SALT—THE BENEFITS OF POPULATION SALT REDUCTION: UPDATE OF EVIDENCE SINCE 2011

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In its 2011 paper *Diet, Physical Activity and Cardiovascular Disease Prevention in Europe*, EHN concluded that average daily salt intake among adults in Europe was probably around 10 g per day and proposed an intermediate population goal for maximal daily consumption of 5 g/day and a more ambitious longer term target of 4 g/day. This document reviews the new scientific evidence on this issue.

1. Key points

- Salt[1] is causally related to blood pressure (BP): the higher the salt intake, the higher the BP, an effect which can be seen from birth.
- A sustained reduction in salt intake (up to 50% of what we eat now) causes a fall in BP in almost everyone across the whole range of BP, although individuals will respond more or less, depending on factors like age, ethnicity, initial levels of BP and body weight.
- High BP contributes to strokes and heart attacks and a reduction in BP is associated with their reduction. The magnitude of the effect is related to the size of the fall in BP.
- It is logical to consider, therefore, that a moderate reduction in salt intake in the population, through a modest reduction in BP, will result in a reduction in the incidence of strokes and some reduction in heart attacks.
- Natural experiments in different countries, direct experiments in primates, migration studies in humans, results from most prospective cohort studies in human populations and some randomised clinical trials support this concept.
- Some prospective observational studies have suggested that lower salt intake might be associated with 'increased' risk of CVD events. These studies, however, suffer from measurement errors that would introduce fatal biases in the results and, hence, erroneous conclusions.
- Well-conducted prospective studies—with sufficient statistical power and in which sodium excretion is accurately measured as an index of sodium intake and with the exclusion from the study population of people who are already unwell—support a graded, positive and linear relationship between sodium intake and both CVD and all-cause mortality.
- The World Health Organization currently therefore recommends targets of 5 g of salt (2 g of sodium) per day with a global target, as part of the global NCD action plan, to achieve a 30% reduction from current consumption by 2025.
- Sodium intakes exceed the recommended levels in almost all countries, so that virtually all populations would benefit from sodium reduction, supported by enhanced surveillance.
- Global actions are underway globally to reduce average population salt consumption.

[1] In this document salt (NaCl sodium chloride) and sodium are used to refer to sodium intake. Please note the following conversion: 2.5g (2,500mg) of salt = 1.0 (1 000mg) of sodium.

- Population salt reduction is amongst the most cost-effective public health initiatives for reducing the burden of CVD.
- Population salt reduction programmes are feasible and effective (and are therefore considered 'preventive' imperative), cost-saving in all settings ('economic' imperative), powerful, rapid and equitable ('political' imperative).

2. Consideration About Targets

From anthropological accounts, evidence in primates and contemporary data from hunter-gatherer human populations still living in remote areas of the world where there is no access to salt, a consumption of as little as 1g of salt (0.4g of sodium) per day is compatible with a healthy life.

Salt consumption in the world varies, but (apart from the isolated populations mentioned above) no country in the world consumes less than 5 g of salt (2.0 g of sodium) per day.

Quality evidence from RCTs of the blood pressure lowering effect of salt reduction suggests a dose-response effect including as little as 5 g of salt (2.0 g of sodium) per day.

Prospective observational and modelling studies suggest a dose-dependent beneficial effect on cardiovascular outcomes.

Based on the best available evidence so far, long-term targets have been set to limit average population intakes to <5 g of salt (2.0 g of sodium) per day. However, it is acknowledged that, although rapid reductions are feasible, population salt reduction must be achieved gradually to allow adaptation of taste preference and an increase in consumer acceptance and demand. Many countries exceed these salt targets several fold.

Short- and medium-term targets have been set by the United Nations (UN) High Level Group for a 30% reduction in population salt consumption by 2025.

3. Background – Need To Update The Previous EHN Report

The 2011 paper *Diet, Physical Activity and Cardiovascular Disease Prevention in Europe* extensively reviewed the role of salt and its effects on human health and concluded:

- the precise amount of daily salt intake among adults in Europe is not known, but probably lies around 10 g per day (*see update in present document*),
- falls in salt intake reduce blood pressure, with clear evidence of a fall in cardiovascular morbidity and mortality (*see update in present document*),
- the mechanisms are still unexplained,
- a maximal daily consumption of 5 g/day seems reasonable for adults (with a longer term ambitious goal of 4 g/day). Policies for a progressive decrease are needed (*see update in present document*).

Since 2011, various publications have become available, ranging from new meta-analyses of RCTs, cohort studies in populations and patients' groups, new methodologies for assessing salt intake, modelling studies on effectiveness and costs,

and policy documents. Critically, public health policies have been developed at the global level, led by a UN General Assembly Resolution in 2011 and by further analyses[3,4] World Health Organization (WHO) action plans and the initiatives of numerous international health agencies and implementation plans have been undertaken for population reductions in salt consumption for the prevention of cardiovascular disease.

Current recommended targets specify an intake of *5g of salt (2g of sodium) per day* with an action plan for a *30% reduction from current consumption by 2025*[1]. However, despite a large level of general scientific consensus, dissenting voices from industry and from some members of the scientific community have created a 'controversy'. The main criticisms are: a) a low salt intake may not lower blood pressure in everyone; b) a lower salt intake, as suggested by guidelines, may cause harm by increasing cardiovascular mortality; c) there is not sufficient evidence to justify current policies.

The following update will summarise new evidence, will respond to these criticisms and will offer updated conclusions.

4. Global Salt Consumption

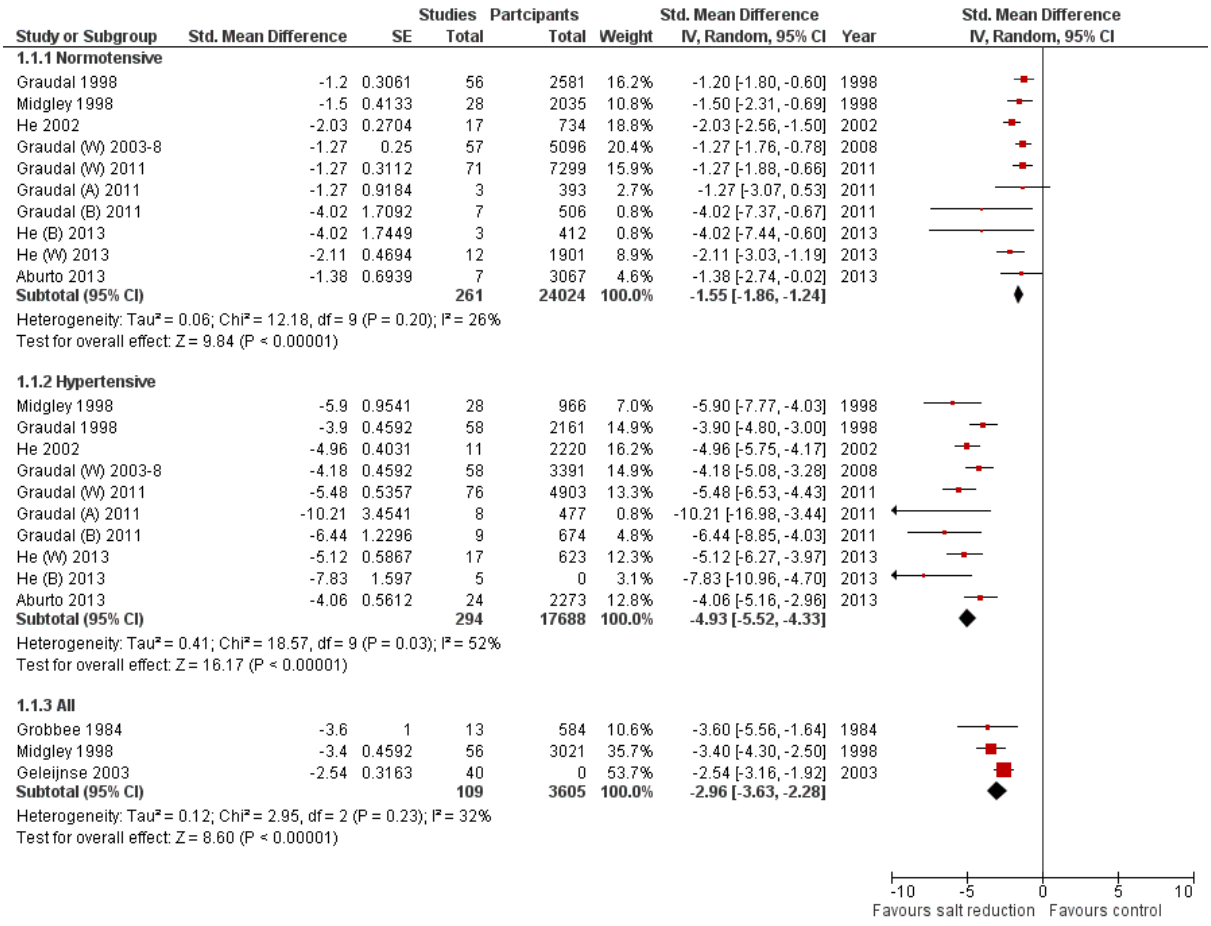
The Global Burden of Disease Nutrition and Chronic Disease Expert Group (NutriCoDE) has recently published two reports on comprehensive and comparable estimates of sodium intake globally[5] and estimates of global attributable deaths from cardiovascular causes above levels of 5 g salt (2 g of sodium) per day,[6] i.e., the World Health Organization recommended targets.[1] Sodium intakes exceed the recommended levels (often by three fold) in almost all countries with small differences by age and sex.[2] Furthermore, 1.65 million deaths from cardiovascular causes that occurred in 2010 were attributed to sodium consumption above the reference level of 5 g of salt (2.0 g of sodium) per day.[6]

5. Salt And Blood Pressure

Salt is causally related to blood pressure (BP), the higher the salt intake, the higher the BP, with an effect being seen from birth.[7] A small and sustained reduction in salt intake (up to 50% of what we eat now) causes a fall in BP in almost everyone across the whole range of BP, although individuals will respond more or less, depending on factors like age, ethnicity, their initial levels of BP and their body weight. These facts have been proven over and over again and summarised in repeated systematic reviews and meta-analyses of small and large clinical trials in people with and without high BP. Figure 23 shows the collective estimates of all meta-analyses published to date on the effect of salt reduction on BP in adults[8–17] The meta-analyses differ by the time of their analysis, so in the available studies, there are differences in the inclusion criteria (short-term studies of <4 weeks versus longer-term studies of >4 weeks), the proportion of normotensive and hypertensive participants, the study designs (cross-over, parallel group, blinded and open designs) and the proportion of relevant subgroups (gender, age and ethnic group). Despite differences between studies, the range of the pooled and weighted estimates of an effect are all in favour of salt reduction. Furthermore, their 95% confidence intervals are compatible with each other, indicating consistency, with differences between them likely due to random variation. Furthermore, when using very 'short-term salt restriction' trials with very

large changes in salt intake (unlikely to be comparable to 'longer-term more moderate salt reduction' procedures) it has been argued that changes in metabolic and hormone variables that occur may be harmful.[10,13–15] These changes are due to rapid and transient activations of sympathetic adrenergic activity and haemoconcentration, not detected in longer-term and moderate salt reduction trials.[11,16,17] Finally, in 2015, a randomised, placebo-controlled crossover study was published.[5] It examined the effect of sodium or potassium supplementations on blood pressure in 36 participants, whose diet was fully controlled for the duration of the study. The subjects were provided with 2,500 kcal per day, 2 g of sodium and 2 g of potassium per day, and their systolic blood pressure was between 130 and 159 mmHg. In the sodium arm, participants were given 3 g of added sodium (equivalent to 7.5 g of salt per day) for 4 weeks. Twenty-four hour (24h) urinary sodium excretion increased, on average, by 98 mmol per day (~2.3 g of sodium or ~5.8 g of salt per day) compared to placebo. During sodium supplementation, office, 24h and central blood pressures all increased significantly compared to placebo (7.5/3.3 mmHg, 7.5/2.7 mmHg and 8.5/3.6 mmHg, respectively).

Figure 23 Forest-plot summarising the results of published meta-analyses of randomised clinical trials of the effects of salt reduction on systolic blood pressure. Results are reported as standard mean difference and 95% confidence intervals (CIs)



In conclusion, the results of these analyses, despite different interpretations at the time of their publication, all agree on the following:

(i) salt intake is one of the major determinants of BP in populations and individuals;
(ii) a reduction in salt intake causes a dose-dependent reduction in BP;
(iii) the effect is seen in both sexes, in people of all ages and ethnic groups, with all starting BPs, and is detectable for measurements made in the office, over a continuous 24h period and when measuring central BPs.

Similar results have been described in children.[18,19]

Salt Sensitivity

A moderate reduction in salt intake reduces BP in most but not all individuals. The effect on BP varies largely from person to person.[20] Salt sensitivity has a variety of determinants, including race and ethnicity[21], age[22], body mass index,[23–25] and diet quality, as well as associated disease states (e.g. hypertension, diabetes, and renal dysfunction). It is also partially under genetic control, as these more salt responsive individuals, whether considered 'normotensive' or 'hypertensive'; tend to have a positive family history of hypertension.[26] The BP response to a moderate change in salt intake is normally distributed.[27] Many experimental models have been used for the past 40 years to attempt an individual characterisation of so-called salt sensitivity. These methods have included BP responses to (1) acute and large changes in salt intake, with or without diuretic-induced volume depletion and (2) moderate changes in salt intake over days in normotensive volunteers,[28] patients, or the general population.[29] They also included the response of the renin-angiotensin-aldosterone system[29–31] and the clearance of endogenous lithium, a non-invasive method for assessing segmental renal tubular sodium handling[31] and considered a proxy for salt sensitivity.[32,33] Measures of salt sensitivity are associated with more severe cardiovascular risk factor profiles,[25,34–36] and they are also negative prognostic indicators.[25,34] Although less easy to detect, salt sensitivity is also present in normotensive people. In a small clinical study with a long-term follow-up, normotensive salt-sensitive individuals had a cumulative mortality as high as that of hypertensive patients.[37]

In the last year two comprehensive reviews of the topic have been published.[38,39] Both independent appraisals of the available evidence agree on the following points:

(i) the paradigm of 'salt-sensitivity' has important pathophysiological meaning in understanding individuals' variation in BP response to changes in salt intake;
(ii) knowledge gaps suggest further research in the area;
(iii) due to important limitations (lack of uniformity of assessment across studies, lack of an established method of assessment, lack of reproducibility of current methods, variable definitions) the concept of 'salt sensitivity' is not useful to the practising physician in clinical practice;
(iv) the concept is not relevant or useful in the design and implementation of public health policies based on a moderate reduction in population salt intake, and aiming at a modest shift to the left in the average distribution of salt consumption and BP, with a recognised ensuing reduction in cardiovascular outcomes.[40,41]

Salt And Mortality

High BP contributes to strokes and heart attacks and a reduction in BP is associated with their reduction. The magnitude of the effect is related to the size of the fall in BP. It is therefore conceivable that a moderate reduction in salt intake in a population,

through a reduction in BP, would result in a reduction of strokes and heart attacks. The collective evidence from systematic reviews of prospective longitudinal studies indicates that a lower salt intake is associated with a lower incidence of fatal and non-fatal cardiovascular events, in particular stroke.[17,42] This is also supported by a meta-analysis of the few RCTs available to date that have measured fatal and non-fatal outcomes.[43]

Since 2011, analyses of prospective observational studies have suggested, in some cases, that lower salt intake might be associated with an 'increased' risk of CVD events, in particular heart failure. These studies have been the object of intense scrutiny due to numerous methodological issues present in observational studies that would introduce fatal biases (errors) in the results and, hence, erroneous conclusions.

A comprehensive account of these issues has been published by the American Heart Association.[44] These issues are reported below (Table 6).

Table 6 Methodological issues in the assessment of prospective observational studies of salt consumption and cardiovascular outcomes

Domain 1	**Errors with the greatest potential to alter the direction of association**
	Systematic error in sodium assessment • Lower risk of errors: 24h urine collections for sodium analyses, but some collections have no quality assurance, and do not exclude incomplete collections • Higher risk of errors in methodology: e.g., the use of other general 24h urine collections obtained for other purposes, all dietary assessments, spot and overnight urine collections
	Reverse causality • Lower risk of errors: when participants are recruited from the general population and those with pre-existing CVD excluded • Intermediate risk: when sick populations are not excluded or included despite claims to the contrary; when there is the presence of other CVD risk factors; use in specifically sick populations • Higher risk: specific types of sick populations (e.g.: heart failure, kidney disease, diabetes); removal of sick participants from the analysis changes the direction of the subsequently observed association
Domain 2	**Errors with some potential to alter the direction of association**
	Potential for residual confounding • Incomplete adjustment: not including two or more factors such as age, sex, race, socioeconomic status, cholesterol, BMI or weight, smoking, diabetes; if diet-based assessments of sodium intake are made then the neglect of total calorie intake; if urine-based, adjusting by weight, BMI or assessed creatinine excretion • Imbalance across sodium intake levels: with age difference across sodium groups >5 years; imbalance in sex or race distribution across sodium groups >20% • Inadequate follow-up: low level of follow-up (<80%) or when the quality for outcome assessment is uncertain.
Domain 3	**Errors with the potential to lead to a false null result**
	Random error in sodium assessment • Lower risk of error: more than four 24h urine assessments on average; Food Frequency Questionnaires • Intermediate risk: between two and four 24h urine collections, or corrections for regression dilution bias; dietary reports • Higher risk: urine collection <24 h or single 24h urine collection; single dietary

	recall or 1-day food record
	Insufficient power • Less than 80% power to detect a 10% reduction in relative risk for every standard deviation difference in sodium intake
	Studies using same data but reporting divergent results • NHANES I: analyses in the same age group with the same follow-up by different authors – both inverse and positive associations reported with the use of different selections, adjustments etc. • NHANES III: analyses in different age groups with different follow-up by different authors – both inverse and positive associations reported when again using different analytical approaches.

6. Population-based Cohort studies

Stolarz-Skrzypek et al[45] followed up 3 681 participants without CVD who were members of families that were randomly enrolled in the FLEMENGHO and EPOGH studies in Belgium. They measured baseline salt consumption with a single 24h urine collection and recorded all-cause and cardiovascular mortality for a median period of 7.9 years. Vital status was obtained in all participants; 219 deaths were recorded, of which 84 deaths were cardiovascular. Cardiovascular mortality (p=0.02), but not all-cause mortality (p=0.10), was higher in the group with a lower urinary sodium excretion, when adjusted for confounders. The authors conclude that lower sodium excretion was associated with higher CVD mortality and that the results do not support current recommendations of a generalised reduction in sodium intake at the population level.

Comment: the study presents several weaknesses: (a) the lower sodium group had not only lower urinary volume excretion but also lower urinary creatinine and potassium excretion, suggesting incomplete collections in that group;[46–48] (b) the lower sodium group had paradoxical higher proportion of low socio-economic participants, in contrast with the expectations of a higher salt intake in that group;[49–51] (c) the only statistically significant finding was for CV deaths (n=50 in the low sodium group), in contrast with no significant effects when fatal and non-fatal events were considered together. In particular, there was no effect on stroke events.[52]

O'Donnell et al[53] obtained morning fasting urine samples from 101 945 persons taking part in the Prospective Urban Rural Epidemiology (PURE) study, a cohort study that enrolled and followed up 156 424 persons, aged 37-70 years from 628 rural and urban communities in 17 low- middle- and high-income countries. Salt intake was inferred from estimated 24h urinary sodium excretion calculated with the Kawasaki formula applied to a morning fasting urine sample. They recorded all-cause and major CV deaths for a mean follow-up of 3.7 years. A composite outcome occurred in 3 317 participants. There was a J-shaped association between estimated sodium excretion and CV events: a higher estimated sodium excretion of $\geq$7 g (>17.5 g of salt) per day was associated with increased risks of death and major CV events, with a stronger effect among people with 'hypertension'. On the other hand, an estimated sodium excretion that was below 3 g (7.5 g of salt) per day was also associated with an increased risk of the composite outcome.

Comment: a) the estimated sodium excretion using morning fasting spot urines with Kawasaki or other equations is unreliable and biased, as demonstrated by several studies,[54–57] including validations within the PURE study;[58,59] b) the sodium study

within the PURE study may be affected by selection bias: the sodium study, in fact, included only 65% of the participants; there were fewer from India (5 v 18%) and many more from China (42% v 30%). Moreover, a high proportion of participants had pre-existing ill-health (hypertension, blood pressure medication, pre-existing CHD and CVD); c) the lower sodium group was grossly unbalanced compared to the higher sodium group: it was older and had fewer men, fewer Asians and smokers with more Africans and non-Asians and urban persons; they also had a lower BP, a higher LDL-cholesterol, a history of CVD and diabetes, lower level of physical activity and higher medication use (suggesting reverse causality); d) the lower sodium excretion group (<3 g/day or <7.5 g of salt/day) was unable to discriminate within the range of recommended targets for populations and, therefore, was not informative for policy making.

Joosten et al[60] followed up 7 543 participants free of cardiovascular and kidney disease in the PREVEND study in Gröningen, the Netherlands. They measured baseline salt consumption by two 24h urine collections at baseline and recorded the occurrence of fatal and non-fatal CHD events for a median period of 10.5 years. 452 CHD events were recorded. In the entire cohort, there was no statistically significant association between estimated salt intake and CHD event rate (HR=1.07, 95% CI 0.98-1.18). However, higher sodium excretion was associated with an increased CHD risk amongst subjects with hypertension or with increased NT-proBNP concentrations. No trend for increased risk on low sodium excretion was detected.

Comment. Given the small number of events, the study might have lacked statistical power to statistically detect a small increase in risk in the overall cohort (average 7%). Also, it is apparent from the figure (although not reaching statistical significance) that there was a linear trend between urinary sodium excretion and adjusted risk, with no indication of a J-shaped relation at lower levels of urinary sodium.

Cook et al[61] followed up pre-hypertensive participants during an extended post-trial surveillance in TOHP II (10 years follow-up) and TOHP I (15 years follow-up). 193 fatal and non-fatal cardiovascular events were recorded amongst the 2 275 participants not in a sodium reduction intervention group. Multiple (3-to-7 per individual) 24h urine collections were obtained throughout. There was a linear 17% increase in risk of CVD events per 1 g/day increase in sodium excretion. No J-shaped trend was observed at lower sodium excretion.

Comment. This study design overcomes major methodological challenges of prior studies and, in spite of the relatively small event rate, does detect an overall benefit of lower sodium intake with no evidence of non-linear effects. Assessment of sodium is strengthened by a multiple collections carefully controlled for completeness.

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Pfister et al[62] followed up 9 017 men and 10 840 women (age 39-79 years) participating in the EPIC-Norfolk prospective study in the UK. They estimated baseline salt consumption on a casual spot urine sample obtained at baseline using the Tanaka formula for estimating daily sodium excretion and then recorded 1 210 fatal (n=137) and non-fatal (1,073) incident cases of heart failure (702 men and 508 women) during a mean follow-up of 12.9 years. There was a U-shaped association between estimated urinary sodium and heart failure risk. The risk associated with high

sodium was attenuated when adjusting for blood pressure whereas the risk associated with low sodium was attenuated when adjusting for pre-existing disease.

Comment. The study suffers from the following methodological flaws: a) the biased assessment of sodium consumption due to the use of casual spot urines and application of the Tanaka formula; b) a clear selection bias in the low sodium group representing sicker individuals (reverse causality); c) the latter point is supported by the diluting effect of risk in the low sodium group when adjusted for pre-existing disease.

Kalogeropoulos et al[63] followed up 2 642 older adults (71-80 years) without prevalent CVD at baseline participating in a community-based prospective cohort study in Pittsburgh and Memphis, USA (Health ABC Study). They measured baseline salt consumption by a Food Frequency Questionnaire and recorded CVD (n=1 981) and heart failure (HF) (n=2 628) mortality over 10 years of follow-up. In total, 881 had died, 572 of CVD and 398 of HF. The results show no significant association between FFQ-determined dietary sodium intake and mortality from CVD or HF.

Comment. The article was the subject of several comments in the media and in the scientific literature. A variety of sources agreed on the main criticisms: there was a systematic error in the assessment of sodium intake with the use of imprecise methods, such as FFQ; there was a potential for reverse causality possibly due to selection bias with the lower sodium group.[64–66]

Lamelas et al[67] reports from a sub-sample (in four South American countries) of the PURE Study. They obtained morning fasting urine samples from 17 033 persons from Argentina, Brazil, Chile and Colombia. They estimated 24h urinary sodium and potassium excretion from a morning fasting urine sample, using the Kawasaki formula. All-cause mortality and major CVD was the primary outcome with a median follow-up of 4.7 years. A composite CVD outcome occurred in 568 participants (417 deaths, 143 had a CVD event, and 148 a myocardial infarct (MI), 102 had a non-fatal stroke and 41 developed HF). There was a possible J-shaped association between estimated sodium excretion and composite event: a higher estimated sodium excretion ($\geq$7 g/day) was associated with increased risks of death and major CV events, but the effect was attenuated by adjustments. On the other hand, the reported increased risk at lower sodium excretion was never statistically significant.

Comment: this study design suffers from all the limitations reported for the main PURE Study. Specifically, a) the estimated average 24 sodium excretion using a morning fasting spot urines measure recalculated with the Kawasaki or other equations is unreliable and biased, as demonstrated by several studies,[54–57] including validations within the PURE study[58,59] itself; b) the lower sodium excretion group (<3 g/day or <7.5 g of salt/day) was unable to discriminate within the range of previously recommended salt targets of 3 g, 5 g or 6 g/day and, therefore, is not informative for policymaking; c) the analysis of the South American sub-sample is also inconclusive due to a lack of statistical power.

Cook et al[68] followed up pre-hypertensive adults during an extended post-trial surveillance in the TOHP II study with on average a 25.7 year follow-up and in the TOHP I analysis of 22.4 years of follow-up. A total of 77 and 174 deaths respectively

occurred amongst the unique 2 974 participants not in a sodium reduction intervention group. Multiple (three to seven per individual) 24h urine collections were obtained throughout. There was a direct linear association between average sodium intake and mortality (HR: 1.12 per 1g sodium/day [95% CI: 1.00 to 1.26], p=0.05). No J-shaped trend was observed at lower sodium excretion.

Comment. This study design overcomes major methodological challenges of prior studies and, in spite of relatively small event rates, detects an overall benefit of lower sodium intake with no evidence of non-linear effects. The validation of the assessment of sodium excretion is strengthened by the use of multiple urine collections carefully controlled for completeness.

7. Patients' groups

Ekinci et al[69] followed up 638 patients with type 2 diabetes attending a single diabetes clinic. They measured baseline salt consumption with a median number of two 24h urine collections and recorded all-cause and cardiovascular mortality for a median period of 9.9 years. Vital status was obtained in 620 patients; 175 deaths were recorded, of which 75 deaths were of cardiovascular cause. Both all-cause (p=0.017) and cardiovascular (p=0.026) mortality were higher in the group with a lower urinary sodium excretion, when adjusted for confounders. The authors conclude that intervention studies are necessary to establish causality and whether it is appropriate to advocate salt reduction in these patients.

Comment: patients in the lower tertile of estimated sodium excretion were at greater risk of death. They were older, had a longer duration of diabetes and were more likely taking insulin, beta-blockers, and less likely to take ACE inhibitors, and their GFR was lower than in the other sodium groups. This raises the question whether the results were affected by 'reverse causality', due to the selection of sicker patients who were therefore more likely to die in the low sodium group.

Thomas et al[70] followed up 2 807 patients with type 1 diabetes without end stage renal disease (ESRD) in a nationwide multicentre study (FinnDiane Study). They measured baseline salt consumption by a single 24h urine collection and recorded all-cause mortality (n=217) and ESRD incidence (n=126) for a median period of 10 years. There was a U-shaped relationship between sodium excretion and both mortality and ESRD. The authors call for caution before applying salt restriction universally.

Comment. The methodology for measuring compliance and completeness of urine collections are not reported nor are there the mean values presented. From what can be gathered from the published data the risk of incomplete urine collections was highly likely. Reverse causality and residual confounding are also likely explanations of the findings.

O'Donnell et al[71] followed up two cohorts of patients (n=28 880) included in the ONTARGET and TRANSCEND trials which are RCTs of anti-hypertensive therapy in high risk patients. They estimated 24h urinary sodium and potassium excretion from a morning fasting urine sample, using the Kawasaki formula, and recorded CV death, myocardial infarction (MI), stroke, and hospitalisation for congestive heart failure (CHF) for a median follow-up of 56 months. A composite cardiovascular outcome occurred in 4 729 participants, including 2 057 CV deaths, 1 412 non-fatal

MI, 1 282 non-fatal stroke, and 1 213 developed CHF. There was a J-shaped association between estimated sodium excretion and CV events.

Comment: a) there was an inaccurate estimate of sodium intake based on spot urine samples with the use of the Kawasaki equation. The method has been extensively assessed for validity and it has been unequivocally shown to be biased and unable to characterise individuals' sodium excretion (intake),[54–57] including the authors' validation in a subsequent study[58,59] (see above); b) the population group studies was made of old and sick patients with pre-existing conditions (70% hypertensive, 37% with diabetes, 48% with previous MI, 21% with a previous stroke or transient ischaemic attack (TIA) and 3% with atrial fibrillation); c) patients were often on multiple medications (overall 29% were on diuretics, 41% of whom were in the lowest sodium group). The latter two points strongly points to a 'reverse causality' bias as a likely explanation of the mortality findings.

Saulnier et al[72] followed up a prospective inception cohort of 1 439 French patients with type 2 diabetes, in whom the median duration of follow-up was 70 months (SURDIAGENE Study). They report a non-linear relationship between urinary sodium and cardiovascular mortality.

Comment. This is a report of results in a letter with no details provided. The original publication[73] does not report the methodology for assessing sodium excretion. This report is therefore difficult to assess in terms of quality.

Singer et al[74] followed up a cohort of 3 505 hypertensive individuals participating in a worksite hypertension programme. They measured daily urinary sodium excretion with a single 24h urine collection, and obtained mortality data for a mean follow-up period of 18.6 years. Overall there were 1 013 deaths (399 cardiovascular). In adjusted models sodium intake was not significantly associated with cardiovascular mortality. The authors suggest that the inconsistent results cast doubt on whether a single measurement can reliably predict mortality over a prolonged follow-up period.

Comment. This study is inconclusive due to lack of statistical power. However, the authors' conclusion has merit.

Äijälä et al[75] followed up a cohort of 1 405 participants in a population-based study of treated hypertensive patients and matched normotensives. 716 of them completed a food diary from which to calculate dietary sodium consumption and 690 without previous CVD were included (329 men and 361 women). They obtained information on fatal and non-fatal CVD events for a mean follow-up period of 19 years. Overall there were 109 events. In adjusted models sodium intake was significantly associated with increased cardiovascular events, both in men and women.

Comment. This is a small study, the assessment of dietary sodium is inaccurate and the selection of participants (cases and matched control) suggest that they are not fully unselected cases needed for an unbiased analysis.

Mills et al[76] followed up a cohort of 3 757 patients with chronic kidney disease (CKD) from seven locations in the USA. They assessed baseline urinary sodium excretion from a cumulative calibrated measure based on three 24h urine collections

and obtained information on non-fatal composite CVD events (CHF, MI and stroke) for a median follow-up of 6.8 years. 804 composite events (575 of CHF, 305 of MI and 148 of stroke) occurred. The study showed a significant linear association between calibrated 24h urinary sodium excretion and composite CVD events with no evidence of non-linear effects.

Comment. This study design overcomes major methodological challenges of prior studies and, in spite of relatively small event rate, detects an overall benefit of lower sodium intake with no evidence of non-linear effects. Assessment of sodium in strengthened by a calibration of multiple collection carefully controlled for completeness.

Mente et al[77] reported on a pooled analysis of about 134 000 individuals (about 63 500 with hypertension) taken from four independent studies (i.e. PURE, EPIDREAM screnees, ONTARGET and TRANSCEND). They estimated 24h urinary sodium and potassium excretion from a morning fasting urine sample, using the Kawasaki formula, and recorded the primary outcome as a composite of death, myocardial infarction (MI), stroke and heart failure (HF). They reported data for normotensive and hypertensives separately. Hypertension was defined if untreated when baseline BP was ≥140/90mmHg or if participants were prescribed anti-hypertensive drugs at baseline. In hypertensives, higher sodium intake of >7 g (>17.5 g of salt) per day and lower sodium intake <3 g (7.5 g of salt) per day were associated with increased risk compared to those with 4-5 g of sodium (10-12.5 g of salt) per day, whereas in normotensive participants, higher sodium intake was not associated with increased risk but lower sodium intake was.

Comment. This study suffers from flaws that have been repeatedly addressed in previous reports but ignored in the present study. Three areas: i) inappropriate assessment of exposure with spot urines (as extensively explained above); ii) reverse causality by including sick participants that are overrepresented in the 'lower' sodium group; iii) the artificial split of participants into normotensive and hypertensive which is not biologically plausible and reduces the statistical power of analysis and leads to paradoxical and implausible results such as the findings of an 'inverse' relationship between BP levels and cardiovascular outcomes in normotensives, irrespective of their estimated salt intake (Figure 3, bottom panel of original publication[77]). A comprehensive critique of this approach can be seen in published correspondence.[78,79]

8. Assessment of Salt Intake By Urinary Sodium Excretion

Salt intake is extremely variable between individuals as well as from day-to-day in the same person. Therefore, even a single measurement of the daily amount of sodium excreted in the urine (often regarded as the 'gold' standard for assessing individuals' salt consumption) may be inadequate.[80] In a well-conducted physiological study single 24-hour urine collections at intakes ranging from 6 to 12 g salt per day are not suitable to detect a 3 g difference in individual salt intake. Repeated measurements of 24h urinary sodium improve precision, suggesting multiple 24h urine collections over time are necessary to assess a person's salt intake.[80]

On the other hand, there is great interest in replacing 24h urinary sodium with easier methods to assess dietary sodium. A recent systematic review included 1 380 130 participants from 20 studies. The main statistical method for comparing 24h urine

collections with alternative methods was the use of a correlation coefficient. Spot, timed, and overnight urine samples were subject to greater intra-individual and inter-individual variability than 24h urine collections. There was a wide range of correlation coefficients between 24h urine sodium and other measures of sodium excretion.[81] Subsequently, numerous validation studies have been published, comparing 24h urine collections with estimates of daily sodium excretion from spot urines extrapolated with the application of different formulae. The results have been analysed and compared using Bland-Altman plots. There is a global consensus from a variety of population analyses that spot urines (irrespective of the formulas used to estimate daily consumption) lead to biased estimates of 24h urinary sodium excretion with overestimates at lower levels and underestimates at higher levels.[54–59]

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