

REVIEW ARTICLE

MEDICAL PROGRESS

Salt in Health and Disease — A Delicate Balance

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THE FACT THAT SALT (SODIUM CHLORIDE) IS ESSENTIAL FOR LIFE HAS been recognized for millennia. Historically, the exchange value of salt played an important role in establishing trade routes, securing alliances, and provoking revolutions. Homer referred to salt as a divine substance, and Plato described it as especially dear to the gods. Salt has been associated with sexual potency, fertility, and immortality.

In sodium-deficient states, salt consumption is driven by salt appetite — an innate and motivated behavioral response that drives a human or animal to seek and ingest salt-containing foods and fluids.¹ However, under usual circumstances, the ambient salt diet is in excess of physiological need, and in humans, it has been difficult to distinguish innate salt appetite and salt need from salt preference.² The hunger for salt is also influenced by taste, culture, social custom, the widespread availability of salt, and habit independent of the need for salt.³ Despite its historical value and physiological importance, high salt consumption has been recognized as detrimental to health. In this article, we provide an overview of the current understanding of the relation of salt consumption to hypertension and cardiovascular disease.

SALT CONSUMPTION AND ARTERIAL PRESSURE

A high-salt diet convincingly contributes to elevated arterial pressure in numerous animal species, including genetic and acquired models of experimental hypertension. People living in nonindustrial, unacculturated communities with low salt intake have low average blood pressures that increase little with age. Blood pressure increases when such populations adopt modern lifestyles.

Within populations, either slight but significant correlations or insignificant correlations between blood pressure and dietary salt have been observed.^{4,5} A relatively constricted range of sodium intakes — in particular, high sodium intakes — may contribute to the underestimation of the association between blood-pressure level and sodium intake within populations. Studies across populations provide more convincing evidence than within-population studies of the association of salt intake with both blood pressure and the age-related rise of blood pressure in adults.⁶⁻⁸ There is also a modest association between higher salt intake and higher blood pressure in children and adolescents.⁹ Low dietary intake of potassium may increase the effect of sodium on blood pressure, and the relationship between sodium and blood pressure becomes stronger if the urinary sodium:potassium ratio, rather than simply the sodium excretion rate, is considered.⁷

Clinical trials provide definitive evidence of a direct cause-and-effect relation-

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Table 1. Meta-Analyses of the Effect of Salt Reduction on Blood Pressure.*

Study	Persons with Hypertension					Persons with Normal Blood Pressure				
	No. of Trials	No. of Persons	Reduction in Sodium Intake	Reduction in Systolic Pressure	Reduction in Diastolic Pressure	No. of Trials	No. of Persons	Reduction in Sodium Intake	Reduction in Systolic Pressure	Reduction in Diastolic Pressure
			mmol/day	mm Hg	mm Hg			mmol/day	mm Hg	mm Hg
Midgley et al. ¹⁰	28	1131	95	3.7†	0.9	28	2374	125	1.0†	0.1
Cutler et al. ¹¹	22	1043	77	4.8†	2.5†	12	1689	76	2.3†	1.4†
Graudal et al. ¹²	58	2161	118	3.9†	1.9†	56	2581	160	1.2†	0.3
He and MacGregor ¹³	17	734	78	5.0†	2.7†	11	2220	74	2.0†	1.0†

* The numbers in the sodium intake and blood pressure columns are average reductions. An amount of 17 mmol of sodium is equivalent to 400 mg of sodium or 1.0 g of sodium chloride.

† The reduction in the blood-pressure value was significant.

ship between salt consumption and blood pressure. Although meta-analyses are potentially subject to criticism owing to variations in the inclusion and exclusion criteria of the trials and other variations among the study protocols, several meta-analyses of randomized clinical trials have consistently shown that persons with hypertension have a greater response to a reduced salt intake than do persons with normal blood pressure¹⁰⁻¹³ (Table 1). In a meta-analysis of 10 controlled trials involving a total of 966 children (median age, 13 years; range, 8 to 16), a 42% reduction in salt intake was associated with small but significant reductions of both systolic pressure (-1.17 mm Hg ; 95% confidence interval [CI], -1.78 to -0.56) and diastolic pressure (-1.29 mm Hg ; 95% CI, -1.94 to -0.65).¹⁴

Trials involving abrupt and severe salt restriction have shown significant increases in plasma renin activity, serum aldosterone, and plasma levels of noradrenaline and adrenaline, total cholesterol, and triglycerides.^{12,15} The implication is that these neural and hormonal responses may have adverse cardiovascular consequences. Studies assessing a long-term (>6 months) modest reduction of salt intake have shown only small increases in renin activity and little or no change in sympathetic tone or plasma lipid levels.

“SALT SENSITIVITY” OF BLOOD PRESSURE

Blood-pressure responses to salt are heterogeneous and are normally distributed within populations. Although salt sensitivity is a continuous,

not a binary, trait, depending on the methods used for assessment and the definition of salt sensitivity, approximately 30 to 50% of persons with hypertension and a smaller percentage of persons with normal blood pressure are thought to have salt-sensitive blood pressure.¹⁶ Phenotypes associated with salt-sensitive blood pressure include low-renin hypertension, older age, African American ethnicity, obesity, and the metabolic syndrome.^{17,18}

Blood-pressure responses to salt may be modified by other components of the diet. Low dietary intakes of potassium and calcium potentiate the salt sensitivity of blood pressure.¹⁹ Conversely, high dietary intakes of potassium and calcium attenuate the development of salt-induced hypertension in several animal models. In genetic experimental models of hypertension, blood-pressure responses to salt are modulated by the protein, carbohydrate, and fat composition of the diet. In addition, the full expression of salt-sensitive hypertension depends on the concomitant intake of sodium and chloride, rather than sodium with some other anion.²⁰ However, in usual diets, it has been estimated that more than 85% of sodium is consumed as sodium chloride.

Experimental models of hypertension provide convincing evidence of a genetic susceptibility to salt sensitivity. The most intensely studied experimental model of salt-sensitive hypertension has been the Dahl rat, developed by Lewis K. Dahl nearly 50 years ago and inbred by John Rapp. In consomic rats (in which otherwise genetically identical animals differ by one chromosome), transfer of any one of several chromosomes from

normotensive Brown Norway rats into Dahl salt-sensitive rats attenuates or abolishes salt-induced hypertension and proteinuria.²¹ Knockout mice lacking genes for γ melanocyte-stimulating hormone, atrial natriuretic peptide and its receptor, the prostaglandin EP₂ receptor, or the bradykinin receptor all have salt-sensitive hypertension. The heritability of salt-induced increases in blood pressure may also be unrelated to genetic polymorphisms. In the normotensive Sprague-Dawley rat, either a high or a low salt intake during pregnancy is associated with a reduced number of renal glomeruli and proteinuria in the offspring,²² and animals with a reduced number of nephrons become progressively more salt-sensitive with age in terms of blood pressure.

Limited clinical data are available concerning the heritability of salt sensitivity. As compared with whites with normal blood pressure, blacks with normal blood pressure have slower sodium excretion after intravenous administration of a sodium load and have greater increases in blood pressure in response to an extremely high salt intake.²³ Among both black families and white families, the blood-pressure response to sodium loading and sodium restriction is highly heritable.^{24,25} In addition, among white twins with normal blood pressure, there is a strong heritable influence on plasma renin activity, the plasma aldosterone concentration, and the efficiency of sodium excretion after infusion of a saline load.²⁶

Monogenic renal tubular disorders resulting in either sodium retention or renal sodium wasting are associated with hypertension and hypotension, respectively.²⁷ However, the causative mutations of these monogenic syndromes of sodium retention are not applicable to the general population or to the vast majority of persons with hypertension. A number of rare alleles in several genes that alter renal salt handling are associated with blood-pressure variation in the general population.²⁸ Preliminary evidence in various patient populations has identified a number of DNA polymorphisms associated with salt sensitivity in genes that may contribute to the regulation of renal sodium transport.^{29,30} Salt sensitivity is also reportedly associated with single-nucleotide polymorphisms in at least a dozen genes that have no apparent physiological basis for the regulation of arterial pressure or sodium balance. For the most part, these observations await confirmation.

SALT CONSUMPTION AND CARDIOVASCULAR DISEASE

It has been projected that a reduction in dietary salt intake by 3 g per day (on the basis of the current average consumption in the United States) would reduce the annual number of new cases of coronary heart disease by 60,000 to 120,000, cases of stroke by 32,000 to 66,000, and cases of myocardial infarction by 54,000 to 99,000 and would reduce the annual number of deaths from all causes by 44,000 to 92,000.³¹ With notable exceptions, results of observational studies generally support an association of high salt intake with cardiovascular end points. In a 2009 meta-analysis of 19 independent cohort samples from 13 studies involving a total of 177,025 participants (follow-up, 3.5 to 19 years) and 11,000 cardiovascular events, Strazzullo et al. reported that a high salt intake is associated with increased risks of stroke and total cardiovascular disease,³² although an inverse trend with respect to the association between salt intake and the risk of cardiovascular disease was observed in three cohorts. Results from several recent observational studies are consistent with the overall conclusions of the meta-analysis by Strazzullo et al.³³⁻³⁵

In contrast, a limited number of observational studies have suggested either no association of cardiovascular disease with salt intake or an increased prevalence of cardiovascular disease with low salt intake.³⁶ On the basis of a post hoc analysis of two populations enrolled in drug trials, O'Donnell et al. reported that both high and low sodium intakes were associated with increased cardiovascular events in a J-shaped curve (24-hour sodium excretion was estimated on the basis of the measured sodium concentration in a fasting morning urine sample).³⁷ As compared with participants who had a baseline sodium excretion of 4 to 6 g per day (10 to 15 g per day of sodium chloride), participants who excreted more than 6 g of sodium (15 g of sodium chloride) per day and those who excreted less than 4 g of sodium (10 g of sodium chloride) per day in that study showed an increase in cardiovascular deaths, strokes, or heart attacks. Studies with negative or paradoxical outcomes have been criticized for a number of methodologic deficiencies, including confounding variables (e.g., coexisting conditions and diuretic therapy) and a short duration of follow-up.

Results of epidemiologic studies and randomized trials suggest that potassium consumption influences the effect of sodium on blood pressure and the risk of cardiovascular disease. Low potassium intake is associated with an increased risk of hypertension, and a high ratio of sodium intake to potassium intake is a more potent risk factor for hypertension and cardiovascular disease than each factor alone.^{34,38} A high potassium intake offers the greatest benefit when sodium intake is high.

All observational studies share intrinsic weaknesses and methodologic limitations. None were designed to address the relation between daily sodium intake and the risk of cardiovascular disease.

In several long-term, prospective, randomized clinical trials, reduced salt intake was reported to result in a decreased incidence of cardiovascular events.³⁹⁻⁴¹ In contrast, on the basis of a meta-analysis of seven randomized trials (involving a total of 6250 participants) with at least 6 months of follow-up, a 2011 Cochrane analysis concluded that reducing dietary salt intake did not decrease the risk of death or cardiovascular disease.⁴² One of the trials in the analysis included patients with heart failure who were simultaneously receiving aggressive treatment with diuretic agents. In addition, trials involving persons with normal blood pressure and those involving persons with hypertension were analyzed separately, potentially resulting in lack of statistical power. On the basis of a meta-analysis that excluded the study in which patients received concomitant diuretic therapy and that combined the normotensive and hypertensive study populations, He and MacGregor concluded that decreased salt intake was associated with a significant reduction in cardiovascular events and a nonsignificant reduction in all-cause mortality.⁴³

Results from trials in discrete patient populations suggest that caution is warranted in recommending rigorous sodium restriction for specific patient groups. An observational study involving 2807 adults with type 1 diabetes (mean age, 39 years) showed that dietary sodium was inversely associated with all-cause mortality and the development of end-stage renal disease (median follow-up, 10 years).⁴⁴ In that study, reduced survival was also observed among adults with high sodium intakes. In a related study involving 638 patients with long-standing type 2 diabetes (mean age, 64 years), low urinary sodium excretion

was associated with increased all-cause and cardiovascular mortality (median follow-up, 9.9 years).⁴⁵ Notably, the patients in that study had multiple coexisting conditions, including renal impairment and cardiovascular disease, at baseline. Clinical trials of a low-sodium diet in combination with high-dose diuretic agents and fluid restriction in patients with congestive heart failure have been reported to show an increase in hospital readmissions and deaths.^{46,47} However, in patients with chronic kidney disease, modest salt reduction is associated with improved clinical outcomes and greater reductions in blood pressure in response to pharmacologic inhibition of the renin–angiotensin system.⁴⁸

Mechanisms of Salt-Induced Hypertension and Target-Organ Damage

In parallel with these observational studies and clinical trials, mechanisms by which a high salt intake may increase blood pressure and lead to adverse cardiovascular outcomes have been studied in the laboratory. Hypertension can be produced in response to a high dietary sodium intake in a number of well-recognized experimentally induced conditions, all of which have the common denominator of a diminution in the renal capacity to excrete sodium.⁴⁹ This “natriuretic handicap” may be due to an intrinsic renal defect. Alternatively, stimuli that result in increased renal tubular reabsorption of sodium chloride may reset the kidneys so that a higher level of renal-arterial perfusion pressure is required to maintain a net sodium balance.

As suggested by Guyton (cited in Cowley’s review⁵⁰), impaired natriuresis may result in a small increase in blood volume, and in response, whole body autoregulation may explain the rise of total peripheral resistance. Whether this sequence of events occurs in either the Dahl salt-sensitive rat or in humans with salt-sensitive hypertension is not clear. What is clear, however, is that salt can activate a number of neural, endocrine or paracrine, and vascular mechanisms, all of which have the potential to increase arterial pressure (Table 2); for a list of relevant references, see the Supplementary Appendix, available with the full text of this article at NEJM.org.

In rats, a high-salt diet leads to accumulation

of hypertonic sodium in the interstitial space.⁵¹ This hypertonicity is sensed by macrophages, which produce an angiogenic protein, vascular endothelial growth factor, in the skin that stimulates lymphatic-vessel growth, creating a third fluid compartment that buffers sodium-induced increases in vascular volume. It has been suggested that failure of this extrarenal regulatory mechanism may lead to salt sensitivity in rats with deoxycorticosterone acetate–salt hypertension.⁵² However, this hypothesis remains speculative because there is no evidence that altering the distribution of salt and body fluids would by itself affect the long-term regulation of arterial pressure.

Independently of its effect on arterial pressure, prolonged salt loading in the rat causes alterations of vascular endothelial-cell function and promotes organ damage (Fig. 1).^{53–55} Administration of excess dietary salt in rats with spontaneous hypertension causes perivascular fibrosis of the coronary arteries, fibrosis of the noncardiac ventricular interstitial matrix, ischemia of both ventricles, and ventricular diastolic dysfunction.⁵⁶ Severe proteinuria and end-stage renal failure develop within 3 weeks and are associated with interstitial fibrosis, renal arteriolar damage, increased glomerular hydrostatic pressure, and glomerular hyalinization.⁵⁷ Although treatment with an angiotensin-receptor antagonist does not reduce arterial pressure in these rats, it prevents or attenuates the salt-induced structural and functional changes in the heart and kidney.^{58,59} High salt intake also results in decreased elasticity and fibrosis of large arteries, potentially worsening hypertension and exacerbating cardiovascular risk.⁶⁰ Like salt excess, high levels of aldosterone are associated with alterations of myocardial and renal structure and function, owing to oxidative stress and vascular inflammation.⁶¹ The proinflammatory effects of aldosterone are amplified by salt, and clinically, target-organ damage has been related to the interdependence of aldosterone and dietary salt.^{62–65}

The most frequent causes of hospitalization among older persons in industrialized societies are cardiac failure and end-stage renal disease. Such target-organ disease may result from long-term consumption of excess salt. Salt intake is an independent predictor of left ventricular mass, and left ventricular mass decreases in response to dietary salt restriction.^{66,67} In patients with hypertension, a high salt intake amplifies the effect of

Table 2. Interrelated Salt-Induced Alterations That May Impair Sodium Excretion and Promote Vasoconstriction.*

Kidney

- Increased activity of the sympathetic nervous system
- Decreased renal medullary blood flow
- Increased formation of reactive oxygen species
- Low bioavailability of nitric oxide
- Defective dopamine-receptor function
- Enhanced vasoconstrictor effects of angiotensin II and vasopressin
- Increased intrarenal generation of angiotensin II
- Overexpression of angiotensinogen in proximal tubule
- Increased expression of aldosterone synthetase
- Activation of the mineralocorticoid receptor
- Decreased production of 20-hydroxyeicosatetraenoic acid, an arachidonic acid metabolite
- Failure of atrial natriuretic peptide to potentiate marinobufagenin-induced inhibition of Na^+/K^+ -ATPase

Nervous system

- Increased sympathetic nervous system activity triggered by sodium concentration in cerebrospinal fluid
 - Enhanced response of vasomotor neurons of the rostral ventrolateral medulla to excitatory amino acids
 - Decreased release of nitric oxide in the paraventricular nucleus
 - Activation of glutamate receptors in the paraventricular nucleus
 - Decreased baroreceptor sensitivity
 - Increased oxidative stress in the brain
 - Production of a ouabain-like compound by the brain
 - Up-regulation of mineralocorticoid receptors in the central nervous system
- #### Blood vessels
- Reduced production of nitric oxide and impaired nitric oxide-dependent vasodilation
 - Increased production of reactive oxygen species
 - Reduced scavenging of free radicals by superoxide dismutase
 - Failure of atrial natriuretic peptide to potentiate marinobufagenin-induced inhibition of Na^+/K^+ -ATPase
 - Potential vascular effect of salt-induced autoimmune inflammatory response

* For a list of relevant references, see the Supplementary Appendix, available at NEJM.org. Na^+/K^+ -ATPase denotes the sodium-potassium pump.

arterial pressure on target-organ damage, including cardiac hypertrophy and microalbuminuria.⁶⁸ Furthermore, in patients who have hypertension with compensated heart failure and a normal ejection fraction, dietary-salt restriction reduces arterial pressure, arterial stiffness, and oxidative stress.⁶⁹ Multifactorial causation of prolonged salt excess, including an interaction with tissue renin-angiotensin systems, may contribute to major target-organ impairment.

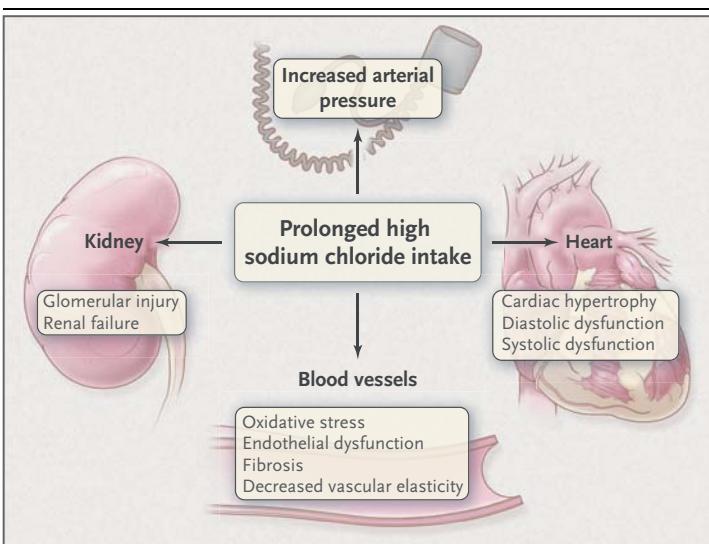


Figure 1. Target-Organ Damage Due to High Intake of Sodium Chloride.

In addition to increasing arterial pressure, a prolonged high intake of sodium chloride has a direct effect on target-organ damage.

RECOMMENDATIONS AND STRATEGIES FOR SALT REDUCTION

In view of the association of a high salt intake with hypertension and cardiovascular and renal disease, many countries have introduced population-based recommendations and initiatives to reduce salt consumption.⁷⁰ Beginning in the early 1970s, Finland implemented population-wide initiatives to reduce salt intake.⁷¹ Between 1979 and 2002, the average 24-hour urinary sodium excretion decreased from more than 5200 mg per day (13.0 g of sodium chloride) to less than 4000 mg per day (10.0 g of sodium chloride) in Finnish men and from nearly 4200 mg per day (10.5 g of sodium chloride) to less than 3000 mg per day (7.5 g of sodium chloride) in Finnish women.⁷² Along with this reduction in sodium intake, there has been a reduction of more than 10 mm Hg in both systolic and diastolic blood pressure and a corresponding decrease of 75 to 80% in the rate of death due to stroke and coronary heart disease.⁷¹ In 2004, with the voluntary engagement of the food industry, the British government introduced a population-based salt-reduction program with the use of a media campaign to increase public awareness and demand for change.⁷³ Sodium intake decreased from 3800 mg per day

(9.5 g of sodium chloride) in 2001 to 3440 mg per day (8.6 g of sodium chloride) in 2008.

In 2005, the U.S. Department of Health and Human Services recommended that adults in the United States consume no more than 2300 mg of sodium per day (5.8 g of sodium chloride) and that those in specific groups (persons 51 years of age or older, persons with hypertension, diabetes, or chronic kidney disease, and persons of African-American ethnicity) consume no more than 1500 mg per day (3.8 g of sodium chloride).⁷⁴ The 1500-mg recommendation applies to about half the U.S. population. The same recommendations were endorsed as part of the *Dietary Guidelines* issued in 2011 by the U.S. Department of Agriculture and the Department of Health and Human Services.⁷⁵ Numerous professional societies, including the American Heart Association, have also endorsed recommendations to reduce sodium intake to less than 1500 mg per day.⁷⁶ In England and Wales, the government-recommended target was 2400 mg of sodium per day (6.0 g of sodium chloride) by 2012.⁷³ The global goal set by the World Health Organization is to reduce sodium intake to less than 2000 mg per day (5 g of sodium chloride) per person by 2025, with some countries aiming for even lower levels in the long term.⁷³

Despite these recommendations, initiatives, and early successes, sodium intake remains high. Data from the National Health and Nutrition Examination Survey suggest that, for over a decade, sodium consumption has been relatively constant in the United States and well above recommended amounts (Fig. 2). Currently, Americans consume a mean of approximately 3400 mg of sodium per day (8.5 g of sodium chloride), with 77% of the sodium coming from packaged, processed, and restaurant foods.⁷⁷ In 2010, the Institute of Medicine recommended that sodium intake be reduced gradually, and emphasized that voluntary approaches for reducing sodium levels in the food supply have not been successful.⁷⁸

Nevertheless, reflecting the difficulty of translating science into public policy,⁷⁹ there remain outspoken critics of these population-based recommendations to reduce sodium consumption.⁸⁰⁻⁸³ Several specific concerns have been expressed. Critics point out that the influence of salt intake on blood pressure is generally too small to mandate policy decisions and that there is substan-

tial variation from one person to another in the blood-pressure response to salt reduction. In addition, critics note that results of studies of the relationship of reduced sodium intake to morbidity and mortality have been inconsistent and that population-based estimates of the reduction in cardiovascular disease that is related to an effect of salt reduction on blood pressure are based on a "surrogate" end point. They also note that a reduction in sodium intake may have an adverse effect on other end points, such as level of lipids, catecholamines, renin, and aldosterone, and that in the general population, a J-shaped curve may characterize the relationship between salt consumption and cardiovascular morbidity and mortality. Critics also note that low salt intake increases the risk of cardiovascular events in specific patient groups (e.g., patients with congestive heart failure who are aggressively treated with diuretic agents and patients with diabetes). In response to concerns that a low level of sodium intake may adversely affect blood lipids, insulin resistance, and the risk of cardiovascular disease, the Institute of Medicine is undertaking a study to "evaluate the results, study design, and methodological approaches that have been used to assess the relationship between sodium and health outcomes."⁸⁴

CONCLUSIONS

Although it has been difficult to separate salt need from salt preference, current levels of salt consumption exceed salt need and are associated with adverse clinical outcomes. High salt intake is associated with high blood pressure and increased rates of cardiovascular disease. Experimental studies continue to provide information about mechanisms for these adverse effects of salt. In clinical trials, a reduction in salt intake is associated with reduced blood pressure, more so in persons with hypertension than in those with normal blood pressure. Although not discussed in the present review, it should be noted that reduced salt intake is associated with greater blood-

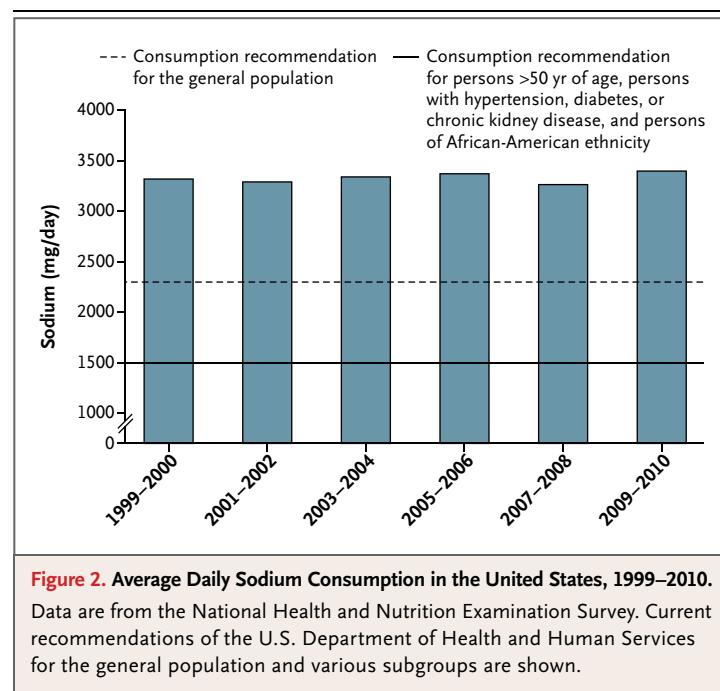


Figure 2. Average Daily Sodium Consumption in the United States, 1999–2010.

Data are from the National Health and Nutrition Examination Survey. Current recommendations of the U.S. Department of Health and Human Services for the general population and various subgroups are shown.

pressure responses to antihypertensive drug therapy, including drug therapy in patients with resistant hypertension.^{85,86} Most, but not all, clinical trials have shown that reduced salt intake is also associated with decreased risks of cardiovascular events and death. Consequently, recommendations for reducing the currently high levels of salt consumption in the general population seem justifiable, although in terms of safety, the lower limit of salt consumption has not been clearly identified. It may be premature to discount the apparently paradoxical cardiovascular outcomes associated with low salt intake, particularly in specific clinical conditions (e.g., type 1 or type 2 diabetes and congestive heart failure that is aggressively treated with diuretic agents). Less-rigorous targets for salt reduction may be appropriate for these and other patient groups.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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