# Presidential Address: 21st Scientific Meeting of the International Society of Hypertension

# Dietary sodium and cardiovascular disease: the 'J'-shaped relation

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## Introduction

High blood pressure is the leading risk factor for stroke and coronary artery disease – the world's leading causes of death. Because sodium metabolism plays a central role in the modulation of blood pressure, it is altogether fitting that its relation to both blood pressure and cardiovascular disease should play a prominent role in this, the 21st Scientific Meeting of the International Society of Hypertension.

My presentation will focus on the health effects of variations in sodium intake in populations. Many clinical situations exist in which either restriction or supplementation of dietary sodium is known to be of enormous benefit – or harm – to human health. By contrast, an appropriate level of dietary sodium for the general population – if there is one – is unknown.

During the past decade, a considerable body of basic, clinical and epidemiological evidence has accumulated to address the link between dietary sodium and health. Thus, discussions about salt need no longer depend upon belief, logic, extrapolation from animal experiments, proxy end points, ecological studies and/or authority. Instead, a substantial body of solid empiric evidence now informs questions about the role of salt in human biology and therapeutics. For example, the relation of salt to blood pressure is now firmly established. Moreover, 10 reported prospective observational studies have addressed the more pressing question of how a reduced salt intake relates to morbidity, mortality and duration of life. Together, these provide a sound basis upon which to construct a unifying hypothesis on how sodium intake may affect health.

## Salt and blood pressure

Multiple clinical trials have established that a reduction of 75–100 mmol/day in sodium intake (more than half the usual US diet), on average, reduces systolic blood pressure by several millimeters of mercury (mmHg), and diastolic blood pressure by 1 or 2 mmHg [1]. Most salt to blood pressure trials were short, and more extended study suggests that despite continued adherence to a lower salt regimen, the pressure effect tends to attenuate over time [2]. However, individual responses vary and can include both a substantial fall, or actually, an increase in pressure, reflecting the interplay of buffering responses to a drop in sodium intake that protect pressure and flow.

In normal circumstances, environmental, behavioral and genetic influences produce wide variation in sodium intake. However, blood pressure is generally maintained in a normal range by the capacity of the kidney to vary sodium excretion from near zero to several hundreds of mmol/day without much change in pressure [3]. 'Salt sensitivity', which is imprecisely defined as a sharp fall in pressure in response to salt restriction, does occur, but may not be immutable. For example, Morris *et al.* [4] have shown that the sensitivity commonly seen in potassium-depleted subjects can be reversed by its repletion. However, when the physiological feedback loop that modulates sodium balance is compromised by genetic disorders or dysfunction of the renin–angiotensin feedback loop, for example, the capacity to buffer variations in salt load is compromised, and blood pressure changes as sodium intake varies [3]. Nevertheless, despite this marked inter- and intra-individual heterogeneity, on average, a substantial reduction in population sodium intake will generate a measurable fall in average blood pressure.

## Other consequences of reduced sodium intake

It is this measurable drop in average pressure that has inspired many authorities to argue that reduced dietary sodium consumption will translate into a net reduction in stroke and heart disease incidence. Attractive as this simple formulation has been, the reality is that restriction

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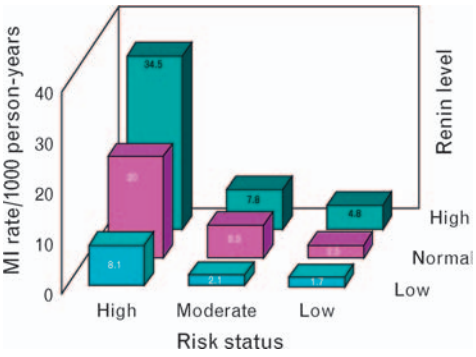
of dietary salt has multiple other consequences – some of which can be harmful.

It is these non-hemodynamic effects of salt restriction that are of most concern. Randomized clinical trials have established that reduced sodium intake is associated with improved calcium balance, increased sympathetic nerve activity [5], a three- to six-fold increase in plasma renin activity and a two- to three-fold increase in aldosterone [1], and decreased insulin sensitivity [6]. Other effects for which evidence exists include reduced left ventricular mass and osteoporosis, and increased incidence of gastric cancer [7–9]. Perhaps of greatest concern, in view of the close correlation between sodium and total caloric intake, and virtually every known nutrient, is the strong possibility that a diet constructed to achieve a reduced sodium content might be associated with a disturbance (or reduction) in the intake of other needed nutrients. History and experience suggest that the possibility of unanticipated effects can be ignored only at one's peril.

My own interest in the sodium to cardiovascular outcomes relation grew out of clinical studies of the renin–angiotensin system (RAS) led by John Laragh. He and his colleagues demonstrated the intimate involvement of the RAS in hemodynamic control through modulation of volume and vasoconstriction. Based on this analysis, he postulated that the renin system, reflected by plasma renin activity (PRA), should be suppressed in persons with hypertension. He further hypothesized that a failure of suppression would have pathological cardiovascular consequences. Findings consistent with this hypothesis were obtained in a prospective observational study of nearly 4000 participants in a worksite-based hypertension treatment program in New York City (Fig. 1) [10]. There was a robust, continuous and independent association of pretreatment PRA and subsequent myocardial infarction among these successfully treated hypertensive patients. More recently, analysis of the PROGRESS Trial has produced similar results [11].

**Fig. 1**




The Worksite Hypertension Program [13]. Plasma renin activity: an independent risk factor for myocardial infarction (MI).

## Sodium intake and cardiovascular disease outcomes

In view of the known strong inverse correlation of sodium intake and PRA, it seemed reasonable to explore the relation of sodium intake to cardiovascular outcomes. Surprisingly, a literature search in the early 1990s yielded only one study linking sodium intake and cardiovascular disease (CVD) outcomes. This single observational study among Japanese migrants acculturated to Hawaiian life found no association of sodium to cardiovascular outcome [12].

In view of the then (and now) near unanimous recommendation by authorities that sodium intake be reduced – especially in hypertensive subjects – the absence of supportive evidence was striking. We therefore examined the relation of 24-h urinary sodium excretion to cardiovascular outcomes among our 3000 worksite hypertensive subjects and found a continuous inverse relation of sodium to CVD morbidity and mortality, largely driven by the association with myocardial infarction in men [13]. Subjects in the lowest quartile of sodium intake were 4.3. times more likely to have a heart attack than were those in the highest.

In the 11 years since that first report linking sodium intake to outcomes, there has been no further report specifically addressing this question in hypertensive patients. In a world of 1 billion hypertensive persons, with perhaps 200 million in treatment, and 200 000 participants in long-term antihypertensive treatment studies, and in the face of unequivocal advice to reduce salt intake, it is curious that no additional observational study has been published to either confirm or challenge those findings.

Since the 1995 report on hypertensive patients, eight additional observational studies addressing the salt to outcome association have been published. The results of these now altogether 10 reports have varied sharply. For example, in Takayama, Japan, a community-based prospective observational study revealed a strong direct association of sodium intake (average intake 5400 mg), as measured by dietary recall, and stroke [14]. In these 29 079 participants (13 355 males), followed for 7 years, there were 269 fatal or non-fatal strokes. A direct association of sodium intake (1st vs 3rd tertile) was found in males but not females.

The most recent report, from our group in New York, examined the experience of 7500 participants in a representative sample of the US population [15]. During 12 years of follow-up, there were 1354 deaths, of which 541 were cardiovascular. A strong, consistent, independent and significant continuous inverse association of dietary sodium and cardiovascular mortality was found – with results indistinguishable from the analysis of the

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**Table 1 Sodium (Na) and cardiovascular disease (CVD): NHANES II [15]. CVD-adjusted mortality hazard ratios (HR)**

| Na | HR | 95% CI | *P* |
|---|---|---|---|
| Na per 1000 mg | 0.89 | 0.80, 0.99 | 0.03 |
| Na mg/cal | 0.80 | 0.68, 0.94 | 0.008 |
| Na < 2300 mg | 1.37 | 1.03, 1.81 | 0.03 |
| Na < residuals adjusted median | 1.22 | 1.01, 1.49 | 0.04 |

CI, confidence interval. Adjusted for age, sex, race, smoking, alcohol, systolic blood pressure, blood pressure history, body mass index, education, physical activity, dietary potassium, history of diabetes, cholesterol, (calories).

NHANES I Follow-up Study [16]. Table 1 describes the relative risk for coronary heart disease (CVD) as estimated by four different analytic techniques designed to avoid the confounding effect of the close correlation between sodium and caloric intake. Subgroup analysis, after stratification by some 27 characteristics, revealed point estimates consistent with the overall findings except for persons with body mass index (BMI) >30 and those older than 55 (neither of which differed significantly from unity).

It is important to note that none of these studies examined the effect of change in sodium intake, but defined associations of regular sodium intake and outcome. Thus, this large body of observational data provides no guidance as to the effect that an intervention to modify sodium intake might have on CVD outcomes. Overall, the experience of more than 130 000 subjects has been reported in 10 published epidemiological studies [12,13,15–21]. During 1 229 899 patient years of observation, 7761 fatal and non-fatal cardiovascular events occurred (Table 2).

Epidemiological data are, of course, imperfect tools by which to establish causality. Occasionally, as in the case of tobacco, when the data are overwhelming and consistent across a variety of settings, therapeutic conclusions can be drawn with confidence. However, when multiple effects have been shown to result from an intervention (low sodium diet), the only way to assess their net effect is by directly linking that intervention to health outcomes. The alternative is to either extrapolate from one or another individual effect, or to guess at what their integrated impact might be. In the absence of a clinical trial, observational data provide the most useful means by which to identify a reasonable hypothesis that accommodates the available data and can be tested if therapeutic consequences are to be considered. It is, therefore, fortunate that a large number of studies link salt intake to cardiovascular morbidity and mortality.

**Table 2 Cohort studies linking sodium to cardiovascular disease (CVD)**

| Study | Subjects | Follow-up (years) | Person-years | End point events |
|---|---|---|---|---|
| HHS [12] | 7895 | 10 | 78 950 | 238 Stroke |
| WSH [13] | 2937 | 3.8 | 10 150 | 55 CHD |
| SHS [20] | 11 629 | 7.6 | 88 380 | 1178 CVD |
| HPS [18] | 43 738 | 8 | 349 904 | 328 Stroke |
| NHANES I [16] | 11 346 | 19 | 215 574 | 1970 Fatal CV |
| MRFIT [17] | 11 696 | 10 | 116 960 | 2714 Fatal CHD |
| NHANES I[a] [19] | 2688 | 19 | 43 788 | 379 Fatal CV |
| NHANES II [15] | 7154 | 13.7 | 98 010 | 541 Fatal CV |
| FHS [21] | 2463 | 10 | 24 630 | 148 Fatal CV |
| Takayama [14] | 29 079 | 7 | 203 553 | 169 Stroke |
| Totals | 131 625 | | 1 289 899 | 7771 |

CHD, coronary heart disease; CV, cardiovascular; FHS, Finish Heart Study; HHS, Honolulu Heart Study; HPS, Health Professionals Follow-up Study; MRFIT, Multiple Risk Factor Intervention Trial; NHANES, National Health and Nutrition Examination Survey; SHS, Scottish Heart Health Study; WSH, Worksite Hypertension Study. [a] 28% obese.

Of course, it is a daunting challenge to assess sodium intake accurately once, much less to establish usual sodium intake. However, when several studies yield similar results, measurement error may be less consequential. In this regard, since all but one of the 'moderate' intake studies took place in the United States, it is fortunate that the consistency of the estimation of US sodium intake has been established by different means. The sodium levels obtained by dietary recall in NHANES II (2718 mg/24 h), was about 10% less than that estimated by 24-h sodium excretion in the four US sites in the Intersalt Study (3005 mg/24 h) [22]. This modest difference may be accounted for by the inability to assess table salt use through dietary recall. It is also interesting to note that most of the 52 sites worldwide studied in Intersalt had sodium intakes around 3 g/day. These US estimates differ from the two 'high' sodium communities (5400 mg/24 h in the Japanese and 4400 mg/24 h in the Finnish Study). The relationships observed between sodium intake and cardiovascular outcomes may reflect a direct effect of sodium. It is also possible that measured sodium may reflect other characteristics of overall diet. Thus, for example, the nature of the impact on cardiovascular events of diets with higher sodium may differ between the US and Japan because of the overall composition of their diets. In other words, the context in which various sodium intakes exist may be more important than the sodium intake itself.

The available data can be divided (although some overlap at the extremes probably exists) into two groups by level of sodium intake. In the first group of eight [12,13,15–20] sodium intake was about 3 g/24 h. These are classified as 'moderate' intake communities (Table 3). The remaining two studies were performed in 'high' sodium environments with intakes of 4.5–5.5 g/24 h (Table 4) [14,21]. In four of the eight 'moderate' intake studies there was no association of intake to CVD (Table 3) [12,17,18,20]. In three, there was a significant inverse relation in the entire group, [13,15,16] and in one [19], there was a direct relationship. This was in the 28% obese subset of participants in NHANES I [16]. In total the NHANES population, by contrast, there was an inverse relationship. This single outlier may reflect the play of chance, selection or

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**Table 3 Health outcomes associated with lower versus higher sodium intake: moderate-intake societies**

| Study | Year | D/U | $Na^+$ (mg/day) | Outcome |
|---|---|---|---|---|
| HHS [12] | 1985 | D | 2000 | L = H |
| WSH [13] | 1995 | U | 2600 | L > H |
| SHS [20] | 1997 | D | ??? | Mixed |
| HPS [18] | 1997 | D | 3000 | L = H |
| NHANES I [16] | 1998 | D | 2400 | L > H |
| MRFIT [17] | 2000 | D | 2921 | L = H |
| NHANES I [19][a] | 2000 | D | 2000 | L < H |
| NHANES II [15] | 2006 | D | 2718 | L > H |

D/U, sodium estimated by diet (D) or 24-h urine collection (U); H, higher sodium intake; HHS, Honolulu Heart Study; HPS, Health Professionals Follow-up Study; L, lower sodium intake; MRFIT, Multiple Risk Factor Intervention Trial; NHANES, National Health and Nutrition Examination Survey; SHS, Scottish Heart Health Study; WSH, Worksite Hypertension Study. [a] 28% obese.

the possibility that the interaction of obesity and dietary sodium intake may influence outcomes. Given the experience of 100 000 subjects with over 1 million years of observation, it is unlikely that some meaningful benefit among populations with moderate sodium intake has eluded detection.

By contrast, both studies in high-salt communities revealed a continuous and independent direct association of salt intake and CVD (Table 4) – although in neither was the effect seen throughout the studied populations.

## A hypothesis that fits the evidence

The facts that need to be accommodated are:

(1) a reduction of sodium intake by 160 mmol in normotensive persons produces a 1.2 mmHg fall in systolic blood pressure; a reduction of 118 mmol in hypertensive persons produces a 3.9 mmHg systolic fall [1];
(2) the bulk of evidence in moderate-intake societies suggests either no association or an inverse relationship, with a positive association in one subgroup analysis; and
(3) a direct association of higher sodium with increased CVD in two high-salt populations.

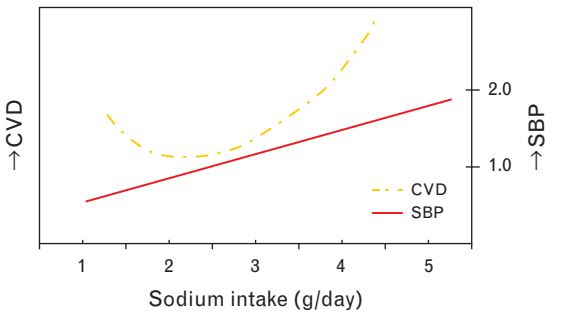
The dissociation between the blood pressure and the cardiovascular effects is analogous to that seen with alcohol intake [23]. The findings in the moderate-salt studies could be explained by an increase in PRA, aldosterone, sympathetic nerve activity and, perhaps, insulin resistance, as well as a diet altered to accomodate the sodium intake that also produced an unanticipated adverse effect. Some, or all of these adverse effects may overwhelm any benefit related to a lower blood pressure. In a high-salt environment, where overall diet is not likely to be compromised by consuming less sodium, the blood pressure effect might dominate and translate into a health benefit.

**Table 4 Health outcomes associated with lower versus higher sodium intake: high-intake societies**

| Study | Year | D/U | $Na^+$ (mg/day) | Outcome |
|---|---|---|---|---|
| FHS [21] | 2001 | U | ±4600 | L < H |
| Takayama [14] | 2005 | U | ±5400 | L < H |

D/U, sodium estimated by diet (D) or 24-h urine collection (U); FHS, Finish Heart Study; H, higher sodium intake; L, lower sodium intake.

**Fig. 2**




The relation of dietary sodium intake to systolic blood pressure (SBP) and cardiovascular events (CVD). In normotensive persons a decrease in sodium intake of 160 mmol produces a 1.2 mmHg fall in systolic blood pressure.

The task of the epidemiologist is to generate a hypothesis that accommodates all the available evidence – and ideally one that can be tested. Because there is probably overlap between the two groups, and most studies in the moderate group show little or no impact of altering sodium in a wide range around 3 g/day, it seems reasonable to suspect that 'moderate' and 'high' sodium groups represent different parts of an epidemiologic continuum, rather than a bimodal distribution (Fig. 2). This can best be described by a 'J'-shaped curve, with evidence for harm at the low and high extremes, and little effect in the broad middle range. A 'J'-shaped relationship is commonly seen in biology. To establish the validity of the 'J'-shaped relationship presented here, an attractive next step might be to pool individual data points from the multiple studies (as has been done with blood pressure and cardiovascular events) for a more precise assessment of the sodium to outcome relation through the full range of sodium intake.

## Practical implications of the sodium hypothesis

This enormous body of observational data still falls short of proving any causal relationship, nor can it support a policy determination, but it does provide a way forward.

(1) Context matters. It is important to establish the sodium intake of communities and individuals to assess the likely effect of any intervention.
(2) It is unlikely that a health benefit could be achieved by construction of a diet to produce a reduction in sodium intake, in settings such as North America

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where sodium intake is around 3 g/day. In fact, the available evidence suggests the real possibility of harm.

(3) On the other hand, a benefit might well attend reduction of sodium intake in settings, such as much of Asia, where regular daily sodium intake exceeds 4–5 g. This may be particularly true when stroke is the major cardiovascular outcome, since the blood pressure relationship is steeper here than for myocardial infarction.

This hypothesis can be tested. A successful long-term randomized trial of sodium reduction has already been conducted. In the TOPH Trial, 2400 subjects were randomized, and 36–40 month follow-up was achieved in 96% [2]. The mean decline in urinary sodium was 50 mmol at 6 months, and 40 mmol at 36 months. This was achieved in a moderate sodium context where most sodium is consumed in prepared foods. Since observational studies indicate that the appropriate setting for testing reduced sodium intake would be in a high-salt environment, where most salt intake is discretionary, any danger of compromising overall diet would be minimized.

In settings of moderate salt intake, where the data fail to suggest a benefit, and perhaps some harm, there seems little ethical or medical justification for a clinical trial. At the very least, however, in view of the weight of existing observational evidence, any recommendation for widespread sodium reduction in 'moderate' sodium environments should be preceded by accumulation of convincing evidence that a health benefit might be achieved.

## Summary

A substantial body of observational data now supports the hypothesis that the relationship between sodium intake and cardiovascular outcomes is 'J' shaped. While further rigorous observational data are always welcome, they are unlikely to change the thrust of the data already available for the 'moderate' sodium communities. The likelihood that individuals or populations consuming about 3 g of sodium per day would benefit from a diet with less sodium seems remote. By contrast, in settings where sodium intake is 4–5 g or above, similarly obtained evidence suggests that benefit through reduction may be more likely. The next step is to determine whether or not this hoped-for reduction of cardiovascular events can actually be realized by sodium restriction among high salt consumers.

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