



Increased Salt Intake for Orthostatic Intolerance Syndromes: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: Guidelines recommend increased salt intake as a first-line recommendation in the management of symptomatic orthostatic hypotension and recurrent syncope. There have been no systematic reviews of this intervention. We sought to summarize the evidence for increased salt intake in patients with orthostatic intolerance syndromes.

METHODS: We conducted a systematic review and meta-analysis of studies in PubMed, EMBASE, and CINAHL. Interventional studies that increased salt intake in individuals with orthostatic intolerance syndromes were included. Primary outcome measures included incidence of falls and injuries, and rates of syncope and presyncope. Secondary outcome measures included other orthostatic intolerance symptoms, blood pressure, and heart rate.

RESULTS: A total of 14 studies were eligible, including participants with orthostatic hypotension, syncope, postural orthostatic tachycardia syndrome, and idiopathic orthostatic tachycardia (n = 391). Mean age was 35.6 (± 15) years. All studies were small and short-term (<60 mins-90 days). No study reported on the effect of increased salt intake on falls or injuries. Meta-analysis demonstrated that during head-up tilt, mean time to presyncope with salt intake increased by 1.57 minutes (95% confidence interval [CI], 1.26-1.88), mean systolic blood pressure increased by 12.27 mm Hg (95% CI, 10.86-13.68), and mean heart rate decreased by -3.97 beats per minute (95% CI, -4.08 to -3.86), compared with control. Increased salt increased supine blood pressure by 1.03 mm Hg (95% CI, 0.81 to 1.25). Increased salt intake resulted in an improvement or resolution of symptoms in 62.3% (95% CI, 51.6 to 72.6) of participants in short-term follow-up studies (mean follow-up of 44.3 days, 6 studies; n=91). Methodological quality of studies were low with high statistical heterogeneity in all meta-analyses.

CONCLUSIONS: Our meta-analysis provides low-quality evidence of a short-term improvement in orthostatic intolerance with increased salt intake. There were no clinical trials demonstrating the efficacy and safety of increased salt intake on long-term clinical outcomes. Overall, there is a paucity of clinical trial evidence to support a cornerstone recommendation in the management of orthostatic intolerance syndromes.

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KEYWORDS: Falls; Orthostatic hypotension; Orthostatic intolerance; Salt; Syncope

Funding: This work was supported by a European Research Council - Horizon 2020 grant. CSJ was supported by the Irish Clinical Academic Training (ICAT) Programme, the Wellcome Trust and the Health Research Board (grant number 203930/B/16/Z), the Health Service Executive, National Doctors Training and Planning, and the Health and Social Care, Research and Development Division, Northern Ireland.

Conflicts of Interest: None.

Authorship: All authors had access to the data and a role in writing this manuscript.

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INTRODUCTION

Orthostatic hypotension is defined as a sustained fall in systolic blood pressure of a least 20 mm Hg or a fall in diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing.¹ Orthostatic hypotension is a common condition affecting 18.4% of community-dwelling older adults and 22.2% of adults in long-term care facilities.² However, prevalence varies across studies. It can be a debilitating disorder with an increased risk of falls, major injury, and increased morbidity and mortality.^{3,4} Management of this condition is challenging, with many therapies having adverse side effects, including supine hypertension.⁵

Increased salt intake is a cornerstone recommendation in the management of orthostatic intolerance syndromes across clinical guidelines,^{6–11} including a Class I (Level C) recommendation in the European Society of Cardiology-Treatment of Syncope: Orthostatic Hypotension guidance.⁶ However, guidelines vary on the amount of salt recommended (6-10 g/d), none reference clinical trial evidence to support this recommendation, and some include

statements regarding the uncertain benefits and risks of long-term treatment with high salt intake (Table 1). Conversely, hypertension and cardiovascular prevention guidelines recommend low salt intake (<5 g/d).¹²

Accordingly, an estimate of the net benefit of increased salt intake in patients with orthostatic hypotension/intolerance syndromes is required.¹³ To address this gap, we performed a systematic review and meta-analysis to determine the effectiveness and safety of increased salt intake among patients with orthostatic intolerance syndromes.

METHODS

Objectives

We aimed to synthesize the evidence of the efficacy and safety of increased salt intake as a therapeutic intervention in patients with orthostatic intolerance syndromes.

Preparing Our Systematic Review

We adhered to the *Cochrane Handbook for Systematic Reviews of Interventions*.¹⁴ The review protocol was registered with PROSPERO, CRD42019121330.

CLINICAL SIGNIFICANCE

- In patients with orthostatic intolerance syndromes, systematic review and meta-analysis showed that increased salt intake causes a short-term increase in blood pressure and time to presyncope during orthostasis.
- Increased salt intake improved symptoms of orthostatic intolerance in short-term studies.
- There is no report on the effect of long-term increased salt intake on falls or cardiovascular risk. Studies are short-term, small, and of low methodological quality.

Table 1 Guidelines on the Management of Orthostatic Intolerance Syndromes*

Guideline	Recommendation
European Society of Cardiology, 2018: Guidelines for the diagnosis and management of syncope ⁶	Orthostatic Hypotension/Orthostatic Intolerance: 2-3 L of fluids and 10 g of sodium chloride per day.
American Journal of Cardiology, 2017: ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope ⁷	Vasovagal Syncope or Neurogenic Orthostatic Hypotension: 6-9 g (100-150 mmol) of salt per day (Class IIb recommendation).
The National Institute for Health and Care Excellence (NICE), 2015: Orthostatic hypotension due to autonomic dysfunction: midodrine ⁸	Increased water and salt ingestion (no guidance on amount).
American Society of Hypertension (ASH) Guidelines, 2013: ASH Position Paper: Evaluation and Treatment of Orthostatic Hypotension ⁹	6-10 g of sodium chloride and 1.5-2 L of water per day.
American Family Physician, 2011: Evaluation and Management of Orthostatic Hypotension ¹⁰	Sodium may be supplemented by adding extra salt to food or taking 0.5- to 1.0-g salt tablets. A 24-h urine sodium level can aid in treatment. Patients with a value <170 mmol per 24 hours should be placed on 1-2 g of supplemental sodium 3 times per day and be re-validated in 1-2 weeks, with the goal of raising urine sodium to between 150 and 200 mEq.
The European Federation of Neurological Societies (EFNS), 2006: Guidelines on the diagnosis and management of orthostatic hypotension ¹¹	At least 8 g (150 mmol) of sodium chloride per day.

*Table shows the available guidelines on the management of orthostatic intolerance syndromes. The major guidelines are listed in the left-hand column and the specific recommendation on the right.

Search Strategy and Selection Criteria

We searched PubMed, EMBASE, and CINAHL databases from database inception to January 17, 2019. We also searched the bibliographies of retrieved review articles from PubMed to identify additional relevant papers. Reviewers independently screened titles and abstracts using the Rayyan web software.¹⁵ Following this, full-text articles were assessed for eligibility, and disagreements were resolved by consensus.

Eligibility Criteria

Studies were eligible if they included patients with orthostatic hypotension, falls, syncope or presyncope resulting from orthostatic intolerance, or reflex syncope. We also included postural orthostatic tachycardia syndrome and orthostatic tachycardia due to the similarities in treatment with orthostatic hypotension, thereby including a diverse group of orthostatic intolerance syndromes.¹⁶ The intervention of interest was increased salt intake in the form of oral salt supplementation or intravenous saline infusion. Studies required either a placebo or alternative control group (or period) and at least 1 of the following outcome measures: rate of falls or injuries; rate of syncope or presyncope; change in symptoms; change in orthostatic intolerance; change in supine or orthostatic systolic blood pressure; change in supine or orthostatic heart rate; or adverse effects. We included all interventional clinical studies of human participants published in peer-reviewed journals in English.

Data Extraction and Measurements

Data were extracted by reviewers independently in an unblinded fashion, using a predetermined standardized data extraction form. Our primary outcome measures were the effect of salt on falls or injuries and rates of syncope or presyncope. Secondary outcome measures included the effect of increased salt intake on symptoms and other measures of orthostatic intolerance, the effect on physiological parameters including changes in blood pressure and heart rate, and the adverse effects of increased salt intake.

Quality Assessment and Publication Bias

The quality of the evidence and recommendations of the included studies were assessed using the GRADE guidelines and rated as very low, low, moderate, or high-quality.¹⁷

Data Synthesis and Statistical Analysis

We collected descriptive data for a Characteristics of Studies table. The standardized mean difference (SMD) associated with increased salt intake was calculated for head-up tilt orthostatic tolerance or time to presyncope, seated or supine systolic blood pressure, and seated or supine heart rate. The mean difference following intervention was calculated for head-up tilt/standing systolic blood pressure, and head-up tilt/standing heart rate. The effect of the intervention on symptoms of orthostatic intolerance, and adverse

effects were recorded. Weighted pooled treatment effects were calculated using a fixed effects (FE) model.¹⁸ The variability across studies as a result of heterogeneity was estimated with the test for heterogeneity (I^2) statistic. Statistical analysis was performed using the Metafor package on R Statistical Software (V3.4.3).¹⁹

RESULTS

Study Selection

Our initial search retrieved 1168 articles. Following review, 14 studies^{20–31} including 391 participants satisfied full eligibility criteria; see the meta-analyses of observational studies in epidemiology (MOOSE) flow diagram (Supplementary Figure S1, available online).

Description of Included Studies

We included 11 single-arm interventional studies, 1 randomized double-blind placebo-controlled trial, 1 randomized crossover trial, and 1 open-label randomized trial. We report characteristics of included studies in Table 2.

A variety of methods were used to investigate the effect of increased salt intake on blood pressure. Ten studies ($n = 322$) used a head-up tilt method, 2 used an active stand ($n = 33$), and 2 assessed seated or supine blood pressure only ($n = 36$). The method of carrying out a head-up tilt differed across studies (Supplementary Table S1, available online).

Characteristics of Participants

Eleven studies included adults ($n = 302$), and 3 included children ($n = 89$). Mean age was 35.6 (± 15) years (range: 11–65), and 60.1% were female. Participants had a history of syncope or near-syncope (73.6%); orthostatic intolerance, orthostatic hypotension or orthostatic tachycardia (16.9%); postural orthostatic tachycardia syndrome (6.9%); 2.6% were healthy participants. Most studies excluded patients with comorbidities, and some stopped pre-existing medications ($n=99$) (Supplementary Table S2, available online).

Intervention

Increased salt intake was achieved through oral intake in 11 studies (table salt or slow sodium tablets) (range 1.2–10.5 g) and intravenously in 3 studies, using a saline infusion (6.3–9 g). Three studies included a control group. All other studies compared to a control period before salt intervention.

Four studies assessed the immediate effect of increased salt intake ($n=84$, <60 minutes), 4 studies reported the effect over days ($n=118$, 3–10 days), and 6 studies evaluated the effect over weeks ($n=189$, 30–90 days). Mean follow-up was 26.9 days (range 0–90) (Table 2).

Table 2 Characteristics of Included Studies*

Author	Year	Sample Size	Design	Participants	Active	Control [†]	Follow-Up
Mangru	1995	50	Single-Arm Trial	Syncope	6.3 g NaCl	Before Salt	<1 day
El-Sayed	1996	11	Single-Arm Trial, Open	Syncope	7 g NaCl	Before Salt	56 days
El-Sayed	1996	20	Randomized, Double-Blind Placebo Controlled	Syncope	7 g NaCl	Placebo	56 days
De Lorenzo	1997	22	Single-Arm Trial	Orthostatic Hypotension	1.2 g NaCl	Before Salt	56 days
Jacob	1997	13	Single-Arm Trial	Orthostatic Hypotension	9 g NaCl	Before Salt	<1 day
Mtinangi	1998	6	Single-Arm Trial	Orthostatic Hypotension	7 g NaCl	Before Salt	3 days
Mtinangi	1998	6	Single-Arm Trial	Orthostatic Hypotension	7 g NaCl	Before Salt	7 days
Pechère-Bertschi	1998	20	Single-Arm Trial	Orthostatic Hypotension	6 g NaCl	10 Healthy Patients	8 days
Burklow	1999	12	Single-Arm Trial	Syncope	9 g NaCl	Before Salt	<1 day
Cooper	2002	98	Single-Arm Trial	Syncope	6.1 g NaCl	Before Salt	90 days
Claydon	2004	11	Single-Arm Trial	Syncope	6 g NaCl	Before Salt [†]	60 days
Raj	2006	9	Randomized, Crossover Trial	Orthostatic Hypotension	2 g NaCl	473 mL Distilled Water	<1 day
Bellard	2007	86	Randomized, Open Trial	Syncope	1.5 g NaCl	Control Group	10 days
Zhang	2012	27	Single-Arm Trial	Postural Orthostatic Tachycardia Syndrome	10.5 g NaCl for 70 kg	Before Salt	30 days

*Table showing characteristics of included studies. Author name is listed in the first column, followed by year of publication, sample size, study design, participants studied, active arm, control period/group, and length of follow-up.

[†]Control period before intervention with salt.

NaCl = Sodium Chloride.

Primary Outcomes

Effect of Salt Intake on Falls or Injuries. No study reported on the effect of increased salt intake on the rate of falls or injuries.

Effect of Salt Intake on Orthostatic Tolerance and Time to Presyncope. Five studies reported data that were amenable to meta-analysis. Pooled analysis of these 5 studies ($n = 164$; syncope [$n = 152$] and orthostatic hypotension [$n = 12$]) showed higher salt intake increased orthostatic tolerance or time to presyncope by 1.57 minutes (95% confidence interval [CI], 1.26-1.88) $I^2 = 97.2\%$ (Figure 1). A pooled analysis looking at individual populations (i.e., syncope vs orthostatic hypotension) was not possible because of low study numbers.

Secondary Outcomes

Effect of Increased Salt Intake on Symptoms of Orthostatic Intolerance. Among studies reporting on orthostatic intolerance symptoms following increased salt intake (6 studies, 91 participants), 62.3% (95% CI, 51.6 to 72.6), $I^2 = 97.2\%$, reported improvement (or resolution) in symptoms after a mean follow-up of 44.3 days. No study reported on symptoms beyond 60 days. In the only randomized placebo controlled trial ($n=20$) reporting on symptoms, symptomatic improvements were reported in 8/10 in the salt supplement group and 3/10 in the placebo group, relative risk (RR) 2.67 (95% CI, 0.98 to 7.22) after 8 weeks. One study used a questionnaire which was reported to be of demonstrated validity and reliability,²⁰ and 1 study used the Fatigue Impact Scale.³⁰

Changes in Physiological Parameters. Effect of Increased Salt Intake on Mean Change in Supine Blood Pressure.

Pre- and post-intervention seated or supine systolic blood pressure was reported in 6 studies, which were amenable to meta-analysis ($n=174$; orthostatic hypotension or orthostatic tachycardia [$n = 28$], syncope [$n = 119$], postural orthostatic tachycardia syndrome [$n = 27$]). Increased salt intake was associated with a small increase in seated or supine systolic blood pressure: 1.03 mm Hg (95% CI, 0.81-1.25), $I^2: 92.8\%$ (Figure 2).

Effect of Increased Salt Intake on Mean Difference in Mean Change of Head-up Tilt or Standing Systolic Blood Pressure. Mean change in head-up tilt or standing systolic blood pressure before and after increased salt intake was reported for 3 studies ($n=45$; syncope [$n = 12$], orthostatic hypotension [$n = 33$]). Thus, as a result of low trial numbers, this precluded separating based on individual intolerance syndromes. Looking at individual studies, Jacob studied a population with orthostatic intolerance and demonstrated an increase in systolic blood pressure of 11 mm Hg;³¹ Pechère-Bertschi studied an orthostatic hypotension population and recorded an increase of 12.8 mm Hg;²⁴ and Burklow studied a population with unexplained syncope and found a larger increase of 19.3 mm Hg.²³ Pooled analysis across these syndromes demonstrated that following increased salt intake, there was a 12.27 mm Hg increase in the mean change in head-up tilt or standing systolic blood pressure (95% CI, 10.86-13.68), $I^2: 74.1\%$ (Figure 3).

Effect of Increased Salt Intake on Mean Change in Seated or Supine Heart Rate. Mean change in seated or supine

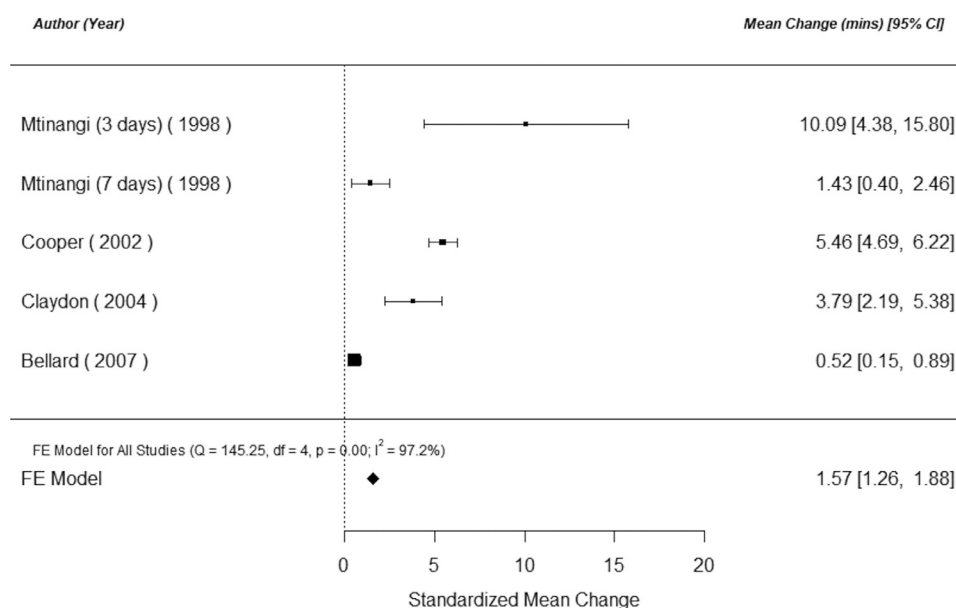


Figure 1 Forest plot of standardized mean change in head-up tilt orthostatic tolerance/time to presyncope following administration of salt. Forest plot showing the effect of salt intervention during head-up tilt on orthostatic tolerance/time to presyncope, $n=164$. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, and the size of the squares reflects the weight of the studies. The combined effect appears as a diamond and the vertical dashed line represents the line of no effect.

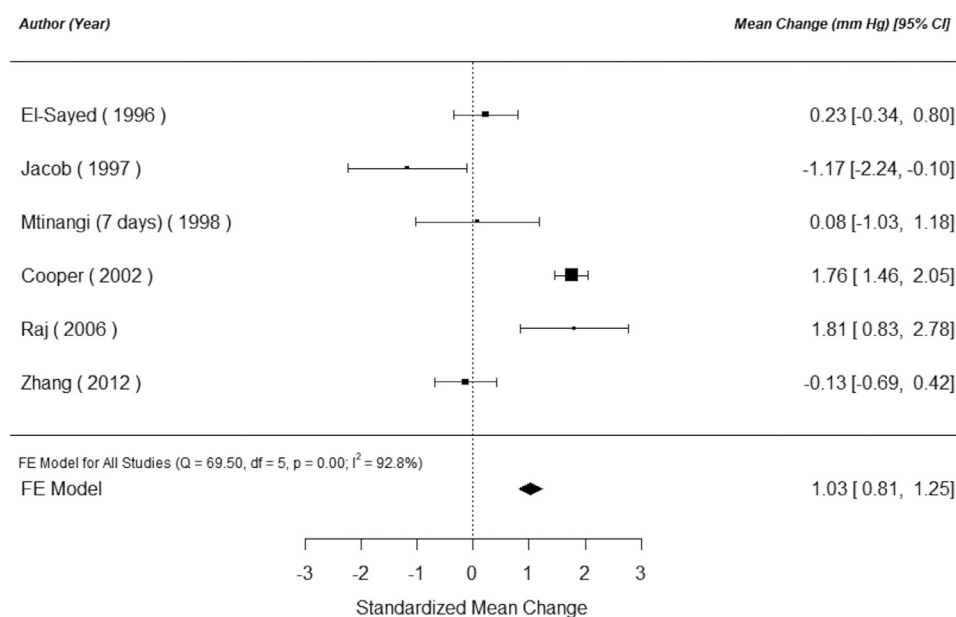


Figure 2 Forest plot of standardized mean change in seated or supine systolic blood pressure following administration of salt. Forest plot showing the effect of salt intervention on seated or supine systolic blood pressure, $n=174$. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, and the size of the squares reflects the weight of the studies. The combined effect appears as a diamond and the vertical dashed line represents the line of no effect.

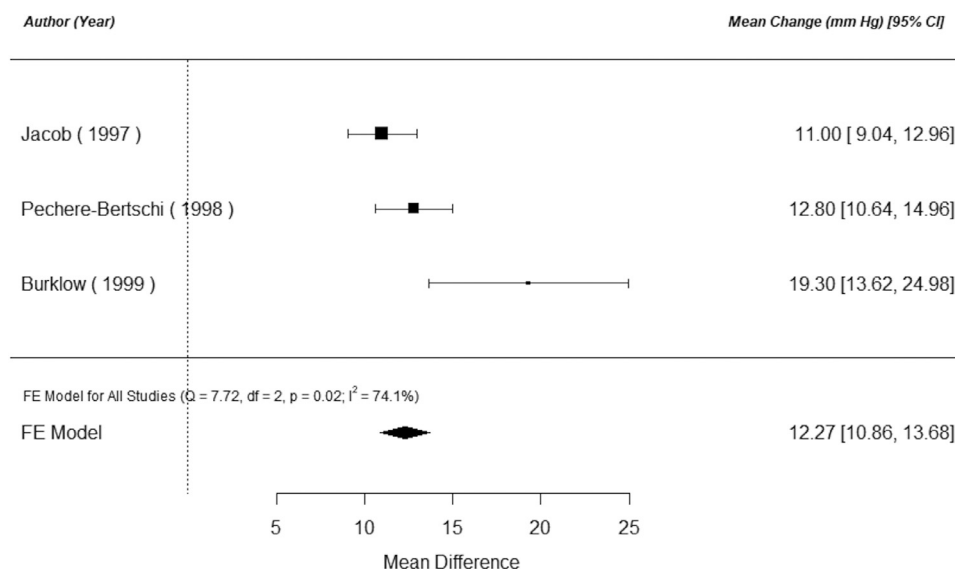


Figure 3 Forest plot of mean difference in mean change of head-up tilt/standing systolic blood pressure following administration of salt. Forest plot showing the effect of salt intervention during head-up tilt on the mean difference in the mean change of systolic blood pressure, $n=45$. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, and the size of the squares reflects the weight of the studies. The combined effect appears as a diamond and the vertical dashed line represents the line of no effect.

heart rate before and after intervention was available for 5 studies, and these were pooled for analysis ($n=60$; syncope [$n = 32$] and orthostatic hypotension or orthostatic tachycardia [$n = 28$]). Mean seated or supine heart rate did not change significantly after salt intervention: -0.08 (95% CI, -0.47 to 0.30), I^2 : 67.9%; (Supplementary Figure S2, available online).

Effect of Increased Salt Intake on Mean Difference in the Mean Change in Head-up Tilt or Standing Heart Rate.

Mean change in head-up tilt or standing heart rate before and after increased salt intake was reported in 4 studies ($n=79$; syncope [$n = 66$] and orthostatic tachycardia [$n = 13$]). Pooled analysis demonstrated that following increased salt intake, there was a -3.97 beats/min change in the mean change in head-up tilt or standing heart rate (95% CI, -4.08 to -3.86), I^2 : 99.7% (Supplementary Figure S3).

Adverse Effects of Increased Salt Intake. The safety and adverse effects of increased salt intake were reported in 6 studies, $n=72$. Of those, 4 reported no adverse events with increased salt intake ($n=32$),^{21,22,27} 1 reported poor tolerance in 2 of 30 patients,²⁰ and 1 reported that most patients experienced nausea with salt capsules ($n=10$).²² Supine hypertension as a potential adverse effect of salt supplementation is reported on above. No study addressed the long-term cardiovascular risk or other safety outcomes of increased salt intake.

Quality of Evidence/Publication Bias

The quality of the evidence was reported as “very low”/“low.” The small participant numbers and poor methodological quality contributed to this assessment. Only 3 trials were randomized. There was no blinding of outcome assessment. There was substantial or considerable heterogeneity among studies as demonstrated by the I^2 . Publication bias could not be assessed because there were less than 10 studies available in each of the outcome measures.

DISCUSSION

Our systematic review supports a short-term pressor effect of increased salt intake in the management of orthostatic intolerance syndromes. Pooled analyses indicate orthostatic tolerance or time to presyncope and systolic blood pressure were increased during orthostatic stress over a follow-up of 3-90 days. Symptom burden was also improved in small, short-term trials (longest follow-up of 8 weeks), but most studies did not include a control group. Increased salt intake resulted in a small increase in short-term seated or supine systolic blood pressure, and a reduction in orthostatic heart rate. We believe this reduction in heart rate represents the pressor effect of increased salt, which results in a lesser drop in orthostatic blood pressure and, thus, resulting in less of a rebound tachycardia. These observations may suggest a preferential effect of salt intake on orthostatic blood pressure, compared to supine blood pressure, potentially related to the effect of salt on increasing both circulating intravascular volume and increasing baroreceptor

sensitivity and peripheral vascular resistance.²¹ We could not determine the longer-term efficacy and safety, or the long-term cardiovascular risk of increased salt intake because of the absence of long-term trials.

Included studies were small with short-term follow up, were of low and very low quality, and considerable clinical and statistical heterogeneity was observed. Pooled analyses were possible on only a small number of relevant outcomes from a small number of studies. Additionally, subgroup analysis by individual orthostatic intolerance syndromes was not possible. There were large differences in study design, particularly in the methods of carrying out an orthostatic challenge, which limits the validity of combining studies.

There are limitations to the external validity of these findings, given that participants were young with few comorbidities and had few existing medications. It is especially difficult to ascertain whether they can be applied to an older, comorbid population. As many older adults with orthostatic hypotension would also be recommended low-salt diets (especially those with co-existing hypertension or heart failure), there is clinical uncertainty about the risk-to-benefit ratio of long-term high-salt diets.

This work highlights the paucity of high-quality data supporting a cornerstone recommendation in the management of orthostatic intolerance syndromes. Our systematic review reports an absence of evidence, rather than evidence of absence, of the long-term clinical benefit of increased salt intake in orthostatic intolerance syndromes (e.g. on incidence of recurrent falls). Our review provides evidence for short-term improvements in orthostatic intolerance symptoms, but meta-analysis included small numbers of participants (n=91) and only one small trial was placebo controlled (n=20), which reported improvement/resolution of symptoms in 30% of those receiving placebo. We do not suggest that current guidelines change, but, rather, should prompt more rigorous long-term evaluation of increased salt intake on clinical outcomes (e.g. falls, syncope) in relevant patient populations. Clinical trials are also required to determine the optimal amount of salt intake in patients with orthostatic intolerance syndromes (i.e. dose-finding studies), and whether regimens should vary by population. The need for high-quality randomized controlled trials of dietary intervention is being increasingly recognised, especially when modifying an essential nutrient or electrolyte.^{32–33} There are ongoing large clinical trials of sodium reduction in populations with heart failure and for secondary stroke prevention.^{34–36} There is also controversy about the optimal salt intake in general populations. While the WHO recommend low salt intake (<5g/day of salt) in the entire adult population,³⁷ based largely on clinical trials of blood pressure, prospective cohort studies report a J-shaped association of salt intake and cardiovascular events/mortality with the lowest risk at a moderate intake range (~7.5–12.5g/day of salt).³⁸ Findings from prospective cohort studies, and the absence of definitive randomised controlled trials, has resulted in calls

to undertake large clinical trials comparing low salt intake to moderate intake in general populations.³⁹

In conclusion, our meta-analysis provides low-quality evidence of a short-term improvement in orthostatic intolerance with increased salt intake. There were no clinical trials demonstrating the efficacy and safety of increased salt intake on long-term clinical outcomes. Our findings highlight the need for robust randomized controlled trials, particularly in older adults with symptomatic orthostatic intolerance syndromes.

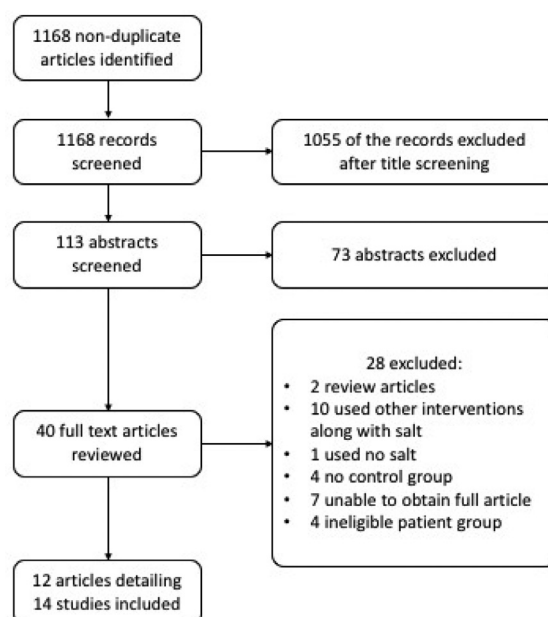
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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amjmed.2020.05.028>.



Supplementary Figure S1 Meta-analyses of observational studies in epidemiology (MOOSE) flow diagram of articles selected for systematic review and meta-analysis. MOOSE flow diagram showing the article selection process. The boxes detail the number of studies available at each stage of review. The arrows direct the flow of study selection. The right-hand side of the diagram illustrates the number of studies excluded, and reasons for exclusion. MOOSE was used due to the observational nature of most clinical studies included (i.e. interrupted time-series).

Supplementary Table S1 Method of Orthostatic Challenge*

Study	Procedure Used	Method of BP and HR Measurement	BP/HR	Salt Intake Record
Mangru, 1995	Tilt Table	Baseline supine measurements. Tilted to 80°, measurements for 30 min until symptomatic.	BP (Dinamap) at 1-min intervals	N/A: IV NaCl
El-Sayed, 1996	Tilt Table	Supine for 20 min, tilted to 60° for 20 min, then lower body pressure at –20 mm Hg and –40 mm Hg for 10 min.	BP: sphygmomanometer. HR: ECG	Self-administered: no diary kept
De Lorenzo, 1996	Tilt Table	Fasted for 4 h. After 10 min supine, the patient was tilted to 70° for 40 min.	BP: automatic sphygmomanometer every 1 min; HR: telemetry	Self-administered: no diary kept
Jacob, 1997	Active Stand	BP and HR measured after 10 min supine and after 3 min standing.	Nil further details	N/A: IV NaCl
Mtinangi, 1998	Tilt Table	Supine for 20 mins, tilted to 60° for 20 mins, and then lower body pressure at –20 mm Hg and –40 mm Hg for 10 min each.	BP: automatic sphygmomanometer. HR: ECG	Self-administered: no diary kept
Pechère-Bertschi, 1998	Active Stand	BP/HR measured at 0, 3, 5, 10, 15, 25, and 30 min, repeated at 30 min standing. The differences between 3 min values/lowest standing BP was recorded.	BP: sphygmomanometer	Self-administered: no diary kept
Burklow, 1999	Tilt Table	Fasted for 6-8 h. ECG/BP data were collected supine. 30 min later, tilted to 80° for 30 min, ECG/BP repeated.	BP: Radial arterial line	N/A: IV NaCl
Cooper, 2002	Tilt Table	Supine on a tilt-table for 20 min. Tilted to 60° for 20 min. Then lower body suction of –20 mm Hg and –40 mm Hg was applied for 10 min each.	Nil further details	Self-administered: no diary kept. 24-h urine was taken in a subset
Claydon, 2004	Tilt Table	Supine for 20 min. Tilted to 60° for 20 min. Then lower body negative pressure of –20 mm Hg and –40 mm Hg was applied for 10 min each.	BP: Continuous photoplethysmography device; HR: ECG	Self-administered: no diary kept
Raj, 2006	Seated/Supine BP	BP measured seated/supine only.	BP/HR: automated vital signs (Dinamap)	Observed ingestion of saline water
Bellard, 2007	Tilt Table	HR/BP were measured supine for 30 min, tilted to 70° for 45 min.	Nil further details	Self-administered: no diary kept
Zhang, 2012	Seated Supine	Seated BP measured before and after salt intake.	Nil further details	Self-administered: no diary kept

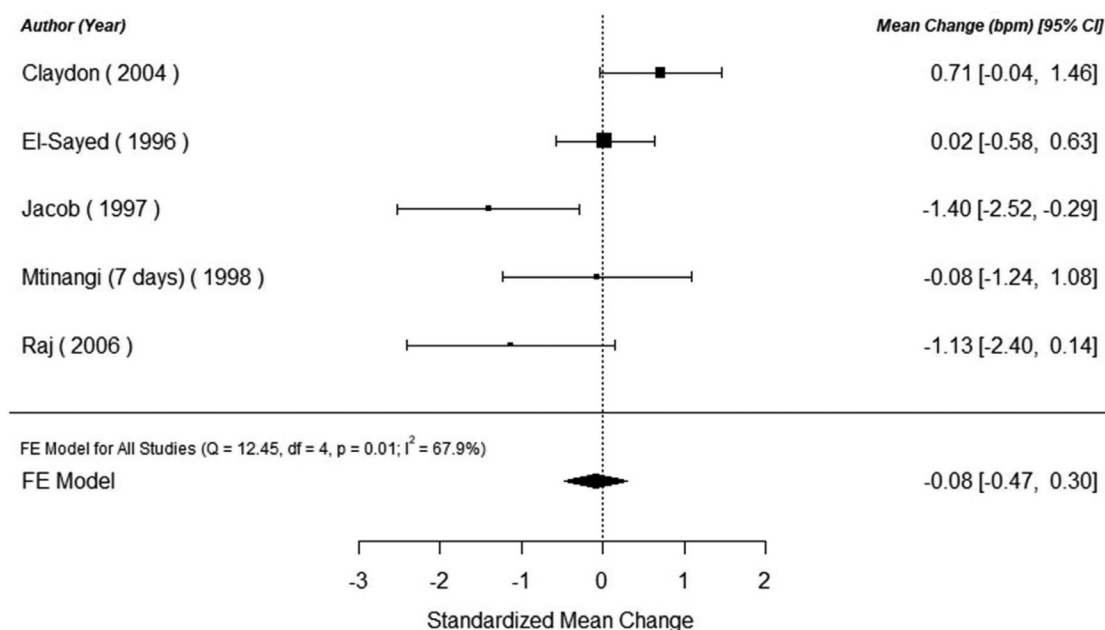
***Table demonstrating method of carrying out an orthostatic challenge.** Author and year of publication are listed in the first column, followed by method of assessing orthostatic intolerance, procedure used, method of measuring blood pressure and heart rate and whether this was intermittent or continuous, and method of recording salt intake.

BP = blood pressure; ECG = electrocardiogram; HR = heart rate; HUT = head-up tilt; IV = intravenous; N/A = not applicable; NaCl = sodium chloride.

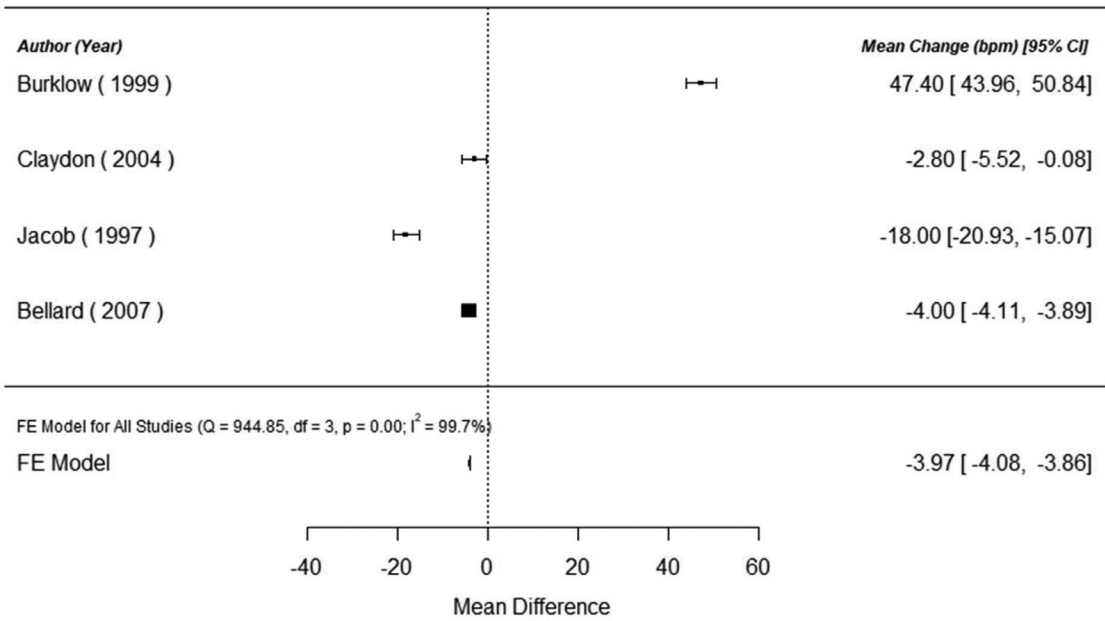
Table S2 Characteristics of Participants: Medications and Comorbidities*

Characteristics of Participants	Medications	Comorbidity Comment
Mangru, 1995	Not listed	Wolff Parkinson-White (n = 1)
El-Sayed, 1996	No medications	Not listed
El-Sayed, 1996	No medications	Not listed
De Lorenzo, 1998	No medications	Not listed
Jacob, 1997	All medications discontinued for 2 weeks	Patients with systemic illnesses affecting the autonomic nervous system were excluded
Mtinangi, 1998	Not listed	Not listed
Mtinangi, 1998	Not listed	Not listed
Pechère-Bertschi, 1998	No medications	Patients suffering from secondary hypotension, venous insufficiency, and secondary dysautonomia were excluded
Burklow, 1999	Not listed	Mild aortic valvular insufficiency (n = 1), mild mitral regurgitation (n = 2)
Cooper, 2002	No medications	Excluded if a history of cardiovascular disease or neurological disorder
Claydon, 2004	No medications	No other medical disorder
Raj, 2006	Not listed	Not listed
Bellard, 2007	Antihypertensives were stopped for 2 days	Excluded if "evidence of disease"
Zhang, 2012	On no medications affecting autonomic tone	No history of chronic debilitating disorder

***Characteristics of Participants: Medications and Comorbidities.** Table further categorizing participants. Author and year of publication are listed in the first column, followed by concurrent medications, and comorbidities in the right-hand side column.



Supplementary Figure S2 Forest plot of standardized mean change in seated or supine heart rate following administration of salt. Forest plot showing the effect of salt intervention on seated or supine heart rate, n=60. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, and the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect.



Supplementary Figure S3 Forest plot of mean difference in head-up tilt/standing heart rate following administration of salt. Forest plot showing the effect of salt intervention during head up tilt on heart rate, n=79. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect.

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(((orthostatic intoleran*[Title/Abstract]) OR orthostatic hypotensi*[Title/Abstract]) OR postural hypotension[Title/Abstract])
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