Is salt substitution ready for prime time?

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Salt substitutes hold great potential for the control of blood pressure and prevention of chronic disease, but the evidence base remains inadequate. Data from a community-based trial in Peru add to this evidence base and support the conduct of large-scale trials to drive the global uptake of salt substitution.

Refers to Bernabe-Ortiz, A. et al. Effect of salt substitution on community-wide blood pressure and hypertension incidence. *Nat. Med.* **26**, 374–378 (2020)

Excess dietary consumption of sodium is estimated to cause approximately 3 million deaths each year, mainly through adverse effects on blood pressure and increased risk of stroke, myocardial infarction and chronic kidney disease[1]. Although a reduction in sodium consumption is advocated by multiple national and international guidelines for blood-pressure control, the evidence that sodium intake can be reduced outside of highly controlled settings is scarce. In a paper published in *Nature Medicine*, Bernabe-Ortiz and colleagues report a novel approach to reducing sodium intake using a community-based salt-substitution strategy that was tested in a stepped-wedge trial performed in rural Peru[2].

Salt substitutes are alternative formulations in which a proportion of the sodium chloride has been replaced by another mineral, usually potassium chloride. Randomized trials have shown that salt substitutes can substantially lower blood pressure, with hypotensive effects mediated by the combined actions of reducing sodium and increasing potassium[3]. Salt substitutes are a potentially attractive mechanism for reducing sodium intake because the intervention requires only that the salt supply is switched to the salt substitute, although additional support might be required to ensure effective incorporation of the salt substitute into food preparation and consumption practices. Salt substitutes can also be used in the commercial manufacturing of food, but the replacement of table salt is of particular interest in low-income and middle-income countries, where salt added during food preparation in the home is the main source of dietary sodium[4].

The trial by Bernabe-Ortiz and colleagues was performed using a cluster–randomized design in six villages and involved 2,376 participants. In accordance with the stepped-wedge methodology, baseline data were collected in every village while participants were using regular salt and then periodically throughout follow-up as the salt substitute (75% sodium chloride and 25% potassium chloride) was progressively introduced into each of the villages. The effect of the salt substitute on the primary outcome of blood pressure was then estimated by comparing the blood pressure values measured in participants while using regular salt with the measurements recorded while using the salt substitute. This type of study design can provide an efficient means of assessing community-based interventions but does require rigorous control of the intervention delivery and follow-up assessments.

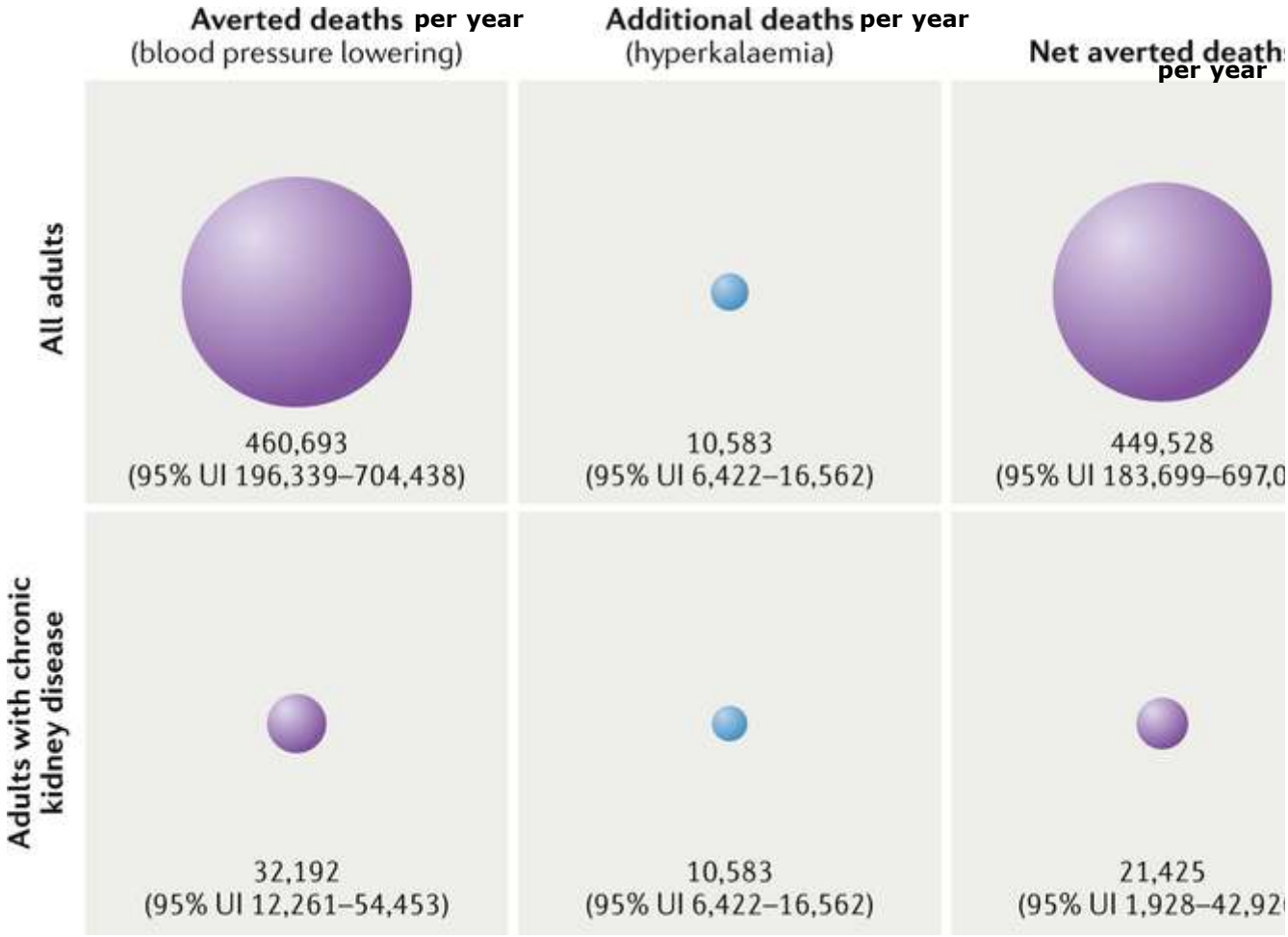
The primary findings from the trial were a 1–2 mmHg reduction in systolic blood pressure and a halving of the risk of incident hypertension[2]. As anticipated, the quantity of potassium excreted in the urine increased, but no corresponding reduction in the quantity of sodium excreted was observed. No serious adverse effects were reported, and the researchers concluded that the data supported the implementation of population-wide salt substitution.

An important challenge to achieving the widespread use of a salt substitute has been concerns about potential harms caused by increased potassium intake[5]. Although potassium is widely available in many fruits and vegetables and is thought to be an important component of a healthy diet, excess potassium might be harmful to individuals with serious impairment of kidney function. In this patient group, elevated dietary intake of potassium might cause hyperkalaemia and increase the risk of cardiac arrhythmias and sudden cardiac death[6], but data describing an increase in this risk with the use of salt substitutes are sparse, with a reliance on case reports. Modelled estimates of the potential benefits and risks associated with population-wide salt substitution in China suggest considerable net benefits for the overall population and even among the subset with chronic kidney disease[7] (Fig. 1).

Annual averted cardiovascular deaths owing to reduction in blood pressure and annual additional deaths owing to elevated serum potassium concentration, both overall (top row) and in individuals with chronic kidney disease (bottom row), estimated using comparative risk assessment models[7]. Net Annual net averted deaths were calculated by subtracting additional deaths from averted deaths. Monte Carlo simulations ($n = 1{,}000$) using uncertainties in model inputs were conducted to generate central estimates and 95% uncertainty intervals (UIs). The areas of the bubbles are proportional to the central estimates.

Fig. 1

Estimated population-wide benefits and risks of replacing regular salt with a potassium-enriched salt substitute in China.



The trial in Peru provides no new data about the balance of risks and benefits in patients with kidney disease because these individuals were excluded. The additional exclusion of all individuals with self-reported cardiovascular disease might explain why no serious adverse events were reported during the entire study period. The absence of any serious harm in the trial provides some reassurance that a pragmatic approach to minimizing risk might be effective, although the generalizability of this finding to other settings is debatable. The exclusion of individuals with cardiovascular disease is a limitation of the trial because high-risk groups have much to gain in the short to medium term from effective lowering of blood pressure[8].

Somewhat difficult to understand is how a very small population-wide effect on blood pressure (a 1.1% reduction) could co-exist with a very large effect on incident hypertension (a 51% reduction)[2]. The absence of an effect on sodium excretion is somewhat surprising but might be explained by participants using a greater quantity of the salt substitute to achieve the same effects on food taste as were achieved with regular salt — in this scenario, an elevation in potassium excretion might be observed while sodium excretion is unchanged. The play of chance might also have influenced some of the trial findings — the study included a large number of individuals, but the cluster design limited the

capacity to reliably quantify small effect sizes and effects on outcomes that were infrequent. Biases could also have been introduced; although the trial was randomized, the intervention was unblinded, and outcomes were assessed with knowledge of the treatment allocation.

On balance, the trial in Peru provides important new information that supports a probable net benefit of a salt substitution strategy for blood pressure control, although aspects of the trial results mean that the study is unlikely to drive widespread global uptake. The small changes in blood pressure and in sodium and potassium excretion are similar to those observed in a large, community-based, cluster–randomized trial of salt substitution performed in rural China[9], and a formal meta-analysis of the two studies might be revealing. Further insight into the extent to which salt substitution was taken up by the populations and options for increasing the blood-pressure-lowering effect with community-based salt substitution will be especially valuable. Although the lowering of systolic blood pressure even by 2 mmHg would be of great public health importance because such a large proportion of global disease burden is caused by elevated blood pressure, larger reductions in blood pressure would be anticipated from a widespread switch to a salt substitute. A large, ongoing trial involving 21,000 individuals recruited from 600 villages in rural China that is designed to assess the effects of salt substitution on stroke should soon be completed and will provide important additional data on efficacy. In particular, this study should definitively address the question of safety because large numbers of strokes, myocardial infarctions and deaths will be recorded[10].

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Competing interests B.N. has received a salt substitute used for research trials from the Beijing Salt Manufacturing Corporation and NuTek. B.N. is the chair of the steering committee for an ongoing, large-scale trial assessing the effects of salt substitution on stroke. M.M. declares no competing interests.

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