

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



The Importance of Population-Wide Sodium Reduction as a Means to Prevent Cardiovascular Disease and Stroke: A Call to Action From the American Heart Association

Lawrence J. Appel, Edward D. Frohlich, John E. Hall, Thomas A. Pearson, Ralph L. Sacco, Douglas R. Seals, Frank M. Sacks, Sidney C. Smith, Jr, Dorothea K. Vafiadis and Linda V. Van Horn

Circulation published online Jan 13, 2011;

DOI: 10.1161/CIR.0b013e31820d0793

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2011 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

The Importance of Population-Wide Sodium Reduction as a Means to Prevent Cardiovascular Disease and Stroke

A Call to Action From the American Heart Association

Lawrence J. Appel, MD, MPH, FAHA; Edward D. Frohlich, MD, FAHA;
John E. Hall, PhD, FAHA; Thomas A. Pearson, MD, PhD, FAHA; Ralph L. Sacco, MD, FAHA;
Douglas R. Seals, PhD; Frank M. Sacks, MD, FAHA; Sidney C. Smith, Jr, MD, FAHA;
Dorothea K. Vafiadis, MS; Linda V. Van Horn, PhD, RD, FAHA

Blood pressure (BP)-related diseases, specifically, stroke, coronary heart disease, heart failure, and kidney disease, are leading causes of morbidity and mortality in the United States and throughout the world. In the United States, coronary heart disease and stroke are the leading causes of mortality, whereas heart failure is the leading cause of hospitalizations.¹ Concurrently, the prevalence of chronic kidney disease remains high and is escalating.^{2,3} The direct and indirect costs of these conditions are staggering, over \$400 billion just for cardiovascular disease (CVD) in 2009.^{1,4} The human consequences are likewise enormous.

The relation between BP and adverse health outcomes is direct and progressive with no evidence of a threshold, that is, the risk of CVD, stroke, and end-stage kidney disease increases progressively throughout the range of usual BP starting at a level of $\approx 115/75$ mm Hg.⁵⁻⁷ Overall, elevated BP is the second leading modifiable cause of death, accounting for an estimated 395 000 preventable deaths in the United States in 2005.⁸ Worldwide, elevated BP accounts for 54% of stroke and 47% of coronary heart disease events; importantly, about half of these events occur in persons without hypertension.⁹

The 2020 goal of the American Heart Association (AHA) is to improve the cardiovascular health of all Americans by 20% while continuing to reduce deaths from CVD and stroke by 20%.⁴ Two of the key metrics for ideal cardiovascular health are a BP of $<120/80$ mm Hg and sodium consumption of <1500 mg/d. The purpose of this advisory is 2-fold: first is to highlight the impressive body of evidence that links sodium intake with elevated BP and other adverse outcomes, and second, to serve as a call to action on behalf of the AHA

for individuals, healthcare providers, professional organizations, governments, and industry to address this major public health issue. See Table for key points.

The Evidence

Excess intake of salt (sodium chloride) has a major role in the pathogenesis of elevated BP. Excess sodium intake also has BP-independent effects, promoting left ventricular hypertrophy as well as fibrosis in the heart, kidneys, and arteries.¹⁰ Evidence on the adverse health effects of excess sodium intake includes results from animal studies, epidemiological studies, clinical trials, and meta-analyses of trials.¹¹ To date, >50 randomized trials have tested the effects of sodium reduction on BP in adults. A meta-analysis¹² of these trials documented that a median reduction in urinary sodium of ≈ 1800 mg/d lowered systolic/diastolic BP by 2.0/1.0 mm Hg in nonhypertensive individuals and by 5.0/2.7 mm Hg in hypertensive individuals. In a subsequent meta-analysis of trials in children, a reduced sodium intake lowered mean systolic/diastolic BP by 1.2/1.3 mm Hg in children and adolescents and lowered systolic BP by 2.5 mm Hg in infants.¹³ The benefits of sodium reduction in persons with poorly controlled BP are striking. In a recent trial of patients with resistant hypertension, reducing sodium intake by 4600 mg/d lowered systolic/diastolic BP by 22.7/9.1 mm Hg.¹⁴

Some of the most persuasive evidence on the effects of sodium on BP comes from rigorously controlled, dose-response trials.¹⁵⁻¹⁷ Each of these trials tested at least 3 sodium levels, and each documented statistically significant, direct, progressive, dose-response relations. The lowest level of sodium intake in

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on January 7, 2011. A copy of the statement is available at <http://www.americanheart.org/presenter.jhtml?identifier=3003999> by selecting either the "topic list" link or the "chronological list" link (No. KB-0187). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Appel LJ, Frohlich ED, Hall JE, Pearson TA, Sacco RL, Seals DR, Sacks FM, Smith SC Jr, Vafiadis DK, Van Horn LV. The importance of population-wide sodium reduction as a means to prevent cardiovascular disease and stroke: a call to action from the American Heart Association. *Circulation*. 2011;123:●●●-●●●.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit <http://www.americanheart.org/presenter.jhtml?identifier=3023366>.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <http://www.americanheart.org/presenter.jhtml?identifier=4431>. A link to the "Permission Request Form" appears on the right side of the page.

(*Circulation*. 2011;123:00-00.)

© 2011 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIR.0b013e31820d0793

Table. Key Points

- Elevated blood pressure (BP) is a leading, preventable cause of mortality and morbidity in the United States and throughout the world.
- The relation of BP and adverse health outcomes is direct, progressive, consistent, continuous, independent, and etiologically relevant throughout the range of usual BP starting at a level of approximately 115/75 mm Hg.
- A diverse body of evidence has implicated excess sodium intake in the pathogenesis of elevated BP.
- Independent of its effects on BP, excess sodium intake adversely affects the heart, kidneys, and blood vessels.
- Current intake of sodium greatly exceeds 1500 mg/d, the upper level of intake recommended by the American Heart Association and the 2010 Dietary Guidelines Scientific Advisory Committee.
- The potential public health benefits of sodium reduction are enormous and extend to virtually all Americans.

each trial was ≈ 1500 mg/d, the level currently recommended by the AHA.⁴ Importantly, the BP response to sodium reduction, while direct and progressive, was nonlinear. Specifically, decreasing sodium intake by ≈ 900 mg/d caused a greater reduction in BP when the starting sodium intake was ≈ 2300 mg/d than when it was ≈ 3500 mg/d. The DASH (Dietary Approaches to Stop Hypertension)-Sodium trial, the largest of the 3 major dose-response trials,^{18,19} also documented that reduced sodium intake significantly lowered BP in each of the major subgroups studied (ie, nonhypertensive individuals, hypertensive individuals, men, women, African Americans, non-African Americans). The benefits of sodium reduction in non-hypertensive individuals were recently corroborated in the GenSalt feeding study, which documented that lowering sodium intake to ~ 1500 mg/d reduced BP in $\sim 2,000$ Asian adults with mean systolic/diastolic BP $< 120/80$ mm Hg.²⁰

Sodium reduction also blunts the age-related rise in BP. Because BP rises with age, about 90% of adults eventually become hypertensive.²¹ The DASH-Sodium trial demonstrated that sodium reduction to a level of ≈ 1500 mg/d lowers BP more in older adults than younger adults.¹⁹ Systolic BP decreased by 8.1 mm Hg in those aged 55 to 76 years, compared with 4.8 mm Hg for adults aged 23 to 41 years. In persons without hypertension, BP decreased by 7.0 mm Hg in those > 45 years of age compared with 3.7 mm Hg in those ≤ 45 years of age. These results demonstrated that sodium reduction can lessen the rise in BP with age²² and also confirmed the well-documented observation of a reduced age-related rise in BP in isolated populations with low sodium intake.²³ Consistent with this evidence, a major trial in the United States documented that a reduced sodium intake can prevent hypertension by $\approx 20\%$.²⁴

Evidence supporting a direct relation of sodium intake and CVD is also accumulating. In a recent meta-analysis of observational studies, a higher sodium intake was associated with an increased risk of stroke and likely CVD.²⁵ To date, 3 trials conducted in general populations have reported the effects of reduced sodium interventions on CVD outcomes. Two of these trials tested lifestyle interventions that focused on reducing sodium intake, and 1 trial tested the effects of a reduced sodium/high potassium salt. In each instance, there was a 21% to 41% reduction in clinical CVD events in those who received a reduced sodium intervention (significant reduction in 2 trials^{26,27}

and a nonsignificant trend in the third²⁸). Hence, direct evidence from trials, albeit limited, is consistent with indirect evidence on the health benefits of sodium reduction.

Independent of its effects on BP, an increased sodium intake has other adverse effects. These include subclinical CVD (ie, left ventricular hypertrophy, ventricular fibrosis, diastolic dysfunction), kidney damage, gastric cancer, and disordered mineral metabolism (ie, increased urinary calcium excretion, potentially leading to osteoporosis).¹¹ It is well-established that sodium loading suppresses the systemic renin-angiotensin-aldosterone system by inhibiting renin release from the renal juxtaglomerular apparatus. Less well appreciated are findings that sodium loading increases oxidative stress and endothelial dysfunction and promotes mitogenic responses (fibrosis in heart, kidneys, and arteries) resulting in cardiac and vascular remodeling.^{10,29–33}

With regard to arterial dysfunction, higher sodium intake is associated with greater increases in large elastic artery stiffness with aging,^{34,35} and reducing sodium intake from moderate levels by $\approx 50\%$ to less than ≈ 1500 mg/d reduces large elastic artery stiffness in otherwise healthy middle-aged and older adults with elevated systolic BP.^{36,37} An acute increase in sodium intake has been shown to impair vascular endothelial function in young adults with normal BP.³⁸ Among middle-aged and older adults with elevated systolic BP, lower sodium intake is associated with enhanced vascular endothelial function, independent of BP or other risk factors.³⁹ A low sodium diet of ≈ 1200 mg/d improves endothelial function in overweight and obese adults with normal BP.⁴⁰ These findings have important clinical implications given that stiffening of the large elastic arteries, independent of BP, is a major independent risk factor for CVD and incident cardiovascular events,^{41,42} whereas vascular endothelial dysfunction is associated with increased cardiovascular events and CVD mortality.^{43,44}

Sodium-induced increases in BP may directly induce renal injury or accelerate kidney disease caused by other conditions such as diabetes mellitus or glomerulonephritis. However, excess sodium intake also has deleterious effects on the kidneys independent of increased BP. Studies in experimental animals and in human beings have shown, for example, that high sodium intake can cause glomerular hyperfiltration and increased albumin excretion, renal oxidative stress, and renal fibrosis independent of BP.^{45–47} A direct association between sodium intake and urinary albumin excretion, independent of BP, has been observed in epidemiological studies.⁴⁷ In a trial of whites, blacks, and Asians with elevated BP, decreasing sodium intake from an average of ≈ 3800 mg/d to ≈ 2500 mg/d significantly reduced 24-hour urinary albumin excretion, an early marker of renal injury.⁴⁸ A retrospective analysis of patients with chronic kidney disease, with an average observation period of 3 years, showed that in patients with a sodium intake > 4600 mg/d, the rate of decline in creatinine clearance and increase in proteinuria were greater compared with patients with a sodium intake < 2300 mg/d, despite similar BP control.⁴⁹ Excess sodium intake also attenuates the beneficial effects of many antihypertensive drugs, especially the antiproteinuric effect of blocking the renin-angiotensin system.⁵⁰ Thus, there is considerable evidence linking increased sodium intake with kidney injury not only through

increased BP but also by effects that appear to be at least partly independent of BP.⁵¹

Some sodium intake is required. An Institute of Medicine Committee set 1500 mg of sodium per day as an adequate intake level, primarily to assure nutrient adequacy.⁵² Based on the DASH-Sodium trial, it is apparent that Western type diets can provide this level of sodium intake and that such a diet also can provide adequate levels of other nutrients.⁵³ In 2005, the US Dietary Guidelines for Americans recommended a sodium intake of <2300 mg/d for the general adult population and stated that hypertensive individuals, blacks, and middle-aged and older adults would benefit from reducing their sodium intake even further to 1500 mg/d.⁵³ Because these latter groups comprise at least 50% of adults and perhaps as high as 70%,⁵⁴ and because ≈90% of US adults will develop hypertension over their lifetime, the goal should be 1500 mg/d, as recommended by the scientific advisory of the 2010 Dietary Guidelines Committee.⁵⁵ The health benefits apply to Americans in all groups, and there is no compelling evidence to exempt special populations from this public health recommendation. Although clinical research has identified groups that experience greater or lesser BP effects from sodium reduction, there is no practical clinical test to assess sodium sensitivity in individuals. Hence, it is not feasible, from a public health perspective, to classify individuals as sodium-sensitive or not.

A Call to Action

The projected benefits of sodium reduction are substantial. Several studies have estimated the societal benefits of population-wide sodium reduction.^{56–58} In the most recent and comprehensive set of projections, Bibbins-Domingo and colleagues⁵⁸ quantified the effects of 400 mg/d to 1200 mg/d reductions in sodium intake on a variety of relevant outcomes. A national effort that reduces sodium intake by 1200 mg/d should result in 60 000 to 120 000 fewer coronary heart disease events, 32 000 to 66 000 fewer strokes, 54 000 to 99 000 fewer myocardial infarctions, and 44 000 to 92 000 fewer deaths, and save 194 000 to 392 000 quality-adjusted life-years and \$10 to \$24 billion in healthcare costs annually. Even if average sodium intake is reduced by just 400 mg/d, the benefits would still be substantial and warrant implementation.

Accomplishing population-wide sodium reduction is similar to achieving other lifestyle modifications, in that a substantial public health approach will be required to facilitate environmental changes that support changes in individual behavior. Indeed, the need for an effective public health approach is even greater for sodium reduction than other lifestyle modifications. For example, in contrast to cigarette smoking, where usage is evident and deliberate by the consumer, the sodium content of our diets is not readily apparent.

More than 75% of consumed sodium comes from processed foods.⁵⁹ Even those who read labels are often left without realistic alternatives to high-sodium foods, and those who eat out, a behavior that has increased more than 200% from 1977 to 1995, are subjected to excessive sodium intakes from routinely served, processed foods.⁵⁵ Some food items are extremely high in sodium. However, from a public health perspective, the problem of excess sodium intake largely reflects the cumulative

intake of common foods that are only moderately high in sodium. Hence, any meaningful strategy to reduce sodium intake population-wide must involve the efforts of food manufacturers, food processors, and restaurant industries, a strategy that is being successfully implemented in other countries. For example, the United Kingdom has a vigorous salt reduction campaign, which has resulted in an estimated population-wide reduction in sodium intake of ≈10%.⁶⁰ Ongoing surveillance is necessary to evaluate the progress of such strategies.

Some scientists still question the evidence supporting population-wide sodium reduction. Common arguments include the absence of a major trial with hard clinical outcomes. It is well-known, however, that such trials are not feasible because of logistic, financial, and often ethical considerations. In fact, there is no trial of weight reduction or increased physical activity on hard clinical outcomes, and only 1 definitive trial of smoking cessation therapy on lung cancer.⁶¹ It also has been argued that sodium reduction might be harmful.⁶² However, the evidence for harm is unpersuasive, based largely on inferences from cohort studies with major methodological limitations, particularly, incomplete assessment of sodium intake and the potential for reverse causality.⁶³

In 2010, the Institute of Medicine issued a report that provides a roadmap for lowering Americans' intake of sodium.⁶⁴ It was noted that for >40 years, efforts to reduce sodium intake of the US population have been unsuccessful. This absence of tangible progress reflects the lack of a substantive, multidimensional, environmentally focused strategic plan with measurable outcomes, joint-ownership, and accountability among the many stakeholders. Specifically, given the ubiquity of sodium in the food supply, the prior focus on encouraging individuals to select reduced-sodium products has been insufficient to meaningfully reduce sodium intake and achieve levels consistent with the Dietary Guidelines for Americans. Such efforts must be accompanied by an overall reduction of the level of sodium in the food supply. The Institute of Medicine made a series of recommendations, many of which involved regulatory actions (eg, setting mandatory national standards for the sodium content of foods). Such a strategy extends the voluntary approaches implemented in New York City.⁶⁵

Conclusion

A compelling and still increasing body of evidence supports the imperative for population-wide sodium reduction as an integral component of public health efforts to prevent CVD, stroke, and kidney disease. The potential public health benefits are enormous and extend to virtually all Americans. The AHA is committed to improving cardiovascular health of the whole population, as recently articulated in its 2020 strategic goals.⁴ Successful sodium reduction requires action and partnership at all levels—individuals, healthcare providers, professional organizations, public health agencies, governments, and industry. The AHA urges a renewed and intensive focus on this critically important public health issue and looks forward to partnering with public and private organizations to achieve our shared goal of population-wide reduction in sodium intake.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Lawrence J. Appel	Johns Hopkins Medical Institutions	None	None	None	None	None	None	None
Edward D. Frohlich	Ochsner Clinic Foundation	None	None	None	None	None	None	None
John E. Hall	University of Mississippi Medical Center	NIH/NHLBI*	None	None	None	None	None	Editor-in-Chief, <i>Hypertension, Journal of the American Heart Association*</i>
Thomas A. Pearson	University of Rochester	None	None	None	None	None	None	None
Ralph L. Sacco	University of Miami School of Medicine	None	None	None	None	None	None	None
Frank M. Sacks	Harvard University/Brigham and Women's Hospital	None	None	None	None	None	None	None
Douglas R. Seals	University of Colorado	None	None	None	None	None	None	None
Sidney C. Smith, Jr	University of North Carolina at Chapel Hill	None	None	None	None	None	None	None
Dorothea K. Vafiadis	American Heart Association	None	None	None	None	None	None	None
Linda V. Van Horn	Northwestern University	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Significant.

References

- Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smolter S, Wong N, Wylie-Rosett J, Hong Y; for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2009;119:480–486.
- Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298:2038–2047.
- United States Renal Data System. *USRDS Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD: 2008.
- Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's Strategic Impact Goal Through 2020 and Beyond. *Circulation*. 2010;121:586–613.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
- Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J. Blood pressure and end-stage renal disease in men. *N Engl J Med*. 1996;334:13–18.
- Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, Ezzati M. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med*. 2009;6:e1000058.
- Lawes CM, Vander Hoorn S, Rodgers A, International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. *Lancet*. 2008;371:1513–1518.
- Frohlich ED. The salt conundrum: a hypothesis. *Hypertension*. 2007;50:161–166.
- He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens*. 2009;23:363–384.
- He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. *J Hum Hypertens*. 2002;16:761–770.

13. He FJ, MacGregor GA. Importance of salt in determining blood pressure in children: meta-analysis of controlled trials. *Hypertension*. 2006;48:861–869.
14. Pimenta E, Gaddam KK, Oparil S, Aban I, Husain S, Dell'Italia LJ, Calhoun DA. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. *Hypertension*. 2009;54:475–481.
15. Johnson AG, Nguyen TV, Davis D. Blood pressure is linked to salt intake and modulated by the angiotensinogen gene in normotensive and hypertensive elderly subjects. *J Hypertens*. 2001;19:1053–1060.
16. MacGregor GA, Markandu ND, Sagnella GA, Singer DR, Cappuccio FP. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. *Lancet*. 1989;2:1244–1247.
17. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER III, Simons-Morton DG, Karanja N, Lin PH, DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med*. 2001;344:3–10.
18. Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG, Conlin PR, Svetkey LP, Erlinger TP, Moore TJ, Karanja N, DASH-Sodium Trial Collaborative Research Group. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med*. 2001;135:1019–1028.
19. Bray GA, Vollmer WM, Sacks FM, Obarzanek E, Svetkey LP, Appel LJ, DASH Collaborative Research Group. A further subgroup analysis of the effects of the DASH diet and three dietary sodium levels on blood pressure: results of the DASH-Sodium Trial. *Am J Cardiol*. 2004;94:222–227.
20. He J, Gu D, Chen J, Jaquish CE, Rao DC, Hixson JE, Chen JC, Duan X, Huang JF, Chen CS, Kelly TN, Gazzano LA, Whelton PK, GenSalt Collaborative Research Group. Gender difference in blood pressure responses to dietary sodium intervention in the GenSalt study. *J Hypertens*. 2009;27:48–54.
21. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA*. 2002;287:1003–1010.
22. Sacks FM, Campos H. Dietary therapy in hypertension. *N Engl J Med*. 2010;362:2102–2112.
23. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. *BMJ*. 1988;297:319–328.
24. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. *Arch Intern Med*. 1997;157:657–667.
25. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ*. 2009;339:b4567.
26. Chang HY, Hu YW, Yue CS, Wen YW, Yeh WT, Hsu LS, Tsai SY, Pan WH. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. *Am J Clin Nutr*. 2006;83:1289–1296.
27. Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ*. 2007;334:885–888.
28. Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). *Arch Intern Med*. 2001;161:685–693.
29. Safar ME, Thuilliez C, Richard V, Benetos A. Pressure-independent contribution of sodium to large artery structure and function in hypertension. *Cardiovasc Res*. 2000;46:269–276.
30. Frohlich ED, Varagic J. The role of sodium in hypertension is more complex than simply elevating arterial pressure. *Nat Clin Pract Cardiovasc Med*. 2004;1:24–30.
31. Varagic J, Frohlich ED, Susic D, Ahn J, Matavelli L, Lopez B, Diez J. AT1 receptor antagonism attenuates target organ effects of salt excess in SHR without affecting pressure. *Am J Physiol Heart Circ Physiol*. 2008;294:H853–H858.
32. Diez J, Frohlich ED. A translational approach to hypertensive heart disease. *Hypertension*. 2010;55:1–8.
33. Lai EY, Onozato ML, Solis G, Aslam S, Welch WJ, Wilcox CS. Myogenic responses of mouse isolated perfused renal afferent arterioles: effects of salt intake and reduced renal mass. *Hypertension*. 2010;55:983–989.
34. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation*. 1985;71:202–210.
35. Avolio AP, Clyde KM, Beard TC, Cooke HM, Ho KK, O'Rourke MF. Improved arterial distensibility in normotensive subjects on a low salt diet. *Arteriosclerosis*. 1986;6:166–169.
36. Seals DR, Tanaka H, Clevenger CM, Monahan KD, Reiling MJ, Hiatt WR, Davy KP, DeSouza CA. Blood pressure reductions with exercise and sodium restriction in postmenopausal women with elevated systolic pressure: role of arterial stiffness. *J Am Coll Cardiol*. 2001;38:506–513.
37. Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension*. 2004;44:35–41.
38. Tzemos N, Lim PO, Wong S, Struthers AD, MacDonald TM. Adverse cardiovascular effects of acute salt loading in young normotensive individuals. *Hypertension*. 2008;51:1525–1530.
39. Jablonski KL, Gates PE, Pierce GL, Seals DR. Low dietary sodium intake is associated with enhanced vascular endothelial function in middle-aged and older adults with elevated systolic blood pressure. *Thromb Haemostasis*. 2009;3:347–356.
40. Dickinson KM, Keogh JB, Clifton PM. Effects of a low-salt diet on flow-mediated dilatation in humans. *Am J Clin Nutr*. 2009;89:485–490.
41. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkatasubramanian L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A, Health ABC Study. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation*. 2005;111:3384–3390.
42. Mitchell GF, Wang N, Palmisano JN, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS. Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. *Circulation*. 2010;122:1379–1386.
43. Halcox JP, Schenke WH, Zalos G, Minicemeyer R, Prasad A, Waclawiw MA, Nour KR, Quyyumi AA. Prognostic value of coronary vascular endothelial dysfunction. *Circulation*. 2002;106:653–658.
44. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol*. 2003;42:1149–1160.
45. Yu HC, Burrell LM, Black MJ, Wu LL, Dilley RJ, Cooper ME, Johnston CI. Salt induces myocardial and renal fibrosis in normotensive and hypertensive rats. *Circulation*. 1998;98:2621–2628.
46. Sanders PW. Salt intake, endothelial cell signaling, and progression of kidney disease. *Hypertension*. 2004;43:142–146.
47. du Caillat G, Ribstein J, Mimran A. Dietary sodium and target organ damage in essential hypertension. *Am J Hypertens*. 2002;15:222–229.
48. He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, MacGregor GA. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. *Hypertension*. 2009;54:482–488.
49. Cianciaruso B, Bellizzi V, Minutolo R, Tavera A, Capuano A, Conte G, De Nicola L. Salt intake and renal outcome in patients with progressive renal disease. *Miner Electrolyte Metab*. 1998;24:296–301.
50. He FJ, Jenner KH, Macgregor GA. WASH-world action on salt and health. *Kidney Int*. 2010;78:745–753.
51. Jones-Burton C, Mishra SI, Fink JC, Brown J, Gossa W, Bakris GL, Weir MR. An in-depth review of the evidence linking dietary salt intake and progression of chronic kidney disease. *Am J Nephrol*. 2006;26:268–275.
52. Institute of Medicine. *Dietary Reference Intakes: Water, Potassium, Sodium Chloride, and Sulfate*. 1 ed. Washington, DC: National Academy Press; 2004.
53. US Department of Health and Human Services and US Department of Agriculture. *Dietary Guidelines for Americans*. 6th ed. Washington DC: US Government Printing Office; January 2005.
54. Centers for Disease Control and Prevention (CDC). Application of lower sodium intake recommendations to adults—United States, 1999–2006. *MMWR Morb Mortal Wkly Rep*. 2009;58:281–283.

55. Dietary Guidelines Advisory Committee. *2010 Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans*. Washington, DC: US Department of Agriculture, Agricultural Research Service; 2010.
56. Asaria P, Chisholm D, Mathers C, Ezzati M, Beaglehole R. Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use. *Lancet*. 2007;370:2044–2053.
57. Palar K, Sturm R. Potential societal savings from reduced sodium consumption in the U.S. adult population. *Am J Health Promot*. 2009;24:49–57.
58. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med*. 2010;362:590–599.
59. Mattes RD, Donnelly D. Relative contributions of dietary sodium sources. *J Am Coll Nutr*. 1991;10:383–393.
60. Food Standards Agency. Dietary Sodium Levels Surveys. <http://www.food.gov.uk/science/dietarysurveys/urinary>. Accessed December 19, 2010.
61. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005;142:233–239.
62. Alderman MH. Reducing dietary sodium: the case for caution. *JAMA*. 2010;303:448–449.
63. Cook NR, Sacks F, MacGregor G. Public policy and dietary sodium restriction. *JAMA*. 2010;303:1917; author reply 1917–1918.
64. Institute of Medicine. *Strategies to Reduce Sodium Intake in the United States*. Washington, DC: National Academy Press; 2010.
65. City of New York. Cutting Salt, Improving Health. <http://www.nyc.gov/html/doh/html/cardio/cardio-salt-initiative.shtml>. Accessed December 19, 2010.

KEY WORDS: AHA Scientific Statements ■ sodium ■ salt ■ blood pressure ■ hypertension ■ cardiovascular disease ■ stroke ■ kidney disease



Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION