



Nutrition in cardiovascular disease

Nutrition in cardiovascular disease: salt in hypertension and heart failure

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There is much evidence for a causal relationship between salt intake and blood pressure (BP). The current salt intake in many countries is between 9 and 12 g/day. A reduction in salt intake to the recommended level of 5–6 g/day lowers BP in both hypertensive and normotensive individuals. A further reduction to 3–4 g/day has a much greater effect. Prospective studies and outcome trials have demonstrated that a lower salt intake is associated with a decreased risk of cardiovascular disease. Increasing evidence also suggests that a high salt intake is directly related to left ventricular hypertrophy (LVH) independent of BP. Both raised BP and LVH are important risk factors for heart failure. It is therefore possible that a lower salt intake could prevent the development of heart failure. In patients who already have heart failure, a high salt intake aggravates the retention of salt and water, thereby exacerbating heart failure symptoms and progression of the disease. A lower salt intake plays an important role in the management of heart failure. Despite this, currently there is no clear evidence on how far salt intake should be reduced in heart failure. Our personal view is that these patients should reduce their salt intake to <5 g/day, i.e. the maximum intake recommended by the World Health Organisation for all adults. If salt intake is successfully reduced, there may well be a need for a reduction in diuretic dosage.

Keywords

Dietary salt • Blood pressure • Left ventricular hypertrophy • Heart failure • Cardiovascular disease

For several million years, the ancestors of humans, like all other mammals, ate a diet which contained a very small amount of salt that existed in natural foods, i.e. <0.5 g of salt (0.2 g sodium) per day.¹ Only ~5 000 years ago, the Chinese discovered that salt could be used to preserve foods. Salt then became of great economic importance and the most taxed, traded commodity in the world, with intake reaching a peak around the 1870s.¹ However, with the invention of the deep freezer and the refrigerator, salt was no longer required as a preservative. Salt intake had been declining, but with the recent large increase in the consumption of highly salted processed foods, salt intake is now increasing again. The current salt intake in many countries is between 9 and 12 g/day.² This large increase in salt intake is relatively recent in evolutionary terms. It presents a major challenge to the physiological systems to excrete these large amounts of salt through the kidneys. The consequence is a gradual rise in blood pressure (BP),^{3,4} thereby increasing the risk of stroke, heart attack, heart failure, and renal disease. Furthermore, a high salt intake may

have direct effects on stroke,^{5,6} left ventricular hypertrophy (LVH),⁷ progression of renal disease and proteinuria,⁸ independent of but additive to the effect of salt on BP. There is also evidence that a high salt intake is indirectly related to obesity through increased soft drink consumption,^{9,10} associated with a higher risk of renal stones and osteoporosis,¹¹ and probably a major cause of stomach cancer.^{12,13} The evidence on these harmful effects of salt has been comprehensively examined in several recent review articles.^{3,14} In this paper, we focus on the evidence relating salt to BP, LVH, heart failure, and total cardiovascular disease.

Salt and blood pressure

Raised BP is a major cause of cardiovascular disease, responsible for 62% of stroke and 49% of coronary heart disease.¹⁵ Importantly, the risk is not limited to those with hypertension (i.e. systolic BP ≥ 140 or diastolic ≥ 90 mmHg), but throughout the range of

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BP, starting at 115/75 mmHg.¹⁶ It has been shown that a high salt intake, a low consumption of fruit and vegetables (i.e. low potassium intake), obesity, excess alcohol intake, and lack of physical exercise all contribute to the development of high BP. However, the diversity and strength of the evidence is much greater for salt than for other factors. The evidence for salt comes from studies in animals, human genetics, epidemiology, migration, population-based intervention, and treatment trials.³ These studies have consistently shown that dietary salt intake is a major cause of raised BP.

Experimental studies in various species of animals, e.g. rat, dog, chicken, rabbit, baboon, and chimpanzee, have shown that salt intake plays an important role in regulating BP.^{17,18} A study in chimpanzees (98.8% genetic homology with man) demonstrated that an increase in salt intake from 0.5 g/day, which is close to humans' evolutionary intake, to 10–15 g/day which is similar to our current salt intake, caused progressive and large increases in BP.¹⁷ A more recent study demonstrated that even a modest reduction in salt intake had a significant effect on BP in chimpanzees. Additionally, the fall in BP was as large as or larger for salt intakes at or below the recommended levels of 5–6 g/day.¹⁸

Genetic studies of rare Mendelian form of high or low BP have shed light on the salt-BP relationship. About 20 different genes have been identified.¹⁹ Most of these genes affect sodium handling by the kidney and can have a dramatic effect on the BP of affected individuals.^{19,20} Although such genetic disorders are very rare, these studies clearly indicate the importance of salt intake in regulating BP in humans. Additionally, recent studies have suggested a key role of salt consumption as an effect modifier in BP genetics.²¹

Numerous epidemiological studies^{22–26} have shown that non-acclimated tribes who have a salt intake of <3 g/day have a lower BP, e.g. 96/61 mmHg for adult Yanomamo Indians, and their BP does not rise with age.²⁴ However, undeveloped tribes who have access to salt, e.g. the Qash'qai in Iran, develop high BP and a rise in BP with age similar to that which occurs in Western communities, but they live a lifestyle similar to non-acclimated societies.²⁵ In spite of this evidence, it was felt necessary to set up a large international study on salt and BP (INTER-SALT)⁴ using standardized methods for measuring 24-h urinary sodium and BP. The intention was to study communities with a wide range of salt intake, e.g. from 0.5 to 25 g/day. A total of 10 079 individuals from 52 centres around the world were recruited into the study. However, among these 52 communities, only 4 had a low salt intake (i.e. ≤ 3 g/day) and the majority lay between 6 and 12 g/day and none had the high salt intake as originally envisaged. Nevertheless, the study demonstrated a significant positive relationship between salt intake and BP. There was also a highly significant positive relationship between salt intake and the increase in BP with age (Figure 1). It was estimated that an increase of 6 g/day in salt intake over 30 years would lead to an increase in systolic BP by 9 mmHg.⁴

One criticism of the INTERSALT study made by the Salt Institute (a public relations company defending the interests of salt extractors and manufacturers worldwide) was that when the four communities consuming lower salt were excluded, there was no overall relationship remaining between salt intake and BP.

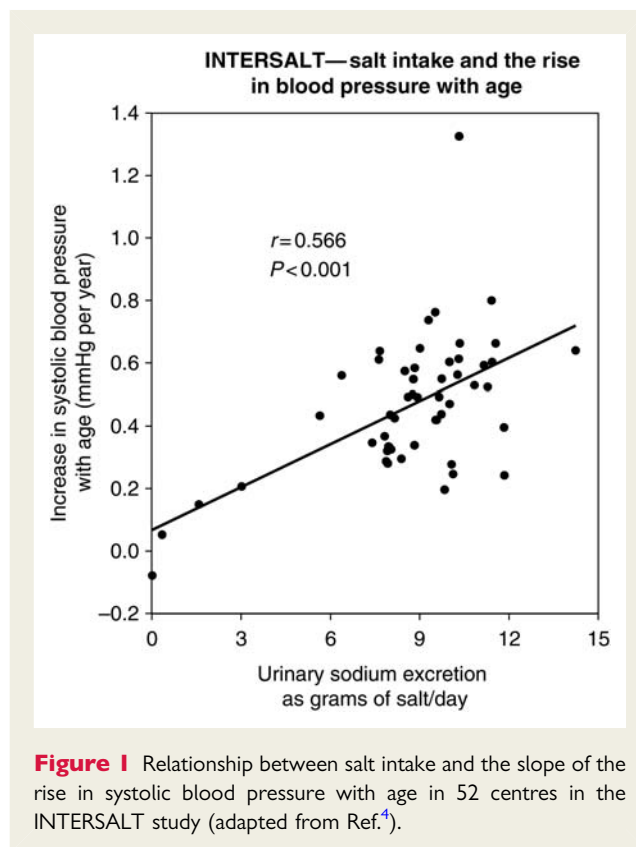


Figure 1 Relationship between salt intake and the slope of the rise in systolic blood pressure with age in 52 centres in the INTERSALT study (adapted from Ref.⁴).

The INTERSALT's investigators re-analysed their data and showed that the highly significant within-population association between salt intake and BP across all 52 centres was virtually unchanged when the 4 low-salt populations were excluded, and the association between salt intake and the rise in BP with age persisted across 48 centres.^{4,27,28} Other epidemiological studies, e.g. the international study of macro- and micro-nutrients and BP,²⁹ and the Norfolk Cohort of the European Prospective Investigation into Cancer,³⁰ have lent further support for the important role of salt intake in determining the levels of population BP.

Migration studies, e.g. the Luo migrants in Kenya and the Yi migrants in China, have shown that migration from isolated low-salt societies to an urban environment with a high salt intake is associated with an increase in BP.^{31,32}

Population-based intervention studies have shown that when salt intake is decreased, there is a reduction in population BP.^{33,34} One of the most successful intervention studies was conducted in two similar villages in Portugal³³ where salt intake was very high (~ 21 g/day) and the prevalence of hypertension and stroke was also very high. During 2 years of intervention through vigorous, widespread health education to reduce the consumption of salt especially from foods that had previously been identified as the major sources of salt, there was a difference of $\sim 50\%$ in salt intake between the two villages (i.e. intervention vs. control). This was associated with a difference of 13/6 mmHg in BP (Figure 2). Another community-based intervention trial in two rural villages in north-eastern Japan reduced salt intake by 2.3 g/day through dietary counselling for 1 year. This reduction in salt

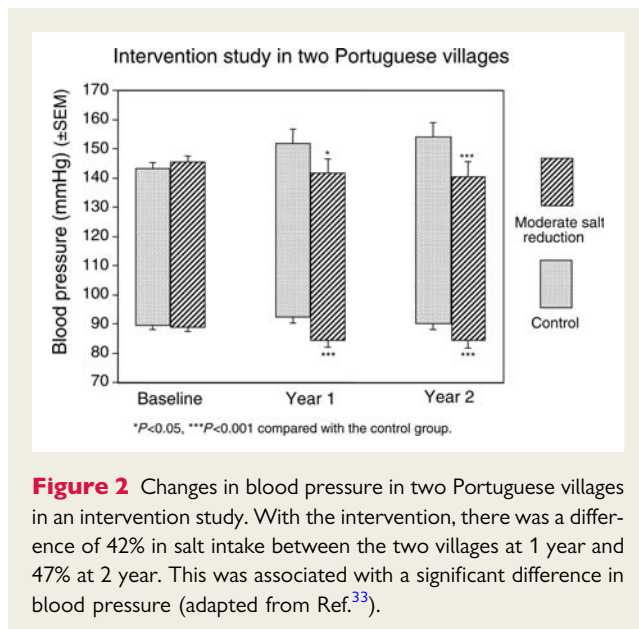


Figure 2 Changes in blood pressure in two Portuguese villages in an intervention study. With the intervention, there was a difference of 42% in salt intake between the two villages at 1 year and 47% at 2 year. This was associated with a significant difference in blood pressure (adapted from Ref.³³).

intake was associated with a decrease of 3.1 mmHg in systolic BP.³⁵ Several other studies,^{36,37} however, failed to achieve a reduction in salt intake in the intervention group, it is therefore not surprising that there was no change in BP in such studies.

There have been a large number of randomized trials looking at the effect of a reduction in salt intake on BP in both hypertensive and normotensive individuals. Several meta-analyses of these trials have been performed.^{38–42} In two meta-analyses,^{39,41} it was claimed that salt reduction had very little effect on BP in individuals with normal BP and a reduction in population salt intake was not warranted. However, these two meta-analyses are flawed. Both included trials of very short duration with many comparing the effects of acute salt loading to abrupt and severe salt restriction, e.g. from 20 to <1 g/day for only a few days. It is known that such acute changes in salt intake increase sympathetic activity, plasma renin activity, and angiotensin II,⁴³ which would counteract the effects on BP. Furthermore, most BP-lowering drugs do not exert their maximal effects within a few days. This is particularly true with diuretics which are likely to work by a similar mechanism to that of salt reduction. It is therefore inappropriate to include the acute salt restriction trials in a meta-analysis that attempts to apply them to public health recommendations for a longer term modest reduction in salt intake. A meta-analysis by Hooper *et al.*⁴² attempted to look at whether salt reduction for ≥ 6 months caused a fall in BP. However, most trials included in this meta-analysis achieved only a very small reduction in salt intake. It is, therefore, not surprising that there was only a small, but still significant fall in BP. A more recent meta-analysis of randomized trials of 1 month or longer, demonstrated that a modest reduction in salt intake caused significant and important falls in BP in both hypertensive and normotensive individuals.⁴⁴ Furthermore, there was a dose–response to salt reduction. A reduction of 6 g/day would lower BP by 7/4 mmHg in hypertensives and 4/2 mmHg in normotensives (Figure 3).⁴⁴

The best way to study the dose–response relationship between salt intake and BP is to look at the BP responses to several levels of

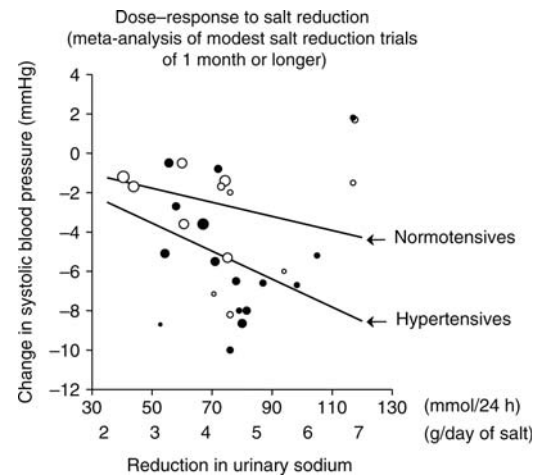
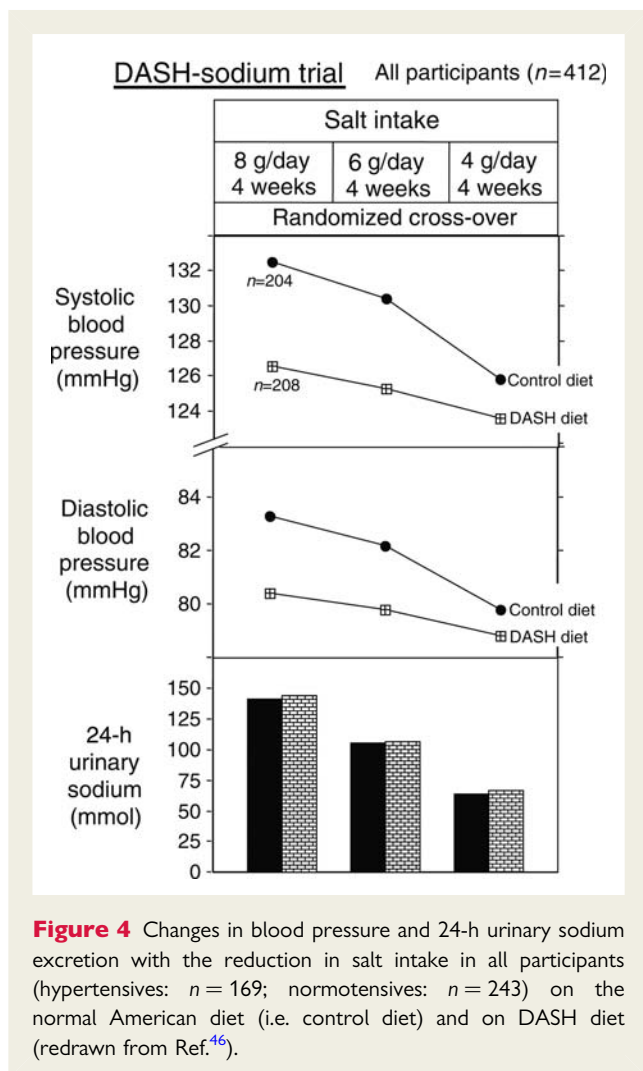


Figure 3 Relationship between the reduction in 24-h urinary sodium and the change in systolic blood pressure in a meta-analysis of modest salt reduction trials. The open circles represent normotensives and the solid circles represent hypertensives. The slope is weighted by the inverse of the variance of the net change in blood pressure. The size of the circle is in proportion to the weight of the trial.

salt intake. So far, there are only two well-controlled trials that studied three levels of salt intakes.^{45,46} One is the randomized double-blind cross-over trial in 20 individuals with untreated essential hypertension, where salt intake was reduced from 11.2 to 6.4 and 2.9 g/day, each for 1 month.⁴⁵ Blood pressure was 163/100 mmHg with a salt intake of 11.2 g/day, and reduced to 155/95 mmHg when salt intake was decreased to 6.4 g/day (i.e. a decrease of 8/5 mmHg). Blood pressure fell further to 147/91 mmHg when salt intake was reduced to 2.9 g/day (i.e. a further fall of 8/4 mmHg). After the trial was completed, individuals continued the low salt intake. Among these 20 participants, 19 were followed up for one further year and the BP sustained at the lowest level (i.e. 145/90 mmHg) with the lowest salt intake of 3.0 g/day.⁴⁵ The other well-controlled trial that has looked at the dose–response is the DASH (Dietary Approaches to Stop Hypertension)-Sodium study which is a feeding trial with all foods and drinks provided to all participants for the entire study.⁴⁶ A total of 412 individuals with normal or mildly raised BP were randomized into two groups, i.e. the normal American diet and the DASH diet which is rich in fruits, vegetables, and low-fat dairy products. Within each group, participants were given three levels of salt intake 8, 6, and 4 g/day in a randomized cross-over design, each for 1 month. The results demonstrated a clear dose–response to salt reduction both on the normal American diet and the DASH-diet (Figure 4).⁴⁶ From these well-controlled trials, it is clear that the current recommendations to reduce salt from 9–12 to 5–6 g/day will have a major effect on BP, but are not ideal. A further reduction to 3 g/day will have a much greater effect. It is important to note that the current recommendations are based on the feasibility of reducing population salt intake to 5–6 g/day,⁴⁷ but not on the potential maximum



beneficial effects of salt reduction. Therefore, these are viewed as interim targets. Recently the UK government's health advisory agency, the National Institute for Health and Clinical Excellence has recommended a reduction in the population's salt consumption to 3 g/day by 2025.⁴⁸

It has been shown that, for a given reduction in salt intake, the fall in BP was larger in individuals of African origin, in older people and in those with raised BP compared with whites, young people and individuals with normal BP, respectively.⁴⁹ These differences in the fall in BP were, at least in part, due to the differences in the responsiveness of the renin-angiotensin system.^{50,51} The term 'salt sensitivity' has been commonly used to describe the variations of BP response to salt reduction. However, almost all of the studies on 'salt sensitivity' have used a protocol of very large and sudden changes in salt intake. As described previously, these studies are irrelevant to the public health recommendations of more modest reduction in salt intake for a prolonged period of time. There is strong evidence that a modest reduction in salt intake should be carried out universally in the entire population. A reduction in population salt intake lowers population BP. Even a small reduction in BP across the whole population would have

a large impact on reducing the appalling burden of cardiovascular disease.⁵²

A reduction in salt intake is additive to other dietary and lifestyle changes for lowering BP.^{46,53} The DASH-Sodium trial demonstrated that the combination of a low salt and the DASH diet had a greater effect on BP than either intervention alone, though the combined effects were not as great as the simple addition of each separate intervention (Figure 4).⁴⁶ The Trial of Non-pharmacologic Interventions in the Elderly (TONE) demonstrated that a combination of salt reduction and weight loss were more successful than either intervention alone in maintaining satisfactory BP control after withdrawal of antihypertensive medication in older people who were obese and had hypertension.⁵³ The Trial of Hypertension Prevention (TOHP) II also showed that salt restriction combined with weight reduction had a greater effect on reducing the incidence of hypertension during the first 6 months of the study in overweight people with high-normal BP. However, this effect did not sustain over the following 30 months due to the failure of maintaining lower salt and weight.⁵⁴

A reduction in salt intake is also additive to antihypertensive drug treatments, enhances BP control, and reduces the need for drug therapy.^{53,55} Salt restriction is particularly effective in lowering BP when the renin-angiotensin system is blocked by an angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker because the reactive increase in plasma renin activity and thereby angiotensin II that occurs with salt reduction, offsets the falls in BP.⁵⁵ In this respect, black hypertensive patients are usually considered as poor responders to a blocker of the renin-angiotensin system and better responders to a diuretic because of their low baseline plasma renin activity. However, in a group of black hypertensive individuals who were on a lower salt intake, i.e. ~6 g/day, a better BP response to an angiotensin-converting enzyme inhibitor than to a diuretic was found in a randomized cross-over trial.⁵⁶ These results suggest that a reduction in salt intake may restore the BP response to drugs that block the renin-angiotensin system even in black hypertensive population.⁵⁶ The TONE study demonstrated that, in elderly hypertensive individuals after withdrawal of medication, a very modest reduction in salt intake of only 2.4 g/day reduced the occurrence of high BP, resumption of medication and cardiovascular events by 32% ($P < 0.001$) during a follow-up period of 28 months.⁵⁷

Salt and left ventricular hypertrophy and left ventricular dysfunction

Left ventricular hypertrophy is an important predictor of cardiovascular outcomes.⁵⁸ Raised BP is a major risk factor for LVH and long-term treatment of hypertension has been shown to result in regression of existing LVH.⁵⁹ A reduction in salt intake lowers BP, and therefore could reduce the risk of LVH. Increasing evidence also suggests that salt intake may have a direct effect on LVH independent of BP.^{60,61} A review of nine cross-sectional studies in which salt intake and LV mass were assessed, has shown a close positive correlation between the two, with correlation coefficients ranging from 0.22 to 0.61.⁷ The relationship

was independent of other confounding factors including BP.⁷ A reduction in salt intake has been shown to decrease LV mass in hypertensive individuals.^{62–64} A study in 10 hypertensive men showed that when salt intake was reduced from 6.2 to 1.7 g/day for 6 weeks, there was a significant decrease in echocardiographically determined LV mass.⁶² Two other studies (one reduced salt intake by ~5 g/day for 1 year and the other reduced salt intake by 2 g/day for 4 years) demonstrated that salt reduction in combination with other dietary and lifestyle changes had a significant effect on reducing LV mass.^{63,64}

Diastolic dysfunction, characterized by abnormalities of ventricular filling, can be present in hypertensive individuals without overt hypertrophy, and may represent an early marker of end-organ damage. Up to 50% of individuals with hypertension have evidence of diastolic dysfunction.⁶⁵ Treatment trials have demonstrated that lowering BP improves diastolic function even in individuals with mild hypertension and irrespective of the type of antihypertensive agent used.⁶⁶ A reduction in salt intake lowers BP and could therefore have a beneficial effect on diastolic function. It is of interest that some cross-sectional studies have shown that a higher salt intake as measured by 24 h urinary sodium excretion was associated with impaired LV diastolic function in hypertensive individuals⁶⁷ and in patients with type II diabetes.⁶⁸ Clearly, further studies are needed, in particular, to investigate whether a longer term modest reduction in salt intake, as currently recommended, has a significant effect on cardiac function.

The pathophysiological mechanisms for a link between salt and LV function are not fully understood. Experimental studies in rats demonstrated that an increase in salt intake for a few weeks not only caused LVH, but also led to widespread interstitial fibrosis in the left ventricle and intramyocardial arteries and arterioles.⁶⁹ Tissue culture experiments showed that increasing bath sodium concentration in an amount similar to the increase in plasma sodium which was seen with an increase in salt intake, caused marked cellular hypertrophy in both arterial smooth muscle and cardiac myocytes.⁷⁰ The hypertrophy was due to an increase in the rate of protein synthesis and a decrease in the rate of protein degradation.⁷⁰

Salt and cardiovascular disease

A reduction in salt intake lowers BP and, as raised BP throughout its range is a major cause of cardiovascular disease, salt reduction would be predicted to reduce cardiovascular risk. Based on the fall in BP from a meta-analysis of randomized salt reduction trials,⁴⁴ it was estimated that a reduction of 6 g/day in salt intake would reduce stroke by 24% and coronary heart disease by 18%. This would prevent ~35 000 stroke and coronary heart disease deaths a year in the UK⁷¹ and ~2.5 million deaths worldwide.

Prospective cohort studies have shown that a higher salt intake is related to an increased risk of cardiovascular disease. A recent meta-analysis of 13 cohort studies with 177 025 participants for a follow-up between 3.5 and 19 years, showed that an increase of 5 g/day in salt intake was associated with a 23% increase in the risk of stroke and a 14% increase in total cardiovascular disease.⁷² After excluding one study which had serious

methodological problems,⁷³ the pooled analysis showed that a 5 g/day increase in salt intake was associated with a 17% increase in cardiovascular disease risk (Figure 5).⁷²

Outcome trials have demonstrated that a reduction in salt intake leads to a decrease in cardiovascular risk. A follow-up study of individuals who took part in two large randomized salt reduction trials, Trial of Hypertension Prevention (TOHP) I and II, showed a significant effect of salt reduction on cardiovascular disease.⁷⁴ In the original trials, over 3000 participants with an average baseline BP of 127/85 mmHg were randomized to a reduced salt group (for 18 months in TOHP I and 36–48 months in TOHP II) or to a control group. Compared with the control group, individuals in the intervention group reduced their salt intake by 25–30%

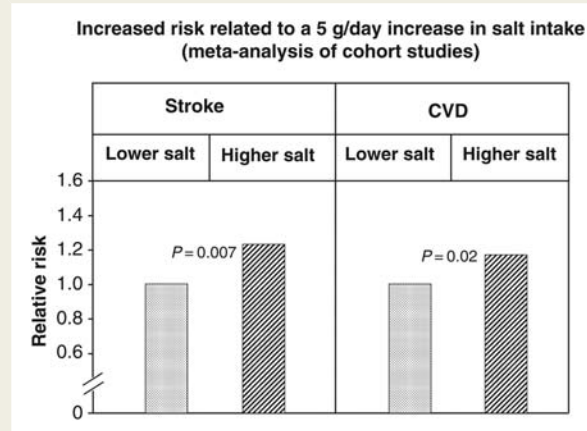


Figure 5 Relative risk of stroke and total cardiovascular disease (CVD) associated with a 5 g/day increase in salt intake in a meta-analysis of cohort studies (adapted from Ref.⁷²).

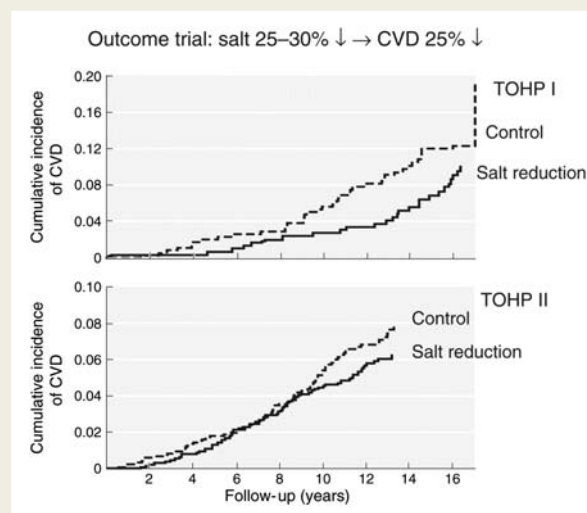


Figure 6 Cumulative incidence of cardiovascular disease (CVD) by salt intervention group in the Trial of Hypertension Prevention (TOHP) I and II, adjusted for age, sex, and clinic (adapted from Ref.⁷⁴).

from an average of ~ 10 g/day. This resulted in a fall in BP of 1.7/0.9 mmHg at 18 months (TOHP I) and 1.2/0.7 mmHg at 36 months (TOHP II). After the original trials were completed, participants were not given further dietary advice. A follow-up study at 10–15 years post trial showed that individuals who were originally allocated to the reduced-salt group had a 25% lower incidence of cardiovascular events after adjusting for confounding factors (Figure 6).⁷⁴ Another outcome trial of over 2.5 years in elderly Taiwanese veterans ($n = 1981$) showed that switching from the usual salt (i.e. sodium chloride) to potassium-enriched salt (49% sodium chloride, 49% potassium chloride, 2% other additives) with a subsequent reduction of 17% in salt intake and an increase of 76% in potassium intake, as measured by urinary sodium/creatinine and potassium/creatinine ratio, caused a 40% decrease in cardiovascular mortality.⁷⁵ These results were likely to be attributable to both a reduction in salt and an increase in potassium intake.

Salt and heart failure

Raised BP is a major cause of heart failure with hypertension preceding the development of heart failure in $\sim 90\%$ of patients.⁷⁶ Blood pressure treatment trials of 2–5 years have demonstrated that lowering BP could reduce heart failure by over 50%.⁷⁶ Left ventricular hypertrophy and LV dysfunction are also important independent risk factors for heart failure. As described previously, a high salt intake increases BP and the risk of LVH and LV dysfunction, thereby increasing the risk of heart failure (Figure 7). A prospective cohort study in 10 352 men and women has shown that a higher salt intake was associated with a higher risk of developing heart failure over a follow-up period of 19 years. This association was found in overweight individuals, but not in those with normal weight.⁷⁷ Similarly, the administration of drugs that promote sodium and fluid retention, such as non-steroidal anti-inflammatory drugs⁷⁸ or thiazolidinediones,⁷⁹ have been shown to increase the risk of congestive heart failure significantly.

In a healthy person, the balance between salt intake and excretion is crucial in the control of extracellular volume. When salt intake is increased, there is retention of salt and thereby water. This expands extracellular volume. The increase in extracellular volume is a trigger for various compensatory mechanisms to allow an increase in urinary sodium excretion but at the expense of continued retention of salt and water. With an increase of 5 g/day in salt intake, e.g. from 5 to 10 g/day, there is an increase

of ~ 1.0 – 1.5 L in extracellular volume. This corresponds to a gain of 1.0–1.5 kg in body weight.⁸⁰ In patients with heart failure, there is already retention of salt and water. A high salt intake aggravates this, thereby exacerbating heart failure symptoms and progression of the disease. Even in well-compensated heart failure, a sudden increase in salt intake (e.g. eating a very salty meal) causes a rapid increase in extracellular volume and may precipitate left ventricular failure.

A lower salt intake is the primary dietary strategy for the management of heart failure. A study by Hummel *et al.*⁸¹ in 443 heart failure patients with preserved systolic function showed that advice for salt-restricted diet was associated with a lower rate of hospital readmission and death 30-days after hospital discharge. On the contrary, a recent randomized trial by Paterna *et al.*⁸² suggested that a lower salt intake had detrimental renal and neurohormonal effects with worse clinical outcome. In this trial, 232 compensated heart failure patients were randomized to receive a normal salt intake of 120 mmol/day (7.1 g) or a lower salt intake of 80 mmol/day (4.7 g), with all participants taking high-dose oral furosemide (250–500 mg, twice a day) and restricting fluid intake to 1000 mL/day. At the same time, all patients were on captopril 75–150 mg/day and 87% of the patients were on spironolactone 25 mg/day. The results showed that individuals who were on the lower salt intake had a higher rate of hospital readmission due to worsening of heart failure and mortality during a follow-up period of 6 months. A further study by the same group of researchers used a similar protocol on salt intakes, but the normal and lower salt intake was combined with different doses of furosemide (250 or 125 mg, twice a day) and different amount of fluid intake (1000 or 2000 mL/day).⁸³ A total of eight groups of different combinations were studied and each group involved around 50 patients with compensated heart failure. The results indicated that a combination of normal salt intake with high dose of diuretic and fluid intake restriction was a better approach in terms of neurohormonal responses and clinical outcome, when compared with other combinations including a lower salt intake.

It is important to note that, in the above trials^{82,83} particularly the first one,⁸² patients were on high-dose furosemide, angiotensin-converting enzyme inhibitor and spironolactone, and they were already on the verge of sodium and water depletion. It is therefore not surprising that a lower salt intake is harmful under such circumstances, particularly when no attempt was made to lower the dose of furosemide or spironolactone. In the second trial,⁸³ the dose of furosemide was lower compared with that in the first trial. However, furosemide at a dose of 125 or 250 mg, twice a day, when combined with angiotensin-converting enzyme inhibitor and spironolactone, could still lead to sodium and water depletion. A lower salt intake would aggravate this. Additionally, in the second trial⁸³ there were only ~ 50 participants in each group and the number of cases with outcome, especially mortality, was very small. Therefore, the results from the above trials need to be interpreted with caution.

Diuretics are commonly prescribed for patients with heart failure and clinical signs or symptoms of fluid retention. However, the use of diuretics is not without side effects, and this is particularly true with high doses. If diuretics are suddenly

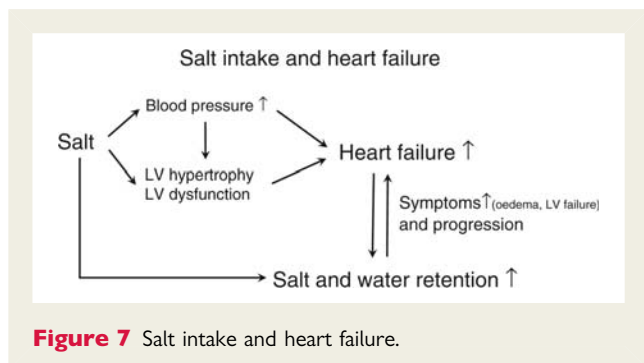


Figure 7 Salt intake and heart failure.

withdrawn in patients with a normal salt intake, there is rebound retention of salt and water.⁸⁴ This is because the compensatory mechanisms that are induced to maintain sodium balance in the presence of the diuretic are still acting several days after the effect of the diuretic has worn off. There are two ways to mitigate this rebound retention of salt and water. One is to gradually reduce the dose. The other and better way is to place the patient on a low salt diet so that only a small amount of salt can be retained when diuretic treatment is stopped.⁸⁴ Nevertheless, most patients with heart failure will need to continue with the diuretic treatment, however, even in these patients, a lower dose of diuretic may be sufficient if salt intake is reduced.

The question is how far salt intake should be reduced in patients with heart failure? Disappointingly there is no clear evidence to address this question. Although all authority bodies have recommended salt restriction in patients with heart failure, many of the guidelines are either vague or set a level which is even higher than those recommended for the general population, e.g. 2.0–2.4 g/day of sodium ('restricted') and 3.0–4.0 g/day ('moderate restriction').⁸⁵ These are equivalent to a salt intake of 5.0–6.0 and 7.5–10 g/day, respectively. Obviously these recommended levels are too high. The European Society of Cardiology Guidelines⁸⁶ state that '*Sodium restriction is recommended in symptomatic heart failure to prevent fluid retention. Although no specific guidelines exist, excessive intake of salt should be avoided. Patients should be educated concerning the salt content of common foods.*' This recommendation is graded as 'Class IIa' which is defined as '*Weight of evidence/opinion is in favour of usefulness/efficacy.*' The level of evidence for this recommendation is classified as 'C', i.e. '*Consensus of opinion of the experts and/or small studies, retrospective studies, registries.*' Clearly well-controlled trials are needed to study what level of salt intake should be in heart failure. Our personal view is that salt intake should be reduced to <5 g/day, i.e. the maximum intake recommended by the World Health Organisation for all adults. If patients are successful in reducing salt intake, there may well be a need for a reduction in the dose of diuretics.

Salt reduction is a cost-effective public health measure to reduce cardiovascular disease

Several studies have shown that a reduction in salt intake is one of the most cost-effective interventions to reduce cardiovascular disease in the population.^{87–93} For instance, a recent study in the USA showed that even a very modest reduction in salt intake of only 10% which could be easily achieved, as demonstrated in the UK,⁹⁴ would prevent hundreds of thousands of strokes and heart attacks over the lifetimes of adults aged 40–85 years who are alive today, and could save >\$32 billion in medical expenses in the USA alone.⁹³ A larger decrease in salt intake would result in a larger health improvement and greater cost savings.⁹¹ The UK salt reduction campaigns which started in 2003/2004 have been successful and the average salt intake, as measured by 24 h urinary sodium, has fallen from 9.5 to 8.6 g/day by May 2008.⁹⁴ The campaigns, which cost just £15 million,

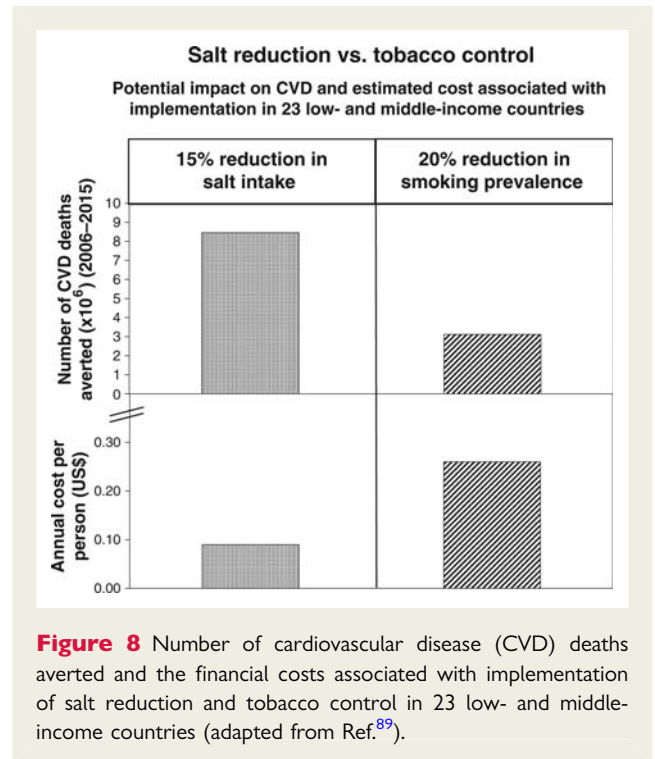


Figure 8 Number of cardiovascular disease (CVD) deaths averted and the financial costs associated with implementation of salt reduction and tobacco control in 23 low- and middle-income countries (adapted from Ref.⁸⁹).

led to ~6000 fewer cardiovascular deaths per year, saving the UK economy ~£1.5 billion per annum.^{48,95}

Asaria et al.⁸⁹ estimated the effects and cost of strategies to reduce salt intake and control tobacco use for 23 low- and middle-income countries that account for 80% of chronic disease burden in the developing world. They demonstrated that, over 10 years (from 2006 to 2015), a 15% reduction in mean population salt intake could avert 8.5 million cardiovascular deaths and a 20% reduction in smoking prevalence could avert 3.1 million cardiovascular deaths. The modest reduction in salt intake could be achieved by a voluntary reduction in the salt content of processed foods and condiments by manufacturers combined with a sustained mass-media campaign aimed to encourage dietary change within households and communities. The cost for implementing such salt reduction programmes was estimated to be US\$0.09 per person per year. The cost for tobacco control, including both price and non-price measures, was US\$0.26 per person per year (Figure 8).⁸⁹ These figures clearly suggest that a reduction in salt intake is more, or at the very least just, as cost-effective as tobacco control in terms of reducing cardiovascular disease on its own, the leading cause of death and disability worldwide.

Conclusions

The evidence for a causal relationship between chronic high salt intake, high BP, and cardiovascular disease is very strong. The totality of the evidence for salt is more robust than for any other dietary variables considered to be important in the prevention of cardiovascular disease. A reduction in salt from the current intake of 9–12 g/day to the recommended level of <5–6 g/day

will have major beneficial effects on health along with major cost savings in all countries around the world.

Each country should adopt a coherent and workable strategy to reduce salt intake. In most developed countries, ~80% of salt is hidden in foods, i.e. added by the food industry.⁹⁶ It is therefore vital to persuade the food industry to make a gradual and sustained reduction in the amount of salt they add to foods. Several countries, e.g. Finland and the UK, have successfully carried out salt reduction programmes and salt intake has already fallen.^{94,97} Many other countries, e.g. Australia, Canada, and the USA, are also stepping up their activities to reduce salt intake. In many developing countries, where most of the salt consumed comes from salt either added during cooking or from sauces, public health campaigns are needed to encourage consumers to use less salt. A modest reduction in population salt intake worldwide would result in a major improvement in public health—similar to the provision of clean water and drains in the late nineteenth century in Europe.

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References

- MacGregor GA, de Wardener HE. *Salt, Diet and Health*. Cambridge: Cambridge University Press, 1998.
- Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. *Int J Epidemiol* 2009;**38**:791–813.
- He FJ, MacGregor GA. Reducing population salt intake worldwide: from evidence to implementation. *Prog Cardiovasc Dis* 2010;**52**:363–382.
- Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ* 1988;**297**:319–328.
- Tobian L, Hanlon S. High sodium chloride diets injure arteries and raise mortality without changing blood pressure. *Hypertension* 1990;**15**:900–903.
- Perry IJ, Beevers DG. Salt intake and stroke: a possible direct effect. *J Hum Hypertens* 1992;**6**:23–25.
- Messerli FH, Schmieder RE, Weir MR. Salt. A perpetrator of hypertensive target organ disease? *Arch Intern Med* 1997;**157**:2449–2452.
- 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.
- He FJ, Markandu ND, Sagnella GA, MacGregor GA. Effect of salt intake on renal excretion of water in humans. *Hypertension* 2001;**38**:317–320.
- He FJ, Marrero NM, MacGregor GA. Salt intake is related to soft drink consumption in children and adolescents: a link to obesity?. *Hypertension* 2008;**51**:629–634.
- Cappuccio FP, Kalaitzidis R, Duneclift S, Eastwood JB. Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism. *J Nephrol* 2000;**13**:169–177.
- Joossens JV, Hill MJ, Elliott P, Stamler R, Lesaffre E, Dyer A, Nichols R, Kesteloot H. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol* 1996;**25**:494–504.
- Tsugane S, Sasazuki S, Kobayashi M, Sasaki S. Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer* 2004;**90**:128–134.
- Mohan S, Campbell NR. Salt and high blood pressure. *Clin Sci (Lond)* 2009;**117**:1–11.
- World Health Report 2002: Reducing risks, promoting healthy life. Geneva, Switzerland: World Health Organisation, 2002. www.who.int/whr/2002 (Access verified 28 May 2010).
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. 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.
- Denton D, Weisinger R, Mundy NI, Wickings EJ, Dixon A, Moisson P, Pingard AM, Shade R, Carey D, Ardaillou R, Paillard F, Chapman J, Thillet J, Michel JP. The effect of increased salt intake on blood pressure of chimpanzees. *Nat Med* 1995;**1**:1009–1016.
- Elliott P, Walker LL, Little MP, Blair-West JR, Shade RE, Lee DR, Rouquet P, Leroy E, Jeunemaitre X, Ardaillou R, Paillard F, Meneton P, Denton DA. Change in salt intake affects blood pressure of chimpanzees: implications for human populations. *Circulation* 2007;**116**:1563–1568.
- O'Shaughnessy KM. Dissecting complex traits: recent advances in hypertension genomics. *Genome Med* 2009;**1**:43.
- Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001;**104**:545–556.
- Eap CB, Bochud M, Elston RC, Bovet P, Maillard MP, Nussberger J, Schild L, Shamlaye C, Burnier M. CYP3A5 and ABCB1 genes influence blood pressure and response to treatment, and their effect is modified by salt. *Hypertension* 2007;**49**:1007–1014.
- Page LB, Damon A, Moellering RC Jr. Antecedents of cardiovascular disease in six Solomon Islands societies. *Circulation* 1974;**49**:1132–1146.
- Uzodike VO. Epidemiological studies of arterial blood pressure and hypertension in relation to electrolyte excretion in three Igbo communities in Nigeria. Thesis (MD). University of London 1993.
- Mancilha-Carvalho JJ, de Oliveira R, Esposito RJ. Blood pressure and electrolyte excretion in the Yanomamo Indians, an isolated population. *J Hum Hypertens* 1989;**3**:309–314.
- Page LB, Vandeventer DE, Nader K, Lubin NK, Page JR. Blood pressure of Qash'qai pastoral nomads in Iran in relation to culture, diet, and body form. *Am J Clin Nutr* 1981;**34**:527–538.
- Pavan L, Casiglia E, Braga LM, Winnicki M, Puato M, Pauletto P, Pessina AC. Effects of a traditional lifestyle on the cardiovascular risk profile: the Amondava population of the Brazilian Amazon. Comparison with matched African, Italian and Polish populations. *J Hypertens* 1999;**17**:749–756.
- Elliott P, Stamler J. Evidence on salt and blood pressure is consistent and persuasive. *Int J Epidemiol* 2002;**31**:316–319.
- Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M. Inter-salt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. *BMJ* 1996;**312**:1249–1253.
- Zhou BF, Stamler J, Dennis B, Moag-Stahlberg A, Okuda N, Robertson C, Zhao L, Chan Q, Elliott P. Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: the INTERMAP study. *J Hum Hypertens* 2003;**17**:623–630.
- Khaw KT, Bingham S, Welch A, Luben R, O'Brien E, Wareham N, Day N. Blood pressure and urinary sodium in men and women: the Norfolk Cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk). *Am J Clin Nutr* 2004;**80**:1397–1403.
- He J, Klag MJ, Whelton PK, Chen JY, Mo JP, Qian MC, Mo PS, He GQ. Migration, blood pressure pattern, and hypertension: the Yi Migrant Study. *Am J Epidemiol* 1991;**134**:1085–1101.
- Poulter NR, Khaw KT, Hopwood BE, Mugambi M, Peart WS, Rose G, Sever PS. The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *BMJ* 1990;**300**:967–972.
- Forte JG, Miguel JM, Miguel MJ, de Padua F, Rose G. Salt and blood pressure: a community trial. *J Hum Hypertens* 1989;**3**:179–184.
- Tian HG, Guo ZY, Hu G, Yu SJ, Sun W, Pietinen P, Nissinen A. Changes in sodium intake and blood pressure in a community-based intervention project in China. *J Hum Hypertens* 1995;**9**:959–968.
- Takahashi Y, Sasaki S, Okubo S, Hayashi M, Tsugane S. Blood pressure change in a free-living population-based dietary modification study in Japan. *J Hypertens* 2006;**24**:451–458.
- Staessen J, Bulpitt CJ, Fagard R, Joossens JV, Lijnen P, Amery A. Salt intake and blood pressure in the general population: a controlled intervention trial in two towns. *J Hypertens* 1988;**6**:965–973.
- Tuomilehto J, Puska P, Nissinen A, Salonen J, Tanskanen A, Pietinen P, Wolf E. Community-based prevention of hypertension in North Karelia, Finland. *Ann Clin Res* 1984;**16**(Suppl. 43):18–27.
- Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III—analysis of data from trials of salt reduction. *BMJ* 1991;**302**:819–824.
- Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996;**275**:1590–1597.
- Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr* 1997;**65**:643S–651S.
- Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride: a meta-analysis. *JAMA* 1998;**279**:1383–1391.
- Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Systematic review of long term effects of advice to reduce dietary salt in adults. *BMJ* 2002;**325**:628–632.
- He FJ, Markandu ND, MacGregor GA. Importance of the renin system for determining blood pressure fall with acute salt restriction in hypertensive and normotensive whites. *Hypertension* 2001;**38**:321–325.

44. 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.
45. 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;**334**:1244–1247.
46. 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. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001;**344**:3–10.
47. Scientific Advisory Committee on Nutrition, Salt and health. 2003. The Stationery Office. www.sacn.gov.uk/pdfs/sacn_salt_final.pdf (Access verified 15 November 2010).
48. National Institute for Health and Clinical Excellence (NICE). Guidance on the prevention of cardiovascular disease at the population level. <http://guidance.nice.org.uk/PH25> (Access verified 14 July 2010).
49. Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG, Conlin PR, Svetkey LP, Erlinger TP, Moore TJ, Karanja N. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med* 2001;**135**:1019–1028.
50. He FJ, Markandu ND, Sagnella GA, MacGregor GA. Importance of the renin system in determining blood pressure fall with salt restriction in black and white hypertensives. *Hypertension* 1998;**32**:820–824.
51. He FJ, MacGregor GA. Salt, blood pressure and the renin-angiotensin system. *J Renin Angiotensin Aldosterone Syst* 2003;**4**:11–16.
52. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J. Primary prevention of hypertension: clinical and public health advisory from the National High Blood Pressure Education Program. *JAMA* 2002;**288**:1882–1888.
53. Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH Jr, Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Cutler JA. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA* 1998;**279**:839–846.
54. The Trials of Hypertension Prevention Collaborative Research Group. 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. *Arch Intern Med* 1997;**157**:657–667.
55. MacGregor GA, Markandu ND, Singer DR, Cappuccio FP, Shore AC, Sagnella GA. Moderate sodium restriction with angiotensin converting enzyme inhibitor in essential hypertension: a double blind study. *Br Med J (Clin Res Ed)* 1987;**294**:531–534.
56. Falconnet C, Bochud M, Bovet P, Maillard M, Burnier M. Gender difference in the response to an angiotensin-converting enzyme inhibitor and a diuretic in hypertensive patients of African descent. *J Hypertens* 2004;**22**:1213–1220.
57. 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.
58. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;**322**:1561–1566.
59. Devereux RB, Dahlof B, Gerds E, Boman K, Nieminen MS, Papademetriou V, Rokkedal J, Harris KE, Edelman JM, Wachtell K. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. *Circulation* 2004;**110**:1456–1462.
60. Burnier M, Phan O, Wang Q. High salt intake: a cause of blood pressure-independent left ventricular hypertrophy?. *Nephrol Dial Transplant* 2007;**22**:2426–2429.
61. Jin Y, Kuznetsova T, Maillard M, Richart T, Thijs L, Bochud M, Herregods MC, Burnier M, Fagard R, Staessen JA. Independent relations of left ventricular structure with the 24-hour urinary excretion of sodium and aldosterone. *Hypertension* 2009;**54**:489–495.
62. Ferrara LA, de Simone G, Paganini F, Mancini M. Left ventricular mass reduction during salt depletion in arterial hypertension. *Hypertension* 1984;**6**:755–759.
63. Liebson PR, Grandits GA, Dianzumba S, Prineas RJ, Grimm RH Jr, Neaton JD, Stamler J. Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). *Circulation* 1995;**91**:698–706.
64. Jula AM, Karanko HM. Effects on left ventricular hypertrophy of long-term non-pharmacological treatment with sodium restriction in mild-to-moderate essential hypertension. *Circulation* 1994;**89**:1023–1031.
65. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;**289**:194–202.
66. Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourciere Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JM, Thomas JD, Zile MR, Aurigemma GP. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet* 2007;**369**:2079–2087.
67. Langenfeld MR, Schobel H, Veelken R, Weihprecht H, Schmieder RE. Impact of dietary sodium intake on left ventricular diastolic filling in early essential hypertension. *Eur Heart J* 1998;**19**:951–958.
68. Kagiya S, Koga T, Kaseda S, Ishihara S, Kawazoe N, Sadoshima S, Matsumura K, Takata Y, Tsuchihashi T, Iida M. Correlation between increased urinary sodium excretion and decreased left ventricular diastolic function in patients with type 2 diabetes mellitus. *Clin Cardiol* 2009;**32**:569–574.
69. 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.
70. Gu J, Anand V, Shek E, Moore M, Brady A, Kelly W, Adair T. Sodium induces hypertrophy of cultured myocardial myoblasts and vascular smooth muscle cells. *Hypertension* 1998;**31**:1083–1087.
71. He FJ, MacGregor GA. How far should salt intake be reduced?. *Hypertension* 2003;**42**:1093–1099.
72. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 2009;**339**:b4567.
73. Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension* 1995;**25**:1144–1152.
74. 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.
75. 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.
76. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr., Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;**42**:1206–1252.
77. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Dietary sodium intake and incidence of congestive heart failure in overweight US men and women: first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Arch Intern Med* 2002;**162**:1619–1624.
78. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Arch Intern Med* 2000;**160**:777–784.
79. Lipscombe LL, Gomes T, Levesque LE, Hux JE, Jurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA* 2007;**298**:2634–2643.
80. Antonios TF, MacGregor GA. Salt—more adverse effects. *Lancet* 1996;**348**:250–251.
81. Hummel SL, DeFranco AC, Skorcz S, Montoye CK, Koelling TM. Recommendation of low-salt diet and short-term outcomes in heart failure with preserved systolic function. *Am J Med* 2009;**122**:1029–1036.
82. Paterna S, Gaspare P, Fasullo S, Sarullo FM, Di Pasquale P. Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend?. *Clin Sci (Lond)* 2008;**114**:221–230.
83. Paterna S, Parrinello G, Cannizzaro S, Fasullo S, Torres D, Sarullo FM, Di Pasquale P. Medium term effects of different dosage of diuretic, sodium, and fluid administration on neurohormonal and clinical outcome in patients with recently compensated heart failure. *Am J Cardiol* 2009;**103**:93–102.
84. Missouris CG, Cappuccio FP, Markandu ND, MacGregor GA. Diuretics and oedema: how to avoid rebound sodium retention. *Lancet* 1992;**339**:1546.
85. Beich KR, Yancy C. The heart failure and sodium restriction controversy: challenging conventional practice. *Nutr Clin Pract* 2008;**23**:477–486.
86. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Puri SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellems I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC

- (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;**29**:2388–2442.
87. Selmer RM, Kristiansen IS, Haglerod A, Graff-Iversen S, Larsen HK, Meyer HE, Bonaa KH, Thelle DS. Cost and health consequences of reducing the population intake of salt. *J Epidemiol Community Health* 2000;**54**:697–702.
88. Joffres MR, Campbell NR, Manns B, Tu K. Estimate of the benefits of a population-based reduction in dietary sodium additives on hypertension and its related health care costs in Canada. *Can J Cardiol* 2007;**23**:437–443.
89. 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.
90. Murray CJ, Lauer JA, Hutubessy RC, Niessen L, Tomijima N, Rodgers A, Lawes CM, Evans DB. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003;**361**:717–725.
91. 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.
92. 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.
93. Smith-Spangler CM, Juusola JL, Enns EA, Owens DK, Garber AM. Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. *Ann Intern Med* 2010;**152**:481–487, W170–483.
94. Food Standards Agency. Dietary sodium levels surveys, 22 July 2008. www.food.gov.uk/science/dietarysurveys/urinary (Access verified 28 May 2010).
95. Ofcom, Office of Communications. Impact assessment. http://stakeholders.ofcom.org.uk/binaries/consultations/foodads_new/ia.pdf (Access verified 13 July 2010).
96. James WVP, Ralph A, Sanchez-Castillo CP. The dominance of salt in manufactured food in the sodium intake of affluent societies. *Lancet* 1987;**1**:426–429.
97. Karppanen H, Mervaala E. Sodium intake and hypertension. *Prog Cardiovasc Dis* 2006;**49**:59–75.