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Title: Non-Pharmacological management of Orthostatic Hypotension in older people: A systematic review. The SENATOR ONTOP series

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Keywords: Orthostatic hypotension; postural hypotension; orthostasis; non-pharmacological therapy; older people

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Abstract: Objectives
Non-pharmacological therapies are often recommended as a first line treatment for orthostatic hypotension (OH). However, the true effect of non-pharmacological therapy remains unclear, particularly in the older population. We undertook a systematic review evaluating the efficacy of non-pharmacological interventions in older people with OH to provide evidence-based recommendations.

Design
Systematic review of systematic reviews

Setting and Participants
MEDLINE, PubMed, EMBASE, and Cochrane Database of Systematic Reviews, CINHAL and PsychINFO were searched up to June 2018. Two reviewers identified eligible systematic reviews from which primary studies were selected. We included studies both randomized and non-randomized studies that evaluated any type of non-pharmacological intervention and reported outcomes of change in postural drop in systolic blood pressure (SBP) and/or orthostatic symptoms measured using any validated instrument. The Cochrane risk of bias tool was used, with recommendations based on the GRADE approach.

Results
Eleven trials were included. Meta-analysis of lower limb compression showed a reduction in the postural drop in SBP of 9.83 mmHg (95%CI -12.56, -7.11), whereas abdominal compression showed a larger reduction in postural drop in SBP of 12.30mmHg (95%CI -18.20, -6.39). Compression therapy was also beneficial in reducing OH symptoms. However, the quality of the evidence for compression therapy was very poor. One study each was identified for sleeping-head-up (SHU), home based resistance training (HBRT) and multi-component intervention but did not significantly reduce postural SBP drop. Bolus water drinking was effective in one study but the study was of low quality.

Conclusions/implications
There is no high quality evidence to recommend any of the non-pharmacological therapies for the management of OH in older people. Yet, we make a weak recommendation for lower limb and abdominal compression therapy based on very low quality evidence. Large-scale trials are warranted in older people to substantiate the efficacy of non-pharmacological therapies in OH.

Letter
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19 Mar 2019

To
Professor Philip D. Sloane MD, MPH
Editor-in-Chief,
Journal of the American Medical Directors Association

Sub: Submission of the revised version of the manuscript (Manuscript Reference Number: JAMDA-D-19-00103)

Dear Prof/Dr Philip Sloane,

We are submitting the revised version of the above referenced systematic review article entitled **"Non-Pharmacological management of Orthostatic Hypotension in older people: A systematic review. The SENATOR ONTOP series"** to be considered for publication in the Journal of the American Medical Directors Association.

On behalf of all co-authors, I would like to take this opportunity to thank the Editorial Boards for considering our paper and the reviewers for their helpful comments. We have attached the responses to the comments in a separate document named 'Response to Reviewers'. We sincerely hope that the revised version will satisfy the reviewers and the editors and that the revised manuscript will be accepted for publication in JAMDA.

We are looking forward to hear from you.

Yours sincerely,

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*Title Page (Containing author details)

Title page

Non-Pharmacological management of Orthostatic Hypotension in older people: A systematic review. The SENATOR ONTOP series

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Brief summary: Our review revealed there is no strong evidence to recommend any non-pharmacological therapies for treating OH in older people, though lower limb and abdominal compression bandaging may help.

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Abstract

Objectives

Non-pharmacological therapies are often recommended as a first line treatment for orthostatic hypotension (OH). However, the true effect of non-pharmacological therapy remains unclear, particularly in the older population. We undertook a systematic review evaluating the efficacy of non-pharmacological interventions in older people with OH to provide evidence-based recommendations.

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Eleven trials were included. Meta-analysis of lower limb compression showed a reduction in the postural drop in SBP of 9.83 mmHg (95%CI -12.56, -7.11), whereas abdominal compression showed a larger reduction in postural drop in SBP of 12.30mmHg (95%CI -18.20, -6.39). Compression therapy was also beneficial in reducing OH symptoms. However,

the quality of the evidence for compression therapy was very poor. One study each was identified for sleeping-head-up (SHU), home based resistance training (HBRT) and multi-component intervention but did not significantly reduce postural SBP drop. Bolus water drinking was effective in one study but the study was of low quality.

Conclusions/implications

There is no high quality evidence to recommend any of the non-pharmacological therapies for the management of OH in older people. Yet, we make a weak recommendation for lower limb and abdominal compression therapy based on very low quality evidence. Large-scale trials are warranted in older people to substantiate the efficacy of non-pharmacological therapies in OH.

Introduction

Orthostatic hypotension (OH) is extremely common in older people and increases with advancing age[1]. An International consensus statement defined OH as a sustained reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table[2]. Prevalence of OH varies greatly, from 5% to70% depending on the setting or population[3,4]. Saedon et al. reported that the pooled prevalence of OH was 22.2% and 23.9% in community dwelling older people and in long-term care settings respectively[5]. A cross-sectional cohort study involving 653 home-dwelling people aged 75 years and above reported an OH prevalence of 34%[6]. In addition to ageing, polypharmacy is also associated with increased prevalence of OH, being reported in up to 65% of veterans attending a geriatrics clinic[7].

Medications that increase the risk of OH include vasodilators, antihypertensives, β-blockers, calcium antagonists, renin-angiotensin inhibitors, α-blockers, dopaminergic agents, antipsyhotics, antidepressants and sedative-hypnotics[8-12]. OH is significantly associated with coronary heart disease, heart failure, transient ischaemic attacks, isolated systolic hypertension, and carotid stenosis[1,13-15]. The annual rate of OH-related hospitalizations, from a nationwide inpatient sample in 2004 was 36 per 100,000 US adults which increased to 233 per 100,000 in patients aged 75 years or older. OH was the primary diagnosis in 35% of these hospitalizations[16]. Additionally, OH is an independent risk factor for falls[1,17,18] and all-cause mortality[17,19]. In the Atherosclerosis Risk in Communities cohort study, all-cause mortality was 13.7% in those with OH compared to 4.2% in those without[20].

The main goal in the treatment of OH is to alleviate the postural symptoms and improve functional capacity and quality of life rather than achieving a blood pressure target[17,21,22].

The first step in OH treatment involves considering discontinuing or reducing dose of any medications that could potentially cause OH[23]. Non-pharmacological interventions are the first line of treatment for OH and pharmacological treatments are introduced only in severe cases of OH where non-pharmacological treatment is inadequate[17,21,24-26]. Although guidelines exist for managing OH, optimal non-pharmacological management is not well defined for the geriatric population. Indeed, the effectiveness of non-pharmacological treatment has been questioned[27]. There is a significant lack of research evidence in the fast growing population of older people with OH. Hence, we set out to fill this evidence gap as part of the SENATOR-ONTOP work package (Software ENgine for the assessment and Optimization of drug and non-drug Therapy in Older peRsons-Optimal Evidence-Based Non-drug Therapies in Older People)[28] with the view of development of evidence based recommendations for the non-pharmacological interventions for common geriatric conditions.

The aim was to assess the efficacy of non-pharmacological interventions in the treatment of OH in people aged ≥65 years.

Methods

This review of systematic reviews was conducted according to the SENATOR-ONTOP protocol[29]. A literature search was undertaken on EMBASE, PubMed, the Cochrane Database of Systematic Reviews (CDSR), CINAHL, and PsycINFO from inception to 6th June 2018 to identify systematic reviews. Key search terms used included orthostatic hypotension, postural hypotension, orthostasis, orthostatic intolerance, orthostatic syncope and postural blood pressure. There was no language restriction, however authors planned to translate only papers published in Spanish and Italian languages. The search strategy was

restricted to 'human only' studies and publication type was limited to 'systematic review/reviews/meta-analysis'.

Study selection criteria

We included systematic reviews and/or review articles that had evaluated any non-pharmacological intervention for treatment of OH, used at least one medical literature database for evidence searching, included at least one primary study, and evaluated at least one non-pharmacological intervention for the treatment of OH in older people.

We included any comparative study, either randomized or non-randomized clinical trials that investigated the effect of any non-pharmacological intervention in OH. Before-and-after studies (BAS) or repeated measure study design where patients acted as their own controls were included. We excluded observational studies or BAS with historical controls.

We included trials involving older people in which the mean age of participants was ≥65 years. For the purpose of this review, OH was defined as a drop in systolic BP ≥20 mmHg and/or a diastolic BP ≥10 mmHg determined by either active standing or passive tilt test[30]. Though our initial plan was to include only supine to standing OH, due to a lack of eligible studies in older people, we later included studies that evaluated the effect of non-pharmacological intervention in different positons, e.g. supine to seated or seated to standing.

Types of interventions

Our review focused on trials of non-pharmacological interventions administered either alone or in combination with other non-pharmacological interventions. Comparator interventions included placebo, no treatment or sham procedure. We excluded control

interventions of active pharmacological and non-pharmacological treatments as this might not provide accurate efficacy data on the non-pharmacological interventions.

Types of outcome measures

We conducted an online Delphi survey involving international experts from the field of geriatric medicine in order to select the most important outcomes measures for this review. Two outcome measures that were ranked as 'critical' by the Delphi panel for OH were included as the main outcomes for this review. These were:

- Outcome 1: Change is postural systolic BP drop (mmHg) from supine to standing
- Outcome 2: Orthostatic symptoms measured using any validated method.

Data collection and analysis

Two reviewers independently screened the titles and abstracts, and selected potentially relevant review articles for full text review. From the included review articles, we identified eligible primary studies as per inclusion criteria and reference checking was performed to identify any additional eligible primary studies. After removing duplicates using reference manager software (Refworks®), two reviewers independently reviewed the full-text of the eligible primary studies for inclusion or exclusion. At each stage of screening and study selection, any disagreements were resolved by discussion and by consensus with the lead author wherever necessary. Two reviewers independently extracted data using a study specific data extraction form developed for this review.

Analysis

The methodological quality of each SR was assessed using AMSTAR (A Measurement Tool to Assess Reviews) instrument[31]. The risk of bias for all the included primary studies was evaluated using the Cochrane collaboration's recommended risk of bias tool [32]. Risk of bias was rated by two reviewers independently, resolving disagreements by discussion and by consensus with the lead author when required.

The quality of evidence was assessed using the GRADE (Grading of Recommendations Assessments, Development and Evaluation) approach, which classifies evidence into four categories - high, moderate, low and very low[33]. PICO clinical questions were developed for each intervention and outcome, and authors completed grading assessment and summary of findings (SoF) using online software, GRADEpro®[34].

The treatment effect size and heterogeneity were assessed as described in the SENATOR-ONTOP protocol[29]. Meta-analysis and forest plots were created where possible using the version 5.3 of RevMan® software when data from at least two primary studies could be combined. Each type of non-pharmacological intervention was evaluated separately and we chose the generic inverse variance statistical method. When there was not enough information reported on the paper for outcomes data, we contacted study authors by email. The size of the treatment effect was expressed as the mean difference between the intervention and control group. Narrative synthesis of the evidence was undertaken where meta-analysis was not possible.

Results

A total of 2037 articles were retrieved after removing duplicates. We excluded 2029 non-relevant articles after screening titles and abstract, and eight systematic review articles were identified for full text review. We included six review articles after excluding two

144 review articles that did not meet inclusion criteria. Our search did not identify articles in
145 any language other than English. The study selection process is illustrated in the PRISMA
146 flow diagram (**Figure A1**).

147 Of the six review articles included, only one article was of high quality (AMSTAR score 8-11),
148 three were of medium quality (scoring 4-7) and two were of low quality (scoring 0-3). The
149 systematic review articles were heterogeneous, varied extensively in population and the
150 intervention type. Three articles included pharmacological treatment for OH in addition to
151 evaluating the non-pharmacological interventions.

152 From the six review articles, we identified 64 primary studies for abstract screening.
153 Following the full-text review of 30 eligible primary studies, we included 11 primary studies
154 in the review (**Figure A1**). Studies were conducted in Europe, USA, Australia, Japan and
155 Israel between 1999 and 2017. Of the 11 included studies, six were observational studies
156 with BAS design and five were RCTs (4 crossover design and one open RCT).

157 Study sample sizes ranged from 8 to 100 participants and took place in various settings
158 including in-patient hospital wards, outpatient ambulatory departments, and community
159 non-clinical areas (i.e. outside of hospital) and research laboratories. None of the studies
160 reported sample size calculations. Studies included patients with various OH types
161 (symptomatic, persistent OH, progressive OH) from various causes of OH. The definition and
162 measurement of OH, and the outcomes reported varied considerably between studies.
163 Characteristics of the included studies are detailed in **Table 1**.

164 Our review identified seven different types of non-pharmacological interventions from 11
165 studies - lower limb compression, abdominal compression, combination therapy of lower
166 limb and abdominal compression, sleeping with head-up (SHU), bolus water drinking, home

based resistance training (HBRT) and multi-component non-pharmacological intervention. Duration of interventions varied from one single time point assessment to a period of 8 weeks. Studies very rarely reported adverse events due to interventions. Based on non-pharmacological therapies that were identified in our review, we categorised the non-pharmacological interventions into two broad categories, compression therapy and others (**Table 2**).

Figure 1 shows the risk of bias assessment of individual studies Risk of bias of the included studies was high in general, not only for the observational studies, but also for the RCTs mainly due to the type of study design. Risk of bias across studies (**Figure A2**) showed that nearly 75% of the studies had non-random sequence generation and lack of allocation concealment. Many of the studies included in this review used either BAS or crossover study design where patients acted as their own control, which limited the blinding of participants. Selective reporting and other types of bias were common in around 50% of the studies.

Effectiveness of non-pharmacological interventions.

Meta-analysis was performed for two non-pharmacological interventions, lower limb and abdominal compression bandage.

Outcome 1: Change is postural systolic BP drop (mmHg) from supine to seating/standing

Meta-analysis was undertaken on three studies comparing lower limb compression with no lower limb compression in 131 participants acting as their own controls (**Figure 2**). There was a significant improvement with lower limb compression (MD -9.83 mmHg, 95% CI -12.56, -7.11).

Three studies comparing abdominal compression with no abdominal compression on 50 participants acting as their own controls were suitable for meta-analyses (**Figure 3)**.This showed statistically significant benefit for abdominal compression therapy (MD -12.30 mmHg, 95% CI -18.20, -6.39).

One study[35] of graduated elastic compression hosiery (GECH) showed short term benefits in improving symptoms of OH. Maximum mean (SD) SBP drop on standing with and without GECH was 24.5 (7.9) and 52.2 (4.4) mmHg, ($p < 0.005$) respectively. Orthostatic dizziness was abolished in 7 out of 10 patients.

One study[36] investigated the combined treatment effect of lower limb and abdominal compression bandage. Initial lower limb compression showed improvement in orthostatic blood pressure on standing (10±5.56 vs 20±6.85 mmHg), but addition of an abdominal bandage showed no added benefit (10±6.17 vs 26 ±6.85 mmHg).

One study[37] evaluated the physiological effects of SHU at 6-inches for 6 weeks but results showed this was ineffective in improving blood pressure or symptoms.

One study[38] evaluated bolus water drinking where patients were asked to take 480 mL of tap water in less than 5 minutes. Seating to Standing SBP 35 minutes before and after bolus water drinking showed positive effect (83 ± 20 mmHg vs 114 ± 30 mmHg, $p<0.01$) in orthostatic blood pressure drop.

One study[39] investigated home-based resistance-training (HBRT), however the mean reduction in SBP drop from supine to standing (36.8±13.4 at week 1 vs 43.8± 3.4 mmHg at week 8, $p>0.05$) did not show any significant improvement in orthostatic blood pressure.

One study[40] evaluated a twelve component non-pharmacological intervention including: increased dietary salt (10–20 g daily); five glasses (250 mL/glass) of water per day; elevated head of bed (10–15 cm); thigh-high 30 mmHg compression stockings; frequent small meals (6 per day); coffee/tea in the morning; no alcohol use; avoiding exposure to hot ambient temperatures; avoiding strenuous early morning activities, sitting on the side of the bed for 30 seconds before rising in the morning; regular moderate intensity exercise (20 minutes three times a week) and avoiding prolonged standing. The multi-component intervention did not improve SBP on standing, though it quantitatively improved OH symptoms in 7 out of 17 participants.

Outcome 2: Efficacy of non-pharmacological interventions in improving OH symptoms.

Our review identified two studies that had reported orthostatic symptoms using a validated questionnaire. One study[36] investigated the effect of lower limb compression stocking in reducing orthostatic symptoms using a 7-item Specific Symptom Scale Questionnaire for Orthostatic Intolerance (SSS-OI) questionnaire[36]. The baseline SSS-OI score of 35.2±12.1 decreased to 22.5±11.3 (p=0.01) after 1 month therapy, indicating significant symptom improvement. Another study[41] compared no abdominal compression with a conventional elastic abdominal binder in 13 patients with neurogenic OH and measured severity of OH symptoms using Orthostatic Symptoms Scale (OSS)[41]. Median baseline OSS score improved from 5.0 points to -0.5 points five minutes after standing with conventional elastic abdominal binder.

Quality of Evidence GRADE quality assessment and summary of evidence

GRADE quality assessment was very low for all the included studies primarily due to the poor study design, small sample size and short term follow up. **Appendix 3** shows the

Summary of Findings table's for lower limb and abdominal compression therapy for outcome 1.

Discussion

This is the first review of systematic reviews to summarize the evidence based recommendations for the non-pharmacological treatment of OH in an older population. Even though our meta-analysis showed statistically significant benefit favouring lower limb and abdominal compression therapy for management of OH in older people, the quality of included studies was very poor. There was substantial clinical heterogeneity among the three studies included for lower limb compression bandage. Two studies assessed the preventive effect from supine to seated OH and one study evaluated the treatment effect using a tilt table study. The lower limb compression pressure varied from 30 to 60mmHg with different pressures applied at different sites in the limbs. Furthermore, treatment duration varied from 5 to 20 minutes. In terms of population characteristics, two studies included OH patients with no specific cause or OH due to various acute conditions and one study included patients with OH due to acute decompensated heart failure.

Similar to lower limb compression, three studies that evaluated abdominal compression therapy showed large differences in the population included, variation in the abdominal compression pressure from 10 to 20 mmHg and in the definition and measurement of OH. Studies also failed to report information on the effect of OH after discontinuation of compression therapy. GRADE quality was therefore downgraded for both LL and abdominal compression therapy despite the meta-analysis showing positive effect size from the pooled estimate. Therefore, we cannot make strong recommendations for use of compression therapy in OH. In addition, caution should be applied in recommending these non-

pharmacological interventions because the lack of reporting of potential adverse effects is a concern. Our results and conclusions regarding the compression therapy are similar to those of Frith[42]. Interestingly, compression therapy has been recommended by two systematic reviews based on limited evidence but the authors recommended further studies due to lack of good quality evidence[43,44]. In addition, a recent study by Newton and Frith suggested disregarding compression therapy in the aging population[45].

Based on the present review, there is no recommendation for any other types of non-pharmacological interventions in older people with OH as evidence was restricted to a single small and poor quality study for each. Although, combination treatment of sleeping head-up with fludrocortisone is frequently used for treating OH, this recommendation is mainly based on results from two studies which have included only younger people i.e. aged 64 years or younger, and small sample sizes[46,47]. Guidelines indicate the quality of evidence for recommending SHU for OH is low[48].

Similar to the finding by Saedon et al[5], we also observed from our review that OH definition, protocol for measuring orthostatic hypotension, and evaluation of postural symptoms varied greatly among studies. This is a most important factor to note as this might have potential impact on the detection of OH, and thereby efficacy of the interventions. In addition, some studies carried out OH measurements in the fasting state but many did not specify. Therefore, it is uncertain whether these studies evaluated for post-prandial hypotension, which is an important and different entity to be considered in the geriatric population.

Adverse events

None of the included studies in our review reported adverse effects of non-pharmacological therapies except two studies which reported that increased fluid intake in OH people aggravated urinary incontinence and hyponatraemia resulting in confusion[40] and more ankle oedema in the intervention arm of the study evaluating SHU[37].

Strengths and weaknesses of the review

We used an international Delphi survey for selecting the most important outcome measures. We performed meta-analyses for lower limb and abdominal compression therapy after contacting authors which, to our knowledge, is the first review to synthesize evidence for the non-pharmacological treatment for OH in older people. Furthermore, the quality of the evidence was assessed systematically by applying the GRADE quality assessment tool. A limitation of our review is that it may have missed important trials that were published after the last systematic review was published. Our review was focused only on older people with OH. Therefore, it is possible that helpful interventions that have not been sufficiently tested in older people were missed. Almost all the studies excluded participants with recent changes in the prescribed therapy or reduced/discontinued vasoactive medications. However, the effects of medications on OH have not always been reported clearly, which is potentially important in multimorbid older people with polypharmacy. Usual measures of OH used in these studies may not be accurate to detect patients at risk[49]. Also, the recommendations from this review might not be applicable to specific populations of patients such as those with OH due to autonomic failure or spinal cord injury. Our review does not consider compliance issues. This may be relevant as Schoffer et al. reported that patients' compliance was lowest (46% in men versus 100% in woman) with OH for

compression stockings amongst the 12 non-pharmacological therapies that they had investigated[40].

Conclusions/implications

Our review found that there is no strong evidence to recommend any of the non-pharmacological therapies for the management of OH. Nevertheless, we make a weak recommendation based on very low quality evidence for lower limb compression and abdominal compression bandage in treating OH in older people. The results of this review also emphasized the necessity to standardize the method of measuring OH.

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Author contributions

SS: Study design, screening, data extraction, data analysis, interpretation of data and drafting and finalising the manuscript for publication

RLS: Study concept and design, data analysis, interpretation of data, and critical review and approval of final version of the manuscript to be published

PKM and KRM: Study concept and design, supervision, and critical review and approval of final version of the manuscript to be published

IB: Study concept and design, data analysis, and critical review and approval of final version of the manuscript to be published

DOM, AJC and AC: Study concept and design, and critical review and approval of final version of the manuscript to be published

SD: Screening, data extraction and analysis

Sponsor's Role: Sponsor did not play any role in the study design, methods, data collection, analysis and preparation of paper.

Conflict(s) of Interest/Disclosures(s)

None.

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463 **Figure legend**

464 **Figure 1.** Risk of bias summary for individual study. Red (-) = high risk of bias, green (+) = low
465 risk of bias and yellow (?) = unclear risk of bias.

466 **Figure 2.** Forest plot showing the meta-analysis of lower limb compression bandage. *Note:*
467 *Patients acted as their controls, therefore the total sample size is 131.*

468 **Figure 3.** Forest plot showing the meta-analysis of abdominal compression binder *Note:*
469 *Patients acted as their controls in all three studies, therefore the total sample size is 50.*

470 **Figure A1**. PRISMA flow diagram of study selection process. SCI: Spinal Cord Injury.

471 **Figure A2.** Risk of bias graph across all included studies.

472

473

474 **Tables**

Table 1. Characteristics of primary studies.

Author	Study design	Setting & Population	Comorbidities & Type of OH	Definition of OH	Method of OH measurement	Further details on OH assessment	Intervention	Results
Lower limb compression bandage								
Gorelik et al 2004[50]	Randomized crossover study (BAS)	In patient study; Passive Seating-induced OH; 61 patients; aged >65 years	Hospitalized for various acute conditions and remain bedridden for at least 36 hours.	Fall of ≥20 mm Hg in SBP or ≥10 mm Hg in DBP on sitting	Digital cuff BP measurement in supine and 1, 3 and 5min following passive seating (unbandaged & bandaged)	In the morning, prior to assuming sitting position. Excluded patients with previously diagnosed OH and hemodynamic instability	Lower limb compression bandages (30 mmHg pressure) applied from ankle to thighs before sitting	Change in mean SBP un-bandaged 17.8 ± 16.8 vs bandaged 5.3 ± 12.0, (p=<0.001); Symptoms significantly reduced in bandaged compared to un-bandaged.
Gorelik et al 2009[51]	Non-randomized, uncontrolled BAS	In patient study; Seating-induced OH; 49 patients; Aged ≥ 60 years	Acute Decompensated heart failure (chronic, NYHA grade II to IV), furosemide-treated patients	Fall of ≥20 mm Hg in SBP and/or ≥10 mm Hg in DBP on sitting from supine	Digital cuff BP measurement in supine and 1, 3 and 5min following passive seating (unbandaged & bandaged)	In the morning, while fasting and before drug administration; After clinical, hemodynamic stabilization & withdrawal of IV medications	Lower limb compression bandage from the ankle to thigh (40mm Hg pressure) before sitting	Mean change in SBP of un-bandaged 18.3 ± 14.1 vs bandaged 10.9 ± 12.7, (p=0.001). OH Symptoms appeared in 22.4% of un-bandaged vs 12.2% of bandaged (p =0.1).
Abdominal compression								
Yamamoto et al 2006[52]	Uncontrolled BAS	In patient study; 25 patients; Mean age: 68.3 ± 10.9	Chronic hemodialysis with intractable post-dialytic	Improvement in mean SBP after HD with the band ≥25mm Hg	SBP at supine and 1min after active standing, measured with and without	Did not eat and did not administer antihypotensive medications during study;	Abdominal compression with an inflatable abdominal band (air bag inflated	Change in mean SBP after HD without band -36.2 ± 18.0 vs with band -19.4 ± 21.2 mm Hg, (p<0.002)

		years	OH (Drop in SBP ≥15 mm Hg upon standing and hypotensive symptoms soon after HD)		band, following 15 rest after HD	Excluded patients with hypervolemia and chronic hypotension	to 20 mm Hg pressure)	
Fanciulli et al 2016[53]	Randomized cross over study	15 patients; Mean age: 69 years (range 66 to 75)	Parkinson's Disease with symptomatic OH	Not defined, calculated mean SBP and DBP changes 3min after head-tilt up and 3min after active standing.	Both tilt-table at 60° and active standing test, using continuous non-invasive BP monitoring (10min supine, 10min head-up tilt, 5min supine & 5min standing)	Assessed OH between 9am to 12pm, excluded patients with changes in medications 6 weeks preceding enrollment and other major neurological conditions	Elastic abdominal binder (20 ± 2 mm Hg pressure) versus Placebo binder (3 ± 2 mm Hg) on the abdominal wall)	Mean difference in SBP between abdominal binder versus placebo was +10 ± 10.2 mm Hg (P= 0.006)
Figueroa et al 2015[41]	Randomized crossover trial	Autonomic Research laboratory; 13 patients; Median age: 72 years	Neurogenic OH with PD, diabetic neuropathy, MSA or other neurological condition associated with autonomic failure	supine to standing (within 5min of standing) drop of ≥30mmHg SBP and ≥15mmHg DBP	Supine to active standing via continuous beat-to-beat arterial BP using plethysmogra-phy	Withheld anticholinergic, α and β adrenergic agonist for at least 5 half-lives prior to the study, midodrine the night before evaluation, permitted Fludrocortisone doses ≤0.2mg/day	Abdominal compression with conventional elastic abdominal binder (10mmHg pressure for 2min) versus no abdominal binder, remained erect for 5min	Change in median SBP with (-50 mmHg; IQR, -33 to -70mmHg) vs without (-57mmHg; IQR -40 to -76 mmHg) abdominal compression

Lower limb compression combined with abdominal compression

Podoleanu et al 2006[36]	Randomized crossover study	21 patients; Mean age: 70 ± 11 years	Symptomatic progressive OH, not mentioned any specific condition/cause of OH	Progressive decrease in BP with occurrence of symptoms during diagnostic tilt testing	Acute-tilt table test at 60° using noninvasive digital cuff SBP measurement in supine and standing 2 min and 10min and 20min head-up tilt or onset of OH symptoms	Not reported	Lower limb compression bandages (40 to 60 mmHg at ankles & 30 to 40 mmHg at hips) for 10min followed by abdominal compression (20 to 30 mmHg) for 10min vs Sham bandage (5mm Hg overall)	Change SBP after active vs sham Lower limb compression: 10±5.56 vs 20±6.85 mmHg and after adding abdominal compression: 10±6.17 vs 26±6.85 mmHg
Lower limb compression hosiery								
Henry et al 1999[35]	Non-randomized BAS	Geriatric falls clinic; 10 patients; Mean age: 77.2 years; (range 62 to 89)	Persistent (reproducible) symptomatic OH with H/o falls	Sustained drop in SBP of >20 mm Hg (average SBP over the whole 3 min) from supine to standing	Continuous BP reading in 3min supine and 3min passive head up tilt to 90°using digital BP device	Studied each patient least 2 hours after breakfast or lunch	Graduated Elastic Compression Hosiery (GECH), 20–30 mmHg pressure at ankles	Maximum mean SBP without 52.2 (4.4) vs with GECH 24.5 (7.9) mmHg, (p <0.005). orthostatic dizziness was abolished in 7 out of 10 patients
Sleeping-head-up (SHU)								
Fan et al 2011[37]	Open Randomized Controlled Trial	Community dwelling, 100patient; aged ≥ 60 years	OH from all cause	symptomatic OH according to consensus criteria	24hr ABPM & phasic beat-to-beat digital Photoplethys-mography during 5min supine rest & at 2min active standing	Patients performed active stands between 9 and 11 hours; Increased water intake to at least 2 litres a day; Reduction or discontinuation of	SHU at 6 inches versus no head elevation during sleep for 6 weeks	No significant difference in standing SBP, DBP or MAP and symptoms before or after the intervention between groups.

						medications that lower BP at least a month prior to study		
Bolus water drinking								
Shannon et al 2002[38]	BAS	11 patients; Mean age 69.8 years (range 54 to 83)	Severe OH due to primary autonomic failure (Pure autonomic failure & MSA)	Severe OH, No OH criteria defined	Seating BP (every 5 min for 30min) and upright standing BP at 1min using automated brachial BP cuff	Discontinue vasoactive medications & fludrocortisone at least 5 half-lives prior to study, To consume diet containing 150 mmol of sodium and 70 mmol of potassium for at least 3 days before, and not to drink for at least 1.5 hours before testing, Assessed OH at least 2.5 hours after breakfast or lunch	480 mL of bolus water (tap) drinking at room temperature (20° C) in less than 5 minutes. Measured standing BP 35min after bolus water drinking	Standing SBP before and 35min after bolus water drinking was 83±20 vs 114±30 mmHg, (p<0.01); Tolerated standing time improved from 5±3min to 11±10min in 6patients
Home-based resistance-training								
Zion et al 2003[39]	Non-randomised, BAS	8 patients; Median age 73.5 years (range 63 to 81)	No specific cause for OH mentioned	Decrease in SBP of >20 mm Hg or DBP of >10 mm Hg within 3min	Abbreviated title table test after 12-15min of supine rest, and head-up tilt to 60° for 20 min	Overnight fasting, Not to consume caffeinated products within 4 hours of testing, No exercise	Various HBRT exercises using elastic resistance bands (5–8 min of a warm-up, 25 minutes of	Mean change in SBP at week 1 and 8 was 36.8±13.4 vs 43.8±13.4 mmHg, not significant.

				of standing		performed 24 hours prior to testing, refrain from taking midodrine morning dose.	strengthening & 5 min of cool-down/stretching exercises, every other day (4day/week) for 8 weeks	
Multi-component non-pharmacological therapy								
Schoffer et al 2007[40]	BAS	17 Clinic patients; mean age: 69±11 years	OH in patients with idiopathic Parkinson's Disease	Fall of ≥20 mm Hg in SBP and/or ≥10 mm Hg in DBP within 3min of standing	Bedside postural BP testing via automatic sphygmoman-ometry by a physician in supine and standing 1 and 3min	Sustained response to medications, held stable throughout study; Excluded patients with ACS and severe hypertension	12 different types of multi-component non-pharmacological intervention	Multi-component non-pharmacological therapy did not significantly alter the drop in SBP on standing. Quantitatively, 7 of 17 patients noted an improvement in OH symptoms.

OH: Orthostatic hypotension; BAS: before-and-after study; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BP: Blood Pressure; NYHA: New York Heart Association; HD: Haemodialysis; PD: Parkinson's Disease; MSA: Multiple System Atrophy; IQR: Inter Quartile Range; GECH: Graduated Elastic Compression Hosiery; SHU: Sleeping with Head-Up; ABPM:; Ambulatory Blood Pressure Monitor; MAP: Mean Arterial Pressure; HBRT: Home-based resistance-training; ACS: Acute Coronary Syndrome.

Table 2. GRADE Quality of evidence for the various non-pharmacological interventions.

Intervention category	Intervention subtype	No. of studies	GRADE score
Compression therapy	Lower limb compression bandage	3	Very low
	Abdominal compression	3	Very low
	Lower limb combined with abdominal compression	1	Very low
	Lower limb compression with graduated elastic compression hosiery	1	Very low
Others	Sleeping-head-up at 6 inches	1	Very low
	Bolus water drinking (480ml of tap water in <5minutes)	1	Very low
	Home-Based Resistance Training program	1	Very low
	Multi-component non-pharmacological therapy	1	Very low

Figures

Figure 1. Risk of bias summary for individual studies. Red (-) = high risk of bias, green (+) = low risk of bias and yellow (?) = unclear risk of bias.

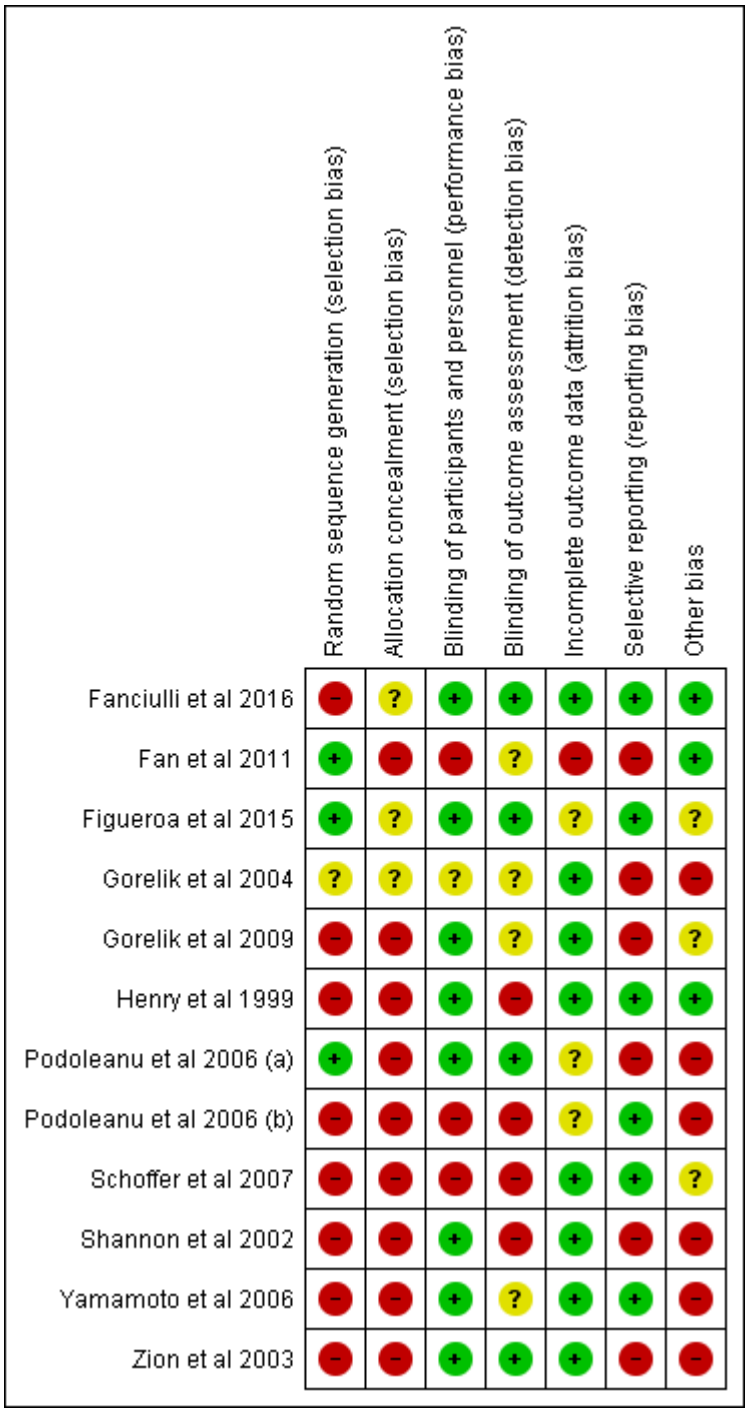


Figure 2. Forest plot showing the meta-analysis of lower limb compression bandage. *Note: Patients acted as their controls, therefore the total sample size is 131.*

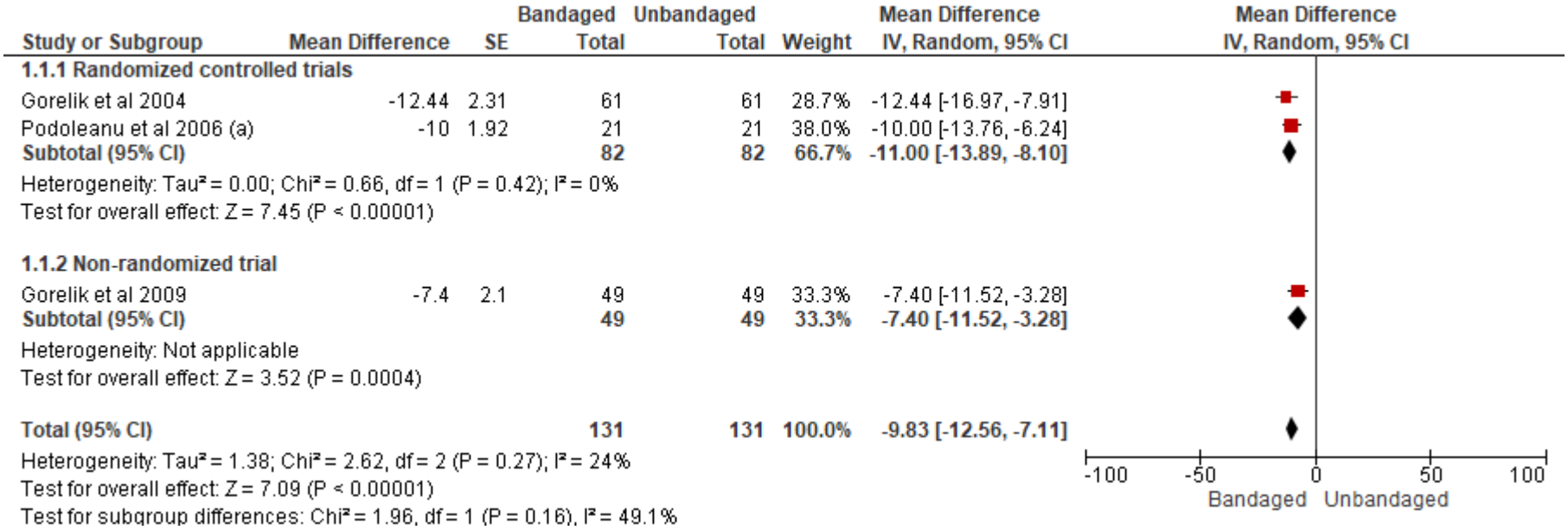
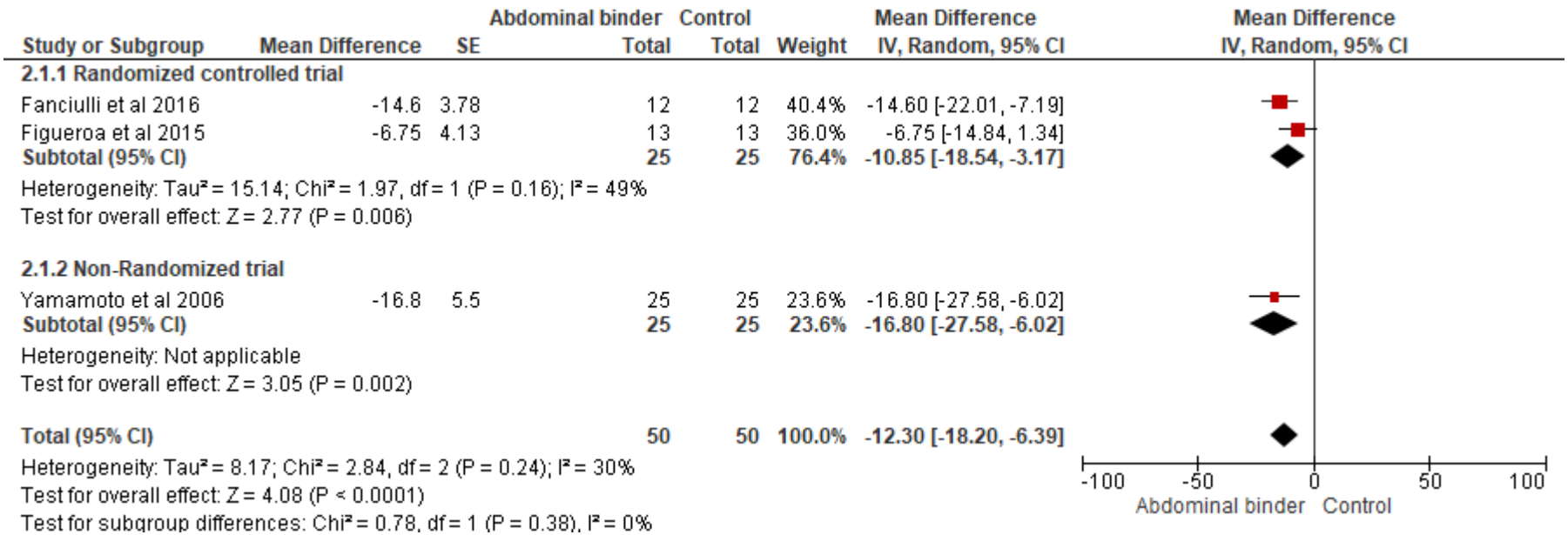


Figure 3. Forest plot showing the meta-analysis of abdominal compression binder *Note: Patients acted as their controls in all three studies, therefore the total sample size is 50.*



506 **Appendices**

507 Appendix 1: PRISMA flow diagram

508 Appendix 2: Risk of bias across studies

509 Appendix 3**:** GRADE Summary of Findings tables for LL and abdominal compression bandage.

Response to Reviewers

Manuscript Reference Number: JAMDA-D-19-00103

Title: Non-Pharmacological management of Orthostatic Hypotension in older people: A systematic review. The SENATOR ONTOP series.

Editor's comments

1. **A good study, but long and needing some tightening up.**

   Thank you for this comment. We have tried our best in reducing the length of the manuscript.

2. **Abstract: when you say "compression therapy" please discuss relative value of abdominal versus lower limb compression.**

   We have now revised the results section of the abstract (**line 19**) to indicate the relative effects of abdominal versus lower limb compression.

3. **Introduction and Discussion - please provide a more broad discussion of treatment approaches to orthostatic hypotension, including identifying medication adjustment (include a list of medications most linked to OH), to help put this topic into context.**

   We updated the introduction (**lines 44-46 and line 56**) and discussion (**line 310**) to provide information on the potential medications that commonly cause OH.

4. **Table 2 - just spell out lower limb everywhere instead of creating an abbreviation.**

   We removed the abbreviation and have now spelled out as 'lower limb'

5. **The PRISMA flow diagram was blank, probably because you have a white font on a white background.**

   We changed the font colour of the PRISMA diagram to 'black'.

6. **Move Figures 1 and 2a to the appendix.**

   We moved Figures 1 and 2a to the appendix and renamed as Figure A1 and Appendix A2 respectively.

7. **Delete Appendices 1 and 2.**

   We deleted the Appendices 1 and 2 and updated the appendices with new list of appendices.

8. **RE reviewer 2 comment 1 --no need to spend too much time on measurement, other than to acknowledge that it is important.**

Thank you for your feedback. We have indicated this in the discussion section (**line 288**) and updated Table 1 where information was available.

Reviewers' comments

Reviewer #1

This is an excellent study. I concur with the conclusions.

Thank you very much for providing such a great comment. We really appreciate your positive feedback.

Reviewer #2

1. **A very important topic, no doubt. Rightfully you have stated that as it is a review of prior studies much information is hard to provide.**

   Thank you for this comment. We agree that, since we are limited to what prior studies report, it is sometimes challenging or impossible to provide the information the reviewer requests below. We have attempted to balance completeness with the Editor's request for brevity as the manuscript is already lengthy.

2. **Nevertheless, when we discuss orthostatic hypotension, there are several basics that need addressing. How was the BP taken: manual or digital? Were the readings are 1 min, 3 mins or both, from supine to sitting or standing?**

   We agree that some of the basic details around measurement can have an important impact on results. Where possible, we provide additional comments on orthostatic blood pressure measurements in Table 1. We now also include a general comment on the potential impact of these details on the results in the discussion (**line 288**).

3. **Was there a relation to meals? The topic of post-prandial hypotension is important and a different entity.**

   Some studies involved measurements in the fasting state but many did not specify. Where possible, we provide additional details in Table 1, and a general comment in the discussion section (**line 292**).

4. **How often was there a benefit to the patient following the discontinuing or reduction in dose of medications? I believe medication effect is very relevant.**

   We agree that medication effects are potentially important but studies tended to exclude participants with recent changes in prescribed therapy or reduced/discontinued vasoactive medications that may affect their BP readings prior to the study. Where information on this was available, this is now shown in Table 1. This is also addressed in a general comment in the limitations section (**line 310**).

5. **What was the duration of therapy for the compression devices? If it was 8 weeks, did the orthostasis tend to recur after discontinuing the compression therapy?**

   On Line **264**, we explain that duration of therapy ranged from 5 to 20 minutes only. Information on the effect after discontinuation is not available. We now add a comment in the discussion to alert readers to this important point (**line 270**).

6. **Was there an attempt to look at the influence of change in meals (less carbohydrates), admn. of caffeine (coffee) after meals and the basic salt intake. This important approach is briefly discussed (lines 230 to 238) and could be elaborated.**

   As reported, we found only one study of a multi-component intervention that included modulation of meals and salt intake. Based on the limited evidence base on older people and the need for brevity, we did not feel we should elaborate further.

7. **If water intake was a means, did you look at foot elevation during the day or at nite?**

   The single study on bolus water drinking did not also include foot elevation.

8. **How did you remove the influence of disorders with autonomic neuropathy (diabetes mellitus, Parkinsons disease)?**

   The influence of autonomic neuropathy could not be fully excluded in the included studies, though this was usually mitigated by the participants acting as their own controls and through use of randomisation.

Supplementary Material

Click here to download Supplementary Material: Supplementary material-revised-Mar 2019.docx

Figure1

Click here to download high resolution image

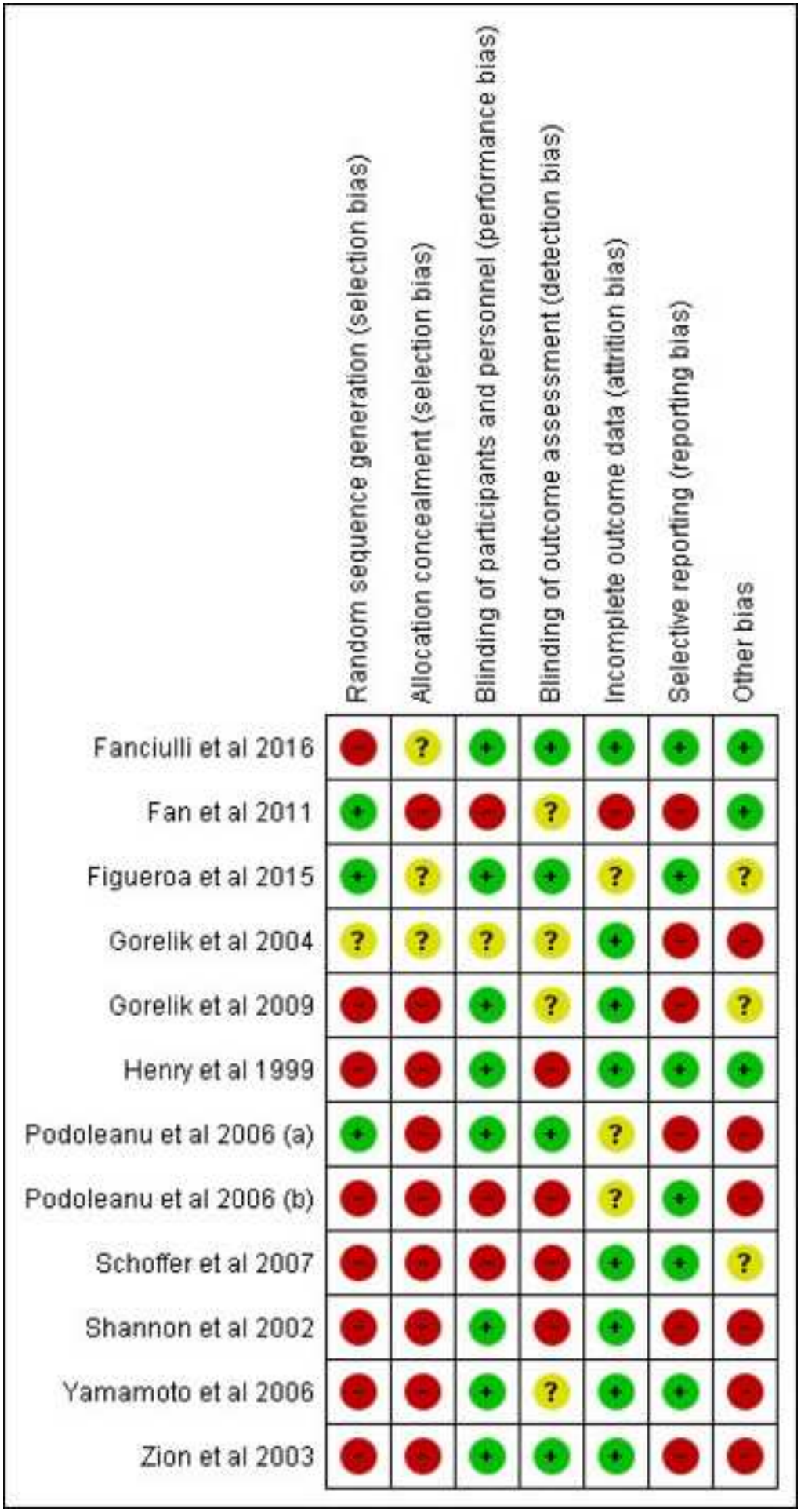


Figure2

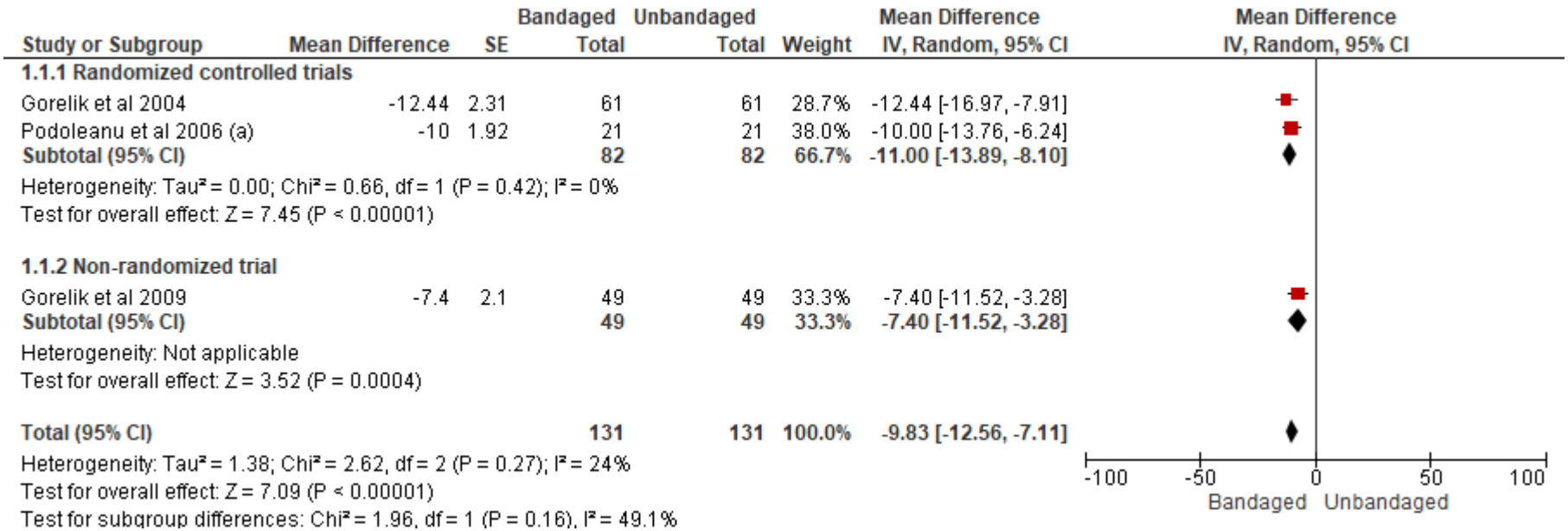
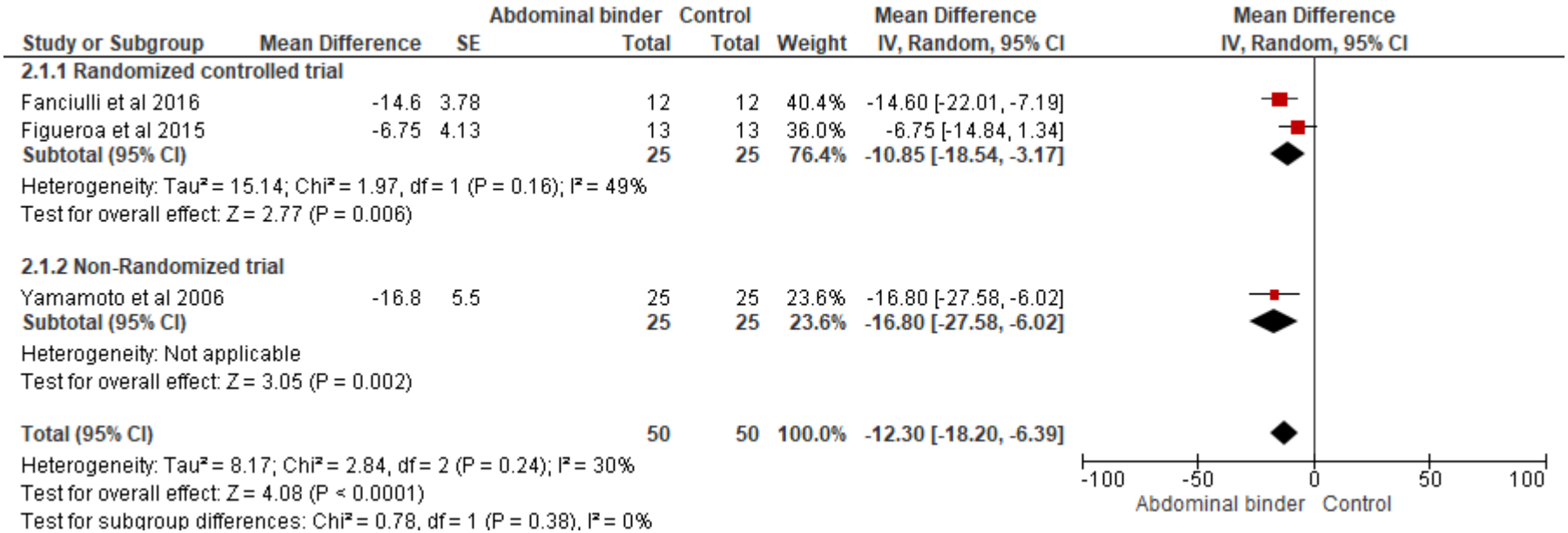
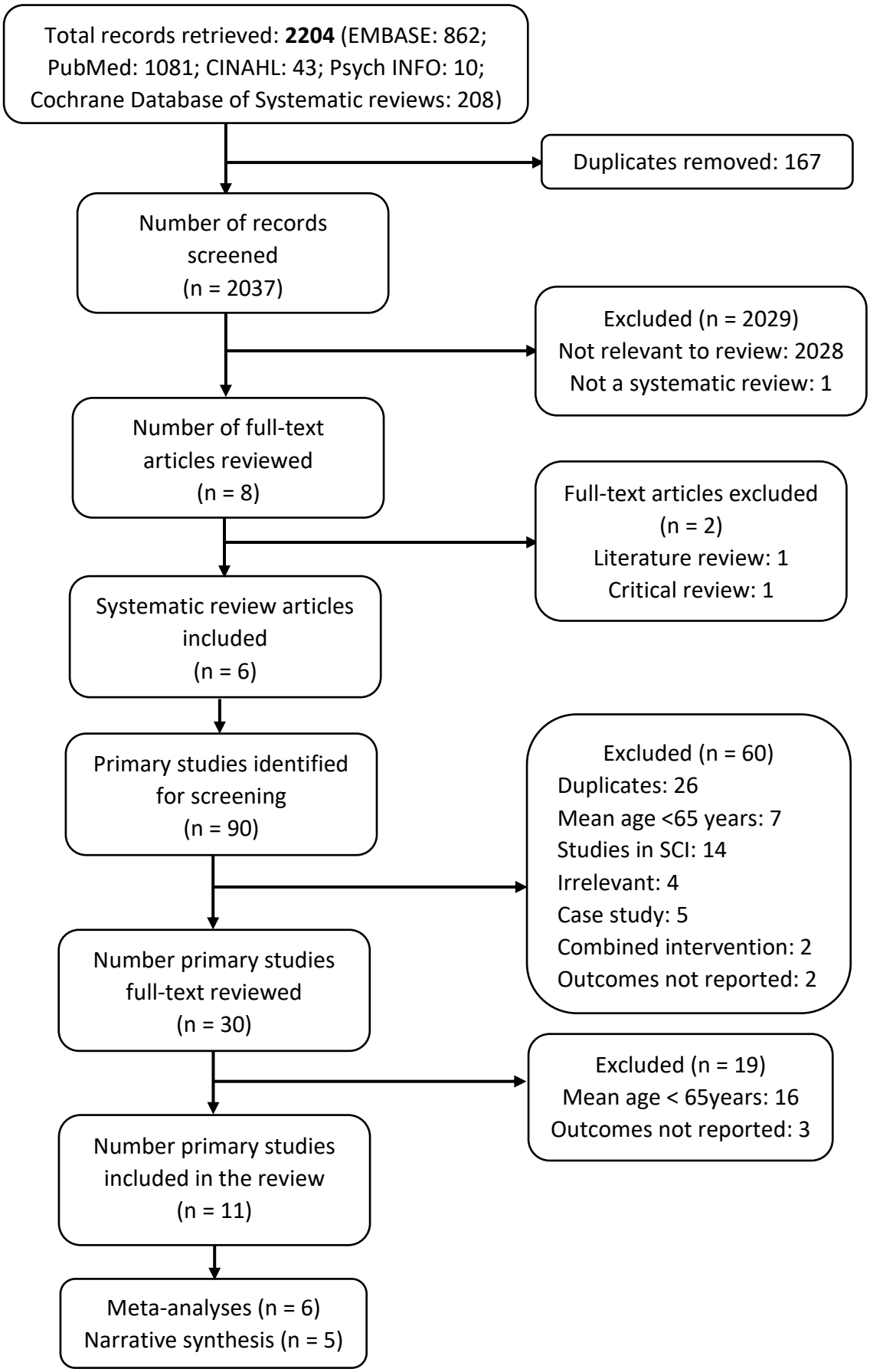

Bandaged
Unbandaged
Mean Difference
Mean Difference
Study or Subgroup
Mean Difference
SE
Total
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Randomized controlled trials
Gorelik et al 2004 -12.44 2.31 61 61 28.7% -12.44 [-16.97, -7.91]
Podoleanu et al 2006 (a) -10 1.92 21 21 38.0% -10.00 [-13.76, -6.24]
Subtotal (95% CI) 82 82 66.7% -11.00 [-13.89, -8.10]
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 7.45 (P < 0.00001)
1.1.2 Non-randomized trial
Gorelik et al 2009 -7.4 2.1 49 49 33.3% -7.40 [-11.52, -3.28]
Subtotal (95% CI) 49 49 33.3% -7.40 [-11.52, -3.28]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.52 (P = 0.0004)
Total (95% CI) 131 131 100.0% -9.83 [-12.56, -7.11]
Heterogeneity: Tau² = 1.38; Chi² = 2.62, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 7.09 (P < 0.00001)
Test for subgroup differences: Chi² = 1.96, df = 1 (P = 0.16), I² = 49.1%
-100
-50
0
50
100
Bandaged
Unbandaged

Figure3


Abdominal binder
Control
Mean Difference
Mean Difference
Study or Subgroup
Mean Difference
SE
Total
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
2.1.1 Randomized controlled trial
Fanciulli et al 2016 -14.6 3.78 12 12 40.4% -14.60 [-22.01, -7.19]
Figueroa et al 2015 -6.75 4.13 13 13 36.0% -6.75 [-14.84, 1.34]
Subtotal (95% CI) 25 25 76.4% -10.85 [-18.54, -3.17]
Heterogeneity: Tau² = 15.14; Chi² = 1.97, df = 1 (P = 0.16); I² = 49%
Test for overall effect: Z = 2.77 (P = 0.006)
2.1.2 Non-Randomized trial
Yamamoto et al 2006 -16.8 5.5 25 25 23.6% -16.80 [-27.58, -6.02]
Subtotal (95% CI) 25 25 23.6% -16.80 [-27.58, -6.02]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.05 (P = 0.002)
Total (95% CI) 50 50 100.0% -12.30 [-18.20, -6.39]
Heterogeneity: Tau² = 8.17; Chi² = 2.84, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 4.08 (P < 0.0001)
Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%
-100
-50
0
50
100
Abdominal binder
Control

FigureA1


Total records retrieved: **2204** (EMBASE: 862; PubMed: 1081; CINAHL: 43; Psych INFO: 10; Cochrane Database of Systematic reviews: 208)
Duplicates removed: 167
Number of records screened (n = 2037)
Excluded (n = 2029)
Not relevant to review: 2028
Not a systematic review: 1
Number of full-text articles reviewed (n = 8)
Full-text articles excluded (n = 2)
Literature review: 1
Critical review: 1
Systematic review articles included (n = 6)
Primary studies identified for screening (n = 90)
Excluded (n = 60)
Duplicates: 26
Mean age <65 years: 7
Studies in SCI: 14
Irrelevant: 4
Case study: 5
Combined intervention: 2
Outcomes not reported: 2
Number primary studies full-text reviewed (n = 30)
Excluded (n = 19)
Mean age < 65years: 16
Outcomes not reported: 3
Number primary studies included in the review (n = 11)
Meta-analyses (n = 6)
Narrative synthesis (n = 5)

FigureA2

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