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# Physical activity and exercise for erectile dysfunction: systematic review and meta-analysis

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## ABSTRACT

**Background** A growing body of evidence suggests that physical activity and exercise may improve erectile function.

**Objective** To conduct a systematic review and meta-analysis evaluating the effects of physical activity modalities and exercise on erectile function in erectile dysfunction trials.

**Methods** A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. We searched 6 electronic databases between January 1990 and July 2016 and hand-searched reference lists for randomised controlled trials. Only patients with a diagnosis of erectile dysfunction were included. The mean differences between intervention and control groups were calculated for meta-analysis.

**Results** 7 studies were eligible, including 478 participants allocated to aerobic, pelvic or combined exercise interventions. Follow-up ranged from 8 weeks to 2 years. The risk of bias in the trials was deemed moderate to high mainly due to impossible blinding of patients and personnel, as well as questionable blinding of outcome assessors. Random-effects meta-analyses were performed. Pooled data showed a statistically significant improvement in erectile function score (mean difference 3.85, 95% CI 2.33 to 5.37). A benefit was still demonstrable after a sensitivity analysis because the mean difference in International Index of Erectile Function (IIEF) score ranged from 3.39 (95% CI 1.92 to 4.87) to 4.28 (95% CI 2.54 to 6.02). A benefit was also detected in short-term and long-term interventions as well as in trials evaluating physical activity and exercise alone or in addition to usual care.

**Conclusions** The present study suggests that physical activity and exercise interventions improve patient-reported erectile dysfunction, particularly aerobic exercise with moderate-to-vigorous intensity.

## INTRODUCTION

Erectile dysfunction is, by definition, the persistent inability of the male to achieve and maintain a penile erection sufficient to perform satisfying sexual intercourse.[1] It is a common clinical entity among men, with prevalence of erectile dysfunction ranging from 8% in men 20–30 years of age to 37% in men 70–75 years of age.[2] This sexual disorder can significantly deteriorate quality of life and is often neglected in clinical practice.[3] Moreover, public concern of erectile dysfunction is mounting concomitant with the incidence and media coverage of this problem. Some authors estimate that by 2025 there will be ~322 million cases worldwide.[4]

Erectile dysfunction is a multifactorial medical disorder that has been linked to numerous aetiologies[5] and is a predictor of future cardiovascular disease. Its presence should instigate a thorough investigation for potentially modifiable cardiovascular disease risk factors.[6–8]

The diagnosis relies essentially on a comprehensive sexual and medical history. Standardised questionnaires may be useful before the medical interview to quantify its severity, however, they are more frequently used in research contexts. The International Index of Erectile Dysfunction (IIEF) is the most employed questionnaire—it consists of 15 questions that analyse every domain of male sexual dysfunction.[9] An abridged version of the IIEF questionnaire (ie, IIEF-5 or the Sexual Health Inventory for Men (SHIM) questionnaires) is an alternative diagnostic tool.[10]

Even though pharmacological therapy is a first-line treatment modality for erectile dysfunction,[11] the role of lifestyle interventions in reducing the burden of erectile dysfunction is increasingly recognised.[12–14] Previous systematic reviews have assessed the association between physical activity and this disorder; however, study selection in these cases was restricted to aerobic activities[15] or patients with prostate cancer.[16] We conducted a systematic review and meta-analysis of published randomised controlled trials (RCTs) to estimate the pooled effect of physical activity and exercise interventions on erectile function in male adults diagnosed with erectile dysfunction.

## EVIDENCE ACQUISITION

### Conduct of systematic review

Our systematic review was performed and reported under the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (see online supplementary text S1).[17] A protocol similar to this systematic review has not been performed.

### Data sources and search strategy

Comprehensive systematic online searches were conducted in July 2016 by two independent authors (ABS and NS) using the following electronic databases and a combination of Medical Subject Headings and keywords: PubMed (Medline); Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Online Library, Wiley; CINAHL Plus (EBSCOhost); SPORTDiscus (EBSCOhost); PsycINFO (EBSCOhost) and Scopus. For these sources, we used the following search strategy: ((erectile dysfunction [mh]) OR (sexual dysfunction [mh] OR sexual dysfunctions [mh]) OR (impotence [mh]) OR (penile erection [mh])

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OR (genital diseases [mh])) AND ((physical activity [keyword]) OR (motor activity [mh]) OR (exercise therapy [mh]) OR (exercise [mh])). Electronic databases were searched from 1 January 1990 to 15 July 2016, and searches were limited to the English language. No other limits were placed during this phase of the study.

Reference lists of relevant review articles and original studies were hand searched to identify studies not found in our database searches. In addition, our group queried both a urological panel of experts and a sports medicine expert to report any published studies not identified by our search.

### Study selection

Two authors (ABS and NS) independently screened the title and abstract of every citation found in our literature search. Studies of potential relevance were the subject of a search for the full-text version, and the eligibility criteria were applied. According to PRISMA recommendations, inclusion and exclusion criteria are based on relevant study characteristics (participants, intervention, comparator, outcome, study design and length of follow-up). Divergent opinions regarding study inclusion were resolved by consensus among three authors (ABS, NS and CM). In particular, published studies were included if: (1) the patient population was composed of adult males with a diagnosis of erectile dysfunction, regardless of aetiology or duration based on diagnostic criteria such as the IIEF questionnaire or a clinical history compatible with erectile dysfunction; (2) the intervention was any form of physical activity alone or in addition to any kind of drug therapy; (3) the comparator was normal physical activity (absence of physical activity or exercise regimen) and/or usual care administered by the attending physician; (4) the outcome was a change in patient-reported penile erection quality as measured by an erectile dysfunction symptom score (eg, IIEF); (5) the study design was a randomised controlled clinical trial and (6) follow-up duration was at least 30 days (if follow-up was done at more than one time frame—the data for the longest one was extracted). The data were extracted into a standardised spreadsheet containing the key study characteristics (table 1).

Non-human articles were excluded from this systematic review as were studies lacking original data (eg, letters, review articles or editorials), articles on unrelated topics, studies not reporting outcome of interest and studies containing fewer than 10 participants. In addition, clinical trials with partial or quasi-random designs were excluded from this systematic review.

### Data extraction and quality assessment

Eligible studies were examined independently by two collaborators (ABS and NS), and any disagreement was settled via discussion among all authors. The study features extracted from each paper include first author, year of publication, predisposing factor for erectile dysfunction, number of patients randomised to control and intervention groups, mean or range age of participants, follow-up duration, a description of the intervention and control groups, mean baseline erectile function score, method of ascertainment of outcome and a summary of the primary study outcome. The latter included the p value and a calculated difference between erectile function score at baseline and follow-up in the intervention group ($\Delta EQ_i$) expressed as a percentage.

Two authors (ABS and NS) evaluated the risk of bias in the selected studies using the Cochrane Collaboration's tool.[25] Factors considered include adequate sequence generation (selection bias), allocation sequence concealment (selection bias), blinding (performance and detection biases), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias.

### Data synthesis and analysis

The results from the included studies were combined to give an overall estimate of treatment effect. The primary outcome was a change in mean erectile function score in the intervention and control groups as well as the p value and CI of the change. Heterogeneity among the included studies was explored qualitatively and quantitatively via the $I^2$ statistic. A random-effects model meta-analysis was used if statistical heterogeneity was present and, if non-existent, a fixed-effects model was used instead. All analyses were conducted using Review Manager V.5.3. Sensitivity analysis was performed by conducting a meta-analysis after removing each study sequentially to ascertain if one study biased the pooled result. If the number of studies was sufficient—and the analysis was considered adequate—subgroup analyses were performed to evaluate the intervention effect in different patient populations and treatment scenarios.

## EVIDENCE SYNTHESIS

### Selection of studies

A total of 5460 articles were identified by our search strategy; five were identified from hand searching reference lists and listening to expert opinions on the subject matter. In total, 53 articles were assessed for eligibility. The study selection process and the reasons for exclusion of the 46 articles are shown in figure 1. Notably, one article was excluded because the full text was not retrievable and attempts to contact the study authors were unsuccessful. We included seven trials in our systematic review (table 1). There was complete agreement between reviewers regarding study selection.

### Key characteristics of included trials

A summary of eligible studies is shown in table 1. The studies were performed in three continents: five from Europe,[18 19 21 23 24] one from Asia[20] and one in Africa.[22] Follow-up ranged from 8 weeks to 2 years. The articles were published between 1 November 2004 and 18 June 2013. A total of 505 participants were randomised, 292 of whom were allocated to the intervention group and 213 to the control group; 27 among them were excluded from statistical analysis across all studies. The mean age among participants ranged from 43 to 69 years. The mean severity of erectile dysfunction was identified as severe,[20 24] moderate[19 22] and mild to moderate[18 21 23] according to the IIEF-5 classification of severity.[10] Predisposing factors for erectile dysfunction also varied among studies: one described no predisposing conditions,[24] two enrolled radical prostatectomy[20] and invasively treated patients with ischaemic heart disease[18], and the remainder included patients with one or more cardiovascular risk factors alone.[19 21–23]

The treatment approach (type of activity) differed among RCTs: four predominantly involved aerobic exercise;[19 21–23] one used a combined[18] (aerobic and resistance exercises) programme; two involved pelvic floor muscle-specific exercises.[20 24] Three trials evaluated physical activity without usual care for erectile dysfunction,[20 23 24] while the remaining four combined physical activity with pharmacological treatment.[18 19 21 22] Four studies included a specific and monitored exercise regimen[18 19 22 24] and three consisted of unsupervised physical activity.[20 21 23] The tool used to evaluate erectile dysfunction

**Table 1** Characteristics of included studies

| Study | Number randomised | Predisposing factor | Mean or range age in years (SD) | Intervention group | Control group | Follow-up duration | Erectile function outcome measure | Mean IIEF score at baseline (SD or range) | Outcome summary ($\Delta EQ_i$; p value) |
|---|---|---|---|---|---|---|---|---|---|
| Kalka *et al*[18] | Intervention n=103 Control n=35 | Invasively treated IHD | Intervention 62.07 (8.59) Control 61.43 (8.81) | Supervised activity: aerobic (cycle ergometer, 3×week, 45 min duration, 10 W maximum load, perceived exertion at level 13 on 15-grade Borg scale), general fitness and resistance (2×week, 8–10 types, 12–15 reps) exercises plus standard medical drug therapy for IHD. | Received general health advice plus standard medical drug therapy for IHD | 6 months Measurement dates: unavailable | IIEF-5 (questions 1–5) | Intervention 12.51 (5.98) Control 12.26 (5.83) | No improvement (15.01%; p<0.05) |
| Maresca *et al*[19] | Intervention n=10 Control n=10 | Metabolic syndrome | Intervention 69.0 (2.8) Control 68.0 (3.6) | Supervised activity: aerobic (cycle ergometer/treadmill, 3 sessions/week, 30 min duration, heart rate target 65% $VO_2$ peak) exercises+5 mg tadalafil/day. | 5 mg tadalafil/day+advice | 2 months Measurement dates: unavailable | IIEF-EF (questions 1–5 +15) | Intervention 10.8 (2.0) Control 11.2 (2.1) | Improves ED (86.11%; p<0.001) |
| Lin *et al*[20] | Intervention n=41 Control n=31 | Radical prostatectomy | 65.75 (6.12) | Unsupervised activity: pelvic floor muscle training consisting of 3 10 s maximum contraction alternating with 3 10 s relaxations (2×day, in 3 positions) after biofeedback training. | No exercise or training sessions | 3, 6, 9, 12 months Measurement dates: November 2007–July 2010 | IIEF-5 (questions 1–5) | Intervention 5.06 (0.24) Control 5.00 (0.00) | Improves ED (60.87%; p=0.014, at 12 months) |
| Maio *et al*[21] | Intervention n=30 Control n=30 | CV risk factors | Intervention 50.14 (6.28) Control 50.32 (6.95) | Unsupervised activity: advised to maintain regular (minimum 3 hours/week) aerobic, non-agonistic physical activity+PDE5-i. | Received PDE5-i alone | 3 months Measurement dates: unavailable | IIEF-EF (questions 1–5 +15) | Intervention 15.8 (4.19) Control 15.5 (4.18) | Improves ED (68.98%; p=0.003) |
| Lamina *et al*[22] | Intervention n=25 Control n=25 | Hypertension | Intervention 62.10 (5.23) Control 64.00 (4.77) | Supervised activity: aerobic (3 sessions/week, bicycle ergometer, 45–60 min each, 60–79% $HR_{max}$, 17 W load)+methyldopa (250 mg and 500 mg daily). | Advised not to increase physical activity +methyldopa (250 mg and 500 mg daily) | 8 weeks Measurement dates: unavailable | IIEF | Intervention 11.50 (5.30) Control 8.10 (4.02) | Improves ED (31.65%; p<0.001) |
| Esposito *et al*[23] | Intervention n=55 Control n=55 | Obesity | Intervention 43.5 (4.8) Control 43 (5.1) | Unsupervised activity: advised to increase physical activity (mainly by walking, but also swimming and aerobic games) and reduce caloric intake to achieve a minimum of 10% weight loss. | General health advice, but no individual programme | 2-year Measurement dates: October 2000–October 2003 | IIEF-5 (questions 1–5) | Intervention 13.9 (4.0) Control 13.5 (4.0) | Improves ED (22.3%; p=0.008) |
| Dorey *et al*[24] | Intervention n=28 Control n=27 | None described | Intervention 58 (22–78) Control 61 (41–72) | Supervised activity: instructed to contract pelvic floor muscles for 10 s followed by 10 s rest (5 30 min sessions in consecutive weeks) with biofeedback control in addition to daily home exercises+advice on lifestyle changes. | Advice on lifestyle changes | 3, 6 months Measurement dates: June 2000–April 2002 | IIEF-EF (6 questions) | Intervention 7.5 (1–28) Control 7.0 (1–17) | Improves ED (129.33%; p=0.004 at 3 months) |

$\Delta EQ_i$, mean variation in erectile quality in the intervention group (values expressed in percentage); CV risk factors, more than one cardiovascular disease risk factor described; ED, erectile dysfunction; $HR_{max}$, maximum heart rate; IIEF, International Index of Erectile Function questionnaire; IIEF-EF, erectile function parameter of IIEF questionnaire; IHD, ischaemic heart disease; DE5-i, phosphodiesterase type 5 inhibitor; $VO_2$, oxygen consumption.

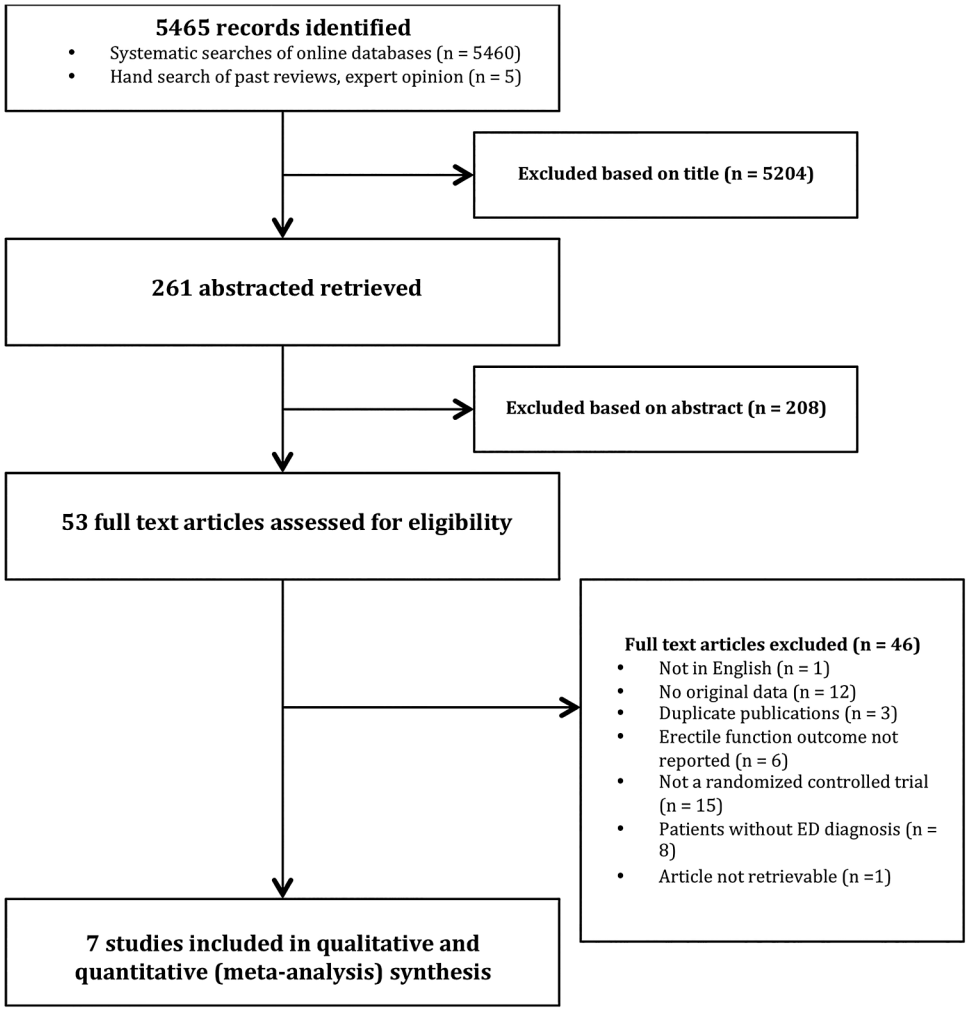


**Figure 1** Literature search and selection process. ED, erectile dysfunction.

was homogeneous among studies since the IIEF questionnaire was applied in all studies. The percentage increase in IIEF scoring ($\Delta EQ_i$) ranged from 15.01% to 129.33% across trials, as shown in table 1.

## Risk of bias in individual trials

Assessment of the risk of bias for each study is summarised in figures 2 and 3, and a detailed evaluation is presented in online supplementary table S1. In general, the risk of bias for each individual study was deemed moderate to high because the risk was considered predominantly unclear or high for three of the seven evaluated criteria. The most common problems during this phase of our review were blinding of patients and medical professionals, which was impracticable across all trials, and questionable blinding of outcome assessors.

## Physical activity, exercise and erectile dysfunction

### Total physical activity

Seven RCTs involving a total of 478 participants were included in the meta-analysis. All trials measured patient-reported erectile function using a tool whose total score allowed for a pooled quantitative analysis. Overall, the meta-analysis found a statistically significant association between increased physical activity and a 3.85-point improvement in erectile function scores (95% CI 2.33 to 5.37; figure 4).

### Subgroup analysis

Differences in the effect of physical activity and exercise modalities were found when analysing different subgroups as shown in online supplementary figure S1. Statistically significant increases in IIEF scores were found in patients with cardiovascular risk factors alone (4.20; 95% CI 2.16 to 6.23) and in those with either coronary heart disease or radical prostatectomy, although this effect was less expressive (2.11; 95% CI 0.76 to 3.45).

Both short-term (<6 months) and long-term activities (≥6 months) were associated with increases in mean IIEF scores. The first showed a superior benefit (5.30; 95% CI 2.40 to 8.21 vs 2.60; 95% CI 1.54 to 3.66).

When studying specific treatment approaches, a statistically significant benefit was found among studies offering physical activity both with no usual care (3.83; 95% CI 1.39 to 6.27) or in addition to usual care (3.91; 95% CI 1.59 to 6.23).

Studies investigating pelvic floor muscle-specific exercises demonstrated no significant improvement in erectile function scores (5.10; 95% CI −1.34 to 11.54).

### Test for heterogeneity across studies

When all seven RCTs were pooled, significant heterogeneity was detected ($p<0.00001$; $I^2=74\%$). Among subgroups, however, heterogeneity varied considerably from non-existent when

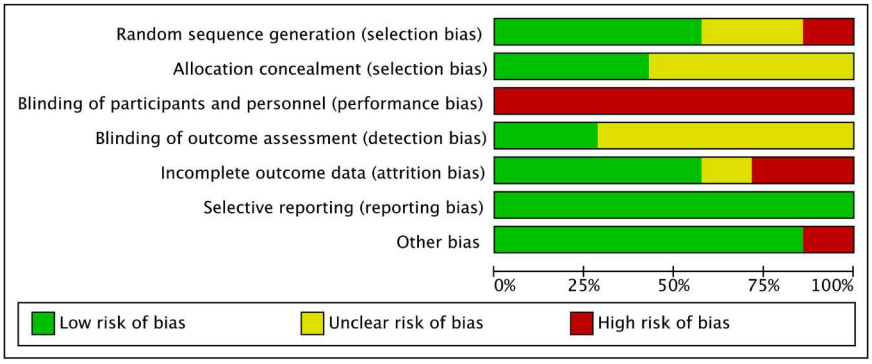


**Figure 2** Risk of bias graph of included randomised controlled trials (n=7): review authors' judgements about each risk of bias item presented as percentages across all included studies.

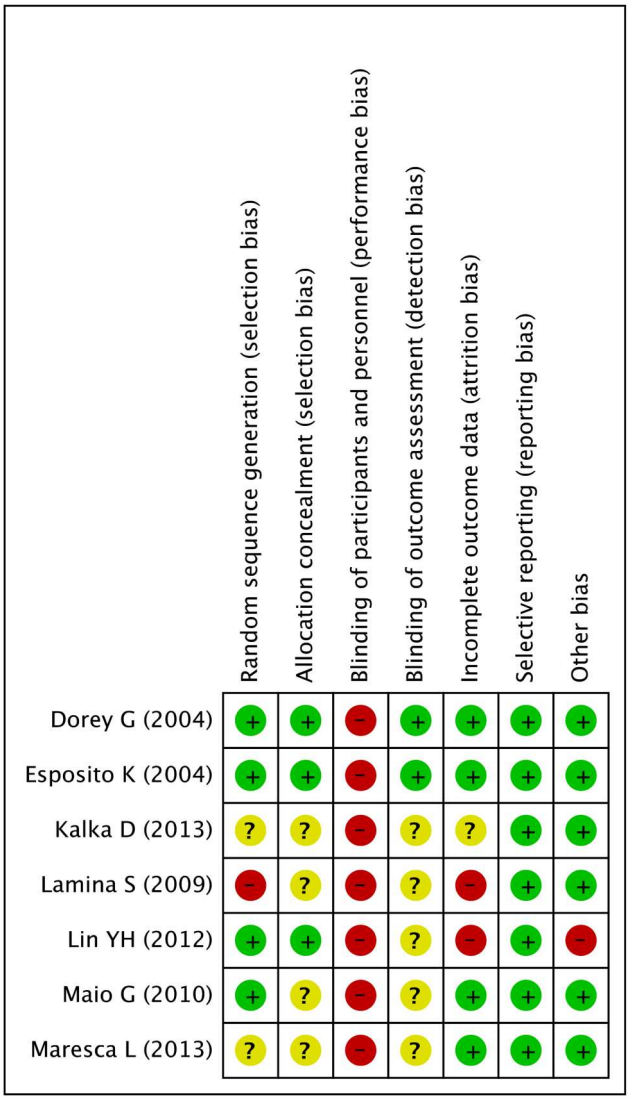


**Figure 3** Risk of bias summary: review authors' judgements about each risk-of-bias item for the included studies.

pooling studies with follow-up superior to 6 months ($p<0.00001$; $I^2=0\%$) or with evidence of target organ disease ($p=0.002$; $I^2=0\%$) to a maximum $I^2$ of 85%. In the sensitivity analysis, heterogeneity ranged from 68% to 79%.

### Sensitivity analysis

When sensitivity analysis was performed (see online supplementary figure S2), we found that the pooled results did not vary substantially. The mean IIEF score ranged from 3.39 (95% CI 1.92 to 4.87) to 4.28 (95% CI 2.54 to 6.02).

## DISCUSSION

Our systematic review indicates that physical activity and exercise improve erectile dysfunction symptoms—there is a 3.85-point increase in the erectile function parameter of the IIEF questionnaire. This benefit is further supported by a sensitivity analysis—there is a statistically significant increase in IIEF scores after omitting each trial sequentially.

Subgroup analyses also suggest that any physical activity and exercise modality is beneficial in patients with increased cardiovascular risk alone, coronary heart disease or radical prostatectomy. Also, both short-term and long-term interventions, whether used alone or concomitantly with usual care, were associated with a beneficial effect. In some subgroups, a small number of trials were included and consequently these analyses might be underpowered.

To the best of our knowledge, this is the first systematic review and meta-analysis evaluating the effects of any physical activity regimen in patients diagnosed with erectile dysfunction. We pooled seven trials involving 478 male participants with a diagnosis of erectile dysfunction from various geographical locations and analysed a broad range of physical activities and exercise programmes. This provides the most complete data on the impact of increased physical exertion on erectile function ever reported.

### Mechanisms

The pathophysiological mechanisms underlying this improvement remain academic at this point. A growing body of evidence suggests that the pelvic floor muscles play a crucial role in penile rigidity. Their efficient contraction prevents the return of venous blood from the penis and increases intracorporeal pressure significantly higher to that of systemic blood pressure.[26] One study demonstrated via electromyography that their contractility was more efficient in men with a normal erectile function than in male patients with erectile dysfunction.[27] However, inefficient long-term supervision, poor characterisation and low intensity/timing of training may have underestimated the true effect of pelvic floor muscle exercises in the work by Dorey *et al*[24] and Lin *et al*,[20] whose patients had the most severe forms of erectile dysfunction. Indeed, a recent meta-analysis[28] suggested that preoperative exercises might be more effective versus postoperative training for the recovery of urinary continence in patients with radical prostatectomy because this may facilitate proper pelvic muscle contraction and provide more incentive to continue these exercises after the intervention. Penile haemodynamics is also dependent on endothelial function. Aerobic exercises have

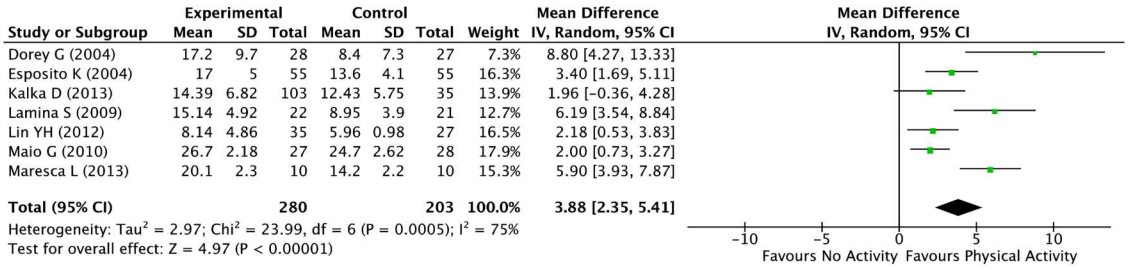


**Figure 4** Forest plot of comparison: 1 increased PhA versus normal PhA, outcome: 1.1 change in average erectile function score for included RCTs. df, degrees of freedom; PhA, physical activity; RCTs, randomised controlled trials.

been shown to improve cardiac output, exercise tolerance and control of cardiovascular risk factors such as hyperlipidaemia, and the glycaemic profile in diabetes and obesity. This decreases oxidative stress and enhances availability of nitric oxide in penile vasculature.[29]

Kalka *et al*[18] reported a non-significant improvement, but this study has important limitations because the patient population consisted mainly of functionally debilitated elderly patients with relevant ischaemic heart disease on drug regimens that can deteriorate both erectile function and exertion tolerance (eg, β-blockers, ACE inhibitors or angiotensin II-receptor antagonist and diuretics).

From a clinical practice perspective, this meta-analysis shows evidence that in patients with erectile dysfunction of non-specific aetiology, aerobic exercise with moderate-to-vigorous intensity may be beneficial. In patients with severe and prostatectomised erectile dysfunction, pelvic floor muscle-specific exercises did not show a statistically significant effect, as opposed to aerobic and resistance activities. In patients with erectile dysfunction associated with cardiovascular risk factors, there is evidence that aerobic exercise with moderate-to-vigorous intensity may be beneficial. Moreover, physical activity and exercise are more effective in improving erectile dysfunction when combined with specific pharmacological therapy.

The patient's perception of improvement at follow-up might also be influenced by psychological factors, independent of the type of activity used, although none of the trials formally quantified changes in patients' well-being.

Our systematic review has important strengths. We performed a thorough and systematic literature search for every published randomised clinical trial reporting on physical activity or exercise interventions, ultimately including trials from developed and developing countries. All trials used the same tool to estimate the change in patient-reported erectile function (IIEF questionnaire) and a consistent benefit was demonstrated after a sensitivity analysis, which further reinforces the consistency of the results.

## Limitations

As is the case for any meta-analysis, our systematic review also has some limitations. The pooled number of participants is relatively small as seven studies were ultimately selected for our quantitative analysis. Such a finding is to be expected because, in clinical practice, the vast majority of physicians are not confident in prescribing physical activity or exercise to their patients, even less so for the treatment of erectile dysfunction. Most of the trials included in the meta-analysis had a moderate-to-high risk of bias. This is relevant because the primary end point was measured by patient-reported questionnaires. Also, the duration of follow-up varied considerably among RCTs—8 weeks to 2 years. As mentioned above, insufficient adherence and supervision of participants may explain why exercise interventions were less effective in long-term trials than in short-term trials. Patients in the trials reported varying degrees of erectile dysfunction. More trials in patients with less severe forms of erectile dysfunction are needed. Finally, none of the studies evaluated the potential harms of the intervention.

Heterogeneity was predictably significant among studies because we included RCTs varying significantly in: (1) activity-related factors such as the type, intensity, duration, presence of supervision and concomitant interventions and (2) patient-related factors including geographic location, age, predisposing factors for erectile dysfunction and severity at baseline. The expression of the pooled results in terms of mean differences rather than the standardised mean difference also contributed to the magnitude of heterogeneity. Even so, except for one study,[18] the remaining six RCTs all showed a significant benefit in patients with erectile dysfunction. As such, we believe it may not be particularly limiting.

In conclusion, this meta-analysis suggests physical activity and exercise as an effective intervention to treat erectile dysfunction, which adds further benefit to those already on medical therapy. Although specific physical activity and exercise modalities are underprescribed in clinical practice to improve sexual function, aerobic exercise with moderate-to-vigorous intensity may be recommended, alone or combined with the pharmacological approach. A shift in the treatment paradigm, including physical activity as an adjunctive therapy, would require a coordinated multidisciplinary team consisting of urology, physiotherapy, sports medicine and nurse specialists trained to treat and follow-up patients with erectile dysfunction.

More wide-scale RCTs aiming at longer follow-up periods are needed to evaluate the long-term benefits of physical activity and exercise, and its potential harms, as well as to better clarify the appropriate timing, frequency, intensity and duration

### What are the main findings

- Research on nonpharmacological approaches for the treatment of erectile dysfunction is growing, but still limited.
- This systematic review and meta-analysis summarises the current knowledge regarding the effects of physical activity and exercise interventions on erectile function in erectile dysfunction trials.
- The results show a significant difference in post-treatment, patient-reported erectile dysfunction scores.

## How might it impact on clinical practice in the future?

- The incorporation of these activities by multidisciplinary groups may further improve outcomes in patients already on pharmacological terapy.
- For healthcare professionals, these results may aid in guiding informed decision-making regarding the treatment of erectile dysfunction patients.
- For clinical researchers, these findings provide an opportunity to publish further studies that address the limitations faced during the course of this systematic review.

## Summary box

- A systematic review and meta-analysis of seven randomised controlled trials of patients with erectile dysfunction.
- Different physical activity and exercise interventions increase short-term and long-term patient-reported erectile function in different patient population and treatment scenarios.
- The pooled evidence supports the need to review current recommendations for prescribing physical activity and exercise to patients with erectile dysfunction.

necessary to optimise its beneficial effects, all the while increasing its awareness in the medical community.

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**Contributors** ABS and CM are the guarantors. All authors except for LFA contributed to the drafting of the manuscript, the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. ABS and NS developed the search strategy. ABS and NS conducted the report screening, study inclusion, data extraction, and result interpretation and discussion.

**Competing interests** None declared.

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