The potential scalability of salt substitutes as an intervention to lower population sodium levels

Antonio Bernabe-Ortiz, MD, PhD,[1] Kathy Trieu, MPH, PhD,[2] Matti Markland, PhD,[2-4] Jason HY Wu, PhD, FAHA,[2] Lorena Saavedra-Garcia, RDN, MsC,[1] Ashleigh C Hart, MPH, BSc,(2) Jie Yu, MD, PhD,[2] Sudhir Raj Thout, MA,[5] J Jaime Miranda, MD, PhD,[1,2] Jacqui Webster, PhD, RPHNutri.[2]

Bernabe-Ortiz A, Trieu K, Markland M, HY Wu J, Saavedra-Garcia L, Hart AC, Yu J, Raj Thout S, Miranda JJ, Webster J. The potential scalability of salt substitutes as an intervention to lower population sodium levels. Salud Publica Mex. 2022;64(Supl 1):S6-S13.
https://doi.org/10.21149/12788

Abstract

Reducing salt intake is one of the most cost-effective interventions to improve population health due to the subsequent reductions in blood pressure. Countries are introducing programs to lower salt consumption. Such programs usually focus on reducing salt in packaged foods and meals alongside campaigns to change consumer behavior. Thus, this paper provides an overview of the rationale for and evidence supporting the use of salt substitutes. Current approaches to salt reduction are insufficient, and more innovative solutions need to be identified. There is good evidence that salt substitutes, where some of the sodium is replaced with potassium, are effective to lower sodium total intake. The main challenge is to understand the pathways to market for salt substitutes. How do we implement programs to promote salt substitutes in different countries? What levels of government intervention are required? With more research and government investment, salt substitutes could be a game changer for increasing the impact of strategies to reduce population salt intake.

Keywords: salt; salt substitute; sodium; potassium; blood pressure; health policy

Bernabe-Ortiz A, Trieu K, Markland M, HY Wu J, Saavedra-Garcia L, Hart AC, Yu J, Raj Thout S, Miranda JJ, Webster J. Potencial escalabilidad de los sustitutos de la sal como una intervención para reducir los niveles de sodio en la población. Salud Publica Mex. 2022;64(Supl 1):S6-S13.
https://doi.org/10.21149/12788

Resumen

La reducción del consumo de sal es una de las intervenciones más costo efectivas para mejorar la salud poblacional debido a la consiguiente reducción de la presión arterial. Algunos países están introduciendo programas para reducir el consumo de sal. Estos programas suelen centrarse en reducir la sal en los alimentos envasados junto con campañas para cambiar el comportamiento de los consumidores. Por lo tanto, este documento proporciona una descripción general de la justificación y la evidencia que respalda el uso de sustitutos de la sal. Los enfoques actuales para la reducción de la sal son insuficientes y, por lo tanto, es necesario identificar soluciones más innovadoras. Existe buena evidencia de que los sustitutos de la sal, en donde parte del sodio es reemplazado con potasio, son efectivos para reducir la ingesta total de sodio. El principal reto es comprender las vías para comercializar los substitutos de la sal en ¿Cómo implementamos programas para promover los sucedáneos de la sal en diferentes países? ¿Qué niveles de intervención gubernamental se requieren? Con más investigación e inversión gubernamental, los sustitutos de la sal podrían cambiar las reglas del juego para aumentar el impacto de las estrategias para reducir el consumo de sal de la población.

Palabras clave: sal; substituto de la sal; sodio; potasio; presión arterial; política de salud

(1) Cronicas, Centro de Excelencia en Enfermedades Crónicas, Universidad Peruana Cayetano Heredia. Lima, Peru.
(2) The George Institute for Global Health, University of New South Wales. Sydney, Australia.
(3) Johns Hopkins Bloomberg School of Public Health. Baltimore, United States.
(4) Uppsala University. Uppsala, Sweden.
(5) The George Institute for Global Health. New Delhi, India.

Received on: April 29, 2021 • **Accepted on:** September 10, 2021 • **Published online:** June 13, 2022
Corresponding author: Antonio Bernabe-Ortiz. Cronicas, Centro de Excelencia en Enfermedades Crónicas, Universidad Peruana Cayetano Heredia. Av. Armendáriz 445, Miraflores. 15074 Lima, Peru.
email: antonio.bernabe@upch.pe

Why salt reduction matters

Nutrition transition, *i.e.*, the change away from traditional diets towards more highly processed packaged foods as countries become more industrialized, is associated with a change in diet patterns, including an increase in consumption of saturated and trans fats, sugar, and salt. A high consumption of salt increases blood pressure levels and is associated with increased risk of heart disease, stroke, and cardiovascular mortality.[1-3] An estimated 1.89 million deaths were attributed to sodium intake in 2019 worldwide.[4]

Cardiovascular diseases have been the leading causes of death globally for the last 15 years.[5] Blood pressure control is closely linked to reduction in cardiovascular risk and, given the rates of non-adherence to medication of hypertension globally, non-pharmacological measures at the population level to improve blood pressure control are required.[6] Reducing sodium intake and increasing potassium intake are recommended dietary interventions to reduce blood pressure. According to the World Health Organization (WHO), high sodium consumption (>2 grams/day, equivalent to 5 g salt/day) and insufficient potassium intake (<3.5 grams/day) contribute to high blood pressure and increase the risk of heart disease and stroke.[7,8] The main source of sodium in our diet is salt, and most people consume too much salt–on average 9-12 grams per day, more than the double of the recommendations of the WHO since 2010.[9,10] Moreover, trends of salt intake in different countries do not appear to be declining.[11]

Most salt in the diet comes from processed foods or is added to food during cooking. A recent systematic review reported that bread products, cereal and grains, and dairy products were the major contributors to dietary salt intake in different populations around the world; but there are considerable differences in the amounts of salt added during cooking or at the table (discretionary salt).[12] In some countries such as China, Indonesia and also Peru, monosodium glutamate, used as a condiment, can be also a major source of sodium.[13,14]

Reducing salt intake has been identified as one of the most cost-effective measures countries can take to improve population health outcomes.[15,16] In randomized controlled trials, reduction in salt intake results in clinically meaningful reductions in both normotensive and hypertensive individuals, and effects appears linear down to levels as low as 1-1.5 grams of sodium per day.[17,18] As a result, strategies have been proposed to reduce salt consumption at the population level, including, but not limited to, consumer's education and awareness campaigns, salt reduction in bread and other products, working with the food industry to reformulate processed foods with a concomitant reduction of salt, the use of front-of-pack labelling schemes such as octagons, or taxation of high-salt products. Yet, there are limitations with focusing only on the provision of dietary salt advice as such information strategies do not necessarily translate on important clinical outcomes.[19]

Salt substitution, where some of the sodium in salt is replaced with other minerals, mainly potassium, has been reported to be effective in reducing both systolic and diastolic blood pressure.[20] This approach is amenable to be adapted and implemented at the population level as salt substitution has little impact on food taste and flavor.[21-24] This paper provides an overview of the rationale for and evidence supporting the use of salt substitutes, including case studies of recent trials, and identify strategies for scale up including research gaps and pathways to increase the use of salt substitutes and broaden the impact on population health.

Growing evidence for salt substitution as a public health strategy

One of the main reasons for the addition of salt to food is to enhance its taste and flavor. Thus, a key barrier to reducing dietary salt is the perception that food is 'tasteless'.[25-27] Many food companies report that they are starting to reach limits in reducing salt levels in foods without adversely impacting taste. Therefore, salt substitution, where some of the sodium is replaced with other minerals such as potassium, magnesium or calcium while maintaining a similar taste, seems to be a promising strategy. Moreover, most salt substitutes available in markets are dominated by potassium chloride as replacement of sodium chloride, and evidence shows that most counties around the globe do not meet the WHO recommendations of potassium intake.[28]

Reduced-sodium salts could be used for both reducing sodium in processed foods as well as salt added, in discretionary way, by consumers during cooking and eating. Food manufacturers are already using salt substitutes in their products and have developed formulations for foods such as cheese[29] or ham.[30] Additionally, reduced-sodium salts are available on the market in many countries, making them a potential option for consumers who add salt during cooking or at table. The replacement of sodium chloride with potassium chloride could also contribute to increased consumption of potassium,[31] a mineral with opposite effects to sodium on blood pressure and cardiovascular risk.[32] Evidence shows that potassium intake reduces blood pressure and higher potassium intake (>90 mmol potassium/day) was associated with 24% lower risk of stroke.[33] Increasing potassium intake is critical since populations

around the world consume it below recommended levels for cardiovascular health.[8]

The effect of reduced-sodium salts on cardiovascular risk factors and outcomes has been evaluated in a number of trials over the last decade. A meta-analysis of randomized controlled trials that included hypertensive, normotensive, and mixed populations, demonstrated that blood pressure reductions were achieved, regardless of the level of substitution.[34,35] On average, salt substitutes decreased systolic blood pressure (SBP) by -7.81 mm Hg (95%CI -9.47, -6.15, p<0,001) and diastolic blood pressure (DBP) by -3.96 mm Hg (95%CI -5.17, -2.74, p<0,001) compared to regular salt. The effects were accompanied by an increase in potassium and calcium intake.[35]

It is also worth noting here that in these trials, the use of salt substitutes did not increase the risk of any adverse side effects, *i.e.*, they appear safe to use, contrary to concerns relating to increased potassium consumption. Most of the studies have been carried out in China;[36-39] nevertheless, other countries such as Peru[20] and India[40] have also demonstrated the impact and safety of salt substitutes. A recent randomized controlled trial conducted in seven villages in Telangana, in South India[40] among 502 participants (mean age, 61.6 ± 12.0 years, 58.8% women) found that provision of a salt substitute (70% sodium chloride/30% potassium chloride blend) over three-month to replace regular salt for home use, resulted in a reduction of 4.6/1.1 mmHg in average systolic blood pressure (SBP)/diastolic blood pressure (DBP) amongst hypertensive cases.[41] The beneficial effect size is comparable to an average reduction of 4/2 mmHg in SBP/DBP typically achieved with the prescription of angiotensin-converting enzyme inhibitor therapy.[42] Participants reported that they used the reduced sodium study salt provided regularly for home cooking, and rated the taste of the study salts provided similarly.

While the blood pressure reductions (and even reduced risks of cardiovascular outcomes) are evident in a number of well-designed clinical trials,[20,35,36,43] the evidence regarding life-threatening hyperkalemia induced by salt substitutes is limited. Although a handful case reports suggest that reckless or deliberately harmful use of potassium supplements and salt substitutes in combination with underlining health conditions may induce hyperkalemia-related complications, there are several lines of evidence indicating that the risks associated with salt substitutes use may be very limited. Trials evaluating the safety of potassium-enriched salt substitutes (≤40% KCl) in at risk groups have not reported any severe events as a result of salt substitute use.[44,45] Recently, a randomized cluster trial found that the rate of serious adverse events attributed to hyperkalemia was not significantly higher with the salt substitute that with regular salt.[46] Importantly, severe adverse effects have not been reported in studies evaluating overall effects of salt substitute, even in large pragmatic trials where strict CKD screening have not been employed[20,36] and thus may have included patients with undiagnosed CKD (*i.e.*, 86% of individuals with CKD stages ≥G3a in China were aware of their condition). In fact, increased potassium intake has even been suggested to hamper CKD progression. Still, more research is needed to understand the health impact of potassium-enriched salt substitutes.

Modeling of salt substitution

Several modelling studies have also estimated the potential public health impact of population-wide replacement of regular salts with reduced-sodium salts. The studies have differed in settings (*e.g.*, country of interest or focus on discretionary salt or packaged foods), methodology (dietary impact estimations, comparative risk assessments, or cost-effectiveness analyses), and model inputs and assumptions. Given the theoretical concerns about potential risk of increased potassium intake leading to life-threatening hyperkalemia (*i.e.*, elevated serum potassium levels) in certain high-risk groups, the modelling studies have also varied in aims (*e.g.*, estimating potential benefits and/or risks of salt substitutes).

Several evaluations of potential benefits and/or risks of population-wide salt substitute use in European countries have been conducted.[31,47,48] A study in the Netherlands concluded that replacement of regular salt with potassium-enriched salt substitutes in foods commonly consumed would result in better compliance to the WHO potassium intake guideline and not exceed the potassium safety recommendations of the European Food Safety Authority Potential.[31] However, this evaluation did not estimate the actual number of deaths or events averted or caused by the reformulations. In contrast, in the UK, the Committee of Toxicity conducted a benefit and risk assessment of a scenario where 15-25% of NaCl in foods would be replaced by potassium salts. The assessment considered both benefits of the expected blood pressure reduction and the potential increase in life-threatening hyperkalemia.[47] It concluded that "at a population level, the potential benefits of using potassium-based reduced sodium salts to help reduce sodium in foods outweigh the potential risks".

Two studies have estimated the potential health effects of promoting reduced-sodium salts in China.[43,49] First, the effects of two different sodium reduction strate-

gies (salt substitutes and sodium restriction spoons) on CVD in China was estimated using a state-transition (Markov) model.[49] Promotion of reduced-sodium salts was estimated to be the more effective strategy of the two, preventing three times more CVD events and deaths compared to sodium reduction using salt-restriction spoons. Over a 10-year period, the salt substitute promotion strategy was estimated to have health effects similar to those estimated for a scenario where the average salt intake would be gradually reduced to 6 g/d after 10 years. The second study utilized a comparative risk assessment framework to estimate both the potential benefits (on blood pressure and related diseases) and risks (*i.e.*, hyperkalemia-related mortality) of increased salt substitute use in China.[43] Replacement of discretionary salt with reduced-sodium salt substitutes was estimated to prevent nearly 500 000 cardiovascular deaths per year through blood pressure reductions while the increased potassium intake could potentially lead to around 10 000 additional hyperkalemia-related deaths per year. When benefits and risks were estimated specifically among individuals with chronic kidney disease, substantial net benefits were estimated also in this high-risk group.

A recent cost-effectiveness analysis utilized a Markov model to estimate the health and economic impact of three types of government interventions to promote salt substitutes (*i.e.*, voluntary, subsidized and regulatory) targeting table salt, bot canh (common seasoning), and fish sauce (together contributing to 70% of sodium intake) in Vietnam.[50] All three policies were estimated to generate substantial health gains compared to no policy, especially for the non-voluntarily approaches. For example, the subsidized approach was estimated to prevent over one million CVD events and the regulatory approach nearly two million CVD events over the population lifetime. All three policies were estimated to be cost saving from a governmental perspective, with healthcare savings due to a reduced CVD burden exceeding any potential policy implementation costs.

Despite the heterogeneous methods used between these modelling studies, the findings suggest in general that substantial public health benefits can be gained by promoting more wide-spread use of reduced-sodium salt substitutes.

Effective community-wide salt substitution

The promising results so far suggest the use of salt substitutes could be a key driver of the gains linked to salt reduction resulting in major public health benefits.[51] Simultaneously reducing sodium intake and increasing potassium intake is more effective at lowering blood pressure and reducing the risk of cardiovascular disease than either intervention alone.[52] However, most of the studies were controlled clinical studies and enrolled individuals with hypertension.[35,36,40,53,54] In contrast, very few effective population-wide salt substitution strategies have been documented so far.[55] A key challenge is that, whilst salt substitutes are already used in some processed foods and on the market for consumers in many countries, consumers' demand alone will not be adequate to ensure sufficient uptake to impact population health outcomes. A pragmatic population-wide salt substitution strategy was implemented using a stepped wedge cluster randomized trial among 2 376 participants (mean age, 43.3 ± 17.2 years) in Peru.[20] Mid-size villages with 350-700 subjects were selected for the study. Of the 20 villages available, six were randomly selected. All adults (≥18 years) from the six selected villages were invited to participate. Using a social marketing campaign, the regular salt of enrolled households was retrieved and replaced, free of charge, with a substitute product containing 75% sodium chloride and 25% of potassium chloride.

Salt substitutes were provided to families for home cooking, but also to small shops, bakeries, community kitchens, street vendors and restaurants, to ensure the full replacement of salt in the whole village (cluster). Each village crossed over from the control condition (no salt substitution) to the intervention (community-wide salt substitution) sequentially, in an order determined by randomization, and remained in the intervention condition until the end of the study. In this way, salt substitution was implemented in all villages, a strategy known as a 'stepped-wedge' design.

An average reduction of 1.23 mm Hg in systolic and of 0.72 mm Hg in diastolic blood pressure, accompanied by a 51% reduction in the risk of developing hypertension among participants without hypertension at baseline (4 673 person-years follow-up) was obtained.[20] The intervention, developed using extensive formative work,[24,56] was highly accepted as shown by complimentary results on the 24-hour urine samples, showing that potassium levels were higher (2.60 ± 1.60 g.) at the end of the study compared to those at baseline (1.97 ± 1.20 g, $p<0.001$).

Primordial prevention requires shifting the entire population distribution of a given risk factor, in this case, blood pressure, in line with Geoffrey Rose's "Sick individuals, sick populations".[57] In so doing, in addition to the wider benefits to entire population, the effects of reductions in blood pressure are higher for higher risk groups, *e.g.*, those who were labeled as having hypertension at baseline and older groups, as reported in the

study.[20] The pragmatic study in Peru showed the effect of a population-wide strategy that shifts the population's distribution of blood pressure, much in line with Geoffrey's proposal of shifting the entire distribution in the population of a given risk factor.[57]

But are small reductions of 1-2 mm Hg in blood pressure meaningful? The Prospective Studies Collaboration conducted a meta-analysis of 61 observational studies of blood pressure and vascular disease in adults and found that, for each 2 mm Hg decrease in systolic blood pressure, stroke mortality and cardiovascular mortality decreased by 10 and 7%, respectively, an effect that was observed in reductions of systolic blood pressure levels up to 115 mm Hg.[58] This indicates that even small reductions in blood pressure at the population level could result in large public health gains.

Our study in Peru demonstrated that these sorts of reductions in blood pressure could be achieved in a real world setting through a population wide intervention. The also showed a reduction in the incidence of hypertension, a meaningful clinical, public health, and patient-relevant outcome.[20] In addition, the salt substitute was acceptable to consumers and no adverse events were reported.

The lessons from the study in Peru convey a pragmatic and feasible strategy that will likely inform worldwide recommendations for sodium reduction and blood pressure lowering,[59,60] and provide further support for the use of salt substitutes as a population-level strategy to prevent hypertension.[55,61]

Next steps for scale up including research gaps and pathways to market for salt substitutes

As outlined above, there is clear evidence from randomized controlled trials, modelling studies, and community interventions, to support the health and economic benefits of salt substitutes as an intervention to reduce sodium intake. Additional evidence from a large-scale salt substitution study of cardiovascular outcomes (*i.e.*, fatal and nonfatal stroke, major cardiovascular events, and total mortality) is expected soon.[62] Salt reduction strategies have huge potential to improve population health and are supported by many governments and international organizations. A recent systematic review showed that 96 countries had some sort of program in place to reduce salt in 2019.[63] This is an increase of 28% from the 75 countries reported in 2015.[64] Whilst this signifies positive progress, the picture is less rosy when we assess the impact of such strategies on salt intake, with only 12 countries reporting that they have reduced salt so far.[63] This is in part due to the time it takes to achieve reductions –even with a comprehensive well-financed strategy, it took the UK government six years to reduce population salt intake by 15%.[65] But the slow progress to date also reflects the limitations of current salt reduction strategies and the need for innovative interventions.

Salt substitutes provide a clear opportunity in this respect as they can work for all countries –they can be used by the industry to reduce sodium levels in commonly eaten processed foods. Plus, low sodium salt available to consumers also provides a particularly important opportunity for many low- and middle-income countries, where most salt is still added to food during cooking and at the table. It is extremely challenging to change behavior in these countries and the burden of chronic disease is high and increasing meaning it is crucial that we find practical solutions.

However, whilst the evidence in favor of using salt substitutes is increasing, there are still some considerable barriers to scaling up this important intervention. These include the potential adverse risks for a small minority of the population, the perception that consumers will not like them, the additional costs, and the fact that consumer choice alone is not likely to lead to sufficient uptake. The WHO is currently reviewing the evidence relating to the risks and benefits of using salt substitutes as part of salt reduction programs and recommendations are expected in late 2021. Even if the recommendations are positive, it will be important that clear advice not to eat salt substitutes or foods with salt substitutes is provided to patients with existing advanced kidney disease. What's more, robust monitoring of adverse health outcomes needs to be undertaken with a view to adapting if needed. But it is highly likely that the adverse impacts will be minimal and will be far outweighed by the health benefits, as has been suggested by modelling studies.[49] Many governments have therefore already taken steps and other countries are considering how they might support the introduction of salt substitutes into their national plans for salt reduction or broader noncommunicable disease prevention programs.

Whilst another barrier, mainly voiced by food companies, could be the perception that consumers will not like reduced-sodium potassium-enriched products, or will be put off by potassium on the label (making it less "clean"), there is little evidence for this. A recent systematic review reported that reformulation via salt replacement was conducted in 20 studies of 24 products.[21] The level of salt reduction ranged from 3% - 75%. Salt substitutes are already used in quite a lot of foods,[66] which indicates they are acceptable to consumers.

Regarding costs for example, potassium-enriched salt is 1.5 more expensive than common salt in China;[36] whereas in Peru, 1 kg of salt substitute costs 60 times

more than common salt.[20] Because potassium-enriched salt is more expensive, strategies such as industry subsidies or taxes on high sodium content food could reduce the costs. A recent study has demonstrated that a modelled subsidized strategy consisting of replacing common salt with potassium chloride in high sodium products would be cost effective even when it requires a high level of investment – the implementation costs will be exceeded by healthcare savings.[50]

In a recent open-label, cluster-randomized trial,[46] the rates of stroke, major cardiovascular events, and deaths from any cause were lower with the salt substitute compared to regular salt among subjects with history of stroke, or individuals aged 60 years and over and had high blood pressure. Thus, sodium reduced foods and reduced sodium salt needs to be the norm, not just an option available to consumers, to ensure that the potential health benefits of this intervention can be reached. This means the main research gap now, is understanding how to roll-out this intervention at scale, so that uptake is at a level that will benefit population health. The implementation study in Peru has provided evidence in support of the effectiveness of one approach that could be scaled up to achieve this. In another study in Vietnam (funded by Vital Strategies) the market feasibility and strategies for large-scale production, distribution and uptake of reduced-sodium seasonings was assessed.

The approach combined semi-structured face-to-face interviews with stakeholders, including salt and fish sauce manufacturers; visits to retailer stores; and a compilation of relevant market data to inform the business case. The main recommendations for the way forwards were initial government regulatory action and alignment to incentivize the food industry to use salt substitutes, including regulations on salt content of foods and consumer education to raise awareness of the harmful impacts of eating too much salt. This could be followed by an industry driven approach at a later stage when there is rising consumer demand in the market. This research is being used to support the Ministry of Health to develop a roadmap for introducing reduced-sodium seasoning products into the Vietnamese market. With three main foods; table salt, bot canh (common seasoning) and fish sauce, constituting around 70% of the total dietary sodium consumed,[67] the potential for population health gain is huge.[55] Whilst it is likely that lessons will be broadly applicable to other countries, context specific implementation research will need to be undertaken to support adaptation to other settings.

In conclusion, salt substitutes are potentially a game changer for improving the magnitude of the impact of national strategies to reduce population salt intake. There is an urgent need to identify pathways to market, including different levels of government intervention required, to support countries to ensure adequate uptake of this life-saving intervention.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

References

1. Li XY, Cai XL, Bian PD, Hu LR. High salt intake and stroke: meta-analysis of the epidemiologic evidence. CNS Neurosci Ther. 2012;18(8):691-701. https://doi.org/10.1111/j.1755-5949.2012.00355.x
2. Poggio R, Gutierrez L, Matta MG, Elorriaga N, Irazola V, Rubinstein A. Daily sodium consumption and CVD mortality in the general population: systematic review and meta-analysis of prospective studies. Public Health Nutr. 2015;18(4):695-704. https://doi.org/10.1017/S1368980014000949
3. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ. 2009;339: b4567. https://doi.org/10.1136/bmj.b4567
4. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1223-49. https://doi.org/10.1016/S0140-6736(20)30752-2
5. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, *et al*. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25): 2982-3021. https://doi.org/10.1016/j.jacc.2020.11.010
6. Aaron KJ, Sanders PW. Role of dietary salt and potassium intake in cardiovascular health and disease: a review of the evidence. Mayo Clin Proc. 2013;88(9):987-95. https://doi.org/10.1016/j.mayocp.2013.06.005
7. World Health Organization. Guideline: Sodium intake for adults and children. Geneva: World Health Organization, 2012.
8. World Health Organization. Guideline: Potassium intake for adults and children. Geneva: World Health Organization, 2012.
9. Carrillo-Larco RM, Bernabe-Ortiz A. Sodium and salt consumption in Latin America and the Caribbean: a systematic-review and meta-analysis of population-based studies and surveys. Nutrients. 2020;12(2):556. https://doi.org/10.3390/nu12020556
10. Johnson C, Praveen D, Pope A, Raj T, Pilliai, RN, Land MA, *et al*. Mean population salt consumption in India: a systematic review. J Hypertens. 2017;35(1):3-9. https://doi.org/10.1097/HJH.0000000000001141
11. Land MA, Neal BC, Johnson C, Nowson CA, Margerison C, Petersen KS. Salt consumption by Australian adults: a systematic review and meta-analysis. Med J Aust. 2018;208(2):75-81. https://doi.org/10.5694/mja17.00394
12. Bhat S, Marklund M, Henry ME, Appel LJ, Croft KD, Neal BN, *et al*. A systematic review of the sources of dietary salt around the world. Adv Nutr. 2020;11(3):677-86. https://doi.org/10.1093/advances/nmz134
13. IHS Markit. Monosodium Glutamate (MSG): Chemical Economics Handbook [internet]. Toronto: IHS Markit, 2018 [cited 2021 Mar 19]. Available from: https://ihsmarkit.com/products/monosodium-glutamate-chemical-economics-handbook.html
14. Kantar. Brand Footprint Latam: A regional ranking of the most chosen consumer brands [internet]. Kantar, 2020 [cited 2021 Mar 19]. Available from: https://kantar.turtl.co/story/brand-footprint-2020-latam/page/5/12
15. Schorling E, Niebuhr D, Kroke A. Cost-effectiveness of salt reduction to prevent hypertension and CVD: a systematic review. Public Health Nutr. 2017;20(11):1993-2003. https://doi.org/10.1017/S1368980017000593

16. Webb M, Fahimi S, Singh GM, Khatibzadeh S, Micha R, Powles J, *et al*. Cost effectiveness of a government supported policy strategy to decrease sodium intake: global analysis across 183 nations. BMJ. 2017;356:i6699. https://doi.org/10.1136/bmj.i6699
17. Filippini T, Malavolti M, Whelton PK, Naska A, Orsini N, Vinceti M. Blood pressure effects of sodium reduction: dose-response meta-analysis of experimental studies. Circulation. 2021;143(16):1542-67. https://doi.org/10.1161/CIRCULATIONAHA.120.050371
18. He FJ, Li J, Macgregor GA. Effect of longer-term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ. 2013;346:f1325. https://doi.org/10.1136/bmj.f1325
19. Adler AJ, Taylor F, Martin N, Gottlieb S, Taylor RS, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease. Cochrane Database Syst Rev. 2014;12(Cd009217). https://doi.org/10.1002/14651858.CD009217.pub3
20. Bernabe-Ortiz A, Sal y Rosas VG, Ponce-Lucero V, Cárdenas MK, Carrillo-Larco RM, Diez-Canseco F, *et al*. Effect of salt substitution on community-wide blood pressure and hypertension incidence. Nat Med. 2020;26(3):374-8. https://doi.org/10.1038/s41591-020-0754-2
21. Jaenke R, Barzi F, McMahon E, Webster J, Brimblecombe J. Consumer acceptance of reformulated food products: A systematic review and meta-analysis of salt-reduced foods. Crit Rev Food Sci Nutr. 2017;57(16):3357-72. https://doi.org/10.1080/10408398.2015.1118009
22. Li N, Prescott J, Wu Y, Barzi F, Yu X, Zhao L, *et al*. The effects of a reduced-sodium, high-potassium salt substitute on food taste and acceptability in rural northern China. Br J Nutr. 2009;101(7):1088-93. https://doi.org/10.1017/S0007114508042360
23. Maleki A, Soltanian AR, Zeraati F, Sheikh V, Poorolajal J. The flavor and acceptability of six different potassium-enriched (sodium reduced) iodized salts: a single-blind, randomized, crossover design. Clin Hypertens. 2016;22:18. https://doi.org/10.1186/s40885-016-0054-9
24. Saavedra-Garcia L, Bernabe-Ortiz A, Gilman RH, Diez-Canseco F, Cárdenas MK, Sacksteder KA, *et al*. Applying the Triangle Taste Test to assess differences between low sodium salts and common salt: evi-dence from Peru. PLoS One. 2015;10(7):e0134700. https://doi.org/10.1371/journal.pone.0134700
25. Ghimire S, Shrestha N, Callahan K. Barriers to dietary salt reduction among hypertensive patients. J Nepal Health Res Counc. 2018;16(2):124-30. https://doi.org/10.3126/jnhrc.v16i2.20296
26. Lacey M, Chandra S, Tzianetas R, Arcand J. Evaluation of actions, barriers, and facilitators to reducing dietary sodium in health care institutions. Food Sci Nutr. 2018;6(8):2337-43. https://doi.org/10.1002/fsn3.814
27. Ponce-Lucero V, Saavedra-Garcia L, Cateriano-Arévalo E, Perez-Leon S, Villareal-Zegarra D, Horna-Alva D, *et al*. Parents' perceptions about salt consumption in urban areas of Peru: formative research for a social marketing strategy. Nutrients. 2020;12(1):176. https://doi.org/10.3390/nu12010176
28. Drewnowski A, Rehm CD, Maillot M, Mendoza A, Monsivais P. The feasibility of meeting the WHO guidelines for sodium and potassium: a cross-national comparison study. BMJ Open. 2015;5(3):e006625. https://doi.org/10.1136/bmjopen-2014-006625
29. Grummer J, Karalus M, Zhang K, Vickers Z, Schoenfuss TC. Manufacture of reduced-sodium Cheddar-style cheese with mineral salt replacers. J Dairy Sci. 2012;95(6):2830-9. https://doi.org/10.3168/jds.2011-4851
30. Armenteros M, Aristoy MC, Barat JM, Toldrá F. Biochemical and sensory changes in dry-cured ham salted with partial replacements of NaCl by other chloride salts. Meat Science. 2012;90(2):361-7. https://doi.org/10.1016/j.meatsci.2011.07.023
31. Van Buren L, Dötsch-Klerk M, Seewi G, Newson RS. Dietary impact of adding potassium chloride to foods as a sodium reduction technique. Nutrients. 2016;8(4):235. https://doi.org/10.3390/nu8040235
32. Binia A, Jaeger J, Hu Y, Singh A, Zimmermann D. Daily potassium intake and sodium-to-potassium ratio in the reduction of blood pressure: a meta-analysis of randomized controlled trials. J Hypertens. 2015;33(8):1509-20. https://doi.org/10.1097/HJH.0000000000000611
33. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ. 2013;346:f1378. https://doi.org/10.1136/bmj.f1378
34. Greer RC, Marklund M, Anderson CAM, Cobb LK, Dalchin AT, Henry M, *et al*. Potassium-enriched salt substitutes as a means to lower blood pressure: benefits and risks. Hypertension. 2020;75(2):266-74. https://doi.org/10.1161/HYPERTENSIONAHA.119.13241
35. Hernandez AV, Emonds EE, Chen BA, Zavala-Loayza A, Thota P, Pasupuleti V, *et al*. Effect of low-sodium salt substitutes on blood pressure, detected hypertension, stroke and mortality: A systematic review and meta-analysis of randomised controlled trials. Heart. 2019;105(12):953-60. https://doi.org/10.1136/heartjnl-2018-314036
36. China Salt Substitute Study Collaborative Group. Salt substitution: a low-cost strategy for blood pressure control among rural Chinese. A randomized, controlled trial. J Hypertens. 2007;25(10):2011-8. https://doi.org/10.1097/HJH.0b013e3282b9714b
37. Jin A, Liu K, Labarthe DR, Feng X, Zhang R, Wang H, *et al*. Impact of salt substitute and stepwise reduction of salt supply on blood pressure in residents in senior residential facilities: Design and rationale of the DECIDE-Salt trial. Am Heart J. 2020;226:198-205. https://doi.org/10.1016/j.ahj.2020.05.013
38. Li N, Yan LL, Niu W, Laberthe D, Feng X, Shi J, *et al*. A large-scale cluster randomized trial to determine the effects of community-based dietary sodium reduction--the China Rural Health Initiative Sodium Reduction Study. Am Heart J. 2013;166(5):815-22. https://doi.org/10.1016/j.ahj.2013.07.009
39. Li N, Yan LL, Niu W, Yao C, Feng X, Zhang J, *et al*. The effects of a community-based sodium reduction program in rural China - A cluster-randomized trial. PLoS One. 2016;11(12):e0166620. https://doi.org/10.1371/journal.pone.0166620
40. Thout SR, Yu J, Tian M, Huffman M, Arnott C, Li Q, *et al*. Rationale, design, and baseline characteristics of the Salt Substitute in India Study (SSIIS): The protocol for a double-blinded, randomized-controlled trial. J Clin Hypertens. 2020;22(8):1504-12. https://doi.org/10.1111/jch.13947
41. Yu J, Thout SR, Li Q, Tian M, Marklund M, Arnott C, *et al*. Effects of a reduced-sodium added-potassium salt substitute on blood pressure in rural Indian hypertensive patients: a randomized, double-blind, controlled trial. Am J Clin Nutr. 2021;117(1):185-93. https://doi.org/10.1093/ajcn/nqab054
42. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs--overview and meta-analyses. J Hypertens. 2015;33(2):195-211. https://doi.org/10.1097/HJH.0000000000000447
43. Marklund M, Singh G, Greer R, Cudgea F, Matsuhita K, Micha R, *et al*. Estimated population wide benefits and risks in China of lowering sodium through potassium enriched salt substitution: modelling study. BMJ. 2020;369:m824. https://doi.org/10.1136/bmj.m824
44. Bistola V, Arfaras-Melainis A, Trogkanis E, Bakosis G, Polyzogopoulou E, Karavidas IN, *et al*. Safety and efficacy of salt substitution with a low sodium-potassium enriched dietary salt in patients with heart failure with reduced ejection fraction: A pilot study. Clin Nutr ESPEN. 2020;35:90-4. https://doi.org/10.1016/j.clnesp.2019.11.004
45. Karppanen H, Tanskanen A, Tuomilehto J, Puska P, Vouri J, Jäntti V, *et al*. Safety and effects of potassium- and magnesium-containing low sodium salt mixtures. J Cardiovasc Pharmacol. 1984;6(suppl 1):S236-43. https://doi.org/10.1097/00005344-198400061-00037
46. Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, *et al*. Effect of salt substitution on cardiovascular events and death. N Engl J Med. 2021;385:1067-77. https://doi.org/10.1056/NEJMoa2105675
47. Scientific Advisory Committee on Nutrition. Potassium.based sodium replacers: assessment of the health benefits and risks of using potassium-

based sodium replacers in foods in the UK. A Joint Statement from the Scientific Advisory Committee on Nutrition and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment [internet]. UK: Scientific Advisory Committee on Nutrition [cited 2021 Feb 15]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/660526/SACN_COT_-_Potassium-based_sodium_replacers.pdf
48. Steffensen IL, Frølich W, Dahl KH, Iversen PO, Lyche JL, Laugsand-Lillegaard IT, *et al*. Benefit and risk assessment of increasing potassium intake by replacement of sodium chloride with potassium chloride in industrial food products in Norway. Food Chem Toxicol. 2018;111:329-40. https://doi.org/10.1016/j.fct.2017.11.044
49. Wang M, Moran AE, Liu J, Coxson PG, Penko J, Goldman L, *et al*. Projected impact of salt restriction on prevention of cardiovascular disease in China: a modeling study. PLoS One. 2016;11(2):e0146820. https://doi.org/10.1371/journal.pone.0146820
50. Taylor C, Hoek AC, Deltetto I, Peacock A, Thi Phuong Ha D, Sieburg M, *et al*. The cost-effectiveness of government actions to reduce sodium intake through salt substitutes in Vietnam. Arch Public Health. 2021;79(1):32. https://doi.org/10.1186/s13690-021-00540-4
51. Farrand C, MacGregor G, Campbell NRC, Webster J. Potential use of salt substitutes to reduce blood pressure. J Clin Hypertens. 2019;21(3): 350-4. https://doi.org/10.1111/jch.13482
52. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, *et al*. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH). N Engl J Med. 2001;344(1):3-10. https://doi.org/10.1056/NEJM200101043440101
53. Geleijnse JM, Witteman JC, Bak AA, den Breeijen JH, Grobbee DE. Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension. BMJ. 1994;309(6952):436-40. https://doi.org/10.1136/bmj.309.6952.436
54. Zhou B, Wang HL, Wang WL, Wu XM, Fu LY, Shi JP. Long-term effects of salt substitution on blood pressure in a rural north Chinese population. J Hum Hypertens. 2013;27(7):427-33. https://doi.org/10.1038/jhh.2012.63
55. He FJ, Tan M, Song J, MacGregor GA. Salt substitution to lower population blood pressure. Nat Med. 2020;26(3): 313-4. https://doi.org/10.1038/s41591-020-0784-9
56. Pesantes MA, Diez-Canseco F, Bernabe-Ortiz A, Ponce-Lucero V, Miranda JJ. Taste, salt consumption, and local explanations around hypertension in a rural population in Northern Peru. Nutrients. 2017;9(7):698. https://doi.org/10.3390/nu9070698
57. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14(1):32-8. https://doi.org/10.1093/ije/30.3.427
58. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13. https://doi.org/10.016/s0140-6736(02)11911-8
59. Ide N, Ajenikoko A, Steele L, Cohn J, Curtis CJ, Frieden T, *et al*. Priority actions to advance population sodium reduction. Nutrients. 2020;12(9):2543. https://doi.org/10.3390/nu12092543
60. Neal B, Marklund M. Is salt substitution ready for prime time? Nat Rev Cardiol. 2020;17(6):325-6. https://doi.org/10.1038/s41569-020-0365-0
61. Valenzuela PL, Carrera-Bastos P, Gálvez BG, Ruiz-Hurado G, Ordovas JM, Ruilope LM, *et al*. Lifestyle interventions for the prevention and treatment of hypertension. Nat Rev Cardiol. 2020;18:251-75. https://doi.org/10.1038/s41569-020-00437-9
62. Neal B, Tian M, Li N, Elliott P, Yan LL, Labarthe DR, *et al*. Rationale, design, and baseline characteristics of the Salt Substitute and Stroke Study (SSaSS)-A large-scale cluster randomized controlled trial. Am Heart J. 2017;188:109-17. https://doi.org/10.1016/j.ahj.2017.02.033
63. Santos JA, Tekle D, Rosewarne E, Flexner N, Cobb L, Al-Jawldeh A, *et al*. A systematic review of salt reduction initiatives around the world: a midterm evaluation of progress towards the 2025 Global Non-Communicable Diseases Salt Reduction Target. Adv Nutr. 2021;12(5):1768-80. https://doi.org/10.1093/advances/nmab008
64. Trieu K, Neal B, Hawkes C, Dunford E, Campbell N, Rodriguez-Fernandez R, *et al*. Salt Reduction Initiatives around the World - A Systematic Review of Progress towards the Global Target. PLoS One. 2015;10(7):e0130247. https://doi.org/10.1371/journal.pone.0130247
65. He FJ, Brinsden HC, MacGregor GA. Salt reduction in the United Kingdom: a successful experiment in public health. J Hum Hypertens. 2014;28(6):345-52. https://doi.org/10.1038/jhh.2013.105
66. Yin X, Liu H, Webster J, Trieu K, Huffman MD, Miranda JJ, *et al*. Availability, formulation, labelling, and price of low-sodium salts worldwide. JMIR Public Health Surveill. 2021;7(7):e27423. https://doi.org/10.2196/27423
67. Do HT, Santos JA, Trieu K, Petersen K, Bach Le M, Troung Lai D, *et al*. Effectiveness of a Communication for Behavioral Impact (COMBI) intervention to reduce salt intake in a Vietnamese province based on estimations from spot urine samples. J Clin Hypertens. 2016;18(11):1135-42. https://doi.org/10.1111/jch.12884