Use of lower-sodium salt substitutes

WHO guideline

World Health Organization

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Abbreviations

ACS	acute coronary syndrome
AE	absolute effect
BMI	body mass index
CI	confidence interval
CVD	cardiovascular disease
DBP	diastolic blood pressure
GFR	glomerular filtration rate
GIFNA	WHO Global Database on the Implementation of Food and Nutrition Action
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IUGR	intrauterine growth restriction
KCl	potassium chloride
LSSS	lower-sodium salt substitutes
MD	mean difference
NaCl	sodium chloride
NCD	noncommunicable disease
NUGAG	WHO Nutrition Guidance Expert Advisory Group
PICO	population, intervention, comparator and outcome
RCT	randomized controlled trial
RR	risk ratio
SBP	systolic blood pressure
uACR	urine albumin-to-creatinine ratio
WHO	World Health Organization

Executive summary

Globally, each year 8 million deaths are associated with poor diet. Of these, 1.9 million are attributable to high sodium intake. Reducing sodium intake is an effective way to reduce noncommunicable diseases (NCDs) such as cardiovascular diseases (CVDs) and chronic kidney disease by lowering blood pressure. It also lowers the risks of other conditions associated with high sodium intake, such as gastric cancer.

Background

In 2012, the World Health Organization (WHO) issued guidance on limiting sodium intake to below 2 grams per day (g/day) to reduce blood pressure and risk of CVDs. Member States agreed on a global target to reduce mean population sodium intake by 30% by 2030 for the prevention and control of NCDs.[1] Despite efforts made by Member States, progress has been slow. The mean global sodium intake remains high – estimated to be 4.3 g/day (range 2 to 7 g/day) in 2019, which is more than double the WHO recommendation and demands urgent and accelerated actions.

Sodium chloride (NaCl) is the most common form of salt added to foods, both by consumers and in food manufacturing. Lower-sodium salt substitutes (LSSS) are alternatives to regular salt[2] both for discretionary use as salt added to foods by the consumer during cooking or when eating and for non-discretionary use as an ingredient present in manufactured foods and foods served at restaurants and other out-of-home settings. LSSS are also used in sodium-containing condiments, such as soy sauce and fish sauce, that are common discretionary sources of dietary sodium in some countries. These alternative salts contain less sodium than regular salt and often include potassium chloride (KCl), with or without other agents, to achieve a flavour similar to regular salt. The replacement of some of the NaCl by KCl may provide advantages, compared with regular salt, in addition to the sodium-lowering effect, because WHO recommends increasing potassium intake from food sources to reduce blood pressure and risk of CVDs. That recommendation does not include obtaining potassium from supplements in tablet form or LSSS to increase potassium intake. The use of LSSS is increasingly considered by national health authorities and public health organizations as a potential sodium reduction strategy to lower blood pressure and CVD risk, and their use is on the rise. However, global guidance on the use of these substitutes is currently lacking. Concerns have been raised about the safety of LSSS that contain potassium, because too high a level of blood potassium (hyperkalaemia) may be harmful, especially to individuals with impaired kidney function. Therefore, it is important to systematically review existing evidence on the health effects of LSSS intake and issue WHO guidance on LSSS use through the current WHO guideline development process.

Objective

The objective of this guideline is to provide guidance on LSSS use for policy-makers, programme managers, health professionals and other stakeholders in their efforts to reduce sodium intake and reduce the risk of hypertension and related NCDs through a range of policy actions and public health interventions.

Methods

This guideline was developed following the WHO guideline development process as outlined in the *WHO handbook for guideline development (2nd edition)*. This process includes a review of systematically gathered

[1] The timeline was extended to 2030 by a World Health Assembly decision in 2019 in order to ensure its alignment with the 2030 Agenda for Sustainable Development.

[2] In this guideline, "regular salt" and "table salt" refer to food-grade salt as defined by the *Codex standard 150-1995: Standard for food grade salt*. Regular table salt is regular salt that an individual adds to foods during food preparation or when eating.

evidence by an international, multidisciplinary group of experts; assessment of the certainty of that evidence via Grading of Recommendations Assessment, Development and Evaluation (GRADE); and consideration of additional, contextual factors when making decisions and translating the evidence into recommendations.

The evidence

Evidence from the systematic review of 26 randomized controlled trials (RCTs) (published between 1986 and 2021) involving 34 961 adults and 92 children was reviewed. No eligible prospective cohort studies were identified. Most RCTs included some people with hypertension, and the largest RCT included only people with an elevated risk of stroke. All trials included in the systematic review specifically excluded participants in whom an increased intake of potassium could potentially cause harm – for example, people with kidney disease, impaired renal function or those using potassium-sparing medications. Some of the trials also excluded people with type 1 or 2 diabetes mellitus. LSSS interventions of any type or duration were included, provided they aimed to replace the dietary intake of any amount of sodium with another mineral or compound, although the majority of trials included in the systematic review (23 of 26 RCTs) investigated the effects of LSSS that replaced sodium with potassium. The NaCl and KCl contents of those LSSS ranged from 41 to 75% and 19 to 50%, respectively.

In adults, assignment to use LSSS compared to regular salt resulted in reductions in diastolic and systolic blood pressure during follow-up periods ranging in length from 56 days to 5 years. The mean reductions were 2.43 mmHg (95% confidence interval [CI] 3.50 lower to 1.36 lower) for diastolic blood pressure (DBP) and 4.76 mmHg (95% CI 6.01 lower to 3.50 lower) for systolic blood pressure (SBP) (*moderate* certainty evidence). The use of LSSS when compared to regular salt showed reductions in risks of:

- non-fatal stroke – risk ratio 0.90 (95% CI 0.80 to 1.01); absolute effect (AE) 20 fewer per 100 000 persons (95% CI 40 fewer to 2 more);
- non-fatal acute coronary syndrome – rate ratio 0.70 (95% CI 0.52 to 0.94); AE 150 fewer per 100 000 person-years (95% CI 250 fewer to 30 fewer); and
- cardiovascular death – rate ratio 0.77 (95% CI 0.66 to 1.00); AE 180 fewer per 100 000 person-years (95% CI 310 fewer to 0 fewer) (*moderate* certainty evidence).

Using LSSS instead of regular salt led to a mean increase of 0.12 mmol/L (95% CI 0.07 higher to 0.18 higher) in the level of potassium in the blood (*moderate* certainty evidence). LSSS compared to regular salt resulted in little to no difference in hyperkalaemia (*moderate* certainty evidence). LSSS compared to regular salt resulted in little to no difference in hypertension prevalence (*low* certainty evidence). No conclusions could be drawn about effects of LSSS on achieving blood pressure threshold or "control" as prespecified by study authors (hereafter referred to as "blood pressure control"), various other heart disease events (e.g. angina, cardiovascular symptoms), death caused by stroke, lower-than-normal blood potassium (hypokalaemia), or other adverse events (*very low* certainty evidence).

The meta-analysis of the effects of LSSS compared to regular salt or no intervention on 24 hour (h) urinary sodium excretion showed considerable heterogeneity. Despite the considerable heterogeneity, the pooled mean difference of the 11 RCTs (−19.98 mmol [−459 mg] sodium/24 h, 95% CI −35.90 to −4.06 mmol/24 h [−825 to −93 mg/24 h], I^2 = 91%, 3885 participants, 11 RCTs)[3] was indicative of a reduction in 24 h sodium excretion on average. There was also substantial heterogeneity in the sizes of the effects of LSSS on 24 h urinary potassium excretion. The pooled mean difference of the 11 RCTs (11.44 mmol [450 mg] potassium/24 h, 95% CI 7.62 to 15.26 mmol/24 h [298 to 597 mg/24 h], I^2 = 82%, 3885 participants, 11 RCTs) indicated that use of LSSS resulted in an increase in 24 h potassium excretion on average. Subgrouping by baseline 24 h urinary sodium excretion and the baseline 24 h urinary potassium excretion did not suggest important differences in the average effects of LSSS on change in DBP and change in SBP between subgroups.

There was only one study in children (3 to 17 years old) (n = 92) looking at the effect of LSSS instead of regular salt on DBP and SBP. No conclusions could be drawn about the effects of LSSS on DBP and SBP in children

[3] The pooled effect was not included in the published systematic review because of the I^2 threshold required by the review protocol. However, it was presented to the Nutrition Guidance Expert Advisory Group to aid assessing the pooled effect and summary statistics. GRADE was not applied to the urinary sodium and potassium outcomes; thus, the finding is not presented with certainty assessment.

(*very low* certainty evidence). No studies included in the systematic review reported on the effect of LSSS on hypertension, blood pressure control, blood potassium, hyperkalaemia or hypokalaemia in children.

For pregnant women, no studies of the effects of LSSS on DBP and SBP, hypertension, blood pressure control, blood potassium, hyperkalaemia or hypokalaemia were found. Thus, no conclusions could be drawn about LSSS effects in pregnant women.

Most trials assessed discretionary use (i.e. salt that an individual adds to foods during food preparation or when eating) of LSSS.

In addition to the systematic review, a contextual factor narrative review was conducted. The review looked at additional, contextual factors related to the implementation of LSSS use. The summary of the contextual review is as follows:

- **Priority of the problem:** The global burden of disease ascribed to high blood pressure and CVDs is substantial.
- **Values and preferences:** Many studies, mainly in low- and middle-income countries, found that most people consider hypertension a serious disease with potential life-threatening consequences.
- **Resource implications:** Studies found that replacing regular salt in table salt and other foods with LSSS was cost-effective. LSSS are 1.7 times more expensive than regular salt based on the median, but overall salt is a low-cost food commodity.
- **Equity and human rights:** Lower-income or less-educated individuals were less likely to use LSSS. The higher price of LSSS was also a barrier.
- **Acceptability:** Moderate uptake of LSSS was observed for discretionary use of LSSS.
- **Feasibility:** Implementation of LSSS would be feasible overall, but several potential barriers to widespread implementation of LSSS were identified. Main barriers for consumers include: limited availability of LSSS, higher price, lack of awareness, bad taste and lack of perceived health benefit. The higher cost of LSSS and the concerns around the potentially increased risk of hyperkalaemia in those with kidney disease are potential barriers preventing governments from promoting LSSS.

Scope of the recommendation

Based on the review of the evidence, the scope of the recommendation was defined as follows:

The recommendation applies to discretionary use of LSSS in the form of table salt but does not apply to discretionary use of sodium-containing condiments (e.g. soy sauce, fish sauce), or non-discretionary salt already present in manufactured foods and foods served at restaurants and other out-of-home settings. The recommendation in this guideline applies to use of LSSS in which NaCl is partially replaced with KCl. The recommendation in this guideline is intended for adults in the general population and excludes individuals with kidney impairments or with other circumstances or conditions that might compromise potassium excretion. The recommendation does not apply to children or pregnant women.

Recommendation and supporting information

Based on a review of the evidence on effects and safety, and consideration of additional contextual factors, WHO generated the following recommendation for LSSS use.

WHO recommendation

To reduce blood pressure and risk of cardiovascular diseases, WHO has recommended reducing sodium intake to less than 2 g/day (*strong* recommendation).[4] In this context, using less regular table salt[5] is an important part of an overall sodium reduction strategy. If choosing to use table salt, WHO suggests replacing regular table salt with lower-sodium salt substitutes that contain potassium (*conditional* recommendation).[6] This recommendation is intended for adults (not pregnant women or children) in general populations, excluding individuals with kidney impairments or with other circumstances or conditions that might compromise potassium excretion.

This recommendation about LSSS should be aligned with the current WHO recommendations on sodium intake *(1)*:

- WHO recommends a reduction in sodium intake to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults (*strong* recommendation). WHO recommends a reduction to <2 g/day sodium (5 g/day salt) in adults (*strong* recommendation).
- WHO recommends a reduction in sodium intake to control[7] blood pressure in children (*strong* recommendation). The recommended maximum level of intake of 2 g/day sodium (5 g/day salt) in adults should be adjusted downward based on the energy requirements of children relative to those of adults.

Reduction of discretionary salt intake constitutes a critical part of an overall sodium reduction strategy, especially in individuals for whom discretionary salt use is a major source of sodium intake. Importantly, the use of LSSS is only one of many means in an overall strategy to reduce sodium intake.[8]

Rationale and remarks

The following provides the reasoning behind the formulation of the recommendation (i.e. rationale) as well as remarks designed to provide context for the recommendation and facilitate its interpretation and implementation. Details of the levels of certainty can be found in the GRADE table in **Annex 6**.

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[4] *Strong* recommendations are those for which the WHO guideline development group is confident that the desirable consequences of implementing the recommendation will outweigh the undesirable consequences in nearly all circumstances and can be adopted as practice or policy in most situations.

[5] "Regular salt" or "table salt" in this guideline refers to food-grade salt as defined by the *Codex standard 150-1995: Standard for food grade salt*. Regular table salt is regular salt that an individual adds to foods during food preparation or when eating.

[6] *Conditional* recommendations are those recommendations for which the WHO guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences generally or in certain settings or when the anticipated net benefits are very small. Therefore, discussion may be required, including about setting-specific issues, before a *conditional* recommendation can be adopted as policy and appropriately implemented.

[7] "Control" for this recommendation refers to the prevention of a deleterious rise in blood pressure with age.

[8] Resolution WHA76(9) (2023) endorsed the updated menu of policy options and cost-effective interventions for reducing salt intake, such as: i) reformulation of food products to contain less salt and the setting of target levels for the amount of salt in foods and meals; ii) implementation of front-of-pack labelling and other interpretive nutrition labelling; iii) establishment of a supportive environment in public institutions such as hospitals, schools, workplaces and nursing homes, to enable lower-sodium options to be provided; iv) a behaviour change communication and mass media campaign for healthy diets; and v) implementing policies to protect children from the impact of food marketing. SHAKE Technical Package for Salt Reduction presents a suite of action menus, which is currently being updated. WHO released the second edition of the WHO global sodium benchmarks for different food categories in 2024 to assist countries set national sodium targets to reduce the sodium content of manufactured foods.

Rationale

- This recommendation is based on evidence of *moderate-to-low* certainty (an assessment of *low* certainty overall according to GRADE guidance when considering findings across all outcomes of interest) from a systematic review *(2)* that assessed the effects and safety of using LSSS[9] compared to regular salt or no intervention. The prioritized outcomes of interest were effects on blood pressure, serum potassium (hyperkalaemia, hypokalaemia), stroke and cardiovascular events and mortality.
- The recommendation to use LSSS is based on findings from 26 RCTs in adults in which assignment to LSSS compared to regular salt resulted in reductions in DBP and SBP over 56 days to 5 years of follow-up. The mean reduction was 2.43 mmHg (95% CI 3.50 lower to 1.36 lower) for DBP and 4.76 mmHg (95% CI 6.01 lower to 3.50 lower) for SBP (*moderate* certainty evidence). The use of LSSS when compared to regular salt showed reductions in risks of non-fatal stroke (risk ratio 0.90 [95% CI 0.80 to 1.01]; AE 20 fewer per 100 000 persons [95% CI 40 fewer to 2 more]), non-fatal acute coronary syndrome (rate ratio 0.70 [95% CI 0.52 to 0.94]; AE 150 fewer per 100 000 person-years [95% CI 250 fewer to 30 fewer]) and cardiovascular death (rate ratio 0.77 [95% CI 0.66 to 1.00]; AE 180 fewer per 100 000 person-years [95% CI 310 fewer to 0 fewer]) (*moderate* certainty evidence).
- The meta-analysis of the effect of LSSS compared to regular salt or no intervention on 24 h sodium excretion showed considerable heterogeneity. Despite the considerable heterogeneity, the pooled mean difference (−19.98 mmol [−459 mg] sodium/24 h, 95% CI −35.90 to −4.06 mmol/24 h [−825 to −93 mg/24 h], I^2 = 91%)[10] were indicative of a reduction in 24 h sodium excretion on average. There was also substantial heterogeneity in the size of the effects of LSSS on 24 h potassium excretion. The pooled mean difference (11.44 mmol [450 mg] potassium/24 h, 95% CI 7.62 to 15.26 mmol/24 h [298 to 597 mg/24 h], I^2 = 82%) indicated that use of LSSS resulted in an increase in 24 h potassium excretion on average. Subgrouping by baseline 24 h urinary sodium excretion and the baseline 24 h urinary potassium excretion did not suggest important differences in the average effects of LSSS on change in DBP and change in SBP between subgroups.
- All studies in the review excluded people for whom increased potassium intake would not be advisable (e.g. those with kidney disease, those taking potassium-sparing diuretics or potassium supplements). Therefore, relevance to general populations that might include people with kidney impairments or with other circumstances or conditions that might compromise potassium excretion was uncertain. Additionally, some of the trials also excluded people with type 1 or 2 diabetes mellitus.
- In these studies, assignment to use LSSS instead of regular salt led to a mean increase of 0.12 mmol/L (95% CI 0.07 higher to 0.18 higher) in the level of potassium in the blood (*moderate* certainty evidence). LSSS compared to regular salt resulted in little to no difference in hyperkalaemia (*moderate* certainty evidence). Very few studies reported on hyperkalaemia and studies that did report on hyperkalaemia also used variable, in some cases unclear, criteria to define the condition. Other potassium-related measures presented in most of these studies were not rigorously collected and reported. Therefore, the information on hyperkalaemia events and other potassium-related measures was unreliable.

[9] LSSS interventions of any type or duration were included in the systematic review, provided they aimed to replace the dietary intake of any amount of sodium with another mineral or compound, although most trials included in the systematic review (23 of 26 RCTs) investigated the effects of LSSS that replaced sodium with potassium.

[10] The pooled effect was not included in the published systematic review because of the I^2 threshold required by the review protocol. However, it was presented to the Nutrition Guidance Expert Advisory Group to aid assessing the pooled effect and summary statistics. The urinary sodium and potassium outcomes were not GRADED; thus, the finding is not presented with certainty assessment.

- The recommendation was assessed as *conditional* because the overall certainty of evidence was *low* according to the GRADE guidance and there was uncertainty about the balance between the benefits and potential harms, especially in settings where a considerable proportion of the population may have undiagnosed conditions for which it would not be advisable to increase potassium intakes (e.g. some low-resource settings).

Remarks

- Reducing sodium intake from both discretionary and non-discretionary use is the preferred strategy for health benefits. LSSS still contain sodium; therefore, to reduce sodium intake, the amount of sodium obtained from LSSS should be less than the amount of sodium that would have been obtained from the regular salt they replace.
- LSSS interventions of any type or duration were included in the systematic review, provided they aimed to replace the dietary intake of any amount of sodium with another mineral or compound. The recommendation statement refers to LSSS that contain potassium because most trials included in the systematic review (23 of 26 RCTs) investigated the effects of LSSS that replaced sodium with potassium, whose NaCl and KCl contents ranged from 41 to 75 % and from 19 to 50%, respectively. In addition, the blood-pressure-lowering effect of LSSS is partly due to potassium content *(3)*; however, the percentage of KCl in the LSSS did not modify the effect in the systematic review.
- This recommendation, which applies to LSSS containing KCl, should be considered in the context of the other WHO recommendations related to potassium intake. WHO recommends consuming foods that naturally contain potassium (such as beans and peas, nuts and green vegetables) as part of a healthy diet. These foods have other nutritional benefits and should be the primary sources of dietary potassium when seeking to increase intake *(1)*.
- This recommendation is for adults in general populations, and excludes individuals with kidney impairments or with other circumstances or conditions that might compromise potassium excretion (e.g. those taking potassium-sparing diuretics or potassium supplements). In some low-resource settings, a considerable proportion of the population may not be aware of having these conditions, and there may be individuals with undiagnosed kidney disease for whom higher potassium intakes over the long term might be of concern, and might require medical supervision and periodic assessment over time. Therefore, the use of LSSS should be implemented in settings with adequate access to health care, where conditions in which increased potassium intakes are potentially harmful (e.g. kidney disease) would not go undiagnosed for a long time. It should be noted that this guideline is not a clinical management guideline. Providing recommendations on how to clinically manage and treat hypertension, kidney diseases and other conditions is beyond the scope of this guideline.
- Discretionary salt in this recommendation is defined as salt that an individual adds to foods during cooking or when eating. It is commonly known as regular salt or table salt. This recommendation applies to discretionary use of LSSS.
- Non-discretionary salt is consumed as already present in manufactured foods and foods served at restaurants and other out-of-home settings. This recommendation does not apply to consumption of LSSS used in manufactured food products or foods sold by markets, restaurants, cafeterias and street vendors. It should also be noted that consumption of LSSS used in sodium-containing condiments, such as soy sauce and fish sauce, which are common discretionary food sources of sodium in some countries, are not included in the scope of the recommendation. There was not enough evidence on the non-discretionary consumption of LSSS (e.g. from manufactured foods) or on condiments to include them in the recommendation. However, as LSSS are increasingly used in manufactured foods and foods consumed away from home, this will alter the baseline

to which discretionary LSSS are added. Such changes must be monitored at the population level to estimate total sodium and potassium intake from both discretionary and non-discretionary sources.

- There was a paucity of data for children, and no studies in children examined discretionary use of LSSS. One RCT conducted in children reported that the non-discretionary use of LSSS in bread showed little to no effect on blood pressure, but the evidence is very uncertain (*very low* certainty evidence). No studies involving pregnant women were found. Therefore, no conclusions can be drawn for children and pregnant women, and this recommendation does not apply to children and pregnant women. However, if a member in a household (including children and pregnant women) is at risk for hyperkalaemia, LSSS should not be used to prepare a family meal to be eaten by the member.
- Currently, just under half of the LSSS available globally are iodized. Action is required to ensure iodization of LSSS in order to align with national policies on salt iodization.

Introduction

Globally, each year 8 million deaths are associated with poor diet. Of these, 1.9 million are attributable to high sodium intakes *(4)*. Reducing sodium intake is an effective way to reduce noncommunicable diseases (NCDs) such as cardiovascular diseases (CVDs) and chronic kidney disease by lowering blood pressure, as well as to lower risks of other conditions associated with high sodium intakes, such as gastric cancer *(5)*.

Background

In its guidance on sodium intake *(1)*, the World Health Organization (WHO) recommends a reduction in sodium intake to <2 grams/day (g/day) sodium (5 g/day salt) to reduce blood pressure and risk of CVDs in adults (*strong* recommendation[11]). WHO recommends a reduction in sodium intake to control[12] blood pressure in children (*strong* recommendation). The recommended maximum level of intake of 2 g/day sodium in adults should be adjusted downward based on the energy requirements of children relative to those of adults.

In 2013, the World Health Assembly endorsed the WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2030 *(6)* (the timeline was extended from 2020 to 2030 by a World Health Assembly decision in 2019) *(7)*. The Global Action Plan provides WHO Member States and international partners with a road map and menu of policy options that collectively contribute to progress on nine global NCD targets. One of the targets agreed to by Member States is a 30% relative reduction in mean population intake of salt (sodium) by 2030, which contributes to meeting the overall goal of a 25% reduction in premature mortality from NCDs. Member States have been striving to achieve the sodium reduction target by implementing multifaceted measures including promoting reformulation of manufactured foods, implementing effective and accurate food labelling and marketing, and using education and communication efforts to increase the awareness of consumers of the need to eat less sodium. To assist countries taking policy actions, WHO released the SHAKE Technical Package for Salt Reduction in 2016 *(8)*. The SHAKE Package is currently being updated to present a comprehensive action package for sodium reduction. Furthermore, WHO released the second edition of the WHO global sodium benchmarks for different food categories in April 2024 *(9)*, which serves as a guide for countries in setting national sodium targets to reduce the sodium content of manufactured foods. Despite the efforts, progress has been slow, and no country has achieved the target yet. The mean global sodium intake remains high and was estimated to be 4.3 g/day in 2019, which is more than double the WHO recommendation *(10)*. Country mean sodium intakes range from 2 g/day to 7 g/day *(11)*. This clearly indicates the need for urgent and further accelerated actions towards sodium reduction.

Rationale

Sodium chloride (NaCl) is the most common form of salt added to foods by consumers or in food manufacturing. Lower-sodium salt substitutes (LSSS) are alternatives to regular salt,[13] both for discretionary use as salt added to foods by the consumer during cooking or when eating and for non-discretionary use as an ingredient present in manufactured foods and foods served at restaurants and other out-of-home

[11] *Strong* recommendations are those recommendations for which the WHO guideline development group is confident that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. *Strong* recommendations can be adopted as policy in most situations.
[12] "Control" for this recommendation refers to the prevention of a deleterious rise in blood pressure with age.
[13] In this guideline, "regular salt" and "table salt" refer to food-grade salt as defined by the *Codex Standard for food grade salt (12)*.

settings. LSSS are also used in sodium-containing condiments, such as soy sauce and fish sauce, that are common discretionary sources of sodium in some countries. LSSS contain less sodium than regular salt and often include potassium chloride (KCl), with or without other agents, to achieve a flavour similar to regular salt. The replacement of some of the NaCl with KCl may provide advantages, compared with regular salt, beyond the sodium-lowering effect *(13, 14)*.

WHO provides recommendation to increase potassium intake from food sources to reduce blood pressure and risk of CVDs (*strong* recommendation) *(15)*. WHO suggests a potassium intake of at least 90 mmol/day (3510 mg/day) for adults (*conditional* recommendation[14]). WHO suggests an increase in potassium intake from food sources to control blood pressure in children (*conditional* recommendation). The recommended potassium intake of at least 90 mmol/day should be adjusted downward for children, based on the energy requirements of children relative to those of adults. This recommendation does not include obtaining potassium from supplements in tablet form or LSSS to increase potassium intake.

The use of LSSS is increasingly considered by national health authorities and public health organizations as a potential sodium reduction strategy to lower blood pressure and CVD risk *(16)*. Their use is on the rise especially in countries where most sodium intake comes from discretionary use. Furthermore, some food manufacturers consider LSSS as a potential solution to advance product reformulation to reduce levels of sodium in manufactured foods when further reducing sodium content in manufactured foods might otherwise compromise taste or safety. However, global guidance on the use of these substitutes is currently lacking. Concerns have been raised about the safety of LSSS that contain potassium, because too high a level of blood potassium (hyperkalaemia) may be harmful, especially to individuals with impaired kidney function.

WHO Department of Nutrition and Food Safety (NFS) has been receiving an increasing number of inquiries from Member States and other stakeholders as to whether WHO recommends the use of LSSS in place of regular table salt as part of policy actions and public health interventions for reducing sodium intake at the population level. Therefore, it is important to review existing evidence on the health effects of LSSS intake in a systematic manner and issue WHO guidance on LSSS use through the current WHO guideline development process.

Objective

The objective of this guideline is to provide evidence-informed guidance on the use of LSSS. The recommendation in this guideline can be used by policy-makers, programme managers, health professionals and other stakeholders in their efforts to promote reduction of sodium intake and reduce the risk of hypertension and related NCDs through a range of public health policy actions and intervention programmes.

The WHO recommendation on LSSS use is an important element of efforts by WHO to implement the NCD agenda and achieve the triple billion targets set up by the 13th General Programme of Work (2019–2025) and the 14th General Programme of Work (2025–2028) that will guide WHO in supporting Member States and partners to promote, provide and protect the health and well-being of all people, everywhere. In addition, the recommendation and other elements of this guideline will support:

- implementation of the political declarations of the United Nations (UN) high-level meetings on the prevention and control of NCDs held in New York in 2011 and 2018, and the outcome document of the high-level meeting of the UN General Assembly on NCDs (A/RES/68/300) held in New York in July 2014;
- implementation of the WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2030;
- Member States in implementing the commitments of the Rome Declaration on Nutrition and recommended actions in the Framework for Action, including a set of policy options and strategies to promote diversified, safe and healthy diets at all stages of life – these were adopted by the Second

[14] *Conditional* recommendations are those recommendations for which the WHO guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences generally or in certain settings or when the anticipated net benefits are very small. Therefore, discussion may be required, including about setting-specific issues, before a *conditional* recommendation can be adopted as policy and appropriately implemented.

International Conference on Nutrition (ICN2) in 2014 and endorsed by the 136th Session of the WHO Executive Board (January 2015) and the 68th World Health Assembly (May 2015), which called on Member States to implement the commitments of the Rome Declaration across multiple sectors;

- achievement of the goals of the UN Decade of Action on Nutrition (2016–2025), declared by the UN General Assembly in April 2016, which include increased action at the national, regional and global levels to achieve the commitments of the Rome Declaration through implementing policy options included in the Framework for Action and evidence-informed programme actions; and
- the 2030 Agenda on Sustainable Development and achieving the Sustainable Development Goals, especially Goal 2 (Zero hunger), Goal 3 (Good health and well-being) and Goal 17 (Partnerships for the goals).

Target audience

The guideline is intended for a wide audience involved in the development, design and implementation of policies and programmes in nutrition and public health. The end users for this guideline are:

- policy-makers at all levels;
- managers and implementers of programmes relating to nutrition and NCD prevention;
- nongovernmental and other organizations, including professional societies, involved in managing and implementing programmes relating to nutrition and NCD prevention;
- health professionals in all settings;
- scientists and others involved in nutrition and NCD-related research; and
- representatives of the food industry and related associations.

How this guideline was developed

This guideline was developed in accordance with the WHO evidence-informed process for guideline development outlined in the *WHO handbook for guideline development (17)*. Because of the complex nature of the guideline topic and the rapidly evolving evidence base, the guideline was developed over successive meetings of the Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health, from December 2019 until December 2021. Additional consultations with NUGAG members were held in 2024 before the finalization of the guideline.

Contributors to the development of this guideline

Development of this guideline was undertaken by the WHO Department of Nutrition and Food Safety. Several groups contributed to the development of this guideline, and additional feedback was obtained from interested stakeholders via public calls for comment as described below.

WHO Steering group

The work was guided by an internal steering group, which included technical staff from WHO with varied perspectives and expertise in the provision of scientific advice on healthy diets (**Annex 1**).

Guideline development group

The guideline development group – the NUGAG Subgroup on Diet and Health – was convened to support the development of this guideline (**Annex 2**). This group included experts who had previously participated in various WHO expert consultations or were members of the WHO expert advisory panels, and others identified through open calls for experts. In forming the group, the WHO Secretariat took into consideration the need for expertise in many disciplinary areas, representation from all WHO regions, and a balanced gender mix. Efforts were made to include subject-matter experts (e.g. in nutrition, epidemiology, paediatrics, physiology); experts in systematic review, programme evaluation and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologies; and representatives of potential stakeholders (e.g. programme managers, policy advisers, other health professionals involved in the health care process). Shiriki Kumanyika served as the chair at the meetings of the NUGAG Subgroup on Diet and Health. The names, institutional affiliations and summary background information of the members of the NUGAG Subgroup on Diet and Health are available on the WHO website,[15] along with information on each meeting of the group.

Systematic review team

A systematic review team with expertise in both systematic review methodologies and the subject matter was identified. The systematic review was conducted by Amanda Brand, Marianne E Visser, Anel Schoonees, and Celeste E Naude from the Centre for Evidence-based Health Care, Division of Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa *(2)*.

The team consulted frequently with the WHO Secretariat to ensure that the review met the needs of the WHO guideline development process.

[15] For a complete list of meetings and information on members of the NUGAG Subgroup on Diet and Health, see https://www.who.int/groups/nutrition-guidance-expert-advisory-group-(nugag)/diet-and-health.

Observers

Observers were identified by the WHO Steering Group to provide valuable insights to the NUGAG Subgroup on Diet and Health on issues relevant to the topic. The following individuals participated as observers: Norm Campbell (University of Calgary, Canada), Bente Mangschou (Norwegian Scientific Committee on Food and Environment, Norway) and Tor A Strand (University of Bergen, Norway). Their role was to observe, although the chair was allowed to ask them for opinions and information. They did not participate in the formulation of recommendations or in decisions on their wording, direction or strength.

Stakeholder feedback via public consultation

A public consultation was held on the draft guideline between 31 March and 30 April 2023. Stakeholders and others with an interest in the guideline were invited to provide feedback on overall clarity, any potentially missing information, setting-specific or contextual issues, considerations and implications for adaptation and implementation of the guideline, and gaps in the evidence to be addressed by future research. The consultation was open to everyone. Declaration of interest forms were collected from those submitting comments, and were assessed by the WHO Secretariat, following the procedures for management of interests described in the next section. Comments will be summarized, and together with WHO responses to the summary comments, posted on the WHO website. Comments that helped to improve clarity and usability of the draft guideline were considered in finalizing the guideline document.

External peer-review group

External experts with diverse perspectives and backgrounds relevant to the topic of this guideline were invited to review the draft guideline to identify any factual errors, and comment on the clarity of the language, contextual issues, and implications for implementation (**Annex 3**).

Management of conflicts of interest

Financial and intellectual interests of the members of the NUGAG Subgroup on Diet and Health, those serving as external peer reviewers, and individuals who prepared systematic reviews or contributed other analyses were reviewed by members of the WHO Secretariat, in consultation with the WHO Department of Compliance and Risk Management and Ethics, when necessary. Declared interests of members of the NUGAG Subgroup on Diet and Health and of the systematic review team were reviewed before their original engagement in the guideline development process and before every meeting. In addition, each member of the NUGAG Subgroup on Diet and Health (and members of the systematic review team, if present) verbally declared their interests, if required, at the start of each meeting of the group. Declared interests of external reviewers were assessed before they were invited to review the draft guideline. In addition to reviewing interests declared by the individuals themselves, an internet search was conducted for each contributor to independently assess financial and intellectual interests for the 4 years before their engagement in the development of the guideline, which was repeated as necessary. The overall procedures for management of interests outlined in the *WHO handbook for guideline development (17)* were followed.

Interests declared by members of the NUGAG Subgroup on Diet and Health, external reviewers, members of the systematic review team and a methods expert, and the process for managing any identified conflicts of interest are summarized in **Annex 4**.

Guideline development process

The guideline was developed via a process of scoping, defining key questions and outcomes, gathering and assessing evidence, and formulating recommendations.

Scoping of the guideline

The scientific literature was reviewed to identify important populations, outcomes and other topics relevant to the health effects of LSSS use. Existing systematic reviews on the topic were identified. The last search date was 2 October 2019. The information gathered was compiled and used to generate the key questions

and outcomes that would guide the selection of existing systematic reviews or the undertaking of a new systematic review.

Defining key questions and prioritizing outcomes

Proposed key questions in the population, intervention, comparison and outcome (PICO) format were discussed by the NUGAG Subgroup on Diet and Health, which reviewed the scoping review in order to assess the need for the guidance on the use of LSSS (**Annex 5**).

Relevant health outcomes related to use of LSSS were identified during the scoping process. The priority health outcomes varied by population, and are listed in **Annex 5**. Critical health outcomes considered for adults were blood pressure (systolic, diastolic, hypertension, blood pressure control), serum potassium, hyperkalaemia, hypokalaemia, stroke, cardiovascular events including dysrhythmia, sudden death, and CVD mortality. Important health outcomes were all-cause mortality, measures of kidney function (e.g. serum creatinine, albuminuria, urine albumin-to-creatinine ratio (uACR), glomerular filtration rate (GFR)), adverse events, anti-hypertensive medication use, diabetes, hyponatraemia, glucose, total cholesterol, triglycerides, and body mass index (BMI). Dehydration, bone health and neurologic performance (after stroke) were not considered important outcomes. For pregnant women, outcomes were identical to those for adults, but also included pre-eclampsia, eclampsia, pre-term birth, intrauterine growth restriction (IUGR), birthweight, and gestational diabetes. Critical health outcomes for children were identical to those for adults, but also included growth as an important outcome.

Evidence gathering and review

Following the scoping review, a systematic review was commissioned to assess the effects and safety of replacing regular salt with LSSS on health outcomes of interest in adults, pregnant women and children. The last search date was 18 August 2021. This systematic review was published on 10 August 2022 *(2)*.

Assessment of certainty in the evidence

GRADE[16] methodology was used to assess the certainty (i.e. confidence) in the evidence identified in the systematic review.

GRADE assessments assigned by the systematic review team were discussed by the NUGAG Subgroup on Diet and Health and the systematic review team, and refined as necessary under the guidance of a methodologist with extensive expertise in GRADE methodology. GRADE assessments are summarized in **Annex 6**.

The four levels of the GRADE certainty of evidence are interpreted as detailed in **Table 1**. The certainty of the evidence is stated for each outcome of interest, and the certainties of the outcomes inform the overall certainty of the evidence.

Table 1. Description of the interpretation of the GRADE four levels of certainty of evidence

Certainty	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

[16] GRADE working group: http://www.gradeworkinggroup.org

Additionally, contextual factor narrative review was conducted *(18)*. The last search date was 20 April 2022. The following contextual factors that may affect the use of LSSS were included: priority of the problem being addressed; values and preferences related to the health outcomes; resources required; cost–effectiveness, equity and human rights; acceptability; and feasibility.

Formulation of the recommendation

In formulating the recommendation and determining its strength, the NUGAG Subgroup on Diet and Health assessed the evidence in the context of the certainty in the evidence, desirable and undesirable effects of the intervention, and contextual factors (**Annex 7**). To facilitate explicit and transparent decisions, the GRADE evidence to decision framework was used. This framework includes clear criteria on balance of benefits and harms, priority of the problem, values and preferences, certainty of evidence, resource implications, equity and human rights, acceptability and feasibility, all of which may determine the direction and strength of recommendations. Decisions were made by consensus facilitated by the guideline methodologist and the NUGAG chair. Judgements, additional considerations, research gaps, implementation considerations and points about monitoring and evaluation discussed by the NUGAG Subgroup on Diet and Health were documented.

The NUGAG Subgroup on Diet and Health used their judgements for the evidence to decision criteria to determine the direction and strength of the recommendation, including the certainty of evidence.

Summary of evidence

Here, the evidence from a commissioned systematic review is summarized, including the characteristics of the studies included in the review and the main results.

Systematic review

The systematic review was completed to identify, appraise and synthesize the available evidence from the scientific literature.

Systematic review characteristics

The systematic review intended to identify all randomized controlled trials (RCTs) and prospective cohort studies that assessed the effects and safety of LSSS in comparison with regular salt or no active intervention in adults, children and pregnant women.

A total of 26 RCTs, reported in 74 full-text records and reporting on 34 961 adult participants, were identified and included in the review. Of these, 16 trials randomized individual participants and 10 randomized clusters. No eligible prospective cohort studies were identified. One RCT reported a cross-over design for which only first-phase data were used.

No eligible studies were found on pregnant women. One cluster-RCT compared LSSS to regular salt in families, which analysed data from 90 adults and 92 children. Four other trials were conducted in households or families, and the remainder of the trials were conducted on individual adults.

The durations of the 16 individual RCTs ranged from 3 months to 2 years. For the 10 cluster-RCTs, the durations ranged from 2 months to nearly 5 years.

Trials in adults were mostly conducted in Asia – China (*n* = 11), India (*n* = 1), Japan (*n* = 1) and Taiwan, China (*n* = 2). Studies were also conducted in Brazil (*n* = 1), Finland (*n* = 1), France (*n* = 2), Italy (*n* = 2), Netherlands (Kingdom of the) (*n* = 1), Norway (*n* = 1), United Kingdom of Great Britain and Northern Ireland (*n* = 1) and Peru (*n* = 1). The cluster-RCT that included children (3–17 years) was from Denmark (*n* = 1).

Some trials were conducted only on participants with hypertension (*n* = 11), others on participants with and without hypertension (*n* = 11), or only participants with normal blood pressure (*n* = 1) or those who were pre-hypertensive (*n* = 1). Blood pressure statuses at baseline in the remaining studies were unknown (*n* = 2). All 26 trials specifically excluded participants in whom an increased intake of potassium could cause harm – for example, people with kidney disease, impaired renal function or those using potassium-sparing medications or potassium supplements. Some studies also excluded people with type 1 or 2 diabetes mellitus.

In most trials, the interventions consisted of LSSS containing potassium chloride (KCl) in varying amounts (i.e. 19–50% KCl). In 23 studies, combinations of potassium and/or magnesium and/or calcium salts were used as sodium substitutes in the LSSS intervention; two studies assessed an intervention consisting of NaCl combined with 3% chitosan; and one study assessed an intervention consisting of bread made with salt with reduced sodium content. Three studies assessed LSSS with an unknown KCl content. Four cluster-RCTs and six individual RCTs assessed the effects of interventions using LSSS containing ≥30% KCl, while the remainder of the trials used LSSS containing <30% KCl. One RCT included two LSSS intervention arms, both including ≥30% KCl.

In 22 studies, the LSSS intervention was administered as a discretionary intervention (at the individual, household, institution or salt supply chain level). Most trials replaced the supply of regular salt with LSSS within each household, to be used during food preparation or when eating. Approaches used in trials included the following:

- LSSS were made available for purchase at local village shops at either a subsidized price (same as regular salt) in half of the intervention villages, or at a regular price (approximately double that of regular salt). A community-based health education programme to promote the use of LSSS was implemented via public announcement systems, bulletin boards, and specially developed promotional materials.
- Participants were provided with LSSS as salt for household food preparation and for use as table salt.
- LSSS were used during food preparation in nursing home intervention kitchens.

A few trials included LSSS as a non-discretionary use or a combination of both non-discretionary and discretionary uses. Approaches used in trials included the following:

- Bread was the exclusive method of LSSS implementation by incrementally replacing normal salt with LSSS.
- LSSS were incorporated into prepared test foods, such as processed main dishes, bread, cheese, luncheon meats, soups or smoked sausage, or seasonings containing LSSS, such as miso and soy sauce.
- LSSS replaced the supply of regular salt in villages in the supply chain, including in households, food vendors, bakeries, community kitchens and restaurants. A social marketing and education strategy promoting LSSS in each village was aimed at women, who were responsible for household food preparation.

In addition to the interventions, some trials had additional instructions to the participants, or included co-interventions:

- Participants in four studies were instructed not to change their dietary habits during the study period.
- Participants in two trials were advised to either reduce their salt intake or avoid salt-rich foods.
- Participants in some trials received co-interventions such as lifestyle advice about eating less fat and sugar and doing more physical exercise, or a hypocaloric diet with increased physical exercise.

Results of the systematic review

ADULTS

Results for LSSS intervention compared to regular salt in adults (≥18 years) are summarized in **Table 2**. GRADE assessments for each outcome can be found in **Annex 6**.

Table 2. Summary of findings for LSSS intervention compared to regular salt in adults (≥18 years)

Outcome	Anticipated absolute effects[a] (95% CI)			Relative effect (95% CI)	No. studies	No. participants	Certainty (GRADE)
	Risk with regular salt	Risk with LSSS intervention	Risk difference (95% CI)				
Change in DBP[b]	Mean change −0.74 mmHg	Mean change −3.87 mmHg	MD 2.43 mmHg lower (3.50 lower to 1.36 lower)	NA	19 RCTs	20 830	*Moderate*
Change in SBP[b]	Mean change −1.32 mmHg	Mean change −7.48 mmHg	MD 4.76 mmHg lower (6.01 lower to 3.50 lower)	NA	20 RCTs	21 414	*Moderate*
Hypertension prevalence[c]	58 019 per 100 000 persons	56 278 per 100 000 persons (52 217 to 59 759)	1 741 fewer per 100 000 persons (5 802 fewer to 1 741 more)	RR 0.97 (0.90 to 1.03)	1 RCT	2 566	*Low*
Blood pressure control[d]	12 782 per 100 000 persons	27 098 per 100 000 persons (16 872 to 43 586)	14 316 more per 100 000 persons (4 090 more to 30 805 more)	RR 2.12 (1.32 to 3.41)	2 RCTs	253	*Very low*
Cardio-vascular events: various[e]	1 623 per 100 000 persons	1 980 per 100 000 persons (795 to 4 933)	357 more per 100 000 persons (828 fewer to 3 310 more)	RR 1.22 (0.49 to 3.04)	5 RCTs	982	*Very low*
Cardio-vascular events: non-fatal stroke	198 per 100 000 persons	178 per 100 000 persons (158 to 200)	20 fewer per 100 000 persons (40 fewer to 2 more)	RR 0.90 (0.80 to 1.01)	3 RCTs	21 250	*Moderate*
Cardi-vascular events: non-fatal ACS	512 per 100 000 person-years	358 per 100 000 person-years (266 to 481)	150 fewer per 100 000 person-years (250 fewer to 30 fewer)	Rate ratio 0.70 (0.52 to 0.94)	1 RCT	20 995	*Moderate*
Cardio-vascular mortality	786 per 100 000 person-years	605 per 100 000 person-years (472 to 786)	180 fewer per 100 000 person-years (310 fewer to 0 fewer)	Rate ratio 0.77 (0.60 to 1.00)	3 RCTs	23 200	*Moderate*
Stroke mortality	405 per 100 000 person-years	259 per 100 000 person-years (134 to 506)	145 fewer per 100 000 person-years (270 fewer to 100 more)	Rate ratio 0.64 (0.33 to 1.25)	2 RCTs	21 423	*Very low*
Change in blood potassium[b]	Mean change 0.01 mmol/L	Mean change 0.09 mmol/L	MD 0.12 mmol/L higher (0.07 higher to 0.18 higher)	NA	6 RCTs	784	*Moderate*
Hyper-kalaemia	88 per 100 000 persons	91 per 100 000 persons (40 to 209)	4 more per 100 000 persons (47 fewer to 121 more)	RR 1.04 (0.46 to 2.38)	5 RCTs	22 849	*Moderate*

Outcome	Anticipated absolute effects[a] (95% CI)			Relative effect (95% CI)	No. studies	No. participants	Certainty (GRADE)
	Risk with regular salt	Risk with LSSS intervention	Risk difference (95% CI)				
Hypo-kalaemia	One small trial in younger, hypertensive participants receiving potassium supplementation due to the use of potassium-depleting diuretics reported no hypokalaemia events in the intervention (n = 12) or control (n = 10) group.		NA	Not esti-mable	1 RCT	22	*Very low*
Adverse events: other	Eight trials reported other adverse events, with a total of 25/1 094 (2.3%) and 14/1 015 (1.4%) diverse adverse events reported across studies in the intervention and control groups, respectively (not pooled).		NA	Not pooled	8 RCTs	2 109	*Very low*

ACS: acute coronary syndrome; CI: confidence interval; DBP: diastolic blood pressure; MD: mean difference; NA: not applicable; RR: risk ratio; SBP: systolic blood pressure

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Per-group mean changes are unweighted means obtained from primary studies where change was either reported or could be calculated.

[c] Hypertension is defined as reported, or SBP >140 mmHg or DBP >85 mmHg.

[d] Blood pressure control is defined as achieving blood pressure threshold (control) as prespecified by study authors.

[e] Various other cardiovascular events e.g. angina, cardiovascular symptoms.

Primary outcomes for adults

Change in diastolic blood pressure (DBP, mmHg)

Average reductions in DBP ranged from 0.6 mmHg to 11.33 mmHg with LSSS and from a reduction of 7 mmHg to an increase of 2.6 mmHg with regular salt in the 19 trials that reported this outcome. The meta-analysis showed reductions of DBP on average between LSSS and regular-salt groups (mean difference [MD] −2.43 mmHg, 95% confidence interval [CI] −3.50 to −1.36, I^2 = 88%, 20 830 participants, 19 RCTs, *moderate* certainty evidence). This effect was confirmed by sensitivity analyses, including only trials with low or unclear overall risk of bias and including only trials that randomized participants at the individual level – that is, by excluding cluster-RCTs. Subgroup analyses suggested there may be no differences in average effects between subgroups based on study duration, participants' characteristics and intervention type. Follow-up ranged from 4 weeks to 60 months.

Change in systolic blood pressure (SBP, mmHg)

Average reductions in SBP ranged from 1.5 mmHg to 15.25 mmHg with LSSS and from a reduction of 6.8 mmHg to an increase of 4 mmHg with regular salt in the 20 trials that reported this outcome. The meta-analysis showed reductions of SBP on average between LSSS and regular-salt groups (MD −4.76 mmHg, 95% CI −6.01 to −3.50, I^2 = 78%, 21 414 participants, 20 RCTs, *moderate* certainty evidence). This effect was confirmed by sensitivity analyses, including only trials with low or unclear overall risk of bias and including only trials randomizing participants at the individual level – that is, by excluding cluster-RCTs. Subgroup analyses suggested there may be no differences in average effects between subgroups based on study duration, participants' characteristics and intervention type. Follow-up ranged from 4 weeks to 60 months.

Hypertension prevalence and incidence (as reported, or SBP >140 mmHg or DBP >85 mmHg)

One study that followed participants for 18 months reported on hypertension prevalence (risk ratio (RR) 0.97, 95% CI 0.90 to 1.03, 2566 participants, 1 RCT, *low* certainty evidence), with 725 participants in the LSSS group and 738 participants in the regular-salt group having prevalent hypertension at the end of the study. AE for this outcome was 1741 fewer per 100 000 persons (95% CI 5802 fewer to 1741 more). The stepped-wedge cluster trial (unclear overall risk of bias) reported on incident hypertension in 1914 participants represented by 2712.3 person-years at risk in the LSSS group and 1961.1 person-years at risk in the regular-salt group, and found a reduction in hypertension with LSSS compared to regular salt (hazard ratio (HR) 0.45, 95% CI 0.31 to 0.65).

Blood pressure control[17]

Two small studies reported on this outcome (RR 2.12, 95% CI 1.32 to 3.41, I^2 = 0%, 253 participants, 2 RCTs, *very low* certainty evidence). AE for blood pressure control was 14 316 more per 100 000 persons (95% CI 4090 more to 30 805 more). The two trials reporting this outcome had follow-up at 8 weeks and 3 months.

Cardiovascular events: various

For the five trials reporting this outcome, very few participants from either group presented with various other cardiovascular events (e.g. angina, cardiovascular symptoms). Event numbers ranged from zero to eight with LSSS and from zero to five with regular salt. The meta-analysis of the RR was 1.22 (95% CI 0.49 to 3.04, I^2 = 0%, 982 participants, 5 RCTs, *very low* certainty evidence) when comparing LSSS and regular salt. AE for various other cardiovascular events was 357 more per 100 000 persons (95% CI 828 fewer to 3310 more). Two trials reporting this outcome had follow-up at ≤3 months, while three followed participants for 3 to 12 months.

Cardiovascular events: non-fatal stroke

The meta-analysis combining data from three trials resulted in an RR of 0.90 (95% CI 0.80 to 1.01, I^2 = 0%, 21 250 participants, 3 RCTs, *moderate* certainty evidence) when comparing LSSS with regular salt. This result translates to an AE for non-fatal stroke of 20 fewer per 100 000 persons (95% CI 40 fewer to 2 more). Sensitivity analyses, including only trials with low or unclear overall risk of bias and including only trials randomizing participants at the individual level – that is, excluding cluster-RCTs – did not reflect this benefit of LSSS; instead they showed highly imprecise results indicating little to no effect, or harm. The pooled effect was driven by a large secondary prevention trial including a large proportion of participants with previous stroke. The evidence was consequently downgraded once for indirectness as results could not readily be generalized to the wider adult population.

Cardiovascular events: non-fatal acute coronary syndrome

The single large cluster-RCT contributed data to this outcome at a mean follow-up time of 4.75 years, reporting rates of 3.79 events per 1000 person-years in the LSSS group and 5.12 events per 1000 person-years in the regular-salt group. The rate ratio was 0.70 (95% CI 0.52 to 0.94, 20 995 participants, one RCT, *moderate* certainty evidence) and AE for non-fatal acute coronary syndrome was 150 fewer per 100 000 person-years (95% CI 250 fewer to 30 fewer), when comparing LSSS with regular salt in this large secondary prevention trial in which most of the participants had a history of previous stroke. Results of this trial could not readily be generalized to the wider adult population, and the evidence was consequently downgraded once for indirectness.

Cardiovascular mortality

The number of cardiovascular mortality events per 1000 person-years in the three trials reporting on this outcome ranged from 4.53 to 22.94 in the LSSS groups and 7.81 to 26.30 in the regular-salt groups. The meta-analysis comparing LSSS with regular salt resulted in a rate ratio of 0.77 (95% CI 0.60 to 1.00, I^2 = 35%, 23 200 participants, three RCTs, *moderate* certainty evidence). AE for cardiovascular mortality was 180 fewer per 100 000 person-years (95% CI 310 fewer to 0 fewer). A sensitivity analysis including only

[17] Achieving blood pressure threshold or "control" as prespecified by study authors.

trials with low or unclear overall risk of bias confirmed this effect. The pooled effect was driven by the large secondary prevention trial including a large proportion of participants with previous stroke. The evidence was consequently downgraded once for indirectness as results could not readily be generalized to the wider adult population.

Stroke mortality

The number of stroke mortality events per 1000 person-years in the two trials reporting on this outcome ranged from 2.01 to 6.78 in the LSSS groups and 5.85 to 8.79 in the regular-salt groups. The meta-analysis comparing LSSS with regular salt resulted in a rate ratio 0.64 (95% CI 0.33 to 1.25, I^2 = 45%, 21 423 participants, two RCTs, *very low* certainty evidence). AE for stroke mortality was 145 fewer per 100 000 person-years (95% CI 270 fewer to 100 more). The pooled effect was driven to a considerable extent by the large secondary prevention trial including a large proportion of participants with previous stroke. The evidence was consequently downgraded once for indirectness as results could not readily be generalized to the wider adult population.

Change in blood potassium (mmol/L)

Average changes in blood potassium ranged from a reduction of 0.2 mmol/L to an increase of 0.38 mmol/L with LSSS and from a reduction of 0.2 mmol/L to an increase of 0.3 mmol/L with regular salt in the six trials that reported this outcome. The meta-analysis showed increases of blood potassium on average between LSSS and regular-salt groups (MD 0.12, 95% CI 0.07 to 0.18, I^2 = 0%, 784 participants, six RCTs, *moderate* certainty evidence). This effect was confirmed by sensitivity analyses, including only trials with low or unclear overall risk of bias and including only trials randomizing participants at the individual level – that is, excluding cluster-RCTs. Subgrouping participants by risk of hyperkalaemia suggests there may be no differences in average effects between participants not at risk, at unclear risk and at possible risk of hyperkalaemia. The trials reporting on this outcome reported results at 56 days, 5 weeks, 12 weeks and between 1 and 1.5 years each, while two trials reported results at approximately 6 months.

Hyperkalaemia

A very small number of participants presented with hyperkalaemia in both groups across the trials that reported this outcome. The number of participants with hyperkalaemia in the five trials reporting this outcome ranged from zero to 11 with LSSS and from zero to nine with regular salt. From the meta-analysis, RR was 1.04 (95% CI 0.46 to 2.38, I^2 = 0%, 22 849 participants, five RCTs, *moderate* certainty evidence) when comparing LSSS to regular salt. AE for hyperkalaemia was 4 more per 100 000 persons (95% CI 47 fewer to 121 more). A sensitivity analysis including only trials with low or unclear overall risk of bias confirmed this effect, though this result was highly imprecise. A sensitivity analysis including only trials randomizing participants at the individual level – that is, excluding cluster-RCTs – was not informative due to zero events in both trial arms. Subgrouping participants by risk of hyperkalaemia suggests there may be no differences in average effects between participants not at risk, at unclear risk and at possible risk of hyperkalaemia. These five trials reported results after 3 months, 12 months, 1 to 1.5 years, 2 years and a mean of 4.75 years follow-up.

Hypokalaemia

A single small trial reported no hypokalaemia events in either trial arm comparing LSSS and regular salt in young participants with hypertension requiring potassium supplementation due to the use of potassium-depleting diuretics (RR and 95% CI not estimable, 22 participants, one RCT, *very low* certainty evidence). This study reported outcomes at 12 weeks.

Secondary outcomes for adults

Adverse events: other

The number of participants with other adverse events in the eight trials reporting this outcome ranged from zero to 17 with LSSS and from zero to seven with regular salt. The events reported were highly diverse and not suitable for pooling in a meta-analysis (2109 participants, eight RCTs, *very low* certainty evidence). The reported events include influenza, dorsalgia, fever, nephrosis, nephritis, appendicitis, respiratory symp-

toms, abdominal/intestinal symptoms, and unspecified serious adverse events. Subgrouping participants by risk of hyperkalaemia suggests there may be no important clinical differences in average effects between participants not at risk, and those at possible risk, of hyperkalaemia. Four trials reporting on other adverse events reported these at ≤3 months, three reported on this outcome at 3 to 12 months and one trial reported other adverse events at >12 months.

Change in 24 h urinary sodium excretion (mmol/24 h)

Eleven trials reported on change in 24 h urinary sodium excretion. Average changes in this outcome ranged from a reduction of 75.5 mmol (1730 mg) sodium/24 h to an increase of 20.2 mmol (460 mg) sodium/24 h with LSSS and from a reduction of 31 mmol (710 mg) sodium/24 h to an increase of 11 mmol (250 mg) sodium/24 h with regular salt across the trials. Three trials reporting on this outcome followed up participants for 4, 5 and 8 weeks; five trials followed up participants for 3, 4, 9, 18 and 60 months each; three trials reported on the outcome at approximately 6 months. The meta-analysis of the effect of LSSS compared to regular salt or no intervention on 24 h sodium excretion showed considerable heterogeneity. Despite the considerable heterogeneity, the pooled mean difference of the 11 RCTs indicated that use of LSSS resulted in a decrease in 24 h sodium excretion on average (MD −19.98 mmol [−459 mg] sodium/24 h, 95% CI −35.90 to −4.06 mmol/24 h [−825 to −93 mg/24 h], I^2 = 91%, 3885 participants, 11 RCTs).[18] Subgrouping by baseline 24 h urinary sodium excretion did not suggest differences in the average effects of LSSS on change in DBP or change in SBP between subgroups.

Change in 24 h urinary potassium excretion (mmol/24 h)

Eleven trials reported on change in 24 h urinary potassium excretion. Three trials reporting on the outcome followed up participants for 4, 5, and 8 weeks, five trials followed up participants for 3, 4, 9, 18 and 60 months each; three trials reported on the outcome at approximately 6 months. The pooled effect indicated that use of LSSS resulted in an increase in 24 h potassium excretion on average (MD 11.44 mmol [450 mg] potassium/24 h, 95% CI 7.62 to 15.26 mmol/24 h [298 to 597 mg/24 h], I^2 = 82%, 3885 participants, 11 RCTs). Subgrouping by baseline 24 h urinary sodium excretion, the baseline 24 h urinary potassium excretion, study duration and participants characteristics did not suggest differences in the average effects of LSSS on change in DBP and change in SBP between subgroups.

CHILDREN

Evidence for the effects of LSSS use in children was much more limited than that identified for adults. A single RCT randomizing families as clusters and reporting on 92 children was included in this comparison.

Primary outcomes for children

No studies reported on hypertension, blood pressure control, change in blood potassium, hyperkalaemia or hypokalaemia for children (**Table 3**). GRADE assessments for each outcome can be found in **Annex 6**.

Table 3. LSSS intervention compared to regular salt in children (2 to 18 years)

Outcome	Anticipated absolute effects (95% CI)		Risk difference (95% CI)	No. studies	No. participants	Certainty (GRADE)
	Risk with regular salt	Risk with LSSS intervention				
Change in DBP	Mean change −5.87 mmHg	Mean change −2.1 mmHg	MD 1.28 mmHg higher (1.56 lower to 4.12 higher)	1 RCT	92	*Very low*
Change in SBP	Mean change −6.05 mmHg	Mean change −5.1 mmHg	MD 0.12 mmHg higher (4.41 lower to 4.64 higher)	1 RCT	92	*Very low*

[18] The pooled effect was not included in the published systematic review because of the I^2 threshold required by the review protocol. However, it was presented to the Nutrition Guidance Expert Advisory Group to aid assessing the pooled effect and summary statistics. The urinary sodium and potassium outcomes were not GRADED; thus, the finding is not presented with certainty assessment.

Change in diastolic blood pressure (DBP, mmHg)

The average change in DBP was a reduction of 2.1 mmHg in the group that ate bread containing LSSS and a reduction of 5.87 mmHg in the group that ate bread containing regular salt for the single cluster-RCT that reported this outcome at 4 months follow-up. MD when comparing these groups was 1.28 mmHg (95% CI −1.56 to 4.12, 92 participants, one RCT, *very low* certainty evidence).

Change in systolic blood pressure (SBP, mmHg)

The average change in SBP was a reduction of 5.1 mmHg in the group that ate bread containing LSSS and a reduction of 6.05 mmHg in the group that ate bread containing regular salt for the single cluster-RCT that reported this outcome at 4 months follow-up. MD when comparing these groups was 0.12 mmHg (95% CI −4.41 to 4.64, 92 participants, one RCT, *very low* certainty evidence).

Secondary outcomes for children

Change in 24 h urinary sodium excretion (mmol/24 h)

The average change in 24 h urinary sodium excretion was an increase of 11.4 mmol (262 mg) sodium/24 h in the group that ate bread containing LSSS and a reduction of 3.2 mmol (74 mg) sodium/24 h in the group that ate bread containing regular salt for the single cluster-RCT that reported this outcome at 4 months follow-up. MD when comparing these groups was 14.60 mmol (336 mg) sodium/24 h (95% CI −11.22 to 40.42 mmol/24 h or −258 to 929 mg/24 h, 92 participants, one RCT).

Change in 24 h urinary potassium excretion (mmol/24 h)

The average change in 24 h urinary potassium excretion was a reduction of 1.6 mmol (64 mg) potassium/24 h in the group that ate bread containing LSSS and a reduction of 5.7 mmol (223 mg) potassium/24 h in the group that ate bread containing regular salt for the single cluster-RCT that reported this outcome at 4 months follow-up. MD when comparing these groups was 4.10 mmol (160 mg) potassium/24 h (95% CI −5.13 to 13.33 mmol/24 h or −201 to 521 mg/24 h, 92 participants, one RCT).

Pregnant women

No eligible studies of pregnant women were found.

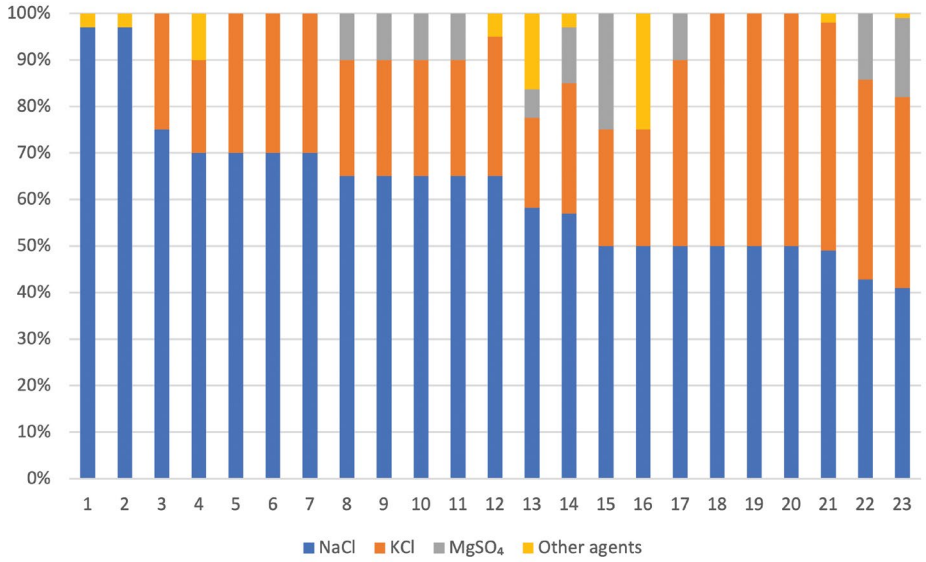
Interpreting the evidence

Several observations were made in interpreting the results of the systematic review, some based directly on data from the review, and others supported by background questions and information that helped to establish the context for the recommendation *(17)*. They are summarized below.

1. Varied types of LSSS were used in the RCTs

The majority of trials included in the systematic review (23 of 26) investigated the effects of LSSS that contain potassium. Since firm conclusions could not be drawn about the effects and safety of LSSS that do not replace sodium with potassium, the recommendation in this guideline applies to LSSS that contain KCl. Effectiveness and safety might be expected to vary depending on the composition of the LSSS used. NaCl and KCl contents of LSSS that contain potassium ranged from 41% to 75% and from 19% to 50%, respectively. Subgrouping by the type of LSSS was conducted for a number of outcomes based on proportion of KCl: ≥30% KCl versus <30% KCl versus unknown versus potassium-free LSSS. The subgroup analyses suggested no differences in average effects, although findings from the subgroup analyses in this systematic review may not all be sufficiently robust and should be interpreted with caution. In the review, subgroup analyses were often limited by very few studies or participants contributing information to certain subgroups. Some studies indicate that the blood-pressure-lowering effect of LSSS is partly due to potassium content *(3)*. In addition to NaCl and KCl, LSSS used in the trials had various other agents, such as magnesium and calcium (See **Fig. 1**).

Fig. 1. Composition of LSSS used in the RCTs included in the systematic review



Note: Other agents included calcium, chitosan, folic acid, iodine, lysine and potassium citrate. One study that assessed LSSS use in bread and three studies with unknown KCl content are not included in the figure. One study appears twice in the figure above because it included two LSSS intervention arms (#18 and #22).

2. Generalizability of the evidence on safety to people at risk of high blood potassium

The systematic review found no meaningful increase in hyperkalaemia with LSSS when compared to regular salt, with little or no difference in effect for this important safety outcome at maximal follow-up of 5 years. It should be noted, however, that the evidence on hyperkalaemia presented in the review has several limitations. Very few studies reported on this important safety outcome, and studies that did report on hyperkalaemia also used variable, in some cases unclear, criteria to define the condition. Other potassium-related measures were not rigorously collected and reported. Therefore, the information on hyperkalaemia events and other potassium-related measures was unreliable. Most studies included in the review also had strict inclusion and exclusion criteria with regard to risk factors for hyperkalaemia. All included trials specifically excluded participants in whom an increased intake of potassium could cause harm – for example, people with kidney disease, impaired renal function or those using potassium-sparing medications. Only seven trials included participants judged to be at possible risk of hyperkalaemia, and four trials included participants at unclear risk of hyperkalaemia (unclear mostly because of limited reporting of the criteria assessed). Only five trials reported on this outcome, two including participants judged to be at possible risk and one including participants at unclear risk, and all information included in the meta-analysis of the systematic review came from participants judged to be at possible or unclear risk of hyperkalaemia. There was a discussion about whether the hyperkalaemia outcome should be downgraded for indirectness because the study populations have been screened and were therefore not at especially high risk of hyperkalaemia. In 75% of the trials, more than 50% of participants were hypertensive, and therefore the participants may be at moderate risk of hyperkalaemia. No downgrading for indirectness was applied for the hyperkalaemia outcome.

Finally, it should be noted that most studies that assessed safety were of limited duration and did not provide evidence of long-term safety.

Caution should be taken when applying these results directly to the general population, which is likely to include people for whom an increased intake of potassium could cause harm, and to settings where a considerable proportion of the population may have undiagnosed conditions such that increased potassium intake is potentially harmful.

3. Interpretation of the increase in blood potassium

Assignment to use LSSS instead of regular salt led to a mean increase of 0.12 mmol/L (95% CI 0.07 to 0.18) in blood potassium. To understand the clinical significance of this increase, indirect evidence exists from a

systematic review and meta-analysis of RCTs that evaluated the effect on circulating potassium and renal function of increasing potassium intake with supplements *(19)*. The reviewed trials did not include people or patients with renal impairment. The study showed that a short-term moderate increase in potassium intake using supplements (average 45 mmol or 1755 mg/day; range 22–140 mmol or 858–5460 mg/day) caused an increase in circulating potassium levels of 0.14 mmol/L (95% CI 0.09 to 0.19). This is comparable to that observed in the LSSS trials. The study also showed that potassium supplements did not seem to cause severe hyperkalaemia or deterioration in renal function in healthy people and patients whose kidney function is not impaired.

4. Lack of evidence for people without high baseline cardiovascular risk

The body of evidence involved trials that mainly restricted participants to those at high baseline cardiovascular risk, most of whom had elevated blood pressure at enrolment. Studies included only participants with hypertension (11 of 26), normal blood pressure (1 of 26), pre-hypertension (1 of 26), or included a mix of participants with and without hypertension (11 of 26). This information was unrecorded in the remaining studies (2 of 26). The largest study included only participants with an elevated risk of stroke at baseline. Due to limited data on adults without elevated blood pressure, the effect modification by hypertension status on the relationship between LSSS use and outcomes could not be reliably evaluated.

5. Generalizability of the evidence on non-discretionary use of LSSS

Most included trials investigated the implementation of LSSS as a discretionary intervention (i.e. replacement for regular table salt), which restricted the generalizability of the findings to discretionary LSSS implementation. Therefore, NUGAG was unable to draw firm conclusions about non-discretionary LSSS implementations such as their use in manufactured foods and foods sold in restaurants and other out-of-home settings. It was not possible to extrapolate the findings on discretionary LSSS use to non-discretionary use because the impacts on effectiveness and safety may vary depending on the degree and range of salt substitution as well as intakes of such foods, for which data were very limited. Moreover, considerations for the contextual factors would also differ from those associated with discretionary use of LSSS. Furthermore, the contribution of discretionary salt to total sodium intake varies considerably across countries and settings *(20)*. Most of the included trials were conducted in China, where discretionary sources account for the majority of salt consumption. In contrast, in western countries, most salt intake comes from non-discretionary sources. This variation is an important consideration when decisions are made about the implementation of LSSS, because the absolute intakes of LSSS may vary across settings, potentially leading to variable impacts on both effectiveness and safety.

6. Children, pregnant women and household

No conclusion can be drawn about benefits and potential harms in children because there is only one trial in which children were exposed to LSSS-containing bread and outcomes were reported in children, and the results of this trial were imprecise. There is no evidence on benefits or potential harms for pregnant women. Therefore, the recommendation in this guideline does not apply to children and pregnant women.

If LSSS are used for cooking to prepare family meals, children in the home will consume LSSS. In some of the trials, the unit of allocation was the village or the household, but in these trials the exclusion criteria were applied to the whole household: if someone in the household had impaired renal function, then the household would not participate in the trial. In trials in which households were the unit of allocation, the outcomes were only measured in adults. Because of the exclusion criteria applied to the whole household, a household where there is anyone (including children and pregnant women) with kidney disease or otherwise at high risk of hyperkalaemia should not use LSSS. Therefore, if a member in a household (including children and pregnant women) is at risk for hyperkalaemia, LSSS should not be used to prepare a family meal to be eaten by the member.

7. Additional analyses of effects of LSSS on sodium and potassium excretion or intake

Additional analyses to be included in the systematic review were requested by the NUGAG Subgroup on Diet and Health in December 2021; they were:

- addition of 24 h urinary sodium excretion as an outcome;
- addition of 24 h urinary potassium excretion as an outcome;
- subgrouping of blood pressure outcomes based on baseline 24 h urinary excretion of sodium; and
- subgrouping of blood pressure outcomes based on baseline 24 h urinary excretion of potassium.

This information was considered necessary to understand the extent to which dietary sodium intake was reduced and potassium intake was increased by using LSSS, whether the LSSS intervention was acceptable to participants, and whether and how they actually used it. Despite the heterogeneity, nine of the 11 RCTs showed a reduction in 24 h sodium excretion on average, and the pooled MD and its 95% CI were all indicative of a reduction. The pooled effect indicated that use of LSSS resulted in an increase in 24 h potassium excretion on average. Subgrouping by baseline 24 h urinary sodium excretion and the baseline 24 h urinary potassium excretion did not suggest differences in the average effects of LSSS on change in DBP and change in SBP between subgroups. The effects observed in the RCTs were likely due to the combination of sodium reduction and potassium increase.

8. Additional analyses of studies published after the systematic review search date

It was raised during the public consultation that a cluster-RCT *(21)* was published after the search date (18 August 2021) of the systematic review *(2)*. This trial would have been eligible for inclusion in the systematic review. The crucial question was whether the new study would add data on safety in a significant manner, as the current evidence base notably lacks such data, and this lack contributes to the uncertainty about the balance between the benefits and potential harms. Additional analyses were conducted incorporating data for relevant primary outcomes reported by this study. Since there were no consequential changes to pooled effects or certainty of evidence on which the recommendation is based, the systematic review will not be formally updated for the guideline at this time (see section 'Updating the guideline').

Contextual review

In addition to the systematic review described in the previous section, a contextual factor narrative review was conducted *(18)*. The review looked at additional contextual factors related to the implementation of LSSS. Evidence for this process was gathered via comprehensive searches of relevant scientific databases and by identification of high-quality studies, including existing systematic reviews, when available. Evidence on the contextual factors is summarized in an evidence to recommendation table in **Annex 7**.

Briefly, findings of the contextual review are as follows:

- **Priority of the problem:** The global burden of disease ascribed to high blood pressure and CVDs is substantial.
- **Values and preferences:** Many studies, mainly in low- and middle-income countries, found that most people consider hypertension a serious disease with potential life-threatening consequences.
- **Resources implications:** Studies found that replacing regular salt in table salt and other foods with LSSS was cost-effective. But LSSS are 1.7 times more expensive than regular salt based on the median, noting that overall salt is a low-cost food commodity.
- **Equity and human rights:** Lower-income or less-educated individuals were less likely to use LSSS. Higher price of LSSS was also a barrier.
- **Acceptability:** Moderate uptake of LSSS was observed for discretionary use of LSSS.
- **Feasibility:** Implementation of LSSS would be feasible overall, but several potential barriers to wide-spread implementation of LSSS were identified. Main barriers for consumers include limited availability of LSSS, higher price, lack of awareness, bad taste and lack of perceived health benefit. The higher cost of LSSS and the concerns around the potentially increased risk of hyperkalaemia in those with kidney disease is a potential barrier preventing governments from promoting LSSS.

Evidence to recommendations

In translating the evidence into recommendations, the NUGAG Subgroup on Diet and Health assessed the evidence in the context of the certainty in the evidence, desirable and undesirable effects of the intervention, priority of the problem being addressed, values and preferences related to the health outcomes, resources required, cost–effectiveness, the potential impact on equity and human rights, acceptability, and feasibility of implementing the intervention in different settings. As the recommendation applies to the discretionary use of LSSS, the NUGAG Subgroup on Diet and Health made its decisions on the following factors in the context of implementing discretionary use of LSSS, rather than implementing LSSS use as a food additive in manufactured foods.

An evidence to recommendation table can be found in **Annex 7**.

Overall certainty in the evidence

The overall certainty in the evidence was considered *low*. This judgement is based on the certainty of evidence across the critical outcomes. This is with acknowledging that there is some evidence of benefit that was of *moderate* certainty.

Balance of desirable and undesirable effects

The NUGAG Subgroup on Diet and Health concluded that the balance between desirable and undesirable effects probably favours the intervention (i.e. LSSS use in comparison to not using LSSS), while noting uncertainty about the balance between the benefits and potential harms, especially in settings where a considerable proportion of the population may have undiagnosed kidney disease for which it would not be advisable to increase potassium intakes.

For desirable effects, NUGAG considered that the extent of the benefit varies by outcome, but that the effects would be considered small, which reflects the expected effects in the general population because the evidence relates mainly to participants at high cardiovascular risk (e.g. high blood pressure, history of stroke). Additionally, the evidence base relates to discretionary use and not to non-discretionary use as a food additive.

For undesirable effects, adverse events were very varied and therefore were not pooled in the systematic review. Very few studies reported on hyperkalaemia, and studies that did report on hyperkalaemia also used variable, in some cases unclear, criteria to define the condition. Other potassium-related measures presented in most of these studies were not rigorously collected and reported. Therefore, the information on hyperkalaemia events and other potassium-related measures was unreliable. Consequently, serum potassium was considered probably the most relevant outcome for safety. Considerations were that patients with overt kidney disease were excluded by the included trials, and that most studies that assessed safety were of limited duration and did not provide evidence of long-term safety. In addition, the undesirable effects may vary with access to health care. Overall, NUGAG concluded that the undesirable effects varied depending on the setting and population.

Priority of the problem

The global burden of disease attributable to high blood pressure and CVDs is substantial. In 2019, an estimated 828 million adults worldwide had hypertension (SBP >140 mmHg), and there were an estimated 523 million prevalent cases of CVDs, which had nearly doubled between 1990 and 2019. There were approximately 18.6 million deaths from CVDs, which was a marked increase since from 12.1 million in 1990 *(22)*. NUGAG concluded that the problem was a priority, while noting a large variation in disease burden due to hypertension and CVDs worldwide.

Values and preferences

NUGAG concluded that there is probably no important uncertainty about, or variability in, how much people value the main outcomes.

The studies showed that generally people felt high blood pressure and CVDs were serious conditions that affected quality of life. Many studies, mostly carried out in low- and middle-income countries, examined the beliefs that people hold towards hypertension and CVDs. Most people believed hypertension is a serious disease that leads to stroke, heart attack and death *(23–30)*. People also viewed hypertension as a "silent killer" *(31, 32)* that can kill suddenly *(23, 33–35)*. Some people described how hypertension and CVDs could affect quality of life *(24, 31, 36)*; however, in several studies, the authors reported that some participants felt unaffected by hypertension, especially if it was well controlled with medication *(23, 24, 29-32, 37)*.

No studies that examined people's views on the importance of hyperkalaemia, hypokalaemia, or serum potassium were identified.

Feasibility

NUGAG concluded that the intervention is probably feasible to implement.

A systematic review identified 87 LSSS, about half of which are iodized *(38)*. At least one LSSS was available in 47 countries, and more than half of these were high-income countries. Implementation of LSSS must be in line with the country's iodization programme and the level of iodization must be adequately recalibrated. Stakeholders, including academics and government and industry representatives, recognize that limited availability and low market share of LSSS are barriers to widespread implementation of LSSS *(39)*. The price of LSSS is between 1.1 and 14.6 (median 1.7) times higher than the price of regular salt *(38)*. Studies in China among the general population have found that the main reasons people do not use LSSS for discretionary use are lack of awareness, bad taste, cost, difficulty in purchasing, and lack of perceived health benefits *(40, 41)*. The higher cost of LSSS is also a barrier for industry *(39)* and governments *(42, 43)*, as are concerns around the potentially increased risk of hyperkalaemia in those with kidney disease *(39, 44, 45)*. The higher cost of LSSS and the concerns about the potentially increased risk of hyperkalaemia in those with kidney disease is a potential barrier preventing governments from promoting LSSS.

It has also been acknowledged that the use of LSSS will not reduce consumer preference for salty tastes *(45, 46)*. Furthermore, it is uncertain whether promotion of LSSS will automatically reduce sodium intakes *(39)*, with the results of several trials indicating that participants consumed more of the LSSS that contain potassium and therefore sodium intakes either were unchanged *(47, 48)*, or decreased by less than expected, while potassium intakes increased. Industry has signalled that it would like to use salt substitutes that contain potassium, especially for products for which it believes it is challenging to reduce sodium without compromising acceptability *(42)*. One barrier for industry has been labelling requirements; industry prefers to use the term "potassium salt" for potassium chloride on food labels *(49, 50)* and this term is now allowed in the USA *(51)*.

Acceptability

NUGAG judged that LSSS use would probably be acceptable to key stakeholders.

Potassium chloride, contained in most LSSS, has bitter and metallic tastes. Therefore, partial instead of full replacement of sodium chloride is typically used to minimize the off tastes associated with potassium chloride, with or without other agents. Studies showed good overall consumer acceptability for LSSS with up to about 30% of sodium chloride replaced with potassium chloride *(52–54)*.

There appears to have been moderate uptake of LSSS for discretionary use in China (about 23–37%) *(40, 41, 55)*. A study conducted in South Africa also confirmed a high level of acceptance *(43)*. Further, RCTs included in the systematic review showed overall good acceptance of the LSSS intervention by participants, as demonstrated by the results of 24 h urinary sodium and potassium excretion.

It is also noted, though, that the public might find the promotion of LSSS a confusing message, because the primary goal and the main public health messages thus far have been to reduce discretionary salt use. This is especially important for countries where discretionary use is a major source of sodium intake.

Equity and human rights

In China, using LSSS for discretionary salt has been encouraged since 2010, and studies have shown that there has been a differential uptake, with adults with lower levels of education or income less likely to use LSSS *(41, 55)*. The higher cost of LSSS may prevent some people from using them *(40, 52)*. Human rights treaties recognize the right of everyone to food that is sufficient, adequate and safe *(56)*.

While various economic status and health systems of countries could affect equity differently, the NUGAG Subgroup on Diet and Health concluded that health equity would probably be reduced.

Resources required

NUGAG concluded that resources required would vary based on country and context.

The costs would depend on the specific context in which discretionary use of LSSS is implemented. Proportion of sodium intake from discretionary use varies across different regions of the world. If a government makes a policy decision to encourage LSSS, particularly in countries where discretionary use of salt is a large source of sodium intake, there would be costs incurred in relation to LSSS use. They would arise from regulatory process such as programme management, health promotion and advocacy, trainings and meetings, mass media, office supplies and rents, law enforcement, monitoring of sodium and potassium intakes and the proportion of at-risk people in the population and the level of substitution of potassium in salt products, subsidies, as well as the additional cost of LSSS. LSSS are 1.7 times more expensive than regular salt based on the median, but overall salt is a low-cost food commodity. Approval of LSSS could require regulatory costs but in countries where LSSS are available, such costs are probably not high. If implementing, LSSS should be placed as part of sodium reduction strategy and its use must be aligned with country's fortification and iodization programmes if required.

Cost–effectiveness

NUGAG judged that using LSSS is probably cost-effective.

Four studies were identified that modelled the cost–effectiveness of implementing LSSS in a population. All four studies found that replacing regular salt in table salt (China) *(57)*, table salt and stock cubes (Cameroon) *(58)*, table salt, fish sauce and bot canh, a traditional condiment (Viet Nam) *(59)*, or table salt and manufactured food (New Zealand) *(60)* with LSSS was cost-effective. The models from China, Viet Nam and New Zealand probably underestimated the costs associated with the intervention; nevertheless, the estimated net cost savings were robust to various changes to the underlying model assumptions. In addition, the model from Cameroon *(58)*, which more fully costed the intervention, suggested that widespread implementation of LSSS is likely to be cost-effective. Similar health gains and cost savings were predicted from a mandatory 25% reduction of sodium (without replacement with LSSS) in all manufactured foods in New Zealand, and from a school-based education programme to reduce household sodium intakes in Cameroon.

Scope of the recommendation

The recommendation applies to discretionary use of LSSS, but does not apply to discretionary use of sodium-containing condiments (e.g. soy sauce and fish sauce) that are common discretionary food sources of sodium in some countries. The recommendation also does not apply to non-discretionary salt consumed as already present in manufactured foods and foods served at restaurants and other out-of-home settings. There was not enough evidence to substantiate such uses of LSSS to include them in the recommendation.

The recommendation in this guideline applies to LSSS in which NaCl is partially replaced with KCl. Most trials included in the systematic review (23 of 26 RCTs) investigated the effects of LSSS that replaced sodium with potassium.

The recommendation in this guideline is intended for adults in general populations. It excludes individuals with kidney impairments or with other circumstances or conditions that might compromise potassium excretion (e.g. those taking potassium-sparing diuretics and potassium supplements). The recommendation does not apply to children and pregnant women, because evidence was very uncertain or not found, and therefore it was not possible to draw a conclusion.

This guideline is not a clinical management guideline. Providing a recommendation on how to clinically manage and treat hypertension, kidney diseases and other conditions is beyond the scope of this guideline.

Recommendation and supporting information

Based on a review of the evidence on effects and safety, and consideration of additional contextual factors, WHO generated the following recommendation for LSSS use.

WHO recommendation

To reduce blood pressure and risk of cardiovascular diseases, WHO has recommended reducing sodium intake to less than 2 g/day (*strong* recommendation).[19] In this context, using less regular table salt[20] is an important part of an overall sodium reduction strategy. If choosing to use table salt, WHO suggests replacing regular table salt with lower-sodium salt substitutes that contain potassium (*conditional* recommendation).[21] This recommendation is intended for adults (not pregnant women or children) in general populations, excluding individuals with kidney impairments or with other circumstances or conditions that might compromise potassium excretion.

This recommendation about LSSS should be aligned with the current WHO recommendations on sodium intake *(1)*:

- WHO recommends a reduction in sodium intake to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults (*strong* recommendation). WHO recommends a reduction to <2 g/day sodium (5 g/day salt) in adults (*strong* recommendation).
- WHO recommends a reduction in sodium intake to control blood pressure in children (*strong* recommendation). The recommended maximum level of intake of 2 g/day sodium (5 g/day salt) in adults should be adjusted downward based on the energy requirements of children relative to those of adults.

Reduction of discretionary salt intake constitutes a critical part of an overall sodium reduction strategy, especially in individuals for whom discretionary salt use is a major source of sodium intake. Importantly, the use of LSSS is only one of many means in an overall strategy to reduce sodium intake *(61)*.[22]

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[19] *Strong* recommendations are those for which the WHO guideline development group is confident that the desirable consequences of implementing the recommendation will outweigh the undesirable consequences in nearly all circumstances and can be adopted as practice or policy in most situations.

[20] "Regular salt" or "table salt" in this guideline refers to food-grade salt as defined by the Codex standard 150-1995: Standard for food grade salt. Regular table salt is regular salt that an individual adds to foods during food preparation or when eating.

[21] *Conditional* recommendations are those recommendations for which the WHO guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences generally or in certain settings or when the anticipated net benefits are very small. Therefore, discussion may be required, including about setting-specific issues, before a *conditional* recommendation can be adopted as policy and appropriately implemented.

[22] Resolution WHA76(9) *(62)* endorsed the updated menu of policy options and cost-effective interventions for reducing salt intake, such as: i) reformulation of food products to contain less salt and the setting of target levels for the amount of salt in foods and meals; ii) implementation of front-of-pack labelling and other interpretive nutrition labelling; iii) establishment of a supportive environment in public institutions such as hospitals, schools, workplaces and nursing homes, to enable lower-sodium options to be provided; iv) a behaviour change communication and mass media campaign for healthy diets; and v) implementing policies to protect children from the impact of food marketing. SHAKE Technical Package for Salt Reduction presents a suite of action menus, which is currently being updated *(8)*. WHO released the second edition of the WHO global sodium benchmarks for different food categories in 2024 to assist countries set national sodium targets to reduce the sodium content of manufactured foods *(9)*.

Rationale and remarks

The following provides the reasoning behind the formulation of the recommendation (i.e. rationale) as well as remarks designed to provide context for the recommendation and facilitate its interpretation and implementation. Details of the levels of certainty can be found in the GRADE table in **Annex 6**.

Rationale

- This recommendation is based on evidence of *moderate*-to-*low* certainty (an assessment of *low* certainty overall according to GRADE guidance when considering findings across all outcomes of interest) from a systematic review *(2)* that assessed the effects and safety of using LSSS[23] compared to regular salt or no intervention. The prioritized outcomes of interest were effects on blood pressure, serum potassium (hyperkalaemia, hypokalaemia), stroke and cardiovascular events and mortality.
- The recommendation to use LSSS is based on findings from 26 RCTs in adults in which assignment to LSSS compared to regular salt resulted in reductions in DBP and SBP over 56 days to 5 years of follow-up. The mean reduction was 2.43 mmHg (95% CI 3.50 lower to 1.36 lower) for DBP and 4.76 mmHg (95% CI 6.01 lower to 3.50 lower) for SBP (*moderate* certainty evidence). The use of LSSS when compared to regular salt showed reductions in risks of non-fatal stroke (risk ratio 0.90 [95% CI 0.80 to 1.01]; AE 20 fewer per 100 000 persons [95% CI 40 fewer to 2 more]), non-fatal acute coronary syndrome (rate ratio 0.70 [95% CI 0.52 to 0.94]; AE 150 fewer per 100 000 person-years [95% CI 250 fewer to 30 fewer]) and cardiovascular death (rate ratio 0.77 [95% CI 0.66 to 1.00]; AE 180 fewer per 100 000 person-years [95% CI 310 fewer to 0 fewer]) (*moderate* certainty evidence).
- The meta-analysis of the effect of LSSS compared to regular salt or no intervention on 24 h sodium excretion showed considerable heterogeneity. Despite the considerable heterogeneity, the pooled mean difference (−19.98 mmol [−459 mg] sodium/24 h, 95% CI −35.90 to −4.06 mmol/24 h [−825 to −93 mg/24 h], I^2 = 91%)[24] were indicative of a reduction in 24 h sodium excretion on average. There was also substantial heterogeneity in the size of the effects of LSSS on 24 h potassium excretion. The pooled mean difference (11.44 mmol [450 mg] potassium/24 h, 95% CI 7.62 to 15.26 mmol/24 h [298 to 597 mg/24 h], I^2 = 82%) indicated that use of LSSS resulted in an increase in 24 h potassium excretion on average. Subgrouping by baseline 24 h urinary sodium excretion and the baseline 24 h urinary potassium excretion did not suggest important differences in the average effects of LSSS on change in DBP and change in SBP between subgroups.
- All studies in the review excluded people for whom increased potassium intake would not be advisable (e.g. those with kidney disease, those taking potassium-sparing diuretics or potassium supplements). Therefore, relevance to general populations that might include people with kidney impairments or with other circumstances or conditions that might compromise potassium excretion was uncertain. Additionally, some of the trials also excluded people with type 1 or 2 diabetes mellitus.
- In these studies, assignment to use LSSS instead of regular salt led to a mean increase of 0.12 mmol/L (95% CI 0.07 higher to 0.18 higher) in the level of potassium in the blood (*moderate* certainty evidence). LSSS compared to regular salt resulted in little to no difference in hyperkalaemia (*moderate* certainty evidence). Very few studies reported on hyperkalaemia and studies that did report on hyperkalaemia also used variable, in some cases unclear, criteria to define the condition. Other potassium-related measures presented in most of these studies were not rigorously collected and reported. Therefore, the information on hyperkalaemia events and other potassium-related measures was unreliable.

[23] LSSS interventions of any type or duration were included in the systematic review, provided they aimed to replace the dietary intake of any amount of sodium with another mineral or compound although the majority of trials included in the systematic review (23 of 26 RCTs) investigated the effects of LSSS that replaced sodium with potassium.

[24] The pooled effect was not included in the published systematic review due to the I^2 threshold according to the review protocol, but was presented to NUGAG for the purposes of assessing the pooled effect and summary statistics.

- The recommendation was assessed as *conditional* because the overall certainty of evidence was *low* according to the GRADE guidance and there was uncertainty about the balance between the benefits and potential harms, especially in settings where a considerable proportion of the population may have undiagnosed conditions for which it would not be advisable to increase potassium intakes (e.g. some low-resource settings).

Remarks

- Reducing sodium intake from both discretionary and non-discretionary use is the preferred strategy for health benefits. LSSS still contain sodium; therefore, to reduce sodium intake, the amount of sodium obtained from LSSS should be less than the amount of sodium that would have been obtained from the regular salt they replace.
- LSSS interventions of any type or duration were included in the systematic review, provided they aimed to replace the dietary intake of any amount of sodium with another mineral or compound. The recommendation statement refers to LSSS that contain potassium because most trials included in the systematic review (23 of 26 RCTs) investigated the effects of LSSS that replaced sodium with potassium, whose NaCl and KCl contents ranged from 41 to 75 % and from 19 to 50%, respectively. In addition, the blood-pressure-lowering effect of LSSS is partly due to potassium content *(3)*; however, the percentage of KCl in the LSSS did not modify the effect in the systematic review.
- This recommendation, which applies to LSSS containing KCl, should be considered in the context of the other WHO recommendations related to potassium intake. WHO recommends consuming foods that naturally contain potassium (such as beans and peas, nuts and green vegetables) as part of a healthy diet. These foods have other nutritional benefits and should be the primary sources of dietary potassium when seeking to increase intake *(1)*.
- This recommendation is for adults in general populations, and excludes individuals with kidney impairments or with other circumstances or conditions that might compromise potassium excretion (e.g. those taking potassium-sparing diuretics or potassium supplements). In some low-resource settings, a considerable proportion of the population may not be aware of having these conditions, and there may be individuals with undiagnosed kidney disease for whom higher potassium intakes over the long term might be of concern, and might require medical supervision and periodic assessment over time. Therefore, the use of LSSS should be implemented in settings with adequate access to health care, where conditions in which increased potassium intakes are potentially harmful (e.g. kidney disease) would not go undiagnosed for a long time. It should be noted that this guideline is not a clinical management guideline. Providing recommendations on how to clinically manage and treat hypertension, kidney diseases and other conditions is beyond the scope of this guideline.
- Discretionary salt in this recommendation is defined as salt that an individual adds to foods during cooking or when eating. It is commonly known as regular salt or table salt. This recommendation applies to discretionary use of LSSS.
- Non-discretionary salt is consumed as already present in manufactured foods and foods served at restaurants and other out-of-home settings. This recommendation does not apply to consumption of LSSS used in manufactured food products or foods sold by markets, restaurants, cafeterias and street vendors. It should also be noted that consumption of LSSS used in sodium-containing condiments, such as soy sauce and fish sauce, which are common discretionary food sources of sodium in some countries, are not included in the scope of the recommendation. There was not enough evidence on the non-discretionary consumption of LSSS (e.g. from manufactured foods) or on condiments to include them in the recommendation. However, as LSSS are increasingly used in manufactured foods and foods consumed away from home, this will alter the baseline

to which discretionary LSSS are added. Such changes must be monitored at the population level to estimate total sodium and potassium intake from both discretionary and non-discretionary sources.

- There was a paucity of data for children, and no studies in children examined discretionary use of LSSS. One RCT conducted in children reported that the non-discretionary use of LSSS in bread showed little to no effect on blood pressure, but the evidence is very uncertain (*very low* certainty evidence). No studies involving pregnant women were found. Therefore, no conclusions can be drawn for children and pregnant women, and this recommendation does not apply to children and pregnant women. However, if a member in a household (including children and pregnant women) is at risk for hyperkalaemia, LSSS should not be used to prepare a family meal to be eaten by the member.
- Currently, just under half of the LSSS available globally are iodized. Action is required to ensure iodization of LSSS in order to align with national policies on salt iodization.

Uptake of the guideline and future work

Dissemination

The guideline will be disseminated through:

- the WHO e-Library of Evidence for Nutrition Actions *(63)*, which is an online library of evidence-informed guidance for nutrition interventions that provides policy-makers, programme managers, health workers, partners, stakeholders and other interested actors with access to the latest nutrition guidelines and recommendations, as well as complementary documents, such as systematic reviews, and biological, behavioural and contextual rationales for the effectiveness of nutrition actions;
- relevant nutrition webpages on the WHO website, including a summary of the guideline in all six official WHO languages;
- the electronic mailing lists of the WHO Department of Nutrition and Food Safety, and the UN Standing Committee on Nutrition;
- the network of the six WHO regional offices and country offices; and
- the WHO collaborating centres.

The guideline will also be disseminated at various related WHO meetings, as well as at global and regional scientific meetings.

Translation and implementation

The recommendation in this guideline can be used by policy-makers, programme managers, health professionals and other stakeholders in their efforts to promote reduction of sodium intake and reduce the risk of hypertension and related NCDs through a range of public health policy actions and intervention programmes. Efforts should be targeted to the general population.

The recommendation in this guideline should be used in conjunction with other WHO guidance on healthy diets – in particular, guidelines relating to sodium *(1)* and potassium *(15)*, as well as free sugars *(64)*, total fat *(65)*, saturated fatty acid and *trans*-fatty acids *(66)* and carbohydrates *(67)* to guide effective policy actions and intervention programmes to promote healthy diets and nutrition, and prevent diet-related NCDs.

It is important for policy-makers and programme managers to keep in mind that reducing sodium intake from both discretionary and non-discretionary use is the preferred strategy. Further efforts are needed to lower the populations' sodium intakes to below 2 g/day.

As noted in the remarks section, the use of LSSS should be implemented in settings with adequate access to health care, where kidney disease would not go undiagnosed for a long time. The recommendation can be interpreted as "Implement the recommendation to use LSSS if safety considerations can be accounted for, and monitor carefully because of potential risks of hyperkalaemia or other indicators of impaired potassium excretion that would be contraindications to LSSS use."

It is challenging at the global level to define the settings or subpopulations where the conditions apply due to differences across countries in the way systems are set up. Conditionality gives each country the ability to assess their own situation, design and implement an adequate approach. This will require substantial discussion and involvement of various stakeholders.

Key considerations by policy-makers and programme managers when discussing the implementation of the recommendation on the LSSS use at a country level include:

- proportion of at-risk population; that is, people in the population with kidney disease or other conditions, for whom an elevated level of potassium intake should be avoided;
- demographics and trends of such at-risk populations in the country (e.g. age profile);
- access to health care (i.e. ability to detect and diagnose problems with kidney health);
- mode of use (e.g. discretionary or non-discretionary) and types of products used (e.g. table salt or manufactured foods);
- monitoring of the level of substitution of potassium in products, of sodium and potassium intakes, and of any change in the proportion of the population that is at risk;
- warning labels and health claims on products;
- consumer awareness/education on the risks and benefits of LSSS, training and meetings; and
- cost implications including higher prices of LSSS as well as costs incurred due to regulatory processes.

The recommendation applies to the discretionary use of LSSS, and therefore it is most relevant to countries where discretionary salt use is a major source of sodium intake. In populations where discretionary salt use is a small proportion of total sodium intake, measures related to discretionary LSSS will have less impact. In fact, for populations where discretionary salt use is already at very low levels, care should be taken so that consumers do not see LSSS guidance as implying that increasing their discretionary salt use with LSSS is more desirable than keeping discretionary salt use very low. Increasing discretionary salt use would increase sodium intakes. Meanwhile, some countries have already begun to implement or consider implementing the use of LSSS for non-discretionary use. This will alter the baseline to which discretionary LSSS are added. Such changes must be monitored at the population level to estimate total sodium and potassium intake from both discretionary and non-discretionary sources. For reference purposes, examples of approaches taken by some countries on the use of LSSS in manufactured foods, foods served at restaurants and other out-of-home settings and in condiments other than regular salt are provided in **Annex 8**. **Although such use of LSSS is beyond the scope of this guideline, the information is provided for reference purposes**.

WHO has been supporting Member States with their efforts to reduce sodium intake. In 2013, the World Health Assembly endorsed the updated menu of policy options and cost-effective interventions for reducing sodium intake, such as: i) reformulation of food products to contain less sodium and the setting of target levels for the amount of sodium in foods and meals; ii) implementation of front-of-pack labelling and other interpretive nutrition labelling; iii) establishment of a supportive environment in public institutions such as hospitals, schools, workplaces and nursing homes, to enable lower-sodium options to be provided; iv) a behaviour change communication and mass media campaign for healthy diets; and v) implementing policies to protect children from the impact of food marketing. WHO has been supporting countries to implement "Best buys and other recommended interventions for the prevention and control of noncommunicable diseases, second edition" *(61)*. To assist countries taking policy actions, WHO released the SHAKE Technical Package for Salt Reduction in 2016 *(8)*. The SHAKE Package is currently being updated to present a comprehensive action package for sodium reduction. Furthermore, WHO released the second edition of the WHO global sodium benchmarks for different food categories in April 2024 *(9)*, which serves as a guide for countries in setting national sodium targets to reduce the sodium content of manufactured foods.

Monitoring and evaluation

The impact of this guideline can be evaluated by assessing its adoption and adaptation across countries. Evaluation at the global level will be through the WHO Global database on the Implementation of Food and Nutrition Action (GIFNA)[25] – a centralized platform developed by the WHO Department of Nutrition and Food Safety for sharing information on food and nutrition actions in public health practice implemented around

[25] https://gifna.who.int/

the world. GIFNA currently contains information on thousands of policies (including laws and legislation), food and nutrition actions and programmes in more than 190 countries. GIFNA includes data and information from many sources, including the second *WHO global nutrition policy review* conducted in 2016–2017 *(68)*. By providing programmatic implementation details, specific country adaptations and lessons learned, GIFNA serves as a platform for monitoring and evaluating how guidelines are being translated into various policy actions and intervention programmes to address the issues related to sodium intake in various countries. Countries are encouraged to submit data with WHO to facilitate information and experience sharing.

Research gaps and future initiatives

Based on the results of the systematic review and discussions with the NUGAG Subgroup on Diet and Health, a number of questions and gaps in the current evidence that should be addressed by future research were identified. Further research is needed to achieve a better understanding of:

- the safety implications of widespread LSSS use (discretionary and non-discretionary) on explicitly defined measures of hyperkalaemia;
- how monitored trials that include participants who may be at risk of hyperkalaemia, and evidence from prospective cohort studies that include participants that are representative of the general population, can provide evidence that is more generalizable to widespread population-level LSSS implementation;
- the effectiveness and safety of LSSS on a participant population that is representative of the general population such as normotensive people and people without history of CVD;
- the effectiveness and safety of LSSS in children and pregnant women;
- the impact of LSSS on hyponatraemia events, especially in older people and those using certain classes of medication used to treat hypertension;
- whether LSSS use sustainably decreases overall sodium intake, or whether it results in dietary compensation through behavioural modifications; such as, for example, an increased sodium intake from non-discretionary salt use;
- data on the extent to which LSSS use reduces sodium intake, and increases potassium intake (when LSSS that contain potassium are used) over the longer term, using reliable measures of dietary sodium and potassium intake, such as 24 h urinary excretion;
- evidence on the use of LSSS in manufactured foods as well as in sauces and condiments, and the implications for guidance on total potassium intake;
- evidence on the use of LSSS in people with relatively low baseline sodium intakes;
- evidence on the use of other types of LSSS (e.g. LSSS that do not contain potassium);
- assessment of sodium intake in populations, and the level and extent of iodization in LSSS, to help countries recalibrate iodization levels in salt in the context of increased LSSS use;
- the effectiveness of multicomponent, multisectoral strategies that include LSSS to further inform decision-making to reduce sodium intake and CVD risk; and
- evidence on the resource implications of LSSS use to inform considerations related to population-level implementation.

Updating the guideline

WHO regularly updates its guidelines and recommendations to reflect the latest scientific and medical knowledge. This guideline will therefore be updated as part of the ongoing efforts of WHO to update existing dietary goals and nutrition guidance for promoting healthy diets, nutrition and the prevention of NCDs. Because the evidence base for LSSS use is rapidly evolving, the literature will be monitored on a regular basis. It is planned that the recommendation in this guideline will be reviewed when new data and information become available that might alter the overall body of evidence such that re-evaluation is needed. The WHO Department of Nutrition and Food Safety, together with partners in other departments

within the WHO Secretariat, will be responsible for coordinating the updating of this guideline, following the formal procedure described in the *WHO handbook for guideline development (17)*. At the time the guideline is due for review, WHO will welcome suggestions for additional questions that could be addressed in a potential update of the guideline.

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Annexes

Annex 1.
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Annex 4.
Summary and management of declarations of interests

Members of the guideline development group (NUGAG Subgroup on Diet and Health)

Interests declared or otherwise identified independently for the following members during the development of this guideline are summarized below.

Member	Interests declared/identified	Action taken
Mary L'Abbé	▶ Iodine Global Network: Member, Board of Directors (2020–2021) ▶ WHO: Director, WHO Collaborating Centre on Nutrition Policy for NCD Prevention (2015–2021) ▶ PAHO: Chair, Pan American Health Organization of the WHO (PAHO) Technical Advisory Group (TAG) to Mobilize Cardiovascular Disease Prevention through Dietary Salt/Sodium Control Policies and Interventions (2015–2021) ▶ PAHO: Member/Chair PAHO consultation meetings for setting sodium reduction targets and other sodium related work) (2012–2021) ▶ Resolve to Save Lives, Vital Strategies: Technical adviser on trans-fats (2018–2019) ▶ Heart and Stroke Foundation of Canada: Member, Council on Mission: Priorities, Advice, Science and Strategy Advisory Panel (CoMPASS) (2013–2021) ▶ World Obesity, World Federation of Public Health Associations: Delegate representative to the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) and to Codex Committee on Food Labelling (CCFL) (2018–2021) ▶ National Nutrient Databank Conference (NNDC): Steering Committee member (2017–2021) ▶ Nestle Nutrition: External peer reviewer for two research proposals, attended peer-review meeting (2018) ▶ US *National Academies of Sciences, Engineering, and Medicine (NASEM)*: Member, NASEM Panel on Global Harmonization of DRIs (2017–2018) ▶ World Obesity: Member, Scientific and Technical Advisory Network (2014–2021) ▶ International Network for Food and Obesity/NCDs Research, Monitoring and Action Support (INFORMAS): Member, International Network for Food and Obesity/ NCD Research (2012–2021) ▶ Marketing to Kids Coalition: Member and Technical Adviser, Health Canada discussion on policy options regarding Marketing to Children (2016–2021)	Each engagement was assessed in the context of the topic of this guideline. While meeting expenses were often covered by the relevant agencies listed, no income or honorariums were paid. The engagements have been on a variety of nutrition topics, none of which were determined to be directly relevant to the objective of this guideline, and were therefore not considered to represent a conflict of interest. The sources of research funds were not considered to represent a conflict of interest for this guideline. Nor were the topics covered by the research funds which focused primarily on assessing dietary quality, ways of promoting healthy diets (including sodium reduction strategies), and food labelling. Because none of the interests were directly relevant to the objective of this guideline, it was therefore determined that these declared interests do not constitute any conflict of interest for the work being undertaken by the NUGAG Subgroup on Diet and Health.

Member	Interests declared/identified	Action taken
	▶ Statistics Canada and Health Canada: Technical Adviser on analysis of dietary intake patterns for 2015 Canadian Community Health Survey (2015–2021) ▶ Health Canada: Technical Adviser on various projects: nutrient profiling for front-of-pack labelling, restricting marketing to children, updating Canada's Food Guide, developing a Canada Food Guide Adherence Tool "what to eat" (2016–2021) ▶ Received research funding from various agencies: Canadian Institute of Health Research (CIHR), Institute for the Advancement of Food and Nutrition Sciences, Alberta Innovates and Alberta Health Services, Health Canada, Sanofi-Pasteur – University of Toronto – Université Paris – Descartes International Collab Research Pilot and Feasibility Program, International Development Research Centre – NCD Prevention Program, Burroughs Wellcome Foundation, Fonds de recherche Société et culture Québec, Heart and Stroke Foundation of Canada (2012–2021)	
Barbara Schneeman	▶ US Agency for International Development: employed as higher education coordinator from 2015 to 2016, where she worked with the higher education community to increase engagement with USAID ▶ US Food and Drug Administration: employed through 2012 (retired in 2013) ▶ Head of the US delegate to the Codex Committees on food labelling and on nutrition and foods for special dietary uses (CCNFSDU): she presented the US positions in these Codex forums (up to 2012) ▶ Monsanto: Member of advisory committee discussing role of agriculture in addressing climate change and improving food and nutrition security (2014–2017) ▶ McCormick Science Institute: Member of advisory committee reviewing research proposals on spices and herbs (2014–2021) ▶ Ocean Spray: Temporary adviser on health claim petitions related to cranberries that were submitted to US Food and Drug Administration (2014–2015) ▶ General Mills: Temporary adviser on US labelling requirements for nutrition declarations (2014–2016, and 2018) ▶ DSM: Temporary adviser on Codex Alimentarius processes (2014–2015) ▶ Hampton Creek: Temporary adviser on labelling standards for mayonnaise (2014–2015) ▶ Washington DC law firm: Temporary adviser on labelling of genetically modified foods (2014–2015) ▶ NASEM: member of the National Academies and member/Chair of the Dietary Guidelines Advisory Committee, involved in reviewing the evidence in developing the national dietary guidelines for the US, *Dietary Guidelines for Americans* — Nominated to the Dietary Guidelines Advisory Committee of the USA by representatives from the North American Branch of the International	Each engagement was assessed in the context of the topic of this guideline. Meeting expenses and honorariums were paid in some instances. With the exception of membership on the advisory committee for the McCormick Science Institute and the US Dietary Guidelines Advisory Committee, the engagements have all been on topics unrelated to the objective of this guideline, primarily providing expert advice on US regulatory issues, such as food labelling (i.e. nutrient declarations, health claims, other types of labelling), or presenting the process for developing the dietary guidelines for the US, *Dietary Guidelines for Americans*. Engagement on the advisory committee for the McCormick Science Institute included tasks to review research proposals submitted for funding by the institute. Studies include evaluation of the use of spices and herbs to support consumers adjust, e.g. to recommendation on reducing intake of added sodium and sugars. No submitted or funded projects have involved salt substitutes. The focus of these engagements was not considered to pose a risk for the guideline development.

Member	Interests declared/identified	Action taken
	Life Sciences Institute; the American Beverage Association; American Bakers Association, Grain Chain; Grocery Manufacturers Association USA Dry Pea & Lentil Council, American Pulse Association — Received honorariums for presentation on the process to develop the Dietary Guidelines for Americans and policies for food labelling in the US at various scientific meetings organized by PMK Associates (IFT & AOCS), McCormick Institute, Fiber Assoc-Japan, and Mushroom Council ▶ International Food Information Council (IFIC): Member Board of Trustees, which ensures that IFIC upholds its responsibilities as a 501(c)(3) non-profit (2021) ▶ International Life Science Institute North America: Government liaison and evaluating research and organizing webinars on the microbiome (2018) ▶ International Dairy Foods Association: presented webinar on the work of the 2020 Dietary Guideline Advisory Committee for which she received no remuneration (2020)	Regarding her membership on the US Dietary Guidelines Advisory Committee, the work was done for a national authority and therefore was not considered a conflict of interest. With respect to her nomination to the US Dietary Guidelines Advisory Committee by various industry groups, there is no relationship or affiliation between nominator and nominee. It was therefore determined that these declared interests do not constitute any conflict of interest for the work being undertaken by the NUGAG Subgroup on Diet and Health.

No other members of the NUGAG Subgroup on Diet and Health declared any interests (or the declared interests clearly did not represent a conflict of interest), nor were any interests independently identified (see **Annex 2** for the list of members of the NUGAG Subgroup on Diet and Health).

Methods expert

The methods expert did not declare any interests, nor were any interests independently identified.

Members of the Systematic review team

No members of the systematic review teams declared any interests, nor were any interests independently identified.

Members of the external peer-review group

Member	Interests declared/identified	Action taken
Amos Laar	▶ Research Support (Grants – 2a) Measuring the healthiness of Ghanaian children's food environments to prevent obesity and Non-Communicable Diseases (MEALS4NCDs) – Research Grant (International Development Research Centre IDRC), Canada) ▶ Healthier Diets 4 Healthy Lives (HD4HL) Project (IDRC, Canada & The Rockefeller Foundation)	Given the nature and topic of the research funding, it was not considered to represent a conflict of interest for serving as an external reviewer of this guideline.
Pasquale Strazzullo	▶ An unpaid member of WASSH (World Action on Salt, Sugar and Health), a non-profit organization advocating the need to reduce salt and sugar intake at the population level ▶ Coordinator of the Working Group on Salt and Health of the Italian Society of Human Nutrition, a non-profit association. The Group has released several public statements concerning the benefits of salt intake reduction at the population level	Given the nature and topic of the engagement, it was not considered to represent a conflict of interest for serving as an external reviewer of this guideline.

No other members of the external peer-review group declared any interests (or the declared interests clearly did not represent a conflict of interest), nor were any interests independently identified (see **Annex 3** for the list of external peer reviewers).

Annex 5.
Key questions in PICO format

PICO questions

The following PICO questions were assessed:

1. What is the effect of replacing salt (sodium chloride) with low-sodium salt substitutes on [outcome] in adults?
2. What is the effect of replacing salt (sodium chloride) with low-sodium salt substitutes on [outcome] in adults with high risk of hyperkalaemia?
3. What is the effect of replacing salt (sodium chloride) with low-sodium salt substitutes on [outcome] in children?
4. What is the effect of replacing salt (sodium chloride) with low-sodium salt substitutes on [outcome] in children with high risk of hyperkalaemia?
5. What is the effect of replacing salt (sodium chloride) with low-sodium salt substitutes on [outcome] in pregnant women?
6. What is the effect of replacing salt (sodium chloride) with low-sodium salt substitutes on [outcome] in pregnant women with high risk of hyperkalaemia?

Population	▶ Adults (including pregnant women) ▶ Children (2 years and older) General population including those with disease and risk factors, such as hypertension, cardiovascular disease (CVD), diabetes, renal impairment, etc. Adults and children in low-, middle- and high-income countries. In each, consider population characteristics, such as age, gender, ethnicity, country/region (urban/rural), socioeconomic status/demographic factors/sanitation, health background and health status, patterns of sodium and potassium intake.
Intervention/exposure	Use/intake of low-sodium salt substitute (ensure the ability to isolate the effect from the other aspects of the intervention or comparator)
Comparator	Use/intake of regular salt (NaCl)
Outcome	**Adults and children** ▶ Blood pressure (systolic, diastolic, hypertension, blood pressure control) ▶ Serum potassium, hyperkalaemia, hypokalaemia ▶ Stroke ▶ Cardiovascular events including dysrhythmia, sudden death ▶ CVD mortality ▶ All-cause mortality ▶ Measures of kidney function (e.g. serum creatinine, albuminuria, urine albumin-to-creatinine ratio (uACR), glomerular filtration rate (GFR)) ▶ Adverse events ▶ Anti-hypertensive medication use ▶ Diabetes ▶ Hyponatraemia ▶ Glucose, total cholesterol, triglycerides, body mass index (BMI)

	Pregnant women ▶ Blood pressure (systolic, diastolic, hypertension, blood pressure control) ▶ Serum potassium, hyperkalaemia, hypokalaemia ▶ Cardiovascular events including dysrhythmia, sudden death ▶ Pre-eclampsia, eclampsia ▶ Measures of kidney function (e.g. serum creatinine, albuminuria, uACR, GFR) ▶ Stroke ▶ Pre-term ▶ Intrauterine growth restriction ▶ Adverse events ▶ Birthweight ▶ All-cause mortality ▶ CVD mortality ▶ Anti-hypertensive medication use ▶ Gestational diabetes ▶ Diabetes ▶ Glucose, total cholesterol, triglycerides, BMI **Children** ▶ Blood pressure (systolic, diastolic, hypertension, blood pressure control) ▶ Serum potassium, hyperkalaemia, hypokalaemia ▶ Growth ▶ Measures of kidney function (e.g. serum creatinine, albuminuria, uACR, GFR) ▶ Adverse events ▶ Cardiovascular events including dysrhythmia, sudden death ▶ Bone health ▶ All-cause mortality ▶ CVD mortality ▶ Hyponatraemia ▶ Anti-hypertensive medication use ▶ Glucose, total cholesterol, triglycerides, BMI ▶ Stroke

Annex 6.

GRADE evidence profiles

Question: LSSS intervention compared to regular salt in adults

Certainty assessment							No. of participants		Effect		Certainty
No. of participants (studies)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LSSS	Regular salt	Relative (95% CI)	Absolute (95% CI)	
Change in DBP											
20 830 (19 RCTs)	randomized trials	not serious	serious[a]	not serious	not serious	none	10 611	10 219	–	**MD 2.43 mmHg lower** (3.5 lower to 1.36 lower)	⨁⨁⨁◯ *Moderate*
Change in SBP											
21 414 (20 RCTs)	randomized trials	not serious	serious[b]	not serious	not serious	none	10 903	10 511	–	**MD 4.76 mmHg lower** (6.01 lower to 3.5 lower)	⨁⨁⨁◯ *Moderate*
Hypertension											
2566 (1 RCT)	randomized trials	serious[c]	not serious	not serious	serious[d]	none	725/1294 (56.0%)	738/1272 (58.0%)	**RR 0.97** (0.90 to 1.03)	**1741 fewer per 100 000 persons** (from 5802 fewer to 1741 more)	⨁⨁◯◯ *Low*
Blood pressure control											
253 (2 RCTs)	randomized trials	serious[e]	not serious	serious[f]	serious[g]	none	35/120 (29.2%)	17/133 (12.8%)	**RR 2.12** (1.32 to 3.41)	**14 316 more per 100 000 persons** (from 4090 more to 30 805 more)	⨁◯◯◯ *Very low*

Certainty assessment							No. of participants		Effect		Certainty
No. of participants (studies)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LSSS	Regular salt	Relative (95% CI)	Absolute (95% CI)	
Cardiovascular events: various events*											
982 (5 RCTs)	randomized trials	not serious	not serious	serious[h]	very serious[i]	none	10/489 (2.0%)	8/493 (1.6%)	**RR 1.22** (0.49 to 3.04)	**357 more per 100 000 persons** (from 828 fewer to 3310 more)	⨁◯◯◯ *Very low*
Cardiovascular events: non-fatal stroke											
21 250 (3 RCTs)	randomized trials	not serious	not serious	serious[j]	not serious	none	19/10 646 (0.2%)	21/10 604 (0.2%)	**RR 0.90** (0.80 to 1.01)	**20 fewer per 100 000 persons** (from 40 fewer to 2 more)	⨁⨁⨁◯ *Moderate*
Cardiovascular events: non-fatal acute coronary syndrome											
20 995 (1 RCT)	randomized trials	not serious	not serious	serious[j]	not serious	none	3.79/1000	5.12/1000	**Rate ratio 0.70** (0.52 to 0.94)	**150 fewer per 100 000 person-years** (from 250 fewer to 30 fewer)	⨁⨁⨁◯ *Moderate*
Cardiovascular mortality											
23 200 (3 RCTs)	randomized trials	not serious	not serious	serious[j]	not serious	none	6.36/1000	7.86/1000	**Rate ratio 0.77** (0.60 to 1.00)	**180 fewer per 100 000 person-years** (from 310 fewer to 0 fewer)	⨁⨁⨁◯ *Moderate*
Stroke mortality											
21 423 (2 RCTs)	randomized trials	not serious	not serious	serious[j]	very serious[k]	none	2.82/1000	4.05/1000	**Rate ratio 0.64** (0.33 to 1.25)	**145 fewer per 100 000 person-years** (from 270 fewer to 100 more)	⨁◯◯◯ *Very low*

Certainty assessment							No. of participants		Effect		Certainty
No. of participants (studies)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LSSS	Regular salt	Relative (95% CI)	Absolute (95% CI)	
Change in blood potassium											
784 (6 RCTs)	randomized trials	serious[l]	not serious	not serious	not serious	none	417	367	–	**MD 0.12 mmol/L higher** (0.07 higher to 0.18 higher)	⨁⨁⨁◯ *Moderate*
Hyperkalaemia											
22 849 (5 RCTs)	randomized trials	serious[m]	not serious	not serious	not serious	none	12/11 452 (0.1%)	10/11 397 (0.1%)	**RR 1.04** (0.46 to 2.38)	**4 more per 100 000 persons** (from 47 fewer to 121 more)	⨁⨁⨁◯ *Moderate*
Hypokalaemia											
22 (1 RCT)	randomized trials	serious[c]	not serious	very serious[n]	not serious	none	0/12 (0.0%)	0/10 (0.0%)	not estimable		⨁◯◯◯ *Very low*
Adverse events: other											
2109 (8 RCTs)	randomized trials	serious[l]	not serious[o]	not serious	serious[p]	none	25/1094 (2.3%)	14/1015 (1.4%)	not pooled		⨁◯◯◯ *Very low*

CI: confidence interval; MD: mean difference; RR: risk ratio
* Various other cardiovascular events; for example, angina, cardiovascular symptoms

GRADE certainty of evidence

- ***High* certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
- ***Moderate* certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- ***Low* certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- ***Very low* certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by 1 for inconsistency: substantial heterogeneity (I^2 = 88%), not explained by subgroup analyses (study duration, ethnicity, BP status, type of LSSS, baseline Na excretion) or meta-regression (type of LSSS, baseline Na excretion, overall risk of bias).
b. Downgraded by 1 for inconsistency: substantial heterogeneity (I^2 = 78%), not explained by subgroup analyses (study duration, ethnicity, BP status, type of LSSS, baseline Na excretion) or meta-regression (type of LSSS, baseline Na excretion, overall risk of bias).
c. Downgraded by 1 for risk of bias: All information is from a study at unclear overall risk of bias.
d. Downgraded by 1 for imprecision: 95% CI is consistent with the possibility of important benefit and unimportant harm (minimally important threshold: 5000 per 100 000).

[e] Downgraded by 1 for risk of bias: The majority of information is from a study at unclear overall risk of bias.
[f] Downgraded by 1 for indirectness: majority of information is from a study using an LSSS with 97% NaCl (table salt).
[g] Downgraded by 1 for imprecision: 95% CI was consistent with the possibility of unimportant and important benefit (minimally important threshold 5000 per 100 000).
[h] Downgraded by 1 for indirectness: pooled effect is driven by a large study in high-risk individuals (participants selected based on high risk of future vascular disease) that is less likely to be directly applicable to the general population.
[i] Downgraded by 2 for imprecision: using the optimal information size (OIS) approach, the ratio of the upper to the lower boundary of the CI is more than 3 (RR); 18 events in total.
[j] Downgraded by 1 for indirectness: pooled effect is driven by a large secondary prevention trial (73% of participants with previous stroke) that is less likely to be directly applicable to the general population, and that reported limited data on safety outcomes.
[k] Downgraded by 2 for imprecision: the ratio of the upper to the lower boundary of the 95% CI is more than 3.
[l] Downgraded by 1 for risk of bias: The majority of information is from studies at high or unclear overall risk of bias.
[m] Downgraded by 1 for risk of bias: The majority of information is from a study at high overall risk of bias.
[n] Downgraded by 2 for indirectness: All information is from a study including younger hypertensive participants with a different rationale for administering LSSS (potassium supplementation due to the use of potassium-depleting diuretics).
[o] Downgraded by 1 for inconsistency: Other adverse event outcomes were too diverse to pool.
[p] Downgraded by 1 for imprecision: 39 events in total, OIS not met (not rare events).

Question: LSSS intervention compared to regular salt in children

Certainty assessment							No. of participants		Effect		Certainty
No. of participants (studies)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LSSS	Regular salt	Relative (95% CI)	Absolute (95% CI)	
Change in DBP											
92 (1 RCT)	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	40	52	–	**MD 1.28 mmHg higher** (1.56 lower to 4.12 higher)	⨁◯◯◯ *Very low*
Change in SBP											
92 (1 RCT)	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	40	52	–	**MD 0.12 mmHg higher** (4.41 lower to 4.64 higher)	⨁◯◯◯ *Very low*

CI: confidence interval; MD: mean difference

GRADE certainty of evidence

- ***High* certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
- ***Moderate* certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- ***Low* certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- ***Very low* certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by 1 for risk of bias: all information is from a study at unclear overall risk of bias.
b. Downgraded by 1 for indirectness: LSSS was delivered in bread only (non-discretionary) for 4 months.
c. Downgraded by 1 for imprecision: wide 95% confidence interval including both reductions and increases in blood pressure.

Annex 7.
Evidence to recommendation table

Assessment

Priority of the problem **Is the problem a priority?**		
Judgement	**Research evidence**	**Additional considerations**
☐ No ☐ Probably no ☐ Probably yes ■ **Yes** ☐ Varies ☐ Don't know	The global burden of disease attributable to high systolic blood pressure and cardiovascular diseases (CVDs) is substantial. In 2019, an estimated 828 million adults worldwide had hypertension (systolic blood pressure >140 mmHg) *(1)*, and there were an estimated 523 million prevalent cases of CVDs, with 18.6 million deaths from CVDs *(1)*. The prevalence of CVDs nearly doubled between 1990 and 2019, and the number of annual deaths also increased markedly from 12.1 million in 1990 *(1)*. Modifiable risk factors such as unhealthy diets, physical inactivity, tobacco use and harmful use of alcohol are major risk factors for CVDs. High sodium intakes are of particular concern because they have been associated with increased risk of CVDs causing an estimated 1.9 million deaths globally each year *(2)*.	There is large variation in disease burden due to hypertension and CVDs worldwide.
Desirable effects **How substantial are the desirable anticipated effects?**		
Judgement	**Research evidence**	**Additional considerations**
☐ Trivial ■ **Small** ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	Lower-sodium salt substitutes (LSSS) compared to regular salt: **Adults** Change in diastolic blood pressure (DBP): mean difference (MD) −2.43 mmHg (95% confidence interval [CI] −3.50 to −1.36) Change in systolic blood pressure (SBP): MD −4.76 mmHg (−6.01 to −3.50) Non-fatal stroke: Absolute effect (AE) 20 fewer/100 000 person-years (−40 to 2) Non-fatal acute coronary syndrome: AE 150 fewer/100 000 person-years (−250 to −30) Cardiovascular mortality: AE 180 fewer/100 000 person-years (−310 to 0) Change in blood potassium: MD 0.12 mmol/L (0.07 to 0.18) Hypertension: AE 1741 fewer per 100 000 persons (−5802 to 1741) Blood pressure control: 14 316 more per 100 000 persons (4090 to 30 805) Various other cardiovascular events: 357 more per 100 000 (−828 to 3310) Stroke mortality: 145 fewer per 100 000 person-years (−270 to 100)	The extent of the benefit varies by outcome, but the effects would be small, which reflects the expected effects in the general population, whereas the evidence relates mainly to participants at high cardiovascular risk (e.g. high blood pressure, history of stroke). Additionally, the evidence base relates to discretionary use and not to non-discretionary use as a food additive.

Judgement	Research evidence	Additional considerations
	Children Change in DBP: MD 1.28 mmHg (−1.56 to 4.12) Change in SBP: MD 0.12 mmHg (−4.41 to 4.64) No evidence about the effects of LSSS on hypertension, blood pressure control, blood potassium in children. **Pregnant women** No eligible studies in pregnant women were found.	

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
☐ Large ☐ Moderate ☐ Small ☐ Trivial ■ **Varies** ☐ Don't know	LSSS compared to regular salt: **Adults** Adverse events: Eight trials reporting on diverse adverse events (not pooled) Hyperkalaemia: 4 more/100 000 (−47 to 121) Hypokalaemia: (one small trial) 12 events in the intervention versus 10 in control Change in blood potassium: MD 0.12 mmol/L (0.07 to 0.18) **Children** No evidence about the effects of LSSS on hyperkalaemia and hypokalaemia in children was identified. **Pregnant women** No eligible studies in pregnant women were found.	For undesirable effects, adverse events were very varied and therefore were not pooled in the systematic review. Very few studies reported on hyperkalaemia, and studies that did report on hyperkalaemia also used variable, in some cases unclear, criteria to define the condition. Other potassium-related outcomes presented in most of these studies were not rigorously collected and reported. Therefore, the information on hyperkalaemia events and other potassium-related measures was unreliable. Consequently, serum potassium was considered the most relevant outcome for safety. Patients with overt kidney disease were excluded by the included trials, and most studies that assessed safety were of limited duration and did not provide evidence of long-term safety. In addition, the undesirable effects may vary with access to health care, setting and population.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
☐ Very low ■ **Low** ☐ Moderate ☐ High ☐ No included studies	**Adults** The overall certainty of evidence for effects in adults of LSSS compared to regular salt is *low*. Certainties of evidence for key outcomes are listed below. Change in DBP: *moderate* Change in SBP: *moderate* Non-fatal stroke: *moderate* Non-fatal acute coronary syndrome: *moderate* Cardiovascular mortality: *moderate* Change in blood potassium: *moderate* Hypertension: *low* Blood pressure control: *very low* Various other cardiovascular events: *very low* Stroke mortality: *very low* Hyperkalaemia: *moderate* Hypokalaemia: *very low* Other adverse events: *very low* **Children** Change in DBP: *very low* Change in SBP: *very low*	See GRADE evidence profiles for certainty of evidence for all outcomes (**Annex 6**). The overall certainty in the evidence was considered *low*. This judgement is based on the certainty of evidence across the critical outcomes. This is with acknowledging that there is some evidence of benefit that was of *moderate* certainty.

Values and preferences

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ■ **Probably no important uncertainty or variability** ☐ No important uncertainty or variability	The studies showed that generally people felt high blood pressure and CVDs were serious conditions that affected quality of life. Many studies, mostly carried out in low- and middle-income countries examined the beliefs that people hold towards hypertension and CVDs. Most people believed hypertension is a serious disease that leads to stroke, heart attack and death *(3–10)*. People also viewed hypertension as a "silent killer" *(11, 12)* that can kill suddenly *(8, 13–15)*. Some people described how hypertension and CVDs could affect quality of life *(6, 10, 12, 16)*; however, in several studies, the authors reported that some participants felt unaffected by hypertension, especially if it was well controlled with medication *(5, 6, 8, 10–12, 17)*. No studies were identified that examined people's views on the importance of hyperkalaemia, hypokalaemia, or serum potassium. No studies were identified that explored the importance of the critical health outcomes in children.	

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ■ **Probably favours the intervention** ☐ Favours the intervention ☐ Varies ☐ Don't know	Based on a comparative risk assessment in China, the estimated net effect from adopting a salt substitute containing potassium in the population was 450 000 fewer deaths annually from CVDs, comprising 461 000 averted deaths from systolic blood pressure reduction and 11 000 additional deaths from increased serum potassium in patients with chronic kidney disease *(18)*.	There is uncertainty about the balance between the benefits and potential harms, especially in settings where a considerable proportion of the population may have undiagnosed conditions for which it would not be advisable to increase potassium intakes.

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ■ **Varies** ☐ Don't know	**Cost to government:** • Programme management, health promotion and advocacy, trainings and meetings, mass media, office supplies and rents, law enforcement/monitoring, subsidies, as well as the additional cost of the salt substitute. A study that modelled the cost–effectiveness of implementing LSSS in Cameroon: Replacement of 35% of the sodium chloride in table salt and stock cubes with potassium chloride was estimated to cost about US$ 174 million over the lifespan of the cohort of adults in Cameroon in 2016 *(19)*. **Cost to consumers:** Higher price of LSSS • Among salt manufacturers that produced both LSSS and regular salts (n = 38), the price of LSSS is between 1.1 and 14.6 (median 1.7) times higher than the price of regular salt (range: 1.1 to 14.6) *(20)*. **Cost to industry:** • Use of LSSS results in higher manufacturing costs *(21)*.	The costs would depend on the specific context in which discretionary use of LSSS is implemented. Proportion of sodium intake from discretionary use varies around the world. LSSS are 1.7 times more expensive than regular salt, but overall salt is a low-cost food commodity. Approval of LSSS could incur regulatory costs, but in countries where LSSS are available such costs are probably not high. If implementing, LSSS should be placed as part of a sodium reduction strategy and its use must be aligned with country's fortification and iodization programmes where required.

Cost–effectiveness

Does the cost–effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ■ **Probably favours the intervention** ☐ Favours the intervention ☐ Varies ☐ No included studies	Four studies were identified that modelled the cost–effectiveness of implementing LSSS in a population. The countries modelled were China *(22)*, Cameroon *(19)*, Viet Nam *(23)* and New Zealand *(24)*. All four studies found that replacing regular salt (NaCl) in table salt (China) *(22)*, table salt and stock cubes (Cameroon) *(19)*, table salt, fish sauce and bot canh, a traditional condiment (Viet Nam) *(23)*, or table salt and manufactured food (New Zealand) *(24)* with LSSS was cost-effective. • **Cameroon:** estimated cost about US$ 174 million over the lifespan of the cohort of adults in Cameroon in 2016 and gain 368 400 health-adjusted life years. Net cost savings of US$ 648 million • **China:** gain 1 185 000 quality-adjusted life years annually, and the cardiovascular health care cost savings were estimated to be 4.1 billion international dollars annually • **Viet Nam:** 1) voluntary approach: net cost saving of US$ 200 000/year 2) subsidized approach: US$ 2 600 000/year 3) regulatory approach: US$ 14 500 000/year The models from China *(22)*, Viet Nam *(23)* and New Zealand *(24)* probably underestimated the costs associated with the intervention; nevertheless, the estimated net cost savings were robust to various changes to the underlying model assumptions. In addition, the model from Cameroon *(19)*, which more fully costed the intervention, suggested that widespread implementation of LSSS is likely to be cost-effective. Similar health gains and cost savings were predicted from a mandatory 25% reduction of sodium (without replacement by LSSS) in all manufactured foods in New Zealand *(24)*, and from a school-based education programme to reduce household sodium intakes in Cameroon *(19)*.	

Equity and human rights

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
☐ Reduced ■ **Probably reduced** ☐ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	In China, using LSSS for discretionary salt has been encouraged since 2010, and studies have shown that there has been a differential uptake, with adults with lower levels of education or income less likely to use LSSS *(25, 26)*. The higher cost of LSSS may prevent some people from using them *(27, 28)*. Human rights treaties recognize the right of everyone to food that is sufficient, adequate and safe *(29)*.	Various economic status and health systems of countries could affect equity differently.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
☐ No ☐ Probably no ■ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	Potassium chloride, contained in most LSSS, has bitter and metallic tastes. Therefore, partial instead of full replacement of sodium chloride is typically used to minimize the off tastes associated with potassium chloride, with or without other agents. Studies showed good overall consumer acceptability for LSSS with up to about 30% of the sodium chloride replaced with potassium chloride *(30–32)*. There appears to have been moderate uptake of LSSS for discretionary use in China (about 23–37%) *(25, 26, 28)*. A study conducted in South Africa also confirmed a high level of acceptance. Further, randomized controlled trials included in the systematic review showed overall good acceptance of the LSSS intervention by participants as demonstrated by the results of 24 h urinary sodium and potassium excretion.	The public might find the promotion of LSSS a confusing message since the primary goal and the main public health message thus far have been to reduce discretionary salt use. This is especially important for countries where discretionary use is a major source of sodium intake.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
☐ No ☐ Probably no ■ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	A systematic review identified 87 LSSS, about half of which are iodized *(20)*. At least one LSSS was available in 47 countries, and more than half of these were high-income countries. Stakeholders, including academics and government and industry representatives, recognize that limited availability and low market share of LSSS are barriers to widespread implementation of LSSS *(33)*. The price of LSSS is between 1.1 and 14.6 (median 1.7) times higher than the price of regular salt (NaCl) *(20)*. Studies in China among the general population have found that the main reasons people do not use LSSS for discretionary use are lack of awareness, bad taste, cost, difficulty in purchasing, and lack of perceived health benefits *(26, 28)*. The higher cost of LSSS is also a barrier for industry *(33, 34)* and governments *(35, 36)*, as are concerns around the potentially increased risk of hyperkalaemia in those with kidney disease *(18, 33, 37)*. The higher cost of LSSS and the concerns about the potentially increased risk of hyperkalaemia in those with kidney disease are potential barriers to governments from promoting LSSS. It has also been acknowledged that the use of LSSS will not reduce consumer preference for salty tastes *(37, 38)*. Furthermore, it is uncertain whether promotion of LSSS will automatically reduce sodium intakes *(33, 34)*, with the results of several trials indicating that participants consumed more of the LSSS that contain potassium, so that sodium intakes either were unchanged *(39, 40)*, or decreased by less than expected, while potassium intakes increased. Industry has signalled that it would like to use salt substitutes that contain potassium, especially for products for which it believes it is challenging to reduce sodium without compromising acceptability *(37, 41)*. One barrier for industry has been labelling requirements; industry prefers to use the term "potassium salt" for KCl on food labels *(21, 41)* and this term is now allowed in the USA *(42)*.	Implementation of LSSS must be in line with country's iodization programme and the level of iodization needs to be adequately recalibrated.

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Annex 8.
Examples of country approaches regarding the LSSS use

Below are examples of various approaches adopted by certain countries regarding the LSSS use in manufactured foods, foods served at restaurants and other out-of-home settings and condiments other than regular salt. **While such use of LSSS is beyond the scope of this guideline, the information is provided for reference purposes.**

Ireland

Since 2003 the Irish food industry has been working on reformulation of manufactured foods to reduce salt. The main sources of salt in the Irish diet are manufactured foods (especially meat and fish products, bread, soups and sauces), which make up about 70% of the total intake. In 2005, the Food Safety Authority of Ireland (FSAI) has advised against the use of potassium-based salt substitutes *(1)*.

In 2016, the Scientific Committee of the FSAI reviewed its previous advice and concluded that potassium-based salt substitutes could be used by the food industry when reduction of salt could be detrimental to food safety and/or to the physical or organoleptic properties of foods *(2)*.

Following the recommendation from the FSAI's Scientific Committee, FSAI developed best-practice guidelines for the food industry on the use of potassium-based salt substitutes to minimize any perceived risk to vulnerable people *(3)*. In this document, FSAI notes that the use of potassium-based salt substitutes by the food industry has emerged as an option to help with reformulation to reduce salt but that the use of potassium-based salt substitutes must be tempered by concerns about the possible vulnerability of some population subgroups to excessive consumption of potassium.

FSAI recommends that the food industry:

I. Examine any technical and/or food safety limitations identified that prevent further salt reduction as part of a reformulation programme of existing manufactured food products or development of new products.

II. Be aware that the use of potassium-based salt substitutes should not be solely for the purpose of flavour maintenance; that is, saltiness or flavour enhancement. There is a public health obligation on the food industry to continue to work on reducing the perception of saltiness in manufactured foods by the Irish population.

III. When manufactured food is reformulated with the addition of potassium-based salt substitutes, consideration should be given to the communication of relevant information (including total potassium content) to vulnerable groups; for example, people with chronic kidney disease (CKD) who may consume those manufactured foods.

FSAI provides best-practice guidance for using potassium-based salt substitutes for reformulation of manufactured foods.

Singapore

To tackle excessive sodium intake in the population, the Singapore government adopts a multipronged strategy to address Singaporeans' key sources of sodium intake, including salt, sauces (e.g. soy sauce, oyster sauce and fish sauce) and seasonings added during food preparation.

One key pillar of the strategy is encouraging the substitution of regular salt with lower-sodium alternatives (e.g. salt that contains potassium). These alternatives can reduce the sodium content in foods by at least 25% without compromising taste when used as a one-for-one replacement for regular salt, beyond supplementing one's potassium intake. Clinicians and professional bodies have also advised that salt that contains potassium is safe for individuals with early-stage CKD, while individuals with late-stage CKD should limit consumption of all forms of salt, whether regular or containing potassium.

A key approach Singapore has taken is industry partnership to help grow the availability, and promote adoption, of lower-sodium alternatives. Singapore provides grant support to manufacturers of salt and sauces to drive the development of lower-sodium products and support trade promotions of these products through distribution and retail channels to encourage use by food operators. With grant support, the wholesale prices of most lower-sodium ingredients supplied to food operators are comparable to those of regular versions.

To build consumer awareness, Singapore runs a multiyear public education campaign on sodium reduction. This is accompanied by its labelling programme, the Healthier Choice Symbol, to nudge consumers in their purchasing decisions at points of sale. Singapore will also be extending its labelling programme to impose a graded label, Nutri-Grade, and advertising prohibition for key contributors to sodium intake, including salt, sauces, seasonings and instant noodles *(4)*.

United Kingdom of Great Britain and Northern Ireland

In 2013, the United Kingdom's Department of Health and Social Care (DHSC) asked the Scientific Advisory Committee on Nutrition (SACN) to provide advice on the potential risks and benefits of reducing the sodium (salt) content of foods using potassium-based sodium replacers. SACN and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) conducted a benefit–risk assessment on the impact and benefit of substituting sodium with potassium. SACN-COT jointly concluded as follows *(5)*:

- Overall, at a population level, the potential benefits (i.e. reduced blood pressure and reduced stroke incidence) of using potassium-based sodium replacers outweigh the potential risks (i.e. an increase in hyperkalaemia in individuals with previously undiagnosed chronic renal impairment).
- The beneficial effects at an individual level are likely to be small but will impact a large proportion of the population.

Three recommendations for the United Kingdom's (UK) government were also made in the joint statement *(5)*:

- The government should consider encouraging food companies to explore the use of potassium-based sodium replacers to help reduce sodium levels in foods, up to the levels of substitution and in the foods considered in the modelling performed for this benefit–risk assessment.
- Risk managers should consider how to monitor the level of substitution of potassium for sodium in foods and the types of foods in which substitution is used. If these become materially different from those assumed for the modelling performed for this benefit–risk assessment, the government should reassess the balance between benefits and risks.
- If the age structure of the UK population, or the percentage of people with CKD or potassium intakes become materially different from those assumed for the modelling performed for this benefit–risk assessment, the government should reassess the balance between benefits and risks.

The preferred approach for the voluntary salt reduction programme in the UK, set out in 2020, is for businesses to gradually reduce the overall saltiness of their products, which will allow people's palates to adjust to less salty foods, and that it is a business decision if and how they wish to use sodium replacers *(6)*.

Responsibility for the programme transferred from Public Health England, to the Office for Health Improvement and Disparities, part of DHSC, in 2021.

United States of America

The updated nutrition facts label final rule issued by the Food and Drug Administration (FDA) in 2016 (81 FR 33742) and required on most food packages by January 2020, requires a declaration of potassium on the nutrition facts label – both the absolute amount per serving as well as the percentage daily value *(7)*.

In 2020, US FDA issued a final guidance allowing food manufacturers to use the term "potassium salt" in the ingredient list on food labels as an alternative to the common or usual name "potassium chloride". This enforcement discretion may help facilitate consumers' choices to decrease their sodium consumption, if manufacturers use potassium chloride as a substitute ingredient for some sodium chloride *(8)*.

In April 2023, the FDA proposed to amend the standard of identity regulations that specify salt (sodium chloride) as a required or optional ingredient. This was to permit the use of salt substitutes in standardized foods, to reduce the sodium content *(9)*. The proposed rule, if finalized, is expected to provide flexibility to facilitate industry innovation in the production of standardized foods lower in sodium while maintaining the basic nature and essential characteristics of the foods. The public commenting period closed in August 2023.

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