

Do Older Adults With Reduced Bone Mineral Density Benefit From Strength Training? A Critically Appraised Topic

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Clinical Scenario: Reduced bone mineral density (BMD) is a serious condition in older adults. The mild form, osteopenia, is often a precursor of osteoporosis. Osteoporosis is a pathological condition and a global health problem as it is one of the most common diseases in developed countries. Finding solutions for prevention and therapy should be prioritized. Therefore, the critically appraised topic focuses on strength training as a treatment to counteract a further decline in BMD in older adults.

Clinical Question: Is strength training beneficial in increasing BMD in older people with osteopenia or osteoporosis? **Summary of Key Findings:** Four of the 5 reviewed studies with the highest evidence showed a significant increase in lumbar spine BMD after strength training interventions in comparison with control groups. The fifth study confirmed the maintenance of lumbar spine density due to conducted exercises. Moreover, 3 reviewed studies revealed increasing BMD at the femoral neck after strength training when compared with controls, which appeared significant in 2 of them. **Clinical Bottom Line:** The findings indicate that strength training has a significant positive influence on BMD in older women (ie, postmenopausal) with osteoporosis or osteopenia. However, it is not recommended to only rely on strength training as the increase of BMD may not appear fast enough to reach the minimal desired values. A combination of strength training and supplements/medication seems most adequate. Generalization of the findings to older men with reduced BMD should be done with caution due to the lack of studies. **Strength of Recommendation:** There is grade B of recommendation to support the validity of strength training for older women in postmenopausal phase with reduced BMD.

Keywords: bone diseases, osteopenia, osteoporosis, resistance training, healthy aging

Clinical Scenario

Reduced bone mineral density (BMD) and as a consequence a reduced bone strength is a serious health impairment in older adults.¹ Generally, 2 states within the reduction range of BMD are distinguished: osteopenia and osteoporosis.^{2,3} Osteopenia is the mild state in which BMD is decreased.² This state is often considered to be a precursor or risk factor for developing osteoporosis^{2,3}; therefore, it is comprehensibly called “borderline” osteoporosis.⁴ Osteoporosis, also known as bone loss, is a metabolic disease of the bone system, which is characterized by gradually decreasing bone mass and deteriorating microarchitecture of bone tissue.^{1,4,5} People of all ages may develop reduced BMD, but the majority of patients are older females and males.⁵ This disorder may go unnoticed for years, and in many cases it is recognized only after the occurrence of painful fractures (eg, femoral neck, spinal, forearm, humerus, rib, and pelvic).¹ These fractures often cause great suffering to people and thus severely limit their quality of life.^{1,4,5} Reduced BMD and specifically severe osteoporosis is a global health problem^{1,5-8}; worldwide there are around 200 million people with osteoporosis.⁹ Obviously, women are more prone to suffer from reduced BMD than men (eg, osteoporosis prevalence ranged from 9% to 38% for women and 1% to 8% for men).¹⁰ Finding solutions to this health problem is a critical issue. Health promotion, prevention, and therapy should be prioritized.

Although previously, reduced BMD was detected only when it led to the first bone fracture (ie, osteoporosis), today a person’s BMD can be measured accurately and reliably using bone densitometry (dual-energy X-ray absorptiometry).¹¹⁻¹³ Dual-energy X-ray absorptiometry measures BMD in gram per square centimeter and provides a *T* score, which is used as a proxy (ie, indirect measurement) for bone strength.¹ Persons with *T* scores between +1.0 and -1.0 are classified as healthy, while persons with *T* scores between -1.0 and -2.5 are diagnosed with osteopenia and -2.5 or lower with osteoporosis.^{4,14} This method is recommended by the World Health Organization.^{11,14}

If reduced BMD is recognized, the next step is to select a suitable and promising therapy to increase the BMD or prevent deterioration.¹ In general, supplements and/or medicines are used as the main treatment.⁹ To be more precise, the basic treatment consists of supplementations with calcium and vitamin D.¹⁵ In addition, the patients often have to take antiresorptive or osteoanabolic medication.^{15,16} Although this treatment is beneficial, applying these medicines can cause one or more side effects (eg, kidney stones, bothersome gastrointestinal effects including bloating and constipation, cardiovascular disease, upper gastrointestinal irritation, flu-like illness, venous thromboembolism, and breast cancer).^{17,18} The consequence of these side effects is the frequent decision to end the necessary treatment.^{17,18} Therefore, it seems sensible to search for an alternative solution to treat reduced BMD with less or without negative side effects.

One of the proposed alternatives to supplements/medicine is strength training.^{9,19} Strength training indeed is suggested to counteract the degeneration of bone substance, especially in older adults.²⁰ Besides that, it improves muscle strength and coordination skills, therefore, supports the preservation of stability, which is important factor in the prevention of falling.^{20,21} Strength training

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can also increase the resilience of tendons, ligaments, and joints.²² Furthermore, it leads to higher efficiency of the cardiovascular and immune system.^{22,23} Last but not least, it is believed to relieve pain and improves mood and well-being.^{23,24} For all these reasons, it might have a very positive influence on the quality of life. However, the advantages of strength training seem apparent and no disadvantages are mentioned so far, it is largely unknown whether strength training can be a reasonable treatment option to increase BMD in older adults suffering from osteoporosis or osteopenia.²⁵ For that reason, recent literature was explored to find an answer to the following question.

Focused Clinical Question

Is strength training beneficial in increasing BMD in older people with osteopenia or osteoporosis?

Summary of Search, “Best Evidence” Appraised, and Key Findings

- The literature was searched for studies of level 3 evidence or higher that investigated the effect of strength training on BMD in older adults with reduced BMD (ie, osteoporosis or osteopenia) in July 2019.
- The search of the literature yielded 14 possible studies for inclusion.
- Five studies^{26–30} met the inclusion criteria and were critically appraised using the 27-item modified Downs and Black checklist³¹ in which individual studies were categorized as excellent (26–28/28), good (20–25/28), fair (15–19/28), or poor ($\leq 14/28$) quality (Appendix 1).³²
- Four of the 5 reviewed studies^{26–28,30} showed a significant increase in lumbar spine BMD after strength training interventions in comparison with control groups (lack of strength training).
- The fifth study²⁹ confirmed maintaining of lumbar spine BMD due to conducted exercises.
- Three reviewed studies^{26,29,30} showed that strength training interventions increased femoral neck BMD in comparison with control. However, a significant increase was noted only in 2 of them.^{26,30}

Clinical Bottom Line

There is a grade B of recommendation to support the validity of strength training as a means to increase BMD in older women with osteoporosis or osteopenia^{26–30}; therefore, it should be considered as a clinical option for increasing BMD and reducing the negative effects. Furthermore, the review of the studies suggests that the amount of exercise per week and the intensity of the training are important issues of strength training (Table 1). Research by Borba-Pinheiro et al²⁶ indicated that the same strength training program executed 3 times a week was significantly more efficient compared with the same training for 2 times a week. Furthermore, Watson et al³⁰ showed that a difference in intensity of the training (high intensity vs low intensity) led to difference in BMD improvement; more intensity in training was followed by a larger improvement in BMD (Table 1). Although the systematic search did not exclude any sex, it showed lack of studies on older men with reduced BMD and

therefore generalization of the outcomes to this target group should be done with caution. Despite the promising results, indicating strength training as the only treatment is not recommended at this moment. The BMD may not increase fast enough to reach the desired level so that further examinations with strength training and supplements/medicine are needed to confirm this approach.

Strength of Recommendation

According to The Centre for Evidence-Based Medicine Levels of Evidence 2011,³³ there is a grade B of recommendation to support validity of strength training for older women with reduced BMD. This recommendation is based on level 2 of evidence with sufficient consistent findings shown by reviewed studies.

Search Strategy

Terms Used to Guide Search Strategy

- **P**atient/Client group: older adults with reduced BMD
- **I**ntervention: strength training
- **C**omparison: lack of strength training
- **O**utcome: change in BMD

Literature was searched in July 2019 by using combinations of the terms: “osteoporosis” OR “osteopenia” OR “bone loss” (P) AND “strength training” OR “resistance training” (I) AND “bone density” OR “BMD” (O). Titles, abstracts, and/or full texts were used to check for the inclusion and exclusion criteria.

Sources of Evidence Searched

- PubMed
- Web of Science
- Scopus

Inclusion and Exclusion Criteria

Inclusion Criteria

- Studies only on older adults (for women this meant to include only those who are in the postmenopausal phase) with reduced BMD (ie, osteoporosis or osteopenia)
- Studies that investigated strength training interventions
- Limited to publications from 2004 to 2019 in the English language

Exclusion Criteria

- Studies that investigated healthy subjects
- Studies that investigated subjects with other diseases
- Studies that did not measure BMD changes
- Studies without control group (lack of strength training intervention)

Results of Search

Five relevant studies^{26–30} were included after determining eligibility and categorized as presented in Table 2 (based on Levels of Evidence, The Centre for Evidence-Based Medicine, 2011).³³

Table 1 Characteristic of Included Studies

Characteristic	Borba-Pinheiro et al ²⁶	Engelke et al ²⁷	de Matos et al ²⁸	Mosti et al ²⁹	Watson et al ³⁰
Study design	Randomized controlled trial	Controlled trial	Controlled trial	Randomized controlled trial	Randomized controlled trial
Participants	<p>52 women, IG1: n = 20, 56.3 (5.2) y, IG2: n = 16, 60.6 (7.5) y, CG: n = 16, 55.3 (6.8) y, from Tucuruí, Pará-Brazil.</p> <p>Inclusion criteria: (1) female volunteers, (2) aged 50 y and older, (3) with low BMD: T score < -1 SD, (4) different ethnic population, (5) patients being treated with sodium alendronate (70 mg) and/or vitamin D₃ (5600 IU), (6) postmenopausal individuals (self-declared), (7) no previous history of fractures (self-declared), (8) no history for at least 1 y of regular practice of physical activity, and (9) with indication/medical clearance for physical exercises practices.</p> <p>Exclusion criteria: (1) after some sort of surgery in the last 6 mo, (2) early menopause by ovary removal, (3) with uncontrolled hypertension, (4) use of additional bone active medications or hormone replacement therapy, and (5) individuals who were being treated with drugs that induces low BMD, as glucocorticoids.</p>	<p>78 women, IG: n = 48, 55.2 (3.3) y, CG: n = 30, 55.5 (3.0) y, from the Erlangen area, Germany.</p> <p>Inclusion criteria: (1) early postmenopausal (1–8 y) and (2) osteopenia at the lumbar spine or total proximal femur (–1 > DXA T score > –2.5 SD).</p> <p>Exclusion criteria: (1) secondary osteoporosis, (2) inflammatory diseases, (3) known osteoporotic fractures, (4) diseases or use of medication affecting bone within 2 y before the start of the study, (5) cardiovascular diseases, (6) very low physical capacity at ergometry (<75 W), and (7) athletic activity during the last 2 decades.</p>	<p>59 women, IG: n = 30, 57.5 (5.1) y, CG: n = 29, 56.6 (4.6) y, from Portugal.</p> <p>Inclusion criteria: (1) postmenopausal and (2) osteoporosis or osteopenia.</p> <p>Exclusion criteria: any associated diseases.</p> <p>IG was formed by voluntary women, whereas the CG was formed by women who did not want to take part in the exercise program.</p>	<p>16 women IG: n = 8, 61.9 (5.0) y, CG: n = 8, 66.7 (7.4) y, from Norway.</p> <p>Inclusion criteria: (1) at least 2 y postmenopausal; (2) <75 y; and (3) BMD T score between –1.5 and –4.0 at the lumbar spine, femoral neck, or total hip.</p> <p>Exclusion criteria: (1) fractures during the last 2 y; (2) use of glucocorticoids or treatment for osteoporosis, other than calcium and vitamin D; (3) any condition that precluded them from taking part in the exercise testing procedures.</p>	<p>101 women; IG: n = 49, 65 (5) y, CG: n = 52, 65 (5) y, from Australia.</p> <p>Inclusion criteria: (1) postmenopausal, (2) aged 58 y and older, and (3) low bone mass (T score < –1.0 at hip and/or spine).</p> <p>Exclusion criteria: (1) after lower limb joint surgery or injury, (2) recent fracture (within the last 12 mo) or localized back pain, (3) less than 5 y postmenopause, (4) malignancy, (5) uncontrolled cardiovascular disease, (6) cognitive impairment, (7) recent X-ray or radiation treatment, (8) contraindications for participating in heavy physical activity, (9) conditions known to influence bone health (eg, thyrotoxicosis or hyperparathyroidism, Paget's disease, renal disease, diabetes, or immobility), (10) taking drugs (other than osteoporosis medications) known to influence bone (eg, prolonged use of corticosteroids, thyroxine, thiazides, or antiviral agents), and (11) unable to attend the supervised training program is so assigned.</p>
Intervention investigated	<p>13 mo of resistance training in the linear periodization; IG1: 3 × a week 60 min. IG2: 2 × a week 60 min.</p> <p>Following exercises were performed: leg press at 45°, knee extension, plantar flexion, squats, hip adduction, gluts (machine for gluts), elbow flexion, elbow extension, and shoulder adduction. At the beginning and in the end of the training: 10 s of stretches for each muscle group (in the exercises machines).</p> <p>CG: no training</p>	<p>36 mo of low-volume high-resistance strength training and high-impact aerobics; IG: 2 × group training (60–70 min) and 2 × home training sessions (25 min) a week. Group training session: warm-up/endurance, jumping, strength training (periodized), and flexibility training sequences.</p> <p>Home training session: rope skipping, isometric and belt exercises, and stretching. Every 12 wk change of exercises.</p> <p>CG: no training</p>	<p>12 mo of weight exercise protocol (longitudinal forces in closed kinetic chain), periodized, 4 stages, 3 mo each stage. General principles of classic weight training in each session: warm-up and aerobic exercises, then performing the weight exercises using either machines or free weights (30–40 min), followed by cooldown and stretching for about 5 min.</p> <p>CG: no training</p>	<p>3 mo of supervised maximal strength training; IG: 3 × a week.</p> <p>Training session: 1 exercise (squat exercise machine). First warm-up including 2 sets of 8–12 repetitions at 50% of 1RM, followed by 4 sets of 3–5 repetitions at 85%–90% of 1RM. Training loads were evaluated each training session and increased, if needed.</p> <p>CG: no training</p>	<p>8 mo of supervised HIPRT and impact loading; IG: 2 × a week 30 min.</p> <p>Warm-up: up to 2 sets of deadlifts at 50%–70% 1RM.</p> <p>HiPRT exercises: deadlift, squat and overhead press; with weight progressively increasing to maintain an intensity of 80%–85% 1RM. Impact loading applied via jumping chin ups with drop landings.</p> <p>CG: 2 × a week 30 min. Unsupervised low-intensity home-based exercise.</p>

(continued)

Characteristic	Borba-Pinheiro et al ²⁶	Engelke et al ²⁷	de Matos et al ²⁸	Mosti et al ²⁹	Watson et al ³⁰
Outcome measures related to bone loss	BMD: LS (L ₂ -L ₄), FN, trochanter, total femur, and total BMD	BMD: LS (L ₁ -L ₄), proximal femur, and forearm.	BMD: LS (L ₁ -L ₄) and hip (neck, trochanter, intertrochanter, and Ward's triangle).	BMD: LS (L ₁ -L ₄), FN, and total hip.	BMD: LS and FN.
Main findings	In IG1, all BMD outcomes showed a significant ($P < .05$) improvement after intervention ($\Delta = 0.07\%$ - 0.12%). IG1 was significantly more efficient ($P < .05$) compared with IG2 regarding BMD variables ($\Delta = 0.07\%$ - 0.12%). IG1 and IG2 groups were significantly more efficient ($P < .05$) compared with CG regarding total BMD (IG1 $\Delta = 0.09\%$, IG2 $\Delta = 0.06\%$). CG's total BMD remained stable. Power: 94%-99% for BMD outcomes.	IG: nonsignificant increase in LS-BMD (DXA $\Delta = 0.8\%$). CG: significant decrease in LS-BMD (lumbar DXA $\Delta = -3.3\%$; $P < .001$). Between-group differences were significant ($P < .001$) for spinal measurements (lumbar DXA $\Delta = -4.1\%$; $P < .001$). At the proximal femur, BMD was maintained in the IG ($\Delta = -0.2\%$), whereas a significant reduction occurred in the CG ($\Delta = -1.9\%$) ($P < .001$); between-groups differences again were significant ($\Delta = 2.1\%$; $P < .001$). At the forearm, both groups lost BMD significantly (IG $\Delta = -2.8\%$, CG $\Delta = -3.8\%$; $P < .001$).	IG: nonsignificant increase in LS-BMD ($\Delta = 1.17\%$) and nonsignificant decreases in hip BMD ($\Delta = -0.07\%$). CG: a significant loss in LS-BMD ($\Delta = -2.26\%$; $P = .01$) and nonsignificant decrease in hip BMD ($\Delta = 0.60\%$). Changes in LS-BMD observed in the IG ($\Delta = 0.010$ [0.043] g/m ²) were significantly different to those observed in the CG ($\Delta = -0.018$ [0.039] g/m ²) ($P < .01$). No differences were observed for hip BMD between IG ($\Delta = -0.006$ [0.032] g/m ²) and CG ($\Delta = -0.005$ [0.031] g/m ²).	IG: LS-BMD pretest 0.759 (0.061), posttest 0.762 (0.062); FN-BMD pretest 0.651 (0.084), posttest 0.655 (0.088); Total hip-BMD pretest 0.751 (0.125), posttest 0.756 (0.123). CG: LS-BMD pretest 0.826 (0.118), posttest 0.818 (0.121); FN-BMD pretest 0.620 (0.055), posttest 0.635 (0.059); Total hip-BMD pretest 0.782 (0.057), posttest 0.775 (0.058). Difference within and between groups were not significant.	IG: FN-BMD and LS-BMD significantly increased compared with losses in the CG; FN-BMD IG $\Delta = 0.3\%$ (2.6%) vs CG $\Delta = -1.9\%$ (2.6%), $P = .004$; LS-BMD IG $\Delta = 2.9\%$ (2.8%) vs CG $\Delta = -1.2\%$ (2.8%), $P < .001$.
Level of evidence	2	2	2	2	2
Modified Downs and Black checklist ³¹	Good (22/28)	Good (21/28)	Fair (16/28)	Good (22/28)	Good (23/28)
Conclusion	Strength training 3 times a week significantly increased BMD (LS, FN, trochanter, total femur, and total BMD) compared with lack of training. Strength training 2 times a week significantly increased total BMD compared with lack of training.	Strength training significantly increased BMD in LS and proximal femur compared with lack of training.	Strength training significantly increased LS-BMD compared with lack of training.	Strength training increased BMD (LS, FN, and total hip); however, insignificantly compared with lack of training.	Strength training significantly increased BMD (LS and FN) compared with low-intensity home-based exercise.

Abbreviations: IRM, 1-repetition maximum; BMD, bone mineral density; CG, control group; DXA, dual-energy X-ray absorptiometry; FN, femoral neck; HiPRT, high-intensity progressive resistance training; IG, intervention group; LS, lumbar spine.

Table 2 Summary of Study Designs and Level of Evidence Based on CEBM 2011³³

Level of evidence	Study design	Number located	References
2	Randomized controlled trial	3	Borba-Pinheiro et al ²⁶ Mosti et al ²⁹ Watson et al ³⁰
2	Controlled trial	2	Engelke et al ²⁷ de Matos et al ²⁸

Abbreviation: CEBM, Centre for Evidence-Based Medicine.

Best Evidence

The studies in Table 2 were identified as best evidence and selected for inclusion in this critically appraised topic. These studies were included, because they measured the change in BMD after strength training intervention in older adults with osteoporosis or osteopenia and comparing with BMD changes in control group.

Implications for Practice, Education, and Future Research

The research reviewed in this critically appraised topic indicated that strength training is an effective therapy to increase BMD in older women with osteoporosis or osteopenia.^{26–30} It also led to establishing the following implications for practice. Based on the results of the included studies it appears that the most beneficial is applying of strength training 2 to 3 times a week.²⁶ The favorable length of the training is estimated between 30 and 60 minutes; this depends on the intensity and volume of given workout program (Table 1). Incorporation of these guidelines into a training program should lead to the increasing of BMD.^{26–30} Strength training of lower intensity, volume, or timeframe might not increase BMD significantly, but can contribute to the maintenance of a certain level.³⁴

At this point, it is important to emphasize that in case of strength training, a crucial element are the resistance level and the nature of the training itself.⁹ To impact muscles and bones sufficiently to prospectively increase BMD, the resistance level of strength training has to be a minimum of 70% of 1-repetition maximum or at least “moderate intensity.”^{12,13,35} This was also confirmed by research included here (Table 1). However, it is important to consider the level of experience when selecting adequate resistance level of the training.⁹ Starting a training program with inadequate resistance level of the training would be irresponsible and potentially dangerous behavior, especially in older adults with reduced BMD.²⁵ Beginners should start with muscle endurance training (ie, lower resistance levels and higher number of repetitions).³⁶ Following increase of the intensity combined with the reduction of the repetition number results with a transition to hypertrophy training and finally maximal strength training.³⁶ The nature of the training should provide an osteogenic effect on bones.³⁷ Muscle actions (muscle loading) and impact forces (gravitational loading) are mechanical forces acting on the skeleton and causing metabolic response in bone tissue.³⁸ Aquatic exercises (eg, swimming) or cycling reduce the gravity force affecting the body making them convenient for older adults, but provide no or not enough impact on bone (no impact activity).^{8,39,40} Therefore, these exercises are not useful as means of complementing the treatment of osteoporosis or even preventive measure.^{8,39,40} The studies included in this critically appraised topic showed the

relevance of impact loading and high-intensity exercises on bone stimulation. It has been proven that they are not only safe, but also sufficient to improve BMD.^{26–30}

Some limitations of this study needs to be acknowledged. First, an important fact to mention is the lack of studies on older men with reduced BMD. A different response in older men after strength training intervention might exist, because they have significantly more muscle tissue ($\pm 25\%$) and muscular strength ($\pm 30\%$) than their female peers.⁴¹ Second, no studies were found that focus on strength training as an alternative for medication therapy in older adults with reduced BMD. For this, a randomized controlled trial is needed including 4 groups (ie, intervention and control groups with and without medication intake) in the best case with a large representative number of subjects. Third, the included studies did not all provide similar outcomes and the effect sizes of their results. Reporting similar outcomes, the effect sizes or estimated thereof would facilitate the interpretation of treatment effect. Finally, although our literature search was conducted in 3 prominent databases, a more extensive search covering more databases is recommended for future searches.

This critically appraised topic showed level B evidence that strength training has a positive and significant influence on bone density in older female adults with reduced BMD. In addition, it seems worth mentioning that it also has a positive effect on strength gain, pain reduction, functional autonomy, and quality of life.^{26,27,29,30} However, it is not recommended to only rely on strength training to increase bone density at this moment. The BMD may not increase fast enough to reach a sufficient value. A combination of strength training and supplements/medication seems most adequate but further examinations are needed to be able to recommend differently. This critically appraised topic should be reviewed in approximately 2 years (2021) to determine if there is any additional best evidence that may alter the practical bottom line for this clinical question.

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Appendix 1 Outcomes Critical Appraisal Using the Modified Downs and Black Checklist³¹

		Borba-Pinheiro et al ²⁶	Engelke et al ²⁷	de Matos et al ²⁸	Mosti et al ²⁹	Watson et al ³⁰
REPORTING						
1	Hypothesis/aim/objective clearly described	1	1	1	1	1
2	Main outcomes in Introduction/Methods clearly described	1	1	1	1	1
3	Patient characteristics clearly described	1	1	1	1	1
4	Interventions of interest clearly described	1	1	1	1	1
5	Principal confounders in each group of subjects to be compared clearly described	2	2	2	1	2
6	Main findings clearly described	1	1	1	1	1
7	Estimates of random variability provided for main outcomes	1	1	1	1	1
8	All adverse events of intervention reported	1	1	1	1	1
9	Characteristics of patients lost to follow-up described	1	1	0	1	1
10	Actual probability values reported for main outcomes	0	1	1	1	1
EXTERNAL VALIDITY						
11	Subjects asked to participate were representative of source population	0	0	0	0	0
12	Subjects prepared to participate were representative of source population	0	0	0	0	0
13	Staff, places, and facilities of treatment were representative of source population	1	1	1	1	1
INTERNAL VALIDITY—BIAS						
14	Study participants blinded to treatment	0	0	0	0	0
15	Blinded outcome assessment	0	0	0	0	1
16	Any data dredging clearly described	1	1	1	1	1
17	Analyses adjust for differing lengths of follow-up	1	1	1	1	1
18	Appropriate statistical tests performed	1	1	1	1	1
19	Compliance with interventions was reliable	1	1	1	1	1
20	Outcome measures were reliable and valid	1	1	1	1	1
INTERNAL VALIDITY—CONFOUNDING						
21	All participants recruited from the same source population	1	1	0	1	1
22	All participants recruited over the same time period	1	1	0	0	1

(continued)

(continued)

		Borba-Pinheiro et al ²⁶	Engelke et al ²⁷	de Matos et al ²⁸	Mosti et al ²⁹	Watson et al ³⁰
23	Participants randomized to treatment	1	0	0	1	1
24	Allocation of treatment concealed from investigators and participants	0	0	0	0	0
25	Adequate adjustment for confounding	1	1	0	1	1
26	Losses to follow-up taken into account	1	1	0	1	1
POWER						
27	Sufficient power to detect treatment effect at a significance level of .05	1	0	0	1	0
TOTAL SCORE		22/28	21/28	16/28	22/28	23/28

Note: 2 = yes (applies only to point 5); 1 = yes; 0 = no or unable to determine. Score range: 28–26 excellent; 25–20 good; 19–15 fair; ≤14 poor.²¹