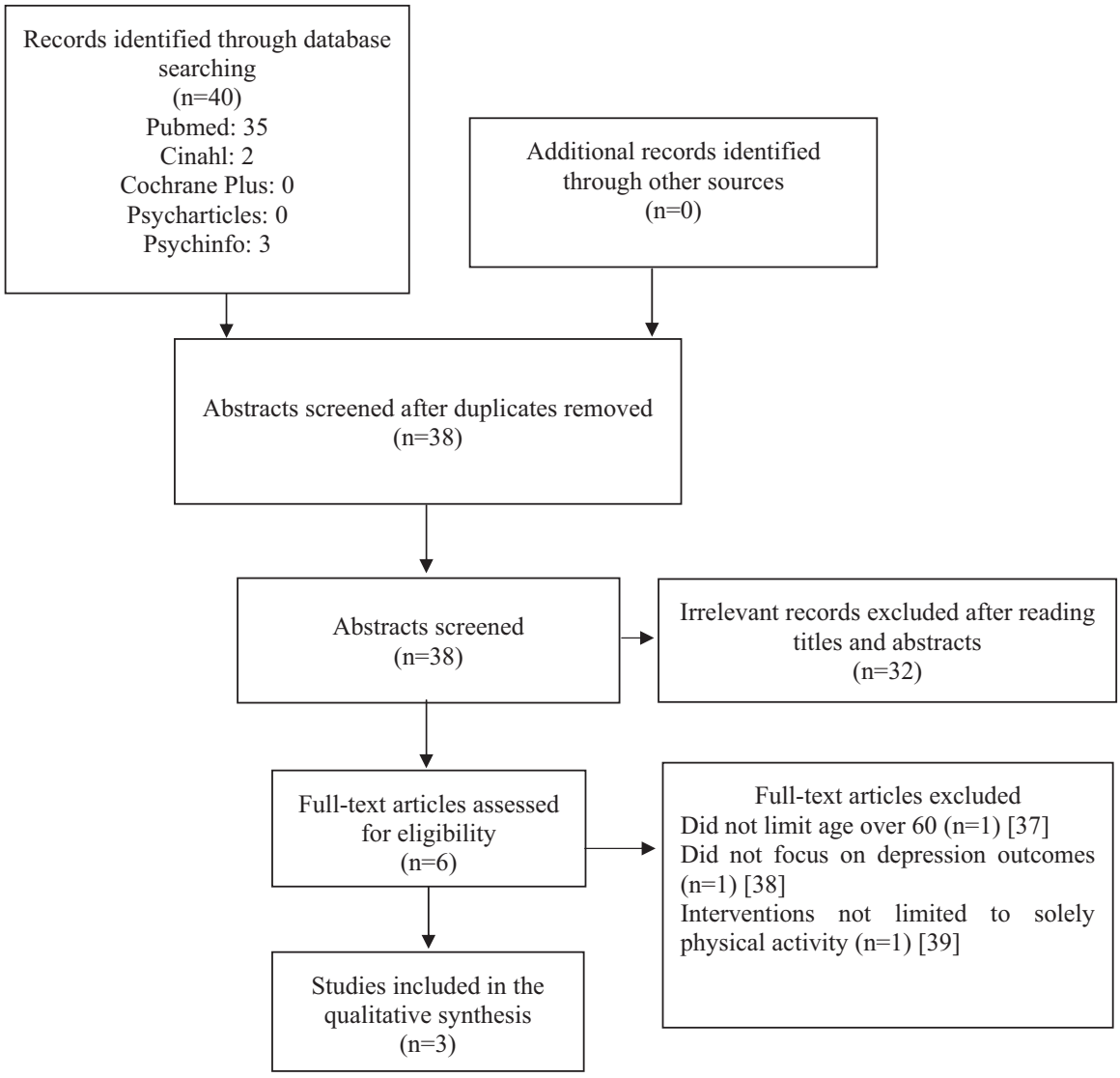

Fig. 1. Flow diagram showing the identification, screening, eligibility and those included for the systematic review.

100% consensus regarding the extracted data.

2.5. Meta-analysis

Where possible, we set out to conduct a random effects pooled meta-analysis of the included effect sizes (SMD) to investigate the influence of exercise on depressive symptoms. We pooled the SMD, 95% confidence intervals weighted for sample size to give a new effect size across all studies (Ioannidis, 2009). We assessed heterogeneity using the I^2 statistic (Higgins and Thompson, 2002) and assessed publication bias with Egger test (Egger et al., 1997).

3. Results

3.1. Search results and study characteristics

The initial electronic database search resulted in 52 valid hits of which 49 articles were excluded with reasons (listed in Fig. 1). Finally, 3 articles met eligibility criteria, which were included in this systematic review and meta-analysis.

3.2. Description of the included meta-analyses

The 3 meta-analyses included similar search periods, from inception to 2009–2011. There was some variation in the aims across the 3 meta-analyses. Forsman et al. (Forsman et al., 2010) focused on the prevention of depression through exercise. Bridle et al. (Bridle et al., 2012) reported the effect of exercise in improving late life depression, and Patel et al. (Patel et al., 2012) assessed yoga as an exercise modality on older adults. There were no overlapping studies within the included meta-analyses. Comparator conditions included in the papers include many different interventions such as 'telephone discussion with researcher about health status', 'physician advice for usual care', 'no intervention, waiting list' and 'exercise advice and information about local exercise options' (Bridle et al., 2012).

Table 1 summarizes the studies characteristics including the aim, search strategy, search period, inclusion criteria, included studies, and participants' characteristics. The meta-analyses varied in the number of studies included (ranging from 3 to 9).

3.3. Review findings

Findings are showed following the PICO search strategy (Population, Interventions, Comparisons and Outcomes) (Higgins and Green, 2011).

3.3.1. Population

In total, 16 unique cohorts of participants involving 1487 participants were included, with sample size of included studies ranging in each of the cohorts from 14 to 672. The mean age range was 63.5–77.5 and the percentage of female participants ranged from 69% to 71%. All participants met depression eligibility criteria determined by the following measures:

a) By the Center for Epidemiological Studies–Depression Scale (CES-D) and GDS (Patel et al., 2012),
b) By depressive symptoms as measured by depression rating scales (such as the Geriatric Depression Scale) (Forsman et al., 2011)
c) By clinician diagnosis, symptom checklist, or a three-question depression screen validated for use in primary care (Bridle et al., 2012).

Studies included older adult's participants living in nursing

Table 1
Studies characteristics.

First author (year)	Aim	Search strategy	Search period	Inclusion criteria	Included RCTs, n	Participants, n (% female); age, years mean
Forsman et al. (2011) [30]	To assess the effectiveness of physical exercise compared with no intervention for the prevention of depression in older people.	AgeLine, ASSIA, CENTRAL, CINAHL, Embase, Medline, OpenSIGLE, Sociological Abstracts, Social Services Abstracts, PsycINFO, and Web of Science	From inception to October 2009	Prospective controlled studies with all participants aged 65 years or older, or an average participant age of 70 years or older. No depressive disorder at the time of enrolment.	3	277 (71); 77
Bridle et al. (2012) [31]	Effect of exercise on depression among older adults, assess whether the effect varies depending on the depression criteria.	CDSR, DARE, UK-NRR, CCT, HSRProj, CENTRAL, Medline; Embase, PsycINFO, SSCI, SportsDiscus, AMED, CINAHL, BioMed Central, HealthPromis, Index of Conference Proceedings, Theses, SIGLE and GreyLit	From inception to January 2011	Randomised controlled trials (RCTs) of exercise interventions for depression among older people. Sample: mean age was over 60 years.	9	667 (69); 65–80
Patel et al. (2012) [32]	The goal was to review systematically the comparative effectiveness of yoga, compared with other exercise interventions.	Medline/PubMed, PsycInfo, CINAHL, Scopus, and Web of Science	From inception to November 2010	Randomized controlled trials. Participants 60 and older. Yoga, compared to another intervention. Studies published in English language.	4	543 (71); 63.5–77.5

homes or other similar institutions (Bridle et al., 2012; Patel et al., 2012), living independently (Bridle et al., 2012; Forsman et al., 2011; Patel et al., 2012), receiving health services at home (Bridle et al., 2012; Forsman et al., 2011), or living in senior communities (Forsman et al., 2011; Patel et al., 2012).

3.3.2. Interventions

In the meta-analysis of Bridle et al. (2012) exercise interventions typically involved exercising for three to five, 30–45 min sessions per week for 3–4 months (see Table 2). Forsman et al. (2011) included different types of physical exercise involving individual or group exercise. Patel et al. (2012) assessed yoga interventions which varied in frequency from once to twice a week, for 12 weeks to 14 months.

In the study of Bridle et al. (2012), 68% (417 of 616) of eligible patients agreed to participate in the trials of which at least three-quarters achieved the minimum criteria for adherence. Patel et al. (2012), found in one trial that adherence was greater when following yoga (77%) compared toexercise (69%), and home exercises (54%). Forsman et al. (2011) did not provide any trial adherence data.

3.3.3. Comparisons

Exercise was compared to treatment as usual, waiting list, or no intervention in two meta-analyses (Bridle et al., 2012; Forsman et al., 2011) and versus yoga (Patel et al., 2012) in another.

3.3.4. Outcomes measures

All studies main outcome measure were depressive symptom checklist including the Center for Epidemiologic Studies Depression Scale (CES-D) and the Geriatric Depression Scale (GDS) (Bridle et al., 2012; Patel et al., 2012).

3.4. Results of individual meta-analyses

Results of the individual meta-analyses are summarized in Table 2. Forsman et al. (Forsman et al., 2011) did not find significant effect on depressive symptoms for exercise (SMD = −0.10; 95% CI = −0.36 to 0.16). Bridle (Bridle et al., 2012) found that exercise reduced depressive symptoms (SMD = −0.34; 95%CI (−0.52 to −0.17)) including those diagnosed with major depressive disorder (SMD = −0.38, 95% CI −0.67 to −0.10). Patel et al. (Patel et al., 2012) found that exercise may be effective in reducing depressive symptoms (SMD = −0.57 (−1.17 to 0.04)).

3.5. Adverse events

Very little information was reported about potential adverse events. Patel (Patel et al., 2012) found that presence or absence of adverse events was not reported by most of the cohorts (7 of 11). When they were reported, no serious adverse events were found from the exercise interventions.

3.6. Methodological quality of the included meta-analyses

Overall, two meta-analyses were considered as moderate quality (Forsman et al., 2011; Patel et al., 2012) and Bridle (Bridle et al., 2012) scored 9 indicating it was high quality. The AMSTAR summary scores and points for individual items are summarized in Table 3.

3.7. Pooled summary effect size across meta-analyses

It was possible to pool the SMD from the 3 individual meta-analyses with 541 older adults in the exercise and 583 older adults in the 'control' arms respectively. This established that exercise

Table 2
Review findings.

First author (year)	Exercise intervention examined	Outcomes	Assessment tools	Major findings (ES and SMD)	Conclusions
Forsman et al. (2011) [30]	Physical exercise: not clearly defined	Depression and depressive symptoms, functional level and quality of life	3; 277 (71); 77; not specified	SMD = −0.10; 95%CI = −0.36 to 0.16; not significant	No statistically significant effect on depressive symptoms was found for physical exercise.
Bridle et al. (2012) [31]	Exercise was defined as any planned or structured movement of the body performed systematically in terms of frequency, intensity and duration	Depression severity, diagnosis type, control vs intervention group	9; 667 (69); 65–80; on depression PHQ-9, GDS, HSCL-20, CES-D, HRSD, BDI, CSDD	SMD = −0.34; 95%CI (−0.52 to −0.17), irrespective of whether participant eligibility was determined by clinical diagnosis (SMD = −0.38, 95% CI −0.67 to −0.10) or symptom checklist (SMD = −0.34, 95%CI −0.62 to −0.06).	Findings suggest that, for older people who present with clinically meaningful symptoms of depression, prescribing structured exercise tailored to individual ability will reduce depression severity.
Patel et al. (2012) [32]	Yoga: not clearly defined.	Maximal aerobic consumption capacity, depression, HRQOL	4; 543 (71); 63.5–77.5; on depression CES-D, GDS	SMD = −0.57 (−1.17 to 0.04), which was a moderate effect size in the direction of yoga reducing depression scores to a greater extent than comparison activities did, although this reduction was not statistically significant.	Small studies with mixed methodological quality suggested that yoga may be superior to conventional exercise interventions in older adults people. The precision of the estimates remains low. Larger studies are necessary to define better the intersection of populations, settings, and interventions in which yoga is most beneficial.

*ES = effect size; SMD = standard mean difference; PHQ-9, Patient Health Questionnaire-9; GDS, Geriatric Depression Scale; HSCL-20, Hopkins Symptom Checklist-20; CES-D, Center for Epidemiologic Studies Depression Scale; HRSD, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; CSDD: Cornell Scale for Depression in Dementia.

Table 3
Results of the AMSTAR checklist items of the meta-analyses.

Items identified through the analysis	Forsman (2011)	Bridle (2012)	Patel (2012)
1. Was an "a priori" design provided?	Yes	Yes	Yes
2. Was there duplicate study selection and data extraction?	Yes	Yes	Yes
3. Was a comprehensive literature review performed?	Yes	Yes	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	Yes	No
5. Was a list of studies (included and excluded) provided?	No	No	No
6. Were the characteristics of the included studies provide?	Yes	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented?	Can't answer	Yes	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes
10. Was the likelihood of publication bias assessed?	No	Yes	No
11. Was the conflict of interest stated?	No	No	No
Total mark	*6*	*9*	*7*

Note: AMSTAR study quality ratings ranged from 0 to 11.

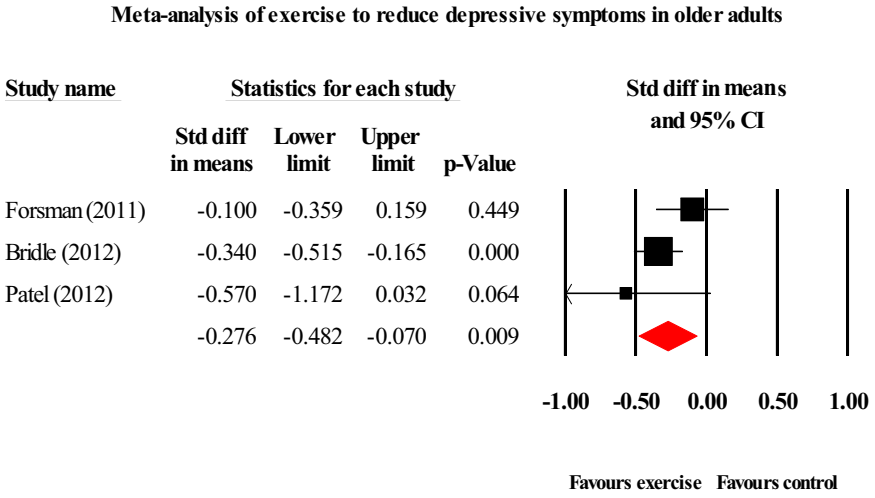

Fig. 2. Pooled meta-analysis investigating the impact of exercise on depressive symptoms.

significantly improved depression among older adults SMD −0.276, (95% CI −0.482 to −0.070, p=0.009) and is displayed in Fig. 2. There was limited heterogeneity (I^2=37%) and no evidence of publication bias (Begg=−0.446, p=0.88).

Finally, as seen in Fig. 3, we pooled the two meta-analyses together that compared exercise (n=442) versus control (n=410) demonstrating that exercise significantly reduced depression (SMD =−0.240, 95% CI −0.472 to −0.008, p=0.04, I^2=52%).

4. Discussion

4.1. General findings

To our knowledge this is the first umbrella review of meta-analyses to investigate the impact of exercise on depression among older adults. We identified 3 meta-analyses published within the last 5 years and found that overall exercise significantly reduces depressive symptoms (SMD −0.276, 95% CI −0.482 to

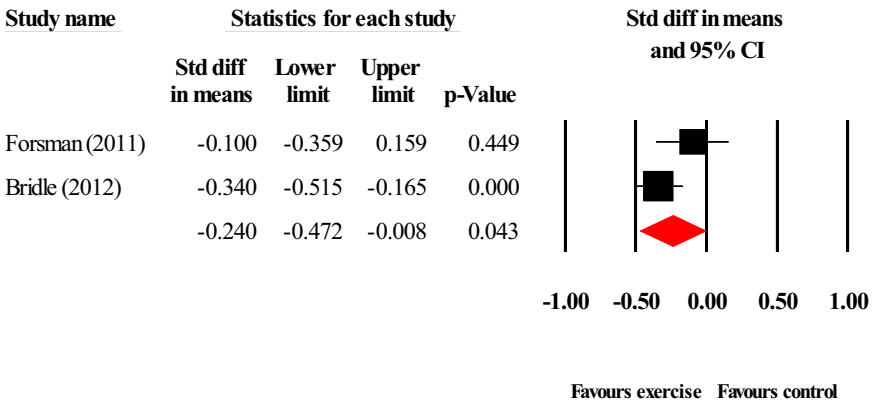

Fig. 3. Pooled meta-analysis investigating the impact of exercise on depressive symptoms excluding yoga.

−0.070, p=0.009). The results remained true when we pooled data from 852 older adults that engaged in non-yoga based exercise versus controls (SMD=−0.240, 95% CI −0.472 to −0.008, p=0.04, I^2=52%). Given that exercise has a plethora of wider health benefits among older adults including preventing cardiovascular disease (Naci and Ioannidis, 2013), prevention of falls (Stubbs et al., 2015) and prevention of disability (Tak et al., 2013), we might recommend that exercise should be considered as an essential part of the treatment of older adults with depression. Additionally, since no serious adverse events were reported, exercise might be considered as a safe intervention in this population. However, we would like to highlight the need for more, well controlled RCT of exercise in older adults with depression in order to strength the above recommendations since one study did not found exercise to provide positive effect (Forsman et al., 2011).

4.2. Practical implications and recommendations for health care professionals when using exercise as a therapeutic strategy in older adults

This overview provides a first attempt for an analysis and synthesis of reviews that might be used as an evidence map to inform practitioners and policy makers about the effectiveness of exercise interventions on depression in older adults. Clinicians, health care policy makers, and clinical guideline developers, who rely on systematic reviews and RCTs to help them make informed choices, may use the summary of findings tables of this overview as an entry point to the current evidence (see Tables 1 and 2). The quality appraisal results can also be used to identify reviews and primary studies of high quality with minimal flaws in both their design and execution that can be trusted to support decision making or address specific questions and details not covered in this overview (see Table 3). Until more evidence becomes available, we recommend that, based on the current evidence, these health care decision makers and practitioners follow at a minimum the latest guidelines from the National Institute for Health and Clinical Excellence (National Institute for Health and Clinical Excellence, 2010) for exercise as a management strategy for depression. These guidelines recommend structured, supervised exercise programs, three times a week (45–60 min) over 10–14 weeks, at low-intensity for mild to moderate depression. Moreover, the guideline for improving mental health prescribes an accumulation each week of a minimum of 150 min of exercise at moderate intensity or a minimum of 75 min at vigorous intensity, in bouts of at least 25 min over 3–5 days per week. In the same way, before any detailed evidence-based FITT-recommendations can be recommended, health care decision makers and practitioners who are faced with implementing exercise programs treatment settings for older adults need to consider the complexity of these programs when interpreting the results of the systematic reviews. For example, health care professionals should take into account that older adults with depression accumulate often many barriers for participation in exercise programs such as a low self-concept, loss of energy, interest and motivation and generalized fatigue (Knapen et al., 2009). In order to improve the patient's motivation and to optimize effects of any exercise program at any age, the following 10 recommendations for health care professionals are useful (Knapen et al., 2009):

1. Anticipate the barriers for participation by an acquaintance conversation.
2. Give information about mental and physical health benefits of exercise, also at an older age.
3. Help older adults with depression to find a form of exercise that suits them.
4. Draw up an individual plan with the patient taking into account emotional, cognitive and physiological and physical components of depression.
5. Create exercise programs based on initial physical fitness assessment and measurement of perceived exertion during exercise.
6. Formulate realistic objectives improving exercise compliance and motivation.
7. Adapt the moderate exercise stimulus to the individual's physical abilities, training status, expectations and goals, side effects of psychotropic medication, exercise tolerance and perceived exertion.
8. Follow the program with exercise cards and provide regular progress feedback to the patients.
9. Focus on perceived fitness gains, achievement of personal goals, mastery experiences and sense of control over the body and its functioning.
10. Involve significant others and family members (children and grandchildren in the exercise programs).

4.3. Future research

Future randomized control trials and meta-analyses should (1) continue to evaluate the long-term effects of exercise, (2) continue to evaluate the effects of exercise as compared to other treatments, (3) not only focus on the effects of exercise on depression but also on how to improve adherence to exercise protocols, (4) clarify the effectiveness of different intervention modalities (frequency, intensity, time and type=FITT principles) for older people with depression to allow determination of exercise dose-response, if possible at all. Future meta-analyses will however continue to face the challenges associated with long-term findings such as variable follow-up assessment time-points across studies and the handling of data for patients who drop out of studies during the follow-up period. Despite these obstacles, the examination of long-term effects has critical implications for the viability of treatments, treatment recommendations and decision making, and the determination of cost-benefit ratios and economic efficiency. As Patel et al. (2012) suggested, given the low number of participants in the trials, it is important to assess barriers to participation in further research. Bridle et al. (2012) advised that new RCTs should stratify randomisation by depression severity, receipt of antidepressant medication and/or level of regular exercise. As uptake of exercise in this population will be the crucial driver for cost-effectiveness, interventions should include integrated strategies, based on behaviour change techniques, to maximise uptake of and adherence to exercise regimens. Although meta-analyses have gained increasing recognition as a valid procedure for evaluating the efficacy of a treatment, limitations of this approach should be kept in mind when drawing conclusions from this review. At a minimum, future meta-analytic research in the field of exercise on late life depression should apply established operational definitions of both exercise (following FITT-principles) and the targeted population in order to improve measurement accuracy when assessing effects.

4.4. Strengths and limitations

A strength of our umbrella review is that we conducted a comprehensive search including only the highest level of evidence (meta-analyses of RCTs) and condensed this in one place to make it readily accessible for clinicians. Moreover, we provided a pooled effect size across the included studies to demonstrate the beneficial influence of exercise on depression. However, whilst this is the first umbrella review of its kind, a number of limitations should be acknowledged which are largely reflected by limitations in the original studies and paucity of data. First, there were a

relative small number of eligible meta-analyses with some heterogeneity and variation in the aims. Second, the included studies often analysed the effect of interventions using different summary measures. Third, the included studies recruited predominantly female participants (69–71%). And fourth, the survival bias which might have been present within the included studies (i.e. only the participants who were benefitting from exercise taking part in follow-up assessments. It is unknown if the included studies uses intention-to-treat or per-protocol analyses. Nevertheless, allowing for these caveats our results are a first and might be of high interest to clinicians and researchers in the area. Our umbrella review may bring some directions towards considering exercise as an effective way to reduce depressive symptoms in older adults. We therefore might recommend that exercise should form a central part of the treatment of older adults with depression. However, as earlier stated, further research is needed to be able to provide a more solid and robust recommendation.

Conflict of interests

Authors declare that there are none.

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