2010 Dietary Guidelines Advisory Committee:

Systematic Reviews of the Sodium, Potassium and Water Subcommittee

USDA's Nutrition Evidence Library supported the 2010 Dietary Guidelines Advisory Committee as it conducted systematic reviews on diet and health. This document includes archives from www.NEL.gov of the complete evidence portfolios for all NEL systematic reviews conducted by the Sodium, Potassium and Water Subcommittee. The *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010* summarizes these systematic review findings and provides interpretations and implications related to these reviews.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

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CHAPTER 1. OVERVIEW AND NEEDS FOR FUTURE RESEARCH

OVERVIEW

Dietary intakes of sodium, potassium and water have substantial health effects. Excessive sodium intake, especially when accompanied by inadequate potassium intake, raises blood pressure (BP), a well-accepted and extraordinarily common risk factor for stroke, coronary heart disease (CHD) and kidney disease.

Adverse effects of sodium on BP appear to begin early in life. Because of worsening BP levels in children in the United States, the 2010 Dietary Guidelines Advisory Committee (DGAC) decided to evaluate available research on the health effects of sodium in children, as well as update the 2005 DGAC's review of research on the health effects of sodium in adults.

While the vast majority of research on the health effects of sodium, potassium and water on adults was published before 2005 and synthesized in the 2005 DGAC report, the Subcommittee conducted a NEL systematic review to build upon those findings and add relevant new literature from updated searches. The new focus involves considerably more effort in reviewing the emerging and growing evidence on the BP effects of sodium in children.

Elevated BP is a highly prevalent, etiologically relevant and modifiable risk factor for cardiovascular and renal diseases. A low intake of dietary potassium, especially in the presence of high sodium intake, has been implicated in the pathogenesis of elevated BP. The 2005 DGAC reviewed available evidence from the relationship between potassium intake and BP and concluded that an increased intake of potassium lowers BP. The 2010 DGAC performed an updated search of literature published since 2005 to identify new research on the relationship between potassium intake and BP.

Recommendations for water are made to prevent the deleterious, primarily acute, effects of dehydration. These effects include impaired cognitive function and motor control. Although a low intake of water has been associated with an increased risk of kidney stones and other chronic diseases, this evidence was insufficient for the 2005 DGAC to establish quantitative recommendations for water consumption.

The 2010 DGAC conducted exploratory literature searches on the relationship of water intake with hydration, kidney stones, body weight, and cancer. These searches revealed that for the purposes of identifying health problems related to water intake in the general population, little additional evidence on these topics has been published after the 2005 DGAC report.

NEEDS FOR FUTURE RESEARCH

1. Conduct studies, including clinical trials, in children to determine the effects of sodium on BP and the age-related rise in BP.

- Rationale: The problem of elevated BP begins in childhood, well before BP levels cross the threshold that defines hypertension (HTN) in adults (140/90mmHg).

2. Conduct trials that determine the effects of sodium reduction on clinically relevant non-blood pressure variables, such as left ventricular mass, proteinuria and bone mineral density (BMD).
   - Rationale. An inclusive body of evidence suggests that the benefits of a lower sodium intake extend beyond reduced BP. Evidence from cross-sectional studies has documented that sodium is directly associated with left ventricular mass and proteinuria. Clinical trials have also documented that a higher intake of sodium increases urinary calcium excretion.

3. Conduct controlled trials that test whether increased potassium intake through supplements or potassium-rich foods increase BMD.
   - Rationale: A consistent body of evidence from observational studies indicates that increased intake of potassium from foods is associated with greater BMD and with evidence of reduced bone turnover. Data from small trials also have documented that increased intake of potassium reduces bone turnover.

4. Conduct dose-response trials that test the main and interactive effects of sodium and potassium intake, as well as possible impact of other minerals (e.g., calcium, magnesium) on BP and other clinically relevant outcomes.
   - Rationale: There remains a need for dose-response trials, particularly for potassium, that span a clinically relevant range of dietary intake. Also, the interactive effects of sodium and potassium are of considerable interest.

5. Investigate the role of increased total fluid intake as a means to prevent chronic diseases.
   - Rationale: A few studies suggest that increased fluid consumption might reduce the risk of bladder cancer, urinary tract infections, kidney stones, and colon cancer. However, this evidence was insufficient to make recommendations on fluid intake.

CHAPTER 2. POTASSIUM AND BLOOD PRESSURE IN ADULTS

WHAT IS THE RELATIONSHIP BETWEEN DIETARY POTASSIUM INTAKE AND BLOOD PRESSURE IN ADULTS?

Conclusion statement

Considerable evidence has demonstrated that a higher intake of potassium is associated with lower blood pressure in adults.

Grade

Strong

Evidence summary overview

A total of 10 articles met the inclusion criteria and were reviewed. Of the 10 articles, five were systematic reviews/meta-analyses, four were randomized controlled trials (RCTs) and one was a three period, non-randomized cross-over trial. Two trials compared potassium chloride (KCl) to potassium citrate (K-cit), one trial without a placebo group. Potassium citrate is the form most similar to that provided naturally in food. Six studies were judged as positive quality and four were neutral in quality.

Enrollment criteria differed among the studies. Three systematic review/meta-analyses included trials that studied hypertensive or normotensive populations, or both. One systematic review/meta-analysis and one RCT studied just hypertensive subjects. Three RCTs and one non-randomized trial enrolled non-hypertensive individuals. The trials were conducted in China, New Zealand, Okinawa and the United Kingdom. Two systematic review/meta-analysis included studies from Australia, Germany, Italy, Japan, Kenya, Netherlands, New Zealand, the United Kingdom and the US; two did not identify the study locations. The five systematic reviews/meta-analyses had some overlap between included trials; this ranged from five out of five (Dickinson et al, 2006) to 25 out of 55 (Burgess et al, 1999).

Each study reported the effects of potassium intake, either from supplements or diet, on blood pressure (BP) in adults. Considering all studies, there was a significant reduction in either systolic blood pressure (SBP) or diastolic blood pressure (DBP) in all but one study and significant reductions in both SBP and DBP in four studies. Among the four RCTs studies judged to be of positive quality, there was a significant reduction in SBP or DBP in each study.

Three meta-analyses of these trials document that, on average, increased potassium intake lowers BP (Cappuccio and MacGregor, 1991; Geleijnse, 2003; Whelton, 1997). In the meta-analysis by Whelton et al, (1997), average net SBP/DBP reductions from a net increase in urinary potassium excretion of 2g per day (50mmol per day) were 4.4/2.5mmHg among hypertensive individuals and 1.8/1.0mmHg among non-hypertensive individuals. A meta-analysis (Dickinson et al, 2006) did not detect a significant effect of potassium on BP, but this meta-analysis applied especially restrictive exclusion criteria (just hypertensive individuals, with at least eight weeks of treatment) and included only five trials. The review by Burgess (1999) was not a formal

meta-analysis. These BP reductions tended to be greatest in hypertensive individuals and Blacks.

Mostly on the basis of literature reviewed for the Dietary Guidelines 2005 (DG2005), we conclude that increased potassium intake lowers BP (Evidence Level: Strong).

Evidence summary paragraphs

Systematic Reviews/Meta-analyses

Burgess E et al, 1999 (neutral quality) a systematic review of 55 studies was conducted to update evidence-based Canadian recommendations for dietary or supplemental cation intake, including potassium, for the prevention and treatment of HTN in otherwise healthy adults (except pregnant women). MEDLINE was searched for reviews, meta-analyses, observational studies and RCTs published in English or French from 1966 to 1996. Included health outcomes were changes in BP, morbidity and mortality. Articles were reviewed, classified according to study design and graded using Canadian Hypertension Society principles. Higher value was placed on the prevention of cardiovascular morbidity and premature death from untreated HTN. The panel concluded that the evidence did not support potassium supplementation to prevent BP increases in normotensives or to reduce BP in hypertensives. The panel did find that potassium supplementation may be effective in reducing BP in hypokalemic patients during diuretic therapy. The panel recommended that, for prevention of HTN and reduced risk of stroke-related mortality, daily potassium intake should be 60mmol or more through dietary intake, not supplementation.

Cappuccio F et al, 1990 (positive quality) a meta-analysis conducted in England, analyzed 19 clinical trials that studied the effect of potassium supplementation on BP. The studies included a total of 586 participants; 412 with essential hypertension. Pooled analysis of the effect of potassium supplementation estimated a 5.9mmHg reduction in SBP (95% CI: -6.6 to -5.2mmHg) and 3.4mmHg reduction in DBP (95% CI: -4.0 to 2.8mmHg). Analysis of only hypertensive subjects found that the magnitude of the blood pressure lowering effect was greater. Systolic blood pressure decreased 8.2mmHg (95%CI: -9.1 to -7.3mmHg) and DBP decreased 4.5mmHg (95%CI: -5.2 to -3.8mmHg). Weighted regression analysis showed a significant relationship between decrease in BP and the duration of supplementation ($P<0.05$ and $P<0.01$ for SBP and DBP, respectively). The authors concluded that non-pharmacological approaches for BP control in subjects with uncomplicated essential HTN should include a recommendation for increased potassium intake.

Dickinson et al, 2006 (positive quality), a Cochrane systematic review and meta-analysis of trials conducted in the US, Australia, Kenya, Germany and Italy, evaluated the effects of potassium supplementation on health outcomes and BP in adults with HTN. One of the exclusion criteria was treatment duration of at least eight weeks. After exclusion criteria were applied, five RCTs of parallel or crossover design that compared oral potassium supplements with placebo, usual care, or no treatment were identified that included a pooled total of 425 participants whose SBP was>140mmHg and DBP was>85mmHg without a known primary cause. Compared to control subjects, potassium supplementation resulted in a statistically non-significant reduction in SBP (mean difference: -11.2, 95% CI: -25.2 to 2.7) and DBP (mean difference: -5.0

(95% CI:-12.5 to 2.4). Excluding one trial in an African population with very high baseline BP resulted in small overall reductions in BP (SBP mean difference= -3.9, 95% CI: -19.9, 5.7; DBP mean difference= -5.5, 95% CI: -14.5 to 3.5). Two trials administering lower (fewer doses of potassium showed greater reductions in BP than three trials administering >100mmol per day, which was significant for DBP (mean differences in the two trials= -17.00 (95% CI: -19.25, -14.75) and -10.50 (95%CI: -16.32, -4.68) mmHg). While the authors concluded the effect of potassium supplementation on BP is uncertain, this meta-analysis applied especially restrictive exclusion criteria.

Geleijnse et al, 2003 (neutral quality) a meta-analysis, conducted in the Netherlands, examined RCTs to assess BP response to sodium and potassium intake in adults. MEDLINE (January 1995-March 2001) and reference lists of systematic reviews were searched and 27 trials (N=30 strata) met the criteria for review, which included a minimum duration of two weeks. Data on changes in electrolyte intake and BP during intervention were collected, along with data on mean age, gender, body weight, initial electrolyte intake and initial BP of the study populations. Weighted meta-regression was used to analyze the effect of potassium intake on BP. Analyses were repeated with adjustment for potential confounders. Increased potassium intake (median: 44mmol per 24 hours) resulted in a 2.42mmHg decrease in SBP (95% CI:-3.75, -1.08mmHg) and a 1.57mmHg decrease in DBP (95%CI:-2.65, -0.50). Blood pressure response was larger in hypertensives than normotensives, (SBP: -3.51 vs. -0.97mmHg, P=0.089; DBP: -2.51 vs. -0.34mmHg, P=0.074). The authors concluded that increasing potassium consumption could help reduce BP, especially in populations with HTN.

Whelton P et al, 1997 (positive quality) a meta-analysis, conducted in the US, examined 33 RCTs to assess the effect of potassium supplementation on BP in adults (pooled N=2,609 participants). Included studies were published before July 1995 in the English language. A standardized protocol was used to extract information on sample size, duration, study design, potassium dose, participant characteristics and treatment results. Each trial's results were weighted by the inverse of its variance, then a random-effects model was used to pool findings. One trial was excluded because an extreme BP lowering effect was noted. After exclusion, pooled analysis found that potassium supplementation was associated with a 3.11mmHg reduction in mean SBP (95% CI:-1.91 to -4.31mmHg) and 1.97mmHg reduction in mean DBP (95% CI: -0.52 to -3.42mmHg), both P<0.001. It was also reported that the effects of treatment appeared to be enhanced in studies in which participants were concurrently exposed to a high intake of sodium. The authors concluded that low potassium intakes may contribute to the onset of high BP and that increased potassium intake should be considered as a recommendation for prevention and treatment of HTN, especially for individuals who are unable to reduce their sodium intake.

Randomized Controlled Trials

Braschi et al, 2008 (positive quality) a randomized, double-blind placebo-controlled trial conducted in the United Kingdom, compared the effect of supplementation with KCl or K-cit on BP in predominately healthy, normotensive volunteers (N=90, age range 33.8 to 36.9 years, body mass index (BMI) across groups: 22.55 to 25.2kg/m2.

After a two week run-in, subjects were randomly assigned to receive KCl (30mmol K), K-cit (30mmol K) or placebo for six weeks. Urinary electrolyte excretion, plasma electrolytes, BP, BMI and heart rate were measured at baseline and end of intervention. At baseline, mean K excretion was over 70mmol per day in each group. Compared with placebo, KCL significantly reduced SBP, DBP and mean arterial pressure (MAP) by 5.2, 4.3 and 4.7mmHg respectively. Corresponding reductions for K-citrate were 6.7, 4.3 and 5.2mmHg (all statistically significant). The BP changes induced by K-cit and KCl were NS different from each other, and were not related to baseline urinary electrolytes. There was a greater treatment-related effect observed in those with higher baseline SBP (P=0.007). This study documented that a modest dose of potassium, only 30mmol per day, reduces blood pressure. Even though there was no significant difference between the KCL and K-Cit groups, the study was likely underpowered to detect a difference in BP.

He et al, 2005 (positive quality), a randomized cross-over trial conducted in the United Kingdom, compared the effects of supplementation with KCl (96mmol K) and K-cit (96mmol K) on BP in 14 hypertensive Caucasian adults (11 males, three females; mean age: 51+9 years; baseline BP=151+16/93+7mmHg; 24-hour urinary K=164+36mmol). Subjects were randomly assigned to first receive KCl or K-cit for one week, followed by the other intervention, with a one-week washout period in between. Blood pressure, body weight and plasma and urinary electrolytes were measured at baseline and at the end of each treatment period. After KCl, BP was 140+12/88+7mmHg (SBP: P<0.001, DBP: P<0.01 compared to baseline) and urinary K was 164+36mmol. After K-cit, BP was 138+12/88+66mmHg (SBP: P<0.01, DBP: P<0.05 compared to baseline) and urinary K was 160+33mmol. There were NS differences in BP between treatments. Plasma K values were significantly higher after both interventions (KCl: 4.6+0.3mmol per L; K-cit: 4.6+0.3mmol per L) than at baseline (4.2+0.3mmol per L) (P<0.001). Study limitations include the small number of subjects and the lack of a placebo group. Overall, the authors concluded that KCl and K-cit have a similar effect on BP. Even though there was NS difference between KCL and K-Cit, the study was likely underpowered to detect a difference in BP.

He J et al, 2009 (positive quality). This non-randomized, controlled three-week feeding trial, conducted in rural China, examined gender differences in BP response to dietary sodium and potassium intake. The interventions included seven days on a low-sodium diet (51.3mmol per day), seven days on a high-sodium diet (307.8mmol per day) followed by seven days on a high-sodium (307.8mmol per day) plus potassium supplementation (60mmol per day), with no washout period between interventions. Subjects were 1,906 adults (1,010 men and 896 women), SBP 130-160 and DBP 85-100mmHg; including eligible siblings and offspring, aged 18-60 years, who participated in the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study. During the interventions, meals were prepared without salt. Staff added prepackaged salt to individual meals prior to serving and observed subjects' consumption. Food records were kept for each meal. At baseline and in each phase of the intervention, three timed urine specimens were collected (one 24-hour and two overnight) to assess dietary compliance. Nine BP measurements were obtained during the three-day baseline observation and the last three days of each intervention using a random-zero sphygmomanometer. For an assessment of the effects of potassium on BP, only the

last two periods are relevant (high salt/low potassium, compared to high salt/high potassium). In men, potassium lowered SBP by 4.4 and DBP by 1.5mmHg (each statistically significant). In women, potassium also lowered BP (SBP reduction of -4.5 and DBP of -2.1mmHg); the DBP reduction in women was slightly, but significantly higher than that observed in the mean (P=0.007). Study strengths include excellent compliance, inclusion of an arm with increased potassium, rigorous methods and conduct of a trial in an understudied, non-overweight population. Limitations include the short duration of each intervention phase (seven days), lack of a washout period, non-randomized order of diets, pre-post evaluation and single ethnic group (rural Chinese). Overall, results from this trial suggest that an increased intake of potassium lowers BP in a pre-hypertensive and hypertensive generally lean, Asian population.

Hilary Green et al, 2000 (neutral quality), a randomized crossover double-blind controlled trial conducted in New Zealand, evaluated the effect of high-calcium skim milk or potassium-enriched high-calcium skim milk on BP compared with non-enriched skim milk. Healthy subjects (N=19 males, mean age=55+11 years, BMI=27.0+2.3kg/m2; 19 females, mean age=50+10 years, BMI=25.7+4.6kg/m2) who were not receiving pharmacologic treatment for HTN, replaced their usual liquid milk with two servings (480ml) per day of reconstituted skim milk powder (SMP) (720mg Ca, 885mg K, 64mg Mg, 197mg Na), high-calcium SMP (1,075mg Ca, 855mg K, 75mg Mg, 208mg Na) or potassium-enriched high-calcium SMP (1,040 Ca, 1,585mg K, 71mg Mg, 195mg Na) for four weeks each, in randomized order, with a four-week washout periods between each milk intervention. Sitting and standing BP were recorded at baseline and at weeks two and four of each intervention. Ambulatory BP (eight hours) was also recorded at the start and end of each intervention. Changes in body weight, physical activity and food intake were monitored; there were NS changes during the study. The authors reported only pre-post changes and do not perform between-group statistical tests. The potassium-enriched high-calcium milk intervention decreased sitting SBP from 125+18 to 117+16mmHg (P<0.001) and ambulatory SBP (138+13 to 135+11mmHg, P<0.05) and DBP (80+8 to 78+9mmHg, P<0.05). Standing SBP decreased on each of the milk interventions: SMP: 127+16 to 124+16mmHg; high-calcium SMP: 130+18 to 126+17mmHg (P<0.05), potassium-enriched high-calcium SMP: 130+16 to 122+15mmHg (P<0.05). The authors conclude that increased calcium and potassium may help to prevent the development of HTN. However, the lack of between-group statistical testing is a major limitation which makes it impossible to reach this conclusion.

Tuekpe et al, 2006 (neutral quality), an RCT conducted in Okinawa, examined whether increasing the consumption of the yellow-green Okinawan vegetables used in Okinawan dishes increases potassium intake. Subjects (N=39 normotensive, normal weight females; 20-30 years old) were randomly assigned to receive an average weight of 371.4g per day of five typical yellow green Okinawan vegetables (2.6kg per week, delivered twice weekly) for 14 days. Urinary potassium was collected via 24-hour urine sample pre- and post-intervention. The intervention group consumed an average of 144.9g of Okinawan vegetables per day. Urinary potassium excretion increased significantly (363.5mg per day, P=0.047) from pre- to post-intervention in the intervention group with NS changes in the control group. Post-intervention urinary potassium excretion correlated positively with vegetable consumption in both the

intervention (r=0.79, P<0.0001) and control (r=0.58, P=0.008) groups, as well as with the Okinawan vegetable intake in the intervention group (r=0.73, P=0.0004). Changes in BP were NS; all subjects were normotensive and of normal weight. The authors found that increasing the consumption of yellow-green Okinawan vegetables typically significantly increased urinary potassium, a reflection of increased potassium intake. The trial was likely underpowered to detect a difference in BP.

Overview table

Author, Year, Study Design, Class, Rating	Population	Significant Systolic Blood Pressure Reduction	Significant Diastolic Blood Pressure Reduction	Caveats
Braschi A and Naismith DJ 2008 Study Design: Randomized, doubleblind placebo-controlled trial with parallel arm design. Class: A Positive Quality	Normotensive.	+	+	None.
Burgess E, Lewanczuk R et al, 1999 Study Design: Review (panel) Class: R Neutral Quality	Hypertensive and Normotensive (not pooled). Systematic Review 55 trials (18 epi; 37 RCT).	Ø	Ø	None.

Cappuccio F and MacGregor G, 1991 Study Design: Meta-analysis Class: M Positive Quality	Hypertensive and Normotensive; N=586. Systematic Review/Meta-analysis 19 RCTs (13 HTN, Six NTN).	+	+	SBP: P<0.05. DBP: P<0.01.
Dickinson HO et al 2006 Study Design: Systematic Review/Meta-analysis Class: M Positive Quality	Hypertensive. N=425. Systematic Review/ Meta-analysis five RCT.	Ø	+ (two trials).	None.
Geleijnse JM, Kok FJ et al, 2003 Study Design: Meta-analysis Class: M Neutral Quality	N=30 strata. Meta-analysis (27 RCT for K).	+	+	SBP: P=0.089. DBP: P=0.074. BP response greater in HTN subjects.
He FJ et al 2005 Study Design: Randomized cross-over trial Class: A Positive Quality	Hypertensive.	+	+	Small sample size, N=14.

He J, Gu D et al, 2009 Study Design: Non-randomized trial Class: M Positive Quality	Normotensive.	+ (Age and Baseline BP). Ø (Gender).	+ (Gender and Baseline BP). Ø (Age).	None.
Hilary Green J, Richards JK, and Bunning RL 2000 Study Design: Randomized double blind controlled trial Class: A Positive Quality	Normotensive.	+	+	Δs in office DBP were NS. Ambulatory BP was significant.
Tuekpe MK et al 2006 Study Design: Randomized Controlled Trial Class: A Neutral Quality	Normotensive.	Ø	Ø	Study designed to examine urinary K excretion, not BP.
Whelton, Appel et al, 1998 Study Design: Randomized controlled study Class: A Positive Quality	N=2,609; 44 evalutated two times in separate protocols. Meta-analysis (33 RCTs).	+	+	SBP and DBP: P<0.001.

Research recommendations

Conduct controlled trials that test whether increased potassium intake through supplements or potassium-rich foods increase bone mineral density.

- Rationale: A consistent body of evidence from observational studies indicates that increased intake of potassium from foods is associated with greater bone mineral density and with evidence of reduced bone turnover. Data from small trials also have documented that increased intake of potassium reduces bone turnover.

Search plan and results

Inclusion criteria

- Randomized controlled trials: 2000 to 2009 adults (19 and older)
- Human subjects
- English language
- International
- Sample size: Minimum of 10 subjects per study arm; preference for larger sizes, if available
- Dropout rate: Less than 20%; preference for smaller dropout rates
- Ages 19 years and older; using research for adults and elderly
- Populations: Healthy and those with elevated chronic disease risk (hypertension, CHD and CVD, Type 2 diabetes mellitus, metabolic syndrome and obesity).

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Malnourished or third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- Cohort and case-control studies
- Articles not peer reviewed (Web site, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

PubMed: ("Hypertension"[mh] OR "blood pressure"[MeSH Terms]) AND ("Potassium"[mh] OR "Potassium, Dietary"[mh] OR potassium[majr])

Date searched: Jan 2000 - Nov 2009

Summary of articles identified to review

- Total hits from all electronic database searches: 410
- Total articles identified to review from electronic databases: 25
- Articles identified via handsearch or other means: 4
- Number of Primary Articles Identified: 5

- Number of Review Articles Identified: 5
- Total Number of Articles Identified: 29
- Number of Articles Reviewed but Excluded: 19

Included articles (References)

Systematic Review and Meta-analysis

1. Burgess E, Lewanczuk R, Bolli P, Chockalingam A, Cutler H, Taylor G, Hamet P. Lifestyle modifications to prevent and control hypertension. 6. Recommendations on potassium, magnesium and calcium. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. *CMAJ.* 1999 May 4; 160(9 Suppl): S35-S45. PMID: 10333852 (Hand search from DRI 2005.)
2. Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *J Hypertens.* 1991 May; 9(5): 465-473. PMID: 1649867 (Hand search from DRI 2005.)
3. Dickinson HO, Nicolson DJ, Campbell F, Beyer FR, Mason J. Potassium supplementation for the management of primary hypertension in adults. *Cochrane Database Syst Rev.* 2006 Jul 19; 3: CD004641.
4. Geleijnse JM, Kok FJ, Grobbee DE. Blood pressure response to changes in sodium and potassium intake: A metaregression analysis of randomised trials. *J Hum Hypertens.* 2003 Jul; 17 (7): 471-480. PMID: 12821954. (Hand search from DRI 2005.)
5. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA.* 1997 May 28; 277 (20): 1,624-1,632. PMID: 9168293. (Hand search from DRI 2005.)

Primary Studies

1. Braschi A, Naismith DJ. The effect of a dietary supplement of potassium chloride or potassium citrate on blood pressure in predominantly normotensive volunteers. *Br J Nutr.* 2008 Jun; 99 (6): 1,284-1,292.
2. He FJ, Markandu ND, Coltart R, Barron J, MacGregor GA. Effect of short-term supplementation of potassium chloride and potassium citrate on blood pressure in hypertensives. *Hypertension.* 2005 Apr; 45 (4): 571-574. Epub 2005 Feb 21.
3. He J, Gu D, Chen J, Jaquish CE, Rao DC, Hixson JE, Chen JC, Duan X, Huang JF, Chen CS, Kelly TN, Bazzano LA, Whelton PK; GenSalt Collaborative Research Group. Gender difference in blood pressure responses to dietary sodium intervention in the GenSalt study. *J Hypertens.* 2009 Jan; 27 (1): 48-54.
4. Hilary Green J, Richards JK, Bunning RL. Blood pressure responses to high-calcium skim milk and potassium-enriched high-calcium skim milk. *J Hypertens.* 2000 Sep; 18 (9): 1,331-1,339.
5. Tuekpe MK, Todoriki H, Sasaki S, Zheng KC, Ariizumi M. Potassium excretion in healthy Japanese women was increased by a dietary intervention utilizing home-parcel delivery of Okinawan vegetables. *Hypertens Res.* 2006 Jun; 29 (6): 389-396.

Excluded articles

Article	Reason for Exclusion
Ando K, Matsui H, Fujita M, Fujita T. Protective effect of dietary potassium against cardiovascular damage in salt-sensitive hypertension: Possible role of its antioxidant action. *Curr Vasc Pharmacol.* 2010 Jan 1.	Publication is theoretical.
Beyer FR, Dickinson HO, Nicolson DJ, Ford GA, Mason J. Combined calcium, magnesium and potassium supplementation for the management of primary hypertension in adults. *Cochrane Database Syst Rev.* 2006 Jul 19; 3: CD004805.	Does not answer question: Examined combinations of mineral supplements.
Buyck JF, Blacher J, Kesse-Guyot E, Castetbon K, Galan P, Safar M, Hercberg S, Czernichow S. Differential associations of dietary sodium and potassium intake with blood pressure: A focus on pulse pressure. *J Hypertens.* 2009 Jun; 27 (6): 1, 158-1, 164.	Study design is cross-sectional.
Chang HY, Hu YW, Yue CS, Wen YW, Yeh WT, Hsu LS, Tsai SY, Pan WH. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. *Am J Clin Nutr.* 2006 Jun; 83 (6): 1, 289-1, 296.	Does not included blood pressure (BP) in analyses.
Charlton KE, Steyn K, Levitt NS, Zulu JV, Jonathan D, Veldman FJ, Nel JH. Diet and blood pressure in South Africa: Intake of foods containing sodium, potassium, calcium, and magnesium in three ethnic groups. *Nutrition.* 2005 Jan; 21 (1): 39-50.	Study design is cross-sectional.
Cohen DL, Townsend RR. What effect does potassium have on blood pressure? *J Clin Hypertens (Greenwich).* 2008 Feb; 10 (2): 158-159.	Publication is editorial.
Cook NR, Obarzanek E, Cutler JA, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: The Trials of Hypertension Prevention follow-up study. Trials of Hypertension Prevention Collaborative Research Group. *Arch Intern Med.* 2009 Jan 12; 169 (1): 32-40.	Does not include BP in analyses.

Delgado MC, Delgado-Almeida A. Red blood cell potassium and blood pressure in adolescents: A mixture analysis. *Nutr Metab Cardiovasc Dis.* 2002 Jun; 12 (3): 112-116.	Study population was adolescents.
Di Legge S, Spence JD, Tamayo A, Hachinski V. Serum potassium level and dietary potassium intake as risk factors for stroke. *Neurology.* 2003 Jun 10; 60 (11): 1, 870. Comment on: *Neurology.* 2002 Aug 13; 59(3): 314-320.	Does not include BP in analyses.
Gu D, Rice T, Wang S, Yang W, Gu C, Chen CS, Hixson JE, Jaquish CE, Yao ZJ, Liu DP, Rao DC, He J. Heritability of blood pressure responses to dietary sodium and potassium intake in a Chinese population. *Hypertension.* 2007 Jul; 50 (1): 116-122.	Does not include BP as an independent variable. Focus was heritability of BP response.
Jan RA, Shah S, Saleem SM, Waheed A, Mufti S, Lone MA, Ashraf M. Sodium and potassium excretion in normotensive and hypertensive population in Kashmir. *J Assoc Physicians India.* 2006 Jan; 54: 22-26.	Study design is case control.
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CHAPTER 3. SODIUM AND BLOOD PRESSURE IN CHILDREN

WHAT IS THE EFFECT OF A REDUCED SODIUM INTAKE ON BLOOD PRESSURE IN CHILDREN FROM BIRTH TO AGE 18 YEARS?

Conclusion statement

A moderate body of evidence has documented that as sodium intake decreases, so does blood pressure in children, birth to 18 years of age.

Grade

Moderate

Evidence summary overview

Of the 15 trials, 14 were randomized controlled clinical trials (RCTs) (Calabrese et al, 1985; Cooper et al, 1984; Gillum et al, 1981; Hofman et al, 1983; Howe et al, 1985; Howe et al, 1991; Lucas et al, 1988; Myers, 1989; Palacios et al, 2004; Pomeranz et al, 2002; Sinaiko et al, 1993; Trevisan et al, 1981; Tuthill and Calabrese, 1985; Whitten and Stewart, 1980). Five of the RCTs earned a positive quality rating (Gillum et al, 1981 Hofman et al, 1983; Howe et al; 1991 Sinaiko et al, 1993; Tuthill and Calabrese, 1985); and seven earned a neutral quality rating (Calabrese et al, 1985; Cooper et al, 1984; Howe et al, 1985; Myers, 1989, Palacios et al, 2004; Pomeranz et al, 2002; Whitten and Stewart, 1980). Two RCTs earned a negative quality rating (Lucas et al, 1988; Trevisan et al, 1981). One non-randomized controlled study (positive quality rating) was the largest and longest trial, a two-period cross-over study conducted in two boarding schools (Ellison et al, 1989). Results of these studies support the conclusion that a reduced sodium intake appears to lower blood pressure in infants and children.

Four prospective studies also provided evidence that supported the conclusion statement. One was a 15-year follow-up study (Geleijnse et al, 1997, positive quality) of the infant study subjects in the RCT conducted by Hofman et al, 1983 in the Netherlands. Three additional studies were prospective longitudinal cohort studies (Geleijnse et al, 1990, positive quality; Brion et al, 2008, neutral quality; and Smith et al, 1995, negative quality).

Ten of the 14 RCTs achieved contrasts in sodium intake of 40% or more between treatment groups or periods (Cooper et al, 1984; Hofman et al, 1983; Howe et al, 1985; Howe et al, 1991; Lucas et al, 1988; Myers, 1989; Palacios et al, 2004; Pomeranz et al, 2002; Tuthill and Calabrese, 1985; Whitten and Stewart, 1980). Two other RCTs achieved contrasts of 7 to 12% (Calabrese et al, 1985; Trevisan et al, 1981); and two achieved less than a 2% difference between treatment groups (Gillum et al, 1981; Sinaiko et al, 1993). Although the extent of sodium reduction often appeared large, the data often came from dietary recalls or dietary histories, rather than 24-hour urine collections.

Additionally, 12 of the 15 intervention studies showed a decrease in systolic (SBP) and/or diastolic (DBP) blood pressure on the low sodium diet (Calabrese et al, 1985;

Cooper et al, 1984; Ellison et al, 1989; Hofman et al, 1983; Howe et al, 1985; Howe et al, 1991; Myers, 1989; Palacios et al, 2004; Pomeranz et al, 2002; Sinaiko et al, 1993; Trevisan et al, 1981; Whitten and Stewart, 1980). In eight of those 12 intervention studies, the decrease was statistically significant for all, or a subset, of the study population (Calabrese et al, 1985; Ellison et al, 1989; Hofman et al, 1983; Howe et al, 1985; Myers, 1989; Pomeranz et al, 2002; Sinaiko et al, 1993; Trevisan et al, 1981). Three studies reported no change in blood pressure on a low sodium diet (Gillum et al, 1981; Lucas et al, 1988; Tuthill and Calabrese, 1985).

Results from two of the three prospective cohort studies tend to support the results of the intervention trials. Two studies (Brion et al, 2008; Geleijnse et al, 1990) involved prospective cohorts that were followed for seven years. In the study by Brion et al, 2008, higher sodium (Na) intake at four months of life (but not at seven months or seven years) was associated with increased SBP at seven years of age. This was consistent with a greater difficulty excreting a sodium load by infants under four months of age. In the cohort study by Geleijnse et al, 1990, a higher Na/K ratio was associated with a greater increase in slope of blood pressure (BP) change over time. In the infant cohort study by Smith et al, 1995 (negative quality), neither the contrast in sodium intake, nor the actual BP was provided. The authors indicated that in the multivariate analysis, the amount of salt added to the diet approached clinical significance (P=0.0751).

The third prospective cohort study was a long term, 15-year follow-up study (Geleijnse et al, 1997, positive quality) of an RCT conducted among infants who participated in the initial trial between birth and six months of age. In this study, SBP and DBP at follow-up were still lower among children initially assigned to the low sodium diet during infancy. The difference for SBP was statistically significant (P<0.05) and for DBP was of borderline significance (P=0.08).

In aggregate, these data indicate that sodium reduction modestly lowers BP in infants and children. While the degree of BP lowering was usually small, in the range of -1 to -5mmHg, such an effect, if sustained over time, could translate into reduced BP in adults, as well as reduced prevalence of hypertension. Furthermore, if a reduced sodium intake blunts the age-related rise in BP in children, then the effects of sodium reduction will be greater than projected from these studies. Nonetheless, it must be acknowledged that most of the studies had one or more methodological limitations, particularly small sample size (and consequently inadequate statistical power), brief duration (typically less than one month), and inadequate or uncertain contrast in sodium intake.

Evidence summary paragraphs

Brion et al, 2008 (neutral quality). This study was a prospective cohort study begun in infancy to examine the associations between sodium (Na) intake and blood pressure at age seven years. This study was conducted in England. Subjects included 533 children initially studied at four months of age, and 710 children studied at eight months of age, who were followed to seven years of age. Sodium intake was estimated from data collected from food diaries and information obtained from food manufacturers. Mean sodium intake at four months was 7.2mmol per day and 0.4% of children exceeded recommended levels for infant sodium intake. At eight months,

mean Na intake was 23.1mmol per day and 73.0% of children exceeded recommended Na intake levels. Mean BP at seven years of age in children initially assessed at four and/or eight months of age was 98.4±9.4/56.4±6.7mmHg. Sodium intake at four months of age was positively associated with SBP at age seven years (P=0.02). Sodium intake at eight months of age and at seven years of age was not significantly associated with BP at age seven years, however. These findings are consistent with evidence that before the age of four months, infants are less able to excrete excess Na loads.

Calabrese EJ & Tuthill RW, 1985 (neutral quality). This study was a randomized, controlled, three-arm parallel trial that examined the effects on blood pressure of 12 weeks of a reduced sodium (Na) intake in children. The trial was conducted in the United States. Subjects were 171 children, mean age nine years. Trios of children matched by sex, school, and baseline BP were randomly assigned to one of three different types of water for cooking and drinking purposes. The Na concentration of bottled water was 10mg per L for the low-Na group and 110mg per L for the two high Na groups (water bottled directly from their own high Na concentration water distribution system; or water from the low Na concentration drinking water community with added sodium added up to 110mg per L). The final analysis was completed on 164 children. Sodium intake was estimated from monthly first morning urine specimens and from weekly 48-hour diet records kept by the children with help from parents and teachers. UNa from first-morning urine samples decreased from 141 to 128mmol per L in the low-salt group and increased from 121 to 124mmol per L in the control group. For all subjects combined, the low Na water intervention reduced SBP -0.80±0.80mmHg, and DBP -1.50±1.65mmHg. The decrease in BP was only significant for females however. Among females, SBP decreased over 12 weeks from 97.7±10.1 to 92.4±8.5mmHg, and DBP decreased from 56.1±9.2 to 47.4±11mmHg. None of the differences in UNa excretion were statistically significant over the study period for any group, and BP changes did not correlate with UNa excretion. Strengths of the study include the controlled intake of water sodium levels. Limitations of the study which could have influenced outcome include the use of spot urine samples rather than 24-hour samples to measure sodium excretion; lack of control over school lunch preparation; dietary assessment methodology of unknown validity (records kept by children); and lack of description of the statistical methods.

Cooper et al, 1984 (neutral quality). This study was a randomized, controlled, two period-crossover trial that examined the effects on BP of 24 days of a reduced sodium (Na) intake in adolescent children. The trial was conducted in the United States. Participants were 124 healthy adolescents (mean age 16 years) at a boarding school. During the low Na period, the intervention aimed to reduce the Na content the food service from 200 to 60mEq per 24-hours. The final analysis was completed on 113 children. Sodium intake was estimated from weekly timed overnight urine samples, and the Na content of foods consumed for 24 hours was analyzed for a random sub-sample of three students per week. Overnight UNa was reduced from 31 in the control group to 13mmol per eight hours in the group that received the reduced Na intervention. Analysis of foods found that the control diet contained ~110mEq Na per day (rather than the predicted 200mEq per day), and the intervention diet ~45mEq per day. Across all subjects there was a nonsignificant decrease in BP (SBP: -

0.6±0.7mmHg and DBP: -1.4±1.0) associated with the reduced Na intervention (net of control). In those individuals with a BMI below the median (BMI<23kg/m2), there was a statistically significant fall in SBP (P<0.05). A strength of the study was adherence to the diet in this institutional setting. Limitations of the study, which might lead to a spurious null result, include predicted sodium content of the control diet (110 vs. 200mEq per day); the short duration of intervention (24 days); and the lack of blinding of students as to their treatment groups.

Ellison et al, 1989 (positive quality). This study was a non-randomized, concurrently controlled, two-period crossover trial that examined the effects on blood pressure of six-months of a reduced sodium (Na) intake in adolescents. The trial was conducted in the United States. Participants were healthy adolescents (mean age 15 years) at two boarding schools, 341 subjects during the control school year, and 309 subjects during the low sodium (Na) intervention year. The intervention occurred in each boarding school during alternate school years. Sodium intake was estimated from food diaries, with an average of 4.5 food diaries per subject obtained during baseline and follow-up period. Food diaries showed that average salt intake was reduced by 15-20%. Students measured their own BP every week using an automatic BP device connected to a computer. Baseline BP was taken as the mean of all recordings obtained during four weeks at the beginning of the BP associated with the low-Na intervention: SBP -1.7mmHg (95% CI=-0.6, -2.9, P=0.003), and DBP -1.5mmHg (95% CI=-0.6, -2.5, P=0.002). There was no evidence of bias that would lead to a spurious association. Strengths of the study are the long term nature of the interventions (six month school year), the blinding of BP-readings from students; and adherence to the intervention via boarding school food service. A potential limitation is that order (control vs. reduced sodium intervention) was not randomized; however, because the unit of assignment was the school rather than individual, this is not a major problem.

Geleijnse JM et al, 1997 (positive quality). This study was a 15-year follow-up of an RCT that examined the effects on blood pressure of a low or normal sodium diet during the first six months of life. The follow-up study was conducted to determine if contrasting levels of Na intake in infancy are associated with BP differences in adolescence. This study was conducted in the Netherlands. In the infant study, 245 newborn infants were assigned to a normal-Na diet and 231 to a low-Na diet. Infants assigned to the low-Na group received formula that was reduced in Na compared to the normal-Na formula (6.3 vs. 19.2mmol Na per L). The Na intake of the normal-Na group was almost three times that of the low-Na group measured as total intake of Na calculated from the food consumed along with an allowance for breastfeeding based upon the Na in the mother's breast milk. In addition, Na intake was estimated from spot urine collections. Systolic BP was measured every month from the first week until the 25th week. At 25 weeks, SBP was 2.1mmHg lower in the low-Na group than in the normal Na group. The difference between the groups increased significantly during the first six months of life. In the 15-year adolescent follow-up study,167 children (71 low-Na; 96 high Na), or 35% of the original cohort were re-evaluated. Results showed that there was still a significant difference in BP at follow-up between children who were randomly assigned to receive a low-salt diet in infancy (SBP: 3.6mmHg lower (95% CI, -6.6 to -0.5) and DBP: 2.2mmHg lower (95% CI, -4.5 to 0.2), compared to those who received the high salt infant diet. The in children who had been assigned to the low Na

group (N=71) compared with the control group (N=96). This occurred despite the fact that infants went back to their usual salt intake when the double-blind trial stopped at six months of age. There was little evidence of bias that would lead to a spurious association. Strengths of the study include the long duration of follow-up after randomization and the approach to data analysis, which took into account potential confounders. A limitation of the study was the loss to follow-up of individuals who originally enrolled in the trial when they were infants. Overall, these findings suggest that sodium intake in infancy is an important determinant of BP later in life.

Geleijnse et al, 1990 (positive quality). This study was a prospective cohort study to examine the association of sodium and potassium intake with blood pressure during childhood. The study was conducted in the Netherlands. Participants were 233 children, aged 5.9 to 17.0 years of age, who were followed for seven years. Six annual overnight urine samples were collected to estimate 24-hour Na excretion, and slopes of BP change over time were calculated. Results showed that mean SBP increased at a rate of 1.95mmHg per year. There was no significant association between sodium excretion and annual change in SBP (0.003mmHg per year per mmol of Na; 95% CI: -0.006 to 0.012). In contrast, higher potassium (K) excretion was associated with a lower age-related rise in SBP (-0.045mmHg per year per mmol of K; 95% CI: -0.069 to - 0.020)], while a higher Na/K ratio was associated with a greater rise in SBP (0.356mmHg per year per unit; 95% CI 0.069 to 0.642). Urinary electrolyte excretion was not associated with changes in DBP. Strengths of the study include the long term follow-up. Limitations include the relatively small number of participants for a cohort study and use of overnight urine collections to estimate 24-hour electrolyte intake.

Gillum RF et al, 1981 (positive quality). This study was a randomized, controlled, two-arm parallel trial that examined the effects on blood pressure of one-year of a reduced sodium intake in children. The trial was conducted in the United States. Participants were 80 public school children, ages six to nine years, with BP >95th percentile for age and sex but <130/90mmHg. During the low Na period, families received dietary counseling to lower Na intake to 70mEq per person per day. The final analysis was completed on 51 children (15 intervention; 36 controls). Sodium intake was estimated from urine collections and diet histories. Subjects reported 40% lower Na intake in dietary records. Twenty-four hour Na intake at one-year follow-up was significantly lower for active participants of the low-Na intervention group as compared to dropouts and controls (87 vs. 130 and 133mmol per 24-hours). Overnight UNa changed from 31 to 35mmol per 10 hours in the control group, and from 30 to 31 mmol per 10 hours in the intervention group. Overall, there was no significant difference in BP between the intervention and control groups. For the low Na intervention, net change in SBP was 3.00±2.61mmHg, and for DBP was 2.90±5.79mmHg. The BP changes did not correlate with changes in 24-hour Na excretion. Limitations of the study, which might lead to a spurious null result, include the high drop out rate of intervention families (21 of 41 families dropped out). Although the drop-outs occurred before the intervention started, it resulted in a significantly lower sample size, especially for the intervention group. In addition, 24-hour urinary Na excretion data were available for intervention children only.

Hofman A et al, 1983 (positive quality). This study was a randomized, double-blind

parallel arm trial that examined the effects on blood pressure of two levels of sodium intake in infants during the first six months of life. The trial was conducted in the Netherlands. Two hundred forty-five newborn infants were assigned to a normal-Na diet and 231 to a low-sodium diet. Infants assigned to the low-Na group received formula that was reduced in Na compared to the normal-sodium formula (6.3 vs. 19.2mmol Na per L). The Na intake of the normal-Na group was almost three times that of the low-Na group measured as total intake of sodium calculated from the food consumed along with an allowance for breastfeeding based upon the Na in the mother's breast milk. In addition, Na intake was estimated from spot urine collections. Systolic BP was measured every month from the first week until the 25th week. At 25 weeks, SBP was 2.1mmHg lower in the low-Na group than in the normal Na group. The difference between the groups increased significantly during the first six months of life. According to the authors these observations were in agreement with the view that Na intake is causally related to BP level. There was no evidence of bias that would lead to a spurious association. Strengths of the study include high follow-up rates and a large sample size, which compensated for the relatively few number of BP measurements (only one BP per month).

Howe PRC et al, 1985 (neutral quality). This study was a non-randomized, controlled, two-period cross-over trial that examined the effects on blood pressure and other cardiovascular parameters of three weeks on a reduced Na intake in children. The trial was conducted in Australia. Participants were 21 school children, ages 11 to 14 years, all of whom had BP ≥90th percentile for age on initial BP screening. Subjects followed a low Na or high Na diet for three weeks, and then switched to the alternate Na diet for the subsequent three weeks. Sodium intake was estimated from weekly overnight urine samples and from 24-hour dietary recalls conducted at baseline, three and six weeks. The study showed that there was a three-fold decrease in Na intake on the low Na diet; Na excretion values from final urine samples in each diet period reflected a slightly less than a two-fold difference in Na intake between the high and low Na diets. There was a significant difference between the two diet periods in the level of DBP in the girls ($P< 0.05$). Limitations of the study include the lack of randomization to treatment condition, the very small sample size and lack of statistical power, and the use of self-reported dietary recall data.

Howe et al, 1991 (positive quality). This study was a randomized, two-period crossover trial that examined the effects on blood pressure of four-weeks of a reduced sodium (Na) intake in adolescent children. The trial was conducted in Australia. Participants were 103 adolescent schoolchildren, aged 11 to 15 years. During the low Na period, participants received dietary counseling to lower Na intake. The final analysis was completed on 100 children. Sodium intake was estimated from urine collections and diet histories; both types of measurements confirmed that the intervention reduced sodium intake. The estimated difference in 24-hour sodium intake was ~80mmol per day. Overall, there was no significant difference in BP between the two groups, overall and in any subgroup. The BP changes did not correlate with changes in Na excretion. Strengths of the study are a high follow-up rate. Limitations of the study, which might lead to a spurious null result, include variable adherence (the trial was not a controlled feeding study) and the small number of BP measurements (only one set per week), thereby reducing statistical power.

Lucas A et al, 1988 (negative quality). This report included the results of two randomized controlled parallel trials, that were originally part of a larger five centre feeding study among preterm infants to examine the effects on weight gain during initial hospitalization (27 to 37 days) of different infant formulas, with or without breast milk. The trials were conducted in England. Blood pressure was not measured during this initial in-hospital feeding phase. Since the feeding regimens differed significantly in Na content, BP was measured in 347 infants at 18 months of age to assess the effects on BP of infant feeds differing in sodium content. Study 1 compared BP for preterm infants who had originally been randomized to receive either low Na banked donor breast milk plus standard term infant formula (1.8mmol per kg per day Na intake), vs. a high sodium preterm formula (3.6mmol per kg per day Na intake). Study 2 compared BP for preterm infants who had originally been randomized to receive either low Na banked donor breast milk and standard term infant formula plus expressed maternal breast milk, versus high sodium preterm formula plus expressed maternal breast milk. At 18 months of age, no differences in BP were observed between treatment groups for either study 1 or 2. Strengths of the study included the large sample size. Limitations of the study which could have influenced outcomes include lack of information on how many BP measures were taken; lack of information as to which Korotkoff sounds were used for measures of BP; lack of information on whether BP observers were blinded as to original treatment group. Other limitations included the fact that infant feeds differed in many other aspects in addition to sodium content; that subjects included all preterm infants, both sick and healthy; and that the power calculations for the study were based on the number of infants needed to detect a specific amount of weight gain, and not on hypothesized differences in BP.

Myers JB, 1989 (neutral quality). This study was an RCT that examined the effects on BP in children and adults of a series of two week interventions involving reduced and high sodium diets. The trial was conducted in New Castle, Australia. Participants were 200 (final N=172, 99F, 73 M) healthy normotensive hospital employees and local residents with their families in a community; subjects had a mean age of 36.9 years±1.3 years (range three to 77 years) and had an average body mass and height. Of the 172 who completed the study, 23 persons were <20 years. The study consisted of three periods, each lasting two weeks. In the first study period, subjects were on their usual diet. The second and third study periods involved a randomized cross-over design in which a reduced and a high Na diet were consumed by subjects. Mean urinary sodium excretion in those <20 was 66, 133, and 158 during the lowest, usual and highest Na periods. Mean SBP was 105, 108 and 109mmHg, respectively, while corresponding values for DBP were 62, 67, and 64mmHg. Although there were trends in SBP across the sodium intake levels, no statistical tests were performed for the effects of Na on BP in those person <20 years. Limitations are the small sample size of subjects <18 years of age, the very short duration of intervention, lack of controlled feeding, non-randomized assignment of the usual Na period (always first), and incomplete statistical analyses.

Palacios et al, 2004 (neutral quality). This study was a randomized, two-period crossover trial that examined the effects on sodium retention and BP of three weeks of a high sodium diet and three weeks of a reduced Na diet in adolescents. The trial was conducted in the United States. Participants were 40 female adolescents, aged 11-15

years. This was a controlled feeding study with subjects housed in a metabolic unit and provided with all meals and snacks during the three-week diet phases. The final analysis was completed on 36 children. Sodium intake was estimated from daily urine collections which confirmed that the intervention diets achieved the desired levels of sodium intake. The difference in 24-hour Na excretion between the high and low Na periods was 1.7g per day for Black subjects and 2.4g per day for White subjects. Overall, there was no significant difference in BP between the two diet phases, overall or in any subgroup. The BP changes did not correlate with changes in sodium excretion. Strengths of the study are adherence to the diets since the trial was a controlled feeding study, and frequent measurement of Na excretion (daily) and BP (every other day). Limitations of the study, which might lead to a spurious null result, include the small sample size and high attrition rate (only 23 of the 36 girls completed both diet phases), thereby reducing statistical power.

Pomeranz A et al, 2002 (neutral quality). This study was a randomized, controlled, with crossover trial that examined changes in BP during the first two months of life in neonates receiving low-sodium mineral water (LSMW), high sodium tap water (HSTW), or breast milk. The trial was conducted in Israel. Participants were 58 Jewish newborn term infants from families with no history of hypertension. The initial analysis conducted on 58 infants and final analysis on 38 infants. The intervention involved feeding formula diluted with water containing either LSMW or HSTW for eight weeks; a non-randomized control group consisted of breastfed infants. The group consuming the LSMW formula reverted after eight weeks to consuming the high Na formula. On a weekly basis, SBP, DBP and MAP were recorded during the first eight weeks, and then, at week 24 (six months of age), a follow-up BP measurement was performed. Sodium intake was estimated from only one urine sample with urinary Na:creatinine ratio calculated. In comparison with the low Na intake group and breastfed infants, the high Na intake group exhibited a progressive increase in MAP, SBP and DBP from week four that attained significance at weeks six to eight of study period ($P<0.05$). When the LSMW reverted to a high-salt intake after eight weeks, their BP values increased towards those observed in the high sodium intake group. Urinary sodium:creatinine ratio was significantly greater in HSTW than in LSMW. Limitations of the study, which might lead to a spurious association, were the small number of participants and the non-random assignment to the control group. Other limitations include uncertain total Na intake in the groups, the pre-post design of the follow-up between weeks eight and 24 in the LSMW, and the loss to follow-up between weeks eight and 24.

Sinaiko et al, 1993 (positive quality). This three-year study was a randomized, controlled, parallel three-arm trial that examined the effects on BP of reduced sodium (Na) intake, potassium (K) supplement, or placebo in adolescents. The trial was conducted in the United States. Participants were 210 adolescents, mean age 13 years with BP at or above the 85th percentile of BP distribution for age. Adolescents were randomly assigned to either a low Na diet (70mmol Na per day), a K supplement (normal diet plus 1mmol per kg KCl per day), or placebo (normal diet plus placebo capsule). Compliance was measured by percent of expected capsule use and by annual 24-hour urinary Na and Na/K ratios. In the low-Na group, 24-hour UNa was changed from 142 to 162mmol for boys, and from 133 to 119 mmol in girls. In the

placebo group, 24-hour UNa was changed from 159 to 178 mmol in boys and from 150 to 128 mmol in girls. Change in SBP for the low-Na group was: SBP -1.98±1.3mmHg, and DBP: -4.65±1.91mmHg. The low Na group of girls had a statistically significant negative slope compared with placebo. The slope for boys was similar in all treatment groups. Strengths of the study are the long term nature of the interventions (three years), and the blinding of BP-observers. Limitations of the study include variable adherence (the trial was not a controlled feeding study), and that neither girls nor boys in the low Na group were successful in reaching the target level of Na intake. In addition, there were few urinary sodium measures (only once every 12 months); and only 59% of boys and 74% of girls had 24-hour UNa measured at year three, though all had 24-hour UNa measured at baseline.

Smith RE et al, 1995 (negative quality). This study was a prospective cohort study begun in infancy to examine the effect of different variables, including anthropometric indices, aspects of feeding practices (including Na intake), and relationship to maternal BP, on the BP of infants. This study was conducted in South Africa. Participants included 684 Sowetan infants from the Birth-to-Ten cohort. At one year of age, an infant feeding history was obtained retrospectively from the mother of each infant, including questions regarding salting practices, and BP was measured in infants and mothers. Results showed that after adjusting for covariates, there was a non-significant trend toward a dose-related response between salt intake and BP, with a positive linear relationship between BP and quantity of salt added to infant foods. A serious limitation of the study is lack of actual measurement of dietary Na intake (estimated only by maternal history), thus numerical estimates of infant Na intake were completely lacking.

Trevisan M et al, 1981 (negative quality). In this report of two studies, one study was an RCT that examined the effects of reduced Na intake on BP. The trial was conducted in the United States. Participants were 21 students in a Seventh Day Adventist boarding high school who were consuming a lacto-ovo vegetarian diet. The students were randomly assigned to a control group (N=9) or the experimental group (N=12), which received moderate salt restriction for 24 days. The experimental study group (N=12) ate meals that lowered sodium intake by ~70% Na from 216 to 72mmol per day. Random 24-hour urines were collected and random duplicate meals were analyzed for Na content, but neither were reported. Blood pressure was measured once at the end of the intervention period. Overall, there was no significant difference in BP between the groups. Limitations of the study which might have led to a spurious null result were the extremely small sample size, the small number of BP measurements, the short duration of the trial, and lack of reported data on the achieved levels of sodium intake.

Tuthill et al, 1985 (positive quality). This study was an RCT examining if a small amount of Na supplementation with food or water influenced BP in a group of female high school students. This trial was conducted in the United States. Subjects were 216 females enrolled in ninth through twelfth grade at a private boarding school. Baseline data was collected for one week prior to supplementation. All subjects took capsules twice per day, under supervision for eight weeks. Group one received a placebo twice a day, group two received two grams of salt capsules midmorning and a placebo in the evening; group three received two grams of salt capsules in the morning. Blood

pressure measurements were taken after dinner before capsules and a 24-hour urine collection was done on the same day twice a week for each student. Differences in BP between the treatment groups were not statistically significant (mean differences were in the order of 1.4mmHg at maximum). There was no significant relationship between systolic and diastolic blood pressure and level of Na supplementation (0.8g per day). Strengths of the study include the double blind intervention design, and large sample size. A significant weakness of the study, however, was the lack of statistical power. The original power calculations were based on combining data from two schools, however the authors chose to analyze the data from each school separately. With the smaller sample size only a 2.5mmHg difference in BP between groups could be detected, whereas the actual mean differences were in the order of 1.4mmHg at maximum.

Whitten CF and Stewart RA, 1980 (neutral quality). This study was a non-randomized trial in which infants at three months of age were assigned to receive low Na foods (2mEq of Na per 100kcal) or high Na foods (9mEq of Na per 100kcal) for five months. Long-term effects were assessed at eight years of age. This study was conducted in the United States. Subjects were 27 healthy three-month old African American male infants. Follow-up data were collected one, three and five months later. At each of these timepoints, the infants were admitted to the hospital for three days of measurements, including BP and urinary sodium excretion. At five months, mean urine excretion was 11mmol per day and 55mmol per day in the low and high groups. There were non-significant trends after the five month intervention and at eight years such that SBP was greater in the high sodium group compared to the low sodium group (after five months of intervention: mean SBP of 90 vs. 88mmHg; at eight years, 105 vs.103mmHg). Limitations of the study which might lead to a spurious result were the very small sample size, uncertain allocation process, and uncertain analytic strategy. Strengths of the study include the large number of measurements per individual and extended follow-up period.

Overview table

Overview Table Key:

- *** Subjects were defined as salt sensitive if BP at end of run-in period (usual diet) was higher than on the low Na diet but less than on the high Na diet.
- N indicates number of participants, and the number in bracket represents the number of participants in low-salt and control group, respectively; UNa, urinary sodium; ? salt intake, net change in salt intake; ? SBP, net change in systolic BP; ? DBP: net change in diastolic BP; NR: not reported. SM = sphygmomanometer.
- * The Myers study (1989) included adults and children (N=172; ages 3-77yrs), but in the He FJ meta-analysis, only the child participants (N=23, mean age 11yrs) were included in the analysis.
- ** Tuthill- Problem with lack of statistical power: The authors intended to combine the two campus' data and the power to determine a difference of 1.5mmHg would have required the total data set to be combined for an N of 214

(71 in each Rx group). However, they had to analyze each campus separately, so given the smaller sample size only a 2.5mmHg BP difference would be detectable. The actual mean BP differences were in the order of 1.4mmHg at maximum.

Author, Year, Study Design, Class, Rating	Participants/ Location	Study Duration	Intervention Procedure	BP Measurement; Sodium Intake Measurement	Outcome (BP values; mmHg)
Brion MJ, Ness AR et al, 2008 Study Design: Prospective cohort study Class: B Neutral Quality	N=533; Age: Four months. N=710; Age: Eight months. 1,394 infants have data from at least one visit. Final analyses on children with complete information on all confounders. Location: United Kingdom.		Sodium intake was measured in infancy and at seven years; BP measured at seven years. The Avon Longitudinal Study of Parents and Children.	BP measured by Dinamapp 9301. Two readings taken and the mean for each measure calculated. Sodium intake estimated from one-day food diary at four months and three day diary at eight months. Mean sodium intake at: Four months: 7.2 mmol/day Eight months: 23.1 mmol/day.	Difference in salt intake (from food diary) at four months was -0.4 mmol/day between Q1 and Q4 BP. After minimal adjustment (age, sex, energy) sodium intake at four months (but not at eight months or seven years) was positively associated with SBP at seven years 0.98mmHg; P=0.02. An ↑ in E-adjusted Na at four months of 9mmol/day was associated with an ↑ in SBP at seven years of 4.0mmHg BP-lower with Low-Na (four months). Stat-SIG

Calabrese EJ, Tuthill RW et al, 1985 Study Design: Randomized controlled trial Class: A Neutral Quality	N=153 (51+102). Mean age: Nine years, 51% boys. Mean BP: 99/57mmHg. Location: United States.	Duration:12 weeks (three months).	Bottled water with varied salt content (110 or 10mg/L) provided for children's family and school classrooms.	BP was measured with mercury SM; Korotkoff 1 and 5 for SBP and DBP. Mean of three readings used in analysis. Sodium intake estimated from first morning urine specimens (1 x month), and from weekly 48 hour diet records kept by the children.	Δ Salt intake: -11.70% (spot UNa). UNa Δ from 141 to 128mmol/L in the Low-Na group, and from 121 to 124mmol/L in the control group. (Note: Low-Na group only -4mmol/L less than High-Na group at end of study). Net difference in BP: Δ SBP: -0.80 ±0.80 Δ DBP: -1.50 ±1.65 BP-reduced for all, but Stat-SIG for girls only.
Cooper R, van Horn L et al, 1984 Study Design: Randomized, controlled, crossover trial Class: A Neutral Quality	N=113. Mean age: 16 years, 47% boys. Mean SBP: 109/61mmHg Location: United States.	Five-day washout. BP-observer blind. Duration: 24 days.	Control diet: 200 mmol/day salt; Low salt diet: ~60mmol/day salt.	First BP measured with mercury SM. Second and third BP measured with random-zero SM. Mean of second and third BP used. Sodium intake estimated from overnight urine samples.	Δ Salt intake: -57.68% (overnight UNa) Net difference in BP: Δ SBP: -0.60±0.70 Δ DBP: -1.40±1.00. BP-reduced; not stat-sig.

Ellison RC, Capper AL et al, 1989 Study Design: Non-randomized, concurrently controlled, longitudinal investigation, with the applications of the intervention in each of two boarding high schools in alternate school years. Class: C Positive Quality	N=309 for intervention year; N=341 for control year. Mean age: 15 years, 49% male, 77% white. Mean BP: 107/64mmHg. Location: United States.	~Five month washout BP-observer blind. Duration: Six months.	Low-salt year: Salt intake reduced by 15-20% via changes in food purchasing and preparation at boarding school.	Weekly BP measured x 3 by students using a Dinamap 845 device connected to a computer. Mean of second and third BP measures used. Sodium intake estimated from food diaries: 4.5/subject at base and follow up.	Δ Salt intake: -16.20% (from food diary). Net difference in BP: Δ SBP: -1.70±0.56 Δ DBP: -1.50±0.46. BP-reduced; Stat-Sig.

Geleijnse JM, Hofman A et al, 1997 Study Design: Randomized trial Class: A Positive Quality	N=167. 71 from infant low Na group; 96 from infant control group. This was 35% of the original cohort of 476. Location: The Netherlands.	15 year follow-up study of the Hofman et al, (1983) infant study subjects.	The intervention had occurred during the first six months of life, 15 years earlier.	BP measured with the Dinamap 8100 Monitor; four measures of BP and HR taken; last three measures averaged. Sodium intake estimated from spot urine collection in the infant RCT. Overnight urine samples were collected at the 15 year follow up.	A difference in Na intake of 8.8mmol/day between the randomized groups corresponded to a -3.6mmHg lower SBP in children randomized to the low-Na group for the first six month of life. After multivariate adjustment for potential confounders, SBP was -3.6mmHg lower (95%CI,-6.6 to -0.5; P=0.02) and DBP was -2.2mmHg lower (95%CI,-4.5 to 0.2; P=0.08) than Control. For subjects with mean HR >median: Adjusted SBP at follow up was -6.0mmHg (95%CI,-10.5 to -1.5.2; P<0.01).; and adjusted DBP was -4.8mmHg (95%CI,-8.7 to -0.9; P<0.01) * SBP-lower with low Na. Statistically significant.

Gillum RF, Elmer PJ et al, 1981 Study Design: Randomized controlled trial Class: A Positive Quality	N=51 (15+36). Age: Six to nine years, 54% boys. BP >95th percentile for age/sex, but <130/90mmHg. Mean BP: 114/68. Location: United States.	Duration: One year.	Children and parents attended four biweekly sessions; then bimonthly sessions. Goal for sodium intake: 70mmol/day.	BP measured at home; random-zero SM. DBP = Korotkoff fourth sound. BP-observer blind. Sodium intake estimated from overnight urine samples. *[*Note: Compliance with diet records and urine collections was a problem in the intervention group.]*	Overnight UNa+ at one year follow up was significantly lower for active participants of the low-sodium group (87mmol/24-hours) compared to dropouts (130mmol/24-hours) and controls (133mmol/24-hours). Δ Salt intake: –1.36% between Intervention and control groups (30 vs 31 mmol/ 10hr). For Intervention (attenders) minus Controls, the diff in BP at 1 year was: Δ SBP: 3.00±2.61 Δ DBP: 2.90±5.79. Not Statistically Sig.
Hofman A, Hazebroek A et al, 1983 Study Design: Double blind randomized trial Class: A Positive Quality	N=466 (225+241). Newborn, 51% boys. Location: The Netherlands.	Double-blind. Duration: Six months.	Formula and foods provided to subjects. Control formula contained Na that was usual for Dutch formula during the study period. Low Na formula had one-third the sodium as the control formula.	SBP measured in weeks one, five, nine, 13, 17, 21, 25) with a Doppler ultrasound device connected to a random-zero SM. Mean of three readings used. BP observer blind. Sodium intake estimated from three casual urine samples (weeks five, 13, 21) and from the food given to baby, with allowance for the sodium content of breast milk.	Δ Salt intake: -51.10% (from spot UNa). Sodium intake estimated from three casual urine samples (weeks five, 13, 21) was 11.1 mmol/L for the low-Na group, and 22.7 mmol/L for the normal Na group. Δ SBP: -2.00±0.92 (P=0.03). BP-reduced **(Stat-SIG).

Howe PR, Cobiac L et al, 1991 Study Design: Randomized controlled trial with crossover Class: A Positive Quality	N=100. Age: 11-14 years, 52% boys. Equal number from top, middle, and bottom deciles of BP distribution. Mean BP: 115/60mmHg. Location: Australia.	Duration: Four weeks.	Child/parent: weekly diet counseling; low-salt bread during low salt period; salt packets provided in control period. Goal for low-sodium diet: <75mmol/day. For high sodium diet: >150mmol/L.	BP measured with Dinamap monitors; mean of the second and third of three BP readings used in the analysis. BP-observer blind. Sodium intake estimated from spot urine samples.	Δ salt intake: -42.13% (spot U Na/Cr ratio); Difference in UNa was 81mmol/day between end of low and high Na periods. Net difference in BP: Δ SBP: -0.97±0.68 Δ DBP: -0.56±0.71 BP-reduced, but Not stat-sig.
Howe PR, Jureidini KF et al, 1985 Study Design: Non-randomized control trial Class: C Neutral Quality	N=21. Age: 11-14 years, 52% boys. BP≥90th percentile adjusted for age and height. Mean BP: 119/78mmHg. Location: Australia.	Duration: Three weeks.	Parents and children instructed by RD on diet.	BP measured with mercury SM. Korotkoff sound 1 and 4 = SBP and DBP, respectively. Sodium intake estimated from overnight urine samples.	Δ Salt intake: -43.25%(overnight UNa). Net difference in BP: Δ SBP: 0±2.32 Δ DBP: -1.30±1.78. ' BP-reduced **(Stat-SIG).

Lucas A, Morley R et al, 1988 Study Design: Randomized trial Class: A Negative Quality	N=347 preterm infants. Healthy and sick; Five center study. Note: There were four different trials (intervention arms) in the original RCT trial. At this 18-month follow up, the four groups were condensed to two (Study 1 and Study 2). This was done since there was no difference in BP between infants fed donor breast milk or regular formula. Combining the groups would allow them to compare BP between babies fed 'Low-Na' vs. 'Hi Na' diets during their first month of life. Location: United Kingdom.	This was an 18-month follow up of an randomized, parallel, clinical trial. Initial trial duration 27-37 days (while preterm baby was still hospitalized). Follow up with BP measurement at 18 months age.	Random assignment to feeds until hospital discharge (27-37 d): Study 1 (N=110) compared BP for infants originally randomized to either: (1a) Hi-Na Preterm formula, which provided 3.6 (0.07)mmol/kg/day Na; or (1b) Banked donor breast milk (BDBM) and a regular Term infant formula, which provided 1.8 (0.06)mmol/kg/day Na. Study 2 (N=121) compared BP for infants originally randomized to either: (2a) Hi-Na Preterm formula plus expressed maternal breast milk (EMBM), which provided 2.8 (0.07)mmol/kg/day Na; or(2b) Banked donor breast milk (BDBM) and a regular Term infant formula, plus EMBM which provided 1.8 (0.8)mmol/kg/day Na.	SBP and DBP measured with standard mercury SM. Number of measures unknown. Sodium content of the standard infant formula (8.3mmol/L), pre-term formula (19.6mmol/L); banked donor breast milk (7.2mmol/L), and expressed breast milk (11mmol/L) was determined.	Feeding a high sodium preterm formula in the neonatal period did not influence BP at 18 months of age. BP-no difference at 18 months. Age between feeding groups. Study 1: *Low Na:* SBP 97.1 (1.3); DBP 65.4 (1.1); *Hi-Na:* SBP 96.6 (1.3); DBP 66.1 (1.1) Study 2: *Low Na:* SBP 97.8 (0.9); DBP 65.8 (0.7); *Hi-Na:* SBP 96.6 (0.9); DBP 65.5 (0.7) *Note: The power calculations for this study (described in the 1984 report) were based on the number needed to detect a specific amount of weight gain (g/kg/day) and not on BP.*

Myers JB, 1989 Study Design: Randomized trial Class: A Neutral Quality	N=23 <18 years old; Mean age: 11 years. 40% boys. Mean BP: 108/67mmHg . (Adults in this study not included.) Location: Australia.	Two- week run-in on usual diet; then crossover periods: Two weeks on High- Na diet Two weeks on Low-Na diet. *[Note: Very short intervention (two week on each diet).]*	RD advised subjects on study diet based on the diet history and 24-hour UNa	BP measured with a mercury SM with observers blind as to diet of subjects. Sodium intake estimated from 24-hour urine samples.	Δ Salt intake: -58.23% (from 24-hour UNa); UNa excretion was 66mmol/24-hour on the Low Na diet; vs. 158mmol/L on the High Na diet (and 133 on the usual diet). Net difference in BP between diets for all children (N=23): Δ SBP: -3.74 ±1.98 Δ DBP: -1.70±2.17. Net difference in BP between diet phases for salt sensitive children*** (N=5): Δ SBP: -10±5 (P=0.06) Δ DBP: -15±1 (P<0.005). BP-reduced on Low Na. The difference in BP on Low vs. High Na was statistically significant for all subjects (age three-77 years), but it is not clear if the differences were stat-sig for the <18 year group.

Palacios C, Wigertz K et al, 2004 Study Design: Randomized crossover trial Class: A Neutral Quality	N=36. Age: 11–15 years. All girls, 39% white; 61% Black. Mean BP: 113/57mmHg. Location: United States.	Two-week washout in between. Duration: Three weeks. Subjects housed in metabolic unit.	All foods and drinks provided to children; Strict supervision to ensure compliance. Low salt diet: 43mmol/day Na. Control diet: 174mmol/day Na.	Supine BP was measured using mercury SM. K 1 and 5 were taken for SBP and DBP, respectively. Sodium intake estimated from daily 24-hour urine samples, and from six-day diet records.	Δ Salt intake: -70.8%. 24-hour UNa was reduced from 140.8 to 41.1mmol/24-hours. Na excretion was similar in W vs. B girls at low sodium intakes, but significantly lower in B vs. W girls at high Na intake. Net difference in BP between low and high sodium diets: Δ SBP: -2.43±2.72 Δ DBP: 1.06±1.98. SBP and DBP ↓ significantly from baseline to end of follow up for both diets, and for both WF and BF: SBP: 108.6 to >98.7 WF; Low Na DBP: 63.0 to >49.8 WF; Low Na SBP: 107.2 to >101.0 BF; Low Na DBP: 51.8 to >49.5 BF: Low Na. SBP: 108.1 to >98.8 WF: High Na DBP: 47.8 to >45.6 WF: High Na SBP: 102.8 to >97.6 BF; High Na DBP: 53.4 to >49.6 BF; High Na *[Note: This may have been due to the weight loss that occurred during the trial in both groups.]* *BP was significantly lower on both diets; but NS differences between the two diets*

Pomeranz A, Dolfin T et al, 2002 Study Design: Randomized controlled trial with crossover Class: A Neutral Quality	N=58 (25+33). Newborns in the intervention; 15 breast fed infants served as controls. Location: Israel.	BP-observer blind. Duration: Eight week intervention trial; Follow up to age six months.	58 infants were randomly assigned to one of two groups: Formula diluted with low Na spring water; or Formula diluted with high sodium tap water for eight weeks. After the eight week intervention, all infants had formula diluted with High Na tap water to age six months. NMa intake estimated to be 9.5mmol/L (Low-Na group), and 16.6mmol/L (High Na group).	BP measured with the Dinamap 8100 Monitor, (BP and pulse by Doppler). BP measured at home during sleep. Sodium intake estimated from flame photometry analysis of formula powder and of the waters used to dilute the formula.	Δ Salt intake: -53.85% (spot UNa/Cr ratio). Net difference in BP between diets for all subjects: Δ SBP: -5.30±2.06. * At eight weeks, SBP, DBP and MAP were significantly greater in the High-Na group than in the Low-Na group or in the breast fed controls. At 24 weeks, the High-Na group still had SBP, DBP and MAP statistically higher than the breast fed controls. BP for the original Low-Na group (which since age eight weeks had been switched to High-Na water) was still lower than the High-Na group (but not a statistically significant difference). BP was reduced on Low-Na compared with High-Na at eight weeks of age. Stat-Sig.
Sinaiko A, Gomez-Marin O et al, 1993 Study Design: Randomized controlled trial Class: A Positive Quality	N=139 (70+69) students in public schools. Mean age: 13 years, 50% M; 88% white. BP in the top 15th percentile of BP distribution. Mean BP: 114/64mmHg Location: United States.	Duration: Three years.	Diet counseling by RD. Neither boys nor girls reached the target levels of sodium intake for the low sodium period.	Random-zero SM used; Means of two measures; K1 and K5 for SBP /DBP. BP-observer blind. Sodium intake estimated from 24-hour urine samples, but only 59% of boys and 74% of girls had 24-hour UNa at year three. Compliance problem - boys	Δ Salt intake: 0.0337% (24-hour UNa); -16.2 % from food diaries. (UNa ↑ for boys in both Rx groups; but ↓ for girls in the low Na group (133 to 119mmol/day). Overall Δ in BP: Δ SBP: -1.98±1.32 Δ DBP: -4.65±1.91. BP-reduced for Girls - Stat-SIG negative slope on Low Na vs Ctrl.**

Smith RE, Kok A et al, 1995 Study Design: Prospective cohort Class: B Negative Quality	N=972 infants at one year. Birth to Ten cohort of Seweten infants. Location: South Africa.		Examined influence of weight, length, upper arm circumference, age formula feeds started, volume of formula feeds, and maternal BP on child's BP at 18 months of age.	SBP measured at one year of age with hand held aneroid SM and a Doppler ultrasound system. Sodium intake estimated from diet questionnaires completed by the mother.	No quantitative measure of Na intake. In the multivariate analysis, 29.3% of the variance for SBP was accounted for by weight (P=0.0001); upper arm circumference (P=0.0007); age formula started (P=0.0096); length (P=0.0346); and volume of formula feeds (P=0.0598). Amount of salt added to diet approached stat-sig. (P=0.0751) **In the multivariate analysis, variables were entered into the model and factors which did not predict SBP were removed one at a time.*
Trevisan M, Cooper R et al, 1981 Study Design: Study 1: Cross-sectional; Study 2: Randomized trial Class: A Negative Quality	N=21 (12+9). Age: 11-15 years. Mean SBP: 109mmHg. Location: United States.	BP-observer blind. Duration: 24 days.	Children followed either control diet or a diet ~70% lower in sodium.	BP measured with VITA-STAT (automatic device); Mean of two readings, one minute apart. Sodium intake estimated from 24-hour urine samples.	Δ Salt intake: (not stated). Net difference in BP: Δ SBP: -1.25±4.96 Δ DBP: NR. SBP-reduced; Stat-Sig.

Tuthill RW and Calabrese EJ, 1985 Study Design: Randomized control trial Class: A Positive Quality	N=216. High School girls from two campuses of private boarding schools (Grades 9-12). *[Note: Only 47.6% of eligible students at Campus 1, and 32.3% at campus 2 volunteered for the study)* Location: United States. Note: This is not a trial of salt reduction.	Duration: Eight weeks. One week base-data. Eight weeks follow up data.	Three treatment groups took capsules BID: Placebo (dextrose). 0.8g sodium (2g salt) in a.m. with water; 0.8g sodium (2g salt) in p.m. with dinner.	BP was measured in duplicate, twice a week. (Device used not stated). Sodium intake estimated from 24-hour urine samples, twice weekly. Note: There was a rapid rise in BP in the first several weeks which corresponded to the rapid increase in Na excretion that occurred at the same time, probably reflecting a significant Δ in diet as students began their semester at these private boarding schools.	Δ Salt intake ~ -56% for campus 1; but unable to estimate for campus 2 (data in figure form only). Differences in BP between Rx groups were not statistically significant. Mean BP differences were in the order of 1.4mmHg at max. There was no effect on BP of 0.8g sodium added to the usual dietary intake of healthy teenage girls. UNa measures showed that the desired sodium difference between RX groups was achieved. But the study was underpowered.** The authors intended to combine data from two schools, since the power to detect a BP difference of 1.5mmHg required the total data set with N=214 (71 per Rx). But they had to analyze each campus separately, so with this smaller sample size only a 2.5mmHg BP diff could be detected. The actual mean BP differences were in the order of 1.4mmHg at maximum. No BP lowering with low Na.
Whitten CF and Stewart RA, 1980 Study Design: Prospective cohort Class: C Neutral Quality	N=27 (13+14). Age: Three months. All African-American boys. Location: United States.	BP-observer blind. Duration: Five months.	All infant foods were provided; Na intake was 9.25 (control) and 1.93mmol/100kcal (low-salt group).	Air Shield BP Monitor used; Automatic reading every five minutes. BP measured six to 12 x during the three-day hospital stay. Only readings taken during sleep and ~one hour after feeding used in analysis. Sodium intake estimated from 24-hour urine samples.	Δ Salt intake: -79.38% (from 24-h UNa). Δ SBP: –2.00±2.13. * Difference in BP between groups was not significant at eight months and at eight years, but the study may have been insufficiently powered to detect such effects. * Decreased SBP; NS.

Research recommendations

Conduct studies, including clinical trials, in children to determine the effects of sodium on blood pressure and the age-related rise in blood pressure.

- Rationale. The problem of elevated blood pressure begins in childhood, well before blood pressure levels cross the threshold that defines hypertension in adults (140/90mmHg).

Search plan and results

Inclusion criteria

Subjects/Population

- Age: Birth to 18 years
- Setting: US and International
- Health Status: Healthy.

Search Criteria

- Study design preferences: Randomized controlled trials (RCT) or clinical controlled studies, large prospective cohort studies, meta-analyses, systematic reviews
- Study dropout rate: Less than 20%; preference for smaller dropout rates
- Year range: 1970 to present (May 2009)
- Languages: Limited to articles in English
- Other: Article must be published in peer-reviewed journal.

Exclusion criteria

Subjects/Population

- Age: Adult
- Setting: Inpatients
- Health status: Diagnosed with disease or medical condition.

Search Criteria

- Study design: Cross-sectional, pre- and post-intervention
- Size of study groups: Sample sizes less than 10
- Study dropout rate: 20% or greater
- Year range: Prior to 1970
- Authorship: Studies by same author similar in content
- Languages: Articles not in English
- Other: Animal or in vitro studies; abstracts or presentations.

Search terms and electronic databases used

PubMed: ("Hypertension"[mesh] OR "blood pressure"[MeSH Terms]) AND ("Sodium, Dietary"[Mesh] OR "sodium"[MeSH Terms] OR "sodium chloride"[mesh]) Limits: All Child: 0-18 years, Publication Date from 1970 to 2009/03 AND "english and humans"[Filter]

Date searched: Feb. 24, 2009, May 26, 2009

Summary of articles identified to review

- Total hits from all electronic database searches: 990
- Total articles identified to review from electronic databases: 126
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 18
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 18
- Number of Articles Reviewed but Excluded: 108

Included articles

1. Brion MJ, Ness AR, Davey Smith G, Emmett P, Rogers I, Whincup P, Lawlor DA. et al. Sodium intake in infancy and blood pressure at 7 years: Findings from the Avon Longitudinal Study of Parents and Children.*Eur J Clin Nutr.* 2008.
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7. Hofman A, Hazebroek A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. *JAMA.* 1983; 250: 370-373. PMID: 6343656.
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13. Pomeranz A, Dolfin T, Korzets Z, Eliakim A, Wolach B. Increased sodium concentrations in drinking water increase blood pressure in neonates. *J*

Hypertens. 2002; 20: 203-207. PMID: 11821704. Infants (Hand Search 04/07/09)
14. Sinaiko AR, Gomez-Marin O, Prineas RJ. Effect of low sodium diet or potassium supplementation on adolescent blood pressure. *Hypertension.* 1993; 21: 989-994.
15. Smith RE, Kok A, Rothberg AD, Groeneveld HT. Determinants of blood pressure in Sowetan infants. *S Afr Med J.* 1995 Dec; 85(12 Pt 2): 1, 339-1, 342. PMID: 8600606.
16. Trevisan M, Cooper R, Ostrow D, Miller W, Sparks S, Leonas Y, Allen A, Steinhauer M, Stamler J. Dietary sodium, erythrocyte sodium concentration, sodium-stimulated lithium efflux and blood pressure. *Clin Sci (Colch).* 1981; 61: 29S-32S. PMID: 7318331.
17. Tuthill RW, Calabrese EJ. The Massachusetts Blood Pressure Study, Part 2. Modestly elevated levels of sodium in drinking water and blood pressure levels in high school students. *Toxicol Ind Health.* 1985 Sep; 1(1): 11-17. PMID: 3842543.
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Excluded articles

Article	Reason for Exclusion
Adamopoulos PN, Chaniotis F, Kodoyianis S, Boutsicakis J, Madalos P, Kassos D, Gatos A, Moulopoulos S. Table salt and blood pressure in Greek children. *J Hum Hypertens.* 1987; 1(3): 209-213.	Cross-sectional study design.
Antonios TF. Salt intake in early life and cardiovascular risk. *Acta Paediatr.* 2000 Apr; 89(4): 397-398. No abstract available. PMID: 10830448.	Editorial publication.
Arguelles J, Diaz JJ, Malaga I, Perillan C, Costales M, Vijande M.Sodium taste threshold in children and its relationship to blood pressure. *Braz J Med Biol Res.* 2007 May; 40(5): 721-726.	Does not address question. Supports what is known already.
Armstrong BK, Margetts BM, Binns CW, Campbell NA, Masarei JR, McCall MG. Water sodium and blood pressure in rural school children. *Arch Environ Health.* 1982 Jul-Aug; 37(4): 236-245. PMID: 7114905.	Cross-sectional study design.
Basile JN., Ralph H. Johnson. Salt sensitivity predicts mortality independently of elevated blood pressure: a 27-	Editorial publication.

year follow-up study. *J Clin Hypertens (Greenwich).* 2001 Jul-Aug; 3(4): 258-259. VA Medical Center and the Medical College of South Carolina, Charleston, 29403, USA. PMID: 11505946.	
Beretta-Piccoli C, Weidmann P, Brown JJ, Davies DL, Lever AF, Robertson JI. Body sodium blood volume state in essential hypertension: Abnormal relation of exchangeable sodium to age and blood pressure in male patients. *J Cardiovasc Pharmacol.* 1984; 6 Suppl 1: S134-S142. PMID: 6204132.	Adult study population.
Calabrese EJ, Tuthill RW. The Massachusetts Blood Pressure Study, Part 1. The Massachusetts Blood Pressure Study, Part 1. Elevated levels of sodium in drinking water and blood pressure levels in children. *Toxicol Ind Health.* 1985 Sep; 1(1): 1-10. PMID: 3842542.	Does not address question. Focus was sodium in drinking water.
Chen J, Gu D, Jaquish CE, Chen CS, Rao DC, Liu D, Hixson JE, Hamm LL, Gu CC, Whelton PK, He J; GenSalt Collaborative Research Group. Association between blood pressure responses to the cold pressor test and dietary sodium intervention in a Chinese population. *Arch Intern Med.* 2008 Sep 8; 168(16): 1, 740-1, 746. PMID: 18779460.	Adult study population.
Cheung BM, Ho SP, Cheung AH, Lau CP. Diastolic blood pressure is related to urinary sodium excretion in hypertensive Chinese patients. *QJM.* 2000 Mar; 93(3): 163-168. PMID: 10751235.	Adult study population.
Connor SL, Connor WE, Henry H, Sexton G, Keenan EJ. The effects of familial relationships, age, body weight, and diet on blood pressure and the 24 hour urinary excretion of sodium, potassium, and creatinine in men, women, and children of randomly selected families. *Circulation.* 1984 Jul; 70(1): 76-85. PMID: 6723013.	Does not answer question. Focus was familial influence on outcomes.
Cooper R, Liu K, Trevisan M, Miller W, Stamler J. Urinary sodium excretion and blood pressure in children: absence of a reproducible association. *Hypertension.* 1983 Jan-Feb; 5(1): 135-139. PMID: 6848460.	Cross-sectional study design.

Cooper R, Soltero I, Liu K, Berkson D, Levinson S, Stamler J. The association between urinary sodium excretion and blood pressure in children. *Circulation.* 1980 Jul; 62(1): 97-104. PMID: 7379290.	Cross-sectional study design.
Couch SC, Daniels SR. Diet and blood pressure in children. *Curr Opin Pediatr.* 2005; (5): 642-647. PMID: 16160541.	Narrative review.
Daniels SR, Loggie JM, Khoury P, Kimball TR. Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. *Circulation.* 1998; 97: 1, 907-1, 911. PMID: 9609083.	Outcome was left ventricular geometry and hypertrophy.
DeSanto NG, Trevisan M, Capasso G, Giordano DR, Latte M, Krogh V. Blood pressure and hypertension in childhood: Epidemiology, diagnosis, and treatment. *Kidney Int Suppl.* 1988 Sep; 25: S115-S118. PMID: 3054226.	Does not address question. Focus was blood pressurediagnosis and treatment.
Du Cailar G, Mimran A, Fesler P, Ribstein J, Blacher J, Safar ME. Dietary sodium and pulse pressure in normotensive and essential hypertensive subjects. *J Hypertens.*2004; 22: 697-703.	Does not answer question. Adult study population.
Du Cailar G, Ribstein J, Daures JP, Mimran A. Sodium and left ventricular mass in untreated hypertensive and normotensive subjects. *Am J Physiol.* 1992 Jul; 263(1 Pt 2): H177-H181. PMID: 1636756.	Does not answer question. Focus was left ventricular mass.
du Cailar G, Ribstein J, Grolleau R, Mimran A. Influence of sodium intake on left ventricular structure in untreated essential hypertensives. *J Hypertens Suppl.* 1989 Dec; 7(6): S258-S259. PMID: 2534413.	Does not answer question. Focus was left ventricular structure.
Du Cailar G, Ribstein J, Mimran A. Dietary sodium and target organ damage in essential hypertension. *Am J Hypertens.* 2002 Mar; 15(3): 222-229. PMID:11939611.	Cross-sectional study design.
Elghozi JL, Dagher G, Garay RP, Vasmant D, Girard F, Meyer P. A case of juvenile essential hypertension: Implications of erythrocyte net Na+, K+ flux measurement. *Biomedicine.* 1981 Mar; 35(1): 4-6. PMID:	Does not answer the question. Focused on RBC electrolyte changes.

7236847.	
Elliott P. Sodium and blood pressure: a review of the evidence from controlled trials of sodium reduction and epidemiological studies. *Klin Wochenschr.* 1991; 69 Suppl. 25: 3-10. PMID: 1921248.	Narrative review.
Ellison RC, Sosenko JM, Harper GP, Gibbons L, Pratter FE, Miettinen OS. Obesity, sodium intake, and blood pressure in adolescents. *Hypertension.* 1980 Jul-Aug; 2(4 Pt 2): 78-82.	Cross-sectional study design.
Falkner B, Michel S. Blood pressure response to sodium in children and adolescents.*Am J Clin Nutr.* 1997; 65(2 Suppl): 618S-621S. PMID: 9022557.	Narrative review.
Falkner B, Sherif K, Michel S, Kushner H. Dietary nutrients and blood pressure in urban minority adolescents at risk for hypertension. *Arch Pediatr Adolesc Med.* 2000 Sep; 154(9): 918-922.	Cross-sectional study design.
Forte JG, Miguel JM, Miguel MJ, de Pádua F, Rose G. Salt and blood pressure: A community trial. *J Hum Hypertens.* 1989 Jun; 3(3): 179-184. PMID: 2671369.	Adult study population.
Frost CD, Law MR, Wald NJ. By how much does dietary salt reduction lower blood pressure? II--Analysis of observational data within populations. *BMJ.* 1991 Apr 6; 302(6, 780): 815-818. PMID: 2025704.	Narrative review.
Geleijnse JM, Grobbee DE. High salt intake early in life: does it increase the risk of hypertension? *J Hypertens.* 2002 Nov; 20(11): 2, 121-2, 124. Review. No abstract available. PMID: 12409942.	Editorial publication.
GenSalt Collaborative Research Group. GenSalt: rationale, design, methods and baseline characteristics of study participants. *J Hum Hypertens.* 2007 Aug; 21(8): 639-646. Epub 2007 PMID: 17443206.	Does not answer question. Paper describes study design and methodology.
Gómez-Marín O, Prineas RJ, Sinaiko AR. The Sodium-Potassium Blood Pressure Trial in Children. Design, recruitment, and randomization: The children and adolescent blood pressure program. *Control Clin Trials.* 1991 Jun;12(3): 408-23. PMID: 1651211.	Does not address the question. Paper describes study design and recruitment.

Grobbee DE, Hofman A. Does sodium restriction lower blood pressure? *Br Med J (Clin Res Ed).* 1986 Jul 5; 293(6, 538): 27-29. PMID: 3089393; PMCID: PMC1340776.	Adult study population.
Gudmundsson O, Cederblad A, Wikstrand J, Berglund G. Sodium elimination rate and blood pressure during normal and high salt intake in subjects with and without familial predisposition to hypertension. *Acta Med Scand.* 1984; 216(4): 345-352. PubMed PMID: 6516904.	Adult study population.
Hallenbeck WH, Brenniman GR, Anderson RJ. High sodium in drinking water and its effect on blood pressure. *Am J Epidemiol.* 1981 Dec;114(6): 817-26. PMID: 7315830.	Cross-sectional study design.
Harshfield GA, Pulliam DA, Alpert BS, Stapleton FB, Willey ES, Somes GW. Ambulatory blood pressure patterns in children and adolescents: influence of renin-sodium profiles. *Pediatrics* 1991 Jan; 87(1): 94-100.	Cross-sectional study design.
He, Feng J.; MacGregor, Graham A. Importance of salt in determining blood pressure in children: Meta-analysis of controlled trials. *Hypertension.* 2006; 48(5): 861-869. PMID: 17000923.	Meta-analysis. DGAC reviewed the primary studies that were examined in this paper.
He FJ, Marrero NM, MacGregor GA.* Salt intake is related to soft drink consumption in children and adolescents: a link to obesity? *Hypertension.* 2008 Mar; 51(3): 629-634. PMID: 18287345.	Cross-sectional study design.
Hill RM, Gambhir KK, Archer JA, Curry CL. Blood pressure and urinary sodium in black American adolescents. *J Natl Med Assoc.* 1984 Jun; 76(6): 579-585. PMID: 6748101; PMCID: PMC2561707.	Cross-sectional study design.
Hoffman CJ. Does the sodium level in drinking water affect blood pressure levels? *J Am Diet Assoc.* 1988 Nov; 88(11): 1, 432-1, 435. PMID: 3183265.	Does not address question. Focus was drinking water.
Hofman A, Valkenburg HA, Vaandrager GJ. Increased blood pressure in schoolchildren related to high sodium levels in drinking water. *J Epidemiol Community Health.* 1980 Sep; 34(3): 179-181. PMID: 7441137; PMCID: PMC1052072.	Retrospective cross-sectional.

Holden RA, Ostfeld AM, Freeman DH Jr, Hellenbrand KG, D'Atri DA. Dietary salt intake and blood pressure. *JAMA.* 1983 Jul 15; 250(3): 365-369. PMID: 6854900.	Adult study population.
Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Systematic review of long term effects of advice to reduce dietary salt in adults. *BMJ.* 2002 Sep 21; 325(7, 365): 628. Review. PMID: 12242173; PMCID: PMC126303.	Adult study population.
Howe PR, Rogers PF, Smith RM, Jureidini KF. Effects of short-term modification of dietary sodium intake on plasma catecholamines and blood pressure in prehypertensive children. *Clin Exp Pharmacol Physiol.* 1986 Apr; 13(4): 305-309. PMID: 3731534.	Same study as Howe et al, 1985, which is already included.
Ingelfinger JR. Sodium and blood pressure in infancy. *JAMA.* 1983 Jul 15; 250(3): 389-390. PMID: 6854907.	Editorial publication.
Jenner DA, English DR, Vandongen R, Beilin LJ, Armstrong BK, Miller MR, Dunbar D.Diet and blood pressure in 9-year-old Australian children. *Am J Clin Nutr.* 1988 Jun; 47(6): 1, 052-1, 059.	Cross-sectional study design.
Jones MR, Sealey JE, Laragh JH. Effects of angiotensin receptor blockers on ambulatory plasma Renin activity in healthy, normal subjects during unrestricted sodium intake. *Am J Hypertens.* 2007 Aug; 20(8): 907-16. PMID: 17679042.	Study population had cystic fibrosis.
Joshi S, Gupta S, Tank S, Malik S, Salgaonkar DS. Essential hypertension: Antecedents in children. *Indian Pediatr.* 2003 Jan; 40(1): 24-29.	Adult study population.
Karp RJ, Williams C, Grant JO. Increased utilization of salty food with age among preteenage black girls. *J Natl Med Assoc.* 1980 Mar; 72(3): 197-200. PMID: 7392064; PMCID: PMC2552550.	Cross-sectional study design.
Key J, Bondie D, Chico R, Moorehead C, Katch V, Martin M. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med.* 1989 Aug 31; 321(9): 580-585. PMID: 2668763.	Does not answer question. Study examined weight loss and blood pressure(BP).

Knuiman JT, Hautvast JG, Zwiauer KF, Widhalm K, Desmet M, De Backer G, Rahneva RR, Petrova VS, Dahl M, Viikari J, et al. Blood pressure and excretion of sodium, potassium, calcium and magnesium in 8- and 9-year old boys from 19 European centres. *Eur J Clin Nutr.* 1988 Oct; 42(10): 847-855. PMID: 3234325.	Cross-sectional study design.
Law MR, Frost CD, Wald NJ. Dietary salt and blood pressure. *J Hypertens Suppl.* 1991 Dec; 9(6): S37-S41; discussion S47-S49.	Narrative review.
Lawlor DA, Smith GD. Early life determinants of adult blood pressure. *Curr Opin Nephrol Hypertens.* 2005; 14(3): 259-264. PMID: 15821420.	Narrative review.
Legris GJ, Dearborn D, Stern RC, Geiss CL, Hopfer U, Douglas JG, Doershuk CF. Sodium space and intravascular volume: dietary sodium effects in cystic fibrosis and healthy adolescent subjects. *Pediatrics.* 1998 Jan; 101(1 Pt 1): 48-56. PMID: 9417150.	Study population had cystic fibrosis.
Leong GM, Kainer G. Diet, salt, anthropological and hereditary factors in hypertension. *Child Nephrol Urol.* 1992; 12(2-3): 96-105. Review. PMID: 1628278.	Does not address question. Focus was genetics.
Lieberman E. Blood pressure and primary hypertension in childhood and adolescence. *Curr Probl Pediatr.* 1980 Feb; 10(4): 1-35. PMID: 6989558.	Study reports BP in adulthood.
Liebman M, Chopin LF, Carter E, Clark AJ, Disney GW, Hegsted M, Kenney MA, et al. Factors related to blood pressure in a biracial adolescent female population. Hyper*tension.* 1986; 8; 843-850.	Cross-sectional study design.
Liu ZQ, Yang DY, Xu XL, Yang J. Sodium and potassium levels in hypertensive children. *Chin Med J (Engl).* 1989 Oct; 102(10): 759-764. PMID: 2517056.	Does not address question. Study was a saline load test; short intervention (three days).
Luque Otero M, Sa?chez RG, Martell Claros N, Fernández Pinilla C, Martínez Zamora M, Sacristán Sevilla A, Fernández Cruz A. Relationship of blood pressure levels to height, weight and sodium and potassium excretion in Spanish children. *J Hypertens Suppl.* 1985 Dec; 3(3): S391-S393. PMID: 2856748.	Cross-sectional study design. Focus was distribution of BP by age in Spanish children.

Málaga S, Díaz JJ, Arguelles J, Perillán C, Málaga I, Vijande M. Blood pressure relates to sodium taste sensitivity and discrimination in adolescents. *Pediatr Nephrol.* 2003 May; 18(5): 431-434. Epub 2003 Apr 5.	Study examined sodium taste sensitivity and BP in adolescents, not sodium intake.
Maseko MJ, Majane HO, Milne J, Norton GR, Woodiwiss AJ. Salt intake in an urban, developing South African community. *Cardiovasc J S Afr.* 2006 Jul-Aug; 17(4): 186-191. PMID: 17001421.	Does not address question. Adult offspring study population.
Mikkila V, Rasaen L, Raitakari OT, Pietinen P, Viikari J. Longitudinal changes in diet from childhood into adulthood with respect to risk of cardiovascular diseases: The Cardiovascular Risk in Young Finns Study. *European Journal of Clinical Nutrition.* 2004; 58, 1, 038-1, 045.	Study analyses did not include BP change in relation to changes in sodium intake.
Miller JZ, Weinberger MH, Daugherty SA, Fineberg NS, Christian JC, Grim CE.Blood pressure response to dietary sodium restriction in healthy normotensive children. *Am J Clin Nutr.* 1988 Jan; 47(1): 113-119. PMID: 3337029.	Study design was an uncontrolled pre- and post-study.
Miller JZ, Weinberger MH. Blood pressure response to sodium restriction and potassium supplementation in healthy normotensive children. *Clin Exp Hypertens A.* 1986; 8(4-5): 823-827. PMID: 3530556.	Study design was an uncontrolled pre- and post-study. Almost same data as Miller JZ et al, 1988 above.
Mo R, Omvik P, Lund-Johansen P, Myking OL. The Bergen blood pressure study: Sodium intake and ambulatory blood pressure in offspring of hypertensive and normotensive families. *Blood Press.* 1993 Dec; 2(4): 278-283. PMID: 8173696.	The publication was a letter.
Mu JJ, Liu ZQ, Liu WM, Liang YM, Yang DY, Zhu DJ, Wang ZX. Reduction of blood pressure with calcium and potassium supplementation in children with salt sensitivity: a 2-year double-blinded placebo-controlled trial. *J Hum Hypertens.* 2005; 19(6): 479-483.	Did not answer question. Sodium intake was not included in analyses.
Mülhauser I, Prange K, Sawicki PT, Bender R, Dworschak A, Schaden W, Berger M. Effects of dietary sodium on blood pressure in IDDM patients with nephropathy. *Diabetologia.* 1996 Feb; 39(2): 212-219. PMID: 8635674.	Study population had diabetes and neuropathy.

Myers J, Morgan T. The effect of sodium intake on the blood pressure related to age and sex. *Clin Exp Hypertens A.* 1983; 5(1): 99-118. PMID: 6831741.	Adult study population.
Nader PR, Stone EJ, Lytle LA, Perry CL, Osganian SK, Kelder S, Webber LS, et al. Three-Year Maintenance of Improved Diet and Physical Activity. The CATCH Cohort. *Arch Pediatr Adolesc Med.* 1999; 153: 695-704.	Does not answer question. No contrast in sodium intake between treatment groups after intervention.
Neyses L, Dorst K, Michaelis J, Berres M, Philipp T, Distler A, Losse H, Vetter H, Epstein FH, Vetter W. Compliance with salt restriction as a limiting factor in the primary prevention of hypertension. *J Hypertens Suppl.* 1985 Apr; 3(1): S87-S90. PMID: 3916444.	Adult and adolescent study population.
Okoro EO, Uroghide GE, Jolayemi ET. Salt taste sensitivity and blood pressure in adolescent school children in southern Nigeria. *East Afr Med J.* 1998 Apr; 75(4): 199-203.	Does not answer question. Study examined sodium taste sensitivity and BP in adolescents, not sodium intake.
Pazarloglou M, Spaia S, Pagkalos E, Ioannidis H, Askepidis N, Varyemezis V. Evaluation of insulin resistance and sodium sensitivity in normotensive offspring of hypertensive individuals. *Am J Kidney Dis.* 2007 Apr; 49(4): 540-546. PMID: 17386322.	Does not answer question. Study examined insulin and sodium sensitivity, not sodium intake.
Pearce MS, Relton CL, Unwin NC, Adamson AJ, Smith GD. The relation between diarrhoeal episodes in infancy and both blood pressure and sodium intake in later life: The Newcastle Thousand Families Study. *J Hum Hypertens.* 2008 Aug ;22(8): 582-584. Epub 2008 May 22. PMID: 18496557.	Does not address the question for children.
Pomerantz A, Korzets Z, Vanunu D, Krystal H, Wolach. Elevated salt and nirtrate levels in drinking water cause an increase of blood pressure in schoolchildren. *Kidney Blood Pressure Res.* 2000; 23: 400-403.	Cross-sectional study design.
Porter LE, Hollenberg NK. Obesity, salt intake, and renal perfusion in healthy humans. Hyper*tension.* 1998 Jul; 32(1): 144-148. PMID: 9674651.	Does not clearly address the question for children; 18-year-old adolescents grouped with adults.
Poulter N, Khaw KT, Hopwood BE, Mugambi M, Peart WS, Sever PS. Salt and blood pressure in various	Cross-sectional study design.

populations. *J Cardiovasc Pharmacol.* 1984; 6 Suppl 1: S197-S203. PMID: 6204141.	
Robertson JS. Water sodium, urinary electrolytes, and blood pressure of adolescents. *J Epidemiol Community Health.* 1984 Sep; 38(3): 186-194. PMID: 6540793; PMCID: PMC1052350.	Cross-sectional study design.
Robertson JI. Long-term effects of neonatal sodium restriction on blood pressure. *Am J Hypertens.* 1997 Dec; 10(12 Pt 1): 1, 425. PMID: 9443781.	Commentary publication.
Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, Martin M. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med.* 1989 Aug 31; 321(9): 580-585. PMID: 2668763.	Design was an uncontrolled pre- and post- study.
Savoca MR, Domel Baxter S, Ludwig DA, Evans CD, Mackey ML, Wilson ME, Hanevold C, Harshfield GA. A 4-day sodium-controlled diet reduces variability of overnight sodium excretion in free-living normotensive adolescents. *J Am Diet Assoc.* 2007 Mar; 107(3): 490-494. PMID: 17324668.	Does not answer question. Short-term intervention examined sodium excretion.
Schiffl H, Küchle C, Lang S. Dietary salt, intracellular ion homeostasis and hypertension secondary to early-stage kidney disease. *Miner Electrolyte Metab.* 1996; 22(1-3): 178-181. PMID: 8676814.	Study population had renal HTN.
Sempos C, Cooper R, Trevisan M, Ostrow D, Stamler J. Family history of hypertension and rates of sodium transport: absence of an association in population-based studies. *Clin Exp Hypertens A.* 1984; 6(7): 1, 379-1, 393. PMID: 6331918.	Cross-sectional study design.
Simon JA, Obarzanek E, Daniels SR, Frederick MM. Dietary cation intake and blood pressure in black girls and white girls. *Am J Epidemiol.* 1994 Jan 15; 139(2): 130-140.	Cross-sectional study design analysis within a prospective cohort study.
Simonetti GD, Raio L, Surbek D, Nelle M, Frey FJ, Mohaupt MG. Salt sensitivity of children with low birth weight. *Hypertension.* 2008 Oct; 52(4): 625-630. Epub 2008 Aug 11.	Does not answer question. Study examined glomerular filtration rate and salt sensitivity in low-

	birth weight children.
Sorof JM, Forman A, Cole N, Jemerin JM, Morris RC. Potassium intake and cardiovascular reactivity in children with risk factors for essential hypertension. *J Pediatr.* 1997 Jul; 131(1 Pt 1): 87-94. PMID: 9255197.	Does not clearly address the question for children. 18-year-old adolescents grouped with adults.
Staessen JA, Lijnen P, Thijs L, Fagard R. (1997) Salt and blood pressure in community-based intervention trials. *Am J Clin Nutr.* 1997 Feb; 65(2 Suppl): 661S-670S. PMID: 9022562.	Narrative review.
Tekol Y. Irreversible and reversible components in the genesis of hypertension by sodium chloride (salt). *Med Hypotheses.* 2008; 70(2): 255-259. Epub 2007 Aug 6. PMID: 17689201.	Paper presented hypotheses.
Tian HG, Guo ZY, Hu G, Yu SJ, Sun W, Pietinen P, Nissinen A. Changes in sodium intake and blood pressure in a community-based intervention project in China. *J Hum Hypertens.* 1995 Dec; 9(12): 959-968. PMID: 8746640.	Cross-sectional study design.
Tochikubo O, Sasaki O, Umemura S, Kaneko Y. Management of hypertension in high school students by using new salt titrator tape. *Hypertension.* 1986 Dec; 8(12): 1, 164-1, 171. PMID: 3793198.	Study was an uncontrolled pre- and post-study.
Trevisan M, Borrillo J. Na-Li countertransport and blood pressure in childhood. *Child Nephrol Urol.* 1992; 12(2-3): 85-89. Review. No abstract available. PMID: 1628276.	Does not address question. Study examined sodium-lithium transport mechanism.
Trevisan M, Cooper R, Stamler R, Gosch F, Allen A, Liu K, Ostrow D, Stamler J. Dietary salt and blood pressure. *Prev Med.* 1983 Jan; 12(1): 133-137. PMID: 6844292.	Narrative review.
Tucker DT, Smothers M, Lewis C, Feldman H. Effects of decreased dietary salt intake on blood pressure in preschool children. *J Nat Med Assoc.* 1989: 81: 299-302.	Cross-sectional study design.
Tuthill RW, Calabrese EJ. Age as a function in the development of sodium-related hypertension. *Environ Health Perspect.* 1979 Apr; 29: 35-43. PMID: 510240; PMCID: PMC1637368.	Does not address question directly. Study examined BP changes with age.

Tuthill RW, Calabrese EJ. Drinking water sodium and blood pressure in children: A second look. *Am J Public Health.* 1981 Jul; 71(7): 722-729. PMID:7246839; PMCID: PMC1619774.	Cross-sectional study design. DGAC reviewed most recent paper (1985) by these authors on this study population.
Tuthill RW, Sonich C, Okun A, Greathouse D. The influence of naturally and artificially elevated levels of sodium in drinking water on blood pressure in school children. *J Environ Pathol Toxicol.* 1980 Sep; 4(2-3): 173-181. PMID: 7462899.	Cross-sectional study design. DGAC reviewed most recent paper (1985) by these authors on this study population.
Tzemos N, Lim PO, Wong S, Struthers AD, MacDonald TM. Adverse cardiovascular effects of acute salt loading in young normotensive individuals. *Hypertension.* 2008; 51: 1, 525-1, 530.	Study population appears to be adults, including university students. Specific age of subjects not reported.
Uchiyama M, Daman Willems CE, Shah V, Dillon MJ. Sodium transport in erythrocytes: Differences between normal children and children with primary and secondary hypertension. *Clin Exp Hypertens A.* 1986; 8(4-5): 669-671. PMID: 2428549.	Does not answer question. Study examined sodium transport in a hypertensive pediatric population.
Uchiyama M, Otsuka T, Shibuya Y, Sakai K. Urinary sodium and potassium excretion in normotensive children in northern Japan. *J Chronic Dis.*1984; 37(12): 956-958. PMID: 6526931.	Publication was a letter.
Ukoh VA, Ukoh GC, Okosun RE, Azubike E. Salt intake in first degree relations of hypertensive and normotensive Nigerians. *East African Med J.* 2004; 81: 524-528.	Cross-sectional study design. Adult and adolescent study population (15 to 25 years of age).
Walker AR , Walker BF, Daya L, Ncongwane J. Blood pressures of South African Black adolescents aged 16 to 17 years. *Trans R Soc Trop Med Hyg.*1980; 74(5): 595-600.	Cross-sectional study design.
Watson RL , Langford HG, Abernethy J, Barnes TY, Watson MJ. Urinary electrolytes, body weight, and blood pressure. Pooled cross-sectional results among four groups of adolescent females. *Hypertension.* 1980 Jul-Aug; 2(4 Pt 2): 93-98.	Cross-sectional study design.
Watt GC, Foy CJ, Hart JT. Comparison of blood	Does not address question.

pressure, sodium intake, and other variables in offspring with and without a family history of high blood pressure. *Lancet.* 1983 Jun 4; 1(8, 336): 1, 245-1, 248. PMID: 6134040.	Analyses included combination of adults and children.
Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension.* 2001 Feb; 37(2 Part 2): 429-432. PMID: 11230313.	Study population included adults and 18-year-old adolescents.
Weinberger MH. Salt sensitivity is associated with an increased mortality in both normal and hypertensive humans. *J Clin Hypertens (Greenwich).* 2002 Jul-Aug; 4(4): 274-276. PMID: 12147930.	Does not clearly address the question for children. Study population included adults and 18-year-old adolescents.
Welty TK, Freni-Titulaer L, Zack MM, Weber P, Sippel J, Huete N, Justice J, Dever D, Murphy MA. Effects of exposure to salty drinking water in an Arizona community. Cardiovascular mortality, hypertension prevalence, and relationships between blood pressure and sodium intake. *JAMA.* 1986 Feb 7; 255(5): 622-626. PMID: 3944962.	Adult study population.
Wilson DK, Bayer L, Sica D. Variability in salt sensitivity classifications in black male versus female adolescents. *Hypertension.* 1996; 28: 250-255.	Cross-sectional study design.
Wilson DK, Sica DA, Miller SB. Effects of potassium on blood pressure in salt-sensitive and salt-resistant black adolescents. *Hypertension.* 1999 Aug; 34(2): 181-186. PMID: 10454438.	Does not address question. Study examined potassium and salt sensitivity.
Wu Y, Cai R, Zhou B, Xu X. Effects of genetic factors and dietary electrolytes on blood pressure of rural secondary school students in Hanzhong. *Chin Med Sci J.* 1991 Sep; 6(3): 148-152.	Cross-sectional study design.
Yamauchi T, Furuta M, Hamada J, Kondo T, Sakakibara H, Miyao M.Dietary salt intake and blood pressure among schoolchildren. *Ann Physiol Anthropol.* 1994 Nov; 13(6): 329-336.	Cross-sectional study design.
Yu Z, Song G, Guo Z, Zheng G, Tian H, Vartiainen E, Puska P, Nissinen A. Changes in blood pressure, body mass index, and salt consumption in a Chinese	Does not address question of salt intake and BP among children and adolescents. Data

population. *Prev Med.* 1999 Sep; 29(3): 165-172.	analysis combined adolescents with all subjects (15 to 24 years of age).
Zhu KM, He SP, Pan XQ, Zheng XR, Gu YA. The relation of urinary cations to blood pressure in boys aged seven to eight years. *Am J Epidemiol.*1987 Oct; 126(4): 658-663.	Cross-sectional study design.

CHAPTER 4. SODIUM AND BLOOD PRESSURE IN ADULTS

WHAT IS THE RELATIONSHIP BETWEEN SODIUM INTAKE AND BLOOD PRESSURE IN ADULTS AGED 19 AND OLDER?

Conclusion statement

A strong body of evidence has documented that in adults, as sodium intake decreases, so does blood pressure.

Grade

Strong

Evidence summary overview

The 2010 Dietary Guidelines Advisory Committee (DGAC) performed an updated literature search to identify new research on the relationship between sodium intake and blood pressure. The Nutrition Evidence Library (NEL) search identified 47 potential articles (15 systematic reviews/meta-analyses and 32 primary studies). A total of 13 articles, 12 primary studies and one systematic review/meta-analysis met the eligibility criteria and were reviewed. Of the 12 primary studies, nine were randomized trials (Cappuccio, 2006; China Salt Substitute Collaborative Group; Dickinson, 2009; Forrester, 2005; Gates, 2004; He FJ, 2009; Makela, 2008; Pimenta, 2009; Swift, 2005), two (He J, 2009; Schmidlin, 2007) were studies that tested different levels of sodium intake but in fixed order, and one was an observational analysis of a previously published trial (Cook, 2005). Of the 12 primary studies, eight were positive quality (Cappuccio, 2006; China Salt Substitute Collaborative Group; Forrester, 2005; He FJ, 2009; Pimenta, 2009; Swift, 2005) and four were neutral quality (Dickinson, 2009; Gates, 2004; Makela, 2008; Schmidlin, 2007). Enrollment criteria differed substantially by study, with blood pressure criteria that often bridged traditional classification schemes. Still, it appears that five of the studies enrolled normotensive individuals, six enrolled hypertensive individuals and one explicitly enrolled both normotensive and hypertensive individuals. Trials were conducted in Jamaica, Northern Chinese, US, Australia, Finland, Great Britain and Nigeria. Populations were demographically heterogeneous (e.g., enrolling black, white and Asian hypertensives living in Great Britain).

Because previous trials had already confirmed that sodium reduction lowers blood pressure, the individual trials typically addressed other issues, such as the effects of public health interventions in economically developing countries or the effects of sodium reduction on other variables (e.g., vascular function, arterial compliance, proteinuria and heart rate variability). Nonetheless, each reported the effects of sodium reduction on blood pressure. In total, a significant reduction in either systolic or diastolic blood pressure occurred in all but one of these studies, and significant reductions in both systolic and diastolic blood pressure in five studies. The eight methodologically strong studies all showed a significant reduction in systolic or diastolic blood pressure, and significant blood pressure reduction in both systolic and diastolic blood pressure occurred in five of the studies. In several studies, relatively

few blood pressure measurements were obtained; hence, in some cases, the absence of significant findings might have resulted from imprecise or inadequate blood pressure measurement.

The systematic review/meta-analysis of 34 randomized controlled trials (RCTs) (He and MacGregor, 2005, positive quality), which pooled data for 23 trials of hypertensive and 11 trials of normotensive subjects, demonstrated that a modest reduction in sodium intake for four or more weeks had a significant effect on blood pressure in both hypertensive and normotensive subjects. It also found a significant dose-response relationship between sodium reduction and both systolic and diastolic blood pressure. In this meta-analysis, a median reduction in urinary sodium of approximately 1.8g per day (78mmol per day) lowered systolic/diastolic blood pressure by 2.0/1.0mmHg in non-hypertensive and by 5.1/2.7mmHg in hypertensive adults.

In aggregate, these studies reinforce and further strengthen the previous conclusions from the 2005 DGAC report that sodium reduction lowers blood pressure and benefits extend to both non-hypertensive and hypertensive individuals.

Evidence summary paragraphs

Cappuccio et al, 2006 (positive quality). This community-based, randomized cluster trial, conducted in 12 rural and semi-urban West African villages, examined the effect of a health promotion intervention to reduce salt intake on blood pressure (BP). Subjects included 1,013 participants (628 women, 481 rural dwellers) whose mean age was 55 years, average BP was 125/74mmHg and urinary sodium excretion (UNa) was 101mmol per day. A general health promotion intervention that covered several relevant topics was provided to all 12 villages over a six-month period. The six intervention villages received additional advice to not add salt to food when cooking, to limit specific high-salt foods and to soak other high-salt foods in water overnight before eating. Urinary sodium excretion and BP levels were assessed at three and six months for all groups. There was no significant (NS) change in urinary sodium excretion in intervention villages. At six months the intervention group experienced a non-significant reduction in systolic blood pressure (SBP) [2.54mmHg (-1.45 to 6.54)] and a significant reduction in diastolic blood pressure (DBP) [3.95mmHg (0.78 to 7.11), P=0.015), net of change in the control group. In analyses that included all participants, regardless of intervention, there was a direct relationship between the fall in urinary sodium excretion and the fall in BP when adjusting for confounders. A difference in 24-hour UNa of 50mmol was associated with a lower SBP of 2.12mmHg (1.03 to 3.21) at three months and 1.34mmHg (0.08 to 2.60) at six months (both P<0.001). A strength of this study is the high response rate. A major limitation of the study is that it did not achieve a contrast in sodium intake. Overall, this trial should be viewed as a test of a public health intervention in a low-resource environment, not a trial to test the biologic effects of sodium reduction on BP.

China Salt Substitute Study Collaborative Group, 2007 (positive quality). This RCT, conducted in rural northern China, evaluated the long-term effects of a reduced-sodium (Na), high-potassium salt substitute [65% sodium chloride (NaCl), 25% potassium chloride (KCl), 10% magnesium sulfate] compared to normal salt (100% NaCl) on BP among 608 high-risk individuals. There were 585 subjects who completed

the one-year trial, 292 in the salt-substitute group and 293 in the salt group. Mean overall difference in SBP between randomized groups was 3.7mmHg (95% CI: 1.6 to 5.9, P<0.001), and SBP was significantly lower in the salt substitute group than in the normal salt group at the six, nine and 12-month visits (all P<0.02). The magnitude of this reduction increased over time (P=0.001) with the maximum net reduction of 5.4mmHg (2.3 to 8.5) achieved at 12 months. However, there were no detectable effects on DBP at any one time point or overall. Additionally, there was no evidence of any evolution of a difference in DBP over time. Based on first-morning specimens, urinary potassium (K) was slightly higher in the salt substitute group. Strengths of the study include its large sample size, rigorous measurements of BP and high adherence, at least by self report. Limitations included lack of 24-hour urines to assess adherence, as well as impact of existing salt and salty foods that were not removed from the homes. This study is most relevant to those populations in which added sodium is the predominant source of sodium. In this case, replacement of usual table salt (100% Na) with a reduced sodium (65%), higher potassium (25%) and magnesium (10%) leads to large BP reductions in high-risk population.

Cook et al, 2005 (positive quality). This multicenter RCT, conducted in the US, examined the relationship between sodium intake and BP change in 18-month and 36-month periods using data from the Trials of Hypertension Prevention (TOHP) Phase II sodium intervention. The original TOHP II subjects were assigned to receive one of the following: Counseling for weight loss only, counseling for sodium intake reduction to 80mmol per day, counseling for weight loss and sodium intake reduction to 80mmol per day, or usual care with no study-delivered intervention. Sodium intervention and usual care groups were combined for analysis; 1,157 overweight, non-hypertensive men and women were randomized and 880 subjects completed the three-year trial (437 in the sodium reduction interventions and 443 in usual care). At 36 months, there were significant differences between the sodium reduction group and usual care group in change of UNaexcretion (-50.9mmol per day vs. -13.2mmol per day, P<0.0001), urinary sodium/potassium ratio (-0.62 vs. 0.06, P<0.0001), SBP (-1.2mmHg vs. 0.5mmHg, P=0.003) and DBP (-3.3mmHg vs. -2.4mmHg, P=0.04). At 36 months, there was a significant trend of greater SBP decrease with lower quintiles of achieved sodium excretion (P=0.005), but not with DBP (P=0.67). In analyses that corrected for measurement error, the estimated mean reduction in SBP from a 100mmol reduction in sodium was 7.0mmHg at 18 months and 3.6mmHg at 36 months. In other analyses limited to those with 24 hours at all time points, those individuals who maintained reduced sodium intake had significantly lower SBP compared to those who did not reduce their sodium intake. Study strengths include its design, high-quality control, and rigorous analytic methods. Limitations include attenuated adherence over time leading to a modest contrast between active and control groups. Overall, the observational analyses presented in this paper are consistent with dose-response trials, documenting that a dose-dependent relationship of SBP reduction with both the extent of sodium reduction and achieved levels of sodium.

Dickinson KM et al, 2009 (neutral quality). This randomized crossover study compared the effects of a low-salt (LS; 50mmol Na per day) diet with those of a usual-salt (US; 150mmol Na per day) diet on flow-mediated dilatation (FMD). Subjects

included 29 overweight and obese normotensive Australian men and women who followed a LS diet and a US diet for two weeks. Participants received diet counseling on how to achieve the intended dietary goals. The diets were designed to ensure weight stability and had similar potassium and saturated fat contents. At the end of each two-week intervention, FMD, pulse wave velocity, augmentation index and BP were measured. The 24-hour sodium excretion was significantly lower (P=0.0001) with the LS diet (64.1±41.3mmol) than with the US diet (156.3±56.7mmol), while urinary potassium excretion was similar on both diets. Flow-mediated dilatation was significantly greater (P=0.001) with the LS diet (4.89%±2.42%) than with the US diet (3.37%±2.10%), SBP was significantly (P=0.02) lower with the LS diet (112±11mmHg) than with the US diet (117±13mmHg). No significant changes in augmentation index or pulse wave velocity were observed. There was no correlation between change in FMD and change in 24-hour sodium excretion or change in BP. The authors concluded that salt reduction improved endothelium-dependant vasodilation in normotensive subjects independent from change BP; suggesting additional cardioprotective effects of salt reduction beyond BP reduction. Study limitations include the short duration of the intervention and relatively few BP measurements at the end of each feeding period. The effects of a reduced sodium intake on FMD suggest that higher sodium intake, in the range commonly consumed in the US, has deleterious effects on vascular function, apart from the well-known effects of increased sodium on BP.

Forrester T et al, 2005 (positive quality). This randomized crossover study examined the effect of low- and high-salt diets on BP response in 114 normotensive adults living in Nigeria (N=58) and Jamaica (N=56). After a four-week run-in period to determine willingness to adhere to a low-salt diet, subjects completed a two-period crossover study of low-salt (usual diet, 50mEq sodium) and high-salt intake (usual diet +50mEq sodium). Each period lasted three weeks, with a two-week washout that separated the periods. Participants were counseled to follow each diet. Baseline UNa excretion was 86.8 and 125.6mEq per day in Nigeria and Jamaica, respectively. Mean baseline SBP was 125mmHg in Jamaica and 114mmHg in Nigeria. Mean urinary potassium excretion was approximately 50mmol per day in both countries. After adjustment for baseline sodium excretion, period effects, age and sex, the net change in urinary sodium excretion between the low-salt and high-salt interventions was 72.2mEq per day in Nigeria and 78.8mEq per day in Jamaica. The mean difference between baseline sodium excretion and low-sodium phase was 33.6mEq per day in Nigeria and 57.5mEq per day in Jamaica. The mean change in SBP between the low- to high-sodium interventions in both countries was approximately 5mmHg suggesting that that the efficacy of sodium reduction in developing countries equals those noted in more affluent cultures. Study strengths include standardized BP measurements, rigorous methods and a cross-cultural comparison. Study limitations include the short duration of the intervention periods. Overall, this trial confirms that sodium reduction lowers BP in non-hypertensive individuals in two different countries with different levels of baseline sodium intake.

Gates PE et al, 2004 (neutral quality). This randomized, crossover study examined the effects of dietary sodium restriction on large elastic artery compliance and BP. Twelve

untreated US adults (six men and six women; 64 + two years) with stage one systolic hypertension (HTN) were assigned to four weeks of low (57mmol per day) or normal (135mmol per day) sodium intake. Participants ate a reduced sodium diet in each period; the contrast in total dietary sodium intake was achieved with pills (either placebo or slow-release sodium chloride). The amount of pills was titrated to achieve the mean baseline levels of sodium intake. Urinary sodium excretion was reduced by 60% by the end of week one of sodium restriction (54±11mmol per day, P<0.01) vs. baseline (135±14). There was no consistent difference in carotid artery compliance between the low and usual sodium periods. During weeks two to four, 24-hour ambulatory SBP was reduced by approximately 6mmHg in the low compared to usual sodium period. Strengths of this study include multiple outcomes of potential interest, beyond BP. However, limitations were substantial and include a confusing presentation of data, mostly comparisons with baseline rather than comparisons between the low and usual sodium periods and suboptimal presentation of the achieved contrast in sodium. Overall, the results of this study should be viewed as non-contributory.

He FJ et al, 2009 (positive quality). This randomized, double-blind crossover trial, conducted in London, England, examined the effect of a modest reduction in salt intake on BP, 24-hour urinary albumin excretion and pulse wave velocity in three ethnic groups with untreated, mildly raised BP. Participants included 71 whites, 69 blacks and 29 Asians, aged 30 to 75 years, with sitting SBP of 140 to 170mmHg or DBP 90 to 105mmHg. All subjects consumed a reduced salt diet for the first two weeks of the study, then were randomized to either slow sodium or placebo for six weeks, followed by a crossover to the opposite tablets for an additional six weeks. From slow sodium to placebo, UNa was reduced by 55mmol per day, from 165+58 to 110+49mmol per 24 hours (9.7 to 6.5g per day salt, respectively). Blood pressuredecreased from 146+13/91+8 to 141+12/88+9mmHg (P>0.001), urinary albumin from 10.2 (IQR: 6.8 to 18.9) to 9.1 (6.6 to 14.0) mg per 24 hours (P>0.001), albumin/creatinine ratio from 0.81 (0.47 to 1.43) to 0.66 (0.44 to 1.22) mg per mmol (P>0.001) and carotid-femoral pulse wave velocity from 11.5±2.3 to 11.1±1.9 m/s (P>0.01). Strengths of this trial include the diverse study population, the clear presentation of results and the duration of feeding. Limitations are the reporting of subgroup findings without interactions tests and suboptimal description of methods (e.g., source of participants, number of dropouts). Overall, this trial documents that sodium reduction, commonly tested in white and black populations, also lowers blood pressure in Asians with HTN and that the extent of BP appears similar in the subgroups tested (whites, blacks and Asians). Reductions in albuminuria and pulse wave velocity also suggest that sodium reduction has benefits beyond BP reduction.

He and MacGregor, Cochrane 2004, Updated in 2005 (positive quality) a systematic review and meta-analysis of 34 trials assessed the effect of modest salt reduction on BP and whether there is a dose response to salt reduction. Twenty-three trials were conducted with subjects who had elevated BP (N= 802) and 11 trials with normotensive subjects (N=2,220). MEDLINE, EMBASE, and Cochrane library databases were searched for randomized trials with a four-week duration or more (date range 1966 to June 2001; updated search through April 2005). Mean effect sizes

were calculated using both fixed and random-effects models. The relationship between the change in UNa and the change in BP was examined using weighted linear regression. The net change in BP (Fixed Model) was -3.03mmHg for SBP and -1.76mmHg for DBP. In subjects with elevated BP, the median reduction in UNa was 78mmol per 24 hours (4.6g per day of salt), the mean reduction in BP was -5.06 for SBP and -2.70mmHg for DBP. In subjects with normal BP, the median reduction in urinary sodium was 74mmol per 24 hours (4.4g per day of salt) and the mean reduction in BP was -2.03mmHg for SBP and -0.99mmHg for DBP. Weighted linear regression showed a significant relationship between the reduction in urinary sodium and the reduction in BP. The dose response analysis with y-intercept fixed at zero showed a significant dose response to salt reduction for both SBP and DBP. A 100mmol reduction of sodium intake per day (6g salt) predicted a fall of 7.2mmHg for SBP and 3.8mmHg for DBP. This meta-analysis demonstrated that a modest reduction in salt intake for four weeks or more had a significant effect on BP in hypertensive and normotensive subjects. There was also a significant dose response relationship between sodium reduction and both systolic and diastolic blood pressure.

He J et al, 2009 (positive quality). This non-randomized, controlled three-week feeding trial, conducted in rural China, examined gender differences in BP response to dietary sodium and potassium intake. The interventions included seven days on a low-sodium diet (51.3mmol per day), seven days on a high-sodium diet (307.8mmol per day) followed by seven days on a high-sodium (307.8mmol per day) plus potassium supplementation (60mmol per day), with no washout period between interventions. Subjects were 1,906 adults (1,010 men and 896 women), BP range 130 to 160mmHg SBP and 85 to 100mmHg DBP; including eligible siblings and offspring, aged 18 to 60 years, who participated in the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study. During the interventions, meals were cooked without salt. Staff added prepackaged salt to individual meals prior to serving and observed subjects' consumption. Food records were kept for each meal. Three-timed urine specimens were collected, one 24-hour and two overnight, at baseline and in each phase of the intervention to assess dietary compliance. Nine BP measurements were obtained during the three-day baseline observation and the last three days of each intervention using a random-zero sphygmomanometer. Compared to the low sodium arm, the high sodium arm raised SBP by 5.2mmHg in men and 6.3mmHg in women. The increase in SBP on the high compared to low sodium was less than zero in 73.9% of participants and more than four in 60.7%. Systolic BP responses to sodium increased with age, and both SBP and DBP responses to sodium and potassium interventions increased with baseline BP levels. Blood pressure responses to low and high sodium intervention were significantly greater ($P<0.001$) in women than in men. Study strengths include excellent compliance, inclusion of an arm with increased potassium, rigorous methods and conduct of a trial in an understudied, non-overweight population. Limitations include the short duration of each intervention phase (seven days), lack of a washout period, non-randomized order of diets, pre-post evaluation of the 'low sodium diet' and single ethnic group (rural Chinese). Overall, this study documents that increased salt intake raises BP in a generally lean Asian population.

Makela et al, 2008 (neutral quality). This RCT, conducted in Finland, assessed the effects of dietary sodium reduction on BP response and heart rate variability in 80 persons with essential hypertension (SBP of 160 to 200mmHg and DBP of 90 to 110mmHg). Forty persons were randomized to six months of a low-sodium diet (daily sodium intake reduced to less than 70mmol, general advice to lose weight if necessary, and general advice to reduce intake of saturated fats) and 40 were assigned to the control group (not described, but previously reported). Although BP was significantly reduced after six months in the sodium restriction group (SBP from 149.9±14.7 to 130.3±11.8mmHg, P<0.001 and DBP from 98.0±6.4 to 87.1±6.2mmHg, P<0.001), NS difference in the change between groups were detected. Additionally, no changes were seen in cardiac parasympathetic nervous control as measured by heart rate variability. Study strengths include the variety of measurements. Limitations include inadequate description of methods, approach to analysis with multiple BP over time, substantial differences between groups at baseline, and inconsistent description of BP results (e.g., significant time by group interaction in results, yet description of NS differences in BP change between groups). Overall, the results of this study should be viewed as non-contributory.

Pimenta et al, 2009 (positive quality). This randomized, crossover study, conducted in the US, examined the effects of dietary salt restriction on office and 24-hour ambulatory BP in 12 subjects with resistant HTN. Two one-week interventions, a low (50mmol per day) and high (250mmol per day) sodium diet, were separated by a two-week washout period. Potassium intake was high and similar in both diets (3,700mg in the 2,000kcal versions of the diets). Brain natriuretic peptide; plasma renin activity; 24-hour urinary sodium, potassium and aldosterone; 24-hour ambulatory BP monitoring; aortic pulse wave velocity; and augmentation index were compared. At baseline, subjects were on an average of 3.4 anti-hypertensive medications with a mean office BP of 145.8+10.8/83.9+11.2mmHg. Mean UNa excretion was 46.1+26.8mmol per day for the low-salt vs. 252.2+64.6 for the high-salt intervention.
Office SBP and DBP decreased by 22.7 and 9.1mmHg, respectively, for the low- vs. high-salt diet. Plasma renin activity increased, whereas brain natriuretic peptide and creatinine clearance decreased during low-salt intake, indicative of intravascular volume reduction. Study strengths included the crossover, randomized design, use of 24-hour ambulatory BP monitoring and confirmation of dietary adherence with 24-hour urinary sodium excretion measurements. Limitations included the small number of subjects and short duration of the dietary treatment periods. Despite these limitations, this trial documents that sodium reduction lowers BP, even among individuals with resistant HTN who concurrently are taking multiple anti-hypertensive medications.

Schmidlin et al, 2007 (neutral quality). This non-randomized, cross-over trial conducted in the US tested the hypothesis that the sodium component of dietary sodium chloride can have a pressor effect apart from its capacity to complement the extracellular osmotic activity of chloride and plasma volume. The study lasted for 21 days total, with three consecutive seven-day periods: Two sodium-loading weeks separated by a sodium-restricted week. All participants (N=35 non-hypertensive blacks) consumed an eucaloric basal metabolic diet providing 30mmol of sodium and 45mmol of potassium per 70kg of body weight per day, as well as 20g

water per kg of body weight per day during sodium restriction and 35g water per kg of body weight per day during sodium loading. Results were only presented in a stratified fashion (salt sensitive vs. salt resistant), not together. Study strengths include the research question, namely, the impact of the anion (chloride vs. bicarbonate) on BP. Limitations include the fixed order of diets and the focus on stratified results without presentation of overall results. Overall, the results of this study should be viewed as non-contributory.

Swift et al, 2005 (positive quality). This randomized crossover trial, conducted in the United Kingdom, determined the effects of moderate salt reduction on BP and urine protein excretion in 47 non-diabetic black hypertensivesubjects. After a run-in period of four weeks of usual diet, followed by an additional run-in period of two weeks on a reduced salt (approximately 5g salt) diet, participants received either 12 slow-sodium tablets (10mmol sodium per tablet) daily to bring their salt intake back to normal or 12 placebo tablets daily for four weeks. In the 40 subjects who completed the study, reducing salt intake from approximately 10 to approximately 5g per day decreased BP from 159/101±13/8mmHg to 151/98±13/8mmHg ($P<0.01$). Mean protein excretion fell from 93 to 75mg per day ($P<0.008$). Study strengths include its crossover design and validity of measurements, while limitations include the narrow population, namely, black hypertensives. Overall, this trial documents that moderate salt reduction should lower proteinuria, as well as BP.

Overview table

Author, Year, Study Design, Class, Rating	Subjects, Duration, and Location	Intervention Procedure	BP Measurement; Sodium Intake Measurement	Outcome (BP Values, mmHg)
Cappuccio F, Kerry S et al, 2006 Study Design: Cluster randomized trial Class: A Positive Quality	N=1,013 participants from 12 West African villages (628 women; 385 men). Mean age: 55 years. Average BP: 125/74mmHg. Average UNa: 101. Duration: Six months. Location: Africa.	Health promotion intervention was provided to examine the effect of education to reduce salt intake upon BP. All 12 villages received education on a wide range of public health topics. Sessions were conducted daily for the first week of the study and weekly thereafter. Intervention villages received additional advice to not add salt to food when cooking, to limit specific high-salt foods and to soak other high-salt foods in water overnight before eating. Height and weight were measured to determine BMI.	UNa excretion and BP levels were assessed at baseline, three and six months for all groups.	Relationship between salt intake (per 50mmol of UNa per day) and BP: SBP: 2.17mmHg; 95% CI: 0.44 to 3.91; P<0.001 DBP: 1.10mmHg; 0.08 to 1.94; P<0.001 ΔSBP: -2.54mmHg; 95% Ci: -6.54 to 1.45 ΔDBP: -3.95mmHg; 95% CI: -7.11 to -0.78; P=1.015. NS Δ in UNa excretion. However, in all participants, regardless of intervention, there was a consistent relationship between the ↓ in UNa excretion and the ↓ in BP when adjusting for confounders. A difference in 24-hour UNa of 50mmol was associated with a ↓ SBP of -2.12mmHg (-1.03 to -3.21) at three months and -1.34mmHg (-0.08 to -2.60) at six months (both P<0.001).

China Salt Substitute Study Collaborative Group 2007 Study Design: Randomized Controlled Trial Class: A Positive Quality	N=608 high-risk individuals; 585 subjects completed the trial, 292 in the salt-substitute group and 293 in the salt group. Duration: One year. Location: Rural northern China.	Trial examined replacement of salt used in home cooking with salt substitute and the effect on BP. Subjects randomized to salt or salt substitute for all home cooking x 12 months. Reduced-sodium, high-potassium salt substitute (65% NaCl, 25% KCl, 10% magnesium sulfate). Normal salt (100% NaCl).	First morning UNa and K at baseline, six and 12 months. BP measured with Omron automatic sphygmomanometer at baseline, one, two, three, six, nine and 12 months. Dietary salt or substitute used in cooking was assessed by self-report in terms of remaining proportion of home cooking salt from the start of the study remaining.	Mean difference in SBP between groups was 3.7mmHg (95% CI: 1.6 to 5.9, P<0.001). SBP was significantly ↓ in the salt substitute group than in the normal salt group at the six, nine and and 12-month visits (all P<0.02). The magnitude of this reduction ↑ over time (P=0.001) with the maximum net reduction of -5.4mmHg (-2.3 to -8.5) achieved at 12 months. There were no detectable effects on DBP at any time point or overall, and no evidence of any evolution of a difference over time.
Cook NR, Kumanyika SK et al, 2005 Study Design: Randomized controlled trial Class: A Positive Quality	1,157 overweight, non-hypertensive men and women were randomized and 880 subjects completed the three-year trial (437 in the sodium reduction interventions; 443 in usual care). Duration: Three years. Location: US.	Trials of Hypertension Prevention (TOHP) Phase II sodium intervention. The original TOHP II subjects were assigned to receive one of the following: Counseling for weight loss only Counseling for Na intake reduction to 80mmol per day Counseling for weight loss and Na intake reduction to 80mmol per day Usual care (UC) with no study-delivered intervention. Sodium intervention and UC groups were combined for analysis.	Na and K intake during trials estimated from a mean of three to seven 24-hour urinary excretions. Dietary Na intake also estimated from self-reported intake on follow-up questionnaire.	At 36 months, there were significant differences between the Na reduction group and UC group in Δ of UNa excretion (-50.9mmol vs. -13.2mmol per day, P<0.0001), urinary Na/K ratio (-0.62 vs. 0.06, P<0.0001), SBP (-1.2mmHg vs. 0.5mmHg, P=0.003), and DBP (-3.3mmHg vs. -2.4mmHg, P=0.04). At 36 months, there was a significant trend of greater SBP ↓ with lower quintiles of Na excretion (P=0.005), but not with DBP (P=0.67).

Dickinson K, Keough J et al, 2009 Study Design: Randomized crossover trial Class: A Positive Quality	N=29 adults (seven men, 22 women). Age: 52.7±6.0 years. Overweight or obese; BMI range 42.0 to 64.0kg/m^2. Normotensive. Duration: One month. Location: Australia.	Compared the effects of low-salt (LS; 50mmol Na per day) diet with usual-salt (US; 150mmol Na per day) diet on flow-mediated dilataion (FMD). Diets designed for weight stability and similar K and saturated fat contents. 24-hour urine to measure Na and K at baseline and end of each intervention.	ANOVA repeated measures used with and without covariates, including diet order, BP and baseline Na excretion. Pearson correlation used to assess association of Δ between variables. Brachial artery flow mediated dilatation measured after an overnight fast with a 7.5-MHz linear array transducer. Pulse wave velocity by Doppler measures at the carotid and femoral arteries. Augmentation index measured with SphygmoCor BP system. BP measured with automated sphygmomanometer.	FMD: US diet (3.37±2.10%) LS diet (4.89±2.42%) significantly ↑ (P=0.001). SBP: US diet (117±13mmHg) LS diet (112±11mmHg), significantly ↓ (P=0.02). 24-hour UNa: US diet (156.3±56.7mmol) LS diet (64.1±41.3 significantly ↓ (P=0.0001). Pulse wave velocity (m/s): US diet: 10.49 (3.07) LS diet: 10.49 (4.14), No Δ (P>0.05).

Forrester T, Adeyemo A et al, 2005 Study Design: Randomized crossover trial Class: A Positive Quality	N=114 adults from Nigeria (N=58; 34 men, 24 women) and Jamaica (N=56; 34 men, 22 women). Age: 25 to 55 years, (Mean age: Nigeria, 46.6 years; Jamaica, 40.8 years). BMI: Nigeria, 23.1kg/m^2; Jamaica 28.5kg/m^2. Baseline BP normotensive: SB P Nigeria = 125mmHg; SBP Jamaica = 114mmHg. Baseline UNa excretion: Nigeria = 86.8mEq per day; Jamaica = 125.6mEq per day. Duration: Three months Location: Jamaica and Nigeria.	High salt diet: 50mEq ↑ in Na over usual diet at baseline. Low salt diet: 50mEq ↓ in Na from usual diet at baseline. Compared effects of low and high salt diet on mean BP response. After a two-week low-Na diet to assess ability for compliance, subjects had a one- to two-week period with usual diet. Subjects were then randomized to either a high- or low-salt diet for three weeks with a two-week usual diet wash out between crossover to the other three-week study arm.	24-hour urine obtained at baseline and end of each intervention; assayed for Na and K to assess dietary compliance. The following parameters were measured at each clinic visit. BP using both manual manometer and the Omron automatic device. Weight to nearest 0.1kg. Height, waist and hip circumference to nearest 0.1cm.	Net Δ in UNa excretion between the low-salt and high-salt interventions (adjusted for baseline UNa excretion, period effects, age and sex). Nigeria: 72.2mEq per day Jamaica: 78.8mEq per day. There were no net Δs in urinary K. Mean Δ in BP mmHg; average of manual and Omron measures (95% CI). ΔSBP Nigeria: 4.5 (1.6, 7.3) Jamaica: 5.5(3.0, 8.0). ΔDBP Nigeria: 2.7 (0.9, 4.5) Jamaica: 2.8 (0.5, 5.0).

Gates P, Tanaka H et al, 2004 Study Design: Randomized controlled trial Class: A Positive Quality	N=12 untreated older adults (six men, six women) with stage one systolic HTN. Age: 64±2 years. Duration: Eight weeks. Location: US.	Subjects were randomized to four-week periods of reduced and normal Na intake. All subjects consumed ↓ Na diets and took a prescribed number of tablets with each meal, either placebo or slow-release NaCl. The number of tablets taken was based on a once-weekly 24-hour UNa excretion compared to the average of two baseline samples. Subjects received comprehensive dietary education and counseling (at baseline and weekly) to reduce Na intake without Δ in caloric intake or dietary composition.	Carotid artery compliance and β-stiffness index were determined using high-resolution B-mode ultrasound and simultaneous estimates of carotid BP using applanation tonometry. Casual brachial artery BP measurements were made after an overnight fast in the upright seated and supine positions. Ambulatory BP measurements were made during normal daily activity. Dietary assessment was based on three-day diet records with Food Processor software (ESHA) at baseline and the end of each intervention.	UNa excretion: Baseline: 135±14mmol per day Week one of Na restriction: 54±11mmol per day, P<0.01; a ↓ of 60%. Carotid artery compliance: Baseline: 0.11±0.01mm per mmHg Low-Na Week One: 0.14±0.02, P<0.05) an ↑ of 27% Low-Na Week Two: +46%, to 0.16±0.02, P<0.01. Supine resting brachial artery SBP was ↓ by >5mmHg by week one of Na restriction, attaining peak reductions by week two (-12mmHg, P<0.01 vs. baseline). The 24-hour ambulatory SBP was ~3mmHg lower at week one of Na restriction and ~6mmHg lower by week two (P<0.01 vs. baseline).

He Feng J, Marciniak M et al, 2009 Study Design: Randomized, double-blind, crossover trial Class: A Positive Quality	N=169 subjects, from three ethnic groups: 71 whites 69 blacks 29 Asians. Age: 30 to 75 years. With untreated, mildly raised BP: Sitting SBP 140 to 170 or DBP 90 to 105mmHg. Duration: 14 weeks. Location: England.	All subjects consumed a reduced salt diet for the first two weeks. Then they were randomized to slow Na (90mmol per day plus low-Na diet) or placebo for six weeks, followed by a crossover to the opposite tablets for an additional six weeks. Measures were taken at end of each six-week intervention.	BP: 24-hour BP measured with Spacelabs 90207 devices. Mean of two consecutive 24-hour urines measured for urinary Na, K, creatinine, calcium and albumin excretion. Urinary albumin measured by laser immunonephelometry. Samples with measured concentrations less than 2.1mg per L werere-analyzed using a high-sensitivity ELISA. Carotid-femoral pulse wave velocity was measured non-invasively using an automatic device; outcome was mean of 10 cardiac cycles.	From slow Na to placebo, UNa was ↓ by 55mmol per day, from 165±58 to 110±49mmol per 24 hours (9.7 to 6.5g per day salt, respectively). BP ↓ from 146±13/91±8 to 141±+2/88±9 mmHg (P>0.001). Urinary albumin from 10.2 (IQR: 6.8 to 18.9) to 9.1 (6.6 to 14.0) mg per 24 hours (P>0.001). Albumin/creatinine ratio from 0.81 (0.47 to 1.43) to 0.66 (0.44 to 1.22) mg per mmol (P>0.001). Carotid-femoral pulse wave velocity from 11.5±2.3 to 11.1±1.9 m/s (P>0.01). Subgroup analysis found significant ↓ in BP and urinary albumin/creatinine ratio in all groups. The ↓ in pulse wave velocity was significant only in the black ethnic group.

He J, Gu D et al, 2009 Study Design: Non-randomized trial Class: M Positive Quality	N=1,906 adults, eligible offspring and siblings (men 1,010; women 896). Mean BP (mmHg): Men = 115±12.8/75±9.9 ; Women = 114.9±15.4/71±7 1.7. Duration: 24 days. Location: China.	Trial examined gender differences in the association between dietary Na and K intake and BP. Three 7-day dietary interventions: Low Na (51.3mmol per day) High Na (307.8mmol per d) High Na (307.8mmol per day) plus 60mmol K supplement. All meals were provided and consumption was supervised.	BP measured at three-day baseline, last three days of each intervention using a random-zero SM. Na intake estimated from food records; 24-hour urinary excretions of Na and K at baseline and each of the three intervention phases.	Δs in BP response were significantly greater in women than in men (all P<0.001). *Low-sodium diet* ΔSBP: Women: -8.1mmHg (95% CI: -8.6 to -7.6) Men: -7.0 (-7.5 to -6.6) ΔDBP: Women: 4.5 (-4.9 to -4.1) Men: -3.4 (-3.8 to -3.0). *High-sodium diet* ΔSBP: Women: 6.4 (5.9 to 6.8) Men: 5.2 (4.8 to 5.7). ΔDBP: Women: 3.1 (2.7 to 3.5) Men: 1.7 (1.4 to 2.1).

Makela P, Vahlberg T et al, 2008 Study Design: Randomized controlled trial Class: A Neutral Rating	N=80 subjects with mild to moderate essential HTN on non-pharmacological Na restriction. Forty subjects randomized to a low Na diet; 40 assigned to the control group. Duration: Six months. Location: Finland.	Subjects were randomized to a low-Na diet (↓ of daily Na intake to less than 70mmol, general advice to lose weight, if necessary and general advice to ↓ intake of saturated fats) or control group (intervention not described).	BP measured at one-month intervals throughout the study. Na intake was estimated three times during the study, at zero, three and six months. Intake was estimated from seven-day food records using Nutrica software from the Social Insurance Institution, Finland. 24-hour UNa and K excretion was also collected and measured by flame photometry. 24-hour ambulatory ECG carried out at beginning of study and at six months; analyzed with Oxford Medilog Series 4.24. Heart rate variability (HRV): Five time-domain variables were analyzed.	BP ↓ significantly more in intervention group. SBP: 149.9±14.7 to 130.3±11.8mmHg. DBP: 98.0±6.4 to 87.1±6.2mmHg, P<0.001. However, NS differences in the Δ between groups could be detected. 24-hour UNa ↓ significantly (P<0.001) in intervention group, but ↑ in the control group (time x group, P<0.001). NS Δs or differences in Δs were seen in any time or frequency-domain variables of heart rate variability. No correlation in Δs of HRV was found in relation to Na intake during the study.

Pimenta E, Gaddam KK et al, 2009 Study Design: Randomized, crossover trial Class: A Positive Quality	N=12 subjects with resistant HTN. Eight females Four males. Six blacks Six whites. Age: 55.5±9.4 years. On average, 3.4 antihypertensive medications. Duration: One month. Location: US.	Examined the effects of dietary salt restriction on office and 24-hour ambulatory BP. Two one-week dietary Na interventions separated by a two-week washout period: Low (50mmol per day) High (250mmol per day).	Office and 24-hour ambulatory BP monitoring with ABPM monitor (Suntech). 24-hour urine collected to measure urinary Na and K excretion, as well as aldosterone and creatinine. Morning blood specimens analyzed for serum potassium, brain natriuretic peptide, plasma aldosterone, plasma renin activity and urinary aldosterone measured by radioimmunoassay. Aortic pulse wave velocity and augmentation index measured with SphygmoCor system.	Mean UNa excretion: Low Na: 46.1±26.8mmol per day High Na: 252.2±64.6mmol per day. ΔBP for the low- vs. high-salt intervention: ΔSBP: -22.7mmHg ΔDBP: - 9.1mmHg. Plasma rennin activity ↑, whereas brain natriuretic peptide and creatinine clearance ↓ during low-salt intake.

Schmidlin O, Forman A et al, 2007 Study Design: Non-Randomized Controlled Trial Class: C Neutral Quality	N=35 black adults. Salt Sensitive (SS): N=18 (51%; 17 males and one female). Salt Resistant (SR): N=17 (49%; 15 males and two females). After adjusting for age and BMI, the SS subjects' DBP and MAP were significantly different than the SR subjects (P≤0.05). Duration: 21 days Location: US.	Two 7-day Na-loading interventions separated by a Na restricted week. Interventions included: NaCl supplement: 250mmol per 70kg weight per day (≤300mmol per day) $NaHCO_3$supplement: 250mmol per 70kg weight per day (≤300mmol per day) Placebo tablets. All participants consumed a eucaloric basal metabolic diet providing 30mmol of Na and 45mmol of K per 70kg of body weight per day. Subjects consumed 20g water per kg body weight per day during Na restriction and 35g per kg per day during Na loading.	Daily BP measured every four-hours with automated oscillometric device (Dinamap, Criticon Inc.); average calculated. MAP = average of Na restriction days five and six, subtracted from average of days five and six during Na loading with either NaCl or Na HCO_3. Daily 24-hour urine analyzed for Na, Cl and Creatinine. Cumulative Na excretion (week three only): Corrected for creatinine excretion; adjusted for 70kg weight. SS defined as an NaCl-induced ↑ in MAP of at least 5mmHg. Weight measured daily at 6 a.m. Blood samples (by stand-on on last day of each intervention): Plasma renin activity, aldosterone, creatinine hematocrit and serum electrolytes.	In SS (but not SR), BP varied directly and highly significantly with the serum concentration of Na. Average NaCl-induced MAP: SS, 11±2mmHg; SR, 1±2mmHg. MAP ↑ significantly from 90mmHg on low NaCl to 95mmHg with $NaHCO_3$ and to 101mmHg with NaCl. The pressor effect of NaCl strongly predicted that of $NaHCO_3$. In SS subjects, MAP varied directly with plasma Na concentration attained with all Na loading. Both NaCl and $NaHCO_3$induced similar significant ↑ in body weight in SS and SR. Both NaCl and $NaHCO_3$induced significant ↓ in hematocrit values in SS and SR, but were significantly larger with NaCl than $NaHCO_3$. NaCl-induced ↓ in PRA (but not aldosterone) was slightly, but significantly greater in SR than in SS.

Swift PA, Markandu ND et al, 2005 Study Design: Randomized crossover trial Class: A Positive Quality	N=40 non-diabetic black subjects. Hypertensive: SBP≥40mmHg; DBP≥90mmHg. Age: 50±10 years. BMI: 28±4kg/m^2. Duration: 3.5 months. Location: United Kingdom	Initial run-in periods on usual (four weeks) and reduced salt (~5g salt) diets (two weeks). Then subjects received either 12 slow-Na tablets (10mmol Na per tablet) daily to bring their salt intake back to normal or 12 placebo tablets daily for four weeks, then crossed over.	BP and other measurements were made at the end of each run-in period and intervention by trained nursing staff. 24-hour ambulatory BP was performed using SpaceLab 90207 devices, which were fitted in the mornings. BP recordings taken at half-hour intervals from 9 a.m. to 10 p.m. and at hourly intervals from 10 p.m. to 9 a.m.	Reducing salt intake from ~10g to ~5g per day ↓ BP: SBP 8±13mmHg, P<0.001; DBP 3±7mmHg, P<0.009. Mean ↓ in urinary protein excretion with salt reduction: 18±39mg per 24 hours (P<0.008). Relationship between urinary protein excretion and BP: SBP (R=0.07; P=0.70) DBP (R=0.19; P=0.26). Other Findings Significant ↓ in mean daytime and nighttime ABPs, with the ↓ in salt intake (mean 24-hour ↓ of 7/3mmHg).

Research recommendations

Conduct trials that determine the effects of sodium reduction on clinically relevant non-blood pressure variables, such as left ventricular mass, proteinuria and bone mineral density.

- Rationale: An inclusive body of evidence suggests that the benefits of a lower sodium intake extend beyond reduced blood pressure. Evidence from cross-sectional studies has documented that sodium is directly associated with left ventricular mass and proteinuria. Clinical trials have also documented that a higher intake of sodium increases urinary calcium excretion.

Search plan and results

Inclusion criteria

Subjects/Population

- *Age:* Adults, 19 years and older
- *Setting:* US and International
- *Health status:* Healthy, those with elevated chronic disease risk and those diagnosed with the highly prevalent chronic diseases (coronary heart disease, cardiovascular disease, type 2 diabetes, metabolic syndrome, obesity).

Search Criteria

- *Study design preferences:* Randomized controlled trials (RCT), observational follow-up of relevant RCT and systematic reviews
- *Duration:* Intervention arms seven days or more
- *Size of study groups:* The sample size must equal 10 adults for each study group. (For example, this would include 10 patients in the intervention group and 10 patients in the control or comparison group)
- *Study drop out rate:* Less than 20%; preference for smaller dropout rates
- *Year range:* June 2004 to July 2009
- *Languages:* Limited to articles in English
- *Other:* Article must be published in peer-reviewed journal.

Exclusion criteria

Subjects/Population

- *Age:* Less than 19 years
- *Setting:* Inpatients
- *Health status:* None
- *Nutrition related problem/condition:* (i.e., end stage renal disease, congestive heart failure).

Search Criteria

- *Study design preferences:* Cross-sectional, case-control, narrative review
- *Study group size:* Sample sizes <10
- *Study duration:* Intervention arms less than seven days
- *Study drop-out rate:* If the dropout rate in a study is 20% or greater, the study

will be rejected
- *Year range:* Prior to June 2004
- *Authorship:* Studies by same author similar in content.
- *Languages:* Articles not in English
- *Other:* Animal studies; abstracts or presentations.

Search terms and electronic databases used

PubMed: Search terms: ("Hypertension"[mesh] OR "blood pressure"[MeSH Terms]) AND ("Sodium, Dietary"[Mesh] or sodium [mesh] or “sodium chloride”[mesh])

Date searched: 4/06/09; 7/10/09

Summary of articles identified to review

- Total hits from all electronic database searches: 199
- Total articles identified to review from electronic databases: 41
- Articles identified via handsearch or other means: 3
- Number of Primary Articles Identified: 12
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 13
- Number of Articles Reviewed but Excluded: 28

Included articles (References)

Primary Studies

1. Cappuccio FP, Kerry SM, Micah FB, Plange-Rhule J, Eastwood JB. A community programme to reduce salt intake and blood pressure in Ghana [ISRCTN88789643]. A community programme to reduce salt intake and blood pressure in Ghana [ISRCTN88789643]. *BMC Public Health*. 2006 Jan 24; 6:13. PMID: 16433927.
2. Chen J, Gu D, Huang J, Rao DC, Jaquish CE, Hixson JE, Chen CS, Chen J, Lu F, Hu D, Rice T, Kelly TN, Hamm LL, Whelton PK, He J; GenSalt Collaborative Research Group. Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China: A dietary intervention study. *Lancet.* 2009 Mar 7; 373 (9666): 829-835. Epub 2009 Feb 14. PMID: 19223069.
3. China Salt Substitute Study Collaborative Group: A randomized, controlled trial. *J Hypertens.* 2007 Oct; 25 (10): 2, 011-2, 018. PMID: 17885542.
4. Cook NR, Kumanyika SK, Cutler JA, Whelton PK; Trials of Hypertension Prevention Collaborative Research Group. Dose-response of sodium excretion and blood pressure change among overweight, non-hypertensive adults in a three-year dietary intervention study. *J Hum Hypertens*. 2005 Jan; 19 (1): 47-54. PMID: 15343354.
5. Dickinson KM, Keogh JB, Clifton PM. Effects of a low-salt diet on flow-mediated dilatation in humans. *Am J Clin Nutr*. 2009 Feb; 89 (2): 485-490. Epub 2008 Dec 23. PMID: 19106240.
6. Forrester T, Adeyemo A, Soarres-Wynter S, Sargent L, Bennett F, Wilks R, Luke A, Prewitt E, Kramer H, Cooper RS. A randomized trial on sodium reduction in two developing countries. *J Hum Hypertens*. 2005 Jan; 19 (1): 55-60. PMID: 15470483.
7. Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly

improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension*. 2004 Jul;44(1):35-41. Epub 2004 Jun 1. PMID: 15173128.

8. He J, Gu D, Chen J, Jaquish CE, Rao DC, Hixson JE, Chen JC, Duan X, Huang JF, Chen CS, Kelly TN, Bazzano LA, Whelton PK; GenSalt Collaborative Research Group. Gender difference in blood pressure responses to dietary sodium intervention in the GenSalt study. *J Hypertens*. 2009 Jan; 27 (1): 48-54. PMID: 19145767.
9. He Feng J., Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, MacGregor GA. Effect of Modest Salt Reduction on Blood Pressure, Urinary Albumin, and Pulse Wave Velocity in White, Black, and Asian Mild Hypertensives. *Hypertension*, Sep 2009. (Hand search - 21 July 2009)
10. Mäkelä P, Vahlberg T, Kantola I, Vesalainen R, Jula A. The effects of a six-month sodium restriction on cardiac autonomic function in patients with mild to moderate essential hypertension. *Am J Hypertens*. 2008 Nov; 21 (11): 1, 183-1, 187. Epub 2008 Sep 11. PMID: 18787516.
11. Pimenta E, Gaddam KK, Oparil S, Aban I, Husain, Dell'Italia LJ, Calhoun DA. Effects of Dietary Sodium Reduction on Blood Pressure in Subjects With Resistant Hypertension Results From a Randomized Trial. *Hypertension*, Sep 2009. (Hand search - 21 July 2009).
12. Schmidlin O, Forman A, Sebastian A, Morris RC Jr. Sodium-selective salt sensitivity: Its occurrence in blacks. *Hypertension*. 2007 Dec; 50 (6): 1, 085-1, 092. Epub 2007 Oct 15. PMID: 17938378
13. Swift PA, Markandu ND, Sagnella GA, He FJ, MacGregor GA. Modest salt reduction reduces blood pressure and urine protein excretion in black hypertensives: A randomized control trial. *Hypertension*. 2005 Aug; 46 (2): 308-312. Epub 2005 Jun 27. PMID: 15983240

Review Articles (1)

1. He FJ, Macgregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens*. 2008 Dec 25. [Epub ahead of print] PMID: 19110538 (Hand search)

Excluded articles

Primary Articles	Reason for Exclusion
Ajani UA, Dunbar SB, Ford ES, Mokdad AH, Mensah GA. Sodium intake among people with normal and high blood pressure. *Am J Prev Med*. 2005 Dec; 29 (5 Suppl 1): 63-67.	Cross-sectional study design.
Chen J, Gu D, Huang J, Rao DC, Jaquish CE, Hixson JE, Chen CS, Chen J, Lu F, Hu D, Rice T, Kelly TN, Hamm LL, Whelton PK, He J; GenSalt Collaborative Research Group. Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China: A dietary intervention study. *Lancet.* 2009 Mar 7; 373 (9666): 829-835.	Reported on same dataset as He et al, 2009.

Cook NR, Obarzanek E, Cutler JA, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK; Trials of Hypertension Prevention Collaborative Research Group. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: The Trials of Hypertension Prevention follow-up study. *Arch Intern Med.* 2009 Jan 12;169 (1): 32-40.	Did not examine relationship between sodium intake and blood pressure.
Kojuri J, Rahimi R.Effect of "no added salt diet" on blood pressure control and 24-hour urinary sodium excretion in mild to moderate hypertension. *BMC Cardiovasc Disord.* 2007 Nov 6; 7: 34.	Case-control study design.
McNeely JD, WindhamBG, Anderson DE. Dietary sodium effects on heart rate variability in salt sensitivity of blood pressure. Psychophysiology. 2008 May; 45 (3): 405-411.	Study interventions were less than seven days.
Takahashi Y, Sasaki S, Okubo S, Hayashi M, Tsugane S. Blood pressure change in a free-living population-based dietary modification study in Japan. *J. Hypertens*. 2006 Mar; 24 (3): 451-458.	Does not include sodium in analysis.

Meta-Analysis/Review Articles	Reason for Exclusion
Adrogué HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N. Engl J Med*. 2007 May 10;356 (19): 1, 966-1, 978. Review. No abstract available. PMID: 17494929	Review describing mechanisms of disease.
Blaustein MP, Zhang J, Chen L, Hamilton BP. How does salt retention raise blood pressure? *Am J Physiol Regul Integr Comp Physiol*. 2006 Mar; 290 (3): R514-23. Review. PMID: 16467498	Review describing mechanisms of disease.
Cohen HW, Alderman MH. Sodium, blood pressure, and cardiovascular disease. *Curr Opin Cardiol.* 2007 Jul; 22 (4): 306-310.	Narrative review.
Frohlich ED. The role of salt in hypertension: The complexity seems to become clearer. *Nat Clin Pract Cardiovasc Med.* 2008 Jan; 5 (1): 2-3. No abstract available. PMID: 18073713	Editorial publication.
Frohlich ED. The salt conundrum: A hypothesis. *Hypertension.* 2007 Jul; 50 (1): 161-166. Epub 2007 Apr 30. Review. No abstract available. PMID: 17470717	Review hypothesizing mechanisms of disease.
Funatsu K, Yamashita T, Nakamura H. Effect of coffee intake on blood pressure in male habitual alcohol drinkers. *Hypertens Res.* 2005 Jun; 28 (6): 521-527. PMID: 16231758	Does not answer question. Describes effects of coffee and alcohol intake on blood pressure (BP).
Hooper L, Bartlett C, Davey SG, Ebrahim S. Advice to reduce dietary salt for prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2004; (1): CD003656. PMID: 14974027	Does not include BPin analyses.

Iwamoto T, Kita S. Hypertension, Na+/Ca2+ exchanger, and Na+, K+-ATPase. *Kidney Int.* 2006 Jun; 69 (12): 2, 148-2, 154. Epub 2006 Apr 26.Review PMID: 16641927	Does not answer question. Describes a mechanism of Na+/Ca2 and Na+K+ ATPase
Jones DW. Dietary sodium and blood pressure. *Hypertension.* 2004 May; 43 (5): 932-935. Epub 2004 Mar 29. Review. No abstract available. PMID: 15128720	Narrative review.
Karppanen H, Mervaala E. Sodium intake and hypertension. *Prog Cardiovasc Dis.* 2006 Sep-Oct; 49 (2): 59-75.	Narrative review.
Kawano Y, Ando K, Matsuura H, Tsuchihashi T, Fujita T, Ueshima H; Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension. Report of the Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension: (1) Rationale for salt restriction and salt-restriction target level for the management of hypertension. *Hypertens Res*. 2007 Oct; 30 (10): 879-886.	Narrative review.
Kawano Y, Tsuchihashi T, Matsuura H, Ando K, Fujita T, Ueshima H; Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension. Report of the Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension: (2) Assessment of salt intake in the management of hypertension. *Hypertens Res*. 2007 Oct; 30(10): 887-893.	Narrative review.
Khalil RA. Dietary salt and hypertension: new molecular targets add more spice. *Am J Physiol Regul Integr Comp Physiol.* 2006 Mar; 290 (3): R509-513. Review. No abstract available. PMID: 16467497	Narrative review.
Lawlor DA, Smith GD. Early life determinants of adult blood pressure. *Curr Opin Nephrol Hypertens.* 2005 May; 14(3): 259-264. Review.	Narrative review.
Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. *Physiol Rev.* 2005 Apr; 85 (2): 679-715.	Narrative review.
O'Shaughnessy KM, Karet FE. Salt handling and hypertension. *J Clin Invest.* 2004 Apr; 113 (8): 1, 075-1, 081. Review. PMID: 15085183	Narrative review and editorial publication.
Orlov SN, Mongin AA. Salt-sensing mechanisms in blood pressure regulation and hypertension. *Am J Physiol Heart Circ Physiol.* 2007 Oct; 293 (4): H2039-2053. Epub 2007 Aug 10. Review. PMID: 1769354	Does not answer question. Describes molecular salt sensitivitymechanism.
Rodriguez-Iturbe B, Vaziri ND. Salt-sensitive hypertension-update on novel findings. *Nephrol Dial Transplant.* 2007 Apr; 22 (4): 992-995. Epub 2007 Jan 8. Review. No abstract available. PMID: 17210585	Does not answer question. Describes molecular salt sensitivity mechanism.
Rylander R, Arnaud MJ. Mineral water intake reduces blood pressure among subjects with low urinary magnesium and calcium levels. *BMC Public Health*. 2004 Nov 30; 4: 56. PMID: 15571635	Does not answer question. Discusses mineral water.

Weinberger MH. Is salt sensitivity of blood pressure linked to the cardiometabolic syndrome? J *Cardiometab Syndr.* 2006 Summer; 1 (3): 217-219. Review. No abstract available. PMID: 17679824	Editorial publication.
Welsh L, Ferro A. Drug treatment of essential hypertension: The case for initial combination therapy. *Int J Clin Pract.* 2004 Oct; 58 (10): 956-963. Review. PMID: 15587775	Does not answer question. Review addresses drug treatments for HTN.