

**Drinking water salinity and risk of hypertension: A systematic review and meta-analysis**

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**Abstract**

We summarized published epidemiological studies assessing sodium in drinking water and changes in blood pressure or hypertension published in English till 2015 from PubMed, Scopus and Web of Science. We extracted data on blood pressure level or prevalence of hypertension and calculated pooled estimates using an inverse variance weighted random-effects model. The pooled (standardized mean difference (SMD)) in 7 studies (12 datasets) comparing the low and high water sodium exposure groups for systolic blood pressure (SBP) was 0.08 (95%CI: -0.17, 0.34) and for diastolic blood pressure (DBP) was 0.23 (95%CI: 0.09, 0.36). Of the three studies that assessed the association between high water sodium and odds of hypertension, two recent studies showed consistent findings of higher risk of hypertension. Our systematic review suggests an association between water sodium and human blood pressure, more consistently for DBP; but remain inconclusive because of the small number of studies, largely in young populations and of cross sectional design, and methodological drawbacks. In the context of climate change related sea level rise and increasing saltwater intrusion into drinking water sources further research is urgently warranted to investigate and guide intervention in this increasingly widespread problem.

## Introduction

High blood pressure or hypertension is the leading risk factor for deaths and disability globally, contributing 9.4 million deaths and 7.0% of global Disability Adjusted Life Years (DALYs) in 2010<sup>1</sup>. Reducing salt (sodium) intake is one of the major dietary interventions to prevent and control high blood pressure and subsequent cardiovascular risks<sup>2,3</sup>. In Western industrialized countries processed foods contribute 75–80% of daily salt intake, while natural salt content in foods (10–12%) and use of salt during food preparation or consumption (around 10%) contribute the remaining<sup>4,5</sup>. Given that in many countries food has been the major source of dietary sodium<sup>5,6</sup>; the increased intake through water has received less attention<sup>7</sup>. According to one estimate, 2 liters of drinking water containing 20–250 mg/liter of sodium may contribute to around 1.0–12.5% of total sodium intake<sup>8</sup>. In the case of young children and for the population who are on a sodium-restricted diet, this estimate is likely to be much higher as drinking water can contribute up to 44% and 64% of the total intake respectively<sup>9</sup>.

In many low-lying coastal countries increasing salinity levels i.e. sodium content of freshwater resources due to saltwater intrusion, may be contributing to higher salt consumption<sup>38</sup>, therefore increasing risk of developing hypertension<sup>10</sup>. For example, in coastal areas of Bangladesh average sodium levels in drinking water sources have been observed between 2600 and 8210 mg/liter during the dry season. Hence, people in this area are consuming 5.2–16.4g of sodium daily from drinking water alone, which is already significantly higher than the daily recommended level of 2g<sup>7</sup>. Saline water intrusion into freshwater resources in coastal areas is a major impact of climate change and global sea level rise<sup>39</sup>, a change that is already affecting

water resources in Asian megadeltas and large deltas such as the Nile and Mississippi <sup>11</sup>.

The link between sodium in drinking water and occurrence of hypertension is not conclusive<sup>8</sup>. Some studies in the USA, Netherlands and Israel have found a positive relationship between elevated sodium in drinking water and rise in blood pressure <sup>12,13,14,15</sup>. However other studies in USA and Australia did not observe any such relationship <sup>16,17,18,19</sup>. The recent studies in coastal Bangladesh demonstrated an unacceptably high level of sodium in water contributing to high prevalence of hypertension in pregnant mothers <sup>7,20</sup>. We conducted this systematic review of epidemiological studies that examined sodium content in water as exposure and blood pressure as outcome to systematically evaluate the potential relationship between sodium in drinking water and blood pressure rise, in order to make recommendations for future research and promote appropriate intervention strategies.

## **Methods**

### **Search strategy, study selection and data extraction**

We conducted a systematic literature search using the PubMed, Scopus and Web of Science databases to find the studies assessing the relationship between exposure to sodium in drinking water with hypertension or blood pressure level and hand-searched the references of the relevant articles. Our search comprised four categories of keywords or Medical Subject Headings (MeSH) terms by using ‘OR’ within a group and combined them by using ‘AND’ between groups. The four categories were: i) related to "water\*", or "\*water", or "drinking water", or "potable water"; ii) salinity, or sodium, or salt, or "sodium chloride"; iii) "blood pressure", or "high blood pressure", or hypertension; and iv) types of observational studies ("analytic" OR observational OR cross-sectional OR cohort OR follow-up OR "prospective cohort" OR

“retrospective cohort” OR longitudinal OR case-control study). We identified the journal articles published in English till 2015.

Eligibility criteria included: 1) studies using sodium in drinking water as exposure and blood pressure as the health outcome; 2) studies providing quantitative measure for the association between sodium exposure and difference in SBP and DBP level or odds ratio of high-low blood pressure 3) or studies providing available data that enable calculation of the mean, standard deviation (SD) or odds ratio (OR); and 4) studies are published in peer-reviewed journals. Experimental studies, reviews, books, reports and conference abstracts were excluded. We did not consider grey literature because of potential issues with quality and lack of peer-review. We also excluded one study that used hypertension mortality as the only end point <sup>21</sup> and two articles <sup>22,23</sup> that reported on the same study population as other included studies <sup>12,13</sup>. Eight studies were also excluded as they did not report SBP and DBP level <sup>17,18,24,25</sup> or provide information that allowed us to calculate SD <sup>16,26,27</sup> or OR <sup>28</sup>.

We screened the searched articles sequentially by title, abstract, and full-text using the inclusion and exclusion criteria (Figure 1). All the authors discussed and agreed upon the inclusion and exclusion criteria. The first author (MRRT) conducted the literature search, screened the articles based on the criteria and consulted with the second author (SR) to resolve any issue with the eligibility criteria of specific articles. In the first step titles and abstracts for all the articles were screened and reviewed for eligibility. The references in papers selected from the first step for full-text review were also searched manually for additional papers. Duplicates papers from different sources were excluded in the second step. Final selection of papers was made matching against the inclusion criteria. For each study, information on- first author and

year of publication, study design, settings (country), study subjects (sample size, age and sex), sodium level in drinking water (exposure), exposure assessment, outcome (blood pressure) assessment, results (measures of association- mean difference or OR) and confounding factors adjusted for analyses were extracted. The quality of the included studies was evaluated by adapting the criteria that includes a standard procedure for sodium exposure and blood pressure or hypertension assessments, selection and recruitment of study participants, blinding and data collection techniques, control for confounders and appropriateness of analysis, as described by Abhyankar et al. (2012)<sup>29</sup>.

#### Statistical analysis

We extracted SBP and DBP level, and their standard deviation between the lowest and highest water salinity (sodium) areas for the included studies with reported SBP and DBP level<sup>12,13,14,15,19,20,30,31</sup>. In order to be consistent we used unadjusted SBP and DBP level from all studies, as covariate adjusted BP level was not available for all the studies<sup>12,13,14,15,19,20,31</sup>. For the studies<sup>12,13,19, 30,31</sup> that reported separate SBP and DBP level for both male and female we analysed them as two datasets. For the studies<sup>19,20</sup> with more than two groups we compared mean blood pressure difference between the lowest and highest water sodium levels. We calculated pooled estimates for mean difference (standardized mean difference- SMD) in SBP and DBP between the highest and lowest categories of water sodium from individual studies using an inverse- variance weighted random-effects model. Pooled SMD were calculated for all studies and separately for studies conducted in populations exposed to high water sodium levels and for studies conducted in populations exposed to low water sodium levels (categorized as upper level of water sodium above and below 150mg/L). There is no health based cut-off level

for water sodium level other than aesthetic level, which is above 200mg/L<sup>8</sup>. However we had few studies with highest exposures above this level to make a meaningful comparison. Therefore this cut-off point was set to ensure a balance between high and low sodium categories in the analyses. The proportion of the total variation in pooled estimates due to heterogeneity was quantified using the  $I^2$  statistic<sup>33</sup>. The relative influence of each study on pooled effect measure was examined by omitting one study at a time. A funnel plot was used to examine the potential publication bias and further evaluated using Egger's statistic. All statistical analyses were performed using Stata software, version 13.1 SE (StataCorp, College Station, TX, USA).

Three studies<sup>7,20,32</sup> reported the association between high water sodium and hypertension, and all were conducted in pregnant women. Because of the small number of studies and because Khan et al. (2011)<sup>7</sup> measured exposure and outcome in different groups; the findings of these studies were presented descriptively.

## Results

The number of studies included in the final analysis was 10, and they contributed 15 datasets. In order to avoid duplication in the pooled estimate of SMD we refer to number of datasets. Figure [1] provides the numbers of articles removed or included at various stages based on the inclusion and exclusion criteria.

### Characteristics of the studies

Seven studies adopted cross-sectional study designs, two studies were case-control and one study had a retrospective follow-up design (Table 1). Combined, the studies covered water sodium exposure and blood pressure outcome for 8093 participants. Five studies<sup>12,13,19,29,30</sup> reported measures of association for males and females separately, two studies<sup>14,15</sup> included both sexes

and three studies were in females only (pregnant women)<sup>7,20,32</sup>. Only two studies<sup>7,20</sup> were conducted in developing country settings, both in coastal Bangladesh. The highest level of sodium in water ranged from ~100-405 mg/L, except the study in coastal Bangladesh where during the dry season the average level of sodium in drinking water was 2,600-8,210 mg/L depending on the drinking water source<sup>7</sup>. Three of the studies reported a water sodium level below 150 mg/L<sup>12, 13, 31</sup>. Six studies were conducted in children<sup>12,13,14,15,19,30</sup> in school settings, one study was hospital-based<sup>32</sup> and three studies were conducted in the community<sup>7,20,31</sup> (Table 1). Eight studies<sup>12,13,14,15,19,20,30,31</sup> reported SBP and DBP level between high and low water sodium groups. Three studies reported odds of risk of hypertension among the exposed group<sup>7,20,32</sup>.

### Quality assessment

Eight studies<sup>7,13,14,15,19,20,30,32</sup> assessed sodium exposure at the individual level (Table 2). Across the studies different techniques were used to measure average sodium intake either alone or in combination including: 24-hour urinary sodium excretion only (n=3), dietary history only (n=1), dietary record and urinary sodium (24-hour/overnight/spot) (n=4). Four studies<sup>7,19,20,31</sup> did not indicate whether the interviewers were blinded to the water sodium exposure status. Three studies mentioned that the interviewers were not aware of the water sodium exposure status<sup>14,20,32</sup>. Five studies<sup>7,13,19,20,30</sup> considered liquid/ water consumption and estimated the contribution of sodium from water. In general, multiple (three) readings for BP (Armstrong et al., 1982<sup>19</sup> and Hofman et al. 1980<sup>14</sup> recorded BP level twice; Jones et al. 1979<sup>32</sup> and Choi 1984<sup>31</sup> used hospital records of BP) were taken in a resting state and averaged for blood pressure (BP) measurement in all the studies, but estimation of BP level across studies was different (e.g.



Hallenbeck et al. (1981)<sup>30</sup> dropped the first record of BP). The studies (Jones et al., 1979<sup>32</sup>, Khan et al. 2011<sup>7</sup>, 2014<sup>20</sup>) that reported OR and/ or prevalence of hypertension used a standardized definition of hypertension, but Jones et al. (1979)<sup>32</sup> and Khan et al. (2011)<sup>7</sup> lack data on the procedure for BP recordings. Across the studies common covariates measured were height, weight, Body Mass Index (BMI) and dietary habits including salt consumption of the respondents. Out of 10, four studies<sup>7,15,31,32</sup> did not control for any confounding factors (Table 2).

### **Sodium in drinking water and blood pressure level**

Of the 7 studies that reported mean difference in blood pressure between high and low water sodium communities, 4 studies<sup>12,13,14,15</sup> showed high water sodium exposure was associated with a positive difference in both SBP and DBP. The mean positive difference in SBP ranged from 0.6-9.0mmHg and in DBP ranged from 0.3-6.8mmHg. Pomeranz et al. (2000) reported the highest positive mean difference in both SBP and DBP. In contrast, Choi (1984)<sup>31</sup> showed higher SBP and DBP, Hallenbeck et al. (1981)<sup>30</sup> and Armstrong (1982)<sup>19</sup> had higher SBP in low water sodium groups. Among the studies<sup>14,15,19,20,30</sup> in the high water sodium (>150mg/L) category the positive mean difference comparing high and low water sodium exposure ranged from 3.2-9.0mmHg for SBP and 3.0-6.8mmHg for DBP. In the studies<sup>12,13,31</sup> in the low water sodium (<150mg/L) category, a positive mean difference ranged from 2.8-5.1mmHg for SBP and 2.5-5.1mmHg for DBP.

The pooled SMD in SBP and DBP compared between the high and low water sodium in the twelve datasets was 0.08 (95%CI: -0.17, 0.34, p-value for heterogeneity <0.001; I<sup>2</sup> 91.9%) and 0.23 (95%CI: 0.09,0.36, p-value for heterogeneity <0.001; I<sup>2</sup> 70.5%) respectively (Figure 2).

The pooled SMD in SBP and DBP in six datasets with the higher sodium in water category was -0.04 (95%CI: -0.35, 0.43, p-value for heterogeneity <0.001;  $I^2$  90.7%) and 0.27 (95%CI: 0.16, 0.38; p-value for heterogeneity =0.797;  $I^2$  0.0%) respectively (Figure 3a, 3b). The pooled SMD in SBP and DBP in the six datasets with lower sodium in water category was 0.12 (95%CI -0.24, 0.49, p-value for heterogeneity <0.001;  $I^2$  94.0%) and 0.20 (95%CI: -0.03, 0.43; p-value for heterogeneity <0.001;  $I^2$  85.1%) respectively (Figure 3c, 3d).

We also analysed for pooled estimates by distribution of sex among the studies and with the studies that controlled for confounders. In five datasets with reported BP data on male participants separately, the SMD in SBP was 0.05 (95%CI: -0.22, 0.32; p-value for heterogeneity <0.001;  $I^2$  83.6%) and in DBP was 0.16 (95%CI: 0.06, 0.27; p-value for heterogeneity =0.448;  $I^2$  0.0%) (Table 3). In the five datasets with reported BP data on female participants separately, the SMD in SBP was -0.06 (95%CI: -0.57, 0.44; p-value for heterogeneity <0.001;  $I^2$  94.8%) and in DBP was 0.22 (95%CI: -0.10, 0.53; p-value for heterogeneity <0.001;  $I^2$  86.5%). In nine datasets that adjusted for confounders, the SMD in SBP was 0.13 (95%CI: -0.07, 0.34; p-value for heterogeneity <0.001;  $I^2$  80.8%) and in DBP was 0.31 (95%CI: 0.22, 0.39; p-value for heterogeneity =0.460;  $I^2$  0.0%) (Table 3). The influence analysis showed no single study was more influential on the pooled estimate (data not shown). The Begg's funnel plot with pseudo 95% confidence limits showed general symmetry around the median line, and Egger's test revealed no evidence of publication bias (for SBP Egger's bias, -1.92, P, 0.67, for DBP Egger's bias, 0.56, P, 0.80).

### **Sodium in drinking water and hypertension (ORs estimates)**

Three studies measured the association between high water sodium exposure and hypertension

and all were conducted in pregnant women. Of them the recent studies in a coastal sub-district area in Bangladesh <sup>7,20</sup> showed significantly higher average consumption of sodium from drinking water above the recommended level. The hospital-based prevalence of hypertension in pregnancy was 9.28% (95% CI, 7.46-11.12) with a higher proportion of hypertension in the dry season (12.20%) compared to the wet season (5.09%) (Prevalence OR 2.39, 95%CI 1.43-3.99)<sup>7</sup>. In a case control design Khan et al. (2014) <sup>20</sup> further demonstrated a significant dose-response relationship between water sodium level and risk of hypertension in pregnant women. The study by Jones et al. (1979) <sup>32</sup> did not reveal any association.

## Discussion

Our study is the first systematic review and meta-analysis assessing the relationship between water sodium exposure and blood pressure and suggests a small association between elevated sodium exposure in water and a positive mean blood pressure difference, which appears more pronounced on DBP. The association was observed in studies with higher sodium exposure and in studies with young populations. Four studies demonstrated a positive difference in both mean SBP and DBP from higher drinking water sodium exposure <sup>12,13,14,15</sup> and all of them were conducted in developed country settings. The most convincing evidence that supports the relationship, at least for young infants and children, was demonstrated by randomized trials <sup>9,34</sup>. A randomized experimental study with fourth grade students in a community of Massachusetts found that the girls, but not the boys, in the low sodium group had a greater reduction of mean BP ranging from 1.73 – 4.87 mmHg. The effect of the low sodium water was more pronounced for DBP than SBP <sup>34</sup>. Two recent studies in coastal Bangladesh <sup>7,20</sup> also showed consistent associations of drinking water sodium exposure and higher prevalence of hypertension in

pregnant women. More particularly the case-control study by Khan et al. (2014)<sup>20</sup> also demonstrated a dose-response relationship between water sodium level and risks of hypertension in pregnant women.

The importance of isolated high DBP over isolated high SBP has long been debated<sup>40</sup> and remains inconclusive<sup>41</sup>. Observation of more than 80,000 cardiovascular disease presentations indicates that the risks of increased SBP and DBP at different ages on acute and chronic cardiovascular diseases have been disproportionate while high SBP level showed higher risks than high DBP level for major cardiovascular events<sup>42</sup>. The isolated high DBP is more common at a young age<sup>43</sup> and therefore may present a low cardiovascular risk. Although some evidence suggests that isolated high DBP level is significantly associated with increased cardiovascular risk<sup>44</sup>. All the studies that reported BP difference in our analyses were conducted in young populations below 20 years, which might partly explain higher effects on DBP than SBP. Individuals with isolated high DBP have the potential to develop isolated high SBP or systo-diastolic high BP<sup>43</sup>. Excessive salt consumption has been identified as an important predictor to transforming isolated high DBP to systo-diastolic high BP<sup>45</sup>. Given the onset of isolated high DBP at a young age and that it is associated with modifiable risk factors such as sedentary life style and higher body mass index<sup>41</sup>, tracking and controlling isolated high DBP might be of greater public health importance<sup>41</sup>.

In contrast to positive BP difference in above studies, two studies in Australia<sup>19</sup> in young populations (12-14 years) and in the USA<sup>30</sup> in adults (mean 29 years) reported a negative association between water sodium exposure and blood pressure rise. There is no clear explanation for discrepancy of this association in these studies. However Armstrong (1982)<sup>19</sup> had

a small number of participants per group and did not find any significant differences in other factors (e.g. height, weight, physical activity, dietary intake) between the low and high water sodium groups. Choi's (1984)<sup>30</sup> analysis of association was based on secondary data examining the blood pressure level difference between people of two different water sodium areas but lacked data on sodium exposure, blood pressure measurement techniques, any relevant confounders. Furthermore it did not adjust for potential covariates (e.g. residence time, other sources of potable water used). The study by Hallenbeck (1981)<sup>29</sup> demonstrated a significantly higher DBP in both male and female students of high water sodium area, but no such change in SBP in both sexes. Though in this study sodium exposure was assessed at the individual level it was not representative of the study participants, estimated total sodium intake was higher in the low water sodium area in male students and differential living duration between low and high water sodium communities was reported.

The interpretation of the association between water sodium exposure and positive blood pressure difference examined for this review is limited by the small number of studies, more studies in young age groups, the heterogeneity across the studies (as reflected by the high values of the  $I^2$  statistics), the absence of prospective design and few community-based studies. Moreover study specific methodological limitations such as differential and non-standardized individual assessment of sodium exposure including quantifying liquid/water intake to sodium exposure, the interviewer being aware of the participants' exposure status, using different estimates (e.g. mean of two or three BP records and/or discarding first record) to obtain blood pressure level and not accounting for relevant confounders limited the evidence from these studies. Overall the findings of our study are suggestive but not conclusive for an association

between water sodium exposure and positive blood pressure change.

The studies conducted in rural villages of coastal Bangladesh reported almost two-six times higher water sodium level (in ground water mean sodium level was 2600mg/L <sup>7</sup> and 714mg/L <sup>20</sup>) than in the studies that were conducted in other parts of the world, all of them in developed country settings, where the highest level of sodium in water was reported to be around 400mg/L <sup>29</sup>. Though the contribution of water sodium to total intake is considered to be negligible <sup>8</sup>, the water sodium exposure for rural coastal populations like Bangladesh is more likely to be different and higher than that of developed countries where a large share of total sodium intake comes from processed food consumption <sup>5</sup>. People in similar settings to coastal Bangladesh are exposed to high sodium from not only drinking but also cooking water, which is rarely considered. A study among the six tribal communities in the Solomon Islands demonstrated that those who cooked vegetables in seawater had the highest salt intake and exhibited a significantly higher level of systolic and diastolic blood pressures in both sexes and almost all age groups <sup>35</sup>. Moreover potential exposure through accumulation of sodium in produced crops due to increased soil and groundwater salinity in such affected areas also needs to be explored<sup>38</sup>. The total sodium exposure from use of saline contaminated shallow and groundwater sources (e.g. from ponds and rivers, and shallow tube wells) in coastal communities in Bangladesh was well above the recommended level<sup>38</sup>, which was also translated into higher prevalence of blood pressure in pregnant women <sup>7,20</sup>. However, there remains a dearth of evidence regarding the effect of higher water sodium on adult blood pressure in similar settings and if SBP and DBP respond differentially. Further to these findings, biologically, it is plausible that elevated sodium consumed through water would have a similar health effect as elevated

sodium consumed through food.

Saltwater intrusion and increasing water salinity are emerging threats to coastal water resources due to sea-level rise associated with climate change <sup>37</sup>. Water resources in all the eleven Asian mega-deltas and other large deltas such as the Nile and Mississippi are vulnerable to climate change, sea level rise and saltwater intrusion. It is estimated that sea level rise will affect more than 1 million people by 2050 in three megadeltas: the Ganges-Brahmaputra delta in Bangladesh, the Mekong delta in Vietnam and the Nile delta in Egypt <sup>11</sup>. The current recommendation for reducing salt intake that is based on food alone is less likely to be adequate for the large population in low-income countries already exposed to elevated sodium level in water. Around 300 million inhabitants living in Asian Deltas are facing serious contamination problems in their water supply including increasing salt concentration <sup>46</sup>, which is likely to aggravate further with the projected climate change scenario. But the contribution of water sodium to total sodium intake and subsequent health effects has so far received less attention in epidemiological studies. The most recent assessment by WHO of the epidemiological evidence to recommend a level for safe sodium in water was inconclusive <sup>8</sup>. Public health professionals must act immediately to better understand sodium exposure pathways in these high-risk communities, improve the evidence base to establish an exposure-outcome and dose-response relationship using rigorous methodology and identify appropriate preventive measures.

One important limitation of our meta-analyses is that we restricted our analyses to full-text articles published in English. There might have been other unpublished studies that were not available online, that therefore could not be assessed. Despite these limitations, the findings of our review provide useful insights for future research needs in this area.

**Conclusion**

We identified an association between high water sodium and positive blood pressure difference, more consistently for DBP. The evidence is further limited due to the small number of studies, largely in young populations and utilizing cross-sectional designs, and with methodological drawbacks. With the projected increase in salinity of freshwater resources from climate change induced sea level rise and saltwater intrusion, particularly in low-lying and low-income countries, it is pertinent to investigate further the effects of chronic water sodium exposure on blood pressure using designs with increased evidence strength such as prospective studies. Given that the progressive effect of sodium on blood pressure and continued consumption of water with elevated levels of sodium may contribute to escalation of high blood pressure in large populations and other related chronic diseases (e.g. cardiovascular and kidney diseases) in low-lying coastal areas, there is a need for immediate promotion of appropriate prevention strategies. Even a modest rise in blood pressure from chronic water sodium exposure will have substantial impact on morbidity and mortality. Further research is warranted examining the different exposure pathways to total sodium intake in vulnerable populations, contribution of water sodium to total consumption, its effect on blood pressure and subsequent wellbeing and other health outcomes, and identifying appropriate interventions to reduce exposure to this sodium source.

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Table 1: Epidemiological studies on sodium exposure in drinking water and blood pressure or hypertension as outcome

Authors and Year	Study type	Country, Study population (N)	Age (years)	Sex	Drinking water Na level (Mean)	Sodium exposure assessment	Total sodium (food & liquid/water) exposure (Mean gram (sd))	BP assessment and defining hypertension	Variables adjusted
Tuthill and Calabrese 1979 <sup>12</sup>	Cross-sectional study	USA, Massachusetts, 606 high school students	Median - 12.7	Both	8 mg/L vs. 108 mg/L	Dietary history	-	Mean of three measures of BP on the left arm in sitting position after rest for 25 minutes maximum with an aneroid manometer	Adjusted for age, sex, height, weight, length of residence, smoking habits, socio-demographic condition, dietary sodium etc.
Hofman et al. 1980 <sup>14</sup>	Retrospective follow up	Netherlands, 348 primary	7.7-11.7 years	Both	-	No dietary record	2.507 (0.920) (H), 2.254	Mean of two recordings of BP after	Adjusted for weight, height

Authors and Year	Study type	Country, Study population (N)	Age (years)	Sex	Drinking water Na level (Mean)	Sodium exposure assessment	Total sodium (food & liquid/water) exposure (Mean gram (sd))	BP assessment and defining hypertension	Variables adjusted
	study	school children				obtained, 24-hour urine samples	(0.897) (L)	resting for 5 minutes on left arm in sitting position with a random-zero sphygmomanometer	, family history of hypertension
Tuthill and Calabrese 1981 <sup>13</sup>	Cross-sectional study	USA, Massachusetts, 607 high school students	3rd graders	Both	8 mg/L vs. 108 mg/L	24-hour dietary record. First morning urine samples from a subset of 100	Male 2.904 (1.088) (H), 2.557 (0.962) (L); Female 2.851 (1.135) (H), 2.523 (1.01	Mean of three measures of BP in sitting position by three separate nurses blinded to each other's readings.	Adjusted for height, weight and social class



Authors and Year	Study type	Country, Study population (N)	Age (years)	Sex	Drinking water Na level (Mean)	Sodium exposure assessment	Total sodium (food & liquid/water) exposure (Mean gram (sd))	BP assessment and defining hypertension	Variables adjusted
						individuals	3) (L)		
Hallenbeck et al.1981 <sup>30</sup>	Cross-sectional study	Chicago, 638 high school students	Third and fourth year	Both	4mg/L vs. 405mg/L	5 days overnight urine samples in a selected sub-sample, 3 days liquid intake	Male 0.586 (76) (H), 0.722 (73) (L); Female 0.748 (48) (H), 0.748 (62) (L)	Three measures of BP in 5 minutes on the left arm in sitting position with mercury sphygmomanometer; Mean of second and third records was considered	Adjusted for cigarettes and BMI
Armstrong et al. 1982 <sup>19</sup>	Cross-sectional study	Western Australia, 635 high	12-14 years	Both	Ranging from 1.46 to 9.69 mmol/L (29.2mg/L to 193.8mg/L)	24-hour dietary diary. Two	3.661 (H); 4.015 (L)	Two measures of BP after 5 minutes rest in	Adjusted for height, weight, mid

Authors and Year	Study type	Country, Study population (N)	Age (years)	Sex	Drinking water Na level (Mean)	Sodium exposure assessment	Total sodium (food & liquid/water) exposure (Mean gram (sd))	BP assessment and defining hypertension	Variables adjusted
		school students				consecutive 24-hr urine specimens were collected from boys		both sitting and standing positions with London School of Hygiene sphygmomanometer; Single measurement immediately after standing was used	upper arm circumference, dietary sodium intake, pulse rate
Pomeranz et al. 2000 <sup>15</sup>	Cross-sectional study	Israel, 956 school children	9-12 years	Both	25-35mg/L vs. 196mg/L	Dietary salt consumption history, Single	-	Mean of three recordings of BP in sitting position after resting for 25 mins	None

Authors and Year	Study type	Country, Study population (N)	Age (years)	Sex	Drinking water Na level (Mean)	Sodium exposure assessment	Total sodium (food & liquid/water) exposure (Mean gram (sd))	BP assessment and defining hypertension	Variables adjusted
						urine sample		using DINAM AP-Doppler technique	
Jones et al. 1979 <sup>32</sup>	Case control study	Houston, Texas, Jefferson Davis Hospital (JDH), 537 cases (pregnant women) and equal number of matched controls	Mean 18.99 (cases) 18.84 (controls)	Female	Ranged from 19 to 250 mg/L	-	-	Hospital record of blood pressure	Adjusted for age, obstetrical history, or race

Authors and Year	Study type	Country, Study population (N)	Age (years)	Sex	Drinking water Na level (Mean)	Sodium exposure assessment	Total sodium (food & liquid/water) exposure (Mean gram (sd))	BP assessment and defining hypertension	Variables adjusted
Choi YH 1984 <sup>31</sup>	Cross-sectional study	Jackson City, Mississippi, 1052 participants	Mean age 29 years	Both	11 mg/L vs. 94 to 120 mg/L.	No information given	-	Hospital record of blood pressure	None
Khan et al. 2011 <sup>7</sup>	Cross-sectional study	Bangladesh, 343 pregnant women	13-49 years	Female	Dry season 11,400mg/L-12,900mg/L, Wet season 3,800mg/L-3,900mg/L;	No dietary assessment; 24-hr urinary samples	3.4 (maximum 7.7)	Blood pressure measurement at 20 weeks of gestation, standardized hypertension definition used	None
Khan et al. 2014 <sup>20</sup>	Case control study	Bangladesh, pregnant women; Cases-202,	13-49 years; Mean age Cas	Female	Cases- 727.9 mg/L Control- 439.4 mg/L	Cases- spot urine Controls- 24-hr urinary	-	Blood pressure was measured using standard protocol, standardized	Age, parity, SES, Mid upper arm circumference

Authors and Year	Study type	Country, Study population (N)	Age (years)	Sex	Drinking water Na level (Mean)	Sodium exposure assessment	Total sodium (food & liquid/water) exposure (Mean gram (sd))	BP assessment and defining hypertension	Variables adjusted
		Controls-1006	es-23.8 years Controls-23.1 years			ry assessment		zed hypertension definition used	nce

Table 2: Evaluation criteria for study design and data analysis of included epidemiological studies on water sodium and blood pressure or hypertension

	Tuthill & Calabrese 1979 <sup>12</sup>	Hofmann et al. 1980 <sup>14</sup>	Tuthill & Calabrese 1981 <sup>13</sup>	Hallenbeck et al. 1981 <sup>30</sup>	Armstrong et al. 1982 <sup>19</sup>	Pomeranz et al. 2000 <sup>15</sup>	Jones et al. 1979 <sup>32</sup>	Choi 1984 <sup>31</sup>	Khan et al. 2011 <sup>7</sup>	Khan et al. 2014 <sup>20</sup>
Blood pressure was measured on participant at resting state in a seated position, using multiple SBP and DBP measures on the same arm with an appropriately sized cuff	Yes	Yes	Yes	Yes	Yes	Yes	No	-	-	Yes
Obtained SBP and DBP value averaging multiple records/ Had standard hypertension definition	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	Yes	Yes
Sodium exposure assessed from 24-hour urine with either single/multiple day collections	No	Yes	No	No	Yes*	Yes	No	No	Yes	Yes*
Sodium exposure assessed at the individual level	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Quantified liquid/water intake to total sodium exposure	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes
Participation rate was at least 70%	Yes	Yes	Yes	Yes	Yes	-	-	-	Yes	Yes
Inclusion and exclusion criteria for	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

participants' recruitment was clearly stated										
Interviewer was blinded with respect to the participant exposure status	No	Yes	No	No	-	-	Yes	-	-	Yes
Data collected in a similar manner for all participants	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Controlled for relevant confounding factors e.g. age, sex, family history and BMI	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes

\* Only for boys; \*\*only for control population; - no data

Table 3: Summary of pooled SMD in SBP and DBP by study characteristics

		<b>SBP</b>	<b>DBP</b>
<b>Characteristics</b>	<b>No. Of participants</b>	<b>Pooled SMD** (95% CI)</b>	<b>Pooled SMD (95% CI)</b>
Overall N=12*	3747	0.08 (-0.17, 0.34)	0.23 (0.09, 0.36)
Categories by highest level of exposure			
High (>150mg/L) (n=6)	1482	-0.04 (-0.35, 0.43)	0.27 (0.16, 0.38)
Low (<150 mg/L) (n=6)	2265	0.12 (-0.24, 0.49)	0.20 (-0.03, 0.43)
Sex			
Male (n=5)	1552	0.05 (-0.22, 0.32)	0.16 (0.06, 0.27)
Female (n=5)	1435	-0.06 (-0.57, 0.44)	0.22 (-0.10, 0.53)
Controlled for confounders			
Yes (n=9)	2157	0.13 (-0.07, 0.34)	0.31 (0.22, 0.39)
No (n=3)	1590	0.02 (-0.81, 0.84)	0.06 (-0.30, 0.42)

\* Number of dataset

\*\* SMD- standardized mean difference



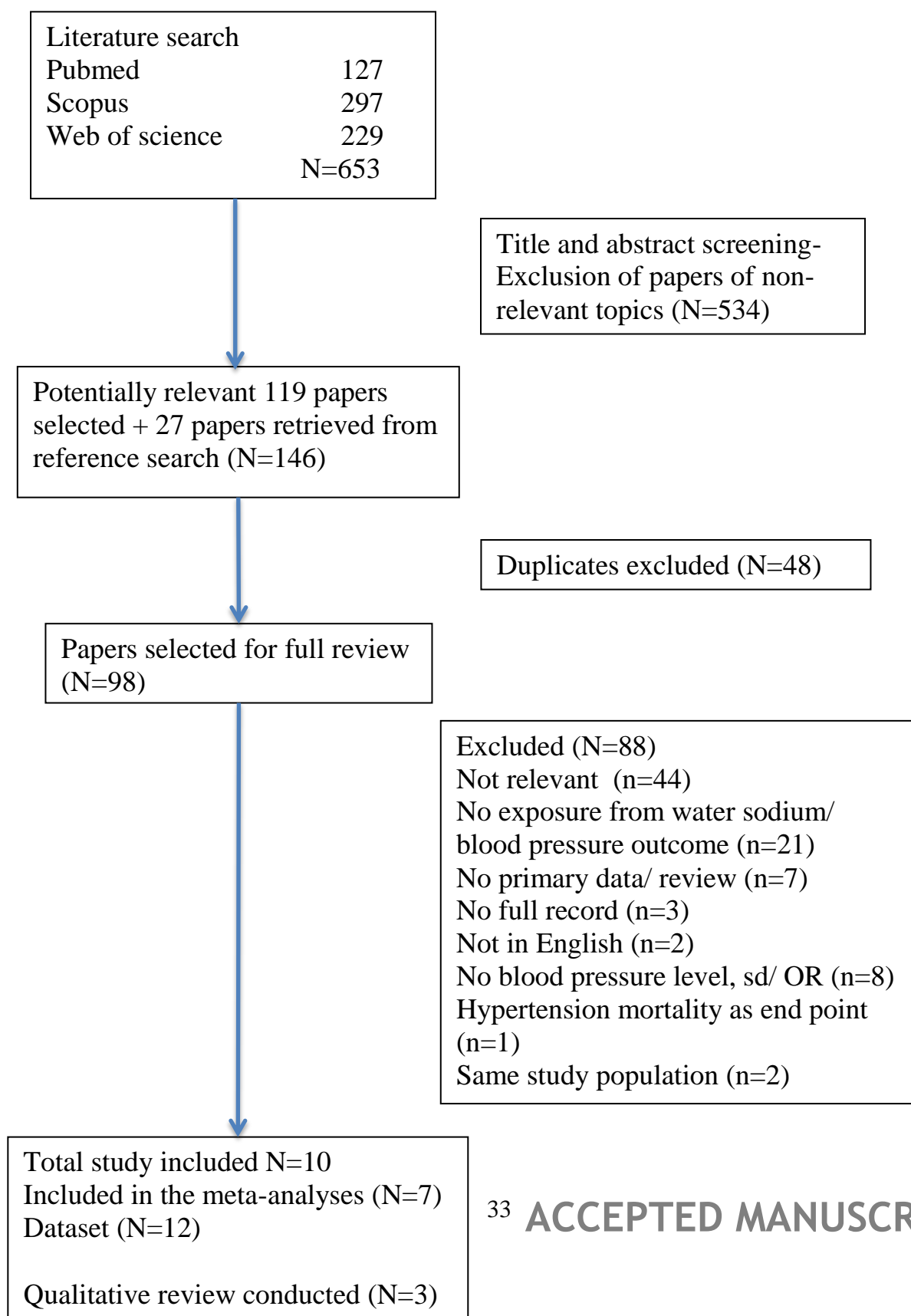
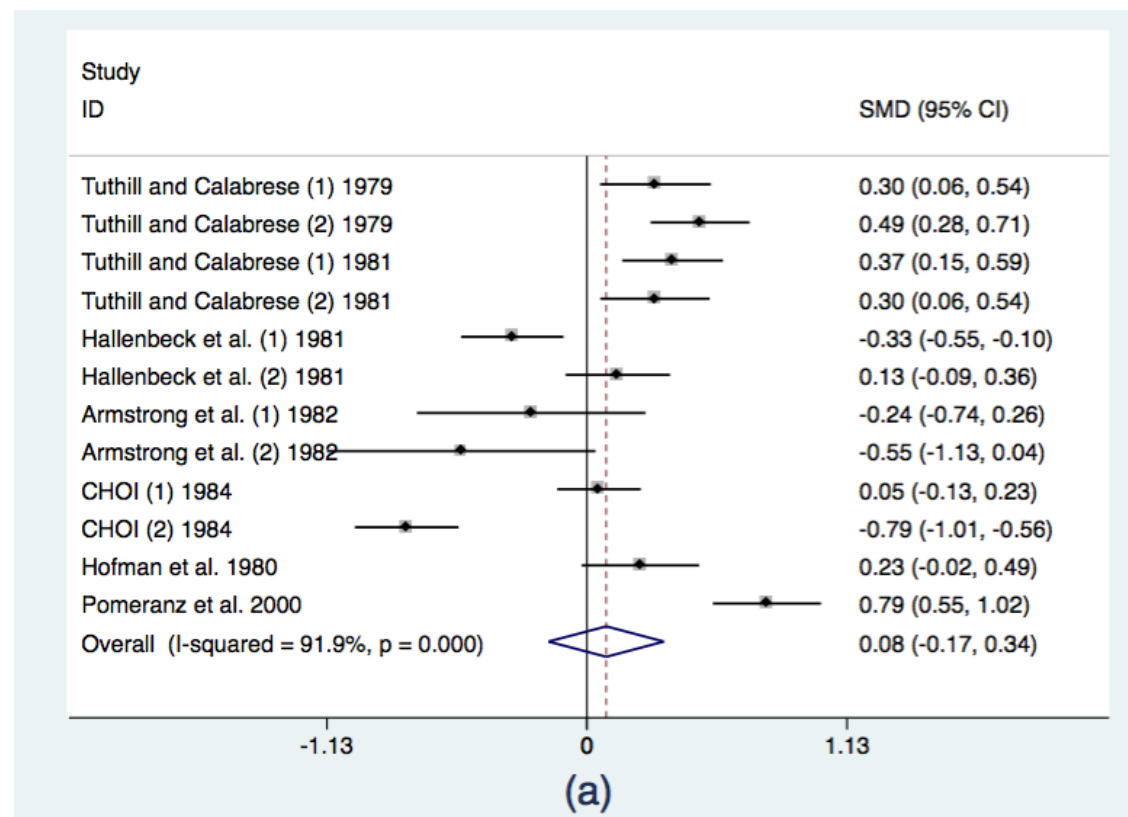


Figure 1: Flowchart presenting the procedure for identifying relevant publications



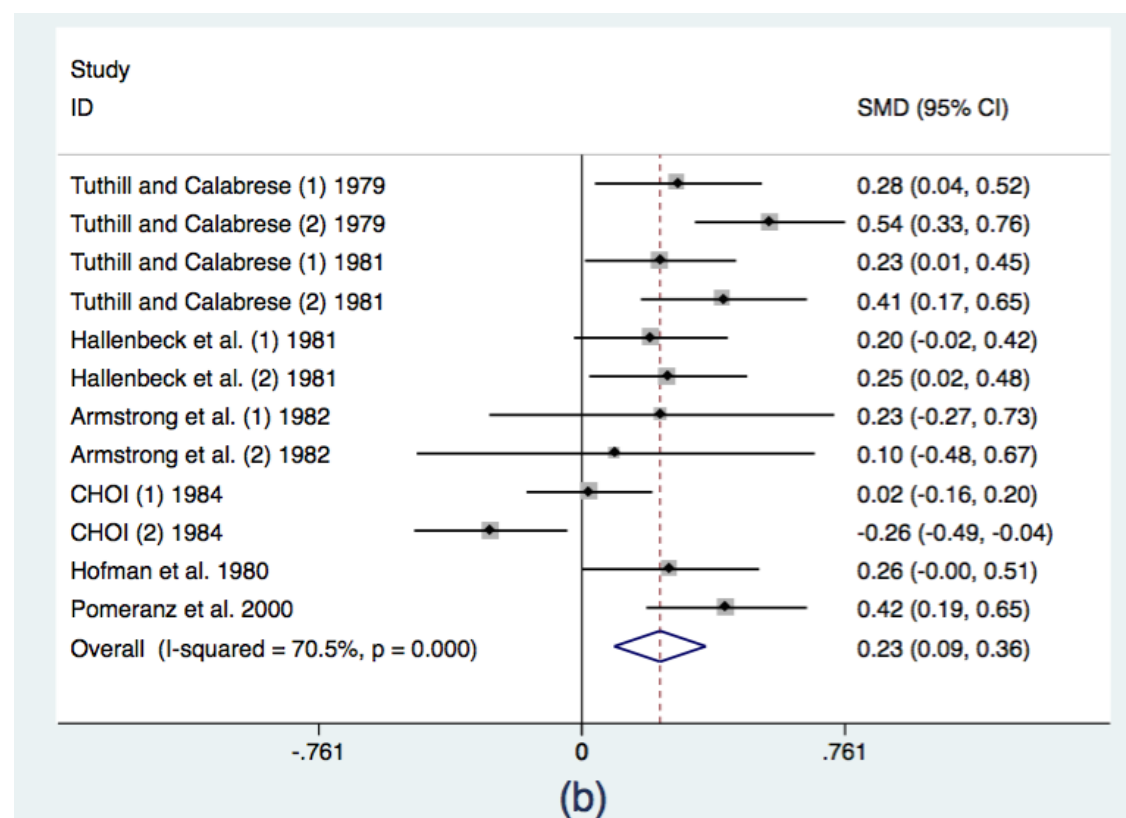
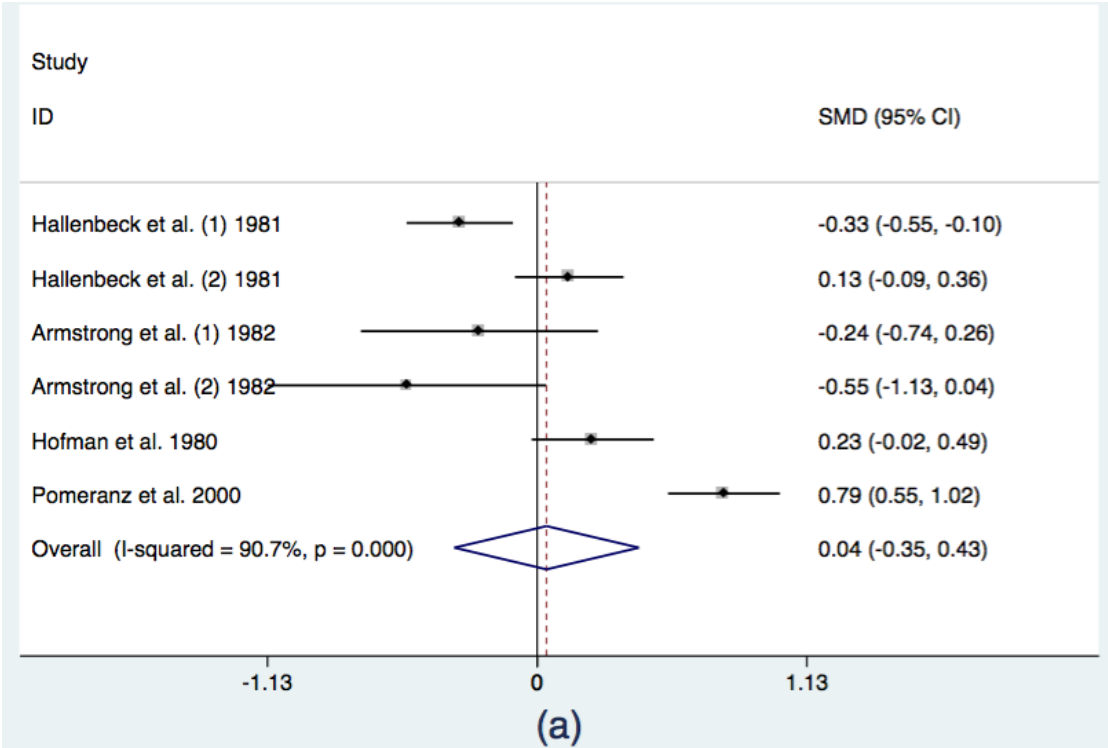
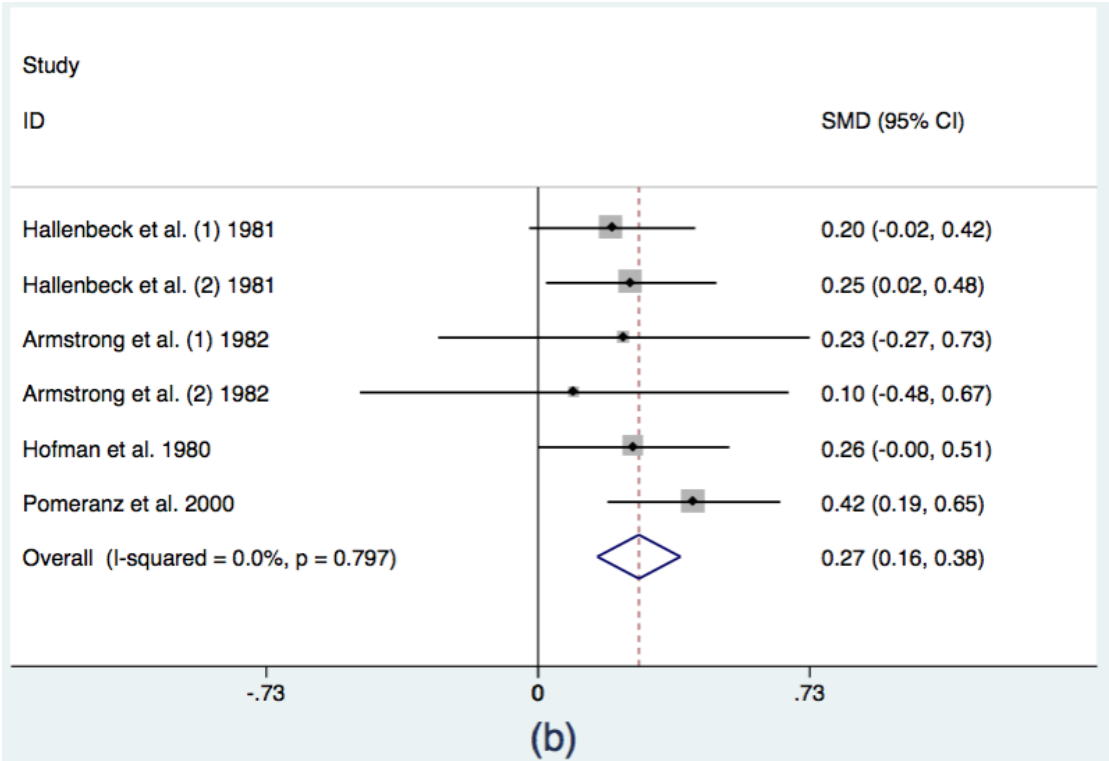
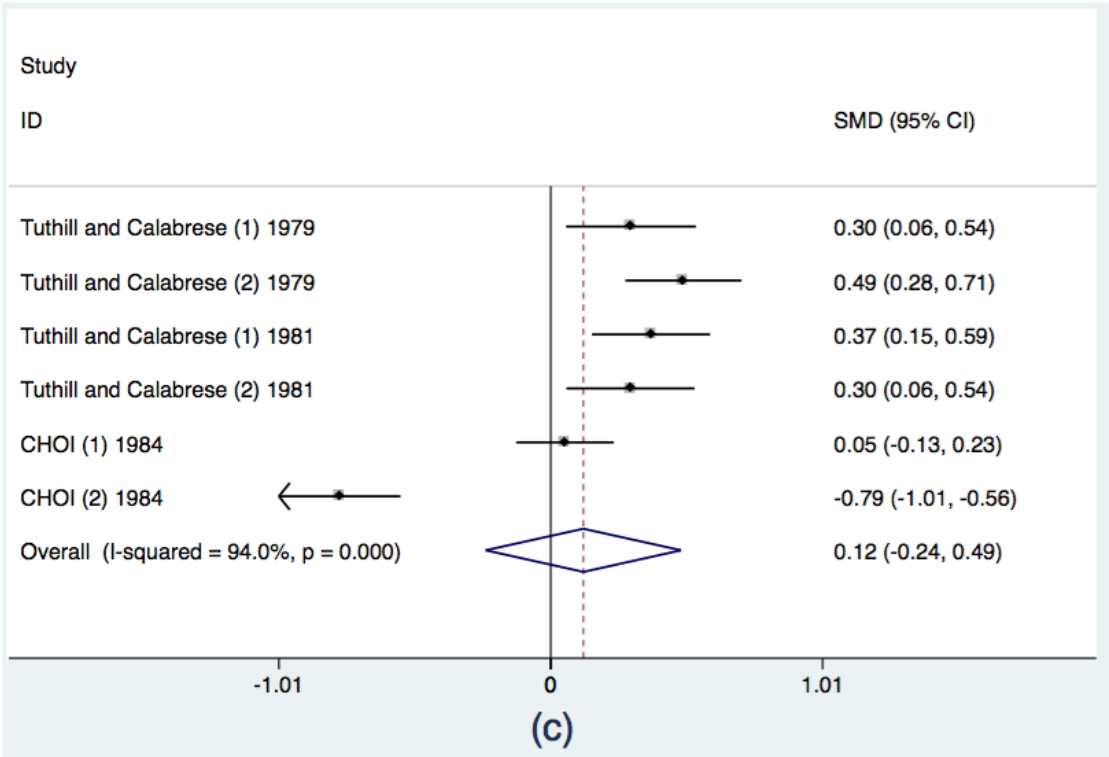


Figure 2: Forest plot showing standardized mean difference (SMD) in SBP (a) and in DBP (b)







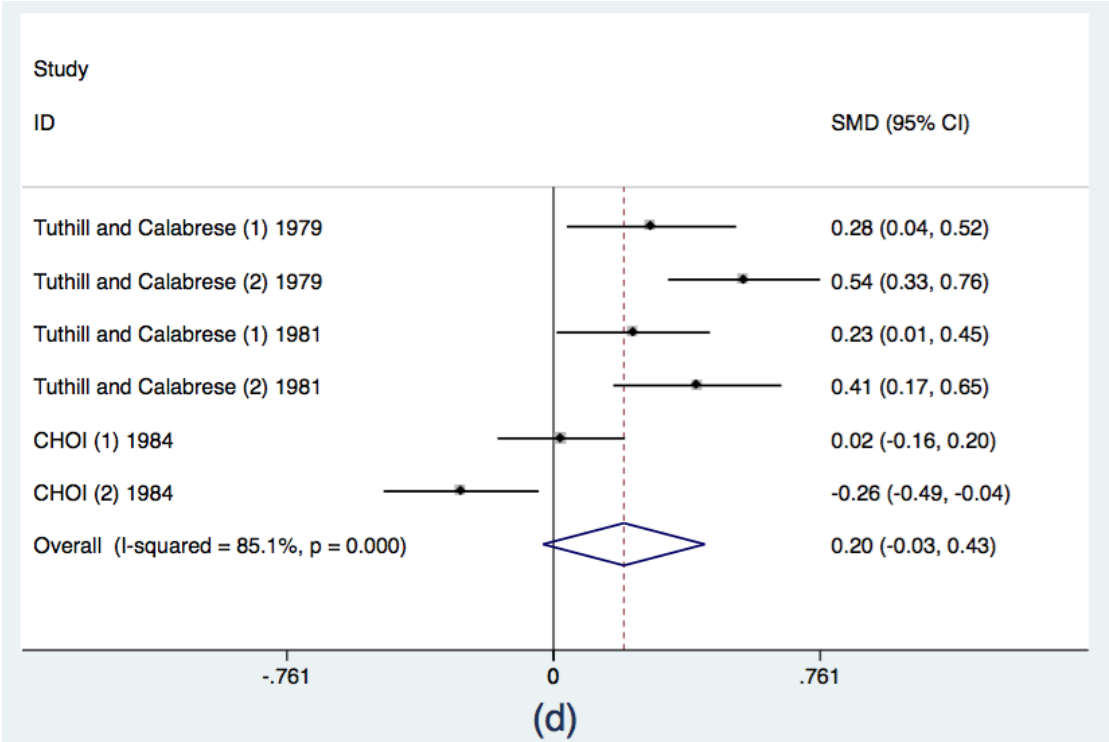


Figure 3: Forest plot showing standardized mean difference (SMD) standardized mean difference (SMD) in SBP (a) and in DBP (b) by higher (>150mg/L) category of highest sodium exposure and SMD in SBP (c) and in DBP (d) by lower (<150mg/L) category of highest sodium exposure