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Original Article

Does whole-body vibration have benefits in patients with multiple sclerosis: a systematic review and meta-analysis

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Abstract: Purpose: To review and assess the effect of whole-body vibration in patients with multiple sclerosis. Method: We conducted a systematic review and meta-analysis of randomized controlled trials of whole-body vibration (WBV) in patients with multiple sclerosis (MS). Effect on mobility, balance, muscle strength, spasm, gait, fatigue, general well-being and side effects were evaluated. Results: Ten randomized controlled trials qualified the inclusion criteria. Meta-analysis revealed no significant benefit of WBV in Berg balance scale (standard mean difference [SMD], 0.06; 95% confidence interval [CI], -0.54 to 0.66; $P = 0.85$; $I^2 = 69\%$) and Timed Up and Go test (SMD, -0.15; 95% CI, -0.41 to 0.10; $P = 0.24$; $I^2 = 0\%$) when compared with outcomes in the control groups. A significant difference in muscle strength was observed in knee extensor (SMD, 0.43, 95% CI, 0.05 to 0.81; $P = 0.03$; $I^2 = 0\%$). There was no sufficient evidence of benefit of WBV in reducing spasm, relieving fatigue, improving gait or for enhancing well-being. Conclusion: Limited evidence supported the benefits of WBV therapy on functions of patients with multiple sclerosis. Larger and more high-quality trials are needed.

Keywords: Multiple sclerosis, vibration, balance, mobility, muscle strength meta-analysis, randomized controlled trials

Introduction

Multiple sclerosis (MS), a progressive neurological disorder with demyelinating lesions in brain and spinal cord [1], which is characterized by a wide range of dysfunction including balance disorder, mobility limitation, muscle stiffness and weakness, cognitive impairment and fatigue [1, 2]. This can profoundly affect the patients' engagement in activities of daily living, and worsen their quality of life [3-5]. Relapsing-remitting MS (RRMS) is the most common type of MS, which is characterized by a cycle of symptomatic flare up and improvement [6]. Therefore, prolonging the periods of remission and improving the quality of life are key objectives of MS treatment [7]. Medications for MS while being modestly effective tend to be poorly tolerated because of the side effects [8]. Moreover, most therapies aim at symptom-relief rather than at physical functional improvement. Multiple rehabilitation interventions are often used in long-term management of MS [9].

Whole-body vibration (WBV), a new physical therapeutic modality, was initially developed for use in the training of elite athletes. However, it is now being frequently used to influence physical capacity, cardiovascular function, hormonal production, bone mass, proprioception, and quality of life in different population subsets, such as patients with cerebrovascular acci-

Table 1. Characteristics of studies included in this review

Authors	Number of Participants	Type of intervention (E/C)	Form of combined exercises	WBV frequency (Hz)	WBV amplitude (mm)	Position	Treatment duration and session of WBV	Outcome measure related to physical function and time point
Schuhfried *et al.* 2005	E/C = 6/6	WBV *vs.* placebo (TENS)	/	1 to (2.0-4.4)	3	Squat position (hip, knee and ankle in slight flexion)	9 min (5 series, 1 min/series, with 1 min rest)	SOT, TUG, FRT. Baseline 15 min, 1-week, 2-week
Schyns *et al.* 2009	G1/G2 = 8/8	WBV and exercise *vs.* exercise	Warm-up massage + strengthening and stretching exercise + cool-down massage	40	2	Not clear	4 weeks (3 sessions/week, 30 s/session, 2-week rest)	MAS, MSSS-88, Nottingham Sensory Assessment, subjects' tactile sensation, 10-MWT, TUG, MSIS-29. Baseline 4-week, 6-week
Broekmans *et al.* 2010	E/C = 11/14	WBV with exercise *vs.* usual lifestyle (non-specific exercise)	Static and dynamic leg squat and lunges	25-40	2.5	Squat position (the exercise including high knee angle between 120° and 130; deep knee angle 90°; wide stance squats, lunges and heel rises)	20 weeks (5 sessions per 2-week, 30-60 min/session, 12 days break in the 10th week)	Maximal isometric (flexion and extension), dynamic and endurance muscle strength (knees) BBS, TUG, 2-MWT, T25FWT. Baseline, 10-week, 20-week
Diego *et al.* 2012	E/C = 18/16	WBV *vs.* Control (no specific information about the control group)	/	6	3	Semi-squat position	5 days (5 periods of 1 min duration)	Krupp scale, BBS, TUG, T 10 m, SOT (condition 1 to 6), COMP, ST, LAT. Baseline Post-intervention
Claerbout *et al.* 2012	El/Ef/C = 18/20/17	WBV-light (low intensity) + exercise + conventional therapy *vs.* WBV-full + exercise + conventional therapy *vs.* conventional therapy	Static unipodal, bipodal squat, dynamic squat, toes-stand and lunge	30-40	1.6	Squat position	3 weeks (10 sessions, from 7 to 13 min/session rest period from 30 s to a maximum of 1 min)	Muscle strength, 3 MWT, TUG, BBS. 1 day before or after the first and last training
Eftekhari *et al.* 2012	E/C = 12/12	Resistance training + WBV *vs.* control (no intervention)	Static stretching movement + cycle ergometer	2-5 to 20	2	Squat, deep squat, deep lunge, sit forward bend, gentle push up and calf massage	8 weeks (three times/week, 3 sessions of 30 s with 1-2 min rest)	Right leg balance, left leg balance and 10-MWT. Baseline, 8-week
Hilgers *et al.* 2013	E/C = 47/37	WBV +exercise *vs.* placebo WBV + exercise	Warm-up exercise (30 s moderate squat with upper limb movement) + 60 s moderate squat	30	Session 1-6: 1 sessions 6-9: 2	squat position	3 weeks (3 sessions/week, 3*60 s/session rest: 5 s)	SST, TUG, 10 MWT, 6 MWT. Baseline 3-week
Wolfsegger *et al.* 2014	E/C = 9/8	WBV + exercise *vs.* placebo WBV + exercise	Ergometer cycle	Week 1 : 2.5-3.0; week 2: 3.5-4.0; week 3: 4.5-5.0	Unclear	Squat position (hip, knee and ankle slight flexion)	3 weeks (Week 1: vibration duration: 45 s, rest: 60 s; Week 2: vibration duration: 60 s, rests: 45 s; Week 3 vibration duration: 60 s, rest: 30 s)	GA, TUG, Baseline, 3-week, 4-week, 5-week
Uszynski *et al.* 2015	E/C = 13/14	WBV + exercise *vs.* exercise	Warm-up (cycle or treadmill) + static squat, dynamic calf raise, static lunges, one leg standing, steps up and down, cool down (stretches)	40	Unclear	Unclear	12 weeks	Muscle strength (isokinetic dynamometer) Vibration threshold Verbal analogue scale Mini-BESTest MSIS version 2 Modified fatigue impact scale. Baseline, 12-week

Ebrahimi *et al.* 2015	E/C = 17/17	WBV + exercise *vs.* control (no physical activities)	Warmed-up (static stretching movements) + cycle ergometer	2-20	2	Squat, deep squat, lunge, sitting forward bend, modified press up position, one leg stance, deep lunge, hip raise	10 weeks (vibration duration: 30 s; rest: 30 s)	EDSS, MFIS, BBS BBS, FRT, 10 MWT 10 MWT, TUG TUG, Chair rise, Modified push-up, 6 MWT, MSQOL-54. Baseline, 10-week

E/C: experimental group/control group; WBV: whole body vibration; TENS: transcutaneous electrical nerve stimulation; SOT: sensory organization test; TUG: timed get up and go test/timed up and go test; FRT: functional reach test; MAS: Modified Ashworth scale; MSSS-88: the multiple sclerosis spasticity scale 88; MSIS-29: the multiple sclerosis impact scale; 10-MWT: 10-meter walk test; BBS: Berg balance scale; 2-MWT: 2-minute walk test; T25FWT: the 25-foot walk test; COMP: global balance; ST: postural strategy; LAT: latency or reaction time; 3 MWT: 3-minute walk test; SST: sit to stand test; 6 MWT: 6-minute walk test; GA: gait analysis; GDNS: Guys Neurological disability scale; MFIS: modified fatigue impact scale; MSQOL-54: Multiple Sclerosis Quality of Life-54 questionnaire.

Table 2. Methodological assessment of studies included in the meta-analysis using the PEDro Scale*

Criterion	Schuhfried *et al.* 2005	Schyns *et al.* 2009	Broekmans *et al.* 2010	Diego *et al.* 2012	Claerbout *et al.* 2012	Eftekhari *et al.* 2012	Hilgers *et al.* 2013	Wolfsegger *et al.* 2014	Uszynski MK *et al.* 2015	Ebrahimi A *et al.* 2015
Eligibility criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Random allocation	1	1	1	1	1	1	1	1	1	1
Concealed allocation	0	0	0	0	1	0	0	0	1	0
Baseline comparability	1	0	1	1	1	1	1	1	1	1
Blind subjects	0	0	0	0	0	0	0	0	0	0
Blind therapists	0	0	0	0	0	0	0	0	0	0
Blind assessors	1	1	0	1	1	0	1	1	1	1
Adequate follow-up	1	0	1	0	1	1	0	1	1	1
Intention-to-treat analysis	1	0	0	0	0	0	0	0	0	0
Between group comparisons	1	1	1	1	1	1	1	1	1	1
Point estimates and variability	1	1	1	1	1	1	1	1	1	1
Total scores	6	4	5	5	7	5	5	6	7	6

*The PEDro scores were taken from the PEDro website, except for studies by Diego *et al.* and Ebrahimi A *et al.*, which were rated by our research team.

dents [10], chronic obstructive pulmonary diseases [11], osteoarthritis [12], osteoporosis [13] and diabetes mellitus [14]. The effect of WBV is thought to be mediated by muscle contraction, facilitation of sensory inputs and stimulation of proprioceptive responses. Recent evidence suggests a stimulant effect of WBV on higher motor centers [15]. Since functional limitation in MS patients is attributable to muscle weakness, sensory abnormalities and central nerve systems deficits, we sought to assess the available evidence on the effect of WBV in MS patients. An increasing number of studies have examined the effect of WBV on functional recovery in MS patients, however, the conclusion is still uncertain [16-18].

The aim of this review was to systematically assess randomized controlled trials (RCT) of WBV among patients with MS.

Materials and methods

Literature search

A literature search for relevant studies was conducted on MEDLINE (1966 to Oct 2015; via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 10 of 12 Oct. 2015), Pubmed (1966 to Oct. 2015), Physiotherapy Evidence Database (PEDro) (1929 to Oct. 2015; via website) and EMBASE (1980 to Oct. 2015; via Ovid). Two of the authors independently identified relevant studies. Keywords used for searching were: (Multiple Sclerosis or MS or Demyelinating Autoimmune Diseases or Demyelinating Diseases) and (Vibration or Whole body vibration and WBV or Biomechanical stimulation) and (Randomized controlled trial or Clinical trial or Controlled clinical trial or Trial or Randomized or Randomly or Placebo). The reference lists of retrieved articles were manually searched to identify any relevant papers. Authors of randomized controlled trials were contacted for additional information, if required. The latest search was performed on 21th June, 2016 on Pubmed to find potential RCTs to update our search.

Inclusion and exclusion criteria

Studies that qualified the following criteria were considered for this review: (1) randomized controlled trials (RCTs) of WBV in MS patients; (2) published in English language; (3) treatment in the control arm included sham WBV intervention, exercise therapy or other conventional treatment modalities; (4) at least one outcome related to muscle strength, functional performance or quality of life was provided.

Articles were excluded if they were: studies conducted on patients with another primary diagnosis (e.g. Parkinson's disease), reports published as conference proceedings, as dissertation or those published on books were excluded.

Outcome measures

Main outcome measures were assessed by various instruments and tools that are used for assessment of individuals undergoing rehabilitation program. Outcomes evaluated were balance (e.g. Berg Balance Scale, BBS [19]), mobility (e.g. Timed Up and Go, TUG [20]), gait (e.g. gait analysis, GA [21]), spasticity (e.g. modified Ashworth scale, MAS [22]), muscle strength (e.g. hand-held dynamometer [23]) and other related outcome measurements. Any side effects and/or adverse events associated with WBV were recorded.

Data extraction and quality assessment

The quality of RCTs was evaluated using the Physiotherapy Evidence-Based Database Scale (PEDro) [24]. Two independent reviewers evaluated each article. Any scoring discrepancy between the two reviewers were resolved with consensus. The PEDro Scale consists of 11 items. The first criterion, item eligibility, is not scored as it is used as a component of external validity. The other criteria included random allocation, concealment of allocation, baseline equivalence, blinding procedure, intention to treat analysis, adequacy of follow-up, between-group statistical analysis, measurement of data variability and point estimates (**Table 2**).

Data analysis

All statistical analyses were performed using RevMan5.3 (http://ims.cochrane.org/revman). Mean and standard deviations for each outcome were extracted for each treatment group and pooled to obtain standard mean difference and 95% Confidence Intervals. Heterogeneity was examined using I^2 statistic. Studies with an I^2 of 25% to 50% were considered to have low

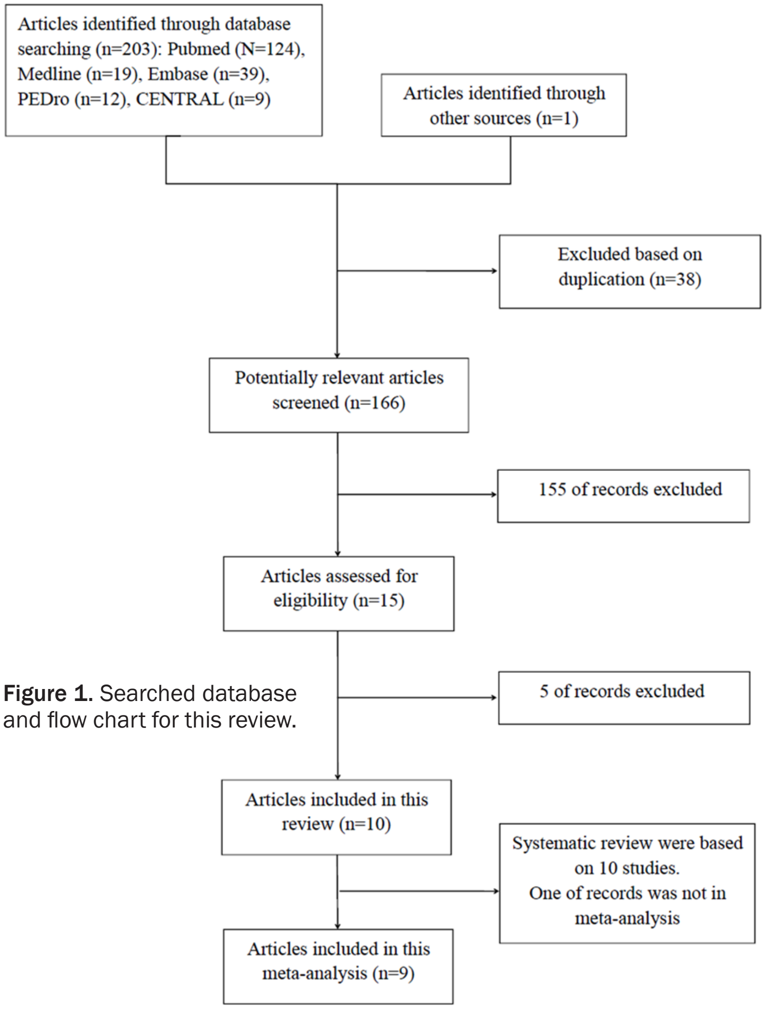

Figure 1. Searched database and flow chart for this review.

heterogeneity, I^2 of values of 50% to 75%, and > 75% were considered indicative of moderate and high level of heterogeneity, respectively. Fixed-effect models were used to combine studies if I^2 test was not significant (P for heterogeneity < 0.1) [25]. Otherwise, random effect models were used. In the event of sufficient studies within each subcategory (e.g., with respect to dose of the WBV and duration of intervention), subgroup analyses were performed to identify sources of heterogeneity and/or to analyze their influence on the effect size. P < 0.05 was considered indicative of a statistically significant between-group difference. Publication bias was not investigated with funnel plots, if < 10 studies were included in the meta-analysis, since in that case, test power is usually too low to distinguish change from real asymmetry [26]. A sensitivity analysis was also used to assess the impact of individual studies on the overall treatment efficacy by examining it after sequential exclusion of one study at a time from the pooled analysis.

Results

Characteristics of trials included in the review

The initial search on databases retrieved a total of 203 citations, of which 166 records were excluded for one or more of the following reasons: nonclinical trials, not relevant to our study, or duplicate publications. Fifteen records were subjected to full-text review, of which five were excluded for the following reasons: non-RCTs (N = 3), one study was a pre-post study [27], and one was a dissertation. Ten studies [28-37] were finally included in our review, and nine of these were included for the meta-analysis [28, 30-37]. Because the study by Schyns *et al.* [29] was excluded as it is a cross-over RCT, which may provide the treatment result with carry-over and learning effects. The study by Claerbout *et al.* [32] had two treatment arms (WBV-light and WBV-full); these were counted as two separate trials to include all data in the analysis. **Figure 1** shows the identification process for selection of trials. Characteristics of included studies are summarized in **Table 1**. Results of assessment of the methodological quality are summarized in **Table 2**.

Quantitative analysis of effects

Results are reported according to various clinical outcomes reflected the effect of WBV.

Measures of muscle tone

Tone was assessed with the Modified Ashworth Scale (MAS) in the study of Schyns *et al.* [29], and tended to increase more for exercise alone compared with WBV plus exercise. The multiple sclerosis spasticity scale 88 (MSSS-88) that quantifies the impact of spasticity in six clini-

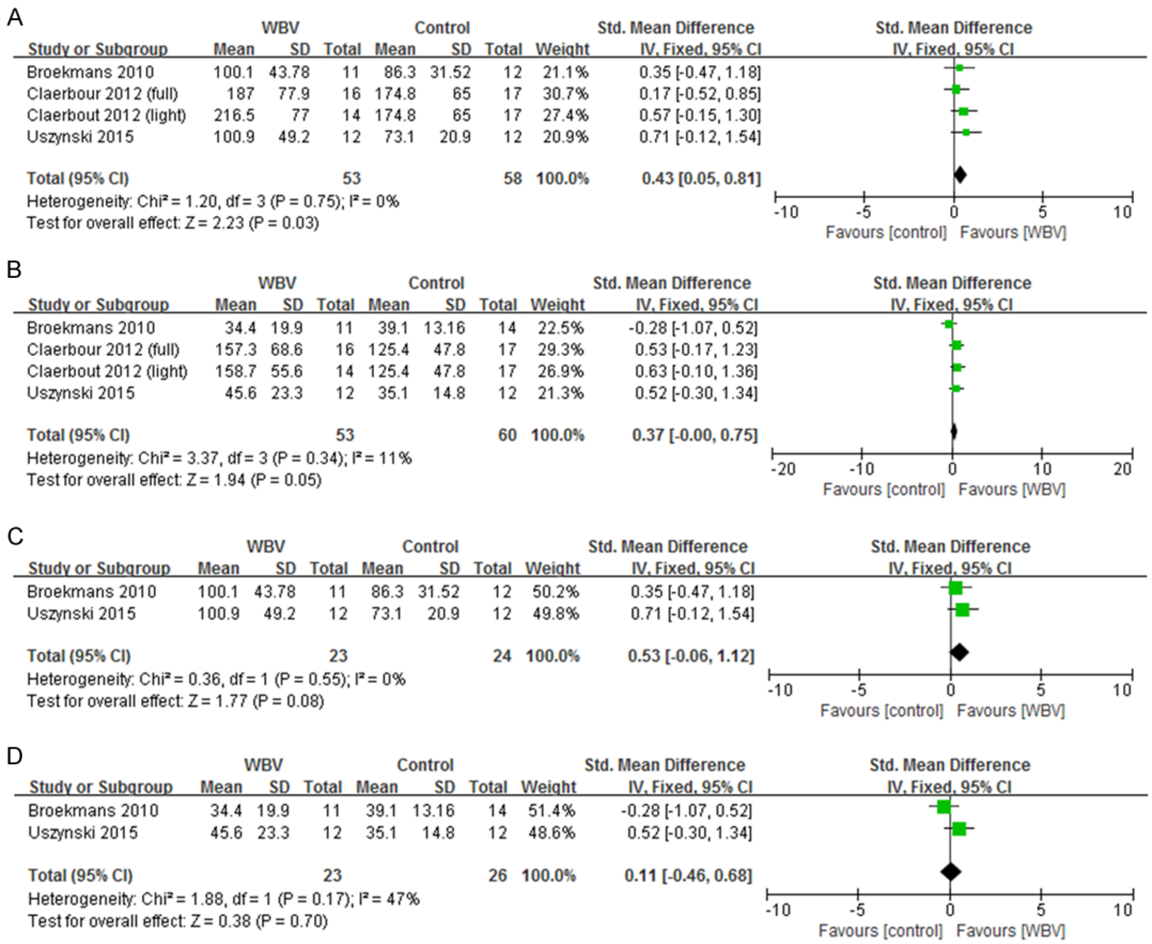

Figure 2. Muscle strength (A) 90 degrees per second for isokinetic knee extension; (B) 90 degrees per second for isokinetic knee flexion; Subgroup analysis of Muscle strength (C) 90 degrees per second for isokinetic knee extension (> 12 weeks); (D) 90 degrees per second for isokinetic knee flexion (> 12 weeks).

cally relevant areas. Results from the MSSS-88 in the study of Schyns *et al.* [29] showed positive benefits from addition of WBV to an exercise program in terms of reducing muscle spasm ($P = 0.02$).

Measures of muscle strength

Five studies [29, 30, 32, 33, 37] investigated the effect on muscle strength. Meta-analysis of three studies [30, 32, 37] show a significant improvement was observed in 90 degrees per second for isokinetic knee extension in favor of WBV in primary analysis, and a trend towards statistically significant difference in favor of the WBV group in isokinetic knee flexion (**Figure 2**).

However, Schyns *et al.* [29] reported no benefit from addition of WBV to exercise therapy with respect to muscle strength, while in the study by Eftekhari *et al.* [33] demonstrated significant improvement of maximal voluntary contraction (MVC) in knee extensors, abduction of scapula, and downward rotation of the scapular girdle muscle groups after eight-week of resistance training plus WBV program.

Measures of balance

Seven studies [28, 30-33, 36, 37] assessed the effect of WBV on balance. In these studies, the duration and parameters of WBV were variable. In total, each patient in WBV arm received approximately 9-minute to 20-week of intervention. Four studies [30-32, 36] used the Berg Balance Scale (BBS), and pooled results revealed standard mean difference of 0.06 (95% CI, -0.54 to 0.66; P = 0.85) with evidence of moderate heterogeneity ($I^2 = 69\%$). Subgroup-analysis of WBV intervention disaggregated by duration and frequency of treatment revealed

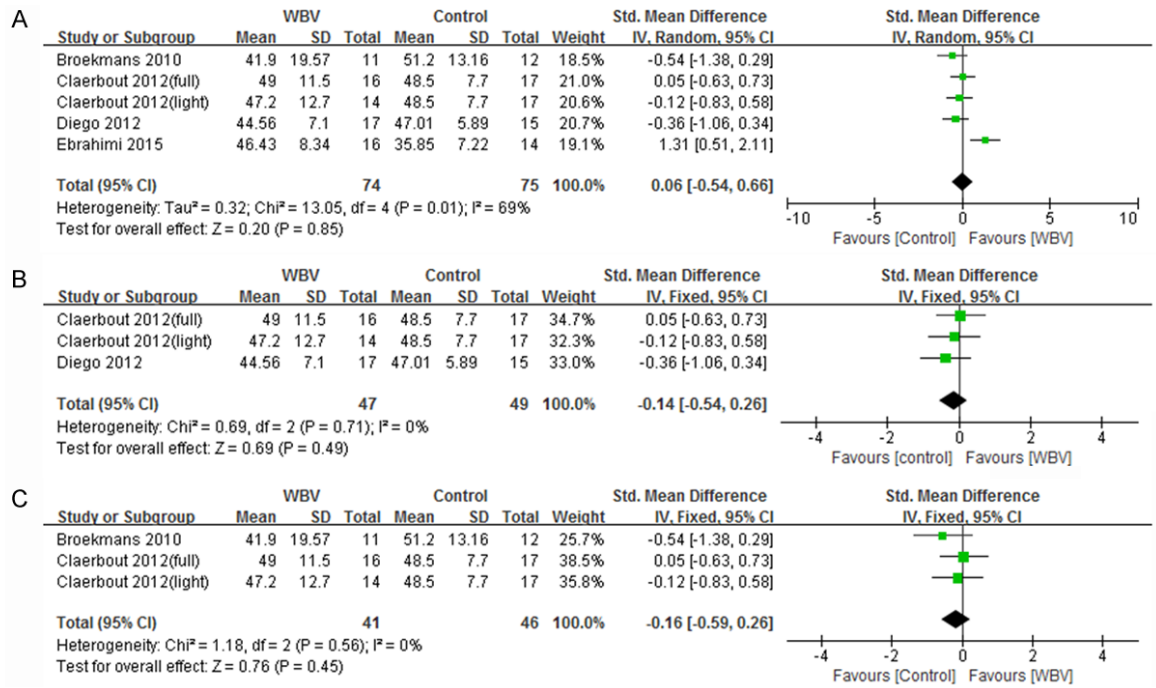

Figure 3. Balance (Berg balance scale) (A) Primary analysis: comparison between the WBV and the control; Subgroup analysis of balance (Berg balance scale) (B) Subgroup analysis: duration < 3-week (short-term); (C) Subgroup analysis: Frequency > 20 Hz (high-frequency).

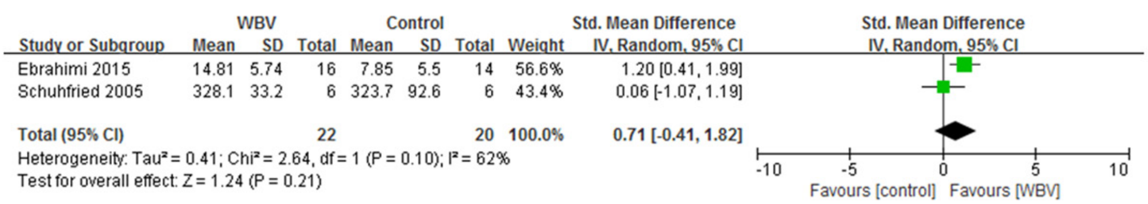

Figure 4. Standing balance (Functional reach test) primary analysis: comparison between WBV and the control.

no significant difference in BBS score achieved with different WBV protocols (**Figure 3**).

Sensory organization test (SOT) was used to assess balance and postural control by using visual and proprioceptive external stimuli [31]. The test includes six sub-tests. Shuhfried *et al.* [28] and Diego *et al.* [31] applied SOT for dynamic posturography to assess the intervention effect. A tendency for higher values on posturographic assessment was observed in the WBV group at all time points of measurement; however, the improvement was not statistically significance [28]. However, Diego *et al.* [31] reported significant within-group improvements in SOT1 ($P = 0.04$), SOT3 ($P = 0.03$) in the treatment arm.

Mini-BESTest provides for assessment of dynamic balance and no significant between-group difference was observed in results of Mini-BESTest in the study by Uszynski *et al.* [37].

Some studies explored the effect of WBV on static balance functions with different outcome measurement tools. Shuhfried *et al.* [28] and Ebrahimi *et al.* [36] used functional reach test (FRT) to measure standing balance; no significant between-group difference was observed in this respect in our meta-analysis (SMD, 0.71, 95% CI, -0.41 to 1.82; $P = 0.21$; $I^2 = 62\%$) (**Figure 4**). Eftekhari *et al.* [33] assessed standing balance by measuring the maximum time for which subjects were able to stand on one leg. They observed a significant increase in double side standing balance after an eight-week treatment regime of WBV plus exercise over that seen in the control group.

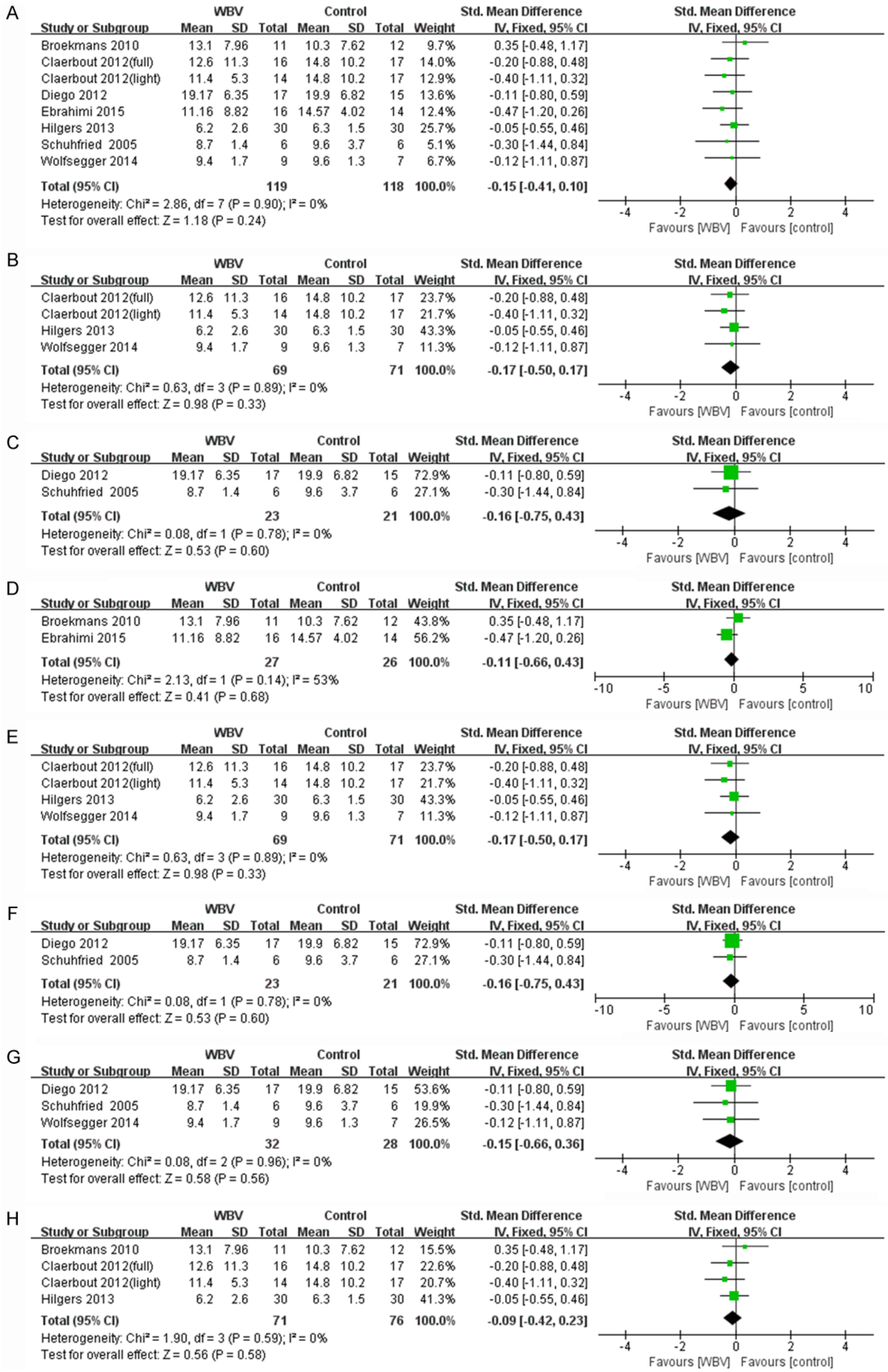
A
WBV | Control | Std. Mean Difference | Std. Mean Difference
Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI
Broekmans 2010 | 13.1 | 7.96 | 11 | 10.3 | 7.62 | 12 | 9.7% | 0.35 [-0.48, 1.17]
Claerbout 2012(full) | 12.6 | 11.3 | 16 | 14.8 | 10.2 | 17 | 14.0% | -0.20 [-0.88, 0.48]
Claerbout 2012(light) | 11.4 | 5.3 | 14 | 14.8 | 10.2 | 17 | 12.9% | -0.40 [-1.11, 0.32]
Diego 2012 | 19.17 | 6.35 | 17 | 19.9 | 6.82 | 15 | 13.6% | -0.11 [-0.80, 0.59]
Ebrahimi 2015 | 11.16 | 8.82 | 16 | 14.57 | 4.02 | 14 | 12.4% | -0.47 [-1.20, 0.26]
Hilgers 2013 | 6.2 | 2.6 | 30 | 6.3 | 1.5 | 30 | 25.7% | -0.05 [-0.55, 0.46]
Schuhfried 2005 | 8.7 | 1.4 | 6 | 9.6 | 3.7 | 6 | 5.1% | -0.30 [-1.44, 0.84]
Wolfsegger 2014 | 9.4 | 1.7 | 9 | 9.6 | 1.3 | 7 | 6.7% | -0.12 [-1.11, 0.87]
Total (95% CI) | 119 | 118 | 100.0% | -0.15 [-0.41, 0.10]
Heterogeneity: Chi² = 2.86, df = 7 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)
-4 -2 0 2 4
Favours [WBV] Favours [control]
B
WBV | Control | Std. Mean Difference | Std. Mean Difference
Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI
Claerbout 2012(full) | 12.6 | 11.3 | 16 | 14.8 | 10.2 | 17 | 23.7% | -0.20 [-0.88, 0.48]
Claerbout 2012(light) | 11.4 | 5.3 | 14 | 14.8 | 10.2 | 17 | 21.7% | -0.40 [-1.11, 0.32]
Hilgers 2013 | 6.2 | 2.6 | 30 | 6.3 | 1.5 | 30 | 43.3% | -0.05 [-0.55, 0.46]
Wolfsegger 2014 | 9.4 | 1.7 | 9 | 9.6 | 1.3 | 7 | 11.3% | -0.12 [-1.11, 0.87]
Total (95% CI) | 69 | 71 | 100.0% | -0.17 [-0.50, 0.17]
Heterogeneity: Chi² = 0.63, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)
-4 -2 0 2 4
Favours [WBV] Favours [control]
C
WBV | Control | Std. Mean Difference | Std. Mean Difference
Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI
Diego 2012 | 19.17 | 6.35 | 17 | 19.9 | 6.82 | 15 | 72.9% | -0.11 [-0.80, 0.59]
Schuhfried 2005 | 8.7 | 1.4 | 6 | 9.6 | 3.7 | 6 | 27.1% | -0.30 [-1.44, 0.84]
Total (95% CI) | 23 | 21 | 100.0% | -0.16 [-0.75, 0.43]
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)
-4 -2 0 2 4
Favours [WBV] Favours [control]
D
WBV | Control | Std. Mean Difference | Std. Mean Difference
Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI
Broekmans 2010 | 13.1 | 7.96 | 11 | 10.3 | 7.62 | 12 | 43.8% | 0.35 [-0.48, 1.17]
Ebrahimi 2015 | 11.16 | 8.82 | 16 | 14.57 | 4.02 | 14 | 56.2% | -0.47 [-1.20, 0.26]
Total (95% CI) | 27 | 26 | 100.0% | -0.11 [-0.66, 0.43]
Heterogeneity: Chi² = 2.13, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 0.41 (P = 0.68)
-10 -5 0 5 10
Favours [WBV] Favours [control]
E
WBV | Control | Std. Mean Difference | Std. Mean Difference
Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI
Claerbout 2012(full) | 12.6 | 11.3 | 16 | 14.8 | 10.2 | 17 | 23.7% | -0.20 [-0.88, 0.48]
Claerbout 2012(light) | 11.4 | 5.3 | 14 | 14.8 | 10.2 | 17 | 21.7% | -0.40 [-1.11, 0.32]
Hilgers 2013 | 6.2 | 2.6 | 30 | 6.3 | 1.5 | 30 | 43.3% | -0.05 [-0.55, 0.46]
Wolfsegger 2014 | 9.4 | 1.7 | 9 | 9.6 | 1.3 | 7 | 11.3% | -0.12 [-1.11, 0.87]
Total (95% CI) | 69 | 71 | 100.0% | -0.17 [-0.50, 0.17]
Heterogeneity: Chi² = 0.63, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)
-4 -2 0 2 4
Favours [WBV] Favours [control]
F
WBV | Control | Std. Mean Difference | Std. Mean Difference
Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI
Diego 2012 | 19.17 | 6.35 | 17 | 19.9 | 6.82 | 15 | 72.9% | -0.11 [-0.80, 0.59]
Schuhfried 2005 | 8.7 | 1.4 | 6 | 9.6 | 3.7 | 6 | 27.1% | -0.30 [-1.44, 0.84]
Total (95% CI) | 23 | 21 | 100.0% | -0.16 [-0.75, 0.43]
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)
-10 -5 0 5 10
Favours [WBV] Favours [control]
G
WBV | Control | Std. Mean Difference | Std. Mean Difference
Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI
Diego 2012 | 19.17 | 6.35 | 17 | 19.9 | 6.82 | 15 | 53.6% | -0.11 [-0.80, 0.59]
Schuhfried 2005 | 8.7 | 1.4 | 6 | 9.6 | 3.7 | 6 | 19.9% | -0.30 [-1.44, 0.84]
Wolfsegger 2014 | 9.4 | 1.7 | 9 | 9.6 | 1.3 | 7 | 26.5% | -0.12 [-1.11, 0.87]
Total (95% CI) | 32 | 28 | 100.0% | -0.15 [-0.66, 0.36]
Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
-4 -2 0 2 4
Favours [WBV] Favours [control]
H
WBV | Control | Std. Mean Difference | Std. Mean Difference
Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI
Broekmans 2010 | 13.1 | 7.96 | 11 | 10.3 | 7.62 | 12 | 15.5% | 0.35 [-0.48, 1.17]
Claerbout 2012(full) | 12.6 | 11.3 | 16 | 14.8 | 10.2 | 17 | 22.6% | -0.20 [-0.88, 0.48]
Claerbout 2012(light) | 11.4 | 5.3 | 14 | 14.8 | 10.2 | 17 | 20.7% | -0.40 [-1.11, 0.32]
Hilgers 2013 | 6.2 | 2.6 | 30 | 6.3 | 1.5 | 30 | 41.3% | -0.05 [-0.55, 0.46]
Total (95% CI) | 71 | 76 | 100.0% | -0.09 [-0.42, 0.23]
Heterogeneity: Chi² = 1.90, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)
-4 -2 0 2 4
Favours [WBV] Favours [control]

Figure 5. Mobility (Time Up and Go test): A. Primary analysis: comparison between the WBV and the control; B. Subgroup analysis: intervention = WBV + EXE VS. EXE; C. Subgroup analysis: intervention = WBV VS. CON; D. Subgroup analysis: intervention = WBV + exercise vs. control; E. Subgroup analysis: duration 3-week; F. Subgroup analysis: duration < 3-week (short-term); G. Subgroup analysis: Frequency < 20-Hz (low-frequency); H. Subgroup analysis: Frequency > 20-Hz (high-frequency).

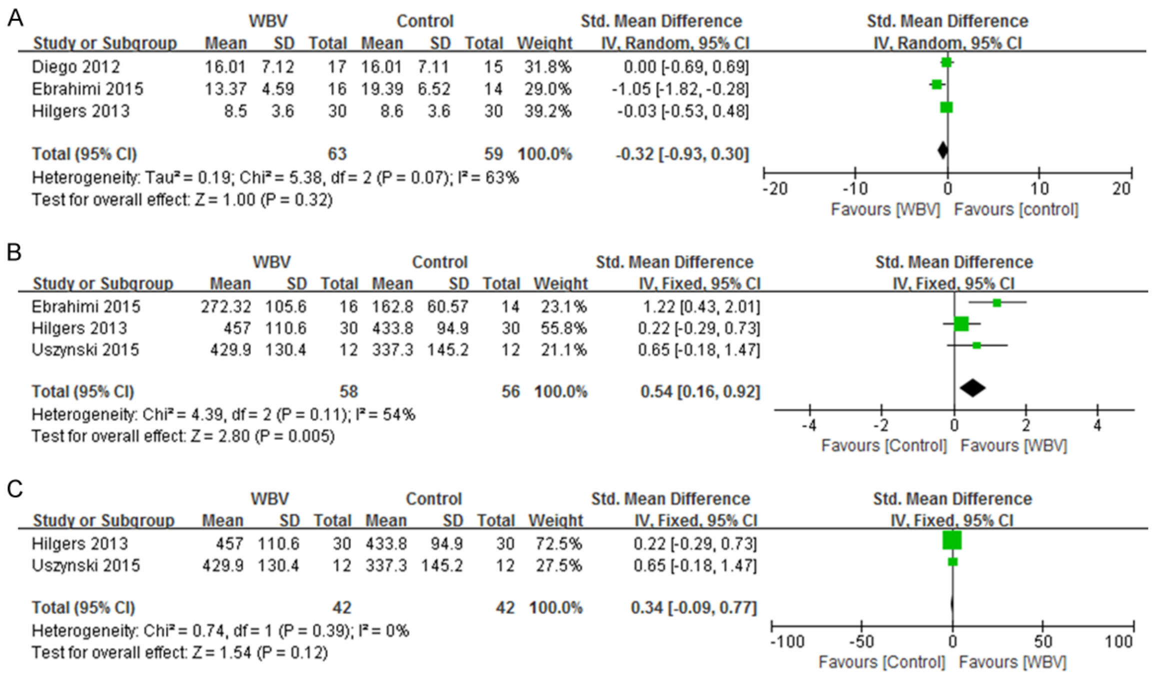

Figure 6. Mobility (walking test) (A) 10-metre walk test; (B) 6-minute walk test; (C) 6-minute walk test (WBV + EXE vs. Placebo WBV + EXE).

Assessment of walking ability

Assessments of walking ability in included studies covered the sit to stand test (SST) [34], timed up and go test (TUG) [28-32, 34-37], 6-min walk test (6-MWT) [34, 36, 37] and 3-min walk test (3-MWT) [32].

Data from seven trials [28, 30-32, 34-37] that used TUG as an outcome measure were also included in the meta-analysis. Schyns *et al. [29]* reported no significant effect of WBV intervention. In the study by Uszynski *et al.* [37], Mann-Whitney U-test revealed no significant between-group difference in TUG scores regardless of the duration of intervention, WBV parameters or patient characteristics (**Figure 5**).

Subgroup analyses by type of intervention, treatment duration and WBV frequency were performed. Experiment groups (WBV plus exercise) in the studies by Claerbout *et al.*, Hilgers *et al.* and Wolfsegger *et al.* [32, 34, 35] showed no significant improvement in TUG over that in the control groups (exercise only). Further, analysis revealed no significant changes in TUG between WBV therapy group and control groups (received no exercise training) [28, 31], and between WBV plus exercise group and control (no exercise training) groups [30, 36].

Meta-analysis revealed no significant benefits of WBV after 3 weeks [32, 34, 35] (SMD, -0.17; 95% CI, -0.50 to 0.16; $P = 0.32$; $I^2 = 0\%$), or < 3 weeks [28, 31] (SMD, -0.16; 95% CI, -0.75 to 0.43; $P = 0.60$; $I^2 = 0\%$).

Three studies [28, 31, 35] that explored the effect of < 20-Hz WBV found no significant differences between the experiment and the control groups (SMD, -0.15; 95% CI, -0.66 to 0.36; $P = 0.56$; $I^2 = 0\%$). Further, three studies [30, 32, 34] showed no improvement with > 20-Hz WBV intervention (SMD, -0.09; 95% CI, -0.42 to 0.23; $P = 0.58$; $I^2 = 0\%$).

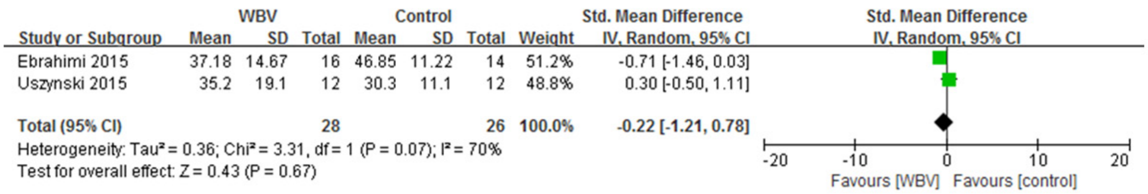

Figure 7. Fatigue (Modified fatigue impact scale) primary analysis: comparison between the WBV and the control.

Five studies [29, 31, 33, 34, 37] investigated the effect of 10-MWT on mobility. No significant result was noted in our primary meta-analysis based on three studies [31, 34, 37] (SMD, -0.32; 95% CI -0.93 to 0.30; $P = 0.32$; $I^2 = 63\%$). The rest study also provided similar result in 10-MWT: Schyns *et al.* [29] demonstrated improved mobility with 10 MWT, but the difference between the intervention and control groups was not statistically significant. Eftekhari *et al.* [33] reported that 8-week resistance training with WBV can reduce the time for 10-MWT, in comparison with no intervention group. For the result of 6-minute walk test, subgroup analysis of pooled data from two studies [34, 37] still showed no significant improvement could be found between WBV plus exercise and Placebo WBV plus exercise (SMD, 0.34; 95% CI, -0.09 to 0.77; $P = 0.12$; $I^2 = 0\%$) (**Figure 6**).

Wolfsegger *et al.* [35] assessed gait velocity, stride length, double support phase and single-step variability as components of gait analysis; however, none of the outcome measures showed a statistically significant difference following 3-week WBV plus exercise intervention compared with placebo WBV plus exercise.

Measures of fatigue

Modified Fatigue Impact Scale (MFIS) was used to assess the effects of fatigue on physical, cognitive, and psycho-social functioning [37]. Two studies [36, 37] evaluated fatigue using MFIS, and no significant difference in favor of WBV therapy was observed in the meta-analysis (SMD, -0.22, 95% CI, -1.21 to 0.78; $P = 0.67$; $I^2 = 70\%$) (**Figure 7**).

Measures of well-being

Multiple Sclerosis Impact Scale (MSIS-29) was used to measure the participants' health-related quality of life, which provides a measure of the physical and psychological impact of multiple sclerosis from the patients' perspective [29, 37]. The result of Schyns *et al.* [29] suggests no added value of WBV in terms of the results. Further, the result of MSIS-29 in the other test [37] showed no statistically significant difference, which is similar to the result of Ebrahimi A *et al.* [36] assessed by MSQQL-54.

Side effects/adverse events

In the study by Schuhfried *et al.* [28], one out of twelve participants complained of increased fatigue, while one patient dropped out due to acute back pain in the study of Wolfsegger *et al.* [35]. Only in one study, did [30] a participant experienced a relapse of MS in the WBV group. We did not find any evidence of the association between WBV and the event. In one study [29], WBV aggravated a pre-existing knee condition in one subject.

Discussion

We performed a systematic review of the effect of WBV therapy in patients with MS and conducted a meta-analysis of the effect of WBV on mobility, balance, muscle strength and fatigue in these patients.

Balance and mobility

Effective balance depends on three sensory inputs: visual, vestibular and somatosensory, which are vulnerable to impairment in MS patients [2, 38, 39]. WBV stimulates the skin receptors, vestibular organs and higher somatosensory cortex [16, 28, 40], which may explain the beneficial effect of vibration on balance and mobility. Approximately 50% of people require walking aids within 15 years of the onset of MS [2, 6], which highlights ambulation rehabilitation as being an integral part of long-term MS management. With obvious heterogeneity of included studies, we tried to analyze the effect from different frequency and duration. However, our meta-analysis revealed no beneficial effect of WBV in improving balance in people with MS as assessed by BBS when compared with the control in all primary analysis and secondary analyses. Diego *et al.* [31] found no significant treatment effect of short-term WBV (five days) on BBS scores. However, improvements in the WBV group were noticed under some conditions in sensory organization test (SOT), which suggests that the potential value of vibration on balance may result from enrichment of sensory inputs. Claerbout *et al.* [32] reported no significant benefit of addition of WBV to an exercise program as assessed by BBS. Similar findings were reported by another study [33], which is inconsistent with other one study [36]. In terms of static standing balance, the pooled data on FRT did not indicate any positive evidence in support of WBV. These inconsistent results are probably due to the variability between the included trials in terms of treatment protocol, characteristics of subjects and duration of intervention.

Assessment tools used in these studies raises some concerns. As Uzynski *et al.* [37] mentioned, absence of "gold standard" measurement tools may have contributed to the inconsistent result on the effect of WBV on balance function. Although the American Physical Therapy Association Neurology Section task force indicated that BBS and FRT were both recommended outcome measure for people with MS [41], we still would like to see future researchers use more reliable and high-tech evaluation methods to explain the influence of WBV on the balance function in patients with MS. Similarly, our meta-analysis revealed no benefits of WBV on improving the mobility, as assessed by various measures such as TUG, and 10-MWT.

There is some evidence of the positive effect of exercise therapy on walking ability in MS [42-45], which is in accordance with the findings reported by Eftekhari *et al.* and Ebrahimi *et al.* [33, 36], but is not with those of the Broekmans *et al.* [30]. On comparing the two studies, we found that the disability level of subjects in the studies by Eftekhari *et al.* and Ebrahimi *et al.* was much lower than that in the study by Broekmans *et al.*, which may have contributed to the discordant results. Also, the exercise protocol needs to be standardized for people with MS, and especially with respect to the combination of appropriate exercise with vibration. Moreover, the effect of vibration on improving mobility in people with MS is not amenable to measurement independent of the effect of exercise program; Schuhfried *et al.* [28] reported a fluctuated result in TUG, while no significant difference was noted in TUG and T-10 m by Diego *et al.* [31]. The variability of parameters of WBV, the duration of WBV and the participants between the studies, may have contributed to the lack of benefit of addition of WBV to a physical exercise program for enhancing mobility. Moreover, the effect of WBV on long distance walking ability of MS patients has also not been investigated.

Muscle strength

Although WBV has shown to be beneficial for lower extremities muscle strength in healthy population [44], we found some inconsistent results in MS population. In the meta-analysis of two studies [34, 37], no evidence of additional benefit of WBV on muscle strength when used in combination with an exercise program. Our study found that WBV therapy may help the extensor muscle strength based on three trails, however, we still did not know whether WBV has additional effects to exercise program in MS population.

Muscle strength should be the primary outcome for people with MS, which was shown to be strongly associated with walking ability [46], further, muscle strength improvement is the most likely clinical outcome liable to be influenced by the vibration-induced muscular reflex. In other neurodegenerative diseases, such as Parkinson's diseases, there is also insufficient evidence to support the WBV pose positive effects in muscle strength [16]. A possible explanation could be that muscle weakness of neurological origin tends to be relatively resistant to rehabilitative training alone. Optimal management of the primary disease in combination with appropriate rehabilitation program is likely to show improved benefit.

Muscle tone

Evidence suggests that vibration can help normalize the muscle tone in patients with cerebral palsy and spinal cord injury [47, 48], by inducing pre-synaptic inhibition or lowering I_a afferent neuron discharge. Based on included trials in this review, it is hard to confirm whether or not WBV is an effective way to reduce the spasticity in people with MS, because only one study [29] evaluated the effect of WBV on spasm, using the MAS and MSSS-88. However, these two measurements are no longer recommended by the American Physical Therapy Association Neurology Section Task Force [41] for use in patients with MS. More trials using reliable outcome measures are needed to arrive at a more definite conclusion on the effect of WBV on spasticity.

Fatigue

We did not find significant improvement in fatigue (MFIS) with WBV intervention in MS. Available evidence shows that the exercise therapy of similar duration may not help reduce the fatigue in people with MS [49]. Because of the obvious heterogeneity and limited amount of studies, more studies are required to clarify whether WBV have additional value in reducing fatigue in MS.

Side effects

Safety of WBV in MS patients is yet to be established. Of note, a new attack is liable to occur in some patients [1]. In order to prevent the disease flare and enable the maximum therapeutic effects, more research into the optimal timing of WBV in people with MS is required. This review was not designed to determine the best timing for commencement of WBV therapy in MS patients, as data on the duration of disease was not reported in most studies.

Additionally, several studies did not report as per the recommendations of the International Society of Musculoskeletal and Neuronal Interactions [50]. Standardized protocol for parameters of WBV is strongly recommended in future studies.

Limitations

There are several limitations in this systematic review and meta-analysis. Firstly, our meta-analysis is based on only a handful of RCTs with small sample sizes. Overestimation of treatment effect is more likely in smaller trials. Secondly, since the subgroup analyses were based only on two or three studies, the conclusions should be interpreted with caution. Thirdly, the protocol of WBV therapy and the characteristics of participants varied greatly. Finally, restricting the scope of the literature search only to English language publications may have excluded some relevant studies from the purview of this study.

Conclusions

In this review, WBV therapy may help improve the extensor muscle strength, but not be associated with any significant effect on balance, mobility, muscle tone, gait and general well-being of patients with MS. No definitive recommendations can be made regarding the use of WBV in people with multiple sclerosis. Further research with standardized protocols and reporting is required to assess the role of WBV therapy in these patients.

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Disclosure of conflict of interest

None.

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