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Review

Effectiveness of exercise-based interventions in reducing depressive symptoms in people without clinical depression: systematic review and meta-analysis of randomised controlled trials

Juan Ángel Bellón, Sonia Conejo-Cerón, Almudena Sánchez-Calderón, Beatriz Rodríguez-Martín, Darío Bellón, Emiliano Rodríguez-Sánchez, Juan Manuel Mendive, Ignacio Ara and Patricia Moreno-Peral

Background

In most trials and systematic reviews that evaluate exercise-based interventions in reducing depressive symptoms, it is difficult to separate treatment from prevention.

Aims

To evaluate the effectiveness of exercise-based interventions in reducing depressive symptoms in people without clinical depression.

Method

We searched PubMed, PsycINFO, Embase, WOS, SPORTDiscus, CENTRAL, OpenGrey and other sources up to 25 May 2020. We selected randomised controlled trials (RCTs) that compared exclusively exercise-based interventions with control groups, enrolling participants without clinical depression, as measured using validated instruments, and whose outcome was reduction of depressive symptoms and/or incidence of new cases of people with depression. Pooled standardised mean differences (SMDs) were calculated using random-effect models (registration at PROSPERO: CRD42017055726).

Results

A total of 14 RCTs (18 comparisons) evaluated 1737 adults without clinical depression from eight countries and four continents. The pooled SMD was −0.34 (95% CI −0.51 to −0.17; $P < 0.001$) and sensitivity analyses confirmed the robustness of this result. We found no statistical evidence of publication bias and heterogeneity was moderate ($I^2 = 54\%$; 95% CI 22–73%). Only two RCTs had an overall low risk of bias and three had long-term follow-up. Multivariate meta-regression found that a larger sample size, country (Asia) and selective prevention (i.e. people exposed to risk factors for depression) were associated with lower effectiveness, although only sample size remained significant when adjustment for multiple tests was considered. According to the Grading of Recommendations Assessment, Development and Evaluation tool, the quality of evidence was low.

Conclusions

Exercise-based interventions have a small effect on the reduction of depressive symptoms in people without clinical depression. It could be an alternative to or complement psychological programmes, although further higher-quality trials with larger samples and long-term follow-up are needed.

Key words

Depression; prevention; exercise; randomised controlled trial; systematic review.

Background

According to the World Health Organization, 322 million people have depression worldwide.[1] Between 2007 and 2017, the depression burden measured as years lived with disability increased by 14.1% and 14.8% for women and men, respectively,[2] ranking third (women) and fifth (men) in the world among 354 diseases. By 2030, it is estimated that depression will be the main cause of disease burden in high-income countries.[3]

Although effective therapies are available for depression, they only reduce disease burden by 30%.[4] In the theoretical situation that all people with depression received the appropriate treatment, the reduction of the disease burden would be limited due to the continuous occurrence of new cases of depression.[5]

Preventing the development of depression

The prevention of depression – which avoids the development of the disease – emerges as a plausible approach to reducing its disease burden.[6] The term primary prevention is reserved for only those interventions that occur before the onset of a disorder. Approaches to prevent the onset of depressive episodes have targeted people with prodromal symptoms not yet meeting the diagnostic criteria of a depressive disorder (indicated prevention), people at elevated risk because they have been exposed to risk factors (selective prevention) and the full population (universal prevention).[7] The overall aim of these three types of preventive intervention is the reduction of the occurrence of new cases. Usually, this is done through a risk-reduction model, and even if outcomes are in the distant future and the goal of fewer cases have not yet been established, the decrease in risk and/or increase in protective factors can be documented,[7] even including estimations of the individual probability of experiencing depression in the future.[8] Depressive symptoms are a good predictor of future incidence of depression,[9] and their reduction can be seen as an indicator of decreased risk. Additionally, the aims of indicated preventive interventions might be to reduce the length of time the early symptoms continue and to halt a progression of severity so that the individuals do not meet, nor do they come close to meeting, DSM diagnostic levels.[7]

In the past two decades, dozens of systematic reviews and meta-analyses of the primary prevention of depression through

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psychological and psychoeducational interventions have been conducted, and from their global analysis it was concluded that these interventions have a small preventive effect, with the quality of evidence being high.[10,11]

Differentiating studies looking at treatment versus prevention

The 2018 Physical Activity Guidelines Advisory Committee Scientific Report suggests strong evidence demonstrates that physical activity reduces the risk of experiencing depression and reduces depressive symptoms in individuals with and without major depression across the lifespan.[12] However, in most of the trials included in the systematic reviews and meta-analyses considered in this report it is difficult to separate treatment from prevention.

A recent meta-analysis of prospective studies found that higher levels of physical activity are consistently associated with lower odds of developing future depression.[13] The authors of a meta-analysis reported that exercise training is effective in reducing the symptoms of depression in sedentary patients with a chronic disease.[14] However, the reportedly higher effectiveness of physical activity in patients with mild-to-moderate depression at baseline might be because of the treatment rather than to the primary prevention of depression. In addition, improvement in symptoms of depression was the primary end-point in only 3 of the 90 trials included. Another meta-analysis revealed that symptoms of depression also improved through physical activity programmes in patients without a diagnosis of clinical depression.[15] Yet, a large number of the trials included had either a before–after design, were non-randomised or evaluated multicomponent interventions (for example exercise + diet) in which the preventive effect of exercise cannot be measured separately.

Aims

The goal of our study was to evaluate the effectiveness of exercise-based interventions for the reduction of depressive symptoms in individuals without clinical depression.

Method

We applied Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews and meta-analyses.[16] The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42017055726). As this meta-analysis is based on published data, no ethical approval was required.

Data sources

We searched six electronic databases: PubMed, PsycINFO, Embase, Web of Science (WOS), SPORTDiscus, OpenGrey (System for Information on Grey Literature in Europe) and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 25 May 2020. We performed a complementary search of the references provided in 56 relevant systematic reviews and meta-analyses (see Supplementary Appendix A available at https://doi.org/10.1192/bjp.2021.5) and those listed in the studies selected. Experts were also contacted to identify further potentially relevant studies.

Search terms included: "physical activity or exercise", "randomised controlled trial", "depressive disorder", "intervention" and "prevention". To increase search sensitivity, search terms were used in their broadest sense. We designed the search strategy based on a preliminary search of PubMed and adapted this for further searches of other databases (see Supplementary Appendix B). Following the removal of duplicates, titles and abstracts were reviewed using our inclusion and exclusion criteria. We then reviewed the full text of the publications selected. In the cases where the information required to determine the eligibility of a study was not provided, the authors were contacted to obtain the information required. Two pairs of reviewers (A.S.-C. with B.R.-M. and D.B. with S.C.-C.), each evaluating half of the records and full-text reports, independently performed the selection. Disagreements within each of the two pairs of reviewers were resolved by consensus or by the intervention of another reviewer (P.M.-P.), when appropriate.

Study selection

Design

We focused the search on randomised controlled trials (RCT), as they provide evidence of causality and are considered the gold standard for clinical trials.[17]

Participants

To ensure that the results obtained in our search were related to the reduction of depressive symptoms in people without clinical depression, we only included RCTs in which participants with depression at baseline, detected through structured standardised interviews (for example, Structured Clinical Interview for DSM-5) or validated self-reports with standard cut-off points (for example, Beck Depression Inventory-II), were excluded. The RCTs enrolling participants with and without depression at baseline were included when results were provided separately for both types of participants, although we only include in the meta-analysis the subsample of individuals without clinical depression at baseline. No restrictions were followed regarding diseases, pathologies or pregnancy. There were also no restrictions based on sociodemographic characteristics (age, gender, education level, etc.), setting (community, primary care, hospital, etc.) or publication language.

Intervention: exercise–physical activity

Although exercise is a subtype of physical activity, for the purpose of this review, we used the terms interchangeably. Exercise and physical activity were defined as any bodily movement generated by skeletal muscles that resulted in energy expenditure above resting levels.[18] The studies selected involved exercise-based interventions and provided data about the frequency, intensity, duration and type of exercise. Studies (or study arms) assessing the effectiveness of interventions combining exercise with another type of intervention known to be effective in the prevention of depression (such as exercise + psychological intervention) were excluded. Studies had to provide objective (for example assessed by accelerometer) or subjective (for example assessed by a questionnaire) evidence that physical activity was performed.

Comparators

Control groups could be usual care, no treatment (only evaluations), waiting list, attention control or any type of placebo. The studies in which the comparator was an intervention that was proven to be effective in the prevention of depression (such as cognitive–behavioural therapy) were excluded.

Outcomes

The outcomes – either primary or secondary – of eligible studies included the reduction of symptoms of depression (as measured through validated scales of symptoms of depression) and/or the incidence of new cases of depression in participants during follow-up (as measured through standardised interviews or validated scales of depressive symptoms using standard cut-offs).

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Data extraction

Data extracted from each study were recorded in an evidence table and extracted by two independent reviewers (P.M.-P. and S.C.-C.). Disagreements between the two reviewers were resolved by consensus or by the intervention of another reviewer (J.A.B.), when necessary. Missing data was resolved by contacting authors when appropriate.

Evaluation of the risk of bias

The methodological quality of the RCTs was assessed using the Cochrane risk-of-bias tool (version 1).[19] From a qualitative approach, RCTs that were assessed to be at low risk of bias for all domains (sequence generation, allocation concealment, blinding of outcome assessors, incomplete data analysis and selective reporting addressed) were considered to have an overall low risk of bias. The item 'blinding of participants and personnel' was excluded from this criterion because the nature of exercise-based interventions makes them difficult to mask. To treat the risk of bias as a quantitative variable for meta-regression analysis, each of the six criteria of the Cochrane tool were assigned 0 points when the risk was low, 1 point when the risk was uncertain, and 2 points when the risk was high. Therefore, the risk of bias of an RCT ranged from 0 (the lowest) to 12 (the highest). Two trained, independent reviewers (S.C.-C. and P.M.-P.) assessed the risk of bias. Disagreements between the two reviewers were resolved by consensus or by the intervention of another reviewer (J.A.B.), when necessary.

Statistical analysis and synthesis

All statistical analyses were performed using 'Stata' version 14.2 and 'Comprehensive Meta-Analysis' (CMA) version 2.2.064.

Measure of effect

We used the standardised mean difference (SMD) between the intervention and the control group as a measure of effect. For each RCT, we calculated the SMD by combining the SMD at different post-test follow-up times into a single estimate as the average, as well as its 95% CI. Negative SMDs indicated a better outcome (reduction of depressive symptoms) in the intervention group. Cohen proposed the following interpretation for this effect size: −0.2 is small; −0.5 medium and −0.8 large.[20] For any RCT that included two different intervention groups (i.e. aerobic versus resistance) and one control group, standard errors in nested comparisons in the same RCT were inflated, following the recommendation of Cates.[21] *A priori*, we selected a random-effects model under the assumption that the RCTs to be included in our meta-analysis were performed in heterogeneous 'populations' that may differ from each other.[22]

Heterogeneity

We assessed the heterogeneity using *I*-squared,[23] which is expressed as a percentage, where heterogeneity is indicated as follows: 0–40% irrelevant, 30–60% moderate, 50–90% substantial, and 75–100% considerable.[19] We also calculated Cochran's *Q*-test and its *P*-value.

Publication bias

We evaluated publication bias by inspecting the funnel plot[24] and the Duval & Tweedie trim-and-fill procedure.[25] We also performed the Begg & Mazumdar rank correlation test.[26]

Analysis of sensitivity

We conducted sensitivity analyses to assess the robustness of the results by repeating the calculation of the pooled SMD in the first and last follow-up evaluation after the intervention, using Hedges's *g* and the profile likelihood method (an alternative to the DerSimonian–Laird method that is more conservative and convenient when the number of studies is small), excluding the RCT that caused the greatest increase in heterogeneity and including only those RCTs with an overall low risk of bias.

Subgroup analysis and meta-regression

We used a mixed-effects model for subgroup analyses with the following *a priori* subgroups:

(a) Participant characteristics: country of origin, clinical status (with or without chronic disease), gender, age (adult (18–64 years)or elderly (>64 years)) and type of prevention (indicated, selective or universal).
(b) Exercise-based intervention characteristics: format (individual, group) verification (objective, subjective), supervision, walking, yoga, intervention duration, session duration, frequency, volume of exercise and intensity.
(c) Methodological characteristics: measure of depression to exclude patients with clinical depression at baseline, measure of outcome, subsample (studies that included participants with and without clinical depression at baseline but give separate outcomes for participants without clinical depression), type of outcome (primary or secondary), type of comparator, qualitative and quantitative level of risk of bias, duration of follow-up and sample size.

We performed multivariate random-effect meta-regressions to assess the impact of study characteristics (considered in advance) on the effect size, adjusting for other covariates and to explain heterogeneity across studies. *A priori*, we forced the variables 'risk of bias' and 'sample size' (as a proxy to quantify publication bias) into the multivariate meta-regression models to adjust for two of the five domains of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality of evidence criteria, for which quantitative variables are available.[27–29]

The *post hoc* analysis strategy to explain the maximum heterogeneity consisted of obtaining the most parsimonious meta-regression model (including the least number of variables) with the best goodness of fit. The normality of the quantitative covariates was checked using the skewness and kurtosis normality test;[30] and transformations were conducted, when appropriate, to approximate normality. We calculated standard errors and 95% CIs using the Knapp & Hartung method.[31] We calculated correlations between covariates to assess potential collinearity. To consider adjustment for multiple tests, we calculated *P*-values with the permutation test following recommendations by Higgins & Thompson.[32] Finally, we used a normal probability plot of standardised shrunken residuals to estimate the goodness of fit of the meta-regression models.

The quality of evidence

The quality of evidence in the domains of risk of bias, consistency, directness, precision and publication bias were taken into account according to the GRADE working group methodology.[33]

Results

Search results

A total of 7640 articles were identified after eliminating duplicates. Of these, 418 articles were included for full-text review and 14 different RCTs[34–47] met the inclusion criteria, which included 18 valid comparisons for the meta-analysis (see Fig. 1).

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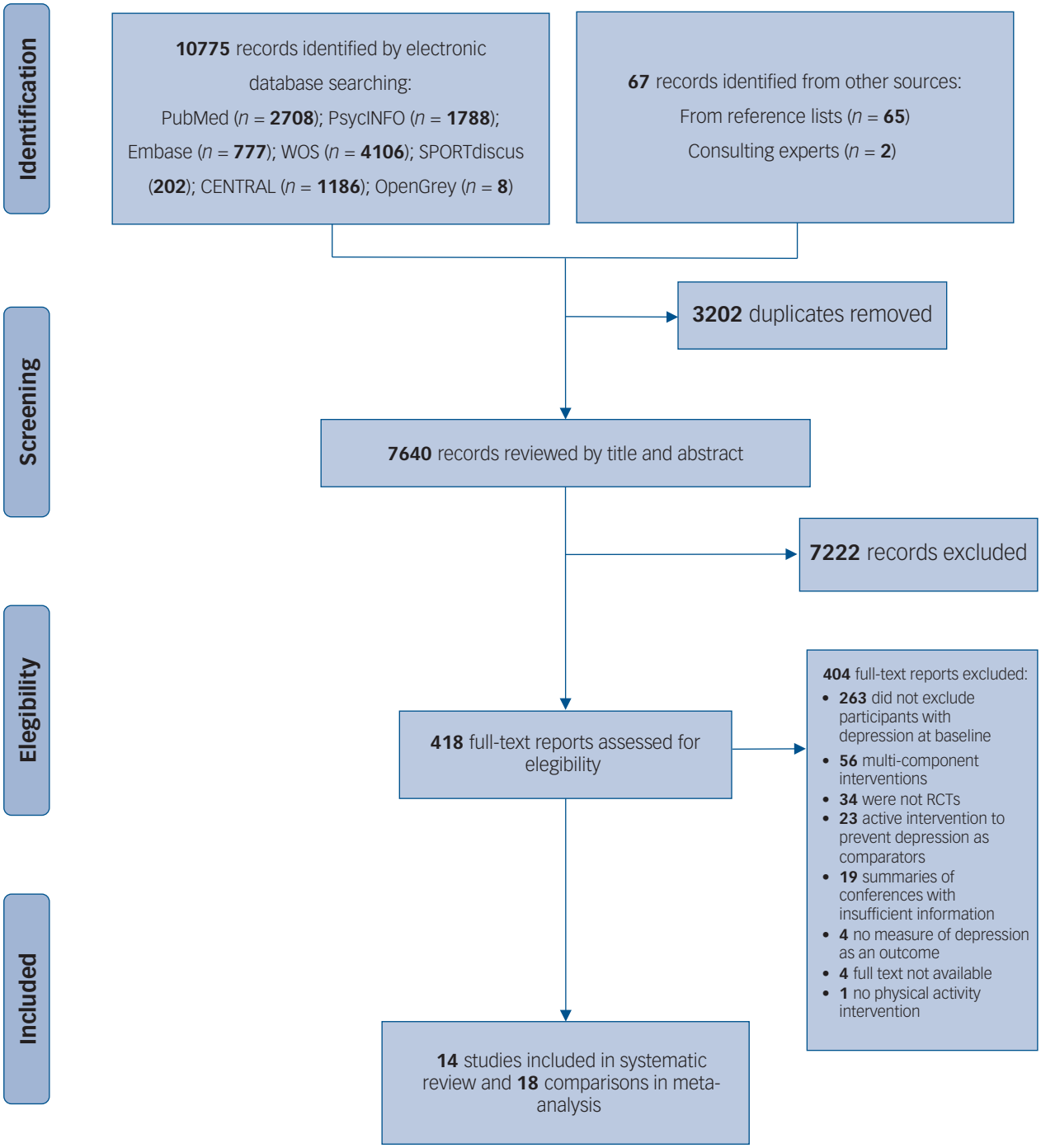

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

RCT, randomised controlled trial.

Characteristics of included studies

The characteristics of the 14 RCTs included are described in Supplementary Table 1. The RCTs were conducted in North America ($n = 6$),[33,38,40,42,46,47] Europe ($n = 3$),[36,41,45] Asia ($n = 3$)[35,39,43] and South America ($n = 2$).[37,44] All were published between 1999 and 2019. Overall, the 14 RCTs evaluated a total of 1737 participants (intervention group 1008; control group 729). Sample sizes ranged from 19 to 501 (median 77; interquartile range 27–124).

Regarding the target population, nine RCTs were aimed at the adult population (18–64 years), and five predominantly concerned elderly people (>64 years).[34,35,41,42,44] Three RCTs included only women (two pre–postnatal[38,45] and one multiple sclerosis[43]). Five included participants with physical chronic diseases (two knee osteoarthritis,[42,44] one low back pain,[46] one multiple sclerosis[43] and one lung cancer[35]). The type of prevention was selective in nine RCTs.

Regarding the exercise-based interventions, nine RCTs provided aerobic exercise. Two RTCs included exclusively walking interventions[35,40] and two Iyengar yoga.[46,47] Most of the interventions were supervised (ten RCTs) and objectively verified (ten RCTs), with sessions of moderate intensity (ten RCTs), under 60 min (nine RCTs)

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Table 1 Effectiveness of exercise-based interventions in reducing depressive symptoms in people without clinical depression

Effectiveness	Number of comparisons	SMD (95% CI)	*P*	I^2, % (95% CI)
Primary analysis[a]	18	−0.34 (−0.51 to −0.17)	<0.001	54 (22–73)
Sensitivity analyses				
At first evaluation post-intervention	18	−0.32 (−0.49 to −0.15)	<0.001	54 (23–73)
At last evaluation post-intervention	18	−0.35 (−0.52 to −0.18)	<0.001	55 (23–73)
Hedges' *g*	18	−0.33 (−0.49 to −0.17)	<0.001	54 (22–73)
Profile likelihood method[b]	18	−0.33 (−0.51 to −0.17)	<0.001	45 (22–73)
Pakkala et al (2008)[41] excluded[c]	17	−0.37 (−0.52 to −0.23)	<0.001	26 (0–59)
Including only RCTs with low risk of bias[e]	2	−0.55 (−0.87 to −0.22)	0.001	0[d]
Woolery et al (2004)[47] excluded[f]	17	−0.30 (−0.45 to −0.14)	<0.001	45 (2–69)

SMD, standardised mean difference; RCT, randomised controlled trial.
a. Taking the different post-intervention evaluations as an average.
b. Between-studies variance estimate (τ^2): 0.042 (95% CI 0.000–0.157).
c. The RCT that most increased heterogeneity.
d. It is not possible to calculate the 95% CI because degrees of freedom ($n - 1$) must be at least 2.
e. Low risk of bias criteria for inclusion (RCTs that scored low risk of bias in sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data addressed and selective reporting): Brenes et al (2007)[34] and Lewis et al (2014).[38]
f. This RCT might be an outlier.

and a frequency of two to four sessions per week (ten RCTs). Most interventions lasted 12 weeks or less (nine RCTs).

Methodological aspects included the following: in 13 RCTs, the primary outcome was the reduction of depressive symptoms; 7 RCTs had follow-up <6 months and only 3 RTCs had follow-up between 12 and 24 months;[37,41,42] 9 RCTs had usual care as a comparator. All RCTs assessed reduction of depressive symptoms as an outcome and only one RCT also assessed the incidence of depression by standardised interview.[38]

Risk of bias

The risk of bias of each of the RCTs is detailed in Supplementary Table 2. Taking into account our standard for considering an RCT as having a qualitative overall low risk of bias, only two RCTs achieved this,[34,38] although the pooled SMD of these was slightly higher than the rest of the RCTs (see Table 1).

Effectiveness of the interventions to prevent depression

Figure 2 shows each of the SMDs of the 18 comparisons for the 14 RCTs. The pooled SMD was −0.34 (95% CI −0.51 to −0.17; $P < 0.001$) for the random-effects model, which indicates that exercise-based interventions had a small, although significant effect on the reduction of depressive symptoms in people without clinical depression. There was moderate heterogeneity across the studies ($I^2 = 54\%$, 95% CI 22–73%) that was significant ($Q = 37.14$; $P = 0.003$). The primary analysis changed very little in the sensitivity analyses (Table 1).

Publication bias

The Begg & Mazumdar test to detect publication bias was not significant ($z = -1.21$; $P = 0.240$). The Duval and Tweedie procedure did not impute any missing RCTs, and the funnel plot is shown in Supplementary Fig. 1. Therefore, no statistical evidence for the presence of publication bias was found.

Subgroup analyses and meta-regression

Supplementary Table 3 shows the subgroup analyses. The effectiveness of exercise-based interventions to reduce depressive symptoms was higher ($P \leq 0.001$) in interventions with objective verification, and it was lower in elderly people, selective prevention, low intensity of exercise and with a larger sample size (>200).

Unadjusted meta-regressions using standard errors by the Knapp & Hartung method, showed that selective prevention, larger sample size and RCTs using a subsample were statistically ($P < 0.05$) associated with lower effectiveness to reduce depressive symptoms; and this was higher in interventions with a group format and RCTs with a waiting list as comparator (Table 2). When adjusted for risk of bias in meta-regression models, group format lost statistical significance; and after adjustment for sample size, only country (Asia) and selective prevention were associated with lower effectiveness (Table 2).

A final meta-regression model including only two moderators explained 100% of the heterogeneity (Table 3) and its goodness of fit was good (see Supplementary Fig. 2). Larger sample size (β (ln) = 0.29 (95% CI 0.16–0.42); $P < 0.001$) and country (Asia) (β = 0.39 (95% CI 0.05–0.73); $P = 0.027$) were significantly associated with lower effectiveness, although the latter did not reach significance when multiplicity adjustment (Higgins & Thompson permutation test) was performed.

Quality of evidence

The initial grading of the quality of evidence was high since we included only RCTs. Although the pooled effect size including only RCTs with an overall low risk of bias was slightly higher than the rest of the RCTs, there were very few RCTs with a low risk of bias, and therefore we reduced the rating from high to moderate. The heterogeneity was moderate, and although this was explained entirely (by 100%) through meta-regression, we reduced the rating from moderate to low. Indirectness was low since the target population, the interventions and our outcome did not differ from those of primary interest. There was no statistical evidence of publication bias. We included a sufficient number of studies, and the total number of participants in our study allowed adequate precision. In summary, the quality of evidence according to GRADE was low.

Discussion

Exercise-based interventions had a small effect on the reduction of depressive symptoms in participants without clinical depression and this result was robust in sensitivity analysis. Most of these interventions were aerobic, of moderate intensity, with two to four sessions a week of 60 min or less, supervised and objectively verified. These findings were derived from 14 RCTs (18 comparisons) including 1737 adult participants (some elderly) from eight countries and four continents. We found no publication bias but there was moderate heterogeneity, 100% of which was explained by only two moderators. There were only two RCTs with a low risk

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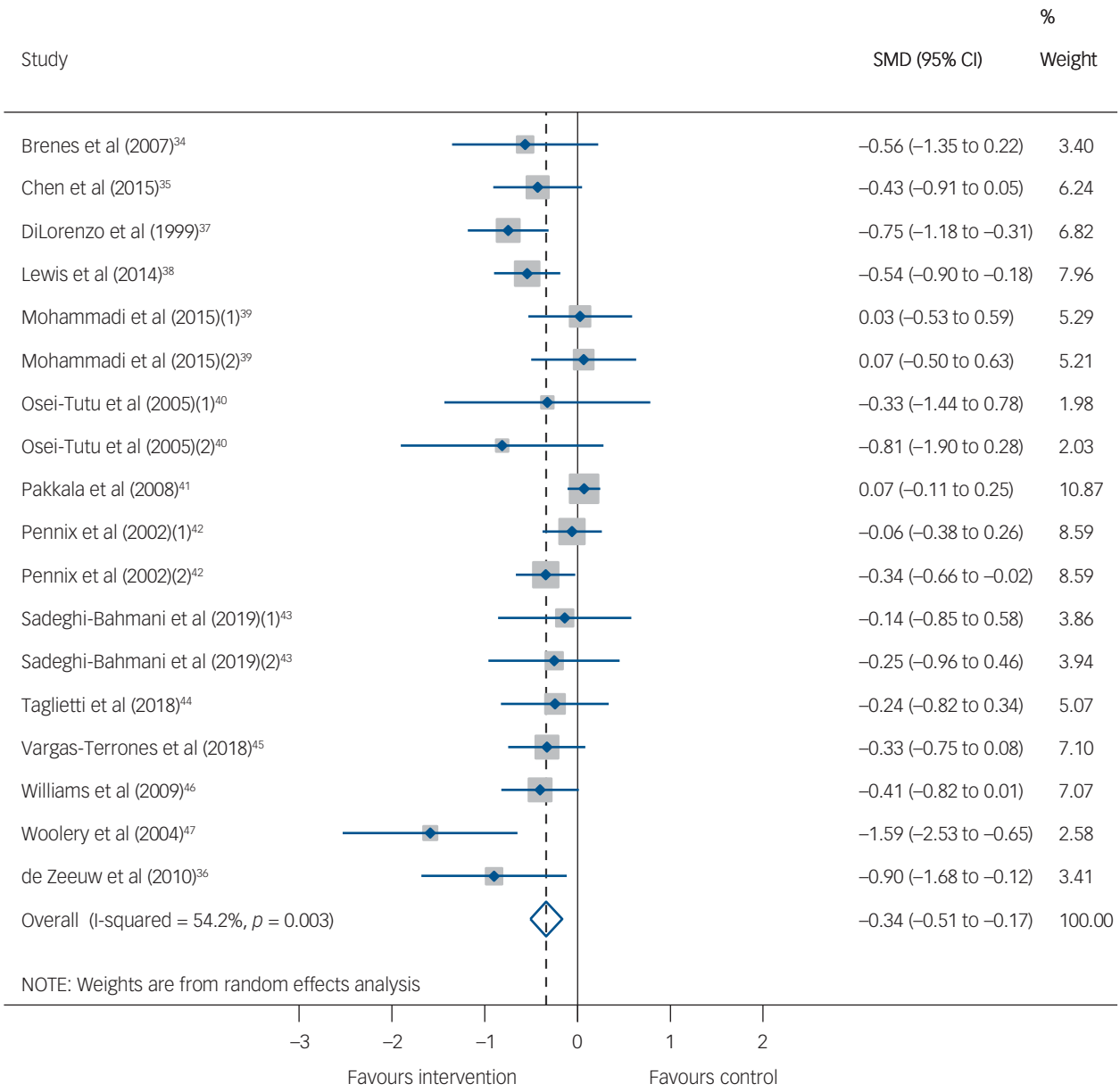

Fig. 2 Forest plot.

SMD, Standardised mean difference.

of bias and three with longer follow-up. Multivariate meta-regression showed that larger sample size, selective prevention and country (Asia) were associated with lower effectiveness. Finally, the strength of evidence, according to GRADE, was low.

Strengths

To the best of our knowledge, this is the first meta-analysis to evaluate the effectiveness of exercise-based interventions for the reduction of depressive symptoms in people without clinical depression through RCTs conducted in adult, including elderly, populations. Our strict inclusion criteria, analysing only RCTs with participants free of depression at baseline, allowed us to clearly distinguish prevention from treatment. Our meta-analysis included a reasonable number of RCTs representing a large population of individuals with different characteristics and from different settings, which supports its external validity.

We used multiple complementary electronic databases, 56 systematic reviews and meta-analyses and supplementary hand searching. The variety of databases utilised, combined with the broad range of search terms and no restriction on study publication language, contributed to a highly sensitive search.

We applied rigorous methodology (PRISMA, GRADE) to the systematic review and meta-analysis process and the evaluation of the strength of evidence. We also performed sensitivity analyses, which support the robustness of the pooled SMDs in different setups (analyses and evaluation times) or when only RCTs with a low risk of bias were included. Finally, subgroup analyses and meta-regression allowed the identification of possible sources of heterogeneity, and multivariate meta-regression let us adjust for confounding biases and multiple comparisons.

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Table 2 Coefficient statistics of unadjusted and adjusted meta-regression on the association between reduction of depressive symptoms (standardised mean difference) and other covariates

Independent variables	Unadjusted coefficient[a]	*P*	Adjusted for risk of bias	*P*	Adjusted for sample size	*P*	Adjusted for risk of bias and sample size	*P*
Participant characteristics								
Country (Asia)	0.239 (−0.178 to 0.654)	0.242	0.230 (−0.193 to 0.652)	0.265	0.389 (0.051 to 0.726)	0.027	0.380 (0.039 to 0.722)	0.032[b,c]
Gender (women)	−0.039 (−0.465 to 0.387)	0.850	−0.094 (−0.532 to 0.344)	0.655	−0.018 (−0.371 to 0.335)	0.914	−0.047 (−0.429 to 0.333)	0.792
Age (elderly)	0.261 (−0.059 to 0.581)	0.104	0.251 (−0.072 to 0.574)	0.118	0.010 (−237 to 0.437)	0.538	0.104 (−0.244 to 0.453)	0.532
Chronic (yes)	0.111 (−0.254 to 0.475)	0.529	0.130 (−0.239 to 0.499)	0.464	0.077 (−0.210 to 0.364)	0.576	0.102 (−0.199 to 0.404)	0.478
Prevention (selective)	0.604 (0.211 to 0.997)	0.005	0.610 (0.175 to 1.056)	0.009	0.442 (0.033 to 0.852)	0.036	0.460 (0.005 to 0.916)	0.048[b,d]
Intervention characteristics								
Type of exercise (aerobic)	−0.040 (−0.399 to 0.320)	0.818	−0.046 (−0.412 to 0.319)	0.790	−0.146 (−0.449 to 156)	0.319	−0.156 (−0.469 to 0.157)	0.304
Walking (yes)	−0.171 (−0.761 to 0.419)	0.548	−0.142 (−0.740 to 0.456)	0.621	0.036 (−0.513 to 0.586)	0.889	0.036 (−0.527 to 0.560)	0.892
Yoga (yes)	−0.412 (−1.00 to 0.178)	0.158	−0.461 (−1.057 to 0.134)	0.120	−0.256 (−0.761 to 0.248)	0.296	−0.315 (−0.852 to 0.223)	0.230
Type of verification (objective)	−0.272 (−0.592 to 0.049)	0.091	−0.238 (−0.592 to 0.116)	0.173	−0.225 (−0.458 to 0.008)	0.057	−0.235 (−0.509 to 0.038)	0.086
Supervised exercise (yes)	−0.221 (−0.562 to 0.119)	0.187	−0.181 (−0.581 to 0.218)	0.349	−0.130 (−0.417 to 0.158)	0.352	−0.115 (−0.473 to 0.243)	0.503
Format (group)	−0.345 (−0.667 to −0.023)	0.037	−0.325 (−0.661 to 0.010)	0.056	−0.196 (−0.526 to 0.134)	0.225	−0.193 (−0.538 to 0.153)	0.251
Duration of intervention (up to 12 weeks)	−0.252 (−0.588 to 0.085)	0.133	−0.217 (−0.595 to 0.161)	0.241	−0.016 (−0.407 to 0.375)	0.932	0.026 (−0.404 to 0.456)	0.899
Frequency of sessions (2–4/week)	−0.070 (−0.456 to 0.317)	0.707	0.054 (−424 to 0.532)	0.812	0.049 (−0.275 to 0.373)	0.752	0.214 (−0.219 to 0.647)	0.307
Duration of sessions (up to 60 min)	−0.163 (−0.504 to 0.178)	0.325	−0.191 (−0.528 to 0.146)	0.245	−0.011 (−0.350 to 0.328)	0.945	−0.033 (−0.394 to 0.328)	0.846
Volume (up to 150 min/week)	−0.240 (−0.566 to 0.086)	0.138	−0.225 (−0.556 to 0.106)	0.169	−0.032 (−0.403 to 0.338)	0.856	−0.033 (−0.418 to 0.352)	0.857
Intensity (low)	0.252 (−0.083 to 0.587)	0.130	0.209 (−0.164 to 0.583)	0.251	0.184 (−0.075 to 0.443)	0.151	0.176 (−0.134 to 0.487)	0.244
Methodological characteristics								
Sample size (ln)	0.220 (0.074 to 0.366)	0.006	0.205 (0.045 to 0.365)	0.015[b,e]	–	–	–	–
Follow-up months (ln)	0.182 (−0.002 to 0.367)	0.053	0.179 (−0.005 to 0.364)	0.056	−0.187 (−0.637 to 0.262)[f]	0.388	−0.150 (−0.674 to 0.374)[f]	0.548
Risk of bias (sqrt)	−0.173 (−0.534 to 0.189)	0.326	–	–	−0.093 (−0.388 to 0.201)	0.509	–	–
Depression exclusion at baseline (standardised diagnostic interview)	−0.053 (−0.544 to 0.439)	0.823	−0.170 (−0.694 to 0.353)	0.499	−0.033 (−0.444 to 0.377)	0.864	−0.107 (−0.574 to 0.359)	0.628
Subsample[g]	0.320 (0.019 to 0.621)	0.038	0.364 (0.090 to 0.638)	0.013	0.125 (−0.255 to 0.506)	0.493	0.206 (−0.209 to 0.621)	0.305
Outcome measure (standardised diagnostic interview)	−0.233 (−0.872 to 0.406)	0.451	−0.527 (−1.198 to 0.145)	0.115	−0.270 (−0.724 to 0.184)	0.225	−0.449 (−0.937 to 0.038)	0.068
Type of outcome (secondary)	0.093 (−0.729 to 0.914)	0.814	0.096 (−0.731 to 0.923)	0.808	0.293 (−0.431 to 1.018)	0.402	0.281 (−0.459 to 1.02)	0.429
Comparator (waiting list)	−1.30 (−2.41 to 0.186)	0.025	−1.234 (−2.376 to −0.092)	0.036	−1.029 (−2.109 to 0.050)	0.060	−1.01 (−2.11 to 0.098)	0.071

ln, Neperian logarithm; sqrt, square root.
a. The coefficient means the change of the dependent variable (SMD between intervention and control groups) with each unit increase of the independent variables. A negative coefficient increases the preventive effect (reduction of symptoms) and a positive coefficient the opposite.
b. Higgins & Thompson permutation test to calculate *P*-values considering multiplicity adjustment (Monte Carlo approach with 20 000 permutations) (see footnotes: c–e).
c. Country (Asia) $P = 0.105$ (95% CI 0.100–0.109).
d. Prevention (selective) $P = 0.120$ (95% CI 0.115–0.125).
e. Sample size (ln) $P = 0.043$ (95% CI 0.041–0.047).
f. The variables follow-up (ln) and sample size (ln) had a high correlation ($R = 0.91$) and as a consequence including both variables the probability of collinearity of the meta-regression model was very high, and so the estimation of coefficients would be biased.
g. Studies that included participants with and without clinical depression at baseline but give separate outcomes for participants without clinical depression.

Table 3 Final meta-regression model

Final model[a]	β (95% CI)[b]	*P*	*P* (95% CI)[c]
Sample size (ln)[d]	0.293 (0.164–0.422)	<0.001	0.0011 (0.0007–0.0017)
Country (Asia)	0.389 (0.051–0.727)	0.027	0.0667 (0.0632–0.0702)

ln, Neperian logarithm.
a. Model $F_{2,15} = 11.85$; $P = 0.0008$; I^2 residual = 0%; adjusted $R^2 = 100\%$.
b. Knapp & Hartung method for estimation of standard error and 95% CI.
c. Higgins & Thompson permutation test to calculate *P*-values considering multiplicity adjustment (Monte Carlo approach with 20 000 permutations).
d. Neperian logarithm transformation.

Limitations

There are several limitations. First, from a qualitative perspective only two RCTs had an overall low risk of bias; therefore, further RCTs of higher quality are needed. Second, only three RCTs had a longer follow-up (12–24 months); consequently, firm conclusions about long-term effectiveness cannot be drawn from our study. Third, applying our selection criteria, we were unable to include RCTs with children and young adolescents because they had some exclusion criteria (for example did not discard participants with depression at baseline) and therefore conclusions cannot be inferred from this population. Fourth, it is difficult to draw conclusions about certain subgroups of interest (such as strength programmes), because of the low number of RCTs included.

Fifth, only one RCT measured the incidence of new cases of depression in the participants and used a standardised diagnostic interview. As we mentioned previously in the introduction section, the reduction of depression symptoms in people without clinical depression is also included in the conceptual framework of depression prevention and has a positive and relevant effect on quality of life and costs.[48] However, standardised diagnostic interviews generally have greater validity than symptom scales and the end-point of preventive intervention is the reduction of the occurrence of new cases of people with depression. Therefore, further RCTs that assess the incidence of new cases of depression through standardised diagnostic interviews are also needed.

Comparison with existing literature

In our systematic reviews and meta-analyses, exercise-based group interventions were more effective than individual interventions in unadjusted meta-regression, although this did not reach statistical significance in the multivariate meta-regression. It has been argued that exercise-based group interventions could reduce depressive symptoms, in addition to physical activity itself, through social support and social learning, although there is no difference between individual and group intervention to prevent depression in the case of psychological interventions.[49] We found a trend toward greater effectiveness when physical activity was objectively verified versus subjective verification, but it was not statistically significant. Social desirability bias may cause participants to respond to physical activity verification questionnaires too optimistically, and variability in mood may influence the ability to accurately respond to self-report questionnaires.[50]

The National Institute for Health and Care Excellence in the UK, in their 2018 update,[51] recommends physical activity programmes in less severe depression (including people with subthreshold depression) detailing the type of physical activity: delivery in groups (usually eight people per group) by a competent practitioner, 45 min of aerobic exercises of moderate intensity, twice a week for 4–6 weeks, then weekly for a further 6 weeks of structured exercise. However, from the results of our systematic review and meta-analyse, no conclusions can be drawn about the characteristics of exercise-based interventions associated with the reduction of depressive symptoms in people without clinical depression.

The effectiveness of yoga to reduce depressive symptoms could be mediated, in addition to physical exercise, by the participant involved in relaxation, mindfulness and meditation.[52] However, regarding the yoga interventions included in our systematic review and meta-analyis,[46,47] we did not find significant differences in the pooled effect size in bivariate and multivariate meta-regression (Table 2).

Attention control is used to achieve some degree of masking of the participants in RTCs. For example, Lewis et al[38] used 'general wellness topics support contact by telephone' as a control group versus an exercise-based intervention. Perhaps this type of control group could have a very small preventive effect for depression and therefore this could reduce the effectiveness of exercise in reducing depressive symptoms. Nevertheless, this was not found in our analyses. Waiting list may be a nocebo condition in RCTs focused on anxiety and depression,[53] which would overestimate the effect of the interventions. In fact, we found higher effectiveness with waiting list as a comparator, but adjusted analysis by multivariate meta-regression cancelled out any statistical significance.

The Physical Activity Guidelines Advisory Committee (PAGAC) in the USA, in its report of February 2018,[12] affirms that physical activity reduces the risk of experiencing depression and depressive symptoms in individuals with and without major depression across the lifespan (PAGAC grade: strong). This evidence was extracted from 38 systematic reviews and meta-analyses. Among the limitations of this overview are the overlap of primary studies in more than one systematic review and meta-analysis, which could contribute to obtaining biased estimates of effectiveness,[54] the inclusion of many low-quality trials, the difficulty of separating people with without clinical depression within the same primary study and the difficulty of separating the effect of exercise when it is in combination with other potentially effective treatments to prevent depression.

In addition to our updated search for primary RCTs, the references of these 38 systematic reviews and meta-analyses and 18 more were also evaluated. Including only RCTs with participants without clinical depression and exclusive exercise-based interventions, we could only incorporate 14 RCTs and, although we found a small preventive effect, the strength of evidence was low according to GRADE.

Practical implications

Physical activity may protect against depression, and/or depression may result in decreased physical activity.[55] Implementing regular exercise is difficult for most people and is even more challenging for those with major depression because of their symptoms of low energy and motivation.[56] From our study we can say that encouraging or prescribing regular exercise could be useful for the reduction of depressive symptoms in people without clinical depression; although, due to the low quality of the evidence, the strength of this recommendation initially would be weak. However, balance between desirable and adverse effects, values and preferences of patients and providers, and costs-effectiveness analyses[33] were not included as outcomes in our systematic review, so any attempt to establish the strength of the recommendation would have high uncertainty. There is evidence that exercise, in addition to having a preventive effect on depression, could help prevent and treat other mental (anxiety, insomnia, dementia) and physical illnesses (cardiovasculars, diabetes, cancer, etc.).[12,57] From this point of view, exercise would have some advantages over psychological programs.

The effect size of psychological interventions and exercise-based interventions for the reduction of depressive symptoms in people without clinical depression could be similar.[10,11] Nonetheless,

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from our study we can conclude that so far the quality of evidence is lower for exercise-based interventions than for psychological interventions.[11] Further RCTs including exercise-based interventions with a low risk of bias, larger samples and longer follow-up are needed as well as others directly comparing psychological versus exercise-based interventions. Finally, studies to establish the optimal type, intensity, frequency and duration of the exercise-based interventions are also required.

The effectiveness of the programmes for the primary prevention of depression might be small. However, if such programmes were scaled to a large part of the population their impact in terms of increased health, quality of life and cost reduction would be relevant.[5,6] If people had two alternatives with similar effectiveness, psychological interventions and exercise-based interventions, the impact would be even greater, since those who are little motivated by psychological programmes could be more motivated by exercise programmes and vice versa. Clinicians could encourage and advise their patients towards either intervention or both, and massive prevention programmes in schools,[58] workplaces[59] and through information and communication technologies[29,60] might also be implemented.

Juan Ángel Bellón, MD, PhD, 'El Palo' Health Centre, Health District of Primary Care Málaga-Guadalhorce, Andalusian Health Service (SAS); Prevention and Health Promotion Research Network (redIAPP), Institute of Health Carlos III (ISCIII); Biomedical Research Institute of Malaga (IBIMA); and Faculty of Medicine, Department of Public Health and Psychiatry, University of Málaga (UMA), Spain; **Sonia Conejo-Cerón**, PhD, Prevention and Health Promotion Research Network (redIAPP), Institute of Health Carlos III (ISCIII); and Biomedical Research Institute of Malaga (IBIMA), Spain; **Almudena Sánchez-Calderón**, MSc, Faculty of Medicine, Department of Public Health and Psychiatry, University of Málaga (UMA), Spain; **Beatriz Rodríguez-Martín**, PhD, Prevention and Health Promotion Research Network (redIAPP), Institute of Health Carlos III (ISCIII); and Faculty of Health Sciences, Talavera de la Reina, Toledo, University of Castilla-La Mancha (UCLM), Spain; **Darío Bellón**, MSc, Faculty of Sport Sciences, University of Castilla-La Mancha (UCLM), Spain; **Emiliano Rodríguez-Sánchez**, MD, PhD, Prevention and Health Promotion Research Network (redIAPP); Institute of Biomedical Research of Salamanca (IBSAL); Primary Care Research Unit of Salamanca (APISAL); and Department of Medicine, University of Salamanca, Spain; **Juan Manuel Mendive**, MD, PhD, Prevention and Health Promotion Research Network (redIAPP), Institute of Health Carlos III (ISCIII); and 'La Mina' Health Centre, Institute of Health Català (ICS), Spain; **Ignacio Ara**, PhD, Faculty of Sport Sciences, University of Castilla-La Mancha (UCLM); GENUD Toledo Research Group, University of Castilla-La Mancha (UCLM), Spain; and CIBER of Frailty and Healthy Aging (CIBERFES), Spain; **Patricia Moreno-Peral**, PhD, Prevention and Health Promotion Research Network (redIAPP), Institute of Health Carlos III (ISCIII); and Biomedical Research Institute of Malaga (IBIMA), Spain

Correspondence: Juan Ángel Bellón. Email: jabellon@uma.es

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Supplementary material

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Data availability

The data that support the findings of this study are available on request from the corresponding author (J.A.B.).

Author contributions

J.A.B., S.C.-C. and P.M.-P. designed the study and the other authors collaborated on the design. A.S.-C., B.R.-M., D.B., S.C.-C. and P.M.-P. participated in the selection of studies and data extraction. S.C.-C., P.M.-P. and J.A.B. assessed the risk of bias. J.A.B. performed the statistical analysis and drafted the manuscript and all authors discussed and approved the final version. J.A.B. is the guarantor.

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Declaration of interest

None.

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