The relationship between dietary sodium intake, alone or in combination with potassium intake, and risk of hypertension in adults

Diet-disease relationship review

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Table of contents:

Purpose of this review

The purpose of this review is to determine whether there are substantiated relationships between dietary sodium intake, alone or in combination with potassium intake, and risk of developing hypertension in adults and if so, the degree of certainty with which this relationship substantiated. The findings of this review will be used to guide the development of claim(s) about this relationship.

This review has been conducted in accordance with a reviewing template prepared by Food Standards Australia New Zealand (FSANZ) and draws on a review conducted by Health Canada in 2000 [1].

Critical appraisal of previous review of this diet-health relationship.

The Health Canada review published in 2000 [1] addresses the question whether lowering sodium intake in a population will reduce the risk of hypertension. The Canadian document draws on the US FDA position, published in draft form in 1991 and revised in 1993, with additional support from 4 meta-analyses [2-5]. The conclusion of the Canadian review supports the FDA position [6] and quantifies the association between sodium restriction of 100 mmol/d as equivalent to a reduction of 1.2 mm Hg in systolic blood pressure in normotensives. In hypertensive individuals sodium restriction results in a reduction of 4 mmHg in systolic and 2 mmHg in diastolic blood pressure.

1 (a) Appraisal of the selection and assessment of evidence in the review.

Were there key studies at the time the Canadian review was prepared that were not considered in their review? If so, would inclusion of these studies have changed the conclusions reached?

The TONE study [7] tested the effect of sodium reduction and weight loss independently and together, in older persons (60-80 y). Compared with usual care, sodium restriction evidenced by a reduction in urinary sodium excretion[1], resulted in a significant reduction in systolic (-3.4 mm Hg) and diastolic (-1.9) blood pressure. Weight loss alone or combined with sodium restriction produced further reductions in blood pressure. The reduction in blood pressure is greater in relatively older compared to younger persons and the authors attribute the large change to enhanced compliance with the intervention and the motivation to reduce dependence on antihypertensive medication. The TONE Study appears in Appendix 1 of the Canadian review and in the tabulation of relevant research (page 33) but is omitted from any further discussion and from the list of cited publications. The reasons for its exclusion are unclear. The Canadian document acknowledges the effect of age on blood pressure (Section 6.2.1, page 18) and the conclusion (6.5, page 20) is unlikely to be affected by the apparent omission of the TONE study.

[1] In humans, urinary excretion of sodium roughly equals sodium intake. In a long-term study in men and women consuming self-selected diets, sodium excretion in urine was 86% of total intake (Holbrook JT et al Am J Clin Nutr 1994; 40: 786-793).

Socioeconomic differences were not included in the Canadian document as factors that are potentially related to blood pressure (Section 5.5, page 14). Analysis of participants' baseline characteristics in TOMHS [8] showed that education and income were inversely correlated with sodium excretion and blood pressure in African Americans. The omission of this report from the Canadian document does not alter its conclusions.

Did the Canadian review correctly interpret the findings of the original US review ?

The US Proposed Rule [9] concluded that the effect of change in dietary sodium on blood pressure is small but statistically significant, and acknowledged the impact on both normo- and hyper-tensive populations, the wide variation in response and the existence of "salt sensitivity". The Final Rule [6] updated the scientific data and concluded that the new evidence strengthens the proposed regulation. The Canadian review has interpreted correctly the US Proposed and Final Rules, and based on new evidence (ie published since the US Final Rule and before the release of the Canadian review in 2000) has provided further support for the proposed health claim.

Was the level of evidence drawn on suitable for substantiating the relationships ?

The key evidence used in the Canadian review is derived from four meta-analyses on the effect of sodium restriction [2-5] and one meta-analysis on the effect of potassium supplementation [10]. The evaluations by Swales [2] and Cutler et al [4] were published as a book chapter and a journal supplement, respectively, and it is unlikely that these meta-analyses were subjected to peer-review. The reports of Midgley et al [3], Graudal et al [5] and Whelton et al [10] appeared in JAMA, a peer-reviewed international journal.

There are differences reported in the outcomes of the meta-analyses that depend on the individuals' characteristics. In normotensive individuals, salt restriction is reported to statistically reduce systolic blood pressure in three meta-analyses [3-5] whereas diastolic blood pressure is lowered in one meta-analysis [4]. Swales [2] reports a reduction is systolic and diastolic blood pressure but the level of statistical significance is not indicated. In hypertensive individuals, salt restriction results in lower systolic and diastolic blood pressure in all meta-analyses [2-5] however, Swales [2] does not indicate the level of significance.

The meta-analysis with the largest number of trials (n=56 in normotensive and n=58 in hypertensive individuals), and published in a peer-reviewed journal [5], concludes that salt restriction results in a statistically significant reduction in systolic and diastolic blood pressure

in hypertensive individuals, and a statistically significant reduction in diastolic blood pressure in normotensive individuals.
The effect of potassium on blood pressure was evaluated in a meta-analysis of 33 trials [10]. Potassium supplementation was found to be associated with a significant reduction in mean systolic (-3.11 mm Hg) and diastolic (-1.97 mm Hg) blood pressure and the effect is greater in studies with a reported higher level of urinary sodium excretion.

Taken together, the outcomes of the meta-analyses provide convincing evidence that salt restriction results in statistically significant albeit small reductions in blood pressure, and potassium enhances blood pressure reduction when sodium intake is high.

Was the interpretation of some or all cited evidence appropriate ? Did the review adequately consider the limitations in the available evidence ?
The interpretation of key evidence [2-5, 10, 11] was appropriate. The INTERSALT Study [11], a cross sectional study involving more than 10,000 individuals demonstrated a positive correlation between urinary sodium excretion and blood pressure. The study is interpreted appropriately and the limitations, particularly the potential difficulties in the statistical evaluations and corrections for potential confounding factors such as salt sensitivity, alcohol intake and BMI, are outlined adequately. Other key references [2-5, 10] were interpreted appropriately, as discussed in Part 1(b) below.

Did the review determine the required changes of intake of sodium (or sodium and potassium) for a reduction in population risk of hypertension to be achieved ?
The required changes in sodium intake were stated in Sections 6.4 and 6.5. In normotensive individuals a decrease of 100 mmol/d in sodium is associated with a reduction of about 1.2 mmHg systolic and about 0.5 mmHg diastolic pressure. In hypertensive individuals a sodium decrease of about 100 mmol/d is associated with reductions of 4 mmHg in systolic pressure and about 2 mmHg in diastolic pressure.
Potassium intake and its relation to blood pressure is discussed briefly (Section 5.4.2). The meta-analysis of Whelton et al [10] showed a significant reduction in systolic and diastolic blood pressure and the effect was enhanced in those with a high sodium intake. A high intake of potassium (120mmol/d) is reported to decrease salt sensitivity in African-Americans.

1(b) Re-analysis of pivotal studies cited in the review

The Canadian review placed substantial weighting on the meta-analyses published since 1991 (Canadian report pp 37-40), with the exception of Law et al [12] which was de-emphasised because it included a large number of trials that were not randomised. The meta-analyses span a range of publication years, combine different numbers of trials in normotensive and hypertensive individuals, and are carried out by different research groups. All analyses show consistently that sodium restriction in hypertensive subjects produces reductions in systolic and diastolic blood pressure that were small but statistically significant. In normotensive individuals, only systolic blood pressure is affected by sodium restriction. The risk of cardiovascular disease rises with blood pressure throughout the normotensive blood pressure range [55] and almost 60% of coronary heart disease events and 45-50% of strokes occur in those with high normal blood pressure. Hence, persons with normal blood pressure may also benefit from lifestyle modification.

The meta-analyses cited in the Canadian Review are re-evaluated as follows:
Swales [2] carried out a meta-analysis on trials published between 1973-1993. Inclusion criteria were that trials should be randomised, longer than 2 week duration, more than 10 subjects in each trial, compliance assessed by urinary sodium excretion, blood pressure independently provided and no dietary changes other than sodium restriction. Sodium restriction was shown to result in modest reductions in blood pressure in hypertensives (Table 1). In normotensive subjects, the very small blood pressure falls were equivalent to those predicted by the INTERSALT study. The statistical significance of the changes reported in Table 1 is not indicated by Swales.

Canadian researchers [3] carried out a meta-analysis on trials published from 1966-1994. The inclusion criteria were that trials had randomized allocation to control and intervention, compliance assessed by urinary sodium excretion, with outcome measures of systolic and diastolic blood pressure. A total of 56 trials met the criteria but demonstrated significant heterogeneity and publication bias. Publication bias was examined further and found to be evident in favour of small trials reporting a reduction in blood pressure. After adjustment for measurement error in urinary sodium excretion, regression analysis showed a decrease in systolic (-3.7 mmHg, $P<0.001$) and diastolic (-0.9 mmHg, $P=0.09$) blood pressure, for a 100 mmol/day reduction in sodium excretion, in the hypertensive trials (28 trials, n=1131 subjects). For the same reduction in daily sodium excretion, the normotensive individuals (28

trials, n=2374 subjects) showed decreases of 1.0 mmHg (P<0.001) and 0.1 mmHg (P=0.64) in systolic and diastolic blood pressure, respectively. Subgroup analysis demonstrated larger decreases in blood pressure in the trials of older hypertensive individuals. In normotensive individuals (14 trials) there was no significant change in blood pressure. The authors state that the results of sodium restriction do not support the (US) Nutrition Labeling and Education Act, and question the wisdom of universal sodium restriction without evidence of long-term benefits.

Cutler et al [4] updated their meta-analysis published in 1991 [13]. For selection in the meta-analysis, trials required random allocation, a design free of confounding, compliance as assessed by urinary sodium excretion, measures of systolic and diastolic blood pressure. A total of 32 trials (n=2,635) were included: 22 trials in hypertensive participants and 12 trials in normotensive patients. Lower intake of sodium was shown to reduce blood pressure in hypertensive and normotensive participants. Linear regression analysis weighted according to sample size, showed a sodium-blood pressure dose response that was more consistent for trials in normotensive patients. Systolic/diastolic blood pressure reductions adjusted to 100 mmol Na/d were -5.8/-2.5 and -2.3/-1.4 mmHg in hypertensive and normotensive individuals, respectively. The meta-analysis yielded no evidence that the sodium restriction reported in the trials would be a safety hazard.

Graudal et al [5] carried out a meta-analysis to estimate the effects of reduced sodium intake on systolic and diastolic blood pressure, body weight, and plasma concentrations of renin, aldosterone, catecholamines, cholesterol and triglycerides. Inclusion criteria included: randomised controlled trials, double-blind, single-blind, or open studies with a parallel or crossover design; sodium intake had to be estimated by a 24 h urinary sodium excretion or from a sample of at least 8 h; the mean age of the participants had to be over 15 y; and studies treating persons with a concomitant intervention, such as antihypertensive medication, were included if the intervention was identical during the low- and high-sodium diets. The median ages of the participants were 49 y and 27 y in the hypertensive and normotensive trials, respectively. The median study duration was 28 d and 8 d in the hypertensive and normotensive trials, respectively. Antihypertensive medication was received by patients in 13 of the 58 studies. In the hypertensive trials (58 studies, n=2161), the final weighted effect of a reduced sodium intake, as measured by urinary excretion (weighted, 118 mmol/d), on systolic blood pressure was -3.9 mmHg (P<0.001), and on diastolic blood pressure was -1.9 mmHg

(P<0.001). In normotensive trials (56 studies, n=2581) the final weighted effect of sodium intake, as measured by urinary excretion (weighted, 160 mmol/d), on systolic blood pressure was -1.2 mmHg (P<0.001), and on diastolic blood pressure was -0.26 mmHg (P=0.12). During the low sodium intervention, the mean body weight was reduced (0.96 kg, P=0.01), plasma total cholesterol increased. Sodium restriction produced dose dependent increases in plasma rennin and aldosterone The authors reiterate the conclusions drawn by Midgley et al [3] that the effect of reduced sodium intake on blood pressure was insufficient to justify a general recommendation for reducing the intake of sodium, although reduced sodium may be used as a supplementary treatment in hypertension.

Whelton et al [10] analysed the effect of potassium on blood pressure, as reported in randomized controlled trials published before 1995. In a meta-analysis of 33 trials (n=2609 participants) potassium supplementation (median dose of 75 mmol/d) was associated with a significant reduction in mean systolic (-3.11 mm Hg) and diastolic (-1.97 mm Hg) blood pressure. Effects of treatment appeared to be enhanced in studies in which participants were concurrently exposed to a high intake of sodium. The authors recommend that increased potassium intake should be considered in the prevention and treatment of hypertension, especially in those who are unable to reduce their intake of sodium.

1(c) Consideration of the validity of the reviewer's conclusions

The Canadian review is an accurate and comprehensive summary of the evidence. The review's recommendations represent correctly the results of meta-analyses that are based on randomized trials and have consistent outcomes. The review concludes that sodium restriction in the normotensive population results in small (1.2 mmHg) reductions in systolic blood pressure for a large (100 mmol/d or about 6 g salt) reduction in sodium intake over the short term. The Canadian review acknowledges that authors of 3 of the 4 meta-analyses do not support a general recommendation on dietary sodium.

In hypertensive individuals, a 100 mmol reduction in sodium intake results in a reduction of 4 mmHg systolic and 2 mmHg diastolic blood pressure. There is consistent support for a recommendation to restrict sodium in older hypertensive people although other influential factors such as weight loss, dietary calcium and potassium are acknowledged.

Potential undesirable effects of sodium restriction are considered in Section 6.3 of the Canadian report. Adverse effects are based on 4 experimental studies and one meta-analysis that report increased mortality, increased plasma rennin an aldostreone, noradrenaline, and cholesterol. In addition fatigue and impaired sexual function were more frequently reported on a low sodium diet than on a normal diet or a weight-reducing diet in hypertensive men. The limitations of these reports are also discussed.

The Canadian recommendations are based on meta-analyses that have consistent outcomes, and the findings are convincing. The cited meta-analyses have clearly defined aims and are based on electronic searches of the evidence (MEDLINE and others) that date back to 1966. In all cases, the results are presented comprehensively and the conclusions are supported by the results as presented.

The Canadian review supports 2 health claims (page 23). The first identifies sodium as the primary factor in affecting blood pressure, and acknowledges a range of other factors that include potassium. The second health claim identifies BMI as the major factor and acknowledges the multifactorial nature of hypertension.

Review of evidence released since the time of the Canadian review.

A search of the literature was undertaken by using MEDLINE, Cochrane and related databases. The search strategy, key words and limits are indicated in Tables 2 and 3. Titles and abstracts (see Appendix 1, 2) were scanned and selected papers retrieved. Additional references were identified from bibliographies of articles and citation searches.

Cross-sectional studies

The EPIC-Norfolk study investigated whether blood pressure is related to differences in sodium intake in free-living populations [14]. In community-living adults (n=23,104; age 45-79 y), mean systolic and diastolic blood pressure increased as the ratio of urinary sodium to creatinine increased, with differences of 7.2 mm Hg for systolic blood pressure and 3.0 mm Hg for diastolic blood pressure ($P<0.0001$) between the top and bottom quintiles. Assessment of urinary sodium was based on a single casual urine sample which is associated with a large within individual variation.

The INTERMAP study [15] examined potential reasons for blood pressure differences that had been reported between northern and southern Chinese (n=839, age 40-59 y) where the average systolic/diastolic blood pressure was 7.4/6.9 mm Hg higher for northern than southern participants, respectively. A total of 18 factors were considered individually, including body mass index, urinary sodium/potassium ratio, urinary sodium, dietary fat, magnesium and vitamin C. These variables reduced north-south blood pressure differences by $\geq$ 10%. When multiple dietary variables (sodium, potassium, magnesium, phosphorus, body mass index) were included in regression models, north-south blood pressure differences were no longer statistically significant. In the USA cohort of INTERMAP (n=2195), an inverse relationship between education level and blood pressure was observed but was no longer significant after correction for multiple dietary factors [16].

NHANES-III data was used to determine the relationship between dietary factors and blood pressure in adults (age>20y; n=17 030) in the USA [17]. Systolic blood pressure was positively associated with higher sodium, alcohol, and protein intakes ($P<0.05$) and negatively associated with potassium intake ($P=0.003$). Diastolic blood pressure was negatively associated with potassium and alcohol intakes ($P<0.001$). A higher intake of calcium ($P=0.01$)

was associated with a lower rate of age-related rise in systolic blood pressure [17]. Regional differences in blood pressure were also examined by the NHANES-III survey (age>18y, n=17752) [18]. Individuals from southern USA were shown to have relatively higher systolic and diastolic blood pressure compared to those from the Midwest, Northwest or West USA. The blood pressure differences between the regions (1-3 mmHg systolic and 1-2 mmHg diastolic) are statistically significant ($P<0.05$). The increased blood pressure in the South corresponded to significantly higher intakes of sodium, fat and cholesterol; and lower intakes of dietary fibre, potassium, calcium, phosphorous, and a number of other micronutrients.

In Chinese vegetarians living in Hong Kong (n=111, age >55y), hypertension (>140/90 mmHg) was observed in 64% of the study population. Compared with normotensives, hypertensive subjects consumed less calcium and had higher urinary excretion of sodium, and a higher urinary sodium/potassium ratio [19]. The authors propose that the higher than expected rate of hypertension in Chinese vegetarians may be attributed to the liberal use of soy sauce. A limitation of this study is the small sample size.

The studies described above, especially those that include large sample sizes, support the relationship reported previously which shows that sodium intake is positively associated with blood pressure and that the relationship is moderated by a number of physiological and dietary factors. These studies do not address the issues of salt sensitivity or cardiovascular endpoints although Southern USA, the region with the highest relative blood pressure, includes the region known as the “stroke belt”.

Prospective studies

A prospective follow up was undertaken in Finnish men (n=1173) and women (n=1263) aged 25-64 y to determine the relationship between 24 h urinary sodium excretion and cardiovascular risk factors [20]. The hazards ratios for coronary heart disease, cardiovascular disease, and all-cause mortality, associated with a 100 mmol increase in 24 h urinary sodium excretion, were 1.51, 1.45, and 1.26, respectively. The frequency of acute coronary events, but not acute stroke events, rose significantly with increasing sodium excretion. When analyses were done separately for each sex, the risk ratios were significant in men only. There was a significant interaction between sodium excretion and body mass index for cardiovascular and total mortality; sodium predicted mortality in men who were overweight.

Froom and Goldbourt [21] compared cardiovascular mortality over an 11 year period in 2 male Israeli cohorts (civil servants, recruited in 1967, n=10048; and industrial workers, recruited 1985-7, n= 2237). Compared to industrial workers, civil servants showed an increase in mortality (hazard ratio 1.18) associated with a higher systolic blood pressure (8.7 mm Hg). Urinary excretion of sodium or potassium are not reported.

Experimental studies

A number of experimental trials have been documented since the publication of the Canadian review. The studies are described below and summarized in Table 4.

Sodium restriction

The Trials of Hypertension Prevention (TOHP), Phase II, tested the effect of sodium restriction as compared to no dietary intervention (usual care) in white (n=956) and black (n=203) adults, aged 30-54 y [22,23]. At 36 months of intervention, urinary sodium excretion was 40.4 mmol/d (24.4%, P<0.0001) lower in the sodium reduction group compared to usual care participants. Decreases in systolic blood pressure were reported at 6 months (2.9 mmHg, P < 0.001), 18 months (2.0 mmHg, P < 0.001), and 36 months (1.3 mmHg, P = 0.02) in the sodium reduction vs usual care groups. The decreases were associated with an overall lower (18%, P=0.048) incidence of hypertension [22]. Further analysis demonstrated a significant dose-response trend in blood pressure change over quintiles of achieved sodium excretion. Systolic blood pressure decreases per 100 mmol/24 h reduction in sodium excretion at 18 and 36 months were 7.0 and 3.6 mmHg after correction for measurement error. At 36 months diastolic blood pressure changes were smaller and not statistically significant [23]. The authors propose that a possible explanation for the smaller effect at 36 months may be the diminution of the dose-response due to the concave-downward shape of the dose-response relationship between sodium and blood pressure [23].

He at al [24] examined the effect of weight loss and sodium restriction in TOHP, Phase I. Individuals that were assigned to the weight loss group or a sodium restricted diet showed no significant differences in weight loss or sodium excretion after 7 y of follow-up. In univariate and multivariate analyses, weight loss resulted in a significant reduction in the odds ratio for hypertension (P<0.02). The effect of sodium reduction was not significant (P=0.37).

Dietary and lifestyle interventions in addition to sodium restriction

The effect of 3 levels of dietary sodium (50, 100 and 150 mmol/d per 2100 kcal) with the DASH diet (rich in fruit and vegetables, and low-fat dairy products) or a typical American (control) diet, were investigated in individuals with and without hypertension [25-28]. Sodium restriction over 30 d, in addition to the DASH diet (DASH-sodium), produced a reduction in systolic blood pressure that was commensurate with the extent of sodium restriction [25-27]. The DASH-sodium diet led to a mean reduction in systolic blood pressure of 7.1 and 11.5 mm Hg in normotensive and hypertensive individuals, respectively [26]. Further subgroup analysis showed that the effect of DASH-sodium on systolic and diastolic blood pressure is greater in older compared to younger individuals [26,27]. The interaction between age and the effect of sodium reduction was observed in normotensive individuals: -3.7 mm Hg systolic for <45 y and -7.0 mm Hg for >45 y with the typical diet, and -0.7 and -2.8 mm Hg with the DASH-sodium diet [27]. Blood pressure became normal or optimal in 71% of persons consuming the control-lower sodium diet and 77% of individuals consuming the DASH-lower sodium diet [28]. Although both the DASH-sodium diet and sodium-restricted diet improved blood pressure control [25-28] the effect is suggested to be mediated by different mechanisms [29]. The DASH diet resulted in significantly lower plasma lipids than the control diet [30,31], but changes in dietary sodium per se had no effect on blood lipids [31].

In individuals with above optimal blood pressure, the PREMIER trial tested the effectiveness of “established recommendations” or “established + DASH diet” as compared with “advice only” over 6 months in adults (n=810). Patients in both intervention groups had significant weight loss and reduction in sodium intake. The 2 intervention groups did not differ significantly - both groups achieved greater reductions in systolic and diastolic blood pressure than did patients in the “advice only” group [32-34].

The effect on blood pressure of a lifestyle intervention that includes the combination of sodium restriction, the DASH diet, weight loss and regular aerobic exercise was evaluated over 9 weeks in hypertensive individuals. The DEW-IT study showed that systolic and diastolic blood pressures were decreased by 12.1 mm Hg ($P<0.001$) and 6.6 mm Hg ($P<0.001$), respectively in the intervention participants (n=20) compared with those in the

control group (n=23). Significant reductions were reported in plasma total cholesterol, LDL and HDL [35].

Nowson et al [36,37] examined the effect of dietary intervention on blood pressure in a community setting. In the context of a self-selected high potassium (80 mmol) diet, a low sodium (50 mmol/d) diet consumed for 4 weeks reduced home-measured systolic blood pressure (- 2.5 mm Hg, P=0.004), compared with the higher sodium (120 mmol/d) diet [36]. Blood pressure measured by the investigators was not statistically different between the low and high sodium diets [36]. Further community-based intervention showed that a low-sodium, high-potassium diet resulted in greater falls in systolic and diastolic blood pressures (-3.5 and -1.9 mmHg, respectively) when compared to a DASH-type diet [37].

Effect of sodium restriction or supplementation in older individuals

The TONE study investigated the effect of sodium restriction in elderly patients with hypertension (n=681, aged 60-80 y). Sodium restriction resulted in mean reductions of 4.3 mmHg (P<0.001) and 2.0 mmHg (P=0.001) in systolic and diastolic blood pressure, respectively [38]. Sub-group analysis showed that the effect of intervention on blood pressure in those aged 70-80 y did not reach statistical significance [38].

Salt sensitivity

Johnson et al [39] supplemented volunteers aged > 60 y, with sodium chloride (50-300 mmol/d) for 14 d, to determine salt sensitivity. Increasing salt consumption resulted in incremental increases in systolic and diastolic blood pressure. The increase in blood pressure occurred with increasing doses of sodium and was significantly greater in older individuals with isolated systolic hypertension.

In healthy volunteers followed-up over 2 y, a significant correlation (P<0.05) between sodium intake and systolic and diastolic blood pressure was observed in 16% and 5% of participants, respectively [40]. The authors conclude that 5-16% of healthy individuals have “salt-dependent blood pressure” and may benefit from a reduction in salt intake. In hypertensive individuals, salt sensitivity is predicted significantly by age and is related to gender, with

highest sensitivity in women with low-renin hypertension and in men with non-modulator hypertension [41].

In the DASH-sodium trial, blood pressure measurements varied significantly over time even when measured by highly trained staff. The authors propose that current study designs that are used to determine whether individuals as salt sensitive, may lead to false positives [42].

Reviews, meta-analyses

Hooper et al [43,44] reviewed the literature to assess the long-term effects of advice to restrict dietary sodium in adults with and without hypertension. The systematic review [44] included randomised controlled trials that aimed to reduce sodium intake over at least 6 months. In normotensive (3 trials, n=2326), untreated hypertension (5 trials, n=387), and in people being treated for hypertension (3 trials, n=801) blood pressures were reduced (systolic by 1.1 mm Hg; diastolic by 0.6 mm Hg) at 13-60 months, as was urinary 24h sodium excretion (by 35.5 mmol/d) in those allocated to low sodium advice. The extent of reduction in sodium intake and change in blood pressure were not related. The authors conclude that intensive interventions provide only small reductions in blood pressure and sodium excretion, and effects on deaths and cardiovascular events are unclear. The authors show that patients on anti-hypertensive medications were able to stop their medication more often on a reduced sodium diet as compared with controls, while maintaining similar blood pressure control [43,44].

The report of Hooper et al [43] has been criticized [45-47] for not providing details about what advice was offered to trial participants and for including studies that do not provide reduced salt foods [45]. While the effect of avoiding discretionary salt is small, Law and Wald [46] claim that the effect of salt reduction as reported by Hooper et al will have been underestimated because the trial participants included people who had already taken steps to avoid using discretionary salt, thereby diluting the observed effect on blood pressure. In addition, the discussion section of the paper by Hooper et al has been criticised because it is selective, and the arguments are said to be largely based on a simplistic, individually based model of health promotion [47].

He and MacGregor [48-50] investigated the effect on blood pressure of reduction in salt intake (from 10 to 5 g/d) over $\geq$ 4 weeks. The duration of the trials is a key difference in the inclusion

criteria in the analyses of He and MacGregor [48-50] and Hooper et al [43,44]. In individuals with elevated blood pressure (17 trials, n=734) the median reduction in urinary sodium excretion was 78 mmol/d (4.6 g/day of salt), the mean reduction in systolic and diastolic blood pressure was -4.97 mmHg and -2.74 mmHg, respectively. In individuals with normal blood pressure (11 trials, n=2220) the median reduction in urinary sodium excretion was 74 mmol/d (4.4 g/day of salt), the mean reduction in systolic and diastolic blood pressure was -2.03 mmHg and -0.99 mmHg, respectively. Weighted linear regression analyses showed a correlation between the reduction in urinary sodium and the reduction in blood pressure [50]. A reduction of 3 g salt/d predicted a fall in systolic and diastolic blood pressure of 3.6-5.6/1.9-3.2 mmHg, respectively [49]. The authors note that Hooper et al [43,44] included trials in which a smaller reduction of salt intake (2 g/d) was achieved and therefore the reported small fall in blood pressure, and the absence of a dose-response to salt reduction are not unexpected.

Geleijnse et al [51] evaluated the blood pressure response to sodium reduction (40 trials) and potassium supplementation (27 trials) in trials lasting more than 2 weeks. Sodium reduction (-77 mmol/24 h) was associated with changes of -2.54 mmHg and -1.96 mmHg in systolic and diastolic blood pressure, respectively. Corresponding values for increased potassium intake (44 mmol/24 h) were -2.42 mmHg and -1.57 mmHg. The blood pressure response was larger in hypertensives than normotensives, both for sodium restriction (systolic: -5.24 vs -1.26 mmHg, $P < 0.001$; diastolic: -3.69 vs -1.14 mmHg, $P < 0.001$) and potassium supplementation (systolic: -3.51 vs -0.97 mmHg, $P=0.089$; diastolic: -2.51 vs -0.34 mmHg, $P=0.074$).

Jurgens and Graudal [52] determined the effects of low- (defined by the authors as “lower than normal”) versus high- (defined as “normal or above normal”) sodium intake on blood pressure, plasma or serum levels of renin, aldosterone, catecholamines, cholesterol and triglycerides. The authors estimate that in Caucasians with normal blood pressure (57 trials), low sodium intake lowered systolic (-1.27 mmHg, $P<0.0001$) and diastolic (-0.54 mm Hg, $P = 0.009$) blood pressure as compared to high sodium intake. In 58 trials of mainly Caucasians with elevated blood pressure, low sodium intake reduced systolic (-4.18 mm Hg, $P <0.0001$) and diastolic (-1.98 mm Hg, $P <0.0001$) blood pressure as compared to high sodium intake. The median duration of the intervention was 8 d in the normal blood pressure trials (range 4-1100) and 28 d in the elevated blood pressure trials (range 4-365). It is noteworthy that multiple regression analyses showed no independent effect of duration on the effect size. In 8 trials in black participants, low sodium intake reduced systolic (-6.44 mm Hg, $P<0.0001$) and

diastolic (-1.98 mm Hg, P=0.16) blood pressure as compared to high sodium intake. The magnitude of blood pressure reduction was also greater in a single trial in Japanese patients. There was also a significant increase in plasma or serum renin (304%, P<0.0001), aldosterone (322%, P<0.0001), noradrenaline (30%, P<0.0001), cholesterol (5.4%, P<0.0001) and LDL cholesterol (4.6%, P<0.004), and a borderline increase in adrenaline (12%, P=0.04) and triglycerides (5.9%, P=0.03) with low- as compared with high-sodium intake. The authors conclude that the magnitude of the effect in Caucasians with normal blood pressure does not warrant a general recommendation to reduce sodium intake.

Publication bias

Swales [53] notes that reviews that are biased by the inclusion of non-randomised trials exaggerate the effect of sodium restriction on blood pressure and citation analysis shows that such reviews are quoted more frequently than those reaching more negative conclusions. Swales suggests that this is an attempt to create an impression of scientific consensus.

Committee Reports

The UK Scientific advisory Committee on Nutrition [54] concluded that "a reduction in dietary salt intake of the population would lower the blood pressure risk for the whole population".

Conclusion

The studies that have appeared since 2000, which include cross-sectional studies, experimental studies and systematic reviews, provide convincing evidence for the relationship between sodium intake and blood pressure. Further, these studies support the findings of the Canadian review [1], namely that sodium restriction has a favourable but small effect on blood pressure reduction. As noted in the Canadian review, researchers remain divided about the potential benefits to public health of implementing widespread programs to lower sodium intake.

The risk of cardiovascular disease rises with blood pressure throughout the normotensive blood pressure range [55] and almost 60% of coronary heart disease events and 45-50% of strokes occur in those with high normal blood pressure. The study in Finns [20] further

supports the relationship between the increased excretion of sodium and cardiovascular disease.

Cross-sectional studies that consisted of large sample sizes, have been carried out in diverse populations (UK [14], China [15], USA [16,17]). The outcomes of these studies point further to the involvement of sodium in addition to other nutrients, such as potassium and calcium, in affecting blood pressure. Prospective studies indicate that a reduction in sodium excretion [20] or blood pressure [21] reduced cardiovascular endpoints however, the results of a systematic review show no clear effect of sodium restriction in intervention trials on deaths or cardiovascular events [44].

A number of trials have been published that report on multifaceted approaches to blood pressure reduction (Table 4). These include sodium restriction in addition to one or more of the following lifestyle factors: weight loss, restricted alcohol consumption, exercise, a diet high in fruit and vegetables and low-fat dairy (DASH). The findings of the lifestyle trials provide convincing evidence for the effect of sodium restriction on blood pressure reduction and for the involvement of multiple factors in the prevention or management of hypertension.

The outcomes of the intervention trials as summarized in systematic reviews [44,50,52], demonstrate a small but statistically significant effect of sodium restriction on blood pressure. In interventions lasting more than 6 months, sodium restriction results in a reduction in systolic/diastolic blood pressure of -1.1/-0.6 mmHg [44]. In short-term trials (>4 weeks), a decrease in sodium excretion corresponds to systolic/diastolic blood pressure reductions of -2.09/-0.99 and -4.97/-2.74 in normotensive and hypertensive populations, respectively [50]. When short-term trials that include mainly Caucasians are analysed, the observed effect of sodium reduction on systolic/diastolic blood pressure is -1.27/-0.54 and -4.18/-1.98 in normotensive and hypertensive participants, respectively [52].

The trial settings and outcomes are applicable to Australia and New Zealand although the inclusion of data from trials with African-Americans may overestimate, to a small degree, the sodium-blood pressure relationship in hypertensive individuals [52]. The evidence available since 2000 is convincing and further supports the conclusion of the Canadian Review that “moderation in intake of sodium may reduce the risk of high blood pressure, a condition

associated with many factors including overweight, excessive alcohol consumption, inadequate intake of dietary potassium, and inactivity".

Relevance of the relationship to Australia and New Zealand.

Hypertension is the most frequently managed medical problem in Australia, accounting for 8.6% of medical consultations and 7.9% of prescriptions [56]. High blood pressure causes the third greatest burden of disease in Australia – over 5% of the total burden of disease and injury, second only to tobacco smoking and physical inactivity [57]. The AusDiab Study found that in 1999-2000 the prevalence of high blood pressure in the Australian population was 28.6 per 100 people with 15.2 per 100 untreated and 13.4 per 100 treated for this condition [58].

The National Heart Foundation encourages individuals to reduce their intake of salt to between 40-100 mmol/d, along with weight reduction, consumption of low sodium/high potassium diets, less alcohol consumption, increased physical activity and cigarette smoking cessation [59]. In a survey carried out in Hobart [60], 36% of women and 6% of men exhibited sodium excretion rates at or below 100 mmol/d, the RDI for sodium, suggesting that a high percentage of individuals, particularly men are consuming sodium in quantities well beyond the RDI.

In an attempt to lower sodium intake, Girgis et al [61] tested the acceptability of salt-reduced bread in healthy volunteers recruited from the staff of Royal North Shore Hospital in Sydney. Volunteers who were allocated to the low-salt group were unable to detect a 25% reduction of salt content of bread and the authors conclude that this is a potential strategy for reducing sodium intake in the population. A similar study was undertaken in Auckland, which showed that a reduction by 10% in the sodium content of bread was not detected by volunteers [62].

A search of the literature (described above), revealed a number of studies that had investigated the relationship between sodium and blood pressure in Australia. Nowson et al [36,37] based at Deakin University in Melbourne, examined the effect of dietary intervention on blood pressure in a community setting. Volunteers were instructed on low sodium and high potassium diets based on resources from a previous national trial (NH&MRC) [63]. In the context of a self-selected high potassium (80 mmol) diet, a low sodium (50 mmol/d) diet consumed for 4 weeks reduced home-measured systolic blood pressure (- 2.5 mm Hg, P=0.004), compared with the higher sodium (120 mmol/d) diet [36]. Blood pressure measured by the investigators was not statistically different between the low and high sodium diets [36].

Further community-based intervention showed that a low-sodium, high-potassium diet resulted in greater falls in systolic and diastolic blood pressures (-3.5 and -1.9 mmHg, respectively) when compared to a DASH-type diet [37]. Compliance with dietary advice was enhanced by the provision of some food items including salt-free bread and salt-free margarine.

Johnson et al [39] working at Princess Alexandra Hospital in Brisbane, supplemented volunteers aged > 60 y, with sodium chloride (50-300 mmol/d) for 14 d, to determine salt sensitivity. Increasing salt consumption resulted in incremental increases in systolic and diastolic blood pressure. The increase in blood pressure occurs with increasing doses of sodium and is significantly greater in older individuals with isolated systolic hypertension.

The evidence summarized in the Canadian review and the new evidence available since its publication (as summarized above) is relevant to Australia and New Zealand. Trials that have been carried out in Australia and New Zealand prior to 2000 have been incorporated in meta-analyses [2-5] and subsequently considered by the Canadian review [1]. The Cochrane systematic reviews that have been published since 2000 also incorporate trials from Australia and New Zealand [44,50,52].

Overall conclusions

4 (a) Public summary

Background

Sodium is a mineral that is plentiful in the food supply, either through natural occurrence or through addition of salt (sodium chloride) or sodium-containing food additives. Australians and New Zealanders tend to have dietary sodium intakes that exceed recommended levels. Potassium is also a mineral that occurs naturally and through addition of food additives.

The purpose of this summary is to determine whether or not there is a substantiated relationship between dietary sodium intake, alone or in combination with potassium intake, and risk of hypertension. It does this by critically appraising a recent Canadian government review of the role of sodium and potassium in hypertension and to update this review with reference to Australian and New Zealand circumstances.

Canadian Review

Health Canada reviewed the literature up to 2000 [1] to address the question whether lowering sodium intake in a population will reduce the risk of hypertension. The Canadian document draws on the US FDA position, published in draft form in 1991 [9] and revised in 1993 [6]. The FDA concluded that the effect of change in dietary sodium on blood pressure is small but statistically significant, and acknowledged the impact on those with normal blood pressure ('normotensive') and those with elevated blood pressure ('hypertensive'), the wide variation in response and the existence of salt sensitivity [6,9]. The Canadian review has interpreted correctly the US Proposed and Final Rules, and based on new evidence (published between 1993-2000) has provided further support for the proposed health claim.

Key evidence summarized in the Canadian review is derived from meta-analyses[1] of the effect on blood pressure of sodium restriction [2-5] and potassium supplementation [7]. The meta-analyses are based on randomized trials, span a range of publication years, combine different

[1] Meta-analyses are studies that combine results from several studies and summarise the findings quantitatively.

numbers of trials in normotensive and hypertensive individuals, and are authored by different research groups. In normotensive individuals, salt restriction is reported to statistically reduce systolic [3-5] and diastolic [4] blood pressure. In hypertensive individuals, sodium restriction is reported to lower systolic and diastolic blood pressure in all meta-analyses [2-5]. Potassium supplementation (median dose of 75 mmol/d) [1] [7] was associated with a significant reduction in mean systolic (-3.11 mm Hg) and diastolic (-1.97 mm Hg) blood pressure and the effect is greater in studies with a reported higher level of urinary sodium excretion.

Potential undesirable effects of sodium restriction are considered in the Canadian report [1]. Adverse effects are based on 4 experimental studies and one meta-analysis that report increased mortality, increased plasma rennin and aldostreone, noradrenaline, and cholesterol. In addition fatigue and impaired sexual function were more frequently reported on a low sodium diet than on a normal diet or a weight-reducing diet in hypertensive men. The limitations of these reports are also discussed.

The Canadian review presents convincing evidence that salt restriction in the normotensive population results in small (1.2 mmHg) reductions in systolic blood pressure for a large (100 mmol/day or about 6 g salt) reduction in sodium intake over the short term. The effect in hypertensive individuals, for an equivalent reduction in sodium, is 4/2 mmHg reduction in systolic/diastolic blood pressure.
The risk of cardiovascular disease rises with blood pressure throughout the normotensive blood pressure range [55] and almost 60% of coronary heart disease events and 45-50% of strokes occur in those with high normal blood pressure. Hence, persons with normal blood pressure may also benefit from lifestyle modification. The review supports two diet-disease relationships. The first identifies sodium as the primary factor in affecting blood pressure, and acknowledges a range of other factors that include potassium. The second relationship identifies BMI as the major factor and acknowledges the multifactorial nature of hypertension.

Update of the Canadian review

A search of the literature was undertaken by using MEDLINE, Cochrane and related databases, to update the Canadian review to 2005.

[1] The average diet provides about 100 mmol/d and common vegetables contain 5-9 mmol/100g.

Cross-sectional studies that consisted of large sample size, have been carried out in diverse populations (UK, EPIC-Norfolk [14]; INTERMAP, China [15], USA [16]; NHANES, USA [17,18]). Evaluation of the NHANES-III data [17,18] showed that systolic blood pressure was positively associated with higher sodium and protein intakes ($P<0.05$) and negatively associated with potassium intake ($P=0.003$). Diastolic blood pressure was negatively associated with potassium and alcohol intakes ($P<0.001$). The large cross-sectional studies support the positive association between sodium intake and blood pressure [14-18], and identify socioeconomic, physiological and dietary factors that modify it. The outcomes of these studies point further to the involvement of sodium in addition to other nutrients, such as potassium and calcium, in affecting blood pressure.

Experimental studies

Experimental studies are those where there is some form of intervention in the diet or lifestyle of participants in order to address a research question, and include randomised and non-randomised, blinded and non-blinded clinical trials. Experimental studies are generally the most persuasive in determining whether or not a diet-disease relationship exists.

In a three-year study of salt restriction, the Trials of Hypertension Prevention (TOHP), Phase II, participants had a decrease in systolic blood pressure (1.3 mmHg, $P=0.02$) that corresponded with a significant dose-dependant reduction in sodium excretion [22,23]. In a seven year follow-up of participants in TOHP, Phase I, the effect of sodium reduction on blood pressure was not significant however, weight loss resulted in a reduction in the Odds Ratio for hypertension ($P<0.02$) [24].

The effects on blood pressure of three levels of dietary sodium (65, 107 and142 mmol/d) with the DASH diet (rich in fruit and vegetables, and low-fat dairy products) or a typical American (control) diet, were investigated [25-28]. Sodium restriction over 30 days, in addition to the DASH diet, produced a reduction in systolic blood pressure that was commensurate with the extent of sodium restriction [25-27]. The DASH-sodium diet led to a mean reduction in systolic blood pressure of 7.1 and 11.5 mm Hg in normotensive and hypertensive individuals, respectively [26] and the effect was more pronounced in older compared to younger individuals [26,27]. In elderly participants (TONE study), sodium restriction resulted in mean

reductions of 4.3 mmHg (P<0.001) and 2.0 mmHg (P=0.001) in systolic and diastolic blood pressure, respectively [28].

In an Australian community setting, Nowson et al [36,37] examined the effect of dietary intervention on blood pressure. In the context of a self-selected high potassium (80 mmol) diet, a low sodium (50 mmol/d) diet consumed for 4 weeks reduced home-measured systolic blood pressure (- 2.5 mm Hg, P=0.004), compared with the higher sodium (120 mmol/d) diet [37]. Further intervention showed that a low-sodium, high-potassium diet resulted in greater falls in systolic and diastolic blood pressures (-3.5 and -1.9 mmHg, respectively) when compared to a DASH-type diet [38].

The effect of multiple lifestyle intervention that includes the combination of sodium restriction, the DASH diet, weight loss and regular aerobic exercise was evaluated in the DEW-IT study. After 9 w, systolic and diastolic blood pressures were decreased by 12.1 mm Hg (P<0.001) and 6.6 mm Hg (P<0.001), respectively in the intervention participants compared with those in the control group [35]. In individuals with above optimal blood pressure, the PREMIER trial showed that patients in the “established recommendations” or “established + DASH diet” intervention groups had significant weight loss and reduction in sodium intake; both groups achieved greater reductions in systolic and diastolic blood pressure than did patients in the “advice only” group [33,34,38].

The findings of the intervention studies provide convincing evidence for the effect of sodium restriction on blood pressure reduction and for the involvement of multiple factors in the aetiology of hypertension.

Experimental studies - salt sensitivity

In healthy volunteers followed-up over 2 y, a significant correlation (P<0.05) between sodium intake and systolic and diastolic blood pressure was observed in 16% and 5% of participants, respectively [40]. The authors conclude that 5-16% of healthy individuals have “salt-dependent blood pressure” and may benefit from a reduction in salt intake. In hypertensive individuals, salt sensitivity is predicted significantly by age and is related to gender, with highest sensitivity in women with low-renin hypertension and in men with non-modulator hypertension [41]. In the DASH-sodium trial, blood pressure measurements varied

significantly over time even when measured by highly trained staff. The authors propose that current study designs that are used to determine whether individuals as salt sensitive, may lead to false positives [42].

Reviews, meta-analyses

Hooper et al [43,44] reviewed the literature to assess the long-term effects of advice to restrict dietary sodium in adults. The systematic review [44] included randomised controlled trials that aimed to reduce sodium intake over at least 6 months. In normotensive (3 trials, n=2326), untreated hypertension (5 trials, n=387), and in people being treated for hypertension (3 trials, n=801) blood pressures were reduced (systolic by 1.1 mm Hg; diastolic by 0.6 mm Hg) at 13-60 months, as was urinary 24h sodium excretion (by 35.5 mmol/d) in those allocated to low sodium advice. The extent of reduction in sodium intake and change in blood pressure were not related. The authors conclude that intensive interventions provide only small reductions in blood pressure and sodium excretion, and effects on deaths and cardiovascular events are unclear [43,44].

The report of Hooper et al [43] has been criticized [45-47] for not providing details about what advice was offered to trial participants and for including studies that do not provide reduced salt foods [45]. While the effect of avoiding discretionary salt is small, Law and Wald [46] claim that the effect of salt reduction as reported by Hooper et al will have been underestimated because the trial participants included people who had already taken steps to avoid using discretionary salt, thereby diluting the observed effect on blood pressure. In addition, the discussion section of the paper by Hooper et al has been criticised because it is selective, and the arguments are said to be largely based on a simplistic, individually based model of health promotion [47].

He and MacGregor [48-50] investigated the effect on blood pressure of reduction in salt intake over $\geq$ 4 weeks. In individuals with elevated blood pressure (17 trials, n=734) the median reduction in urinary sodium excretion was 78 mmol/d, the mean reduction in systolic and diastolic blood pressure was -4.97 mmHg and -2.74 mmHg, respectively. In individuals with normal blood pressure (11 trials, n=2220) the median reduction in urinary sodium excretion was 74 mmol/d, the mean reduction in systolic and diastolic blood pressure was -2.03 mmHg

and -0.99 mmHg, respectively. Weighted linear regression analyses showed a correlation between the reduction in urinary sodium and the reduction in blood pressure [50].

Geleijnse et al [51] evaluated the blood pressure response to sodium reduction (40 trials) and potassium supplementation (27 trials) in trials lasting more than 2 weeks. Sodium reduction (-77 mmol/d) was associated with changes of -2.54 mmHg and -1.96 mmHg in systolic and diastolic blood pressure, respectively. Corresponding values for increased potassium intake (44 mmol/d) were -2.42 mmHg and -1.57 mmHg. The blood pressure response was larger in hypertensives than normotensives, both for sodium restriction (systolic: -5.24 vs -1.26 mmHg, $P < 0.001$; diastolic: -3.69 vs -1.14 mmHg, $P < 0.001$) and potassium supplementation (systolic: -3.51 vs -0.97 mmHg, P=0.089; diastolic: -2.51 vs -0.34 mmHg, P=0.074).

Jurgens and Graudal [52] determined the effects of low- versus high-sodium intake on blood pressure, plasma or serum levels of renin, aldosterone, catecholamines, cholesterol and triglycerides. The authors estimate that in Caucasians with normal blood pressure (57 trials), low sodium intake lowered systolic (-1.27 mmHg, P<0.0001) and diastolic (-0.54 mm Hg, P=0.009) blood pressure as compared to high sodium intake. In 58 trials of mainly Caucasians with elevated blood pressure, low sodium intake reduced systolic (-4.18 mmHg, P<0.0001) and diastolic (-1.98 mmHg, P<0.0001) blood pressure as compared to high sodium intake. The median duration of the intervention was 8 d in the normal blood pressure trials (range 4-1100) and 28 d in the elevated blood pressure trials (range 4-365). It is noteworthy that multiple regression analyses showed no independent effect of duration on the effect size. In eight trials in black participants, low sodium intake reduced systolic (-6.44 mm Hg, P<0.0001) and diastolic (-1.98 mm Hg, P=0.16) blood pressure as compared to high sodium intake. There was also a significant increases in plasma or serum renin (304%), aldosterone (322%), noradrenaline (30%), cholesterol (5.4%), LDL cholesterol (4.6%), adrenaline (12%) and triglycerides (5.9%) with low- as compared with high-sodium intake.

Conclusion

The studies that have appeared since 2000 provide convincing evidence for the relationship between sodium intake and blood pressure. Further, these studies support the findings of the Canadian review [1], namely that sodium restriction has a favourable but small effect on blood pressure reduction. As noted in the Canadian review, researchers remain divided about the

potential benefits to public health of implementing widespread programs to lower sodium intake.

Cross-sectional studies have been carried out in diverse populations [14-18] and their outcomes identify the involvement of sodium in addition to other nutrients, such as potassium and calcium, in affecting blood pressure. Prospective studies indicate that a reduction in sodium excretion [20] or blood pressure [21] reduced cardiovascular endpoints, however in intervention trials there is no clear effect of sodium restriction on deaths or cardiovascular events [44].

A number of trials have been published that report on the effects of sodium restriction in addition to dietary and lifestyle factors, on blood pressure reduction. The findings provide further convincing evidence for the sodium-blood pressure relationship and for the involvement of multiple factors in the prevention or management of hypertension. The outcomes of the intervention trials as summarized in systematic reviews [44,50,52], demonstrate a small but statistically significant effect of sodium restriction on blood pressure. In interventions lasting more than 6 months, sodium restriction by 35 mmol/dresults in a reduction in systolic/diastolic blood pressure of -1.1/-0.6 mmHg [44]. In short-term trials (>4 weeks), a decrease in sodium excretion corresponds to systolic/diastolic blood pressure reductions of -2.09/-0.99 and -4.97/-2.74 in normotensive and hypertensive populations, respectively [50]. When short-term trials that include mainly Caucasians are analysed, the observed effect of sodium reduction on systolic/diastolic blood pressure is -1.27/-0.54 and -4.18/-1.98 in normotensive and hypertensive participants, respectively [52].

The trial settings and outcomes are applicable to Australia and New Zealand although the inclusion of data from trials with African-Americans may overestimate, to a small degree, the sodium-blood pressure relationship in hypertensive individuals [52]. The evidence available since 2000 is convincing and further supports the conclusion of the Canadian review that “moderation in intake of sodium may reduce the risk of high blood pressure, a condition associated with many factors including overweight, excessive alcohol consumption, inadequate intake of dietary potassium, and inactivity”.

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Table 1. Mean weighted reductions in blood pressure (mm Hg) expressed per 100 mmol Na reduction [2].

		Hypertensive BP change			Normotensive BP change	
	No	SBP	DBP	No	SBP	DDBP
Overall	18	-5.44	-4.10	9	-1.48	-0.94
<100 mmol/d achieved	9	-3.30	-3.40	8	-1.63	-0.77
Double-blind trials	6	-5.76	-3.27	2	-1.45	+1.94
Open trials	12	-5.31	-3.36	7	-1.55	-1.19

SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 2. Search strategy for MEDLINE (to March Week 3, 2005)

1	Diet, Sodium-Restricted/ (4248)
2	Sodium, Dietary/ (2793)
3	HYPERTENSION/ (126482)
4	Blood Pressure/ (172927)
5	1 or 2 (6765)
6	3 or 4 (263353)
7	5 and 6 (3713)
8	limit 7 to (humans and English language and yr=2000 - 2005) (332)
9	limit 8 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or journal article or meta analysis or multicentre study or practice guideline or randomized controlled trial or "review" or review, academic or "review literature" or review, tutorial) (283)

Table 3. Search strategy for Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, CCTR (to March week 3, 2005)

1	Diet, Sodium-Restricted/ (356)
2	Sodium, Dietary/ (212)
3	HYPERTENSION/ (9177)
4	Blood Pressure/ (15480)
5	1 or 2 (523)
6	3 or 4 (19722)
7	5 and 6 (388)
8	limit 7 to (humans and English language and yr=2000-2005) [Limit not valid in: CDSR, ACP Journal Club, DARE,CCTR; records were retained] (63)
9	limit 8 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or journal article or meta analysis or multicentre study or practice guideline or randomized controlled trial or "review" or review, academic or "review literature" or review, tutorial) [Limit not valid in: CDSR, ACP Journal Club, DARE; records were retained] (63)

Table 4. Summary of relevant research on sodium and hypertension published between 2000-2005.

<table>
<tr><th>Authors, Reference</th><th>Study design and duration</th><th>Subjects</th><th>Intervention</th><th>Results</th><th>Context of the relationship and conclusions</th></tr>
<tr><td>Kumanyika et al [22];
Cook et al [23];
TOHP, Phase II</td><td>RCT, 9 centres, 36 months</td><td>Adults (30-54 y), N=956 white (681 men, 275 women), n=203 black (86 men, 117 women).</td><td>Usual care or sodium restriction to achieve Na excretion of 80 mmol/24h</td><td>21% of subjects achieved Na restriction target.

Kumanyika et al [9]: BP changes compared with control:
<table>
<tr><td></td><td colspan="3">Months</td></tr>
<tr><td></td><td>6</td><td>18</td><td>36</td></tr>
<tr><td>SBP</td><td>-2.9</td><td>-2.0</td><td>-1.2</td></tr>
<tr><td>DBP</td><td>-1.6</td><td>-1.2</td><td>-0.7</td></tr>
</table>
Cook et al [10]: Estimated BP changes per 100 mmol Na/d (corrected):
<table>
<tr><td></td><td colspan="2">Months</td></tr>
<tr><td>Net BP</td><td>18</td><td>36</td></tr>
<tr><td>SBP</td><td>-7.0</td><td>-3.6</td></tr>
<tr><td>DBP</td><td>-4.8</td><td>-0.8</td></tr>
</table></td><td>Free-living US adult women and men, mostly Caucasians, 110-165% of Metropolitan Life Insurance Company weight standard.

Study results show that sodium restriction lowers BP. The results are largely applicable to Australia and New Zealand; and support the proposed health claim.</td></tr>
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<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>He at al [24]; TOHP, Phase I</td><td>RCT, 18 months. Follow-up after 7 y</td><td>Adults, 87% (n=181) of initial cohort followed-up. Adult men and women, 58% white, 46% college graduates, 18% smokers. No evidence of hypertension, BMI 26.1-36.1. Mean age at baseline : 43y</td><td>Group and individual counseling over 18 months for weight loss and sodium reduction. No further intervention for ensuing 7 y</td><td>Multivariate Odds Ratios (and CI) of hypertension over 7 y follow-up:
<table><tr><td></td><td>OR</td><td>P</td></tr><tr><td>Weight loss</td><td>0.23 (0.07-0.76)</td><td>0.02</td></tr><tr><td>Sodium reduction</td><td>0.65 (0.25-1.69)</td><td>0.37</td></tr></table></td><td>The study results emphasise the importance of weight loss as being more effective than sodium restriction in maintaining long term BP control. The study group includes a high proportion of blacks but the results are largely applicable to Australia and New Zealand. The results do not support the proposed health claim.</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Sacks et al [25]; DASH-sodium</td><td>RCT, 4 centres, 30 d</td><td>390 adults, 57% females, 56% of patients were black, 41% with hypertension, average BMI 29.5. Mean age 47 ± 10 (DASH Diet), 49 ± 10 (Control).</td><td>3 levels of sodium (Low, 50 mmol/2100 kcal; Intermediate, 100; and High, 150 with either a Sodium Restriction (control) or a DASH diet.</td><td>Compared with High Na, Intermediate Na lowered SBP by 2.1 mmHg in the control and 1.3 mmHg in the DASH diet. Reducing Na from Intermediate to Low resulted in additional reductions of 4.6 mmHg during the control and 1.7 mmHg in DASH diet. Reducing sodium from High to Intermediate lowered DBP by 1.1 mmHg in the control and 0.6 mmHg in the DASH diet (the latter was not significant). Reducing sodium from Intermediate to Low resulted in</td><td>The Na restricted diet and the DASH diet lead to BP reduction with greater effects in combination. The effects of DASH-sodium on BP were observed in normo- and hyper-tensives, men, women, blacks and other races.
The study results are largely applicable to</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>additional reductions of 2.4 mmHg during the control and 1.0 mmHg in the DASH diet.</td><td>Australia and New Zealand and support the proposed health claim.</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Appel et al [32]; PREMIER Trial</td><td>RCT, 4 centres, 6 months</td><td>810 adults, 62% women, average age 50y, 34 % blacks, above optimal BP, not taking BP medication</td><td>3 interventions:
(i) established (E)
(ii) established + DASH (E-DASH)
(iii) advice only</td><td>BP changes relative to “advice only” group. All changes are statistically significant.<table><tr><td></td><td colspan="2">Diet</td></tr><tr><td>Net BP</td><td>E</td><td>E-DASH</td></tr><tr><td>SBP</td><td>-3.7</td><td>-4.3</td></tr><tr><td>DBP</td><td>-1.7</td><td>-2.6</td></tr></table></td><td>The main findings are that multiple lifestyle changes (weight loss, sodium reduction, increased physical activity and limited alcohol intake) that include the DASH diet are effective in lowering BP.
The results and setting are applicable to Australia and New Zealand. The results support the proposed health claim but also highlight the role of factors other than sodium.</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Miller et al [35]; DEW-IT</td><td>RCT, 9 weeks</td><td>43 adults (62% women), mean age 54 ± 9 y, overweight, single BP medication</td><td>Lifestyle group included exercise, DASH diet, low sodium.
Comparison made with Control</td><td>Net differences between Lifestyle and Control groups<table><tr><td></td><td>OR</td><td>P</td></tr><tr><td>SBP</td><td>-9.5</td><td>0.000</td></tr><tr><td>DBP</td><td>-5.3</td><td>0.002</td></tr><tr><td>24 h urinary</td><td>-44</td><td>0.07</td></tr></table></td><td>The number of participants in the Control (n=23) and Lifestyle (n=20) groups is small. The intervention is</td></tr>
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<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>group.</td>
<td>
<table>
<tr><td>Na (mmol/l)</td><td></td><td></td></tr>
<tr><td>BMI</td><td>-1.7</td><td>0.000</td></tr>
</table>
</td>
<td>demanding on volunteers.
The main findings are that multiple interventions can improve BP in hypertensive individuals. The results are applicable to Australia and New Zealand. The results support the proposed health claim but also highlight the role of factors other than sodium.</td>
</tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Nowson et al [36]</td>
<td>RCT, 4 weeks</td>
<td>N=108 (64 women, 44 men), average age 47 y, 16 on BP medication</td>
<td>Self selected potassium-rich diets with sodium low (50 mmol/d) or high (120). Blood pressure measured at home (by participants) and by the investigators.</td>
<td>Effect of Low or High sodium on home-measured BP
<table>
<tr><td></td><td>Low Na</td><td>High Na</td><td>P</td></tr>
<tr><td>SBP</td><td>114.9</td><td>117.2</td><td>0.015</td></tr>
<tr><td>DBP</td><td>72.4</td><td>73.3</td><td>0.148</td></tr>
</table>
</td>
<td>The main findings are that a low sodium diet in a community setting reduces home-measured but not investigator-measured systolic BP. The trial was carried out in Australia (Vic) and the findings are relevant to Australia and New Zealand. The findings support the proposed health claim.</td>
</tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr>
<td>Nowson et al [37]</td>
<td>RCT, 4 weeks</td>
<td>N=91 (56 men, 38 women), average age 56 y.</td>
<td>Volunteers randomly assigned to 2 of the following self-selected diets: (i) low Na, high K (LNAHK)
(ii) high Calcium (HC)
(iii) DASH-type diet (OD)</td>
<td>Difference in the changes in home-measured BP differences
<table>
<tr><td></td><td>LNAK-OD</td><td>HC-OD</td></tr>
<tr><td>SBP</td><td>-3.5</td><td>3.1</td></tr>
<tr><td>DBP</td><td>-1.9</td><td>0.8</td></tr>
</table>
</td>
<td>The main findings are that a self-selected low sodium high potassium diet resulted in greater falls in home measured BP than a multifaceted diet such as the DASH-type diet.
The trial was carried out in Australia (Vic) and the findings are relevant to Australia and New Zealand. The findings support the proposed health claim.</td>
</tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Appel et al [38]; TONE Study</td>
<td>RCT, 3 months</td>
<td>N= 681, age 60-80 y, 47% women, 23% black, overweight, taking 1 BP medication,</td>
<td>Assigned randomly to one of 2 groups: reduced sodium or usual lifestyle</td>
<td>Net difference between sodium restriction and usual lifestyle
<table>
<tr><td>SBP</td><td>4.3</td><td>P<0.001</td></tr>
<tr><td>DBP</td><td>2.0</td><td>P<0.001</td></tr>
<tr><td>24 h urinary Na (mmol/l)</td><td>40</td><td>P<0.001</td></tr>
</table>
</td>
<td>Sodium restriction resulted in reductions of 4.3 mmHg in SBP and DBP systolic. The study group includes a moderate proportion of blacks but the results are largely applicable to Australia and New Zealand. The results support the proposed health claim</td>
</tr>
</table>

Table 5. Comparison of some aspects of three Cochrane systematic reviews on sodium and blood pressure.

	Hooper et al [44]	He and MacGregor [50]	Jurgens and Graudal [52]
Inclusion criteria: minimum duration of trials	6 months	4 weeks	8 days
Is the level of Na excretion quantified/evaluated in participants assigned to low Na vs control ?	Y	Y	N
Is there a dose-response in the Na-BP relationship ?	N	Y	N
Are normotensive and hypertensive subjects considered separately ?	N	Y	Y
Are Caucasians and African-Americans considered separately ?	N	N	Y