Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships:

4. Sodium and Hypertension

December 1991

By

Theodore Kotchen, M.D.

Prepared for

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
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Life Sciences Research Office
Federation of American Societies
For Experimental Biology
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Bethesda, Maryland 20814
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon literature reviews and the scientific analyses by knowledgeable investigators engaged in work in specific areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA), in accordance with the provisions of Task Order #9 of Contract No. 223-88-2124. Potential authors and reviewing consultants were identified by the LSRO based on their qualifications, experience, and freedom from conflict of interest, with due consideration for balance and breadth in appropriate disciplines. The author and reviewing consultants were selected with the concurrence of the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB).

On March 14, 1991, the FDA requested submission of scientific data and information on the ten specific topics for which health claims might be made (Federal Register 56:12932–12933). The scientific data and information provided in response to this request were considered by LSRO in preparing this report. Copies of the submitted materials are available for public inspection at the Dockets Management Branch, FDA (Docket No. 91N–0095). Copies of documents cited in this report are available for public inspection at LSRO, FASEB.

Theodore Kotchen, M.D., Professor and Chairman, Department of Medicine, University of West Virginia School of Medicine, Morgantown, WV should be cited as the author of this report. The LSRO acknowledges the efforts of Theodore Kotchen, M.D. and also the critical assistance of Louis Tobian, Jr., M.D., Professor of Medicine, and Chief, Hypertension Section, Department of Internal Medicine, University of Minnesota Hospital and School of Medicine, Minneapolis, MN, and Myron H. Weinberger, M.D., Professor, Department of Medicine, and Director, Hypertension Research Center, Indiana University School of Medicine, Indianapolis, IN, who reviewed several drafts of the manuscript. The appendix tables were prepared by the LSRO staff and author and were critically reviewed by the author and reviewers. Subsequently the draft report and tables were revised by the author, edited by the LSRO scientific staff, and received final concurrence from the author and reviewing consultants.

The evaluation of scientific literature, data, and information submitted to the LSRO was made by the author, reviewers, and the LSRO independently of FDA or any other group, governmental or non-governmental. The author and LSRO accept responsibility for the accuracy of the report conclusions and its appendix tables. This final report was reviewed and approved by members of the LSRO Advisory Committee under authority delegated by the Federation Board. The LSRO Advisory Committee members who reviewed this report were free of conflicts of interest in regard to the subject matter under policies established by the Federation. Upon completion of these review procedures, the report was approved by the Executive Director, FASEB, and transmitted to FDA.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

December 31, 1991
Date

Kenneth D. Fisher, Ph.D.
Director
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I. INTRODUCTION

In terms of a potential impact on blood pressure, no other dietary constituent has been studied as extensively as sodium chloride (NaCl). The mechanisms governing the effects of salt on electrolyte balance in body fluids and on blood pressure have been under investigation for decades. Much of the information on the influence of dietary salt has come from human investigations. Observational studies suggestive of a relationship between dietary salt and blood pressure have been carried out both within and across populations, and, increasingly in recent years, intervention studies seeking to clarify such relationships have appeared. The purpose of this review is to summarize recent observational and intervention studies evaluating the NaCl–blood pressure relationship.

A. WITHIN POPULATIONS STUDIES

Within populations, either low or insignificant correlations between blood pressure and dietary salt have been observed (Elliott, 1991; Frost et al., 1991; Watt and Foy, 1982). Smith et al. (1988) described the relationship between standardized measurements of blood pressure and 24-hour urinary sodium excretion in 7,354 randomly selected 40–59 year old men and women throughout Scotland. Average 24-hour urinary sodium excretion in men and women was 193 mEq ± 77SD and 143 mEq ± 57SD, respectively. Overall, the association between sodium excretion and blood pressure was weakly positive and not statistically significant. Further, in a multiple regression model, sodium excretion did not contribute to the variance of blood pressure, although blood pressure was directly related to body mass index and alcohol intake and inversely related to potassium excretion.

In a randomly selected sample of 8,057 Belgian men and women, there were significant correlations between standardized measurements of diastolic blood pressure and dietary sodium, as assessed by 24-hour food records (Kesteloot and Joossens, 1988). Systolic blood pressure was correlated with sodium intake in men, but not in women.

Two recent reviews have focused on the underestimation of the association between blood pressure and sodium intake within populations (Frost et al. 1991, Watt and Foy, 1982). Within a population, the range of sodium intake is relatively constricted, and this may contribute to an apparent lack of association between NaCl intake and blood pressure. Further, within individuals sodium intake may vary considerably, and consequently a single 24-hour urine collection may not reliably estimate an individual's usual daily sodium intake. Because the within-person variability in sodium excretion may approach or even surpass the between-person variation, it appears that several consecutive urine collections are necessary to adequately characterize an individual's sodium intake (Liu et al., 1979). It has been estimated that as many as 5,700 participants, each collecting a single 24-hour urine, may be required to demonstrate a true regression slope between systolic blood pressure and sodium excretion of 10 mmHg/100 mEq sodium per 24 hours. Further, adjustment for covariates such as body weight, which is measured more precisely than dietary sodium, may result in statistical over adjustment of the blood pressure-sodium relationship. The relationship between dietary sodium and blood pressure is more striking after statistically adjusting for the random error in the estimates of an individual's average sodium intake. Indeed, in the North London Study, an older population with little day-to-day variation of sodium excretion, and with the capacity to identify incomplete urine collections (using a PABA marker), the adjusted coefficient for the sodium/systolic blood pressure relationship was 14.5 mmHg/100 mEq sodium (Elliott et al., 1988).

A recent study that addresses methodologic issues that may contribute to the underestimation of the relationship between blood pressure and salt intake was carried out in four population groups in China
(He et al., 1991). Salt consumption varied considerably among these groups. In approximately 100 men from each of the population groups studied, dietary sodium intake was estimated on the basis of sodium measured in three consecutive 24-hour urine samples and three 24-hour dietary recalls. Overall, systolic and diastolic blood pressures were each significantly correlated with dietary sodium intake and urinary sodium excretion.

B. ACROSS POPULATION STUDIES

Observational studies across populations provide somewhat more convincing evidence for an association between salt intake and blood pressure. Among populations, the prevalence of hypertension is related to salt intake (Dahl, 1972; Elliott, 1991; MacGregor, 1985).

Two early reviews, one by Dahl (1972), cite an association between sodium intake and arterial pressure. In 27 different populations, Gleibermann (1973) documented a significant correlation between salt intake and blood pressure (both systolic and diastolic) in men and women (Dahl, 1972). Estimates of salt intake in many of these populations were based on dietary information in the literature rather than quantitative data on 24-hour urinary excretions.

Using literature derived data from 28 populations around the world, Froment described a slope of 10 mmHg systolic blood pressure/100 mEq sodium intake (Froment et al., 1979). Further, over a 30 year period, the rise of systolic blood pressure with age was 7.7 mmHg lower per 100 mEq decrement in daily sodium intake. Sodium intake was primarily estimated from 24-hour urine collections, although not necessarily from the same studies with blood pressure data, and the regression analyses were strongly influenced by nine populations with low sodium intakes.

In societies that consume a low sodium intake, mean blood pressure is low and among adults, blood pressure does not increase with age. Over 20 unacculturated populations with low blood pressures and unusually low sodium intakes have been described, and when these people were exposed to the acculturation process and especially to a more westernized diet, their blood pressures increased and an age-related upward trend became apparent (Page, 1980; Poulter et al., 1984). Although factors other than low dietary NaCl may have contributed to the lower blood pressures (e.g. high potassium intake, low body weight, no alcohol, high level of physical activity), these striking observations suggest an important causal association between long-term very low salt intakes and lower blood pressures. Indeed, when Samburu soldiers in Kenya were given a daily 16 gram salt ration for periods of a year or more, their blood pressure rose (Shaper et al., 1969).

More recently, the relationship between dietary salt and blood pressure was examined in the Intersalt study (Intersalt Cooperative Research Group, 1988a,b; Rose and Stamler, 1988; Stamler et al., 1991). This is a cross sectional study including 10,079 men and women, aged 20–59 years, in 52 population centers from 32 countries. Blood pressure measurements and 24-hour urine collections were carefully standardized. After adjustment for age and gender, sodium excretion was correlated with systolic blood pressure in 39 of the 52 centers (15 significant) and with diastolic blood pressure in 33 of the centers (4 significant). Overall, both before and after adjustment for body mass index and alcohol intake, there were positive and significant correlations between median sodium excretion and median systolic blood pressure. After additional adjustment for body mass index, alcohol consumption, and potassium excretion, a positive association between systolic blood pressure and sodium excretion persisted in 33 centers (8 were significant); however, significance for the relationship between diastolic blood pressure and sodium excretion was lost. With pooling the regression coefficients from the 52 centers, a significant overall regression coefficient resulted (p< 0.001).
Based on a within-center analysis, sodium excretion was significantly related to systolic blood pressure in men and women aged 40–59 years, but not in 29–39 year old men and women. After adjusting for age and gender, it was estimated that a 100 mEq/day lower sodium intake is associated with a 3.5 mmHg lower systolic blood pressure and a 1.5 mmHg lower diastolic blood pressure; after adjusting for body mass index, alcohol consumption, and potassium intake, these estimates were reduced to 2.2 mmHg systolic blood pressure and 0.1 mmHg diastolic blood pressure. Excluding hypertensives from the analyses did not appreciably change these estimates, suggesting that the relationship between dietary sodium and blood pressure is not restricted to individuals with hypertension.

Four of the population centers examined in the Intersalt study (Yanomamo and Xingu Indians of Brazil and rural populations in Kenya and Papua, New Guinea) were remote and unacculturated. In these populations salt intake was low (1–3 grams NaCl/day vs 9 grams/day in the remaining 48 centers), average body weight was low, and alcohol intake was low or absent (Carvalho et al., 1989). These populations had the lowest blood pressures of all the Intersalt centers, and there was little or no increase of blood pressure with age. Hypertension was virtually absent. After excluding these four low salt centers, the significance of the association between sodium excretion and blood pressure was lost. Similar, but less striking associations were observed between median sodium excretion and median diastolic blood pressure. Median sodium excretion and prevalence of hypertension were positively and significantly correlated for 52 centers, but not after excluding the 4 low salt centers.

Across the 52 centers, after adjusting for age and sex, there was a significant linear relationship between median 24-hour urine sodium excretion and the slope of systolic blood pressure with age ($r = 0.0030 \text{ mmHg/year/mEq sodium}; p < 0.001$). After excluding the four isolated populations with low sodium excretion, this slope remained positive but only at a borderline level of significance ($r = 0.0019; p = 0.06$). After adjustment for body mass index and alcohol consumption, a significant linear association was found between sodium excretion and the slope of systolic blood pressure with age for both 52 centers and the 48 centers. Analyses of the relation between 24-hour urine sodium excretion and the increase of diastolic blood pressure with age also yielded significantly positive findings (Elliott et al., 1989). Based on an analysis of the 48 centers, it was estimated that the rise in systolic blood pressure over a 30-year period (e.g., from age 25 to age 55) would be less by 9 mmHg and the rise in diastolic blood pressure less by 4.5 mmHg if the average sodium excretion were lowered by 100 mEq/24 hours.

To evaluate the relationship between blood pressure and dietary sodium, Law et al. (1991a) recently analyzed data from 24 communities (47,000 people) throughout the world. Although the average blood pressure was higher in economically developed than in underdeveloped communities, the relationship between sodium intake and blood pressure was similar. The authors developed a model for analyzing the relationship between blood pressure and sodium intake. Based on these calculations, a difference in sodium intake of 100 mEq/24 hours was associated with an average difference in systolic blood pressure that ranged from 5 mmHg at age 15–19 years to 10 mmHg at age 60–69 years. The differences in diastolic blood pressure were about half as great. The standard deviation of blood pressure increased with sodium intake, implying that the association of blood pressure with sodium intake in individuals is related to the initial blood pressure.
II. CLINICAL TRIALS

Although epidemiological studies bespeak a relationship between dietary sodium and blood pressure, more convincing evidence can be obtained from experimental studies evaluating the effect of a change in salt intake on a change in blood pressure.

Staessen et al. (1988) evaluated the feasibility and effectiveness of reducing dietary salt, using low cost techniques, in one town in Belgium -- a second town served as a control. The study was principally directed at women. Baseline surveys (including standardized measurements of blood pressure and 24-hour urine sodium excretion) were conducted in random samples of the two towns in 1984–85. Follow-up surveys were repeated five years later. In women aged 20 years or more, urinary sodium decreased by 25 mEq/24 hours in the intervention town, but not in the control town (+8 mEq/24 hours). However, the reductions of systolic and diastolic blood pressures were similar. In men, there were relatively small changes in sodium excretion over time, and blood pressures did not differ in the two towns. The results underscore the difficulty of decreasing salt intake at the community level, and the failure to observe an effect on blood pressure may partly be attributed to the modest reductions in dietary salt.

The Portuguese Salt Trial evaluated the effect of a community health education program on salt reduction and blood pressure in two matched rural communities, of approximately 800 adult inhabitants (Forte et al., 1989). Based on the results of a nutrition survey, initial salt intake was high (360 mEq/day). Over a two year period, blood pressure and overnight urine sodium excretion did not decrease in the control community. In the intervention community, mean systolic and diastolic blood pressures decreased by 3.6/5.0 mmHg at one year and by 5.0/5.1 mmHg at 2 years. A diet survey indicated a 47 percent decrease in salt intake, although overnight urine collections indicated that the reduction of salt intake was only about 10 percent.

In 1986, Grobbee and Hofman (1986) reviewed data from 13 randomized trials on the effect of sodium restriction on blood pressure. The intervention periods were 4 weeks or shorter in 6 of the trials, 5–12 weeks in 3, and a year or longer in two. These trials included both normotensive and hypertensive individuals. Blood pressure changes were statistically significant in three of the trials. The authors concluded that the hypotensive effect of sodium restriction was small and primarily involved systolic blood pressure, which fell by an average of 3.6 mmHg (range 0.5–10.0 mmHg) when the average reduction in sodium intake was 71 mmol/day. The reduction increased with age and in those with higher blood pressures.

In a recent Australian National Health and Medical Research Council Dietary Salt Study, 111 patients with mild essential hypertension were placed on a 80 mEq/day sodium diet and then randomized to receive either 8 tablets of slow release NaCl/day (10 mEq sodium/tablet) or placebo tablets (Australian National Health and Medical Research Council, 1989). After an 8–week intervention, urinary sodium decreased from 142 to 90 mEq/24 hours in the intervention group, but not in the control group. Although differences between the low and high sodium groups diminished in the final week of the study, over the 8–week intervention mean systolic and diastolic blood pressures decreased by 6.1 and 3.7 mmHg, respectively, in the low sodium group and by only 0.6 and 0.9 mmHg in the control group. It has been estimated by the authors that under the conditions of this study the power of detecting a difference in diastolic blood pressure of 2 or 3 mmHg would be 80 percent or 90 percent respectively. In the low sodium group, individuals with higher blood pressures and older individuals had the largest fall in blood pressure.
MacGregor et al. (1989) studied the effect of 3 levels of salt intake for a month each on blood pressure in 20 patients with mild essential hypertension. All patients were instructed to lower their sodium intake to 30–50 mEq/day. Patients were then randomized in a double-blind, three way crossover study (using slow sodium tablets or placebo) to receive total NaCl intakes of 200, 100, or 50 mEq/day for 1 month each. There was a progressive fall in blood pressure as sodium intake was reduced, and the average differences in blood pressure between patients with the highest and lowest sodium intakes were 16 mmHg systolic and 9 mmHg diastolic.

In another randomized, double-blind, crossover trial, both systolic and diastolic blood pressures increased significantly in 95 normotensive adults when a low sodium diet (overnight urine sodium excretion of 19 mEq/8 hours) was supplemented with 96 mEq sodium/day for 4 weeks (Mascioli et al., 1991). Supplemental sodium was provided in capsules, and placebo capsules were administered during the control period. Differences between sodium and placebo periods for systolic blood pressure were 123.9 vs 120.3 mmHg (p< 0.001) and for diastolic blood pressure were 78.7 vs 76.4 mmHg (p< 0.005).

Cutler et al. (1991) recently summarized the results of 23 published randomized, short-term (1–2 months) clinical trials of the effect of moderate NaCl restriction on blood pressure. In aggregate, based on a total of 1,536 subjects, NaCl restriction resulted in a 4.9 ± 1.3 (95 percent confidence limits) mmHg reduction of systolic blood pressure and a 2.6 ± 0.8 mmHg reduction of diastolic blood pressure in hypertensives and a 1.7 ± 1.0 mmHg reduction of systolic blood pressure and a 1.0 ± 0.7 mmHg reduction of diastolic blood pressure in normotensives. These changes were associated with reductions of urinary sodium excretion ranging from 16–171 mEq/24 hours for individual trials. A dose-dependent relationship across trials was found, both in normotensives and hypertensives.

Of potential importance is the fact that all of the above trials were generally short term. Based on observational data among populations, Law et al. (1991a) developed a model to quantitatively predict the reduction of blood pressure associated with a reduction of dietary salt. They subsequently reviewed results of 78 controlled published trials, and using the results of the population based analysis, they calculated a predicted blood pressure reduction for each trial (Law et al., 1991b). In the 45 trials in which NaCl restriction lasted 4 weeks or less, the observed reductions of blood pressure were less than those predicted, whereas in the 33 trials lasting five weeks or longer, there was close agreement between the observed and predicted reductions of blood pressure. This suggests that results of short-term trials may underestimate the impact of salt restriction on blood pressure. In the trials, as in the observational data, the reduction of blood pressure by salt restriction increased with age and with the initial level of blood pressure. The authors predicted that a reduction of dietary sodium by 50 mEq/day in people over 50 years of age would lower systolic blood pressure by 5 mmHg in normotensives and by 7 mmHg in hypertensives; the predicted reductions of diastolic blood pressure were approximately half these values.

Little information is available concerning the effect of sodium restriction on the primary or secondary prevention of hypertension. In hypertensive patients on drug therapy, sodium restriction has been reported to lower blood pressure and to reduce medication requirements (Oberman et al., 1990; Weinberger et al., 1988). Langford et al. (1985) reported that either sodium restriction (mean reduction of 40 mEq/day) or weight loss increased the likelihood of patients with essential hypertension remaining normotensive after stopping prolonged antihypertensive drug therapy.

Over a three year period, the Hypertension Prevention Trial evaluated the effects of the following interventions on blood pressure (using a parallel design) in 841 healthy men and women with diastolic blood pressures in the range of 78–89 mmHg: a) caloric restriction; b) sodium restriction; c) combined caloric and sodium restriction; and, d) combined sodium restriction and a high potassium intake (Hypertension Prevention Trial Research Group, 1990). Compared to controls, in the sodium
restricted groups, the average reductions of overnight urine sodium excretion at 6 months and 3 years were 13 percent and 10 percent, respectively. Blood pressure was reduced by caloric restriction but not by sodium restriction, either alone or in combination with caloric restriction or a high potassium intake. Despite this apparently modest reduction of sodium intake and lack of significant effect of sodium restriction on blood pressure, there was some evidence that fewer individuals in the low salt groups developed hypertension, compared to controls, over the three year period.

In a separate 5-year trial involving 201 men and women with high normal blood pressures, individuals were randomized to a control group or a combined nutritional-hygienic intervention, which consisted of weight reduction in the overweight, reduction of dietary sodium, reduction of alcohol intake, and exercise (Stamler et al., 1989). In the intervention group, sodium excretion, as assessed by periodic measurements in overnight urine collections, was reduced by 25 percent, although only 13 percent of the intervention participants achieved and maintained the goal of 1,800 mg sodium/day. The incidence of hypertension was 8.8 percent among the intervention group versus 19.2 percent among the control group. In multiple regression analyses, there was a significant relationship between change in weight and change in blood pressure, whereas for sodium and alcohol, the relationship with blood pressure was not independently significant.
III. STUDIES IN CHILDREN

In the experimental animal, the impact of a high NaCl intake on blood pressure appears to be more prominent at younger ages (Zicha et al., 1986). Further, in rats, a high salt intake during the perinatal period results in higher blood pressures in the adult (Contreras, 1989; Karr–Dullien and Bloomquist, 1979; McCaughran et al., 1986).

As recently reviewed, relatively little clinical information is available concerning the effect of salt intake on blood pressure in infants and children, and the pattern is inconsistent (Grobbee and Bak, 1989).

Based on a single 24-hour collection in 278 children aged 5–14 years, Berenson et al. (1979) found no significant association between sodium excretion and blood pressure stratum in either blacks or whites. However, in the highest blood pressure stratum, there was a "general tendency" for an association between blood pressure and sodium excretion, and the tendency "appeared" to be stronger in blacks than in whites. This relationship was not verified by statistical analysis.

Cooper et al. (1980) observed a significant correlation between systolic (but not diastolic) blood pressure and urine sodium excretion \((r = 0.386)\) based on the mean of 7 consecutive 24-hour urine collections in 73 normotensive children, aged 11–14 years. The relationship persisted after controlling for height, weight, pulse, age, sex, and race. However, in a subsequent study with additional groups of comparably aged children, using an identical protocol, these same investigators did not find a significant association between average seven day sodium excretion and blood pressure (Cooper et al., 1983).

Geleijnse et al. (1990) studied the relationship between sodium and potassium intake and blood pressure change in a cohort of 233 normotensive children, aged 5–17 years at entry. Annual examinations, for an average followup of seven years, included standardized measurements of blood pressure and estimates of sodium and potassium intake based on measurements in six timed overnight urine collections. There was no significant relationship between the change in systolic blood pressure and sodium excretion, whereas the rate of change of systolic blood pressure was inversely associated with potassium excretion \((r = -0.45 \text{ mmHg/year/mEq}; p = 0.0004)\) and positively associated with the urine sodium/potassium ratio \((p = 0.02)\). Change in diastolic blood pressure was not significantly associated with urine sodium, potassium, or the sodium/potassium ratio.

Results of several studies suggest that there is little or no effect of moderate salt restriction on blood pressure in children. A study of 27 black male newborns fed salted and unsalted diets for between 3 and 8 months of life failed to find any blood pressure differences at either 8 months of age or at followup at age 8 years, when both groups were eating their usual diets (Whitten and Stewart, 1980). However, in a study involving 476 newborns randomized to a low-sodium or a normal-sodium diet during the first 6 months of life, Hofman et al. (1983) observed that the systolic blood pressure difference between the 2 groups increased significantly during the first 6 months of life; at age 25 weeks, systolic blood pressure was 2.1 mmHg lower in the low-sodium group than in the normal-sodium group \((p = 0.01)\).

In school children with blood pressures above the 95th percentile for age and sex, Gillum et al. (1981) reported that a 40 percent reduction of dietary sodium (estimated by food records and urine collections) for 1 year had no significant effect on blood pressure \((n = 15)\) compared to controls \((n = 36)\). In a randomized, crossover trial in 124 adolescents lasting 24 days, Cooper et al. (1984) reported
that reduction of dietary sodium from approximately 110 to 45 mEq/day (estimated in overnight urine collections) had no significant effect on blood pressure.

In the Exeter–Andover Project, dietary sodium of students (approximately 15 years of age) at two boarding schools was reduced by 15–20 percent for 6 months, as estimated by food diaries (Ellison et al., 1989). Baseline sodium intake of boys and girls averaged 163 and 113 mEq/day, respectively. Each school alternately served as control and intervention, and the study design was that of a non-randomized, concurrently controlled, longitudinal investigation. The study included 341 control subjects and 309 intervention subjects. The effect of the sodium intervention on systolic and diastolic blood pressure was −1.7 mmHg (p < 0.003) and −1.5 mmHg (p < 0.002), respectively.

In an uncontrolled study in 149 boys and girls, mean age approximately 10 years (range 2.6–19.8 years), lowering dietary sodium intake by approximately 50 percent (confirmed by 24-hour urine collections) for 12 weeks had no significant effect on systolic blood pressure; diastolic blood pressure decreased significantly (p < 0.05) in girls (54.0 to 52.2 mmHg), but not in boys (Miller et al., 1988).
IV. SALT SENSITIVITY

Within a population, overall responses of blood pressure to NaCl restriction may mask individual variability. Based on arbitrary criteria for blood pressure responses to acute NaCl depletion or acute NaCl loading protocols, it has been estimated that approximately 30–50 percent of hypertensives and 15–25 percent of normotensives are NaCl sensitive i.e. arterial pressure is decreased by 10 mmHg or more by NaCl depletion after NaCl loading (Weinberger et al., 1986), or is increased by more than 5 percent during NaCl repletion after a period of restriction (Sullivan et al., 1988). In normotensive individuals, blood pressure responses to longer term (12 weeks) dietary salt restriction are also heterogeneous. As in the acute studies, individual changes in blood pressure show Gaussian distribution (Miller et al., 1987a).

Falkner and Kushner (1990) evaluated the blood pressure response to addition of 10 grams NaCl (provided as tablets) to the usual diets for 14 days in 121 18–23 year old subjects, including 38 whites and 83 blacks. Overall, it appears that blood pressure was not significantly affected, although this is not clearly stated. According to an arbitrary criterion (5 percent increase of mean arterial pressure), 18.4 percent of whites and 37.3 percent of blacks were considered salt sensitive, although the spectrum of individual responses is not provided. The NaCl load did not augment the blood pressure or heart rate responses to a standardized stress of mental arithmetic.

In acute protocols and clinical trials, NaCl sensitivity of blood pressure is associated with a number of demographic variables, including black race, obesity, older age, and higher levels of blood pressure (Australian National Health and Medical Research Council, 1989; Cutler et al., 1991; Falkner and Kushner, 1990; Flack et al., 1991; Grobbee and Hofman, 1986; Law et al., 1991b; Luft et al., 1991; Miller et al., 1987a; Sullivan, 1991; Sullivan et al., 1987; Weinberger et al., 1986). NaCl sensitivity of blood pressure is also associated with several physiologic variables, including increased forearm vascular resistance in response to a NaCl load, decreased venous compliance, suppressed plasma renin activity in response to NaCl depletion, lower plasma aldosterone, and a shift in the pressure-natriuresis curve (Falkner and Kushner, 1990; Sullivan et al., 1988; Sullivan et al., 1987; Weinberger et al., 1986).

Although it is clear that there is a marked heterogeneity of blood pressure responses to alterations of dietary NaCl in both the experimental animal and in man, currently, there is not a uniform definition of salt sensitivity of blood pressure (Dustan and Kirk, 1988; Grobbee, 1991; Sullivan, 1991). Only limited studies with relatively few subjects suggest that the results of several acute protocols are reproducible (Sharma et al., 1989; Sullivan, 1991; Weinberger and Fineberg, 1991) and that the hypotensive response to acute NaCl depletion predicts the long term blood pressure response to dietary restriction of NaCl. Additionally, there is only limited evidence to suggest that those individuals whose blood pressures increase on a high NaCl intake are the same individuals whose blood pressures decrease on a low NaCl diet (Flack et al., 1991). Until more information is available, caution is recommended before arbitrarily classifying individuals as NaCl sensitive or NaCl resistant.

Experimental models provide convincing evidence for a genetic susceptibility and a genetic resistance to the effects of dietary NaCl on arterial pressure. Structural alterations of the renin gene have recently been described in the Dahl salt sensitive rat, although the relationship of this genetic alteration to salt sensitivity of blood pressure is unclear (Dene et al., 1989; Wang and Rapp, 1989). In man, there may also be a genetic susceptibility to NaCl. A familial resemblance of the change of blood pressure in response to NaCl restriction has been described (Miller et al., 1987b), and it has recently been suggested that a phenotype of haptoglobin is a marker of NaCl sensitivity (Weinberger et al., 1987). However, Watt et al. (1985) have previously reported that blood pressure responses to
eight weeks of NaCl restriction did not differ in subjects with both parents either in the upper or lower third of their age specific blood pressure distributions. They interpreted these results as evidence against a genetic susceptibility to the effect of dietary NaCl on blood pressure.

Physiologic mechanisms that may contribute to NaCl induced elevations of arterial pressure in the susceptible host, in both the experimental animal and in man, include the following: a) a decreased capacity of the kidney to excrete sodium (De Wardener, 1990; Gill et al., 1988); b) increased sympathetic nervous system activity and alterations of arterial and cardiopulmonary baroreflexes (Gill et al., 1988; Mark, 1991; Sakaguchi et al., 1988; Sullivan et al., 1987); and, c) alterations of ion transport in vascular smooth muscle (Weder, 1991).

It has recently been suggested that similar physiologic mechanisms may account for NaCl sensitivity of blood pressure and for hypertension related to insulin resistance (Tuck, 1991). Further, insulin resistance may lead to the development of NaCl sensitivity. Blood pressure of obese individuals tends to be NaCl sensitive, and insulin resistance may be a predictor of NaCl sensitivity of blood pressure in both obese and non-obese humans (Rocchini et al., 1989, 1990).

In the Dahl salt-resistant rat, preliminary data suggest that a high NaCl diet accelerates cerebral arterial disease with brain infarction and a high mortality, in the absence of an increase of blood pressure (Tobian and Hanlon, 1990).
V. INTERACTION OF SODIUM WITH OTHER IONS IN THE DIET

A. CHLORIDE

The full expression of NaCl sensitive hypertension is dependent on the concomitant administration of both sodium and chloride (Bogehold and Kotchen, 1989; Kurtz et al., 1987; Luft et al., 1990). In both experimental models of NaCl sensitive hypertension and in clinical studies with small numbers of hypertensive patients, blood pressure is not increased by a high dietary sodium intake provided with anions other than chloride, and high chloride intakes without sodium have less effect on blood pressure than NaCl. The failure of nonchloride sodium salts to produce hypertension may be related to their failure to expand plasma volume.

B. POTASSIUM

In societies with high potassium intakes, both mean blood pressure and the prevalence of hypertension tend to be lower than in societies with low potassium intakes (Khaw and Barrett–Connor, 1988; Langford, 1991; Svetkey and Klotman, 1990). Several large surveys have also demonstrated a significant inverse correlation between potassium intake and blood pressure among individuals, and this inverse association may be particularly prominent in the presence of a high NaCl diet (Intersalt Cooperative Research Group, 1988a,b; Khaw and Barrett–Connor, 1988; Langford, 1991). Further, a high NaCl intake promotes potassium excretion (Young et al., 1976). The urine sodium/potassium ratio may be a stronger correlate of blood pressure than either sodium or potassium alone (Intersalt Cooperative Research Group, 1988a; Khaw and Barrett–Connor, 1988; Svetkey and Klotman, 1990).

In Intersalt, after adjustment for possible confounders, potassium excretion was negatively associated with systolic blood pressure in 39 of the 52 centers, significantly so in 8 of them (Elliott et al., 1989; Intersalt Cooperative Research Group, 1988a,b). When the center regression coefficients were combined, the negative association was significant (p< 0.001). The sodium/potassium ratio was positively associated with systolic blood pressure; the regression coefficient was positive in 37 centers, significantly positive in 8 of them, and the combined coefficient for all centers was again significantly positive (p< 0.001).

Several relatively small clinical trials have shown that an increased potassium intake decreases blood pressure in patients with hypertension (Khaw and Barret–Connor, 1988; Obel, 1989; Patki et al., 1990; Siani et al., 1987; Svetkey and Klotman, 1990; Veterans Administration Cooperative Study Group on Anti–Hypertensive Agents, 1987). Conversely, potassium depletion induced either by diuretics or by a low potassium diet is associated with an elevation of blood pressure (Krishna et al., 1989; Lawton et al., 1990), and potassium supplementation has been shown to lower blood pressure in diuretic treated, hypokalemic patients (Kaplan et al., 1985). The effect of a high potassium intake on blood pressure is more pronounced in blacks than in whites, in individuals consuming a high NaCl intake (Luft et al., 1979), and in hypertensives compared to normotensives (Barden et al., 1986; Elliott et al., 1989; Khaw and Barrett–Connor, 1988; Krishna et al., 1989; Lawton, 1990; Svetkey and Klotman, 1990). In healthy young white adults and their children, four weeks of modest dietary potassium supplementation appears to have no effect on blood pressure (Miller, et al., 1987c). An increased intake of potassium also appears not to affect blood pressure in individuals on a low NaCl diet (Grimm, 1990), and the blood pressure lowering effect of dietary potassium may be related to its natriuretic capacity (Young et al., 1976).
Potassium loading also prevents or ameliorates the development of hypertension in several animal models of genetic and NaCl induced hypertension (Sato et al., 1991; Svetkey and Klotman, 1990). In the stroke prone, spontaneously hypertensive rat, it has also been reported that high potassium diets protect arterial endothelial cells from intimal lesions attributed to hypertension (Sugimoto et al., 1988), possibly due to a reduction of plasma renin activity (Volpe et al., 1990).

C. CALCIUM

Similar to potassium, within and among populations, there is an inverse association between dietary calcium intake and blood pressure, and calcium deficiency is associated with an increased prevalence of hypertension (Cutler and Brittain, 1990; Grobbee and Waal-Manning, 1990; Harlan and Harlan, 1990; McCarron et al., 1984; Witteman et al., 1989). Calcium is natriuretic, and conversely a high NaCl intake promotes calcium excretion (McCarron et al., 1981). In the HANES-I data, at low but not at high calcium intakes, dietary Na:K (determined by nutrient recall) significantly correlated with blood pressure (Gruchow et al., 1988).

Most clinical trials evaluating the effect of increased dietary calcium on blood pressure have supplemented with 1.0–1.5 grams of elemental calcium/day. Reductions of blood pressure have been modest and inconsistent, and no gradient of calcium effect or threshold intake level has been identified (Grobbee and Waal-Manning, 1990; Harlan and Harlan, 1990; Lyle et al., 1987; Resnick et al., 1983; Zemel et al., 1986). A low calcium intake may amplify the effect of a high NaCl intake on blood pressure in susceptible individuals, and calcium supplementation has been reported to blunt the effect of a high NaCl intake on blood pressure (Hamet et al., 1991; Langford and Watson, 1978; Resnick, 1990; Saito et al., 1989). High dietary calcium also preferentially lowers blood pressure or attenuates the development of hypertension in NaCl sensitive experimental models (Saito et al., 1989).

Low renin, salt-sensitive hypertensive individuals have a metabolic profile of calcium deficiency, including low serum ionized calcium concentrations, and elevations of 1,25 dihydroxyvitamin D3 and parathyroid hormone (PTH) (Resnick et al., 1983, 1986). Similar observations have been made in the Dahl salt-sensitive rat, even before the onset of hypertension (Kotchen et al., 1990). Hypercalcioria and subsequent calcium deficiency may be a consequence of plasma volume expansion in salt-sensitive individuals, and it has been suggested that elevations of 1,25 dihydroxyvitamin D3 and PTH may contribute to increased arterial pressure by elevating calcium content in vascular smooth muscle cells (Resnick, 1987; Strazzullo et al., 1983).
VI. POTENTIAL RISKS OF NaCl RESTRICTION

Severe NaCl restriction in the young rat results in decreased rate of growth, increased heart rate, enhanced cardiovascular vulnerability to blood loss, and "paradoxical" increase of blood pressure due to activation of the sympathetic nervous system and the renin-angiotensin system (Ely et al., 1990; Ott, 1989; Toal and Leenen, 1983).

The older clinical literature also documents several adverse consequences of extremely low NaCl intakes (10–20 mEq sodium/day) in man, e.g. lassitude, anorexia, muscle cramps, hyponatremia, azotemia (Schroeder, 1949; Soloff and Zatuchni, 1949). Efforts to determine whether this degree of NaCl restriction alters serum lipids have disclosed no effects on total cholesterol, HDL cholesterol or triglycerides (Kjeldsen et al., 1987).

There is no evidence that less extreme degrees of salt restriction have any adverse consequences. Although Miller et al. (1987a) have reported that significant percentages of normotensive subjects had higher blood pressures 3 months following a diet containing < 80 mEq sodium/day, these responses may reflect chance variations in blood pressure over time rather than a specific response to dietary NaCl restriction; the majority of subjects showed a decrease in blood pressure, and overall there was a statistically significant reduction of blood pressure on the sodium-restricted diet.
VII. SUMMARY

Both observational data and intervention trials document a small, but consistent effect of dietary NaCl on blood pressure. Currently available data provide little support for the hypothesis that there is a threshold level of dietary NaCl above which further increases will have no additional effect on blood pressure in the general population. Although some of the earlier observational studies across populations were compromised by inappropriate estimates of sodium intake, the carefully standardized Intersalt study (Intersalt Cooperative Research Group, 1988a) and those recently reviewed by Law et al. (1991a) included precautions for quantitative measurement of dietary sodium intake. Although the relation between blood pressure and salt intake is less striking after excluding low salt populations from the Intersalt data, there continues to be a weak, but overall statistically significant association between blood pressure and estimates of salt intake in these studies. For an individual, the clinical impact of the small difference of blood pressure associated with a relatively large difference of NaCl intake may be marginal, however, this association may be more meaningful when extrapolated to a population. Indeed "high salt" populations have a high prevalence of hypertension. A relationship between salt intake and the rate at which blood pressure increases with age persists after adjustment of the Intersalt data for confounding factors. In westernized societies the median dietary sodium intake estimated from urinary data in the Intersalt study (Intersalt Cooperative Research Group, 1988a) is about 150 mEq/day (ca 8.8 g expressed as NaCl). Other studies (James et al., 1987; Smith et al., 1988) estimate intakes of 185 to 190 mEq/day (10.7–11.2 g NaCl) for men and 138 to 145 mEq/day (8–8.4 g NaCl) for women. Food products contributing significantly to dietary sodium have been surveyed by the GRAS select committee (Select Committee on GRAS Substances, 1979) and include dairy products, 10 percent; meat, fish, and poultry, 15 percent; grain and cereals, 30 percent; and vegetables and fruit, 10 percent. British studies suggest that discretionary use of salt accounts for about 15 percent of dietary sodium and manufactured foods may contribute 50 to 75 percent (James et al., 1987). Sodium intakes both considerably higher and lower than the dietary norm have been studied in a number of interventions.

In several short–term clinical trials, increasing dietary NaCl from a moderate to a high level of 250 to 350 mmol per day, had no significant effect on blood pressure in both normotensives and hypertensives (Gill et al., 1988; Kawasaki et al., 1978; Luft et al., 1979; Parfrey et al., 1981; Sagnella et al., 1989). However, in a small number of hypertensive patients, MacGregor observed a dose–response relationship within this range of sodium intakes. He noted graded reduction of blood pressure as dietary sodium was progressively reduced, during 1–month intervals, from 200 to 100 to 50 mEq/day (MacGregor et al., 1989). Blood pressure remained lower for a year when restriction to 50 mEq/day was continued in a subset of these patients. The number of subjects was too small, however, to permit generalization of these observations to the larger population. Additional studies, especially long–term trials (Law et al., 1991), are needed to assess the dose–response relationship between salt intake and blood pressure in both normotensives (Mascioli et al., 1991) and hypertensives.

In salt–sensitive rats, a high NaCl intake has a more pronounced effect on blood pressure in younger animals. However, in humans, it appears that blood pressures of children are less responsive to dietary NaCl than adults, and salt sensitivity of blood pressure increases with age. Unlike rats, humans provide no evidence to support the hypothesis that blood pressure at one age is related to salt intake at an earlier age.

A small reduction of blood pressure associated with restriction of NaCl intake to approximately one–third or one–half of that in the usual western diet has been reported in some earlier trials and in more recent studies with normotensive (Mascioli et al., 1991) and mildly hypertensive subjects (Australian
National Health and Medical Research Council, 1989). When translated to an entire population, the modest reduction of blood pressure associated with moderate NaCl restriction is likely to have a significant impact on cardiovascular disease morbidity and mortality (Rose, 1981). Further, within a population, there is a heterogeneity of blood pressure responses to dietary NaCl, and several demographic and physiologic correlates of salt sensitivity have been identified. The impact of dietary sodium on blood pressure depends on the provision of sodium as the chloride, and in salt-sensitive individuals, high dietary intakes of potassium and calcium attenuate the blood pressure response to a high NaCl intake.

Although severe NaCl restriction (< 20 mEq sodium/day) may have adverse clinical and metabolic consequences, in the absence of an obvious salt losing disorder (e.g., cystic fibrosis, Addison's disease, salt-losing nephritis), there is no evidence that avoiding a high NaCl intake (defined by some arbitrary criterion) will be deleterious to health.
VIII. BIBLIOGRAPHY


* This bibliography contains all reference citations that are either in the text or the appendix tables or both.


APPENDIX

CRITERIA FOR INCLUSION OF ARTICLES IN APPENDIX TABLES

Articles in peer-reviewed journals related to the topic of this review were selected primarily on the basis of date and content. In general, papers appearing in 1987 or thereafter were included, provided that they presented original data from studies in humans. For a study to have been included, sodium intake must have been measured and endpoints identified that would aid in the assessment of putative relationships between sodium and blood pressure. Certain items tabulated for the sake of completeness may not have been cited in the body of the text if their weight or relevance did not add significantly to development of the author's argument. Reviews have not been listed except as they included new data or useful meta-analyses.
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<th>Reference</th>
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<th>Subject Number and Description</th>
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<tr>
<td>Carvalho et al., 1989</td>
<td>Cross-sectional (Selected data from INTERSALT study—four remote populations with low Na intake) International</td>
<td>Subjects selected from the following rural communities: 195 subjects (99 male, 96 female) from Yanomamo, Brazil (YB); 198 subjects (99 male, 99 female) from Xingu, Brazil (XB); 162 subjects (88 male, 74 female) from Papua, New Guinea (PNG); 176 subjects (90 male, 86 female) from rural Kenya (K)</td>
<td>All subjects were asked to refrain from strenuous activity for 30 min prior to BP measurement. BP data were based on the mean of 2 sitting measures taken after subjects emptied their bladders and sat for 5 min. After instruction, subjects collected a 24-hr urine sample in standard 1-liter jars containing boric acid as preservative. Aliquots were refrigerated and subsequently stored at -20°C. Other measures included height and weight and calculated BMI. Na and K assessed by emission flame spectroscopy. Na intake was estimated from 24-hr urine levels.</td>
<td>There were no within-center associations of BP with Na, BMI and alcohol found in these population samples. Ranking of mean estimated Na intake was K-PNG-XB-YB. Key findings were very low BP when compared with findings in other countries (Study mean DBP of 63 vs 74 mmHg in other 46 centers in the INTERSALT survey), lack of hypertension, no increase in BP with age. The level of estimated salt intake was significantly lower in these centers than in the other INTERSALT centers (1-3 g/day vs &gt;9 g/day). BMI and alcohol intake were similarly lower in these rural populations.</td>
<td>No comparisons of socioeconomic or lifestyle variables either within the four groups in this study or between these subjects and subjects surveyed in other INTERSALT surveys.</td>
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<tr>
<td>Elliott et al., 1988</td>
<td>Cross-sectional</td>
<td>A randomly selected subsample of 68 subjects (29 male, 29 female), aged 41-87 yr (mean 59 ± 12 yr) were selected from a larger cohort of 1044 involved in a survey of BP, glucose tolerance and diabetes. A stratified sub-sample of 347 was selected and from this sample 97 subjects were selected. A 39% non-compliance rate resulted in the study size of 68.</td>
<td>Subjects visited clinic twice; first visit had sitting BP, second visit reclining BP. All subjects asked to bring 24-hr urine sample to second visit along with a questionnaire that included start and end times of urine collection and a drug history. In order to corroborate compliance, subjects were asked to take daily PABA tablets. Completeness of 24-hr urine collection checked by recovery of oral PABA (65% recovery of oral load/24 hr was designated a &quot;complete&quot; recovery). Data adjusted for age, sex, BMI. Within person variability of 24-hr Na excretion estimated from 2 collections from 11 subjects.</td>
<td>* had higher mean BP than † (143.8±83.0 vs 139.1±81.1), and significantly higher 24-hr excretion of Na. SBP was significantly associated with 24-hr Na excretion (p&lt;0.02) and to 24-hr Na/creatinine ratio. DBP was similarly related to Na excretion (p=0.04). These effects (regression coefficients) were larger in those cases designated as &quot;complete collectors&quot; based on PABA excretion.</td>
<td>38% noncompliance (of the 97 selected subjects, 35 could not be contacted, and 12 refused to participate). One subject died. Only a 50% (26/58) compliance rate based on PABA excretion. No dietary intake data collected.</td>
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<tr>
<td>Frost et al., 1991</td>
<td>Meta-analysis of 14 published cross-sectional studies International</td>
<td>12,773 people from Europe, Asia and the USA</td>
<td>After adjustment for underestimation due to large variation in within-individual 24-hr Na intakes, regression slopes (SBP/Na) from 14 within-individual studies were compared with slopes from across-population studies.</td>
<td>Adjusted slopes from within-population studies agreed with slopes from across population. 6/14 of studies reviewed demonstrated significant SBP/Na regression slopes. Taken overall relationship significant at p &lt; 0.001.</td>
<td>There was no presentation of actual intake data, nor control for cross-cultural or demographic confounders of sodium intake. Claims that small decrease in SBP, e.g. 2 mmHg/100 mmol Na (5.8 gms salt), in within-population studies could be 23-50% of &quot;true&quot; value. One of 3 studies suggesting that Na reduction reduces SBP and risk of mortality due to stroke, ischemic heart disease.</td>
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<td>He et. al., 1991</td>
<td>Cross-sectional China</td>
<td>Subjects were of 2 ethnic groups, Yi and Han, from 4 areas of Southern China: 119 High-mountain Yi farmers (HMY), mean age 31 ± 12 yr 114 Mountain side Yi farmers (MSY), mean age 36 ± 14 yr 89 Town Yi migrants (TY) mean age 39 ± 13 yr 97 Han town residents (HT) mean age 36 ± 12 yr</td>
<td>To reduce intra-individual variation 24-hr dietary recalls (using food models to estimate portion sizes), 24-hr urine collections, BP measurements, and 1 fasting blood sample were collected on 3 consecutive days from each subject. In addition, demographic, lifestyle and medical history data were collected from all participants. For multivariate analysis adjustments were made for age, BMI, heart rate, alcohol, and energy intake.</td>
<td>Na excretion: HMY&lt;MSY&lt;TY&lt;HT was consistent with dietary Na, Na/K, serum and urinary Na/K, and SBP rankings. Dietary and urinary Na were significantly and positively associated with both SBP and DBP, whereas serum Na showed no association with BP. Dietary, serum and urinary K were negatively associated with SBP. After adjustments for confounding variables, multivariate analysis revealed that an 1 mmol/d increase in Na intake of 100 mmol/d resulted in 1 in both SBP and DBP (2.3 mmHg and 1.8 mmHg respectively), while a similar 1 in K intake resulted in 1 of 8.3 mmHg SBP and 5.7 mmHg DBP.</td>
<td>Methodological precautions to minimize uncertainties in intra-individual Na uptake permit demonstration of BP/Na association in a low Na, non-hypertensive population</td>
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<td>Intersalt Cooperative Res. Group, 1988a,b</td>
<td>Cross-sectional Within-center and across-center International</td>
<td>10,079 subjects (5045 M, 5034 F), aged 20–69, from 62 centers in 22 countries were included in the final analysis</td>
<td>Methods of sample and data collection were standardized across all centers. All subjects were asked to refrain from strenuous activity for 30 min prior to BP measurement. BP data were based on the mean of 2 sitting measures taken after subjects emptied their bladders and sat for 5 min. After measurement, subjects collected a 24-hr urine sample in standard 1-liter jugs containing boric acid as preservative. Aliquots were refrigerated and subsequently stored at −20°C. Other measures included height and weight and calculated BMI. Na and K assessed by emission flame spectrophotometry. Na intake was estimated from 24-hr urine levels. Daily intake of alcoholic drinks exceeding 7 d was assessed by questionnaire. Additional items on questionnaire included: history of hypertension, current medications, education, sociodemographics, and recent changes in diet.</td>
<td>Within individuals: After adjustment for age &amp; sex, Na correlated with SBP in 39 centers (15 significant) and with DBP in 33 (4 significant). Adjustment for BMI, alcohol and K, DBP correlations lost significance. SBP associations were positive in 33 centers (4 significant). SBP/Na relationship was significant in subjects aged 40–59 yr, but not 29–39. K excretion was negatively correlated with BP in individuals after adjustment for confounding variables. BMI and heavy alcohol intake had strong, significant associations with BP within individuals. Across centers: Strongest association with Na is change of BP with age across centers; slope of SBP and DBP vs age correlated significantly with Na after adjustment for age, sex, BMI, and alcohol. Median Na was positively related to median SBP over 62 centers, but not significantly over 48 after removal of 4 low Na remote populations.</td>
<td>BP and urine collection procedures standardized for all centers. 4 remote centers uniquely low in Na, BP, alcohol and slope of BP vs age, skew overall results.</td>
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**Limitations**
- Was a single assessment (event) and therefore did not assess previous or habitual Na exposure
- No assessment of subject compliance or completeness of 24-hr urine sample
- Previous Public Health campaigns in some of the countries had emphasized decreasing Na content of diet
- Treated hypertensives included in the sample thereby artificially reducing the effect of Na on BP
## APPENDIX TABLE 1. OBSERVATIONAL STUDIES - ASSOCIATION OF BLOOD PRESSURE WITH SODIUM INTAKE

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<td>Kesteloot and Joossens, 1988</td>
<td>Cross-sectional Belgium</td>
<td>Subjects were 8058 (4167 ♂, 3891 ♀; aged 25-74, mean 45 ± 13 yr) randomly selected participants in a nutrition survey carried out from 1979-1984. Within the total group, 7143 (3814 ♂, 3329 ♀) subjects were not receiving antihypertensive medications (UT).</td>
<td>The mean of 2 sitting readings was used for BP data. Measures were taken after subjects submitted to a 24-hr dietary recall interview covering the 24 hr preceding the interview (including Sundays). Alcohol intake was estimated by an undescribed method. BMI was calculated from height and weight measures. Heart rate was measured after BP readings. Nonfasting serum samples were obtained from all subjects after BP recordings.</td>
<td>In the UT group, after adjustment for age, BMI, heart rate, alcohol, and calorie intake there was a significant association between Na intake and BP with the exception of SDBP in ♀. There was no independent effect of K on BP. In the total group, significant positive independent relationships existed between dietary Na and DBP in both sexes, between alcohol intake and SBP and DBP in only ♂ and between total caloric intake and SBP only in ♀. Across the whole group, a difference of 13 g salt/d is associated with a change of 2.7 mmHg in SBP and 3.7 in DBP in ♂. For ♀ a difference of 8.3 g salt/d equates to 2.2 mmHg in SBP.</td>
<td>The participation rate varied between 35-46% indicating the potential for selection bias. 24-hr recall are of questionable reliability due to recall bias and inability to account for discretionary use of table salt. In addition, interview data included recall of intake on Sunday by an unaccounted-for number of subjects. Inclusion of weekend days in such dietary surveys introduces a significant source of variability to data as weekends generally are not representative of normal intake. Use of nonfasting blood samples could also introduce significant variability to the data set.</td>
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<td>Law et al., 1991a</td>
<td>Meta-analysis International</td>
<td>The final analysis included studies of 24 communities with data from 47,000 subjects.</td>
<td>Inclusion criteria for consideration included: all studies that estimated 24-hr Na intake from 24-hr urine collections or from Na analysis of replicate diets. Exclusion criteria were any study that estimated 24-hr Na intake by dietary recall or by random (&quot;spot&quot;) urine samples alone, and studies in which the age range of subjects was less than 30 yr. Studies of African, American, Caribbean, and other black populations were also excluded because of the established relationship between race and BP. There was a separate analysis by economic status of communities (developed versus underdeveloped). Separate analyses were performed by 10 yr age groups.</td>
<td>Changes in both SBP and DBP (mmHg per 100 mmol Na/24 hr) increased with age and initial BP. The higher the initial BP, the greater the expected reduction in BP for the same reduction in Na intake. Changes range from 3 mmHg (SBP) and 1 mmHg (DBP) at 15-19 yr and 6th BP centile to 15 mmHg (SBP) and 7 mmHg (DBP) at 60-69 yr and 95th BP centile.</td>
<td>Effects of confounders like BMI, K, and alcohol assumed to be different for developed and undeveloped communities but similar within each class. Separate analyses for 2 classes assumed to give BP/Na regressions unbiased by confounders. May be a useful model. No evidence for a threshold for Na below which there is no effect.</td>
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<td>Smith et al., 1988</td>
<td>Cross-sectional Scotland</td>
<td>7,354 (3754 (\text{M} ), 3600 (\text{F} )), ages 40–45, were randomly selected from Scottish heart health study.</td>
<td>Data included subjects' alcohol consumption (7-d recall), 24-hr urines and blood samples (fasting status unknown), BP (mean of 2 readings), and heart rate.</td>
<td>Age, pulse rate, K excretion, and alcohol show very weak correlation with BP. Association between BP and Na excretion insignificant. Correlation coefficients &lt; 0.1. In multiple regression model Na did not contribute to BP.</td>
<td>As in within–population studies, generally, single 24 hr Na estimates may give intraindividual uncertainty &gt; interindividual with possible underestimate of Na/BP relationship.</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>BP</td>
<td>Blood pressure</td>
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<td>d</td>
<td>Day</td>
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<td>DBP</td>
<td>Diastolic blood pressure</td>
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<td>K</td>
<td>Potassium</td>
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<td>Na</td>
<td>Sodium</td>
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<td>PABA</td>
<td>P-amino benzoic acid</td>
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<td>R</td>
<td>Random</td>
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<td>SBP</td>
<td>Systolic blood pressure</td>
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APPENDIX TABLE 2. INTERVENTION STUDIES - EFFECTS OF SODIUM ON BLOOD PRESSURE

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<td>Australian National Health and Medical Research Council, Dietary Salt Study Management Committee, 1989</td>
<td>Double-blind, placebo-clinical trial Australia</td>
<td>103 subjects (88 &amp; 17 f; mean age ~58 yr) with DBP 90–100 mmHg included in final data set. Subjects were from an original pool of 118 untreated mild hypertensives. Exclusion criteria included: treatment for hypertension, secondary cause of hypertension, complications of hypertension, or evidence of other cardiovascular disease.</td>
<td>Subjects went through 3 phases: screening, run-in phase of 6 wk, and diet phase of 8 wk. Subjects were seen every 2 wk. Subjects were included in the diet phase if they had 4 consecutive sitting DBP readings between 90–100 mmHg. Subjects randomized to 1 of 2 groups: Normal Na (NN), received 8 tablets/d containing 18 mmol NaCl; low Na (LN) received 8 identical placebo tablets/d. During the diet phase all subjects were counselled about lowering or maintaining low Na diet (target intake &lt;80 mmol/d). Measures: at each visit sitting BP, weight, 24-hr urine (at each visit after first), blood (at the third run-in visit and the last diet visit). Each subject gave an &quot;diet history&quot; (details not given) from the 4th visit on.</td>
<td>After multivariate analysis for effects of age, sex, weight, and initial SBP, BP reduction by Na restriction was still significant. Lowering Na intake to target of 80 mmol/d reduced SBP an average 5.5 mmHg.</td>
<td>Blinding is difficult with tablets as opposed to capsules. Small sample. Large range of variation. Response, nonresponder, or self-selection factors not discussed. Procedure for collection of diet data not provided. Intake data not presented. Results apply to mild hypertensives. Study evaluates role of Na in BP reduction rather than in pathogenesis.</td>
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<td>Cutler et al., 1991</td>
<td>Meta-analysis of 23 randomized intervention trials International</td>
<td>Data from a total of 1536 subjects were included in the analysis. 18 of the 23 trials were focused on hypertensive subjects.</td>
<td>Inclusion criteria for study selection included: random allocation of subjects to Na reduction or a control condition, subjects had to be free of antihypertensive interventions, and dependent measures had to include SBP or DBP as opposed to mean arterial BP. All studies included had documentation of Na intake. Studies that had Na levels beyond normal usual range were excluded. Only studies in which 24-hr urinary Na excretion was measured were used.</td>
<td>Reductions in Na urinary excretion were associated with $4.9 \pm 1.3$ mmHg reductions in SBP and $2.8 \pm 0.8$ mm in DBP in hypertensives. SDP and DBP were reduced by $1.7 \pm 0.6$ mm and $1.0 \pm 0.7$ mm respectively in normotensives.</td>
<td>Studies summarized here suggest real but clinically small effects of Na restriction. A dose-dependent relationship across trials was significant for normotensives and for hypertensives provided the models specified a line through the origin. Longer term studies might be more conclusive.</td>
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### APPENDIX TABLE 2. INTERVENTION STUDIES - EFFECTS OF SODIUM ON BLOOD PRESSURE

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<tr>
<td>Forte et al., 1989</td>
<td>Controlled intervention, Community trial, Portugal</td>
<td>Out of ca. 800 in each village, groups of 25 of each sex in each of 3 age groups (15-34, 35-54, and 65-69 yr), were randomly selected for assessment for a total of 150 subjects in each treatment group.</td>
<td>In initial phase all subjects had two BP readings on two 2 (the mean of 4 values used). Early-morning urine samples were provided by all subjects on 2 occasions and the mean electrolyte values were used. A random sample of 10 households in each community provided diet history data. These procedures were repeated at 12 and 24 mo. The intervention group received &quot;vigorously&quot; health education to achieve salt reduction.</td>
<td>Intervention caused significant decrease in BP at 2 yr. In Intervention community, mean SBP and DBP decreased by 3.6/5.0 mmHg at 1 yr and 5.0/5.1 at 2 yr. Salt intake decreased by 47% as estimated by diet survey but ca. 10% by overnight urinary excretion.</td>
<td>Communities are typical because of high initial salt intake (ca 360 mmol/person/day). 80% of population were hypertensive. Findings in this typical population may not apply to those with lower salt intake. Changes in Na intake difficult to quantitate since they are based on diet surveys of only a small portion of the study populations and overnight rather than 24-hr urine samples were used.</td>
</tr>
<tr>
<td>Hypertension Prevention Trial Research Group, 1990</td>
<td>Parallel group design, 4 clinical centers: Birmingham, AL, Jackson, MS, Davis, CA, Minneapolis, MN</td>
<td>A total of 841 healthy subjects (549 males and 292 females; mean age 38.6 yr) with DBP 78-89 mmHg were enrolled in 4 clinical centers.</td>
<td>Subjects randomly assigned to one of 5 groups: control, caloric restriction, Na restriction, Na plus caloric restriction, or Na restriction with concomitant increase in K. Trials were further divided according to BMI into High and Low strata. 3-yr trial with analyses every 6 mo. Participants in the low BMI group (n=211) were randomly assigned to either control or 2 treatments not involving caloric restriction while those in high BMI group (n=630) were assigned to all treatments. Dietary counseling was done in groups rather than individually. Dependent measures were changes in weight, BP, 8-hr overnight Na and K excretion.</td>
<td>BP in uncontrolled controls decreased by 2.6 mmHg In Na-restricted groups overnight Na excretion decreased by 10%. BP reduced by ca. 2 mmHg below controls in calorie-restricted group but not in others. Hypertensive events (DBP &gt; 90 mm or SBP &gt; 140 mm or treatment) over 3 yr reduced from 39% of population to 28% by caloric or Na counseling.</td>
<td>No data on dietary intakes collected</td>
</tr>
<tr>
<td>Law et al., 1991b</td>
<td>Meta-analysis of 70 published studies of effects of salt restriction on BP, International</td>
<td>Only trials with a crossover design (n=68) or parallel control group (n=10) were included. Trials with interventions other than salt restriction assessed patients on antihypertensive medications, or, lacking corroborative data with 24-hr urine collection, were excluded.</td>
<td>For each study observed change in SBP was compared with a value predicted from relationship between Na and BP in across-population studies. Researchers subdivided the data from studies that recruited both subjects with high BP and subjects with normal BP to allow separate assessment of the effect of salt restriction for each category.</td>
<td>Observed reductions in SBP less than predicted in trials of less than 6 wk but similar to predictions in 33 trials of 6 wk. Salt reduction lowers BP in persons with high BP and in those with normal BP. In people aged 50-59 yr, a reduction in daily Na intake of 80 mmol (about 3 g of salt), after a few weeks, lowered SBP by an average of 5 mmHg, and by 7 mmHg in those with high BP; DBP was lowered by about half as much.</td>
<td>Emphasizes importance of longer term studies to assess effects of salt restriction and suggests that the effect of universal moderate dietary salt reduction on mortality from stroke and ischemic heart disease would be substantial. Provides evidence that the effect of salt reduction on BP is larger than has previously been thought. It is unclear exactly how authors controlled for confounding factors in this study.</td>
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**APPENDIX TABLE 2. INTERVENTION STUDIES – EFFECTS OF SODIUM ON BLOOD PRESSURE**

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<tr>
<td>MacGregor et al., 1989</td>
<td>Double-blind, randomized crossover study England</td>
<td>Subjects were 20 mild hypertensives (11♂, 9♀; mean age 57 yr, 15 white, 5 black) with untreated baseline BP 164/101. Subjects were referred by local clinicians and were included if after 2 mo of observation DBP remained within 50–110 mmHg. Exclusion criteria included: cardiovascular or renal disease and use of oral contraceptives or other medications.</td>
<td>All patients were instructed to restrict Na intake during the trial. The crossover design included 3 phases each lasting 1 mo. BP, weight and HR, and blood samples were collected monthly. 24-hr urines were collected twice during the study. Subjects continued on Na restricted diets after completion of the crossover study. 24-hr urines were collected every 3 mo thereafter. 1 mo on NaCl after 6 wk on low NaCl diet. Diet restricted to give 30–50 mmol/d. Slow Na tablets to provide total of 100 or 200 mmol/d.</td>
<td>An apparent linear dose response relationship between BP values and Na intake. Initial mean BP was 164/101, at intake of 50 mmol Na, BP was 147/91; at intake of 100 mmol Na, BP was 155/95; and, at intake of 200 mmol Na, BP was 163/100. 19 patients continued on low Na diet 1 yr after cessation of crossover study. In 16 of these BP stabilized at 145/90 mmHg.</td>
<td>Small study, relevant to mildly hypertensive populations, but offers a model for dose–response studies. Change in BP was 16 mmHg from highest to lowest Na intake (11.6 to 2.4 g salt/d)</td>
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| Mascioli et al., 1991 | Randomized, double-blind, placebo-controlled crossover clinical trial MN, United States | 48 subjects (38♂, 16♀), mean age 52 yr, 47 white, 1 black) were recruited from list of individuals who were ineligible for other clinical protocols conducted by these investigators (no further clarification supplied). Range of seated DBP was 80–89 mmHg and none of the subjects had been diagnosed or treated for hypertension. | 8-hr overnight urines were collected prior to an 8-wk low–Na diet period. Compliance to diet was assessed after 6 wk with 5 consecutive overnight urine samples. Subjects were randomly assigned to one of 2 treatments, NaCl capsules to give 96 in Eq NaCl or placebo. Trial periods were Group 1 (n=28): 4 wk treatment, then 2 wk washout, then 4 wk placebo; Group 2 (n=23): placebo, washout, treatment. | SBP averaged 3.6 mmHg higher during NaCl treatment periods compared with placebo period (p < 0.001). 65% of study participants experienced an increase of SBP when on NaCl capsules compared with placebo capsules. DBP average 2.3 mmHg higher during NaCl capsule treatment periods compared with placebo period (p < 0.005). 65% of study participants experienced an increase of DBP when on NaCl capsules compared with placebo capsules. | Methodologically sound study
Findings consistent with results of Intersalt Cooperative Research Group |
| Sagnella et al., 1989 | Metabolic study England | Six normotensive subjects (4♂, 2♀) ranging in age from 19–21 yr were enrolled. No other details given | The 16-d study had the following sequence: 2-d observation period on normal diet, 4-d equilibration period on low Na, d 5 – d 13 Na intake was increased by 50 mm/d using low Na tablets. D 13 – d 16 subjects remained on peak Na intake of 350 mmol/d. Low Na diet prepared in a metabolic kitchen under supervision of metabolic dietician. Test Na tablets (GIBA, 10 mmol NaCl/tablet). Dependent measures were plasma atrial natriuretic peptide (ANP), aldosterone, and plasma renin activity (PRA). Daily 24-hr urine specimens were collected | ANP rose and aldosterone and PRA fell progressively as Na intake increased. No change in BP
Urinary Na increased with progressive increases in Na intake. | Hormone levels are sensitive and rapid responders to Na load, but BP did not change.
Number of subjects very small |
### APPENDIX TABLE 2. INTERVENTION STUDIES – EFFECTS OF SODIUM ON BLOOD PRESSURE

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<tr>
<td>Steensen et al., 1989</td>
<td>Controlled intervention Community study Belgium</td>
<td>Subjects were from 2 towns of similar demographic make-up. Out of a possible 3286 subjects, 1510 (777♂, 733♀) were included in the final analysis.</td>
<td>Baseline surveys took place in 1979, 1989; follow-up exams 5 yr later. Two visits at each survey involved collection of 24-hr urines, self-administered questionnaires, BP, HR readings, weight, and height. In an intervention aimed at ♂ (since they control food purchase and preparation), 1 of 2 towns was requested by mass media (leaflets, posters, radio and newspapers) to lower salt consumption. The other town served as the control.</td>
<td>24-hr urinary Na decreased by 25 m Eq in ♂ of intervention town. No difference in BP between ♂ in either town. While there were 1 in SBP and urinary Na in ♂ in intervention town they did not differ from those seen in the control ♂. In both intervention ♂ and ♂ &gt;50 yr of age, there were greater 1 in urinary Na excretion than similar control group. There were no significant differences in BP in these latter groups.</td>
<td>Corroborative data, e.g., diet, was insufficient to confirm or refute a relationship between Na and BP. The long period between intervention and follow-up could have confounded the outcomes.</td>
</tr>
<tr>
<td>Stamler et al., 1989</td>
<td>Intervention trial Illinois, United States</td>
<td>201 subjects (174♂, 27♀) with high-normal BP and/or rapid resting heart rate (&gt;80 beats/min) with age range of 30–44 yr. Exclusion criteria included: electrocardiographic abnormalities, history of cardiovascular disease, diabetes, frequent travel, frequent alcohol consumption (&gt;5 drinks/d), special diets, and oral contraceptive use.</td>
<td>In this 5-yr trial, intervention tested was individual guidance to reduce weight, Na and alcohol intake and increase exercise. Subjects were randomly assigned to control and test groups. 7-d diet diaries collected at baseline and annually. 4-d diet diaries collected at least semi-annually. Food models were used to estimate portion sizes. Diaries did not include discretionary salt use. 7 consecutive overnight urine specimens were collected for assessment of Na, K and creatinine at baseline and annually. Intervention group collected specimens semiannually.</td>
<td>Overnight Na urinary excretion was reduced by 25% (2.5 g salt/d) by intervention. Incidence of hypertension was 8.6% in intervention group, 18.2% in controls. In multiple regression analysis BP change was significant associated with weight but not with Na and alcohol.</td>
<td>Study design included several variables known to affect hypertension</td>
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**BP** Blood pressure  
**BMI** Body mass index  
**DBP** Diastolic blood pressure  
**K** Potassium  
**Na** Sodium  
**SBP** Systolic blood pressure
### Appendix Table 3. Studies of Sodium and Blood Pressure in Children

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<tr>
<td>Ellison et al., 1989</td>
<td>Non-randomized controlled intervention with crossover MA, United States</td>
<td>Subjects were 650 (345 ♀, 305 ♂) students with a mean age of 10 yr enrolled in 2 private boarding schools. While all of the students in these schools received the intervention, for logistical reasons only those students taking basic science courses were monitored.</td>
<td>Na intake reduced by 15-20% in 1 of 2 schools for 5 mo, followed by 2-mo follow-up. Reduction was accomplished through changes in food purchasing and preparation. There was no counseling of participants in terms of salt intake reduction. Students were encouraged to eat their normal diet. Intervention and control schools reversed in 2nd yr Na intake assessed by 24-hr diary 1 d/wk for the first 6 wk of school, 2 wk during winter, and 4 wk in the spring. Diaries including documentation of discretionary salt use. Dependent measures were changes in BP between beginning and end of the school year. Baseline BP was the average of all of the BP readings recording during first 4 wk of school. The final BP was the mean of BP reading during final 6 wk of school. Control and intervention groups from the 2 trial periods were pooled in the final analysis.</td>
<td>Na intake decreased from baseline by 4.6% in control ♀ and 2.9% in intervention. Comparable figures for ♂ were 16% and 25%. Overall SBP decreased by 1.7 mm Hg p&lt;0.003 and DBP by 1.5 mm Hg p&lt;0.002 in intervention. Data were adjusted for sex and initial BP.</td>
<td>There was no test of trial differences within schools. Potential for an order effect was not controlled. The school that received the salt restriction first might not have been an appropriate control for the second phase. No comparisons or control for potential differences between schools. No urinary Na measures</td>
</tr>
<tr>
<td>Geleijse et al., 1990</td>
<td>Cohort study The Netherlands</td>
<td>Of 6670 eligible subjects, 233 children (age 5-17 yr, 104 ♀, 125 ♂) were included in the study cohort.</td>
<td>The avg follow-up period was 7 yr. BP was measured 4 wk after selection for the study and yearly thereafter. 24-hr Na and K intakes were calculated from 6 annual timed overnight urine collections. Multiple linear regression was used to assess the associations between electrolyte intake, excretion and the slope of the BP over time line. Other comparisons were made for sex, age, and level of intake (by tertiles, highest third vs lowest third).</td>
<td>There were no significant associations between Na excretion and the change in BP over time. Salt intake varied from 3.6 - 14.7 g/d in this cohort. Slopes of SBP/time (1.95-2.25 mmHg/yr) did not vary with Na but were significantly inversely proportional to K intake. Change in SBP was positively associated with NaK. There was no association between urinary electrolytes and DBP.</td>
<td>No control for potential demographic differences. Large uncertainty in Na values could be expected from methods</td>
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## APPENDIX TABLE 3. STUDIES OF SODIUM AND BLOOD PRESSURE IN CHILDREN

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<tr>
<td>Miller et al., 1968</td>
<td>Intervention IN, United States</td>
<td>Out of a total of 208 children (128 identical twins) providing baseline data, 149 white normotensive subjects (64♂, 85♀) ranging in age from 4–18 yr (mean 10.6 yr) were included in the final data set.</td>
<td>Families were instructed to restrict dietary Na intake to a goal of 60 mmol/d. This goal was to ensure an average Na excretion ≤ 75 mmol/d for the 3-mo trial. After a 2-wk stabilization on restricted diet subjects with 24-hr urinary Na ≤ 60 mEq/d were allowed to continue the trial. Non-twin children collected urine samples every other wk and twin children collected 24-hr urine weekly for a period of 12 wk. 1 member of each twin pair, chosen at random, received a NaCl supplement for the middle 4-wk period in order to return Na intake to baseline levels. Only data for the first 4-wk period of Na restriction were used for the supplemented twin.</td>
<td>There were no differences between supplemented and unsupplemented twins during Na restriction except for urinary excretion of Na. There was a significant (p&lt;0.001) reduction (53 and 41 mEq/d) in 24 hr urinary Na in both sexes. There was no change in ♂ BP while a small but significant (p&lt;0.05) decrease in DBP and mean arterial BP in ♀. Individual mean arterial BP showed normal distribution with extremes of ±14 mm. There was a significant correlation between changes in all BP measures within twin pairs indicating a homogeneity of variance for these dependent measures.</td>
<td>No explanation of why identical twins were used within the pooled data set. The use of a homogeneous group such as identical twins in an otherwise heterogeneous population could influence the outcomes being tested. The authors concluded that there were no easily identifiable dietary characteristics to predict individual BP response to Na.</td>
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**Notes:**
- BP: Blood pressure
- DBP: Diastolic blood pressure
- K: Potassium
- Na: Sodium
- SBP: Systolic blood pressure
### APPENDIX TABLE 4. STUDIES RELATING TO SALT SENSITIVITY

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<tr>
<td>Daston and Kirk, 1988</td>
<td>Metabolic study, AI, United States</td>
<td>There was a total of 156 subjects in the study: 62 normotensive white (21 f, 41 m) 34 normotensive black (13 f, 21 m) 40 hypertensive black (9 f, 31 m). Hypertensive subjects were either untreated or had discontinued medication for 1 mo prior to the study.</td>
<td>All subjects admitted for 10 d. There were 2 protocols. Protocol 1: 3-d control period with 150 mEq Na intake/d was followed by a 4-d depletion period (0 mEq Na/d) and furosemide (1mg/kg in 2 divided doses) and finally a 3-d loading (3.9 mEq Na/kg/d i.v. over 4 hr supplying 3.88 mM of NaCl/kg/d). Protocol 2: The sequence of Na changes reversed, Na load after control period, and salt depletion period was last. Dependent measures included: 4 daily measures of supine brachial arterial pressure and heart rate, daily AM body weight, and 24-hr urine collections. Mean arterial pressure (MAP) was calculated as DBP plus 1/3 pulse pressure. Na balance was calculated by subtracting 24-hr urine from intake. Method for measuring intake was not documented.</td>
<td>MAP rose with load and declined with depletion in both protocols for black hypertensives and in protocol 2 for black normotensives. No effect of Na change on BP in normotensive groups. No correlation between Na balance and changes in MAP</td>
<td>Small or no changes in group average MAP obscured large individual variations. No control or testing for confounding variables such as sex, body weight, or sociodemographic variables Methods used for establishing actual intake used in calculating Na balance were not described. Suggests that interaction of Na with hormonal or other parameters controlling BP may be more important than magnitude of Na retention</td>
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<tr>
<td>Falkner &amp; Kushner, 1990</td>
<td>Metabolic study PA, United States</td>
<td>Study included 121 subjects (63♂, 58♀), ages 18-23 yr, 38 white, 83 black. Subjects with DBP &gt;95 mmHg or on antihypertensive medications were excluded. Subjects were classified as follows: Normotensive (30 whites, 48 blacks) based on Mean Arterial Pressure (MAP) of &gt; 95 mmHg. 18.4% of whites and 37.3% of blacks were Na-sensitive based on the change in MAP after Na loading. (Subjects with ≥ 5% increase in MAP after loading were classified as Na sensitive)</td>
<td>Baseline measures included the mean of 2 overnight urine samples, medical history, anthropometrics, standing, and sitting BP. BP and heart rate before and after 10 min stress (mental arithmetic). Test repeated 14 d after addition of 10g NaCl to usual diet. Subjects scanned at 7 d for BP and weight. Undescribed food survey taken at baseline, d 7 and d 14. Compliance with loading confirmed with overnight urine collection on days 6, 7, 13, and 14.</td>
<td>Na sensitive subjects had a significant increase in weight (p&lt;0.001) after loading period compared to Na insensitive subjects who also had a significantly higher rate of Na excretion (p&lt;0.001). There was a significant negative correlation between change in BP and Na excretion in Na sensitive group. Normotensive blacks accounted for the greatest increases in MAP response to Na loading. Na loading was not associated with any changes in the BP response to stress.</td>
<td>No blinding, placebo or control group included. No evidence for relationship between Na load and mean of BP changes over whole population. Data suggest that Na-sensitivity, especially in blacks, may be related to functional changes in peripheral vascular resistance and reduced rates of Na excretion.</td>
</tr>
<tr>
<td>Flack et al., 1991</td>
<td>Review</td>
<td>Calculation from published data of probabilities of diagnosing Na-sensitivity and Na-resistance cf. Mascioli et al. (1991)</td>
<td>Probabilities of diagnosing salt sensitivity and resistance by chance after identical repeat dietary Na manipulations are ca 0.1 when arbitrary criterion for sensitivity is change of MAP ≥ 5%. Chance probabilities decrease as critical change in MAP is raised. Probability of diagnosing Na-insensitivity on a 2nd experiment was ≥ 0.09</td>
<td>Identifies need for bidirectional criteria (BP increase with salt load and decrease with restriction) for adequate identification of Na-sensitive individuals.</td>
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<tr>
<td>Gill et al., 1988</td>
<td>Controlled metabolic study MD, United States</td>
<td>Subjects were 19 patients (8 ( \Phi ), 11 ( \Phi )) ranging in age from 20-75 yr who were previously diagnosed with idiopathic hypertension. 5 normotensive controls (2 ( \Phi ), 3 ( \Phi )) were recruited Hypertensive subjects discontinued medication for 2 wk prior to admission for the protocol.</td>
<td>Subjects received an isocaloric diet containing 9 mEq NaNa and were challenged with 6 (low), 100 (normal), 240 (high) mEq/d for 7, 7 and 8-4 periods respectively. Na sensitivity defined as increase of MAP ( \geq 6% ) from low to high Na. Dependent measures were: Na metabolism, plasma renin activity (PRA), aldosterone, plasma and urinary NE, and urinary dopamine, and norpinephrine.</td>
<td>8 patients Na sensitive, 11 resistant. Sensitive patients retained more Na than normals. Plasma and urinary NE did not decrease, as would be expected in normals, when Na load was increased nor did urinary DA increase. Resistant patients excreted Na normally and plasma and urinary NE decreased when Na intake increased. Urinary DA was high and did not increase further with Na loading.</td>
<td>Normals had a mean 5% increase in response to Na load, which, by some standards, would be considered salt sensitivity. The salt sensitive group was significantly older and had a greater proportion of ( \Phi ) than the salt resistant group. There were no statistical adjustments for these or other (e.g., BMI) potentially confounding variables. This study suggests that supernormal Na retention and failure to suppress adrenergic activity may be related to salt sensitivity. Leaves open questions on etiology of hypertension in Na-resistant patients.</td>
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<td>Miller et al., 1987a</td>
<td>Uncontrolled community-based intervention IN, United States</td>
<td>Subjects were participants in a larger study of hypertension in families with identical twins. Subjects in this report were 82 normotensive parents (36 ( \Phi ), 46 ( \Phi )).</td>
<td>Subjects and their families were instructed to restrict dietary Na intake to a goal of 60 mmol/d. This goal was to ensure an average Na excretion ( \leq 75 ) mmol/d for the 3-mo trial. After a 2-wk stabilization on restricted diet subjects with 24-hr urinary Na ( \leq 60 ) mEq/d were allowed to continue the trial. Subjects maintained on restricted diet 12 wk during which BP and 24-hr urinary Na measured every other wk.</td>
<td>There was a significant (( p&lt;0.01 )) decrease in MAP during Na restriction. Age was significantly correlated with changes in BP. Change in mean arterial BP for age ( &lt;40 ) was (-0.6\ mmHg) and for age ( &gt;40 ) change was (-5.7\ mmHg). Individual changes in BP showed Gaussian distribution with extremes at ( \pm 16\ mm).</td>
<td>There was heterogeneity of individual responses to Na restriction.</td>
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<tr>
<td>Miller et al., 1987b</td>
<td>Uncontrolled community-based intervention IN, United States</td>
<td>44 families with identical twins aged 4–20 yr</td>
<td>See Miller et al., 1987a, 1988.</td>
<td>Resemblance, a correlational reflection of changes in DBP, SBF, and MAP response to Na restriction, was significant in mother–offspring (p &lt; 0.05), sibling–sibling (p &lt; 0.01) and highly significant (p &lt; 0.001) in twin–twin comparisons. Similar comparisons were only marginally significant (p &lt; 0.10) for father–offspring. The correlation for change in Na excretion was significant for sibling pairs (p &lt; 0.01) and very significant for twins (p &lt; 0.001). There were no associations between excretion and BP in any pair–wise comparisons.</td>
<td>Suggest there might be a partial genetic component in addition to environmental factors involved in the expression of BP effects of Na.</td>
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<tr>
<td>Rocchini et al., 1989</td>
<td>Controlled intervention MI, United States</td>
<td>Subjects included 60 obese adolescents ages 10–16 yr and 18 non-obese adolescents age 10–16 yr. Obesity was defined as weight for height above the 75th percentile for age and sex, and triceps and subcutaneous adipose skin-fold thickness above the 80th percentile for age and sex.</td>
<td>Na sensitivity measured by the response to high (&gt;250 mmol/d) vs low (&lt;30 mmol/d) Na diets for 2 wk. High salt diet was regular diet + 5 NaCl tablets/d (presumably 50mmol/tablet); low Na diet was individually designed 4-d rotating meal plans with 20–30 mmol Na/d. Diets were supposed to be isocaloric. 51 obese subjects completed a 20–wk weight loss program consisting of diet and behavior modification and designed to produce a weight loss of 0.5 kg/wk. This group was further divided into weight loss group (&gt;1 kg lost) and no weight loss group (≤1 kg). Na sensitivity was tested again after weight loss. MAP, cardiac output, and plasma hormones measured before and after switch from high to low Na intake in obese, controls, and obese that had lost weight.</td>
<td>Obese had a significantly larger mean change in MAP after switch from high to low Na than non-obese group (p &lt; 0.001). After the weight loss phase, the weight loss group had a reduced sensitivity of BP to Na while those with no weight loss had no change in Na sensitivity. Other observations included: higher plasma aldosterone and insulin levels in obese subjects; Na sensitivity of MAP was proportional to hyper-insulinemia; and plasma norepinephrine did not increase after switch to low Na in obese subjects.</td>
<td>No random assignment or blinding procedures included in the protocol. No adjustment for confounding variables, i.e., age in this study of pre- and postpubertal adolescents. No documentation of baseline Na intake. Potential underestimation of Na intake during intervention as high Na group at their normal diet (of unknown Na content) while low Na group ate a controlled diet. Dietary comparisons were documented for obese vs non-obese during the controlled low Na period but not high vs low Na. No documentation of weight change in second Na sensitivity test after weight loss protocol. Study concludes that BP of obese adolescent is dependent on dietary Na; however, since this sensitivity may involve insulin, aldosterone or altered sympathetic function, not yet clear if any of these might be a useful marker for Na sensitivity</td>
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<tr>
<td>Sakaguchi et al., 1988</td>
<td>Metabolic study Japan</td>
<td>25 mild hypertensives were admitted, tested for Na sensitivity, and subsequently categorized into 2 groups: 12 Na sensitive (48 ± 8 yr) 13 Na resistant (46 ± 8 yr) Categorization was based on the difference in the averages of the resting SBP taken hourly on the 6th d of 7-d Na depletion and repletion periods.</td>
<td>Patients on low (2-3 g/d) and high Na (22-23 g/d) diets for 7-d periods. 15 hourly SBP's were recorded on the 5th d of each period. Subjects with a significant (p&lt;0.01) increase in SBP after Na load considered sensitive. On the 6th d of each interval, blood samples were collected for measurement of plasma renin activity, plasma aldosterone and norepinephrine, and hematocrit. On the 6th and 7th d, norepinephrine and isoproterenol infusion test (given i.v.) and a 70° tilting test were performed in order to assess cardiovascular and baroreceptor response.</td>
<td>There were similar increases in Na excretion and body weight and decreases in hematocrit during repletion phase in both groups. Baroreceptor slope and decrease in SBP after 70° tilt enhanced by Na in the Na insensitive group only. No group differences in Na dependence of BP change with NE, or in isoproterenol tachycardia</td>
<td>No data on sexual composition, demographics, or baseline Na intake of study groups supplied Study suggests that difference in ability of baroreflex to respond to high Na may be involved in Na sensitivity</td>
</tr>
<tr>
<td>Sharma et al., 1989</td>
<td>Single-blind, randomized crossover study Germany</td>
<td>Two phase study; In phase 1, 40 subjects tested in order to identify the 15+ volunteers for Phase 2 who were divided into two groups: 7 salt sensitive 8 salt insensitive</td>
<td>In Phase 1, subjects selected as salt resistant or sensitive on basis of MAP response to a 7-d reduction of dietary NaCl from 200 to 20 mmol/d. Salt sensitivity defined as a significant (p&lt;0.05) drop &gt; 3 mmHg in MAP after salt restriction. In 2nd test, subjects received placebo or 200 mmol/d supplement to low salt diet for 7 d in a crossover design.</td>
<td>20% of subjects with no familial history of hypertension and 68% of subjects with familial history were salt sensitive. Of 15 subjects, 14 classified same in both parts of study.</td>
<td>Very small number of subjects in short term study No demographics or dietary history presented Data suggest that arbitrary sensitivity classification may be reproducible and indicative of familial tendency to hypertension.</td>
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</table>
# APPENDIX TABLE 4. STUDIES RELATING TO SALT SENSITIVITY

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type/location</th>
<th>Subject Number and Description</th>
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</thead>
<tbody>
<tr>
<td>Sullivan et al., 1988</td>
<td>Metabolic studies</td>
<td>In a subset study of 62 normotensives, 65 with borderline hypertension (BHT—defined as DBP &gt; 90 mm Hg at least 3 occasions and &lt; 90 usually) were evaluated for response to Na depletion and repletion.</td>
<td>BP and hemodynamic parameters measured during normal diet, and after sequential changes to 4 d on 10 mEq Na, 60 mEq Kd, 2 d ad lib, 4 d on 200 mEq Na, and 60 mEq Kd</td>
<td>In studies summarized, Na sensitivity was observed in 15% of white normotensives, 29% of white BHT, 27% of black normotensives, and 60% of black BHT. In 2 of the subset studies reviewed, the incidence of Na—sensitivity was higher in BHT than in normotensive subjects. Na—sensitive subjects were characterized by significantly increased forearm vascular resistance and decreased plasma renin activity and aldosterone concentration.</td>
<td>Sequential changes of dietary Na of short duration Assessment of normal dietary Na intake not described Actual racial or demographic composition of study subsets not supplied</td>
</tr>
<tr>
<td>Weinberger et al., 1987</td>
<td>Metabolic study</td>
<td>A total of 212 patients consisting of 117 normotensives (mean age = 28 yr; 4 black; 68 &amp; , 49 f) and 85 hypertensive (mean age = 42 yr; 20 black; 45 &amp; , 49 f); medication-free for &amp; wk) were admitted for this study.</td>
<td>Blood volume expansion was accomplished by injection of 308 mEq Na/d, followed by low Na diet (10 mEq/d) and furosemide infusion to induce volume contraction. Na sensitivity defined as decrease of MAP ≥ 10 mmHg from high to low Na. Haptoglobin (Hp) phenotypes served as genetic markers and were recorded for all subjects.</td>
<td>Na sensitive members of either normo— or hypertensive groups were significantly older than resistant subjects. Across all subjects independent of race or history of hypertension, those subjects with Hp 1—1 phenotypes were more likely to be Na sensitive, while those with Hp 2—2 were apt to be Na resistant. The group that was heterozygous for Hp 2—1 contained equal numbers of Na sensitive and insensitive subjects.</td>
<td>This study provides preliminary evidence for a possible association of Na sensitivity with Hp phenotype.</td>
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### APPENDIX TABLE 4. STUDIES RELATING TO SALT SENSITIVITY

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<tbody>
<tr>
<td>Weinberger and Fineberg, 1991</td>
<td>Report summarizing results of three metabolic studies. IN, United States</td>
<td>The characteristics of subjects studied in the three studies reported were as follows;</td>
<td>The goals of the 3 studies were as follows;</td>
<td>A. MAP changes were reproducible (r=0.55, p&lt;0.002) on second test after 1 yr 18 of 38 retained and 4 changed from original sensitivity category while 8 became indeterminate.</td>
<td>While this study was based on short-term responses of BP to acute Na deprivation, it does confirm other studies indicating reproducibility of individual sensitivity determinations. Indicates an interesting association between age and Na sensitivity; however, the longitudinal study of Na sensitivity as a predictor of time-dependent BP changes may be somewhat confounded by age differences in experimental groups. Lack of demographic data may impact on the external validity of those studies.</td>
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<tr>
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<td>A. 28 subjects, neither race, sex, nor age was specified, study included both normo- and hypertensive subjects.</td>
<td>Study A. Metabolic study to determine reproducibility in individual subjects of effect of Na and volume depletion</td>
<td>B. Hypertensives had progressive increases in Na sensitivity with increasing decades of age. In normotensives, Na sensitivity increased only at age ≥ 60. No relationship between BMI and Na sensitivity was observed.</td>
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<td>B. A total of 660 subjects demographic composition not given, divided into 2 groups containing 430 normotensive and 230 hypertensive subjects respectively.</td>
<td>Study B. Cross-sectional study of association between age and Na sensitivity of MAP</td>
<td>C. In periods ≥ 10 yr the change in systolic BP in mmHg yr (p&lt;0.001) were -0.32±0.15 and 1.42±0.39 for Na-resistant and Na-sensitive subjects respectively. Corresponding values for diastolic changes were 0.16±0.23 and 0.66±0.33</td>
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<td>C. A total of 31 subjects; 15 Na-resistant, (initial age 29 ± 3 yr) and 16 Na-sensitive (initial age 40 ± 3 yr). No demographic data supplied</td>
<td>Study C. Longitudinal study over 10 yr to determine whether time-dependent changes in MAP differ for populations originally classified as Na sensitive or insensitive</td>
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<td>Blood volume expansion by injection of NaCl followed by low Na intake and frusemide for volume contraction. See Weinberger et al. (1997)</td>
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<td>Na sensitivity defined as a decrease of MAP ≥ 10 mmHg 24 hr after change from high to low Na. Insensitivity defined as decrease &lt; 5 mmHg or an increase.</td>
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**Abbreviations:**
- B: Blood pressure
- BP: Blood pressure
- DBP: Diastolic blood pressure
- Hp: Haptoglobin
- K: Potassium
- MAP: Mean arterial pressure
- Na: Sodium
- SBP: Systolic blood pressure
<table>
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<tr>
<td>Elliott et al., 1989</td>
<td>Cross-sectional study (Data from Intersalt study) International</td>
<td>10,079 subjects (5045 $\sigma$, 5034 $\varphi$), aged 20–69 from 62 centers in 32 countries were included in the final analysis. Data from Intersalt study (see Intersalt Cooperative Res. Group, 1988a,b) examined for relationship by sex and age of BP to Na and K intake. Center-specific regression coefficients combined and weighted to give overall estimates of relationship of BP to each variable. 8 separate analyses for combinations of age and sex.</td>
<td>For $\sigma$ the positive association between SBP and DBP was significant ($p&lt;0.001$) in only the older age groups (40–69 yr); whereas in $\varphi$ it was significant for all age groups and across all ages. For SBP, the pooled analysis ($\sigma$ and $\varphi$) was significant across all ages and for each age group studied. For DBP, the analysis across sexes was significant for the oldest group and the pooled analysis for all ages. In 8 trials, the relationship of BP to Na/K ratio was positive and significant except for $\sigma$ and $\varphi$ age 20–39 and $\sigma$ and $\varphi$ combined, age 20–29. With adjustment for confounding variables, K excretion was negatively and significantly related to the blood pressure of individuals.</td>
<td>See Intersalt Cooperative Res. Group, 1988a,b</td>
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<tr>
<td>Grimm et al., 1990</td>
<td>Randomized, placebo-controlled, double-blind study</td>
<td>Subjects were 287 $\sigma$ (mean age 57 yr) with long-term history of treatment for hypertension. All except 3 subjects were white. Inclusion criteria were: currently medicated with 1 or 2 antihypertensive drugs; had DBP of &lt;95 mmHg on the first of 2 clinic visits, and an average of &lt;90 mmHg over 2 visits. Exclusion criteria were: &lt;5.6 yr-treatment with antihypertensive med, the use of cardiovascular drugs, evidence of cardiovascular disease, weight &gt;150% ideal body weight, incompatible diet, history of renal disease, or documentation of poor compliance with medications. Subjects were randomly assigned to receive either 96 mmol KCl/d (n=143) (12 capsules) or 12 placebo capsules (n=145). In addition all subjects were counselled to follow a low-Na diet with a goal of &lt;80 mmol Na/d. After 12 wk of dietary intervention antihypertensive drugs were discontinued. After withdrawal of meds, patients were monitored for 6 wk and then biweekly for at least 2 yr. Medications were resumed if the DBP was &gt;90 mmHg on 3 consecutive visits 2 wk apart, 95–114 mmHg on 2 consecutive visits or &gt;115 mmHg on a single visit.</td>
<td>86% of participants were taking diuretics, 42% were on $\beta$-blockers. The number on combined medications not supplied. 78 subjects in each groups required reinstatement of meds. Baseline DBP ($p&lt;0.001$), BMI ($p&lt;0.07$), urinary Na excretion ($p&lt;0.04$) and the number of antihypertensive drugs used before randomization ($p&lt;0.001$) were all positively related to reinstatement of meds during the trial. No change in average values for SBP and DBP during follow-up.</td>
<td>Methods for assessing baseline or trial dietary intakes were not described. The mean computed BMI of these subjects was 26 kg/m2, which by some standards is indicative of obesity. There was no analysis of the subjects who did not require reinstatement of medications during the trial (~45% of each group) nor were those reinstated on meds removed from the final analysis. Na/K ratios not presented.</td>
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## Appendix Table 8. Studies on the Interaction of Sodium with Other Dietary Ions

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<tr>
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<tr>
<td>Gruchow et al., 1988</td>
<td>Cross-sectional National survey (NHANES I)</td>
<td>10,361 respondents were included in the final data set. The sample was composed of 9325 whites (4682 male, 4643 female) and 1038 blacks (492 male, 544 female). Subjects were not on antihypertensive medication, special diets, or pregnant.</td>
<td>In order to study the interactions of dietary Na, K, and alcohol, BP and calcium intake, subjects were categorized by 3 levels of calcium intake: &lt; 400 mg/d, 400-800 mg/d, &gt; 800 mg/d. Dietary mineral intakes were based on analysis from 24-hr diet interview. Age distribution of subset weighted to reflect distribution in U.S. population. SBP and DBP were based on sitting BP taken at the physical exam.</td>
<td>Age, BMI, and alcohol were significantly related to both SBP and DBP at all levels of calcium intake. After controlling for age and BMI, Na/K ratio was significantly related to BP, but only in low calcium (&lt;400 mg/d for male, &lt;800 mg/d for female) group. Na and K individually were related to BP in low calcium group, but not significantly. Some data suggest that K may require higher levels of calcium to protect against Na/K effects.</td>
<td>Incomplete measurement of dietary Na and calcium and uncertainty due to the use of 24-hr dietary recall have been cited as reasons for caution in interpreting NHANES data. One of several studies suggesting importance of Na/K ratio. Speaks for a stronger role of Na/K than some other analyses of NHANES I. Despite limitations in diet data, this study is in agreement with studies in other populations that utilized more reliable dietary intake assessment methodologies. Suggests that the Na/K ratio in the diet may contribute to an elevation of BP but only in subjects with low calcium intake.</td>
</tr>
<tr>
<td>Hamet et al., 1991</td>
<td>Cross-sectional Quebec, Canada</td>
<td>182 (66 male, 96 female) normotensive subjects equally distributed from English and French populations of Montreal. Ages ranged from 20-59 yr. Racial composition unknown</td>
<td>Nutritional data computed from 3-d diaries. The time frame for recorded diaries was not given, presumably subjects brought diaries in at the time of first interview. Discretionary Na use was checked by weighed salt shakers; again it was not clear when these shakers were distributed and whether this Na intake was reflected in the diet diaries. BP was recorded twice.</td>
<td>Significant negative correlation of SBP and DBP with calcium persisted after correction for age, weight, alcohol, polyunsaturated fatty acids, and inorganic nutrients. Analysis by tertiles of Na showed no effect. Both SBP and DBP decreased with increasing tertiles of calcium. SBP rose with increasing Na intake in only the lowest calcium tercile. Alcohol potentiated association of SBP and calcium and enhanced effect of Na when calcium intake is low.</td>
<td>Subjects’ selection was not described; therefore, the potential for self-selection bias cannot be discounted. Additional confounder is the timing of the diet diaries and use of discretionary salt shakers supplied for the study participants. BMI or any other reflection of body composition were not computed. Since age, weight and combinations of Na, calcium and alcohol contribute &gt; 30% of variance in BP, nutritional impact of Na, alcohol and calcium should probably be considered conjointly in epidemiological studies.</td>
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<tr>
<td>Khaw and Barrett-Connor, 1988</td>
<td>Cross-sectional CA, United States</td>
<td>A total of 1302 white (584 male, 718 female) subjects, ranging in age from 30-79 yr from a geographically-defined community in CA participated in this study. The subjects in this report represent 30% of a larger cohort from this community who were involved in a survey of heart disease risk factors. This subsample included 15% of the larger cohort plus all subjects identified as hyperlipidemic.</td>
<td>24-hr dietary recall for Na, K, alcohol, and nutrients. Portion sizes estimated with use of food models. Additional salt use estimated from standardized estimate of Na use in recipes incorporated in the diet database used for analysis of recall data.</td>
<td>In both sexes, the age adjusted SBP and DBP was positively correlated with Na/K ratio and negatively with K. There was a significant correlation between age-adjusted BP and Na intake in male only. There was a significant age gradient in Na for the BP and Na/K relationship, indicating increasing sensitivity with increasing age. If relationship is causal, a 10% reduction of calcium to 20 mmol/d in Na (0.6-1.2g of salt) or a 10 to 20 mmol increase in K would be associated with a 2 to 4 mmHg reduction in BP. Adjustments for calcium, alcohol, fiber, saturated fat and calories did not alter relationship of BP with dietary Na/K ratio.</td>
<td>Half of this study sample had hyperlipidemia. There was no inclusion of blood lipid parameters in the data. Questionable reliability 24-hr recall data.</td>
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<tr>
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<td>Krishna et al., 1989</td>
<td>Metabolic study with randomized crossover design PA, United States</td>
<td>Subjects were 10 healthy, normotensive white subjects. Exclusion criteria were BP &gt; 140/90 mmHg, current antihypertensive medication, and body weight &gt; 10% over ideal body weight.</td>
<td>Subjects maintained on a defined diet at home (129–200 mmol Na/d and 60–90 mmol K/d) for 6 d prior to admission. 24-hr urine samples were collected on the 6th d. After admission, fasting blood samples were collected and BP recorded. For the following 9 d subjects maintained on a controlled diet of 0.5–0.7 g/d protein, 30–35 kcal/d, 10 mmol/d K, 400 mg/d Ca, and 500 mg/d Phosphorus. Na content of the diets was held constant with the 5–8 baseline diets (120–200 mmol/d). Subjects were randomly assigned to 1 of 2 trials conducted 4 to 6 wk apart in which they blindly received baseline Na intake plus either placebo or 90 mmol K/d along with the diet defined above for 9 d. On d 10 subjects underwent saline infusion studies involving measurement of urine volume/hr. In addition, BP, Na excretion, creatinine clearance, plasma renin activity, plasma aldosterone, epinephrine, norepinephrine, urinary dopamine, and norepinephrine were measured before, during, and 2 hr after infusion.</td>
<td>Plasma Na and Cl were unchanged in the low K condition. On low K diet, Na excretion decreased from 144 to 100 mmol/d, SBP increased from 119 to 125 mmol/d and DBP from 77 to 81 mm. In the infusion studies plasma aldosterone levels were suppressed after low K, but there were no changes in plasma renin activity or on arginine vasopressin or catecholamine levels. MAP after short saline load increased on low K but not on high K diet.</td>
<td>Subjects maintained on 400 mg/d Ca which is ~1/2 the RDA. There was no mention of the potential for impact of this low Ca intake on dependent measures. Small number of subjects. Subject selection process not detailed. Potential for self-selection bias was not addressed. There was no documentation of subjects' normal dietary electrolyte intake. No description of changes in diets during periods between trials.</td>
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<tr>
<td>Reference</td>
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<td>Kurtz et al., 1987</td>
<td>Metabolic study CA, United States</td>
<td>Out of 7 recruited subjects, 5 hypertensive ( \sigma ) age 53-65 completed the protocol. All of the subjects had a history of hypertension for at least 3 yr confirmed on 3 different occasions with BP readings. None of the subjects had history of renal, cardiac, or hepatic disease.</td>
<td>All medications stopped for 4 wk before the start of the study. Subjects maintained on a defined diet that contained (+10) mmol/kg/d Na and assigned to either placebo (40 capsules/d dextrose) or challenged with (240) mmol Na/d administered orally as chloride or citrate. Randomized challenges were preceded by a 7-d placebo period and were generally 7 d long. BP taken every 4 hr with 5 readings taken/4 hr. Spontaneous urine were collected and fasting blood samples collected in the morning after each challenge and placebo period.</td>
<td>NaCl induced increases of 16 and 8 mmHg in SBP and DBP respectively. No change with citrate, which abolished the increase if given after the chloride. Both salts induced Na retention and weight gain and suppressed plasma renin activity and aldosterone. Only the chloride salt increased plasma volume and calcium excretion.</td>
<td>Well-controlled but small preliminary study suggesting that changes in plasma volume may be important in salt sensitivity. No body composition data supplied No documentation of subjects’ normal dietary patterns</td>
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<tr>
<td>Lawton et al., 1990</td>
<td>Metabolic trial IA, United States</td>
<td>Subjects were 11 borderline hypertensive (BHT), mean age 24.8 yr ( \sigma ), 10 normotensive ( \sigma ) (mean age 23.5 yr). BHT defined as intermittent DBP ( &lt;90) mmHg, normotensive defined as SBP ( &lt;140) mmHg and DBP ( &lt;85) mmHg. All subjects were otherwise healthy.</td>
<td>While on a high Na (440 mEq/d) diet, subjects randomly assigned to both low K (30 mEq/d) and high K (100 mEq/d) conditions. 3-4 wk of ad libium diet between 6-4 trial periods. Test of renal function and circulation were performed on d 6 of each trial period.</td>
<td>Muscle sympathetic nerve activity decreased in the BHT group during low K compared with high K diets and did not change in the normal group. Low K raised SBP 6-7% in both BHT and normals and MAP in BHT only. Lower hematocrit and plasma renin, increased weight, Na excretion and urinary calcium were all compatible with K-dependent volume expansion in both groups.</td>
<td>Subject selection procedure not clearly described; possibility of self-selection bias must be considered. Young subjects who were not blinded were not required to document actual food intake during the trial period. Composition of neither baseline diet nor 3-4 wk ad libium diets between trials were documented Small number of subjects High calorie (~3000 kcal/d), high fat (~40% fat), low carbohydrate (~45%) experimental diets were used. Volume expansion on low K diet may be a factor in increased BP.</td>
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<tr>
<td>Luft et al., 1990</td>
<td>Randomized placebo-controlled crossover trial MI, United States</td>
<td>Subjects were 10 ( \sigma ) and 10 ( \sigma ), 1/2 of each group normotensive (NT), 1/2 hypertensive (HT) 10 subjects (5 NT, 5 HT) were white, 10 (5NT, 5HT) were black. Mean age of all subjects was 36 ( \pm ) 9 yr. Normal BP defined at BP ( &lt;140/90) mmHg; HT defined as medication-free BP ( &gt;140/90).</td>
<td>Protocol had 2 11-d trials. Subjects assigned to experimental diets that were eaten at the clinic. Subjects were given 4-d equilibration period to achieve balance before challenge assignment. The 1-mo challenges consisted of addition of Na as either chloride or bicarbonate to a basal diet offering 60 mmol Na/d. Both regimens increased total Na to 130 mmol/d. Subjects and personnel were blinded to the treatments. All urine was collected during the trial periods.</td>
<td>Neither salt affected BP in normotensives. Bicarbonate decreased SBP but not DBP in hypertensives. Only the chloride induced hypercalcemia.</td>
<td>No baseline data on normal dietary patterns Subject recruitment was not detailed. The experimental diet was relatively low in calcium (~600 mg/d). Effect of bicarbonate small Effects of Na on BP may not be demonstrable at these modest levels of intake.</td>
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### APPENDIX TABLE 5. STUDIES ON THE INTERACTION OF SODIUM WITH OTHER DIETARY IONS

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<tbody>
<tr>
<td>Saito et al., 1989</td>
<td>Randomized placebo-controlled double-blind study Japan</td>
<td>Subjects were 27 borderline hypertensives (BHT-21, 6) with an age range of 30-67 yr. BHT was defined as unmedicated intermittent BP reading of 160/95.</td>
<td>Subjects initially stabilized on diets containing 150 mEq/d Na then 7 d of salt restriction (50 mEq/d), finally, all subjects placed on high salt (300 mEq/d) low calcium (250 mg/d) diet for 7 d during which 13 received placebo, 14 received 2160 mg calcium supplement/d. BP taken on d 7 of each period. Blood collected at same time.</td>
<td>No change in BP after change from normal to low Na diet. MAP increase from end of low salt to end of high salt period was significantly smaller in high calcium group than in placebo (+2.9 and 8.1 mmHg respectively). Na excretion was greater in the calcium group during high salt period. No difference between the groups in Na uptake by erythrocytes, but magnesium was slightly higher in cells from calcium group.</td>
<td>No description of baseline diets or subject recruitment. Suggests effects on Na retention may be related to role of calcium in BF response to Na load.</td>
</tr>
<tr>
<td>Shore et al., 1988</td>
<td>Randomized crossover study England</td>
<td>6 with essential hypertension No other description given All medications were withdrawn for 2 wk prior to the study</td>
<td>After 5 d on 10 mmol Na/d diet subjects assigned to 5 d with either 120 mmol/d of NaCl or 122 mmol/d of Na phosphate with 5 d on the trial diet between challenge periods. 24-hr urines collected for each d of challenge period. Blood collected on the final d of each period.</td>
<td>Supine MAP unchanged by Na phosphate but significantly (p&lt;0.01) increased by 6.9 mmHg after NaCl. Comparable differences observed in standing MAP.</td>
<td>Neither sex nor any other demographic characteristics of subjects reported. Small preliminary study that confirms observations of Kurtz et al. (1987) but at lower more nearly normal Na intake.</td>
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</tbody>
</table>

**Abbreviations:** 
- BMI: Body mass index 
- BP: Blood pressure 
- DBP: Diastolic blood pressure 
- K: Potassium 
- MAP: Mean arterial pressure 
- Na: Sodium 
- SBP: Systolic blood pressure