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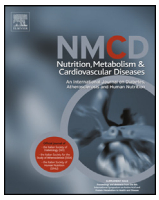

REVIEW

Population dietary salt reduction and the risk of cardiovascular disease. A scientific statement from the European Salt Action Network

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Abstract The publication in the last few years of a number of prospective observational studies suggesting a J-shaped association between levels of salt (sodium) consumption and cardiovascular outcomes has opened a debate on the pertinence of population-wide salt reduction policies to reduce cardiovascular disease burden, and some have even questioned the global World Health Organization guidelines, that recommend a 30% reduction in salt consumption by 2025, aiming at an ideal target of no more than 5 g of salt consumption per day.

In September 2018 the European Salt Action Network (E.S.A.N.), after appraising the quality of publications questioning the appropriateness of population salt reduction, discussed the scientific evidence and identified the pitfalls of recent data. The new evidence was deemed inadequate and, in places, biased by flawed methodology. These were identified in the biased assessment of sodium intake from spot urine and the use of the Kawasaki formula, the biased assessment of the sodium–outcome relationships in prospective observational studies using spot urine samples, the impact of reverse causality in such studies, the inadequate analytical approaches to data analysis, the lack of biological plausibility and the lack of precision in assessing long-term salt consumption, as recently demonstrated in studies using more stringent quality features in their study designs.

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[1] The European Salt Action Network (E.S.A.N.) was established under the auspices of W.H.O. and with the support of the United Kingdom Food Standards Agency. It promotes the harmonization of salt intake reduction programmes in EU countries. Switzerland leads this network, which 39 countries have since joined: Austria, Azerbaijan, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Finland, France, Georgia, Greece, Hungary, Ireland, Israel, Italy, Kazakhstan, Kyrgystan, Latvia, Lithuania, Malta, Moldova, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Serbia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan. WHO/Europe and the European Commission participate as observers. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/policy/member-states-action-networks/reducing-salt-intake-in-the-population.

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On the basis of such appraisal, the E.S.A.N. agreed a statement confirming the support to the implementation of national and regional programmes of moderate reduction in salt intake, as recommended by the World Health Organization.

Introduction

Raised blood pressure (BP) is the first cause of death and disability in adults worldwide, mainly due to cardiovascular disease (CVD). The risk of CVD increases progressively with increasing BP. However, the majority of CVD death and morbidity attributable to BP occur at just suboptimal BP levels such as those between 120 and 140 mmHg systolic, because there are so many individuals in the population with these BP values. Clinical guidelines would not treat the majority of these individuals with drugs. Therefore, a population-approach through non-pharmacological measures (diet and life-style) is the most feasible option, recommended by the WHO [1] and adopted under a UN Resolution of the 66th World Health Assembly in 2013 [2].

Salt, blood pressure and CVD

High salt intake is associated with high blood pressure and a moderate reduction in salt consumption causes a significant reduction in blood pressure [3]. Furthermore, in well-conducted cohort studies [4–7] and in few intervention trials [8], a lower salt consumption is associated with reduced cardiovascular events.

New evidence

However, a number of recent publications from a single research group have generated scientific controversy and confusion in the popular press and the general public. The studies suggest a J-shaped relationship between salt intake and risk of CVD implying that a level of salt intake such as the one suggested by WHO (<5 g per day) is equally dangerous as a level >12 g per day [9–14]. The studies include repeated analyses from the Prospective Urban Rural Epidemiology (PURE) study, and post-hoc analyses from two randomized clinical trials of the effectiveness of combined pharmacological treatment in hypertensive patients (ONTARGET and TRANSCEND), enriched also with data from the screenees of the DREAM trial (EpiDREAM). The methodology used in these studies to explore the effects of different levels of salt consumption on blood pressure and prospective CVD outcomes and mortality suffers from flaws that have been repeatedly addressed in the medical literature in recent years [15,16] (Table 1), and that are still being ignored in more recent publications [13]. Nevertheless, the authors of these papers continue to challenge the WHO's global recommendations to reduce salt intake to less than 5 g per day and call into question what is regarded, by numerous global health organizations, as robust evidence on the role of a moderate salt reduction in the prevention of cardiovascular disease and the need for global public health action.

Brief scientific appraisal of the new evidence

Biased assessment of sodium intake from spot urines and use of Kawasaki formula

All the studies concerned [9–13] use morning voiding urine samples to assess salt intake. This is obtained by extrapolating the data of urinary sodium concentrations to 24 h urinary sodium excretion using the Kawasaki formula [17]. This is an inappropriate method for estimating salt intake in individuals, due to its unreliability and systematic bias [18–20]. This formula relies on urinary creatinine concentration from a spot collection and 24 h urinary creatinine excretion predicted from age, sex, height and weight. One problem lies in the fact that several of these factors, particularly age and urinary creatinine excretion, are closely associated with the outcomes of interest, specifically mortality, so as to lead to multicollinearity and distortions of true relationships. A second problem is that the spot urine method introduces a consistent bias by overestimating at lower levels of salt intake and underestimating at higher levels. This is also present in the validation reported in the PURE study [21], criticized at the time of its publication [22], and even more evident in the Chinese cohort [23], on which later analyses are mainly based. Whilst the use of the Kawasaki formula yields a lower bias compared to the other methods, it is twice as high in the Chinese validation study that in the previous study (−740 [95% CI −1219 to 262] mg/day vs 313 [182 to 444] mg/day) (Fig. 1). However, the authors neglect the presence of a significant bias when estimating individuals' sodium excretion as shown in the Bland–Altman plots, results superimposable to other validations. Furthermore, a 'first void' (overnight) sample was used whereas the Kawasaki equation had been designed to assess' second' void morning samples. There was a very high rate of incomplete collections (>50%), with the bias higher at higher levels of 24 h urinary sodium, likely due to incompleteness [22]. Therefore, spot urine samples are not a valid test to assess salt intake.

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Table 1 Summary of methodological errors identified in recent prospective observational studies of salt consumption and cardiovascular outcomes reporting J-shaped associations. Re-drawn from Reference [15].

Domain 1	Errors with the greatest potential to alter the direction of association
	Systematic error in sodium assessment
	• Lower risk: 24 h urine collections not part of routine clinical practice, no quality assurance, not excluding incomplete collections
	• Higher risk: other 24 h urine collections, all dietary assessments, spot and overnight urine collections
	Reverse causality
	• Lower risk: participants recruited from general population and pre-existing CVD excluded
	• Intermediate risk: sick populations not excluded or included despite stated otherwise; presence of CVD risk factors; specific sick populations
	• Higher risk: specific sick populations (e.g.: heart failure, kidney disease, diabetes); removal of sick participants from analysis changes direction of association
Domain 2	**Errors with some potential to alter the direction of association**
	Potential for residual confounding
	• Incomplete adjustment: not including 2 or more of age, sex, race, SES, cholesterol, BMI or weight, smoking, diabetes; if diet-based, total calories; if urine-based, weight, BMI or creatinine excretion
	• Imbalance across sodium intake levels: age difference across sodium groups >5 years; sex or race distribution across sodium groups >20%
	• Inadequate follow-up: low level of follow-up (<80%) or of uncertain quality for outcome assessment
Domain 3	**Errors with the potential to lead to a false null result**
	Random error in sodium assessment
	• Lower risk: more than four 24 h urine assessments on average; FFQs
	• Intermediate risk: between 2 and 4 24 h urine collections, or corrections for regression dilution bias; dietary reports
	• Higher risk: urine collection <24 h or single 24 h 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 in sodium intake
	Studies using same data with divergent results
	• NHANES I studies: same age group, same follow-up—inverse versus positive association
	• NHANES III studies: different age groups, different follow-up—inverse versus positive association

Biased assessment of sodium–outcome relationships using spot urine samples

The authors of the studies concerned insist on the concept (uncritically repeated in some Editorials) [24,25] that the method could be useful to assess group means. However, they use data on individuals when assessing risk prediction in a cohort study design. It has been long established that several 24 h urine collections are needed to approximate an individual's salt intake with a high degree of confidence (i.e. within 10%) and without bias [26–28]. Cohort studies that use the method of repeated 24 h urine collections to assess salt intake show beyond doubt a graded relationship between sodium excretion and cardiovascular outcomes with no increased risk at lower sodium intakes [4–7].

A recent head-to-head comparison between measures of salt consumption obtained from repeated 24 h urine collections compared to a second morning spot urine in the prospective assessment of salt and mortality shows that there is a graded relationship when salt consumption is assessed with multiple 24 h collections (with no evidence of increased risk at lower levels up to 3 g of salt per day) whereas an 'erroneous' J-shaped curve is generated when using the Kawasaki formula from spot urines [29]. Therefore 'spot' urine collections with the use of the Kawasaki formula are an inappropriate method of studying associations in individuals in prospective studies. This study also shows that a single 24 h urine collection is not sufficient to assess the long-term effects of salt consumption on vital outcomes. Therefore, one single urine test is an inappropriate method for studying associations to assess the long-term effects of salt consumption on vital outcomes.

Potential risk of reverse causality

An important point is the consistent use of sick populations and patient groups to study the implications of a moderate reduction in salt consumption in the general population. The ONTARGET/TRANSCEND study selected 28,800 participants from high risk patients to undergo randomized clinical trials of anti-hypertensive treatments [11]. Reverse causality is an important flaw in their results which are mis-interpreted.

Selected characteristics of the participants are shown in Table 2. Patients were old (average age 66.5 ± 7.2 yrs). However, patients in the lower sodium intake group were 2.4 years older. Whilst in the whole study 71% were men of white European background, the low sodium group had an overrepresentation of women. All had significant previous disease (48% with MIs, 21% CVAs, 70% hypertension and 37% diabetes), all were highly medicated with beta-blockers (57%), diuretics (29%), calcium channel blockers (35%) and ~75% on blockers of the renin-angiotensin system. More interesting the proportion of patients on diuretics was higher in both the low (41%) and the high (43%) sodium groups.

The reported higher cardiovascular mortality in the low sodium group was, in fact, only detected in the composite outcome of total CV death (Table 3). This was exclusively accounted for by excess heart failure in this group, but not excess MI, stroke or non-CV death.

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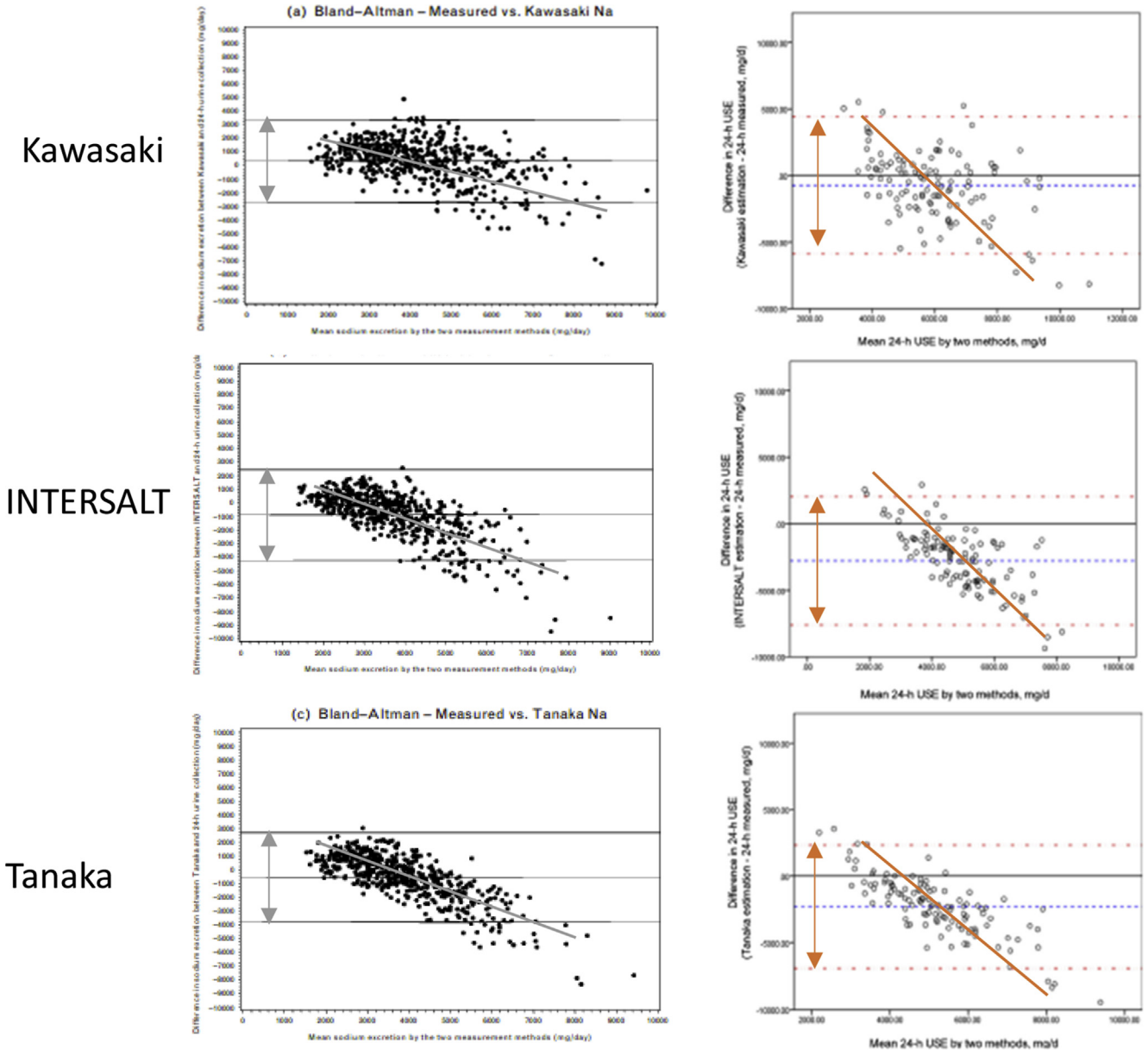

Figure 1 Validation and comparison of three formulae to estimate 24 h urinary sodium excretion from a single morning spot urine sample in the PURE Study. On the right it is the validation in 1083 participants from 11 countries† and on the left it is the validation in 120 participants from the Shanxi Province of China#. Re-drawn from References [21,23], respectively. † 1083 consecutive individuals attending follow-up clinics over a period of 2–6 months; 87 from India, 153 from China and Colombia, 412 from Argentina, Brazil, Malaysia, South Africa, Turkey, 431 from Canada, Sweden, UAE. # 120 participants (60 rural and 60 urban) attending either 3-year or 6-year follow-up visit.

Taken together, the results suggest that the over-representation in the low sodium group of patients with advancing age and illness, at high risk of heart failure, more likely to take diuretics and at higher risk of death explains the high mortality detected in that group and, at the same time, the lower sodium intake that is often associated with reduced calorie intake in this group of patients (reverse causality). Including sick and treated individuals produces misleading results.

Similar attention should be given to the PURE Study [9,10], an on-going epidemiological cohort study that has enrolled 157,543 individuals in 17 countries. The PURE Sodium Study only reported on 101,945 participants (65% of the original cohort) who were able to provide a urine sample [10]. Compared to the overall original cohort, the sodium cohort had fewer participants from India (5 vs 18%) and more from China (42% v 30%), with unbalanced distribution across sodium groups (Table 4). The potential confounding by socio-economic status between countries [30] and within country [31–33] is an important risk when assessing the relationship between sodium consumption and ill-health. Given the study design in PURE and the lack of sufficient adjustments for socio-economic indicators, the lack of adequate adjustment for socio-economic status is a serious problem in PURE.

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Table 2 Selected baseline characteristics of participants in ONTARGET and TRANSCEND by 24 h sodium excretion range.

Variable	Overall (n = 28,880)	Sodium excretion (g/day)				
		<2	2–3.99	4–5.99	6–8	>8
Age (years)	66.5	67.6	67.0	66.5	65.8	65.4†
Women (%)	29.4	53.5	38.0	26.6	20.2	21.0†
White/European (%)	71.4	63.7	70.0	72.4	72.0	73.2†
Previous medical history						
Myocardial infarction	48.4	46.6	48.2	49.0	47.5	45.5*
Stroke/TIA	21.2	23.2	22.9	20.2	20.4	22.7†
Hypertension	69.9	78.2	69.0	67.9	74.1	82.1†
Diabetes mellitus	37.1	39.1	32.2	36.2	45.5	51.6†
Atrial fibrillation	3.3	5.1	3.6	2.9	3.7	3.8†
Medications						
Beta-blocker	57.2	58.2	58.1	57.0	56.2	56.1
Diuretic	28.7	41.0	30.7	25.9	29.0	43.3†
Calcium antagonist	34.6	44.4	32.3	32.3	40.8	50.8†

*p-0.08; †p < 0.001 across sodium excretion groups. Re-drawn from Ref. [11].

Table 3 Association between estimated 24 h urinary sodium excretion and CV events and mortality in ONTARGET and TRANSCEND.

Outcome	Sodium excretion (g/day)						
	<2	2–2.99	3–3.99	4–5.99	6–6.99	7–8	>8
All death	1.19	1.11	1.06	1 reference	1.14	1.29	1.56
	0.99–1.45	0.99–1.26	0.96–1.16		1.02–1.28	1.10–1.52	1.30–1.89
Total CV death	1.37	1.19	1.09	1 reference	1.11	1.53	1.66
	1.09–1.73	1.02–1.39	0.96–1.23		0.96–1.29	1.26–1.86	1.31–2.10
Non-CV death	0.92	1.00	1.02	1 reference	1.18	0.95	1.42
	0.65–1.29	0.83–1.21	0.88–1.18		0.99–1.40	0.71–1.27	1.04–1.94
M.I.	1.10	1.04	1.11	1 reference	1.21	1.11	1.48
	0.80–1.53	0.85–1.27	0.96–1.28		1.03–1.43	0.85–1.44	1.11–1.98
C.H.F.	1.29	1.23	1.07	1 reference	1.04	1.06	1.51
	0.95–1.74	1.01–1.49	0.91–1.25		0.86–1.27	0.79–1.42	1.12–2.05
Stroke	1.06	1.05	0.97	1 reference	0.95	1.06	1.48
	0.76–1.46	0.86–1.28	0.83–1.13		0.79–1.15	0.81–1.40	1.09–2.01

Results are reported as Hazard Ratios (95% C.I.) in a multivariate model. Re-drawn from Ref. [11].

Table 4 Characteristics of the participants in the PURE Sodium Study and the Overall PURE Study in relation to country income level – evidence of selection bias. Re-drawn from Ref. [10].

Characteristics	PURE Sodium Study (n = 102,216)	Overall PURE Study (n = 157,543)
Country income level (%)		
Low income (%)	7.1	22.2
India only (%)	4.8	18.4
Lower middle income (%)	53.6	39.6
China only (%)	42.1	30.0
Upper middle income (%)	25.1	27.9
High income (%)	14.2	10.2

In addition, the low sodium group was 2.8 years older, had fewer men (29.6 v 58.1%), fewer participants from Asian ancestry (33.8 v 73.0%), more with history of cardiovascular disease (9.2 v 7.1%) and diabetes (10.6 v 8.4%), and a greater proportion of people on regular medications, suggesting the presence of self-selected sicker participants in the low sodium group [9]. The self-selection of sicker participants in the low sodium group is the likely result of incorrect assessment of sodium intake. Also, sick people are more likely to die earlier and are also more likely to change their diet. Finally, the EpiDREAM cohort screened people at high-risk of type 2 diabetes, over 70% obese women, with high proportion of treated individuals [13]. None of these studies' results can be generalized to inform current public health strategies for a moderate reduction in sodium consumption in unselected populations or to be considered of good quality to support a causal relationship between low sodium intake and increased cardiovascular mortality.

Analytical approaches to data analysis

A recent analysis from the PURE study attempted to perform a community-based analysis to overcome the above methodological problems. The overestimate at low levels of salt intake and underestimate at higher levels, and associated problems of unreliability and weak estimations, still persist at population level [29]. The same bias is reported in several other populations (irrespective of the formulas used to estimate daily consumption) [18–21,34], making these measures not suitable to assess an individual's sodium excretion (salt intake) in cross-sectional and prospective studies [22]. Community-based

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analysis to overcome methodological problems is, therefore, not the right answer to the previous criticisms.

Two high-impact studies are just re-analyses of the same datasets and a republication of previous data from the ONTARGET and TRANSCEND Trials [11] and from the PURE Study [9,10,12,13] with the addition of EpiDREAM, screenees of the DREAM Trial in one [12]. Not surprising, the results in these 'larger' samples are confirmatory of their previous results. There are several considerations to make: the authors split a continuously distributed biological variable in the population (blood pressure) in a biological meaningless dichotomy of 'hypertension' and 'normotension'. By doing that, they reduce the statistical power of detecting relationships, particularly when studying trends. A similar mistake was made by Taylor et al. [35] leading to misleading conclusions, then corrected by a proper re-analysis of data [8]. In other words, blood pressure, which is the main biological determinant of CV events, is normally distributed, and it is not biologically meaningful to run population-based analyses amongst 'normotensive' and 'hypertensives'.

Lack of plausibility

There is no plausible explanation for the higher CVD risk associated with lower salt intake. The argument that the J-shaped curve may be mediated by a 'harmful' activation of the renin-angiotensin-aldosterone system is an incorrect physiological statement in the circumstances of moderate long-term reduction in salt intake as addressed in previous critics [16,36–38].

As the least dangerous level of salt intake, according to these authors, is exactly the one found in most European, North American and Australian populations (10–12 g per day), their claim would imply a policy of "no-intervention" on salt intake in these countries in spite of the randomized controlled trial evidence of statistically and clinically significant BP reductions achievable in both hypertensive and normotensive individuals by approximately halving the habitual salt intake [3].

Low precision from just one estimate of sodium intake

Studies with more stringent quality features have been able to avoid such biases and have obtained more reliable results [5–7]. *Mills* et al. [5] followed up a cohort of 3757 patients with chronic kidney disease from 7 locations in the USA. They assessed baseline urinary sodium excretion from a cumulative calibrated measure based on three 24 h urine collections and obtained information on non-fatal composite CVD events (heart failure, MI and stroke) for a median follow-up of 6.8 years. 804 composite events (575 of heart failure, 305 of MI and 148 of stroke) occurred. The study showed a significant linear association between calibrated 24 h urinary sodium excretion and composite CVD events with no evidence of non-linear effects. *Cook* et al. [6] followed up pre-hypertensive adults during extended post-trial surveillance in TOHP II (25.7 years follow-up) and TOHP I (22.4 years follow-up). A total of 77 and 174 deaths occurred amongst the unique 2974 participants not in a sodium reduction intervention group, respectively. Multiple (3-to-7 per individual) 24 h urine collections were obtained throughout. There was a direct linear association between average sodium intake and mortality (HR: 1.12 per 1 g sodium/day [95% CI: 1.00 to 1.26], $p = 0.05$). No J-shaped trend was observed at lower sodium excretion. The design of these studies overcome major methodological challenges of prior studies and, in spite of relatively small event rates, they detect 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.

Finally, *Olde Engberink* et al. [7] selected adult subjects (mean age 47 years) with normal renal function, an outpatient 24 h urine sample between 1998 and 1999, and at least 1 collection during a 17-year follow-up. Sodium intake was estimated with a single baseline collection and the average of samples collected during a 1, 5, and 15-year follow-up. 574 subjects with 9776 24 h urine samples were included. Relative to a single baseline measurement, 50% of the subjects had a >0.8 g difference in sodium intake with long-term estimations. As a result, 45%, 49%, and 50% of all subjects switched between tertiles of sodium intake when the 1, 5, or 15-year average was used, respectively. Consequently, hazard ratios for cardio-renal outcomes changed up to 85% with the use of sodium intake estimations from short-term (1-year) and long-term (5-year) follow-up instead of baseline estimations. This study reinforces the concept that relative to a single baseline 24 h sodium measurement, the use of subsequent 24 h urine samples leads to different estimations of an individual's sodium intake, whereas population averages remained similar, with significant impact on the association between sodium intake and long-term cardiovascular and renal outcomes.

Conclusions

The evidence supporting global actions for a moderate reduction in salt consumption to prevent cardiovascular disease is strong and such new controversial studies – in particular the PURE Study - are inappropriate to address the complex associations between salt intake and CVD outcomes and should not overturn the concerted public health action to reduce salt intake globally.

Author contributions

FPC prepared a draft document for discussion at the meeting, contributed to the discussion and prepared the final document. MB chaired the E.S.A.N. meeting in Rome, contributed to the discussion and to the preparation of the manuscript. PS contributed to the discussion and to the preparation of the manuscript. Representatives of Members States associated with the W.H.O. E.S.A.N, affiliated collaborating centres and advisors reviewed and approved the final version.

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Disclaimer

The authors and the members of the ESAN are responsible for the content and views expressed in this publication and they do not necessarily represent the decisions, policy or views of the World Health Organization or the Swiss Federal Food Safety and Veterinary Office.

Conflicts of interest

FPC is a technical advisor to the World Health Organization, unpaid member of CASH, WASH, UK Health Forum, President and Trustee of the British and Irish Hypertension Society. MB in unpaid Chair of the E.S.A.N. PS is unpaid member of WASH and President of the Italian Society of Human Nutrition.

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