Effect of dietary sodium restriction on arterial stiffness: systematic review and meta-analysis of the randomized controlled trials

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Objective: Arterial stiffness is an independent cardiovascular risk factor and sodium intake could be a determinant of arterial stiffness. Nevertheless, the studies that investigated the effect of reducing dietary sodium intake on arterial stiffness in humans provided inconsistent results. Therefore, we performed a systematic review and a meta-analysis of the available randomized controlled trials of salt restriction and arterial stiffness to try and achieve more definitive conclusions.

Methods: A systematic search of the online databases available (from 1996 through July 2017) was conducted including randomized controlled trials that reported arterial stiffness, expressed by carotid–femoral pulse wave velocity (PWV), as difference between the effects of two different sodium intake regimens. For each study, the mean difference and 95% confidence intervals were pooled using a random effect model. Sensitivity, heterogeneity, publication bias, subgroup and meta-regression analyses were performed.

Results: Eleven studies met the predefined inclusion criteria and provided 14 cohorts with 431 participants and 1–6 weeks intervention time. In the pooled analysis, an average reduction in sodium intake of 89.3 mmol/day was associated with a 2.84% (95% CI: 0.51–5.08) reduction in PWV. There was no significant heterogeneity among studies and no evidence of publication bias was detected. No single feature of the studies analyzed seemed to impact on the effect of salt restriction on PWV.

Conclusion: The results of this meta-analysis indicate that restriction of dietary sodium intake reduces arterial stiffness. This effect seems be at least in part independent of the changes in blood pressure.

Keywords: arterial stiffness, blood pressure, cardiovascular disease prevention, meta-analysis, pulse wave velocity, salt, sodium intake

Abbreviations: ACE, angiotensin-converting enzyme; BP, blood pressure; PWV, pulse wave velocity; RAAS, renin–angiotensin–aldosterone system; SE, standard error

INTRODUCTION

Arterial stiffness is an independent cardiovascular risk factor [1,2] and a predictor of all-cause mortality [3]. Arterial stiffness can be assessed by several noninvasive methods of which carotid–femoral pulse wave velocity (PWV) measurement is the one most commonly used [4]. Changes in arterial stiffness were evaluated in several clinical trials of antihypertensive drug treatment [5,6] and in a few studies testing different types of dietary intervention [6,7].

Excess sodium intake exerts well known adverse effects on blood pressure (BP) [8] and has been associated with higher risk of stroke [9,10] and renal dysfunction [11,12]. Accordingly, there is robust evidence from randomized controlled trials that moderate reduction of dietary salt intake safely and effectively reduces BP [13] and the urinary albumin excretion rate in hypertensive and/or diabetic patients [14]. Some evidence from epidemiological and clinical studies also indicated an association between habitual dietary salt intake and PWV [15–17]. This association is supported by experimental evidence in animal models of structural and functional alterations induced by high salt regimens on the arterial wall above and beyond the effect of high BP [18–21]. An abnormal response of the local renin–angiotensin system to high salt intake as well as a reduced bioavailability of nitric oxide [22] have been proposed to play a role in these alterations [20]. A number of intervention studies in man investigated the effect of reduction in salt intake on arterial stiffness, but their results were inconsistent mainly because of the low statistical power of most of them [23–26].

We thus performed a systematic review and meta-analysis of the available clinical trials testing the effect of sodium intake restriction on PWV as a proxy for arterial stiffness, our null hypothesis being that restriction of sodium intake does not affect arterial stiffness.

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METHODS

Data sources and search strategy

This meta-analysis was planned, conducted and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement [27] (Table S1, http://links.lww.com/HJH/A869). We performed a systematic search of the available publications using MEDLINE (from 1966), EMBASE (from 1980) and the Cochrane Library, through July 2017. The search strategy without restrictions is reported in Table S2, http://links.lww.com/HJH/A869. Further information was retrieved through a manual search of references from recent reviews and relevant published original studies.

Study selection and data extraction

Two reviewers (L.D. and E.L.F.) independently extracted the data. Discrepancies about inclusion of studies and interpretation of data were resolved in conference, and consensus was reached after discussion. To be included in the meta-analysis, a published study had to meet the following criteria: original article, adult population study, randomized controlled trial, indication of a difference in PWV between two different sodium intake regimens in one or more patients' cohorts and indication of the number of participants included in the exposed and control group for each cohort.

The main characteristics of the identified studies and the respective populations were recorded and reported in Table 1. Funding sources for the various studies, if any, are reported in Table S3, http://links.lww.com/HJH/A869.

The risk of bias of the studies included in the meta-analysis was assessed according to established criteria [28] and reported in Table S4, http://links.lww.com/HJH/A869.

Statistical analysis

A detailed description of the statistical methods was reported previously [14,29]. Briefly, where available, mean differences and standard error (SE) of the defined outcomes were extracted from the selected publications. If these were not available, mean difference and SE were calculated from the comparison of the outcomes at low sodium and high sodium regimens. Because of the between-study heterogeneity in the unit measure adopted to express PWV, we used in our analysis the between-regimen changes in PWV upon conversion to percentages. The pooled mean difference [and 95% confidence interval (CI)] was estimated using a random-effect estimator based on small-sample adjustments (likelihood-based method) [30,31]. The influence of the individual cohorts or of a particular study was estimated by sensitivity analysis. The Cochrane Q test and the I^2 statistic were used to evaluate statistical heterogeneity across the studies. Funnel plots were constructed and visually assessed for the presence of publication bias [32] and Egger's test was used to test for funnel plot asymmetry. Subgroup and meta-regression analyses were used to identify associations between changes in PWV and relevant study's or patients' characteristics as possible sources of heterogeneity.

All statistical analyses were performed using the Stata Corp. software (version 11; College Station, Texas, USA) [31] and the MIX software (version 1.7; Kitasato Clinical Research Center, Kanagawa, Japan) [33].

Furthermore, in addition to the conventional methods, we applied to the studies included in our review the 'trial sequential analysis', a statistical technique aiming to minimize random error and to evaluate when and whether firm evidence is reached of the hypothesis being tested [34]. An information size (i.e. the number of participants needed to detect or reject an intervention effect) is also estimated. The underlying assumption of trial sequential analysis is that significance testing may be performed each time a new trial is added to the meta-analysis. On the basis of the required information size and of the predetermined type I (5%) and type II errors (20%), trial sequential monitoring boundaries are constructed. If a trial sequential monitoring boundary is crossed before the required information size is reached in the cumulative meta-analysis, firm evidence may have been established and further trials may be superfluous.

Thus, we added the trials according to the year of publication, and if more than one trial was published in a year, trials were added alphabetically according to the last name of the first author. A cumulative z curve of the meta-analysis was constructed with each cumulative z value calculated after including a new trial according to the order of their publication date. The trial sequential analysis was effected using the TSA software (version 0.9.5.5 Beta – 2016; developed by The Copenhagen Trial Unit, Center for Clinical Intervention Research, Copenhagen, Denmark).

RESULTS

Characteristics of the studies included in the meta-analysis

From a total of 4873 publications retrieved, 12 studies were identified that met the inclusion criteria (Fig. 1). As two of them referred to the same cohort [35,36], we included the one that reported more characteristics of the study participants [35]. The relevant features of the 11 included studies [23–26,35,37–42] are provided in Table 1 and Table S3, http://links.lww.com/HJH/A869. Overall, the meta-analysis involved 431 participants from five countries. All but one study recruited both male and female participants, whereas one only female patients [42]. Six studies indicated the patients' ethnicity [26,35,37–39,41].

Two studies provided multiple cohorts including different categories of patients, one stratified by ethnicity [37], another one a group of healthy women stratified by history of preeclampsia [42], all the other studies involved a single group of healthy individuals [24], obese and overweight participants [23,40], patients with diabetes or impaired glucose tolerance [41], hypertensive patients [26,35,39], hypertensive patients with kidney disease [25] or participants with resistant hypertension [38].

With respect to the comparison of the effects of higher vs. lower sodium intake, all the studies were randomized controlled trials with a cross-over design.

Five studies were double blinded with regard to the sodium regimen thanks to the use of slow sodium and identical placebo tablets [25,26,35,37,41], whereas three other studies were single blinded [24,39,40]. Blinding was not specified in one study [38] and, in the remaining studies [23,42], sodium intake was changed through dietary modifications.

TABLE 1. Characteristics of the studies included in the meta-analysis

Reference	Country	Cohort (no. of participants)	Selected features of the study participants	Mean age (years)	Mean BMI (kg/m^2)	Duration of intervention (weeks)	Assessment method	Low vs. high sodium comparison (mmol/24 h)	Changes in SBP/DBP/MBP (mmHg)	PWV at high salt intake (m/s) (changes vs. low)	Study design
Dickinson *et al.* [23]	Australia	Overweight/obese participants (7M, 22W)	SBP < 160 mmHg, no CVD, no antihypertensive therapy, BMI > 27 and <40 kg/m^2	52.7	31.6	2	Doppler transducer	64 vs. 156	−5/−1/−1	10.5 (0)	Crossover (sodium restriction vs. regular sodium)
He *et al.* [37]	England	Hypertensive white patients (56M,15W)	Hypertension (SBP:140–170, DBP: 90–105 mmHg), no antihypertensive therapy	52	28	6	Pressure transducer (Complior)	104 vs. 163	−4/−2/−[a]	11.3 (−0.2)	Crossover double blind (slow-sodium suppl. vs. placebo)
		Hypertensive Black patients (34M, 35W)		50	31			116 vs. 162	−5/−2/−[a]	11.7 (−0.5)	
		Hypertensive Asian patients (23M, 6W)		47	27			108 vs. 176	−2/−2/−[a]	11.3 (−0.1)	
Pimenta *et al.* [38]	USA	Hypertensive White and Black patients (4M, 8W)	Resistant hypertension (with HCT and RAAS-blocking treatment)	55.5	32.9	1	Applanation tonometry (Sphygmocor)	46 vs. 252	−20.1/−9.8/−[a]	10.0 (−0.8)	Crossover (slow-sodium suppl. vs. low-salt diet)
Todd *et al.* [39]	New Zealand	(Pre)hypertensive or hypertensive participants (13M, 21W)	SBP/DBP > 130/85 mmHg or treatment	51.8	25.7	4	Applanation tonometry (Sphygmocor)	60 vs. 200[b]	−5.8/−3.4/–	7.8 (−0.5)	Crossover single-blind (sodium suppl. vs. low-salt diet)
Todd *et al.* [24]	New Zealand	Healthy white patients (5M, 18W)	SBP/DBP < 130/85 mmHg, no treatment; no CVD, BMI < 30 kg/m^2	43.7	25.3	4	Applanation tonometry (Sphygmocor)	60 vs. 200[b]	−0.1/−0.4/–	7.0 (0)	Crossover single-blind (sodium suppl. vs. low-salt diet)
McMahon *et al.* [25]	Australia	CKD patients (15M, 5W)	Hypertension (SBP 130–169, DBP ≥ 70 mmHg), CKD stage 3 or 4 (not transplanted)	68.5	29.3	6	Applanation tonometry (Sphygmocor)	75 vs. 168	−9.7/−3.9/−6[a]	11.1 (−0.5)	Crossover double blind (slow-sodium suppl. vs. placebo)
Jablonski *et al.* [35]	USA	(Pre)hypertensive participants (8M, 3W)	SBP 130–159 mmHg and DBP < 99 mmHg, no treatment, no CVD	60.0	27.2	5	Transcutaneous Doppler flowmeter	77 vs. 144	−11/−4/–	8.43 (−1.4)	Crossover double blind (slow-sodium suppl. vs. placebo)
Dickinson *et al.* [40]	Australia	Overweight/obese normotensive participants (8M, 17W)	BMI: 27–40 kg/m^2, no CVD, SBP/DBP < 140/90 mmHg, no treatment	–	–	6	Doppler transducer	113 vs. 155	−2/−2/−1.7[a]	9.6 (1.1)	Crossover single blind (slow-sodium suppl. vs. placebo)
Gijsbers *et al.* [26]	Netherlands	(Pre)hypertensive white participants (24M, 12W)	No smoking, SBP 130–159 mmHg, no treatment, no CVD, no diabetes	65.8	27.2	4	Applanation tonometry (Sphygmocor)	105 vs. 203	−7.5/−2.7/−[a]	13.1 (0)	Crossover double blind (slow-sodium suppl. vs. placebo)
Suckling *et al.* [41]	England	Diabetic patients, or individuals with impaired glucose tolerance (36MW)	Type 2 diabetes or impaired glucose tolerance, untreated SBP 130–170 mmHg and DBP 70–100 mmHg	58	34	6	Pressure transducer (Complior)	117 vs. 165	−3.3/−1.8/−[a]	12.8 (0.2)	Crossover double blind (slow-sodium suppl. vs. placebo)
Van der Graaf *et al.* [42]	Netherlands	Patient with history of NP (18W)	SBP/DBP < 140/90 mmHg, nonsmokers	36	22.6	1	Applanation tonometry (Sphygmocor)	39 vs. 221	−/−/−4	7.0 (−0.3)	Crossover (sodium restriction vs. high sodium)
		Patient with history of PP (18W)		36	25.3	1		45 vs. 258	−/−/−3	7.0 (0)	

[a]Assessed by ABPM (ambulatory blood pressure monitoring).
[b]8-h overnight urine; CKD, chronic kidney disease; CVD, cardiovascular disease; HCT, hydrochlorothiazide; M, men; MBP, mean blood pressure; NP, normotensive pregnancy; PP, preeclamptic pregnancy; PWV, pulse wave velocity; RAAS, renin–angiotensin–aldosterone system; W, women.

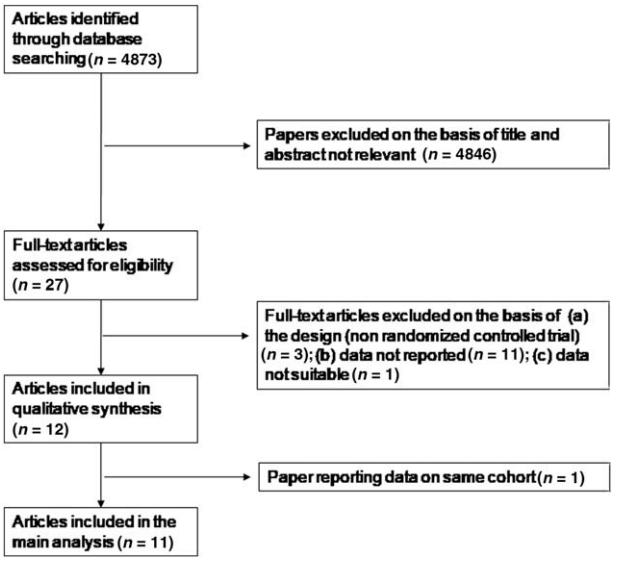

FIGURE 1 Stepwise procedure for selection of the studies. Flowchart indicating the results of the systematic review with inclusions and gexclusions.

In three studies, the participants were on concomitant antihypertensive treatment [25,38,39], whereas in the others, they did not receive any pharmacological treatment. Almost all studies used 24-h urinary sodium excretion as a proxy for sodium intake during intervention, whereas two studies utilized 8-h overnight urine specimens [24,39].

PWV was assessed by different methods, six studies using applanation tonometry (Sphygmocor device; PWV Medical Pty. Ltd., Sidney, New South Wale, Australia), three Doppler transducer (Parks Medical Electronics, Inc., Aloha, Oregon, USA [35]; Accuson Aspen Duplex, Mountain View, California, USA [23,40]), two pressure transducer (Complior device; Colson Medicals, Createch Industrie, Garges les Gonnes, France) [37,41].

The length of intervention ranged from 1 to 6 weeks.

The evaluation of the 'risk of bias' indicated that all but one study were at low risk (Table S4, http://links.lww.com/HJH/A869). External funding sources were declared in all studies (Table S3, http://links.lww.com/HJH/A869).

Effect of sodium intake reduction on pulse wave velocity

In the pooled analysis of the 11 studies (14 cohorts), lower sodium intake (average weighted difference in 24-h urinary sodium excretion = 89.3 mmol or 5.2 g of salt per day) was associated with a significantly lower average PWV (−2.84%; 95% CI: −5.08 to −0.51) compared with the higher sodium regimen. There was no between-study heterogeneity ($Q = 14.8$, $P = 0.32$; $I^2 = 14\%$) (Fig. 2). The funnel plot for

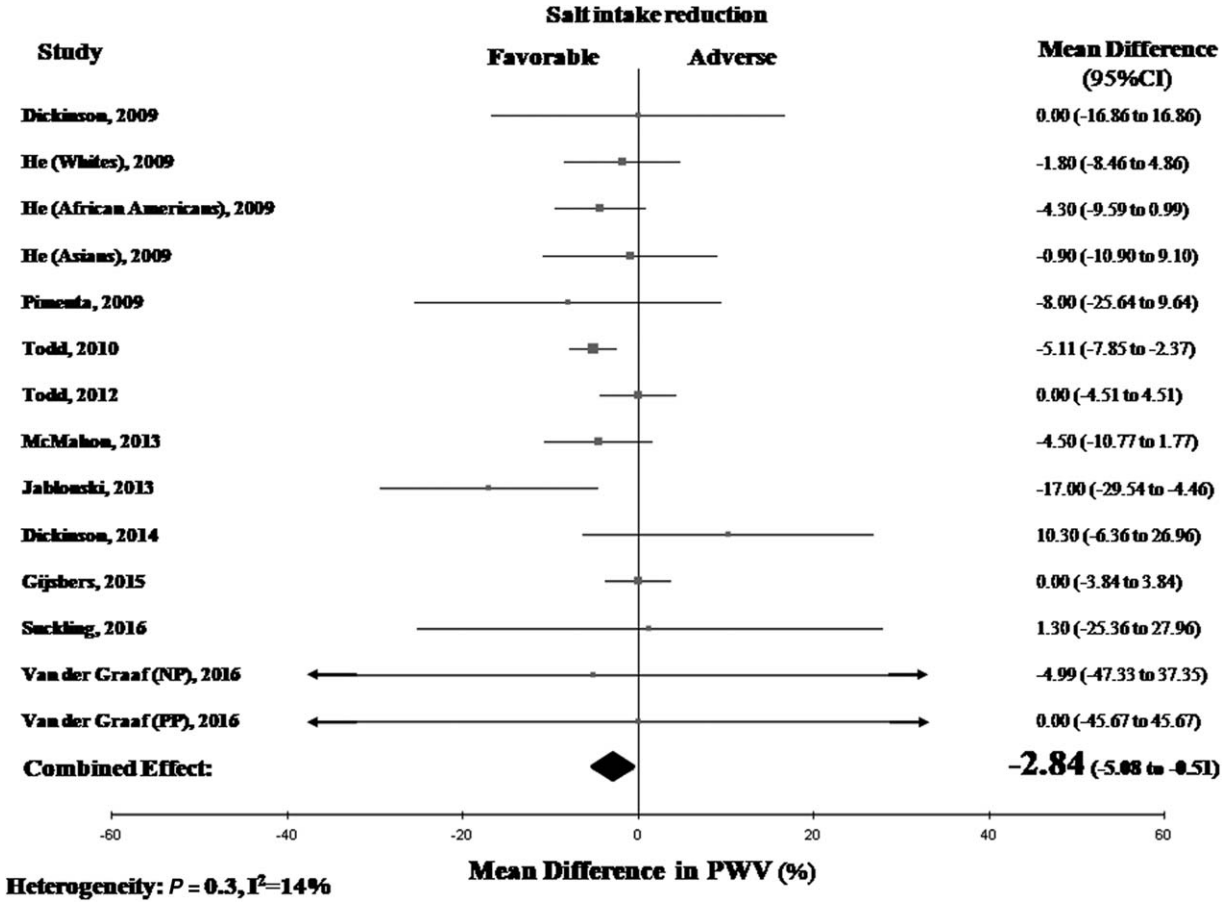

FIGURE 2 Effect of lower salt consumption on carotid–femoral pulse wave velocity. Forest plot of the effect of lower dietary salt intake on pulse wave velocity in 14 population cohorts from 11 published studies. Results are expressed as mean difference and 95% confidence intervals. Squares indicate study-specific relative risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% confidence interval; diamond indicates the overall relative risk with its 95% confidence interval. NP, normotensive pregnancy; PP, preeclamptic pregnancy.

the effect of sodium restriction on PWV was symmetrical on visual inspection, suggesting no significant publication bias, and Egger's test did not find significant evidence of bias ($P = 0.78$) (Appendix Fig. 1, http://links.lww.com/HJH/A869).

As shown in Fig. 2, a trend toward an association between reduced sodium intake and lower PWV was detected in the majority of the cohorts examined but was statistically significant in only two of them. There was no effect in four cohorts and a not significant adverse effect in two involving overweight and obese participants [40] or patients with diabetes or impaired glucose tolerance [41]. Sensitivity analysis showed that the average change in PWV did not vary substantially with the exclusion of any individual study.

The trial sequential analysis showed that, based on an 'a posteriori' estimation, a total of 781 randomized patients (390 per arm) were needed to demonstrate or reject the observed reduction in PWV. The cumulative z curve crossed the trial sequential monitoring boundaries in the direction favoring the effect of salt restriction after the addition of the seventh cohort (out of 14 cohorts available overall). Hence, this analysis suggested that firm evidence of the effect of salt restriction on PWV was actually reached (Appendix Fig. 2A and B, http://links.lww.com/HJH/A869).

Effects of sodium reduction on blood pressure

A meta-analysis of the effects of salt restriction on BP in the same cohorts was carried out. Pooled analyses showed a significant reduction of both SBP (mean difference: −5.82; −8.42 to −3.43 mmHg) and DBP (mean difference: −2.75; −3.67 to −1.87 mmHg) upon reduction of sodium intake. There was high heterogeneity between studies in the SBP analysis, whereas low heterogeneity was found in the DPB analysis. No evidence of publication bias was detected (Egger's test, SBP: $P = 0.29$, DBP: $P = 0.77$). As shown in Fig. 3a and b, there was a reduction of BP during salt restriction in all the cohorts. However, meta-regression analysis did not detect any influence of BP changes on the relationship between salt restriction and PWV (Table 3).

Additional analyses

We carried out an analysis including the results of a most recent study by Jablonski *et al.* [36] in place of the previously published report on the same cohort [34] included in the main analysis. By doing so, the pooled mean difference changed from −2.84 to −3.02% (95% CI: −5.22 to −0.85). Even in this additional analysis, there was neither evidence of heterogeneity among studies (Q: 10.5; $P = 0.65$; $I^2 = 11\%$) nor evidence of publication bias (Egger test; $P = 0.79$).

Exclusion of the study by Dickinson *et al.* [23] that used dietary modification as a mean of changing sodium intake again provided a similar result (mean difference = −2.88%; −5.19 to −0.52). Likewise, pooled results were confirmed also after exclusion of the cohorts at high risk of bias [42] (mean difference: −2.84; −5.10 to −0.49)

The analysis stratified by countries of study implementation suggested a stronger effect of salt restriction in studies performed in the United States of America and Oceania compared with those carried out in Europe (P for heterogeneity = 0.07).

Subgroup analysis in relation to inclusion or not of prehypertensive and hypertensive participants did not detect significant differences (P for heterogeneity = 0.15). Similar result was obtained by subgroup analysis in relation to concomitant antihypertensive drug treatment or not and by subgroup and meta-regression analysis in relation to length of intervention (Tables 2 and 3).

Pharmaceutical funding, study design (i.e. use of placebo and double-blind protocol), instrumental method for measurement of PWV, age, sex, BMI, absolute levels of salt intake and total number of participants were not significant sources of heterogeneity by meta-regression and subgroup analyses (Tables 2 and 3).

DISCUSSION

Main study results

The results of this meta-analysis indicate a direct association between reduction of dietary salt intake and decrease in arterial stiffness in the available randomized controlled trials. An average weighed difference of 89.3-mmol sodium or 5.2 g of salt per day translated into a 2.8% decrease in arterial stiffness. The results were strengthened by the absence of significant heterogeneity among studies, the lack of detectable publication bias, the feature of low risk of bias in all but one study included, the observation of a trend to PWV decrease with salt restriction in the majority of the cohorts under investigation and the results of trial sequential analysis.

On the other hand, the value of our findings is limited to some extent by the relatively short length of intervention (between 1 and 6 weeks) featured by all the studies, and partially by the relatively small number of cohorts available and the small number of participants enrolled in each individual trial.

Additional study results

PWV is known to be associated with BP and age [43,44]. We did not detect significant differences in the effect of salt restriction on PWV as a function of the cohorts' mean age and baseline SBP and DBP. Although sodium restriction reduced SBP and DBP in the pooled analysis of the included trials, the results of meta-regression analysis indicate that the effect of sodium reduction on arterial stiffness was not dependent on the changes in BP. Indeed, in one of the trials included in our meta-analysis, a significantly larger reduction of PWV was observed in black compared with white and Asian hypertensive patients, notwithstanding the fact that the three ethnic groups had similar reductions in BP [37]. Again another study of long-term sodium reduction showed an improvement in arterial stiffness independently of the changes in BP [45]. We did not detect a dose-dependence in the pooled association between salt restriction and reduction of PWV. In principle, this result might be due to the actual lack of a dose-dependence in the range of salt reduction applied in the available studies. It is possible however that the detection of this type of biological association was hampered by confounding factors, first-of-all the different characteristics of the study participants

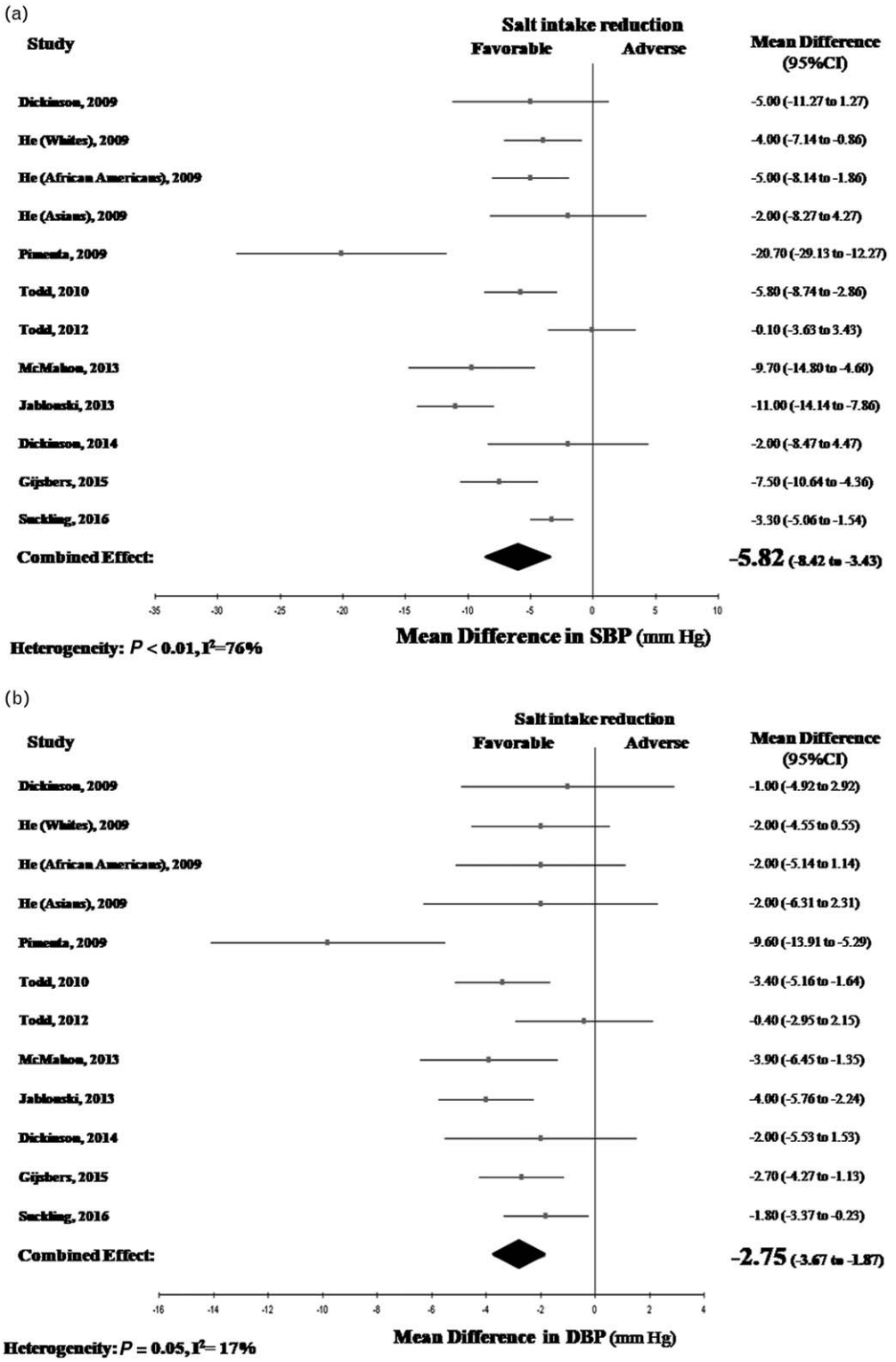

FIGURE 3 (a) Effect of lower salt consumption on SBP. Forest plot of the effect of lower dietary salt intake on SBP in 12 population cohorts from 10 published studies. Results are expressed as mean difference and 95% confidence intervals. Squares indicate study-specific relative risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% confidence interval; diamond indicates the overall relative risk with its 95% confidence interval. (b) Effect of lower salt consumption on DBP. Forest plot of the effect of lower dietary salt intake on DBP in 12 population cohorts from 10 published studies. Results are expressed as mean difference and 95% confidence intervals. Squares indicate study-specific relative risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% confidence interval; diamond indicates the overall relative risk with its 95% confidence interval.

TABLE 2. Subgroup analysis of the effect of sodium intake reduction on pulse wave velocity

	Variables (no. of cohorts)	Pooled mean (%) reduction	95% CI	*P* for heterogeneity
Antihypertensive treatment	Yes (3)	−5.07	−7.56 to −2.58	0.10
	No (11)	−1.70	−4.83 to 1.43	
Length of intervention	<4 weeks (4)	−3.67	−15.01 to 7.68	0.88
	≥4 week (10)	−2.75	−5.42 to −0.08	
Country of origin	Oceania (5)	−2.36	−6.51 to 1.80	0.07
	Europe (7)	−1.47	−4.16 to 1.21	
	USA (2)	−13.95	−24.2 to −3.75	
(Pre)hypertension status	Yes (9)	−3.65	−6.13 to −1.18	0.15
	No (5)	0.60	−4.20 to 7.43	
PWV assessment device	Sphygmocor (7)	−2.60	−5.63 to 0.42	0.99
	Complior (4)	−2.90	−6.68 to 0.90	
	Doppler transducer (3)	−2.89	−20.63 to 14.85	
Pharmaceutical funding source	Yes (4)	−1.16	−5.58 to 3.25	0.27
	No (10)	−4.14	−7.17 to −1.11	
Study design	Double-blind (7)	−3.06	−6.34 to 0.21	0.90
	Single-blind (3)	−3.44	−8.44 to 1.57	
Placebo control group	Yes (8)	−2.66	−6.10 to 0.79	0.88
	No (6)	−3.06	−7.11 to 0.98	

CI, confidence interval.

(e.g. whether hypertensive or not), the interaction between sodium restriction and concomitant antihypertensive drug treatment, and the generally short duration and the unequal length of intervention in the different studies.

In subgroup analyses, there was a pooled reduction in PWV – in the nine cohorts including prehypertensive and/or hypertensive participants (−3.65%), whereas in the five cohorts that enrolled normotensive individuals, a not significant inverse trend was detected (0.60%), but this difference was not statistically significant. A much larger effect of sodium reduction on PWV was also seen in the three cohorts that included hypertensive patients on concomitant antihypertensive drug treatment (−5.07%) than in the 11 cohorts enrolling untreated normotensive or prehypertensive individuals (−1.70%): again, however, this difference was not statistically significant. With regard to the length of intervention, any influence on the effect of sodium reduction was hardly detectable given that most of the studies had similar length.

Finally, although in various studies differences in PWV values were reported according to the measurement methods [46], our subgroup analysis did not detect any difference as a function of the measurement device used in the different studies. In general, although the measurement of PWV is affected by a relatively high intraindividual variability, the process of meta-analysis, with the calculation of a pooled estimate of the effect in a large number of studies, is functional to overcome at least in part this problem.

TABLE 3. Meta-regression analysis of the effect of sodium intake reduction on pulse wave velocity

Variables (no. of cohorts)	ΔPWV (%) (coefficient)	95% CI
Age (years) (13)	0.03	−0.28 to 0.35
BMI (kg/m^2) (13)	0.21	−1.00 to 1.42
Year of publication (year) (14)	−0.65	−1.52 to 0.23
Length of intervention (week) (14)	0.08	−2.11 to 2.26
Number of participants (*n*) (14)	−0.01	−0.16 to 0.13
Sex (% men) (13)	0.02	−0.10 to 0.15
SBP at low salt intake (mmHg) (12)	0.12	−0.11 to 0.35
SBP at high salt intake (mmHg) (12)	0.15	−0.04 to 0.35
DBP at low salt intake (mmHg) (12)	0.19	−0.17 to 0.55
DBP at high salt intake (mmHg) (12)	0.28	−0.02 to 0.58
SBP difference (mmHg) (12)	0.56	−0.17 to 1.29
DBP difference (mm Hg) (12)	1.47	−0.09 to 3.03
Urinary Na at low salt intake (mmol/24 h) (14)	−0.05	−0.15 to 0.06
Urinary Na at high salt intake (mmol/24 h) (14)	−0.03	−0.15 to 0.08
Urinary Na difference (mmol/24 h) (14)	0.01	−0.06 to 0.07

CI, confidence interval.

Possible mechanisms of the effect of sodium intake reduction on arterial stiffness

Our study had no specific potential to address the mechanisms of the effect of sodium intake restriction on arterial stiffness.

In addition to the above discussed possible intermediary role of concomitant BP fall, it is possible that salt restriction exerts direct effects on the arterial wall and its components. A cross-sectional investigation of two groups of Chinese population, respectively, living in a rural low-sodium and an urban high-sodium setting, found a significantly higher PWV in the urban citizens no matter similar mean BP values in the two groups [47]. Similar findings were reported by the same authors in an Australian normotensive population, in which patients dwelling on a low-salt diet had lower PWV compared with those at 'normal' salt intake, upon age and BP matching [45].

Studies on animal models did show pressure-independent effects of changes in dietary sodium intake on arterial structure and function [18,19]. In normotensive rats, a high salt diet was found to induce the endothelial production of transforming growth factor-beta 1 (TGF-β1), a profibrotic factor, without increase in BP [18,19,48]: this action was not counterbalanced by higher nitric oxide bioavailability [48]. In another experimental study in normotensive rats, high salt intake appeared to decrease the expression of endothelial nitric oxide synthase [22]. More recently, sodium

overload was found to decrease the endothelial glycocalyx sodium barrier and to increase endothelial stiffness [49].

Several experimental studies pointed to the local renin–angiotensin–aldosterone system (RAAS) (heart, vessels and kidney) as one of the mediators of vessel wall elasticity [20,50]. A high-sodium regimen has been shown to increase the expression of AT1 receptor in the cardiovascular system [20], which in turn may promote vascular organ damage. Indeed, after administration of an AT1-receptor blocker during salt-loading, there was a decrease in aortic collagen accumulation and an improvement of cardiac, vascular and renal function [12,20,50]. Moreover, high sodium intake was reported to increase the levels of vascular angiotensin-converting enzyme, thereby counteracting the effect of concomitant renin suppression [51].

Dietary salt intake may affect the sympathetic nervous system (SNS) activity according to several reports [52–55]. Experimental studies showed that high salt-sensitivity of BP was associated with evidence of activation of the SNS [52–56]. Changes in plasma and/or cerebrospinal fluid sodium concentration upon variation of salt intake could also modulate the sympathetic nerve activity [57]. In particular, changes in sodium concentration may activate osmoreceptors in the central nervous system [58], thus modulating the activity of the sympathetic neurons in rostral ventrolateral medulla, the main site responsible for basal sympathetic vasomotor tone [59,60].

In humans, an association between salt intake and activation of SNS was supported by the evidence that increased plasma osmolality was associated with significant increments in plasma norepinephrine [61–63] and muscle sympathetic nerve activity, in addition to the rise in BP [62].

In turn, a number of studies suggest that sympathetic nervous activity may affect arterial compliance also independently of the effects on BP. An experimental study in normotensive rats found that sympathectomy increased compliance of femoral and carotid arteries [64]. In humans, sympathetic activation induced a decrease in radial arterial compliance, both directly by affecting the smooth muscle cell tone and indirectly by increasing the BP [65]. To confirm this relationship, in clinical conditions associated with chronic sympathetic activation (e.g. congestive heart failure, etc), a decreased arterial compliance was found [66]. The adverse BP-independent effect of SNS activation on arterial stiffness could be partly explained by yet other mechanisms, such as arterial wall fibrosis promoted by vascular muscle growth and activation of the RAAS [67].

Study strengths and limitations

Major strengths of our meta-analysis are the inclusion of only randomized controlled trials; all but one study provided cohorts at 'low' risk of bias; the results were supported by the lack of statistical heterogeneity among studies; the inclusion of only studies that reported carotid–femoral PWV, the gold standard of noninvasive measurement of arterial stiffness; the measurement of 24-h urinary sodium excretion, a recognized gold standard for monitoring salt intake [68], in all but two studies; and the finding of a trend to reduction of arterial stiffness upon sodium intake restriction in the majority of the cohorts examined. A weakness of our study was its inability to rationally assess a possible association between the extent of salt intake reduction and the observed decrease in arterial stiffness for the reasons discussed above. Also, our study does not allow to draw definitive conclusions about the long-term effects of sodium intake restriction on arterial stiffness, given that none of the trials included in the meta-analysis had an intervention period longer than 6 weeks. Although another possible limitation was given by the small sample size of most of the available studies; however, the trial sequential analysis indicated that the number of included cohorts and participants were actually sufficient to demonstrate the observed effect of sodium restriction on PWV.

Implications for public health

Consistently with the previous demonstration of a favorable effect of sodium reduction on urinary albumin excretion [14], the results of this meta-analysis support the concept of a protective role of lower sodium intake toward organ damage, particularly but not solely, in hypertensive individuals. This concept is obviously in keeping with the recognized beneficial effect of moderate dietary salt restriction on BP [13], but, both in the case of arterial stiffness and in the case of renal dysfunction, the results of the respective meta-analyses leave space to the possibility that direct effects of sodium reduction on arterial wall structure and function contribute at least in part to the favorable outcomes.

The results of the current study have important implications for public health:

(1) Arterial stiffness, as estimated by carotid–femoral PWV measurement, is a recognized predictor of cardiovascular events [2,3,69]. Based on previous studies indicating increments of 14% in all-cause mortality, 15% in cardiovascular mortality and 14% in the incidence of cardiovascular events for each 1 m/s increase in PWV [3], a decrease in PWV upon reduction of salt intake is expected to translate into a substantial reduction in cardiovascular risk.
(2) Based on our results, maximum benefit from salt intake restriction may be expected for hypertensive patients on concomitant antihypertensive drug treatment, nevertheless the benefit may extend to untreated hypertensive and normotensive individuals as well.
(3) As the habitual salt intake in most Western countries is close to 10 g/day, an average reduction of 5 g/day, as in our meta-analysis, would lead to the achievement of the WHO recommended target of 5 g/day for the population: this observation suggests that the results of our study are applicable to real-life conditions and are relevant to population-based strategies for reduction of salt intake [70].

In conclusion, the results of this study show that moderate reduction of dietary sodium intake reduces arterial stiffness, at least in part independently from the hypertensive status and from the concomitant changes in BP. Given the importance of arterial stiffness as predictor of cardiovascular and all-cause mortality, this effect of

moderate sodium intake reduction significantly adds to its recognized value in cardiovascular disease prevention. Our results therefore support the recommendations in favor of moderate dietary salt intake reduction to decrease the risk of cardiovascular diseases.

On research grounds, as a properly powered randomized controlled trial of the effect of long-term moderate salt intake reduction on arterial stiffness is lacking, an effort in this direction is warranted to further support the conclusions of our review and extend current knowledge in this field.

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Conflicts of interest

The remaining authors do not disclose any conflict of interest.

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