The impact of excessive salt intake on human health

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The impact of excessive salt intake on human health

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Abstract | Intake of salt is a biological imperative, inextricably woven into physiological systems, human societies and global culture. However, excessive salt intake is associated with high blood pressure. As this effect likely drives cardiovascular morbidity and mortality, excessive salt intake is estimated to cause ~5 million deaths per annum worldwide. Animal research has identified various mechanisms by which high salt intake drives disease in the kidney, brain, vasculature and immune system. The potential for therapeutic interventions in many of these pathways has yet to be tested. Salt-reduction interventions lower blood pressure but for most individuals, 'hidden' salt in processed foods disconnects salt intake from discretionary control. This problem is compounded by growing inequalities in food systems, which form another hurdle to sustaining individual dietary control of salt intake. The most effective salt-reduction interventions have been implemented at the population level and comprise multi-component approaches, involving government, education and the food industry.

Introduction

Excessive intake of salt (NaCl) — defined as an intake that is surplus to physiological requirements — can raise blood pressure.[1] Such excessive salt intake

is well within the range of typical dietary intake in most modern societies. The mean daily global intake of ~10–15 g NaCl (170–260 mmol)[2-4] far exceeds both physiological requirements and the World Health Organization target of <5g NaCl (85 mmol) per day[5].

Excessive salt intake is associated with high blood pressure in diverse human populations[6]. The crucial question is whether salt exerts a causal influence on patient-centred health outcomes such as myocardial infarction, stroke and death. This is a controversial, fiercely debated[7] area. Some authors argue that there are compelling data to support a causal link between dietary salt intake and cardiovascular disease[8,9]. Others argue that an observational association between low estimated sodium intake and higher mortality shows that salt reduction may be neutral or even harmful in many individuals[10].

The extent to which an individual is susceptible to the health effects of dietary salt depends on their salt intake and their salt-sensitivity; that is, the gradient between salt intake and risk of disease.**Figure 2 | Salt consumption and the effects of interventions on blood pressure and cardiovascular risk. a |** The World Health Organization (WHO)[5] and US National Academy of Sciences (NAS)[48] recommend an upper limit of daily salt intake for all adults of 5 g NaCl (85 mmol) or 5.85 g NaCl (100 mmol), respectively. Kidney Disease: Improving Global Outcomes (KDIGO)[201] and the European Society of Hypertension (ESC)[202] have made similar recommendations for patients with hypertension. However, the daily salt intake of many populations worldwide exceed these recommendations with a global average of ~10–15 g NaCl per day (170–260 mmol)[2,3,10,83,187,189,203.] In remote isolated populations such as the Amazonian Yanomami, daily salt intake is thought to be similar to that in Paleolithic man at ~1g NaCl (20 mmol)[83,203.] Following multi-modal public health interventions, mean daily population salt intake reduced by ~40% in Finland187 and ~15% in the UK184. **b |** Salt-reduction interventions have been shown to lower blood pressure with a linear dose-response relationship in randomized controlled trials (RCTs)[1,30,58.] In these trials, a mean reduction in sodium intake of 80–130 mmol (5–8 g NaCl) induced a ~4 mmHg decrease in systolic blood pressure1,30. The effect size was smaller for interventions lasting longer than 6 months. **c |** The NAS meta-analysis of selected RCTs showed that sodium reduction can reduce the risk of cardiovascular disease (relative risk reduction of ~25 %)[48.] In

observational studies, estimated sodium intake has exhibited either a linear35,52 or J-shaped21,37,38,44 association with cardiovascular disease risk. The J-shaped association can likely be explained by methodological artefacts owing to use of spot urine samples, confounding and reverse causality, rather than a genuine increase in cardiovascular risk at low sodium intakes. Both salt intake and salt-sensitivity of blood pressure are associated with increased risk of cardiovascular disease (CVD) and death[11,12] Diseases including heart failure and CKD also alter individual sensitivity to the health effects of salt (**Box 3)**.

The biological mechanisms whereby salt perturbs normal physiology[13-18], whether salt causes CVD[7] and effective interventions[9,19] to improve health outcomes have been reviewed separately elsewhere. Here, we aim to integrate these disparate areas into a unifying thesis regarding the impact of salt on human health. Given the difficulties in performing definitive long-term RCTs with patient-centred endpoints, we argue that it is necessary to form an opinion based on the total evidence from multiple sources (**Figure 2 | Salt consumption and the effects of interventions on blood pressure and cardiovascular risk. a |** The World Health Organization (WHO)[5] and US National Academy of Sciences (NAS)[48] recommend an upper limit of daily salt intake for all adults of 5 g NaCl (85 mmol) or 5.85 g NaCl (100 mmol), respectively. Kidney Disease: Improving Global Outcomes (KDIGO)[201] and the European Society of Hypertension (ESC)[202] have made similar recommendations for patients with hypertension. However, the daily salt intake of many populations worldwide exceed these recommendations with a global average of ~10–15 g NaCl per day (170–260 mmol)[2,3,10,83,187,189,203.] In remote isolated populations such as the Amazonian Yanomami, daily salt intake is thought to be similar to that in Paleolithic man at ~1g NaCl (20 mmol)[83,203.] Following multi-modal public health interventions, mean daily population salt intake reduced by ~40% in Finland187 and ~15% in the UK184. **b |** Salt-reduction interventions have been shown to lower blood pressure with a linear dose-response relationship in randomized controlled trials (RCTs)[1,30,58.] In these trials, a mean reduction in sodium intake of 80–130 mmol (5–8 g NaCl) induced a ~4 mmHg decrease in systolic blood pressure1,30. The effect size was smaller for interventions lasting longer than 6 months. **c |** The NAS meta-analysis of selected RCTs showed that sodium reduction can reduce the risk of cardiovascular disease (relative risk reduction of ~25 %)[48.] In observational studies, estimated

sodium intake has exhibited either a linear35,52 or J-shaped21,37,38,44 association with cardiovascular disease risk. The J-shaped association can likely be explained by methodological artefacts owing to use of spot urine samples, confounding and reverse causality, rather than a genuine increase in cardiovascular risk at low sodium intakes.). The effects of salt reduction on blood pressure have been tested in individual-level RCTs; the effects of potassium-rich salt-substitutes on cardiovascular disease have been tested in cluster-level RCTs. In observational studies, statistical adjustment for confounders or Mendelian randomization are used to infer a causal role for salt in cardiovascular disease. Animal models have been used to define the likely molecular mechanisms of salt-induced cardiovascular effects. We begin by reviewing the evidence that salt intake affects patient-centred health outcomes. We then highlight the factors that determine individual susceptibility to dietary salt and discuss how best to intervene to reduce salt intake and improve health at the population and individual levels.

Salt and blood pressure

Observational data

The mean global sodium intake is ~170 mmol (4 g Na; 10 g NaCl) per day[2]. Above this threshold, salt intake is positively associated with blood pressure. This observation has been replicated in large, multinational studies in the general population, notably INTERSALT[6], PURE[20] and the UK Biobank cohort[21]. The relationship between salt intake and blood pressure is steeper in patients with hypertension than in those who are normotensive[22]. In addition, a robust negative association exists between potassium intake and blood pressure (**Box 1**).

Mendelian randomisation analysis has been used to infer a causal role for dietary sodium in setting blood pressure. In the UK Biobank cohort, genetic variants that were associated with urine Na/K ratio exerted a probable causal influence on blood pressure[23,24]. Similarly, in East Asian populations, genetic variants that associated with sodium intake were also associated with blood pressure [25,26].

Randomized controlled trial data

Prior to the development of antihypertensive therapies, the low-salt rice diet was used to successfully treat malignant hypertension, but was not tested in RCTs[27].

Subsequent trials in Chimpanzees showed that blood pressure varies in response to interventions in dietary salt[28], an observation that has now been replicated in hundreds of human RCTs.

Two large meta-analyses that quantified the 'dose-response' relationship between sodium intake and blood pressure in adults gave similar results. The first by Huang et al., which included 133 studies with >12,000 participants, included trials of any duration excluding those in pregnant women and patients with chronic kidney disease (CKD)[1]. The analysis showed that in studies that exceeded 14 days in duration, systolic blood pressure fell by ~2.1 mmHg (95% CI 0.9–3.4) per 50 mM reduction in Na. The effect size was roughly half as large in studies of shorter duration. The mean reduction in sodium intake in the intervention group was 131 mmol per day (range of change in sodium intake -336–8 mmol) and the mean reduction in systolic blood pressure was 4.3 mmHg (95% confidence interval 3.6–4.9 mmHg)[1]. This effect size is broadly comparable to that achieved with anti-hypertensive medications: a meta-analysis published in preprint form that included 51 RCTs reported that antihypertensive drugs induce a mean blood pressure decrease of ~5 mmHg compared to placebo[29].

The second meta-analysis by Filippini et al. included 85 trials of >4 weeks' duration and a total of >10,000 participants[30]. A linear relationship between urinary sodium excretion and blood pressure was observed over the range 20–330 mmol per day. The gradient for systolic blood pressure reduction was ~2.8 mmHg (2.3–3.3 mmHg) per 50 mM reduction in Na and the median reduction in Na intake in the intervention group was ~80 mmol per day.

Most published RCTs are fairly small and of short duration. In the meta-analysis by Huang et al., only 5 studies including 3,252 participants had interventions that lasted more than 6 months[1]. However, longer-term population-level salt-substitution interventions have achieved sustained reductions in salt intake and blood pressure, as we discuss in detail below[31-33].

Salt and cardiovascular disease

Observational data

Large observational studies differ in their conclusions regarding the relationship between sodium intake and CVD (supplemental Table 1). A meta-analysis of high-quality prospective cohort studies showed a dose-dependent association between salt intake and CVD, with a ~12% increase in stroke risk for every 100 mmol per day increase in salt consumption[34]. Similarly, a meta-analysis of six prospective cohort studies in over 10,000 healthy, predominantly White adults demonstrated a broadly linear association between sodium intake – estimated from at least two 24h urine collections – and risk of a composite cardiovascular outcome (stroke, MI, coronary revascularisation)[35]. However, some large cohort studies, notably the PURE study, have shown a 'J-shaped curve' with an inverse association between salt intake, CVD and all-cause mortality when estimated salt intake is less than ~170 mmol (~4 g Na; 10 g NaCl) per day[36-40].

Although a well-publicised debate exists regarding the explanation for the 'J-shaped curve', consensus is growing that much of the effect can be explained by methodological artefacts inherent in the estimation of sodium intake using spot urine samples (**Box 2**) or epidemiological analyses (confounding and reverse causation)[19]. The World Hypertension League have been particularly vocal in their criticism of the PURE study, primarily for its reliance on spot urine samples[8,41] Even if the 'J-shaped curve' is predominantly an artefact, low sodium intake could potentially be harmful in certain individuals **(Box 3**). Some have argued that sodium restriction could activate the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous systems with deleterious consequences, but no empirical support for this hypothesis exists[42].

Controversy also exists regarding the upper end of sodium excretion. Most large cohort studies have reported a positive association between estimated sodium intake and CVD for intakes >4–6 g per day (170–260 mmol; 10–15 g NaCl) [22,37,40,43]. However, three analyses of data from the UK Biobank cohort did not replicate this observation [21,24,44]. Whether this discrepancy arises from differences in the study populations or is a methodological artefact is unclear (supplemental Table 1). The most parsimonious explanation is that use of spot urine samples, which underestimate sodium intake at higher levels, flattens any association between salt intake and CVD in this range. Consistent with this effect being a methodological artefact, an analysis of UK Biobank participant data found no significant association

between estimated sodium intake and CVD in the primary analysis, but a significant positive association in a model that did not adjust for BMI[44].

Randomized controlled trial data

Several individually-randomized controlled trials have attempted to determine the effects of salt reduction on CVD and mortality. However, none has had sufficient sample size and duration to give a definitive answer and meta-analyses of these RCTs have reached different conclusions. A Cochrane review concluded that only weak evidence suggests that dietary salt reduction reduces the incidence of CVD[45,46], whereas a contemporaneous analysis by different researchers concluded that dietary salt reduction (~34 mmol (2g) NaCl per day) causes a meaningful reduction in CVD risk (RR 0.80, 95% CI 0.64–0.99)[47]. A US National Academy of Sciences (NAS) report concluded that moderate evidence suggests that dietary sodium reduction (from ~150 to 100 mmol (~3.5 to 2.3 g) NaCl per day) prevents CVD (RR 0.74, 95% CI 0.58–0.93)[48], whereas an associated systematic review concluded that confidence in this observation was low[49]. These discrepancies arise because meta-analyses are highly sensitive to the study inclusion criteria. This issue was exemplified by a meta-analysis in which the researchers reversed their initial opinion that salt restriction reduces all-cause and cardiovascular mortality[50], and in light of additional sensitivity analyses, ultimately concluded that no strong evidence of any effect exists[51].

The conclusion of the NAS report was largely based on a meta-analysis of trials lasting for >12 months and excluding interventions based on salt substitutes; only three trials met these criteria: TOHP-1, TOHP-2 and TONE[52,53]. These trials are potentially informative; they are methodologically sound with a low risk of bias, they were conducted in populations with moderate CVD risk (middle-aged pre-hypertensive adults in TOHP and elderly patients with hypertension in TONE) and they used serial 24h urine collections to accurately define the effect of the low sodium intervention. They also studied the effect of sodium reduction within a clinically relevant range (decrease of ~40 mmol from a baseline of 150–180 mmol per day). However, confidence in the findings of the NAS meta-analysis is limited by the low number of study participants (3,087, of whom 282 experienced a cardiovascular event). Furthermore, as the included trials were conducted in the late 80s and early 90s, when definitions of cardiovascular events and the approach to

CVD prevention differed substantially from the current standards, whether the results are generalizable to a contemporary population is uncertain.

Despite the controversy, two broad points of consensus exist. The first is that the uncertainty could be resolved by better quality data, that is, large RCTs with long enough follow-up to assess robust cardiovascular outcomes. The second is that the barriers to performing such trials are so substantial that they will be rarely, if ever, surmounted. The number of participants required to test the effect of sodium reduction on CVD in an individually randomized controlled trial was estimated to be between 17,000 and 37,000, depending on baseline cardiovascular risk[54]. The estimated cost of such a trial was USD$400–900 million[54].

Cluster-randomized trials enable greater cost-efficiency at the expense of reduced statistical power and precision. This approach has been used to test the effect of potassium-rich salt substitutes in high-risk populations[31,32,55]. The largest such study to date, the SSaSS RCT, included ~21,000 individuals with a history of stroke or aged >60 years with hypertension in rural China[31]. In this study, the intervention, substitution of table salt with 75% NaCl/25% KCl, was randomly assigned to entire villages. This substitution was associated with reductions in the incidence of stroke (~14%), major cardiovascular events (~13%) and all-cause mortality (~12%), without any detectable increase in hyperkalaemia. These effects were broadly consistent with the observed drop in systolic blood pressure of ~3.3 mmHg.

The pragmatic design of SSaSS renders it subject to criticisms of internal and external validity. The control group did not receive a placebo intervention and the unusual table salt in the treatment group might have served as a daily reminder to participants that they were at high cardiovascular risk, encouraging other healthy behaviours (a Hawthorne effect). Moreover, the beneficial effects of sodium reduction could not be differentiated from those of potassium supplementation. This concept is broadly relevant, particularly when renal potassium secretion is compromised (**Box 1**). As patients with kidney disease or who were taking potassium-sparing diuretics were excluded from SSaSS, whether the substitution intervention is safe in these populations is unknown. Nevertheless, in our view, SSaSS provides high confidence that salt reduction reduces cardiovascular risk.

These cluster-randomized controlled trials[31,32,55] prove that intervention at a population level is feasible and cost-effective in populations with discretionary control of dietary salt (that is, when salt is mainly added to food in the home). Beyond this conclusion, one can either take the view that judgement should be reserved until the ideal RCT data are available or can argue – as we do – that the existing evidence from multiple sources should be used to estimate the likely consequences of sodium reduction on CVD in a population. To this end, investigators have used modelling to predict the effect of sodium reduction on CVD from the effect on blood pressure and/or make inferences from observational data.

Modelling data

In RCTs of pharmacological interventions to lower blood pressure, a 5 mmHg reduction in blood pressure confers a ~10% relative risk reduction in major adverse cardiovascular events and a ~6% relative risk reduction in all-cause mortality[56,57]. Thus, the blood pressure reductions that can be achieved using dietary sodium restriction would be expected to confer a clinically meaningful reduction in the risk of stroke, heart failure and death. Models constructed using this reasoning predict that sodium reduction strategies could prevent millions of premature deaths worldwide. The global excess of deaths attributed to excessive sodium intake is estimated at 1–5 million per year[3,58] and sodium reduction strategies could save over 5 million disability-adjusted life-years per year[59,60].

These models rely primarily on blood pressure as a surrogate or intermediate end point on the pathway from salt intake to CVD. In general, surrogate end points must be used with caution[61]; however, blood pressure is recognised as a validated intermediate end point by the US FDA and the EMA because of its incontrovertible role in the causation of stroke, myocardial infarction and heart failure[56,62]. Indeed, given the difficulties in performing a RCT with robust cardiovascular event end points, use of blood pressure as a validated intermediate end point has been essential in obtaining data on the effect of salt reduction on cardiovascular health.

However, the available models are predicated on some partially unverified assumptions. First, that dietary sodium reduction does not activate deleterious pathways that would oppose any beneficial effects of blood pressure lowering. Second, that changes in blood pressure are sustained in the long term. Furthermore,

how effective sodium reduction strategies are at the individual and population levels is unknown.

Salt and other diseases

High sodium intake is associated with stomach cancer[63], obesity, metabolic syndrome[64], autoimmunity[65,66], kidney stones and osteoporosis[9]. These associations are supported by plausible mechanisms in cell and animal models and by epidemiological data.

Salt intake is likely associated with kidney stones and osteoporosis through a common mechanism. In animal models and humans, urinary excretion of sodium and calcium are strongly correlated[67-69]. The majority of renal calcium reabsorption occurs passively in the proximal tubules[70], where it is coupled to sodium and water reabsorption through the effects of water reabsorption on the translumenal calcium gradient and by solvent drag[69]. Salt loading also reduces the expression of claudin 2, an important calcium channel, in the rat proximal tubule[71]. Therefore sodium loading / volume expansion will reduce proximal tubular fluxes and decrease net calcium reabsorption; sodium restriction / volume depletion will do the opposite. This *a priori* reasoning has been used for many years to support a role for sodium restriction in prevention of kidney stones and is supported by one small RCT[72].

For stomach cancer and autoimmune disease, epidemiological and animal data support intriguing mechanistic hypotheses. For example, it has been suggested that high salt intake increases the risk of stomach cancer because it promotes infection with Helicobacter pylori[73,74] and that salt intake promotes autoimmune disease by perturbing T_H17-lymphocyte function[65]. Nevertheless, in the absence of RCTs, we must be guarded about ascribing a meaningful causative role for high dietary salt intake in these diseases.

Determinants of salt intake

The determinants of salt intake are myriad and include cultural, socioeconomic and biological factors. The reasons why salt intake is consistently high are unknown. One possibility is that the inclusion of salt within processed foods[75], which are a dominant food source in many countries, negates discretionary control of salt intake. Even

ostensibly natural cuts of meat include hidden salt[76] due to the common industry practice of injecting saline during processing in a practice known as ‘plumping’ For most people, these practices create an environment in which sustaining a low salt intake is a difficult and resource-intensive choice. However, salt intake is also high in regions where the majority of salt intake is under discretionary control, for example, in many areas of China[75].

The uniformly high salt intake in most populations worldwide raises the question of whether a biological rationale exists for habitual salt consumption far in excess of physiological need. Understanding the mechanism might be important to identify and support individuals who are more sensitive to the adverse effects of high-salt intake and to inform effective salt-reduction strategies at the population level.

Genetic variants

Although salt is an environmental risk factor, its effects might be primarily determined by other modifying exposures, including genetic susceptibilities. Human data support this hypothesis. In the UK Biobank cohort, genetic variants were associated with estimated sodium intake at genome-wide significance. These variants were implicated in the regulation of dietary preferences, behaviour, learning, cognition, thermoregulation and weight loss and were associated with genes expressed in brain, adipose and vascular tissue[23]. Similar observations have been made in other populations. A meta-analysis of GWAS in European populations (n = 6,500) identified seven variants that were associated with urinary sodium excretion[77], including variants in the *CARPTP* and *ZSWIM5* genes, which regulate eating, appetite and neural development. These findings fit well with current understanding of salt biology because, as we discuss below, ‘salt preference’ – a behavioural phenotype – is an important determinant of sodium intake (and hence sodium excretion).

Salt appetite

Salt appetite and salt preference describe different parameters in the afferent arc of salt homeostasis. Salt *appetite* is the innate motivation to find and eat salt evoked by a physiological need relating to salt deficiency. The primordial emotion arose during the transition from aquatic to terrestrial life with selection pressure imposed by the

scarcity of salt across much of the land mass. The sodium content of plants is typically low and animals with predominantly plant-based diets are vulnerable to salt deficiency even if calorific intake is adequate. The evolution of behavioural pathways to ensure adequate salt intake is a protective adaptation to safeguard extracellular fluid volume status. Thus, salt appetite is strongly evident in herbivores; for example, sheep will avidly eat mineral sodium salts to precisely correct deficiency[78], elephants quarry and eat mineral salt as part of their foraging behaviour[79] and the provision of salt-licks has long been used as a strategy for domestication.

For carnivores, the salt content of food is always adequate and they do not exhibit an innate salt appetite, even when sodium depletion is induced experimentally[80]. The earliest hominins preceding *Homo erectus* were omnivorous, eating meat from terrestrial and aquatic animals[81]. Their estimated salt intake of ~1 g (20 mmol; 400 mg Na) per day[82] is similar to, or even slightly higher than, that of present-day isolated populations, such as the Amazonian Yanomami[83]. Whether this salt intake – low by contemporary standards imposed sufficient selection pressure to retain evolved salt appetite is uncertain. On the one hand, chimpanzees retain salt-seeking behaviours when environmental sodium is low[84] and salt-craving is reported in humans with salt-wasting disorders such as Gitelman Syndrome[85] and adrenal insufficiency[86], including a classical case report of a child who consumed salt in mineral form[87]. On the other hands, salt craving is not a consistent feature of salt-wasting disorders and controlled experiments that induce salt-depletion in healthy people do not provide evidence of an innate salt appetite[88].

Salt preference

In contrast to their lack of salt appetite, people display a strong salt *preference*; that is, a desire to eat salty food in the absence of physiological need. Despite an aversive response to mineral salt in isolation, equivalent molar concentrations of salt within the food matrix are highly palatable[89]. The evolution of hedonistic instinct serves two purposes: first, it provides positive reinforcement to a physiological imperative; second it signals satiation, closing the negative feedback loop. In mice, for example, satiation of experimentally-induced salt appetite induces rapid transcription of hypothalamic genes important for gratification and reward. Direct blockade of limbic dopaminergic reward pathways in mice eliminates salt appetite in

the absence of satiety[90]. Thus, while it is probable that salt appetite in humans is at most a vestigial instinct, hedonic preference remains. Coupled with ready accessibility to dietary salt, this preference might provide the key to understanding continuing high levels of salt intake as well as poor long-term adherence to lower salt intake. People mostly experience reduced salt alternatives as unappealing and weeks[91] or months[92] are required to induce the hedonic shift that restores a positive sensory experience at a lower salt threshold, whereupon foodstuffs that were previously palatable are regarded as unpleasantly salty[93].

Salt preference is plastic and influenced by the context of habitual exposure, which makes it difficult to gauge tractability as a means to reduce intake. For example, whether a sustained reduction in salt intake is necessary to induce a preference for foods containing lower sodium levels is not known. Moreover, if this goal is attained, the durability of sensory resetting in the face of fluctuating salt intake is unknown. Nevertheless, the ramifications for clinical management of patients are intriguing. Recognition of salt taste is impaired in people hospitalised with heart failure[94] and recovery of taste may be a prognostic biomarker of improved outcomes[95]. Patients with CKD also have impaired salt-taste acuity and increased salt-preference[96,97], possibly due to structural abnormalities in the taste buds[98].

The salt taste response

Of the five basic tastes, sweet and umami are attractive and promote appetite, whereas bitter and sour are innately aversive. Salt taste is the only modality with a biphasic response ranging from appetitive (<500 mM) to powerfully aversive (>500 mM). In evolutionary terms, this response might serve to ensure adequate salt intake while protecting against the emetic and potentially fatal[99] effects of concentrated salt ingestion[100].

The transduction of appetitive salt taste occurs through at least two distinct pathways. The major pathway is via the amiloride-sensitive sodium channel (ENaC) on the apical membrane of type 1 taste receptor cells in fungiform papillae. Sodium entry depolarises the cell, initiating action potentials in the chorda tympani[101,102]. Studies using conditional knockout strategies have confirmed that ENaC is the dominant salt-taste pathway in mice[103,104]. The molecular nature of the amiloride-insensitive pathway(s), located to the circumvallate and foliate taste buds, has not

been resolved but a role of transient receptor potential cation channel subfamily V member 1 (TRPV1) has been suggested[105]. However, this channel is non-selective and appears broadly tuned to cations and osmolarity[102] and TRPV1-knockout mice exhibit amiloride-insensitive sodium taste[106].

Intriguingly, when sodium is tasted the accompanying anion modulates the information encoded into rodent chorda tympani action potentials[102]. This mechanism might also apply to humans where large anion size increases the latency and reduces the intensity of the salt-taste response, such that monosodium glutamate is experienced as less intensely salty than the equivalent molar amount of sodium chloride[107]. This interaction provides insight into why molecular entities are often perceived differently within the food matrix compared to when experienced in isolation[108]. Thus, modifying the chemical microenvironment within complex structures could potentially maintain the perception of salt taste while achieving a reduction in salt content.

Single nucleotide polymorphisms (SNPs) in ENaC subunits and TRPV1 are associated with salt-taste perception[109] but whether these SNPs influence sodium intake is not clear[110,111]. The available association studies are small and caution must be applied when interpreting the results: ENaC and TRPV1 are also expressed in the gut and kidney so genetic variation in these channels will affect salt homeostasis at multiple points[112].

In the mouse brain, *in vivo* calcium imaging has mapped the organization of the primary gustatory cortex, locating the neuronal activity engaged by salt taste (100 mM NaCl) to a distinct area, spatially segregated from those engaged by other tastants[113]. Taste, appetite, and the motivation of behaviour is integrated between the lamina terminalis in the forebrain (an array of nuclei in the median preoptic area, subfornical organ (SFO), and the organum vasculosum laminae terminalis (OVLT)) and hindbrain (area postrema and nucleus tractus solitaris (NTS)). Projections from some of these areas into the nucleus accumbens integrate salt-appetite with the dopaminergic mesolimbic ‘reward’ system to engage salt-seeking behaviours. Pharmacological blockade of these central reward pathways disengages salt-seeking behaviour in sodium-depleted mice[90]. It is possible that such gratification pathways contribute to salt preference and high salt intake in humans[114] but this has not been extensively examined.

The renin-angiotensin-aldosterone system (RAAS) has a major role in driving the behavioural responses to experimentally-induced sodium appetite. Angiotensin II (ANGII) and aldosterone are synthesized *de novo* within the brain[115]. In rats, brain aldosterone levels increase with salt-restriction and are supressed by high salt intake, but whether this response reflects altered central synthesis is not clear as the majority of aldosterone in brain tissue comes from the circulation[116]. The SFO and OVLT have no blood–brain barrier and neurones express ANGII receptors[117] that receive information about peripheral salt and water homeostasis by detecting circulating ANGII. Distinct groups of type 1 angiotensin II receptor-positive SFO neurones drive thirst and salt appetite and are mutually suppressive via activation of interconnecting GABAergic neurons [118]. However, in rodents aldosterone-sensitive neurones in the NTS are necessary and sufficient to engage salt-appetite[119]. Neuronal activity is increased by salt-deficiency and reduced upon satiety[106] and activation engenders a motivational state specific for sodium rather than thirst or more generalised hunger[120]. This population of neurones express both the mineralocorticoid receptor and the glucocorticoid-metabolising hormone 11β-hydroxysteroid dehydrogenase 2 (11β-HDS2) and are therefore classical aldosterone target cells[121]. Conditional deletion of 11β-HSD2 in the NTS promotes abnormal mineralocorticoid receptor activation and in sodium-replete mice induces a preference for saline solutions and, when given free choice, a large increase in salt intake[122]. Such salt preference in the absence of physiological need is akin to the typical human condition. Notably, ANGII signalling in the SFO and aldosterone signalling in the NTS are synergistic, such that maximum, rapid salt intake is only engaged when both are elevated[119]. This mechanism ensures that salt intake is appropriately promoted in the context of hypovolaemia (which results in high ANGII and high aldosterone levels, but less so when aldosterone is elevated in the context of hyperkalaemia.

Determinants of salt-sensitivity

Salt-sensitivity usually refers to the gradient of the relationship between salt intake and blood pressure. However, a more patient-centred concept is the salt-sensitivity of CVD; that is, the gradient of the relationship of salt intake with cardiovascular risk.

In a substantial proportion of published studies, individuals are classified as having blood pressure that is either salt-sensitive (the minority) or salt-resistant (the majority). Such binary categorisation is useful in a research context, for example because it enables demonstration of an independent association between salt-sensitivity *per se* and cardiovascular morbidity and mortality[11,12], but is generally unhelpful in real-world settings for at least four reasons. First, the categorisation is an artificial construct: in humans, salt-sensitivity of blood pressure is a continuously distributed and reproducible trait[123-126]. Second, the thresholds used to define salt-sensitivity are arbitrary; there is no consensus definition. Third, the protocols that are used to define salt-sensitivity in a research setting are not practical in the clinic[127,128]. Fourth, and most importantly, binary categorisation in a societal context could perpetuate the idea that habitually high salt intake has no adverse health consequences for the majority of the population and therefore pose a barrier to health improvement.

Populations that exhibit increased salt-sensitivity can be identified from RCT data. Sodium restriction induces greater decreases in blood pressure in populations that are older, non-white or hypertensive[1,30]. Evidence from animal models suggests that kidney impairment and diabetes mellitus also induce salt-sensitivity, but no well-controlled studies have been conducted in humans to confirm or quantify this effect. In sum, the sensitivity of an individual to the damaging effects of dietary salt is neither categorical nor static and life events, including normal ageing, will move a person along this spectrum such that the adverse response is exaggerated.

Guyton's hypothesis

The body has many cardiovascular control systems, and yet for over 50 years, mechanistic explanations for salt-sensitivity have been dominated by 'The Guyton Hypothesis', in which the proximate cause of salt-sensitivity is a failure to appropriately regulate renal sodium disposal[129].

As blood pressure increases, so too does renal artery perfusion pressure which in turn stimulates sodium excretion. This relationship – termed 'pressure natriuresis' – was originally described in the isolated, perfused canine kidney[130,131] and is the central tenet of a hypothesis to explain the maintenance salt homeostasis by a simple negative-feedback loop (

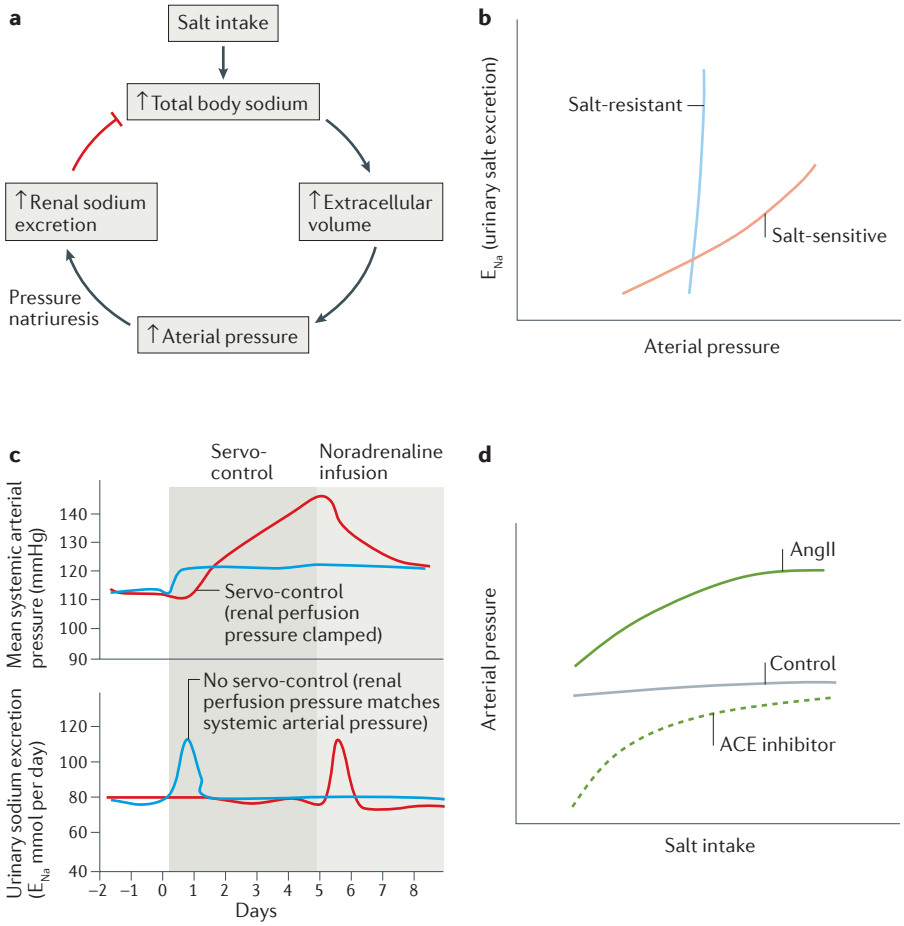

Figure 3A). Constructing a computational model of circulatory function, Guyton and colleagues found that the pressure-natriuresis feedback loop operated with infinite gain – i.e. that any deviation from 'set-point' blood pressure would be corrected exactly by a corresponding change in renal sodium excretion and extracellular fluid volume[132]. They argued that salt-sensitivity in blood pressure therefore *must* reflect some defect in pressure-natriuresis[129,132,133]. Certainly, animals with salt-sensitive blood pressure can be shown also to have a blunted pressure-natriuresis relationship (**Figure 3B**)[130,131,134], but whether this 'blunting' is necessary and sufficient to render blood pressure salt-sensitive in the long term is uncertain and extremely challenging to investigate. A small number of studies in conscious dogs have addressed this, using servo-controllers to dissociate renal perfusion pressure from systemic arterial blood pressure: these experiments showed that blocking pressure-natriuresis causes sustained hypertension over days (e.g. in the context of noradrenaline infusion[135]; **Figure 3C**).

Conceptually, a defect in pressure natriuresis could be intrinsic to the kidney, reflecting hyperactive renal sodium transporters or a defect in the paracrine signalling that controls pressure natriuresis[136]. However the kidney does not operate in isolation and neuroendocrine systems exert powerful modulatory effects on the intrinsic pressure-natriuresis relationship. The RAAS is particularly influential, dynamically adjusting sodium output to match input and thereby minimizing the impact of salt intake on long-term blood pressure. When salt intake is high, the RAAS is suppressed and the pressure-natriuresis system is free to drive commensurately high sodium excretion. When sodium intake is low, the RAAS is activated and ANGII drives renal sodium retention and vasoconstriction, maintaining a blood pressure that would have otherwise fallen. Thus, dynamic modulation of the RAAS with sodium intake is a key factor in salt-resistance of blood pressure. Conversely, when the RAAS is tonically suppressed[137,138] (e.g. with an ACE inhibitor), blood pressure falls; when the RAAS is tonically stimulated[137,139,140] (e.g. in primary hyperaldosteronism), blood pressure rises. In both cases, blood pressure becomes salt-sensitive because the RAAS is unable to dynamically match renal sodium output to input (

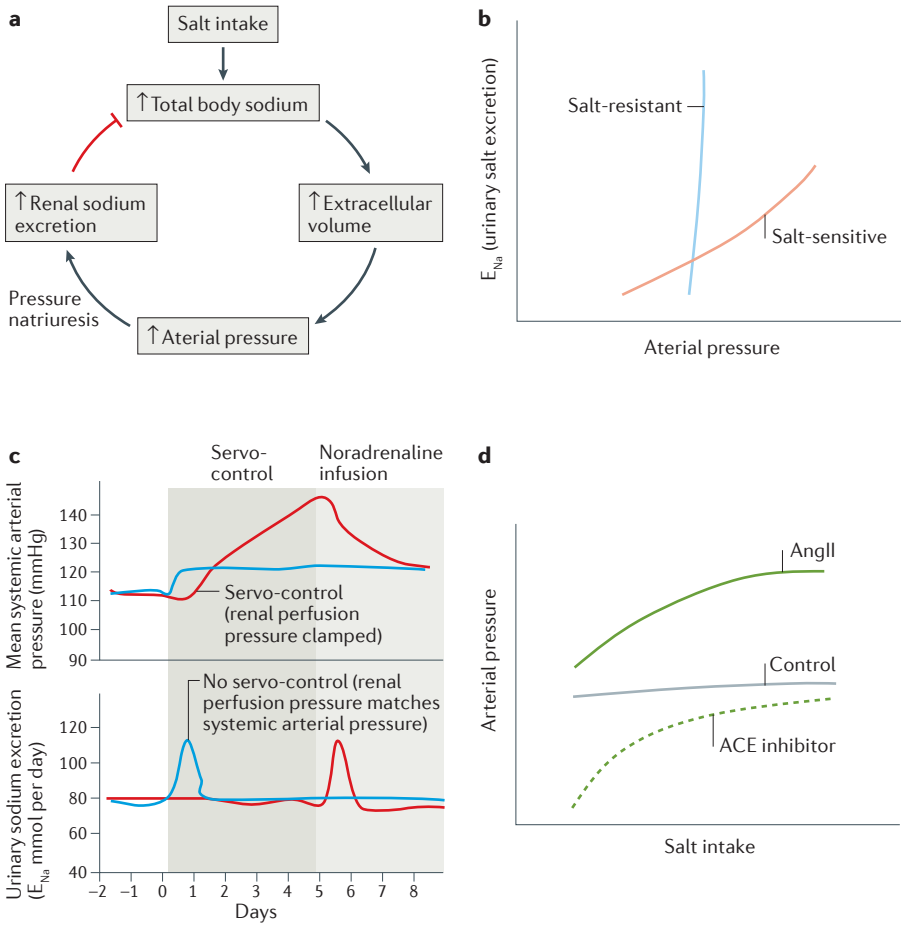

Figure 3D).

Guyton and his colleagues pioneered the use of computational approaches to understand complex physiological systems and introduced new concepts that were profoundly influential in clinical practice and research. However, whether their hypothesis explains salt-sensitive hypertension is controversial and the approach has been criticised for an over-reliance on theoretical modelling rather than empirical data[141,142], for conflating dependent and independent variables (a criticism also levelled at Guyton's venous return curve[143]) and for tautologous reasoning[144,145]. Moreover, predictions made using the model do not consistently replicate experimental outcomes[146].

In our view, a defect in regulating renal sodium excretion is neither necessary nor sufficient for salt-sensitive hypertension. That such a defect is not necessary is evident from studies in which salt-induced hypertension occurs independently of

changes in total body sodium. For example, in African American volunteers, salt-loading induced a positive sodium balance (i.e. an intake exceeding output) and increases body weight and extracellular volume to the same extent in all participants, regardless of whether they were classified as 'salt-sensitive' or 'salt-resistant' [147]. That such a defect is not sufficient is apparent from the many patients who have sodium retention without hypertension (for example, those with nephrotic syndrome, cardiac failure or portal hypertension) and the observation that infusion of sufficient levels of ANGII to blunt the excretion of a sodium load did not increase blood pressure in healthy volunteers[148].

Experiments in animals have illuminated fundamental mechanisms of salt-sensitive hypertension but high-salt models often employ exaggerated, super-physiological salt intake with exposure times restricted to days or weeks, rather than months or years. Although this acute approach pushes homeostatic systems to their limits, such modelling likely provides a poor representation of the chronic, moderate elevations in salt intake observed in human populations. Moreover, manipulation of individual dietary components is easy in animal models but unusual for human diets in which interventions designed to change sodium intake almost always change other dietary parameters (for example, potassium or chloride) that have independent effects on cardiovascular physiology.

The contemporary view

Current evidence indicates that the physiological response to excess salt is complex and involves changes in renal, vascular, neural, metabolic and immune functions[9,127,149,150] (

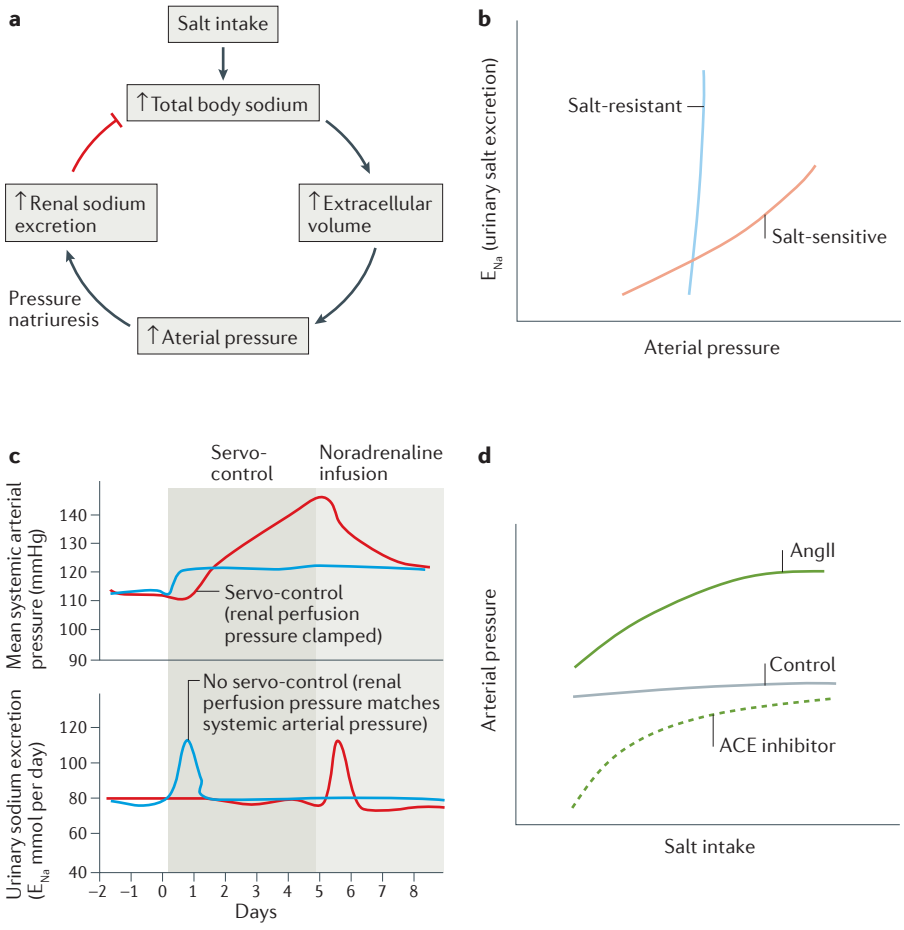

Figure 3). Criticisms of the Guytonian model notwithstanding, renal salt handling and vascular tone are central determinants of salt-sensitive blood pressure changes.

Numerous strands of evidence suggest that the kidneys exert a dominant influence on salt-sensitivity in many settings. In experimental models, salt-sensitivity can be induced by impairing natriuresis through nephrectomy[151] or by infusing ANGII[139] or mineralocorticoids[152]. Differential activation of natriuretic peptide signalling can also contribute to salt-sensitive hypertension: atrial natriuretic peptide levels were lower in salt-sensitive than in salt-resistant subjects in one small study in hypertensive adults[153]. Rodent studies have shown that cross-strain transplantation of kidneys from salt-sensitive donors leads to the development of salt-sensitivity in previously salt-resistant recipients[154] The mechanism of salt-sensitivity sometimes involves volume expansion; a meticulous histochemical analysis found that salt

loading caused an increase in the sodium and water contents of multiple body tissues in salt-sensitive but not salt-resistant rats[155].

Increased vascular tone is also a common feature of most salt-induced hypertension models. People with salt-sensitivity exhibit a blunted drop in systemic vascular resistance after a salt load[147,156]. No convincing support exists for Guyton's hypothesis that this effect is the result of whole-body autoregulation of blood flow. However, there is evidence that high sodium intake induces direct effects on vascular smooth muscle. Using both pharmacological and genetic perturbations in mice with salt-induced hypertension, Iwamoto et al. found that high sodium intake stimulated production of endogenous cardiac glycosides (ouabains), leading to an accumulation of sodium within vascular smooth muscle cells. This sodium was then extruded through the sodium-calcium exchanger NCX1, provoking calcium-dependent vasoconstriction and a rise in blood pressure [157]. Mice carrying a selective PPARγ mutation in vascular smooth muscle cells exhibit global impairment of vasodilation and salt-sensitive hypertension[158]. It would be interesting to investigate the relative contribution of the systemic and renal vascular beds to salt-sensitive hypertension in this model, for example using cross-transplantation studies.

The central and autonomic nervous systems have an important role in salt sensitivity through their effects on vascular tone. In C57BL/6 mice, a widely-used strain that is often considered to be salt-resistant[159], high salt intake raises blood pressure not via renal sodium retention, but by increased sympathetic activity and an augmented vascular response to catecholamines[160]. Salt-induced changes in blood pressure and sympathetic activity are abolished in mice lacking the critical central sodium sensor, Na_X[161].

The immune system is important in establishing salt-sensitive hypertension and in modifying hypertension-induced organ damage. In rats, salt-loading induces VEGF-C secretion by macrophages and blocking this system enhances salt-induced hypertension[162]. VEGF-C stimulates lymphangiogensis; it is hypothesised that this provides an interstitial sodium 'buffer', preventing sodium loads from inducing intravascular volume expansion and raising blood pressure[162]. Whether the proximate stimulus in this pathway is isotonic or hypertonic tissue sodium accumulation is debated[155]. A high-salt diet also induces T helper 17 (T_H17) cells, inciting a pro-inflammatory response[163,164]. T_H17 cells secrete IL-17, which sustains

ANGII-dependent hypertension by stimulating inflammatory signalling pathways in vascular smooth muscle [165] and by stimulating the expression of sodium transporters in the renal tubule[166]. Conversely, salt-wasting tubulopathies are associated with reduced T_H17 cell activation, which may explain the increased prevalence of mucosal infections and allergy in this patient population[167]. In addition, excess dietary salt modifies the gut microbiome in mice and humans, inducing pro-inflammatory changes that perturb diurnal rhythms in blood pressure and drive hypertension[168-170].

Genetic associations

As understanding of the physiology of salt-sensitivity has evolved beyond a simplistic, renal-vascular model to one involving diverse body systems, a parallel shift has occurred in knowledge of the genetic associations of salt-sensitivity. Initially, genetic variants that were associated with salt-sensitivity were identified through studies of rare Mendelian disorders and candidate gene approaches , which implicated genes controlling renal sodium handling[171] and vascular tone[127]. However, these approaches are subject to confirmation bias and do not provide information about the relative importance of genetic variants in the general population.

Unbiased studies of gene-sodium interactions in East Asian populations have identified a small number of genetic variants that are associated with salt-sensitivity of blood pressure with genome-wide significance[25,172,173]. The full functional consequences of these variants are not known, but nearby genes participate in diverse physiological processes including adrenergic and ANGII signalling (*MKNK1*), T-lymphocyte differentiation (*BCL11B*), inflammation (IRAK1BP1) and insulin signalling (*PHIP*).

Salt-reduction strategies

Expert guidelines advocate dietary salt restriction in a range of populations owing to the proven beneficial effects on blood pressure and projected beneficial effects on CVD (supplemental Table 2). However, these recommendations are not universally accepted. In a review published in 2020, an international group of experts stated that insufficient evidence exists to support the widespread recommendation to limit

sodium intake to <2.3 g per day (~100 mmol; 5.85 g NaCl)[174]. They recommended salt restriction only in populations with a mean sodium intake >5 g per day (~220 mmol; 13 g NaCl). Others have argued that because sodium intake in many populations worldwide is within a range that is associated with long life-expectancy and low rates of CVD (130–200 mmol per day; 8–12 g NaCl), attempts to reduce sodium intake are neither desirable nor possible[10]. We do not follow the logic of these arguments, which place an undue emphasis on low-quality observational data and ignore the many other environmental and genetic determinants of health.

One argument against population-level intervention is that if only 20–40% of healthy individuals have salt-sensitive blood pressure, the majority of people will not benefit from reductions in salt intake. At least five counterarguments, in our view, support population-level intervention. First, salt reduction strategies have been effective in whole populations but are relatively untested when applied to individuals in the longer term. Second, accessible methods of identifying at-risk, 'salt-sensitive' individuals are lacking. Even if salt intake could be effectively reduced only in individuals with hypertension, this approach would exclude the 40–50% of these individuals in whom hypertension is undiagnosed (estimated to number in the tens of million in the USA alone)[175-177]. Third, any risk-stratification is likely to become increasingly complex in an ageing population with a high prevalence of multimorbidity; identifying approaches to account for several interacting health conditions will be challenging[178]. Fourth, most societies have already fully adopted the principle that it is acceptable to intervene in many individuals to improve the lives of a small subset. This principle provides a foundation for public health interventions as well as for the prescription of most cardiovascular medicines, including statins[179]. Finally, intervention at the population level provides an opportunity to redress health inequalities. Maintaining a healthy diet requires knowledge, time and money[180]. In a survey of ~4,700 adults in the USA, adherence to a low-salt Dietary Approaches to Stop Hypertension (DASH) diet correlated with higher income and educational attainment[181]. Intervention at a population level would remove these socioeconomic barriers to dietary salt reduction.

Population-level interventions

At least 96 nations have implemented population-level salt-reduction strategies[182]. However, salt intake still exceeds the recommended thresholds in many populations (**Figure 2**). The success of salt-reduction strategies in Finland and the UK demonstrate that wholesale reduction in salt intake is possible. In these countries, multi-modal strategies involving third-sector lobbying groups, government and industry led to sustained reductions in population salt intake of ~40% and ~15%, respectively[183-187]. These reductions are likely to have contributed to a parallel improvement in cardiovascular outcomes[188]. In the UK, robust monitoring of salt intake and labelling of food salt content enabled the use of a target-based approach that resulted in a ~30% reduction in the salt content of processed foods during the first phase of the program[184]. Despite further targeted reductions, government failures such as tasking the food industry to self-regulate without robust, external monitoring of salt content in foods, stalled the decline in population salt intake[189]. Systematic reviews of salt-reduction strategies report that multi-component interventions involving legislation, mandatory reformulation of processed foods and food labelling are the most effective approaches to reduce salt intake[190,191].

A large meta-analysis that included >2 million observations in 11 countries, confirmed that food labelling legislation results in a reduction in salt content[192]. Given that other dietary constituents including potassium and fructose[193] also modulate blood pressure and cardiovascular risk, the most effective interventions would likely rely on holistic dietary changes at multiple levels within society, including policy, industry, healthcare and education. Novel population-level interventions involving the provision of salt substitutes[31,32], salt-restriction spoons[194] and education have also led to substantial reductions in salt intake in clinical trials.

Individual-level interventions

Individual-level interventions have achieved sizeable reductions in salt intake, averaging around 100–130 mmol (6.0–7.5 g NaCl) in the short term (**Figure 2**)[1,58]. However, even in the context of clinical trials, achieving a sodium intake of <5g NaCl (85 mmol) per day as recommended by the WHO[5] has proven to be extraordinarily difficult. In a meta-analysis of RCTs in patients with heart failure, the mean achieved sodium intake in groups with a targeted intake of <1.5 g (65 mmol) per day ranged from 1.9 to 4.6 g (~80–200 mmol) per day[195]. Furthermore, reductions in salt intake

might not be sustained in the longer term. The Huang et al. and Filippini et al. meta-analyses of sodium-reduction RCTs discussed above found that interventions lasting for longer than 12 weeks or 6 months, respectively, induced smaller reductions in blood pressure than did shorter interventions[1,30]. In small RCTs in Dutch patients with CKD, patient-centred interventions aimed at reducing sodium intake reduced sodium excretion at 3 months but these differences were not sustained at 6 months[196,197]. These findings are perhaps not surprising given the powerful cultural and biological forces driving salt intake. They suggest that the biggest obstacle to improved health outcomes is not a lack of understanding about how and why salt causes disease but rather a lack of evidence of how to intervene most effectively at the individual level.

Many factors shape the optimal salt-reduction strategy for individuals. To our knowledge, attempts to evaluate the effect of family-based interventions and feedback using spot urine samples or genetic risk scores to identify individuals most likely to benefit from salt restriction have been limited to small, uncontrolled studies. Individuals vary in the extent to which they prefer to use dietary rather than pharmacological means to reduce total body sodium. Although short-term studies indicate that diuretics and dietary sodium restriction exert broadly equivalent short-term effects on body water and blood pressure[198], whether they confer similar long-term benefits on disease outcomes is unknown.

The efficiency of salt-reduction strategies could potentially be increased by leveraging knowledge of the biology of salt preference. For example, amiloride effectively blocks salt taste when applied topically to the lingual epithelium and in mice, targeted knockout of ENaC in taste receptors reduces salt preference and salt intake[104]. In humans, one small trial suggested that therapeutic doses of amiloride may limit salt intake without inducing any conscious perception of change in taste[199]. It would be productive to explore this potential therapeutic benefit in larger clinical trials.

Conclusions

Overwhelming evidence indicates that excessive intake of dietary salt raises blood pressure. In addition, evidence from multiple sources suggests that excessive salt

intake causes CVD, particularly in high-risk populations. This hypothesis is yet to be confirmed unequivocally in a RCT of sodium restriction, but the cost of such a trial is likely to be prohibitive.

Powerful socioeconomic, cultural and biological drivers explain the high dietary salt intake that is observed in many countries worldwide. The extent to which individuals are susceptible to salt-induced disease outcomes depends on salt preference and salt-sensitivity of blood pressure, which are determined by genetic, demographic and environmental factors. The high burden of 'hidden salt' in processed foods can make it difficult for individuals to control salt intake, but does not render them completely powerless. Exercising individual discretion is a crucial part of any salt reduction strategy and individuals should be given the tools and knowledge to facilitate this approach.

Multi-component interventions have achieved sustained reductions in salt intake in large populations, whereas individual-level interventions have achieved sizeable reductions in salt intake over days to weeks in clinical trials. The effectiveness of individual salt-reduction strategies outside of clinical trials is uncertain as is whether such strategies can sustain reductions in blood pressure in the long term (months to years). Reformulation of foods to reduce salt content is a successful strategy to lower population salt intake but requires government intervention to ensure fair commercial competition. Strategies legislating for reformulation, encouraging reformulation by robust monitoring of reduction targets and even taxation of salt used in food manufacturing have been used to reduce population salt intake with some success[180], but require governments to look beyond short-term political impact to a long-term view of public health.

Author contributions

All authors contributed to researching the data, discussing the content, writing the text and reviewing or editing the manuscript before submission.

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Competing interests

The authors declare no competing interests.

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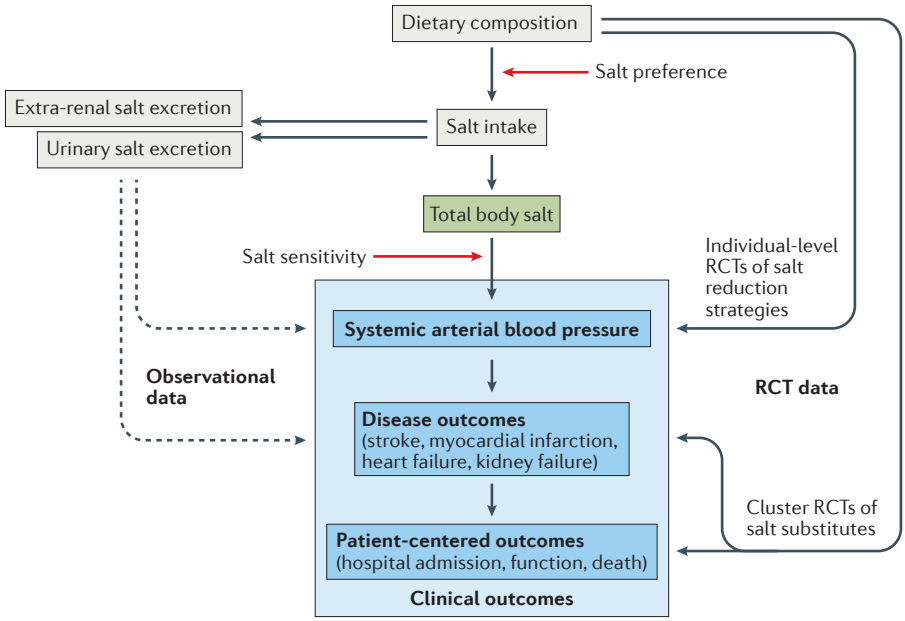

Figure 1 | The pathway from salt intake to clinical outcomes. Dietary salt intake is determined by the salt content of available foods and by individual food choices, which are influenced in part by salt preference — the desire to eat salt in the absence of physiological need. In many societies, a large proportion of dietary salt comes from consumption of processed food, which limits discretionary control of salt intake. Net salt balance (intake minus excretion) determines total body salt, which in turn determines systemic arterial blood pressure. The gradient of the relationship between dietary salt intake and blood pressure is termed 'salt sensitivity'. Sustained elevations in blood pressure (hypertension) are a leading cause of stroke, myocardial infarction and heart failure. Evidence from large observational datasets demonstrates the relationship between salt intake (estimated from urinary sodium excretion) and clinical outcomes including blood pressure and cardiovascular disease[35]. Randomised controlled trials (RCTs) have tested the efficacy of salt reduction strategies in lowering blood pressure and reducing the risk of cardiovascular disease. Individually-randomized trials have had sufficient statistical power to test the effect of salt reduction on blood pressure[1,30], but not cardiovascular endpoints. Cluster-randomized trials of salt-substitution (reducing sodium and increasing potassium intake) have tested effects on cardiovascular disease and mortality[200].

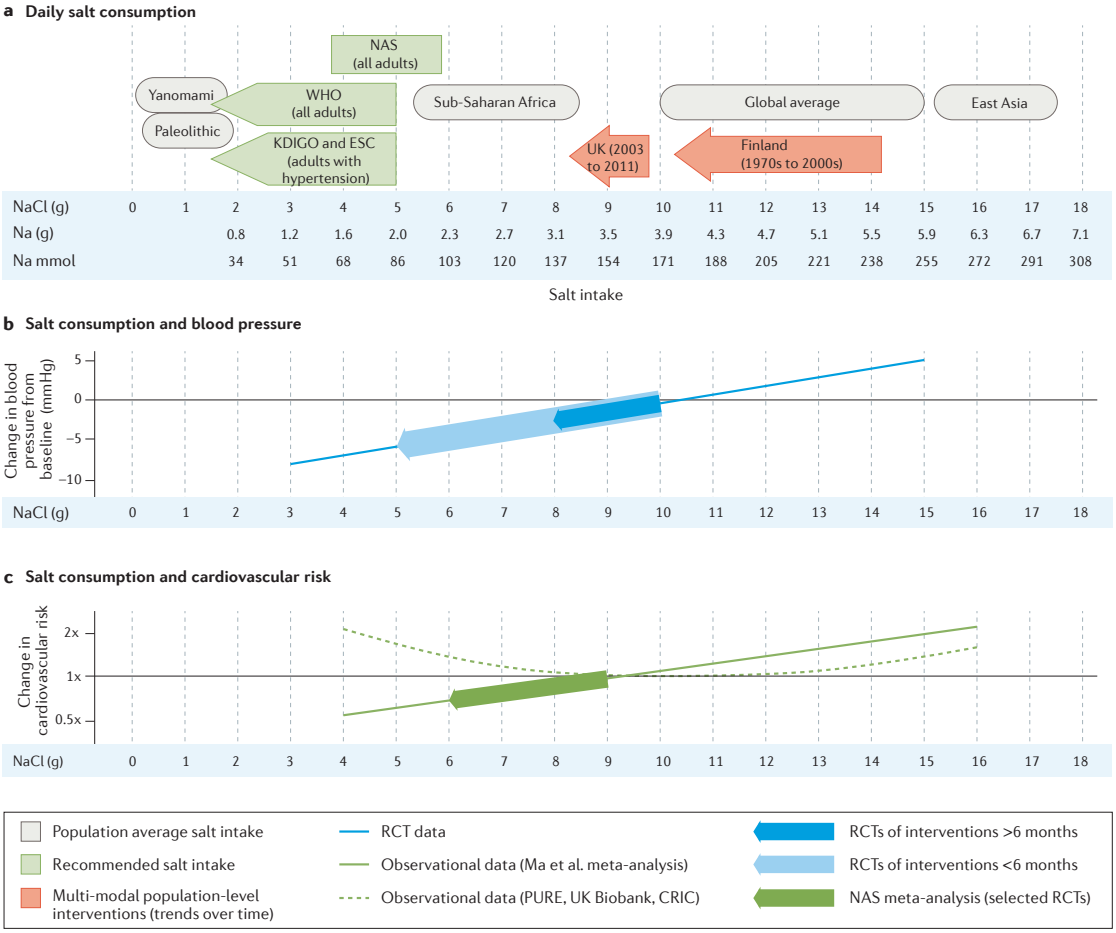

Figure 2 | Salt consumption and the effects of interventions on blood pressure and cardiovascular risk. a | The World Health Organization (WHO)[5] and US National Academy of Sciences (NAS)[48] recommend an upper limit of daily salt intake for all adults of 5 g NaCl (85 mmol) or 5.85 g NaCl (100 mmol), respectively. Kidney Disease: Improving Global Outcomes (KDIGO)[201] and the European Society of Hypertension (ESC)[202] have made similar recommendations for patients with hypertension. However, the daily salt intake of many populations worldwide exceed these recommendations with a global average of ~10–15 g NaCl per day (170–260 mmol)[2,3,10,83,187,189,203]. In remote isolated populations such as the Amazonian Yanomami, daily salt intake is thought to be similar to that in Paleolithic man at ~1g NaCl (20 mmol)[83,203]. Following multi-modal public health interventions, mean daily population salt intake reduced by ~40% in Finland[187] and ~15% in the UK[184]. **b |** Salt-reduction interventions have been shown to lower blood pressure with a linear dose-response relationship in randomized controlled trials (RCTs)[1,30,58]. In these trials, a mean reduction in sodium intake of 80–130 mmol (5–8 g NaCl) induced a ~4 mmHg decrease in systolic blood pressure[1,30]. The effect size was smaller for interventions lasting longer than 6 months. **c |** The NAS meta-analysis of selected RCTs showed that sodium reduction can reduce the risk of cardiovascular disease (relative risk

reduction of ~25 %)[48]. In observational studies, estimated sodium intake has exhibited either a linear[35,52] or J-shaped[21,37,38,44] association with cardiovascular disease risk. The J-shaped association can likely be explained by methodological artefacts owing to use of spot urine samples, confounding and reverse causality, rather than a genuine increase in cardiovascular risk at low sodium intakes.

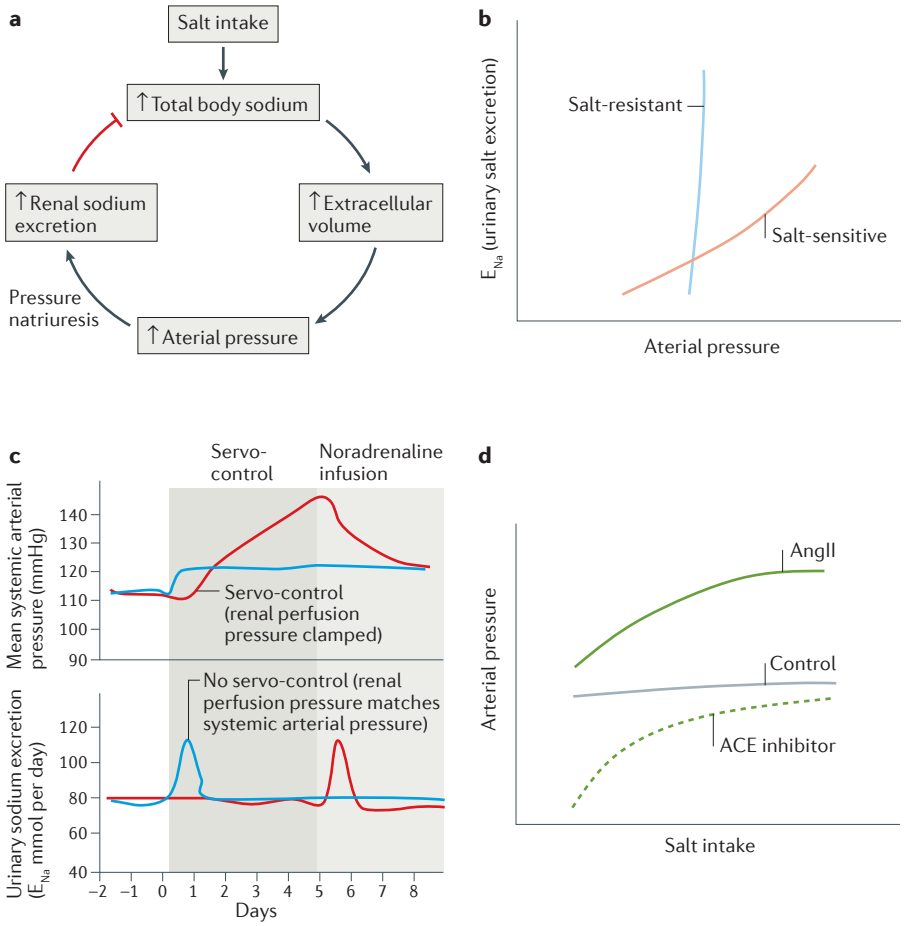

Figure 3 | Guyton & Hall's approach to studying salt sensitivity. A) Guyton proposed the 'kidney-fluid' mechanism: total body salt homeostasis is maintained by a negative-feedback loop in which pressure-natriuresis is the critical limb. In this model, an increase in total body salt causes an expansion of extracellular volume and a rise in arterial pressure. This in turn provokes an increase in urinary salt excretion ('pressure natriuresis'), restoring total body salt and extracellular volume[132]. Any impairment in pressure natriuresis will result in salt-sensitive hypertension[133]. **B) The acute pressure-natriuresis relationship.** In isolated kidney preparations[130,131] and intact organisms[134], an acute rise in arterial pressure (renal perfusion pressure) provokes an increase in urinary sodium excretion. The gradient of this relationship is steeper in salt-resistant rat strains than in salt-sensitive strains[134], in keeping with a model in which defective renal sodium excretion causes salt-sensitivity in blood pressure. **C**) The importance of pressure-natriuresis in chronic blood pressure regulation was demonstrated by Hall and co-workers, using conscious dogs in which renal perfusion pressure was servo-controlled through an

implanted, inflatable aortic occluder. In control animals, infusion of noradrenaline caused a modest rise in mean arterial pressure (< 10 mmHg) and an increase in renal sodium excretion. When renal perfusion pressure was clamped, the same noradrenaline infusion caused a progressive rise in MAP (of up to 40 mmHg) but no change in renal sodium excretion. When the renal perfusion pressure was no longer servo-controlled, renal sodium excretion increased and blood pressure returned to near-basal levels. (Reproduced from Hall *et al., 1988*[135]*).* **D) The chronic 'salt-loading renal function curve'.** This type of analysis was used by Guyton and Hall to plot the steady-state relationships between mean arterial pressure and urinary sodium excretion in conscious dogs[137,139]. In one experiment, dogs were implanted with femoral artery catheters and allowed to recover for three weeks. Sodium intake was controlled by supplementing a sodium-deficient diet with intravenous saline infusions over a range of 5–500 mmoles per day. Blood pressure and renal sodium excretion were measured ~7 days after switching to a new sodium intake, so that intake and excretion were in balance. When RAAS function was unperturbed, arterial pressure was salt-resistant. When dynamic RAAS function was suppressed at low levels (with ACE inhibition) or high levels (with ANGII infusion), then blood pressure became salt-sensitive. (Reproduced from Figure 6 in Hall *et al.* 1980[137]; note that in its original form, salt excretion was plotted as the dependent variable

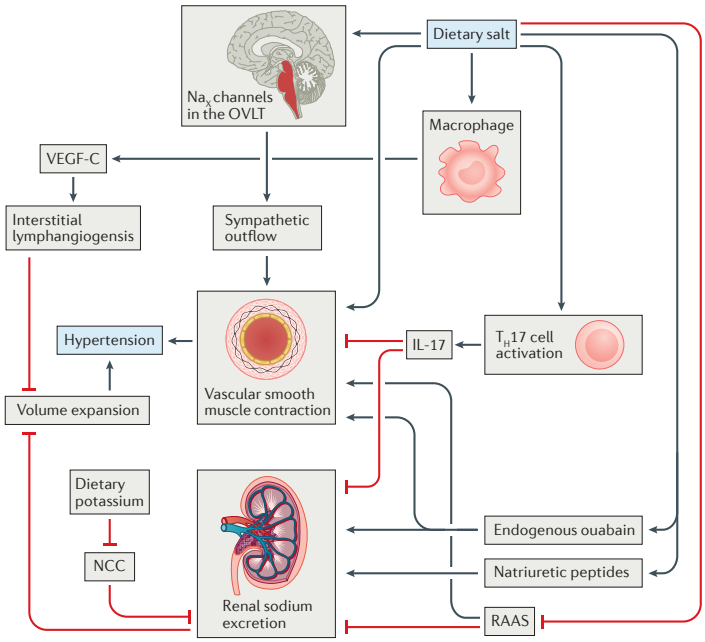

Figure 4 | Potential mechanisms of salt-sensitive hypertension. Current knowledge of the mechanisms of salt-sensitive hypertension is largely based on findings in animal models. Salt acts on multiple systems: kidneys, vasculature, brain and the immune system**Kidneys.** Sodium is primarily excreted in the urine and so the kidneys play a central role in determining sodium balance. Sodium accumulation can lead to volume expansion and hypertension[155]. Net renal sodium excretion is inhibited by the RAAS and stimulated by potassium intake, which inhibits sodium reabsorption through NCC[204]. Defective release of counter-regulatory natriuretic peptides (e.g. ANP) might also contribute to renal sodium retention in some populations[153]. **Vasculature.** Salt loading stimulates vascular smooth muscle contraction through a PPARγ-dependent pathway[158] and by simulating production of endogenous ouabain which then triggers calcium entry through NCX1[157]. **Brain.** Dietary salt loads activate the sympathetic nervous system[160], an effect mediated through the sodium-sensing channel, Na_X in the OVLT[161]. **Immune system.** Salt loading acts on macrophages and T-lymphocytes to stimulate production of VEGF-C[162] and IL-17[163] respectively. VEGF-C stimulates lymphangiogenesis, buffering interstitial sodium and preventing vascular volume expansion[162]. IL-17 potentiates the effects of ANGII in vascular smooth muscle[165] and the renal tubule[166]. **Key:** black arrows = stimulatory pathways; red arrows = inhibitory pathways. **Abbreviations:** OVLT, organum vasculosum lamina terminalis; NCC, thiazide-sensitive NaCl co-transporter; VEGF, vascular endothelial growth factor; RAAS, renin-angiotensin-aldosterone system; PPARγ, peroxisome proliferator-activated receptor gamma; NCX1, sodium-calcium exchanger 1; VEGF-C, vascular endothelial growth factor C; IL-17, interleukin-17; ANGII, angiotensin II.

Box 1: Potassium and blood pressure

A negative association exists between potassium intake, blood pressure, cardiovascular disease[24,35,37] and incident chronic kidney disease (CKD)[205]. Many interventions that aim to reduce sodium intake, such as DASH diets[206] and salt substitutes[32], also increase dietary potassium content and unravelling the independent effects of these cations is difficult. Moreover, potassium-rich diets tend to be plant-based and may contain other constituents with beneficial effects on health.

A meta-analysis of randomized controlled trials reported that oral potassium supplementation was associated with a mean systolic blood pressure reduction of 3.1 mmHg (95% CI 1.9–4.3 mmHg)[207]. Another meta-analysis demonstrated a non-linear dose-response relationship between potassium supplementation and blood pressure and found that potassium supplements were particularly effective at lowering blood pressure in individuals with hypertension and/or high sodium intake[208] The results of cluster-randomized trials of salt substitutes in which table salt was replaced by 75% NaCl/25% KCl, provide further evidence that potassium supplementation can improve blood pressure and cardiovascular risk[31,32]. Several mechanisms likely contribute to the beneficial effects of potassium supplementation. In particular, dietary potassium inhibits the distal tubular sodium-chloride transporter, inducing a thiazide-like effect[204,209].

The beneficial effects of potassium supplementation have obvious implications for the general population and particularly for patients with CKD. Many of these patients are routinely advised to restrict potassium intake owing to the risk of hyperkalaemia. However, this advice could potentially be harmful with respect to cardiovascular outcomes[210]. Small observational and open-label interventional studies have suggested that potassium-rich diets are generally well-tolerated in patients with CKD stage 4-5[211-213]. However, these studies were under-powered for safety outcomes.

Box 2: Estimation of salt intake

Accurate estimation of sodium intake is a key requirement for large-scale studies examining the relationship between dietary sodium and health outcomes , yet no standardised, universally accepted method exists. Food frequency questionnaires and dietary recall are inaccurate for estimation of sodium intake, with a tendency for under-reporting[214-216]. By contrast, estimating sodium intake using urinary excretion, predicated on an assumption of sodium balance, offers an objective, measured variable. Two approaches are widely used for such estimation: 24h urine collections and spot urine collections.

24h urine collections

As ingested sodium must be excreted, 24h sodium output in the urine should provide a robust estimate of approximately contemporaneous sodium intake and is the reference standard. Empirically, ~95% of ingested sodium is recovered in the urine, but even at constant intake considerable variation in 24h excretion exists[217]. Estimates of the usual intake of an individual vary depending on whether a single or multiple, non-consecutive 24h measurements are used. This variation can have important ramifications for study findings, for example altering the hazard ratio of the effect of dietary salt on cardiorenal outcomes[218]. Under controlled intake conditions, precision is improved when estimates are based on three non-consecutive 24h collections[219]. The International Consortium for Quality Research on Dietary Sodium/Salt recommend that 24h collections are used to estimate sodium intake in individuals and populations[220]. Nevertheless, error persists[219], a significant failure rate for complete collection is reported[221] and the financial cost of this approach is high.

Spot or short duration urine collections

Sodium intake can be estimated from spot or short duration urine samples using formulae that take into account some or all of the following variables: urine creatinine concentration, age, sex, height and urine potassium concentration[222,223]. All of these variables are subject to potential bias and none of the equations correlate well with 24h urine sodium excretion at extremes of intake. They tend to over-estimate 24h urine sodium excretion at low levels and under-estimate it at high levels. This effect can explain why 24h sodium excretion demonstrates a linear correlation with blood

pressure, whereas the relationship is J-shaped when sodium intake is estimated from spot urine samples[222,224,225].

The advantage of spot urine samples is that they are cheap and easy to collect. They are therefore suitable for very large study populations[223,226] and biobanks[227], which can be used to determine the relationship between sodium intake and a range of phenotypic and genotypic characteristics. This facility should not detract from the major message that the J-shaped curve, an artefact introduced by estimating sodium intake from spot urine collections, results in an important perception barrier against population-based interventions to reduce salt intake.

Box 3: Salt restriction in patient populations

Heart failure

For decades, sodium restriction was an undisputed cornerstone of management in heart failure[228]. However, expert guidelines now acknowledge that some uncertainty exists (**Error! Reference source not found.**). The literature became difficult to interpret following the retraction of two **[Au: two?]** high-profile studies from the same research group[229,230]. Small randomized controlled trials (RCTs) have demonstrated no beneficial effect of sodium restriction on body weight or symptom score during or after hospitalisation with acute decompensated heart failure[231,232]. Moreover, infusion of hypertonic saline was associated with improved diuresis in a small, inadequately-blinded RCT and in an observational study[233,234]. The effects of sodium restriction in chronic heart failure are currently being evaluated in the phase III SODIUM-HF trial[235].

Chronic kidney disease

Small but meticulous balance studies have shown that patients with advanced chronic kidney disease (CKD; glomerular filtration rate (GFR) <20 ml/min/1.73 m^2) re-equilibrate sodium excretion to match intake at a slower rate than healthy individuals and have pronounced salt-sensitivity of blood pressure[236]. Among patients with IgA nephropathy and GFR >60 ml/min, salt-sensitivity of blood pressure was apparent even in those without overt hypertension[237].

Despite these findings, surprisingly few data on sodium restriction in patients with CKD are available and most are observational. In CRIC study participants with mild-to-moderate CKD, higher urinary sodium excretion (greater than ~4 g (170 mmol) per day) was associated with an increased risk of cardiovascular disease[38]. Sodium intake was also associated with CKD progression in the CRIC cohort of ~4,000 US adults[238] and in the KNOW-CKD cohort of ~1,200 Korean adults[239]. In patients with autosomal dominant polycystic kidney disease, sodium intake was associated with rate of GFR decline; mediation analysis suggested that this effect was mediated by vasopressin signalling and not by blood pressure[240].

Randomized crossover trials in patients with early CKD found that sodium restriction reduces extracellular volume, body weight and blood pressure[198,241]. However, two Cochrane reviews found insufficient evidence to make well-founded conclusions regarding the effects of sodium restriction on CKD progression[242,243]. Low-quality evidence suggested that sodium restriction can reduce albuminuria and that this effect was increased in patients treated with renin-angiotensin blockers. In a *post-hoc* analysis of the RENAAL and IDNT trials, the cardiovascular and renal benefits of angiotensin receptor blockade were only realised in patients with the lowest tertile of sodium intake[244]. A meta-analysis of RCTs including ~500 participants found that sodium restriction reduced albuminuria, with a greater effect size in patients taking RAS inhibitors[245]. The lack of conclusive data has led to calls for a RCT to test the effects of dietary sodium restriction on CKD progression[246].

Kidney failure

Patients with kidney failure on dialysis have a greatly reduced capacity to excrete sodium and therefore might be expected to exhibit an extreme salt-sensitive phenotype. Indeed, very early in its development, haemodialysis was shown to reduce total body sodium and blood pressure[247]. Patients on dialysis are a unique group because interventions aimed at reducing total body sodium can be targeted at dialysis parameters. Systematic reviews of a limited evidence base have found that setting low dialysate sodium reduces interdialytic weight gain and blood pressure, but increases serum sodium levels,[248] and that dietary sodium restriction reduces blood pressure but has no consistent effect on interdialytic weight gain[249]. Despite the blood pressure effect, setting low dialysate sodium did not reduce left ventricular mass in an RCT of 99 patients on haemodialysis[250].

Nephrotic syndrome

Sodium restriction is widely prescribed for nephrotic syndrome and has entered medical dogma without, to our knowledge, a single supportive RCT. This approach is advocated based on first principles (reducing salt intake will help to correct a state of total body salt excess) and evidence from rodent models in which salt restriction reduced kidney fibrosis and improved short-term survival[251,252]. As such reasoning

does not always translate into clinical benefits, further research in this area would be productive.

Individuals in whom salt restriction may be harmful

For the vast majority of people, dietary sodium restriction would not be harmful, particularly given the prevalence of supra-physiological consumption. However, salt restriction could be harmful in individuals with a low baseline salt intake or with excessive salt losses. In frail elderly patients, salt restriction could potentially cause hypotension, falls and acute kidney injury, particularly in the context of use of drugs such as RAS inhibitors that block the normal physiological responses to volume depletion. Similarly, salt restriction is probably harmful in patients with salt-losing states such as adrenal insufficiency, Gitelman syndrome, Bartter syndrome and other renal tubulopathies.

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