Use of non-sugar sweeteners

WHO guideline

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Abbreviations

ADI	acceptable daily intake
BMI	body mass index
CI	confidence interval
CVDs	cardiovascular diseases
eLENA	WHO e-Library of Evidence for Nutrition Actions
FAO	Food and Agriculture Organization of the United Nations
GINA	WHO Global database on the Implementation of Nutrition Action
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
HDL	high-density lipoprotein
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kJ	kilojoules
LDL	low-density lipoprotein
LMIC	low- and middle-income country
MD	mean difference
NCD	noncommunicable disease
NSS	non-sugar sweeteners
NUGAG	WHO Nutrition Guidance Expert Advisory Group
OR	odds ratio
PICO	population, intervention, comparator and outcome
RCT	randomized controlled trial
UN	United Nations
WHO	World Health Organization

Executive summary

Background

High intake of free sugars has been linked to overweight and obesity, which affects nearly 40% of the global adult population and millions of children, and, in turn, diet-related noncommunicable diseases (NCDs), which are the leading causes of death worldwide. In response, the World Health Organization (WHO) has issued recommendations to reduce the intake of free sugars. Various measures are being taken to reduce consumption of free sugars as part of global efforts to address the epidemic of obesity and associated diseases.

Non-sugar sweeteners (NSS)[1] are low- or no-calorie alternatives to free sugars that are generally marketed as aiding weight loss or maintenance of healthy weight, and are frequently recommended as a means of controlling blood glucose in individuals with diabetes. Individual sweeteners undergo toxicological assessment to establish safe levels of intake (i.e. acceptable daily intake, or ADI). However, there is no clear consensus on whether NSS are effective for long-term weight control or if they are linked to other long-term health effects at habitual intakes within the ADI.

Since the release of updated WHO guidance on free sugars intake in 2015, interest in the potential utility of NSS in reducing sugars intake has increased. Therefore, it was considered necessary to review the evidence in a systematic manner, and issue WHO guidance on NSS use through the WHO guideline development process.

Objective, scope and methods

The objective of this guideline is to provide guidance on the use of NSS to be used by policy-makers, programme managers, health professionals and other stakeholders in efforts to reduce free sugars intake, promote healthy diets, and prevent unhealthy weight gain and diet-related NCDs. Because the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health focuses on providing guidance on the prevention of unhealthy weight gain and diet-related NCDs, providing guidance on the management of diabetes in individuals with pre-existing diabetes is beyond the scope of this guideline. Therefore, the guidance in the guideline may not be relevant for individuals with existing diabetes. The guidance is based on evidence of health effects of NSS use at levels already considered safe (i.e. within the ADI), and is not intended to provide updated or alternative guidance on safe or maximal levels of intake.[2]

The guideline was developed following the WHO guideline development process, as outlined in the *WHO handbook for guideline development*. This process includes a review of systematically gathered evidence by an international, multidisciplinary group of experts; assessment of the certainty in (i.e. quality of)

[1] For the purposes of this guideline, NSS are defined as all synthetic and naturally occurring or modified non-nutritive sweeteners that are not classified as sugars. Sugar alcohols and low-calorie sugars are not considered to be NSS.

[2] Safe levels of intake are based on toxicological assessments of individual NSS, which are undertaken by authoritative bodies such as the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) before individual NSS are approved for commercial use. In 2021, JECFA was requested to re-evaluate the safety of aspartame (https://www.fao.org/fao-who-codexalimentarius/sh-proxy/fr/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FCircular%252520Letters%252FCL%2525202021-81%252Fcl21_81e.pdf). In 2019, an international Advisory Group identified the evaluation of aspartame as a high priority for the International Agency for Research on Cancer (IARC) Monographs programme during 2020–2024 (https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf). The two evaluations will be complementary: IARC will assess the potential carcinogenic effect of aspartame (hazard identification), while JECFA will update its risk assessment exercise, including reviewing the ADI and aspartame diet exposure assessment. IARC's hazard identification is planned for 6–13 June 2023, and JECFA's risk assessment for 27 June – 6 July 2023.

that evidence via the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework; and consideration of additional, potentially mitigating factors[1] when translating the evidence into recommendations.

The evidence

Evidence from a recent systematic review and meta-analyses of randomized controlled trials (RCTs) and prospective observational studies found that higher NSS consumption by adults led to lower body weight and body mass index (BMI), compared with not consuming NSS or consuming lower amounts of NSS, when assessed in short-term RCTs, but was associated with increased BMI and risk of incident obesity in long-term prospective observational studies. Effects on body weight and BMI from RCTs are observed only when intake of NSS is compared with intake of free sugars, and are likely mediated at least in part by a reduction in energy intake. No other significant effects or associations on measures of body fatness were observed in either RCTs or prospective cohort studies.

Long-term NSS use was associated with increased risk of type 2 diabetes, cardiovascular diseases (CVDs) and mortality in prospective cohort studies conducted in adults. However, significant effects were not observed on intermediate markers of disease such as fasting glucose, fasting insulin or blood lipids when assessed in short-term RCTs.

Evidence from studies conducted in children and pregnant women was more limited than that identified for adults. One RCT conducted in children reported a reduction in several measures of body fatness when sugar-sweetened beverages were replaced with beverages containing NSS; however, no effect was observed when results for BMI *z*-score[2] were combined with those from a second trial. Results from prospective observational studies did not suggest any significant associations between NSS use and measures of body fatness. Two RCTs conducted in children reported lower indicators of dental caries with use of the NSS stevia. All other identified studies reported no significant associations between NSS use and prioritized health outcomes in children.

Meta-analysis of three prospective observational studies found an increased risk of preterm birth with higher NSS use during pregnancy, but associations observed between birth weight or weight of offspring later in life and NSS use during pregnancy were inconsistent. Single prospective observational studies reported associations between NSS use during pregnancy and outcomes in offspring, including increased risk of asthma and allergies, and poorer cognitive function.

Recommendation and supporting information

This recommendation should be considered in the context of WHO recommendations to reduce free sugars intake and other guidance promoting healthy diets, including WHO guidelines on carbohydrates, total fat, saturated and *trans*-fatty acids, polyunsaturated fatty acids, sodium and potassium.

WHO recommendation

WHO suggests that non-sugar sweeteners not be used as a means of achieving weight control or reducing the risk of noncommunicable diseases (*conditional recommendation*).

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[1] These include desirable and undesirable effects of the intervention, priority of the problem that the recommendation addresses, values and preferences related to the recommendation in different settings, the cost of the options available to public health officials and programme managers in different settings, feasibility and acceptability of implementing the recommendation in different settings, and the potential impact on equity and human rights.

[2] BMI *z*-scores are adjusted for sex and age relative to standardized reference values.

Rationale

- The recommendation is based on evidence of *low* certainty overall, from a systematic review that assessed the health effects of higher compared with lower intake of NSS.[1] The systematic review found no evidence of long-term benefit on measures of body fatness in adults or children, and potential undesirable effects from long-term use in the form of increased risk of type 2 diabetes, CVDs and mortality in adults. Limited evidence suggests potential undesirable effects in the form of increased risk of preterm birth with NSS use during pregnancy.
- Specific findings from the systematic review supporting this recommendation are as follows.

Adults

Evidence from randomized controlled trials (RCTs) was as follows.

- NSS use in any manner[2] resulted in reduced sugars and energy intake, lower body weight and lower BMI in short-term RCTs (all *low* certainty evidence), the majority of which lasted 3 months or less. NSS use did not significantly affect other measures of body fatness or intermediate markers of cardiometabolic health, including glucose, insulin or blood lipids (*very low* to *moderate* certainty evidence). Evidence from a small number of longer-term trials lasting 6–18 months did not suggest an effect on body weight but was difficult to interpret because of many differences in how these trials were conducted and results reported.
- When intake of NSS was directly compared with intake of free sugars (i.e. one group in a trial received NSS, and another group received free sugars), those receiving NSS had lower body weight and BMI, similar in magnitude to the results when NSS was used in any manner. However, most of these trials provided foods and beverages containing NSS or free sugars in addition to existing diets and therefore did not directly measure the effects of replacing free sugars with NSS. When NSS were compared with nothing/placebo or water (i.e. one group in a trial received NSS, and another group received nothing/placebo or water), no effects on body weight or BMI were observed.
- When NSS were assessed specifically as replacements for free sugars in a small number of RCTs (i.e. habitual consumers of foods or beverages containing free sugars were asked to switch to versions containing NSS in place of free sugars), the effect on body weight was significantly weakened relative to that observed for NSS used in any manner, and an effect on BMI was no longer observed.

Evidence from prospective observational studies, with up to 10 years of follow-up, was as follows.

- Higher intakes of NSS were associated with higher BMI and increased risk of incident obesity, but not other measures of body fatness (*very low* to *low* certainty evidence).
- Higher intakes of NSS were associated with increased risk of type 2 diabetes, CVDs and CVD mortality, and all-cause mortality in long-term prospective observational studies with average follow-up of 13 years (*very low* to *low* certainty evidence), but were not associated with differences in overall cancer incidence or mortality (*very low* certainty evidence).
- Use of NSS (predominantly saccharin) was associated with increased risk of bladder cancer as assessed in case–control studies (*very low* certainty evidence).

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[1] Many RCTs compared use of NSS with no use of NSS, whereas prospective observational studies compared different levels of NSS use. To maintain consistency in comparing results across study designs, results are therefore generally reported for effects of higher compared with lower intake, noting that, in most trials, "lower intake" may in fact be no intake.

[2] NSS were consumed by the participants in the RCTs in a variety of ways, including in pre-mixed beverages, powders or drops to be added to beverages by the participants themselves, solid foods, and capsules. To test for inherent properties of NSS, all forms of NSS were combined in the main analysis regardless of how they were consumed. Additional analyses assessed the individual ways of consuming NSS separately.

Children

One RCT conducted in children reported a reduction in several measures of body fatness when sugar-sweetened beverages were replaced with those containing NSS (*moderate* certainty evidence). However, when results for BMI *z*-score were combined with those from a second trial, no effect was observed (*moderate* certainty evidence), and results from prospective observational studies did not suggest any significant associations between NSS use and measures of body fatness (*very low* certainty evidence). All other identified studies reported no significant associations between NSS use and prioritized health outcomes in children.

Pregnant women

Meta-analysis of three prospective observational studies found an increased risk of preterm birth with higher NSS use during pregnancy (*low* certainty evidence), but associations between birth weight or weight of offspring later in life and NSS use during pregnancy were inconsistent (*very low* certainty evidence). Other individual prospective observational studies reported associations between NSS use during pregnancy and outcomes in offspring, including increased risk of asthma and allergies, and poorer cognitive function (*very low* certainty evidence). No associations were observed between NSS use and risk of gestational diabetes.

- The lack of evidence for long-term benefit of NSS use on measures of body fatness assessed in RCTs and potential long-term effects of NSS use observed for adults in prospective observational studies were considered to be relevant for women during pregnancy, and were reasonably expected to be relevant for children and adolescents as well. Therefore, in addition to the limited direct evidence for children and pregnant women, the evidence from RCTs and observational studies in adults was extrapolated to children, adolescents and pregnant women without downgrading for indirectness.
- In reviewing the evidence and formulating the recommendation, the NUGAG Subgroup on Diet and Health noted the following.
    - Because the primary role of NSS use is presumably to reduce free sugars intake (and consequently risk of unhealthy weight gain and disease associated with excess free sugars intake), the currently available evidence on which to base a recommendation on NSS is largely indirect – that is, most RCTs comparing intake of NSS with intake of free sugars did not explicitly assess the replacement of free sugars with NSS.
    - Because weight loss and maintenance of a healthy weight must be sustained over the long term[1] to have a meaningful impact on health, evidence of minor weight loss or reduced BMI over several months or less, as observed in the RCTs, without additional evidence of long-term impact, does not represent a health benefit.
    - The discordant results between the RCTs and prospective cohort studies suggest that the small amount of weight loss resulting from NSS use in short-term experimental settings may not be relevant to the effects of long-term NSS use in the general population.

    In addition, the NUGAG Subgroup on Diet and Health noted that:

    - there were no identified undesirable effects or other mitigating factors that would argue against not using NSS;
    - NSS are not essential dietary factors and have no nutritional value; and
    - use of NSS is not the only way to achieve a reduction in free sugars intake; viable alternatives exist that are compatible with features of a healthy diet including consumption of foods with naturally occurring sugars, such as fruit, and unsweetened foods and beverages.

    Based on the evidence and other considerations noted above, the NUGAG Subgroup on Diet and Health concluded that the lack of evidence to suggest that NSS use is beneficial for body weight or other measures of body fatness over the long term, together with possible long-term undesirable effects

[1] Ideally, healthy body weight is maintained throughout the life course.

in the form of increased risk of NCDs and death, outweighed any potential short-term health effects resulting from the small reductions in body weight and BMI observed in RCTs.

- Because of lack of certainty about the overall balance of desirable and undesirable effects associated with long-term NSS use for reducing NCD risk, including the possibility that reverse causation [1] may have contributed to one or more of the associations observed between long-term NSS use and risk of disease in prospective observational studies, a conservative approach was taken, leading to a conditional recommendation.

Remarks

- With the exception of individuals with diabetes (as noted below), this recommendation is relevant for everyone: children and adults of any age, including pregnant and lactating women.
- The objective of this guideline is to provide guidance on the use of NSS in efforts to prevent unhealthy weight gain and diet-related NCDs, in the context of reducing free sugars intake. Assessing the health effects of NSS on individuals with pre-existing diabetes with the aim of providing guidance on disease management was beyond the scope of the guideline. Consequently, in the evidence reviewed, studies conducted exclusively in individuals with pre-existing diabetes were excluded, and in studies with mixed populations, diabetes was often controlled for as a potential confounding characteristic. Therefore, although individuals with diabetes can also reduce free sugars intake without the need for NSS, the recommendation does not apply to individuals with existing diabetes.
- The recommendation is relevant for all NSS, which are defined in this guideline as all synthetic and naturally occurring or modified non-nutritive sweeteners that are not classified as sugars. Common NSS include acesulfame K, aspartame, advantame, cyclamates, neotame, saccharin, sucralose, stevia and stevia derivatives. Because low-calorie sugars and sugar alcohols (polyols) are sugars or sugar derivatives containing calories, they are not considered NSS, and therefore the recommendation does not apply to these sweeteners.
- In this recommendation, "use" of NSS means consumption of foods or beverages that contain NSS, or the addition of NSS to food or beverages by the consumer.
- Many medications, and personal care and hygiene products contain NSS in small amounts to make them more palatable. The recommendation in this guideline does not apply to such products.
- "Weight control" in this recommendation refers to weight loss in cases of existing overweight or obesity, and preventing unhealthy weight gain by maintaining a healthy weight.
- The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has set acceptable daily intakes (ADIs) for most commercially used NSS. Evidence supporting this WHO recommendation comes from a systematic review of studies in which NSS were consumed in amounts within the ADI set by JECFA, either because this was explicitly stated in the study or it was reasonably inferred that the ADI was not being exceeded.[2]
- The recommendation in this guideline was made based on evidence that suggests that there may be health effects associated with NSS use irrespective of which NSS is being used – that is, NSS as a class of compounds, despite individual NSS having different chemical structures, may have an impact on health. It is recognized that NSS are not a homogeneous class of compounds: each has a unique chemical structure. As a result, individual NSS have different sweetness intensities and organoleptic properties, and are processed differently by the body. Although limited evidence suggests that individual NSS may also differ in some of their physiological effects in humans, the evidence is currently insufficient to make recommendations for individual NSS.

[1] A phenomenon sometimes observed in prospective cohort studies whereby those already in a pre-disease state or with increased risk of disease increase their exposure to the risk factor of interest, erroneously leading to the conclusion that increased exposure to the risk factor of interest leads to increased risk of disease.

[2] For prospective cohort studies, it was generally not possible to determine the absolute highest intakes because the highest quantile was generally a specified amount or more (e.g. ≥2 servings per day). Although it is possible that some adults may have exceeded the ADI in some of these studies, the number doing so would probably have been an extremely small percentage of the entire group. The likelihood that children exceed the ADI is greater given their lower body weight; however, it is still expected to be a small percentage in most populations.

- Efforts to reduce free sugars intake should be implemented in the context of achieving and maintaining a healthy diet. Because free sugars are often found in highly processed foods and beverages with undesirable nutritional profiles, simply replacing free sugars with NSS results means that the overall quality of the diet is largely unaffected. Replacing free sugars in the diet with sources of naturally occurring sweetness, such as fruits, as well as minimally processed unsweetened foods and beverages, will help to improve dietary quality, and should be the preferred alternatives to foods and beverages containing free sugars.

Introduction

Background

Escalating rates of overweight and obesity are a threat to the health of billions of people across the globe. In 2016, more than 1.9 billion adults aged 18 years and older were overweight *(1)*. Of these, more than 600 million were obese. In 2020, more than 38 million children under 5 years of age were overweight – an increase of nearly 6 million during the past 20 years *(2)*. High body mass index (BMI) was responsible for an estimated 4 million deaths in 2017 *(3)*, with greater increases in BMI in the overweight and obesity range leading to a greater risk of mortality *(4)*. Obesity is also a risk factor for many noncommunicable diseases (NCDs), including cardiovascular diseases (CVDs), type 2 diabetes and certain types of cancer. NCDs are the leading causes of death globally and were responsible for an estimated 41 million (71%) of the 55 million deaths in 2019 *(5)*. Obesity and certain NCDs also increase the likelihood of becoming severely ill from COVID-19 infection *(6–10)*.

A high level of free sugars intake is associated with poor dietary quality *(11)*, obesity *(12)* and risk of NCDs *(13)*, and the World Health Organization (WHO) has issued guidance on limiting free sugars intake to reduce the risk of unhealthy weight gain and dental caries *(14)*. Since the release of the WHO guideline on free sugars intake, interest in the potential utility of non-sugar sweeteners (NSS)[1] to reduce sugars intake at the population level has increased.

Referred to by a variety of names, including high-intensity sweeteners, low- or no-calorie sweeteners, non-nutritive sweeteners, non-caloric sweeteners and sugar-substitutes, NSS have been developed as an alternative to free sugars. They are widely used as an additive in pre-packaged foods, beverages and personal care products (e.g. toothpaste, mouthwash), as well as added to foods and beverages directly by the consumer. Because of their ability to impart sweet taste without calories, NSS are generally marketed as aiding weight loss or maintenance of healthy weight. They are incorporated into prepared and packaged foods and beverages in a number of ways, including individually, in combinations of different NSS or in combination with free sugars *(15)*. NSS are also frequently recommended as a means of controlling blood glucose levels in individuals with diabetes. NSS include a wide variety of synthetically derived chemicals and natural extracts that may or may not be chemically modified, and are generally many times sweeter than sugars, which allows them to be added to foods and beverages in very small quantities. Common NSS include acesulfame K, aspartame, advantame, cyclamates, neotame, saccharin, sucralose, stevia and stevia derivatives; certain D-amino acids, and several plant proteins and other extracts also impart a sweet taste.

NSS elicit sweet taste through binding and activation of sweet-taste receptors located in the oral cavity, with subsequent signalling to the brain *(16)*. Sweet-taste receptors have more recently been found at sites outside the oral cavity, including the gastrointestinal tract, pancreas, brain and adipose tissue *(17)*, and may be involved in various metabolic effects of NSS observed in a large body of in vitro, animal and human studies *(18–22)*.

Individual NSS undergo toxicological assessment by various authoritative bodies, such as the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA), to establish safe levels of intake (i.e. acceptable daily intake, or ADI). Although results of randomized controlled trials (RCTs) have generally suggested that NSS may have limited impact on glucose metabolism and result in lower body weight (when coupled with energy restriction) in the short term, there is no clear consensus

[1] For the purposes of this guideline, NSS are defined as all synthetic and naturally occurring or modified non-nutritive sweeteners that are not classified as sugars. Sugar alcohols and low-calorie sugars are not considered to be NSS.

on whether NSS are effective for long-term weight loss or maintenance, or if they are linked to other long-term health effects at intakes within the ADI. In addition, although individual NSS interact with the same sweet-taste receptor to elicit sweet taste and likely result in the same physiological effects to some extent, they are not a homogeneous class of compounds: each has a unique chemical structure, which is reflected in different sweetness intensities, organoleptic properties and routes of processing by the body *(15)*. As a result of these differences, individual NSS may have different physiological effects in humans *(19)*.

Global trends in NSS use are unclear because NSS have yet to appreciably enter some markets, and robust longitudinal intake data are not readily available for many low-and middle-income countries (LMICs) *(23, 24)*. Nevertheless, available data indicate that the number of foods and beverages containing NSS and NSS use are significant in diverse settings worldwide *(23–28)*. Although intake rarely appears to exceed the ADI *(29)*, NSS availability and use (predominantly in the form of consumption of beverages containing NSS) appear to be increasing in many locations – for example, in New Zealand, Norway, Slovenia and the United States of America (the United States) *(30–34)*. This corresponds with a decline in consumption of sugar-sweetened beverages – for example, in the United States and Norway *(31, 33)*. Evidence suggests that the shift from free sugars to NSS occurring in the United States and elsewhere may also be occurring in other countries as global efforts to reduce the intake of free sugars intensify, particularly in settings that are implementing multiple policy actions to reduce free sugars intake *(23)*.

Rationale

Following the work of the 1989 WHO Study Group on Diet, Nutrition and the Prevention of Chronic Diseases *(35)*, and the 2002 Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases *(36)*, WHO guidance on free sugars intake was updated and released in 2015 *(14)*. Since the release of that guideline, interest has increased in guidance on whether incorporating NSS into policy actions and interventions aimed at reducing free sugars intake may be effective and appropriate. At the same time, NSS availability and their use by consumers have increased. Therefore, it was considered important to review the evidence in a systematic manner, and issue WHO guidance on NSS use through the WHO guideline development process.

Scope

This guideline is an extension of the larger effort to update the dietary goals for the prevention of obesity and diet-related NCDs originally established by the 1989 WHO Study Group on Diet, Nutrition and the Prevention of Chronic Diseases *(35)* and updated by the 2002 Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases *(36)*. It is intended to complement other WHO guidance on healthy diets, particularly the WHO guideline on sugars intake *(14)*. The recommendation in this guideline is intended for the general population of children and adults, including pregnant women. The guidance in this guideline is based on evidence of health effects of NSS use at levels already considered safe by JECFA)[1], and is not intended to update or replace existing guidance on safe or maximal levels of intake. Safe levels of intake are based on toxicological assessments of individual NSS, which are undertaken by authoritative bodies before individual NSS are approved for commercial use.[2] Because the work of the Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health is focused on providing guidance on the prevention of unhealthy weight gain and diet-related NCDs, providing guidance on the management of diabetes in individuals with pre-existing diabetes is beyond the scope of this guideline.

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[1] http://www.fao.org/food-safety/scientific-advice/jecfa/en/

[2] In 2021, JECFA was requested to re-evaluate the safety of aspartame (https://www.fao.org/fao-who-codexalimentarius/sh-proxy/fr/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FCircular%252520Letters%252FCL%2525202021-81%252Fcl21_81e.pdf). In 2019, an international Advisory Group identified the evaluation of aspartame as a high priority for the International Agency for Research on Cancer (IARC) Monographs programme during 2020–2024 (https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf). The two evaluations will be complementary: IARC will assess the potential carcinogenic effect of aspartame (hazard identification), while JECFA will update its risk assessment exercise, including reviewing the ADI and aspartame diet exposure assessment. IARC's hazard identification is planned for 6–13 June 2023, and JECFA's risk assessment for 27 June – 6 July 2023.

Objective

The objective of this guideline is to provide evidence-informed guidance on the use of NSS. The recommendation in this guideline can be used by policy-makers and programme managers to address NSS use in their populations through a range of policy actions and public health interventions.

The WHO recommendation on NSS use is an important element of WHO's efforts in implementing the NCD agenda and achieving the "triple billion" targets set by the 13th General Programme of Work (2019–2023), including 1 billion more people enjoying better health and well-being. 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, which was adopted by the 66th World Health Assembly held in May 2013 (the timeline was extended to 2030 at the 72nd World Health Assembly held in May 2019);
- implementation of the recommendations of the high-level Commission on Ending Childhood Obesity established by the WHO Director-General in May 2014;
- 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 International Conference on Nutrition (ICN2) in 2014 and endorsed by the 136th Session of the WHO Executive Board held in January 2015 and the 68th World Health Assembly held in 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, particularly Goal 2 (Zero hunger) and Goal 3 (Good health and well-being).

Target audience

This 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 thus:

- policy-makers at the national, local and other 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;
- educators teaching nutrition and prevention of NCDs at all levels; 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 (37)*. Because of the complex nature of the guideline topic and the rapidly evolving evidence base, the guideline was developed over several meetings of the NUGAG Subgroup on Diet and Health, beginning in 2016.

Contributors to the development of this guideline

This guideline was developed by the WHO Department of Nutrition and Food Safety (formerly the Department of Nutrition for Health and Development). Several groups contributed to the development of this guideline, and additional feedback was received from interested stakeholders via public consultation, 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 an interest 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 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 multiple 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). Professor 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,[1] along with information on each meeting of the group.

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**).

Systematic review teams

Systematic review teams with expertise in both systematic review methodologies and the subject matter were identified.

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[1] 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.

- A team from the University of Freiburg in Germany and the University of Pécs in Hungary, consisting of Ingrid Töws, Szimonetta Lohner, Daniela Küllenberg de Gaudry, Harriet Sommer and Joerg Meerpohl, completed the original systematic review on NSS use and prioritized health outcomes commissioned by WHO and published in 2019 *(38)*.
- Magali Rios-Leyvraz, WHO consultant, and Jason Montez of WHO completed the updating and expansion *(39)* of the original 2019 systematic review.

Teams consulted frequently with the WHO Secretariat to ensure that the reviews met the needs of the WHO guideline development process.

Stakeholder feedback via public consultation

Two public consultations were held during the development of this guideline: one at the scoping phase of the process in 2016 (feedback was received from a total of 13 individuals and organizational stakeholders) and one on the draft guideline in July 2022 (feedback was received from a total of 45 individuals and organizational stakeholders). 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 additional gaps in the evidence to be addressed by future research. The consultation was open to everyone. Declaration of interest forms were collected from all those submitting comments, which were assessed by the WHO Secretariat, following the procedures for management of interests described in the next section. Comments were summarized, and together with WHO responses to the summary comments, posted on the WHO website.[1] Comments that helped to focus the scope of the guideline or improve clarity and usability of the draft guideline were considered in finalizing the scope and the guideline document.

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, where necessary. Declared interests of members of the NUGAG Subgroup on Diet and Health and of the systematic review teams 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 teams, 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 (37)* were followed.

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

Guideline development process

Scoping of the guideline

The scientific literature was reviewed to identify important populations, outcomes and other topics relevant to the health effects of NSS use. Existing systematic reviews on the topic were identified. 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 new systematic reviews.

[1] https://www.who.int/groups/nutrition-guidance-expert-advisory-group-(nugag)/diet-and-health

Defining key questions and prioritizing outcomes

The questions were based on the needs of Member States and international partners for policy and programme guidance. The population, intervention, comparison and outcome (PICO) format was used in generating the questions (**Annex 5**). The PICO questions were first discussed and reviewed by the WHO Secretariat and the NUGAG Subgroup on Diet and Health, and were then made available for public comment in 2016.

The key questions that guided the systematic reviews undertaken are as follows.

- What is the effect on prioritized health outcomes in adults, children and pregnant women of higher intake of NSS compared with lower intake?
- What is the effect on prioritized health outcomes in adults, children and pregnant women of replacing free sugars with NSS?

Priority health outcomes considered for adults were overweight and obesity, dental caries, type 2 diabetes, CVDs, cancer, chronic kidney **curse**, eating behaviour (including sweet preference) and several cognitive parameters. Priority health outcomes for children were identical to those for adults, but also included asthma and allergies. Biomarkers of type 2 diabetes and CVDs (e.g. fasting glucose, fasting insulin, blood lipids) were implicitly included in the outcomes. Pregnant women were not treated as a separate population in the original scope of the guideline, but rather included in the context of adults. Subsequently, outcomes relevant to pregnancy and childbirth were added to those for adults, including gestational diabetes, birth outcomes, and health outcomes of offspring early in life. Additionally, all-cause mortality was not originally prioritized but was subsequently added based on screening of relevant studies.

Evidence gathering and review

Two systematic reviews were conducted to assess the relationship between NSS use and health outcomes of interest in adults and children.

- A review of RCTs and observational studies that assessed the effects of NSS use in adults and children. This review, completed in 2019, did not include or assess studies in which NSS were not specified by name or type *(38)*.
- An update of the 2019 review of RCTs and observational studies that assessed the effects of NSS use in adults and children, and included studies in which NSS were not specified by name or type, as well as studies conducted exclusively in pregnant women *(39)*. This review was published in 2022.

Because the 2022 review is the most up to date and comprehensive, it was used in the development of this guideline.

Assessment of certainty in the evidence

The GRADE[1] methodology was used to assess the certainty (i.e. confidence) in the evidence identified in the systematic reviews. GRADE assessments assigned by the systematic review teams were discussed by the NUGAG Subgroup on Diet and Health and the systematic review teams, and refined as necessary under the guidance of an expert with extensive expertise in GRADE methodology. GRADE assessments are summarized in **Annex 6**.

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 recommended intervention, the priority of the problem that the intervention would address, values and preferences related to the effects of the intervention in different settings, the cost of the options available to public health officials and programme managers in different settings, the feasibility and acceptability of implementing the intervention in different settings, and the potential impact on equity and human rights (**Annex 7**) . Based on the evidence and additional factors, the NUGAG Subgroup on Diet and Health developed the recommendation and associated remarks by consensus.

[1] http://www.gradeworkinggroup.org/

Summary of evidence

Systematic review characteristics

A systematic review of RCTs and observational studies that assessed the health effects of NSS use in adults, children and pregnant women identified 283 unique studies, including 50 RCTs, 97 prospective cohort studies and 47 case–control studies *(39)*.[1] Only studies in which NSS were consumed in amounts within the ADI,[2] either because this was explicitly stated in the study or it was reasonably inferred that the ADI was not being exceeded, were included in the systematic review.[3] Because assessing the effects of NSS use in individuals with diabetes was beyond the scope of this guideline,[4] studies specifically assessing the effects on individuals with pre-existing diabetes or including only such individuals were not included in the review.[5]

RCTs

The systematic review included 45 RCTs conducted in adults, four in children, and one including both adults and children. No RCTs in pregnant women were identified.

Trial duration in adults (including follow-up post-intervention) ranged from 7 days to more than 3 years. Trials in adults were conducted in lean (*n* = 10), mixed weight (*n* = 20) or exclusively overweight (*n* = 15) populations. Thirteen of the trials used an unspecified NSS in their intervention, 12 used aspartame, six used sucralose, three used stevia, one used saccharin, five used a mix of more than one NSS, one used advantame, and four tested multiple NSS separately (saccharin, aspartame, rebaudioside A/stevia, sucralose; sucralose, stevia; aspartame, acesulfame K). Most trials assessed the effects of NSS via consumption of NSS-containing beverages. Trials in adults were conducted in Australia (*n* = 2), Denmark (*n* = 2), France (*n* = 2), Greece (*n* = 1), the Republic of Korea (*n* = 4), Iran (Islamic Republic of) (*n* = 1), Latvia (*n* = 1), Mexico (*n* = 6), New Zealand (*n* = 2), Switzerland (*n* = 1), Thailand (*n* = 1), the United Kingdom of Great Britain and Northern Ireland (the United Kingdom) (*n* = 7), the United States (*n* = 14) and multiple countries (*n* = 1).

RCTs in children lasted from 6 weeks to 18 months. Two trials used stevia in the intervention arm, one used a mix of sucralose and acesulfame K, and one used sucralose. One trial in children was conducted in each of the following countries: India, Italy, Netherlands (Kingdom of the) and South Africa.

The single trial conducted in adults and children included a mixed-sex population, with aspartame in the intervention arm, and was conducted in the United States.

Interventions in the trials included:

- dietary advice (with or without the provision of food) to effect behaviour change (e.g. replacing sugar-sweetened foods and/or beverages with foods and/or beverages containing NSS or that were unsweetened);

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[1] Several relevant non-randomized intervention studies, cross-sectional studies and ongoing or registered RCTs were also identified and noted in the systematic review *(39)*.

[2] As assessed by JECFA (http://www.fao.org/food-safety/scientific-advice/jecfa/en/).

[3] For prospective cohort studies, it was generally not possible to determine the absolute highest intakes because the highest quantile was generally a specified amount or more (e.g. ≥2 servings per day). Although it is possible that some adults may have exceeded the ADI in some of these studies, the number doing so would likely have been an extremely small percentage of the entire group *(23, 24, 29)*. The likelihood that children exceed the ADI is greater given their lower body weight; however, it is still expected to be a small percentage in most populations *(24)*.

[4] See the section *Scope*.

[5] With the exception of studies assessing type 2 diabetes as an outcome (in which individuals with existing diabetes were screened out), prospective cohort studies were generally conducted in a given population at large and therefore could have included some individuals with pre-existing diabetes. Many cohort studies tested statistical models that adjusted for diabetes as a potential confounder.

- supplemental foods and beverages containing sugars or NSS (in addition to existing diet);
- asking habitual users of NSS to discontinue use; and
- providing NSS in capsule form compared with a placebo.

The focus of the trials was not always on assessing the effects of NSS; many had the primary goal of testing the effects of sugars intake and used NSS as a control.

Prospective cohort studies

The systematic review included 64 prospective cohort studies conducted in adults (representing 35 unique cohorts), 15 cohort studies in children (representing 13 unique cohorts), one cohort study in children and adults (representing one unique cohort) and 17 cohort studies in pregnant women (representing 12 unique cohorts). Of the studies in adults, 47 were of mixed sex, 15 were exclusively female, and 2 were exclusively male. All studies of children were of mixed sex, except one that was exclusively girls. Follow-up in cohort studies in adults ranged from 2 years to more than 30 years, in children from 8 months to 10 years, and in pregnant women from 8 months to 16 years. All but 11 of the cohort studies conducted in adults, one cohort study in pregnant women and all cohort studies in children exclusively assessed associations between NSS-containing beverages and health outcomes. The remaining cohort studies mostly assessed associations between NSS-containing beverages and foods together. Cohort studies in adults were conducted in Australia (*n* = 3), France (*n* = 4), Japan (*n* = 1), Mexico (*n* = 1), the Russian Federation (*n* = 1), Spain (*n* = 4), the United Kingdom (*n* = 1), the United States (*n* = 44) and multiple countries (*n* = 5). Cohort studies in children were conducted in Australia (*n* = 1), Denmark (*n* = 1), the United Kingdom (*n* = 1) and the United States (*n* = 12). The cohort study in children and adults was conducted in Australia. Cohort studies in pregnant women were conducted in Canada (*n* = 1), Denmark (*n* = 6), Germany (*n* = 1), Iceland (*n* = 1), Netherlands (Kingdom of the) (*n* = 1), Norway (*n* = 2), Slovenia (*n* = 1), the United Kingdom (*n* = 1) and the United States (*n* = 3).

Case–control studies

The systematic review included 41 case–control studies (42 datasets) assessing cancer outcomes in adults. All case–control studies were conducted in populations of mixed weight. Two were conducted exclusively in males, three exclusively in females and the rest in mixed-sex populations. Twenty-two studies assessed unspecified sweeteners, 11 multiple sweeteners, seven saccharin and two aspartame. Studies were conducted in Argentina (*n* = 2), Canada (*n* = 4), Denmark (*n* = 3), Egypt (*n* = 1), France (*n* = 2), Italy (*n* = 2), Japan (*n* = 2), Lebanon (*n* = 1), China (*n* = 2), Serbia (*n* = 1), Spain (*n* = 1), Sweden (*n* = 2), the United Kingdom (*n* = 2), the United States (*n* = 15) and multiple countries (*n* = 1). Two studies conducted in the United States assessing cancer in children were also included.[1]

Results of systematic review

Adults

Results for adults are summarized in **Table 1**.

Body fatness

Systematic review and meta-analyses of RCTs found that, at the end of the trials, those consuming more NSS had lower body weight than those consuming less or no NSS (–0.71 kg) and lower BMI (–0.14 kg/m^2), although the latter was not statistically significant. In contrast, higher intakes of NSS[2] were associated with a higher BMI (0.14 kg/m^2) and a 76% increase in risk of incident obesity, as assessed by meta-analyses of prospective cohort studies.

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[1] In addition, three case–control studies assessing outcomes other than cancer in adults were included in the review but were not assessed as part of the evidence base because data were available from higher-quality RCTs and/or prospective observational studies.

[2] Many RCTs compared use of NSS with no use of NSS, whereas prospective observational studies compared different levels of NSS use. To maintain consistency in comparing results across study designs, results are therefore generally reported for effects of higher compared with lower intake, noting that, in most trials, "lower intake" may in fact be no intake.

Table 1. Summary of results from meta-analyses of RCTs and observational studies for higher compared with lower intake of NSS in adults

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty
Body weight (kg)				
RCT	MD −0.71 (−1.13 to −0.28)	29	2 433	Low
Observational (cont)	MD −0.12 (−0.40 to 0.15)	4	118 457	Very low
Observational (H/L)	MD −0.01 (−0.67 to 0.64)	5	11 874	Very low
BMI (kg/m2)				
RCT	MD −0.14 (−0.30 to 0.02)	23	1 857	Low
Observational	MD 0.14 (0.03 to 0.25)	5	80 583	Very low
Obesity				
Observational	HR 1.76 (1.25 to 2.49)	2	1 668	Low
Type 2 diabetes				
Observational (bev)	HR 1.23 (1.14 to 1.32)	13	408 609	Low
Observational (TT)	HR 1.34 (1.21 to 1.48)	2	62 582	Low
Fasting glucose (mmol/L)				
RCT	MD −0.01 (−0.05 to 0.04)	16	1 494	Moderate
Fasting insulin (pmol/L)				
RCT	MD −0.49 (−4.99 to 4.02)	10	759	Low
HbA1c (%)				
RCT	MD 0.02 (−0.03 to 0.07)	6	411	Moderate
HOMA-IR				
RCT	MD 0.03 (−0.32 to 0.38)	11	786	Low
High fasting glucose				
Observational	HR 1.21 (1.01 to 1.45)	3	11 213	Low
All-cause mortality				
Observational	HR 1.12 (1.05 to 1.19)	8	860 873	Very low
CVD mortality				
Observational	HR 1.19 (1.07 to 1.32)	5	598 951	Low
CVDs				
Observational	HR 1.32 (1.17 to 1.50)	3	166 938	Low
CHD				
Observational	HR 1.16 (0.97 to 1.39)	4	205 455	Very low
Stroke				
Observational	HR 1.19 (1.09 to 1.29)	6	655 953	Low
Hypertension				
Observational	HR 1.13 (1.09 to 1.17)	6	234 137	Low
Systolic blood pressure (mmHg)				
RCT	MD −1.33 (−2.71 to 0.06)	14	1 440	Moderate
Diastolic blood pressure (mmHg)				
RCT	MD −0.51 (−1.68 to 0.65)	13	1 137	Moderate
LDL cholesterol (mmol/L)				
RCT	MD 0.03 (−0.03 to 0.09)	12	1 193	Low
Cancer mortality				
Observational	HR 1.02 (0.92 to 1.13)	4	568 175	Very low
Cancer (any type)				
Observational	HR 1.02 (0.95 to 1.09)	7	942 600	Very low

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty
Bladder cancer				
Observational (CC)	OR 1.31 (1.06 to 1.62)	26	28 589	Very low
Chronic kidney disease				
Observational	HR 1.41 (0.89 to 2.24)	2	18 372	Very low
Energy intake (kJ/day)				
RCT	MD –569 (–859 to –278)	25	2 208	Low
Sugars intake (g/day)				
RCT	MD –38.4 (–57.8 to –19.1)	12	1 239	Low

bev: beverages; BMI: body mass index; CC: case–control; CHD: coronary heart disease; CI: confidence interval; cont: continuous; CVD: cardiovascular disease; HbA1c: haemoglobin A1c; H/L: highest versus lowest; HOMA-IR: homeostasis model assessment of insulin resistance; HR: hazard ratio; LDL: low-density lipoprotein; MD: mean difference; OR: odds ratio; RCT: randomized controlled trial; TT: tabletop.

Significant associations between NSS use and other measures of body fatness were not observed in meta-analyses of RCTs or prospective cohort studies.

Results of subgroup analyses of RCTs suggest that the effect of NSS on body weight and BMI may differ by comparator. Adding NSS to the diet compared with nothing (or placebo) and adding NSS to the diet compared with sugars (either NSS replacing sugars or both NSS and sugars being added to the diet in separate arms of a trial) both resulted in decreases in body weight and BMI, with the largest effects when NSS were compared with sugars. However, NSS compared with water showed no effect on body weight and a non-significant increase in BMI. When RCTs were limited to those that gave explicit instructions to habitual consumers of sugar-sweetened beverages or sugar-containing foods to replace these foods and beverages with alternatives sweetened with NSS, the effect on body weight remained but was slightly attenuated and became statistically non-significant (mean difference [MD] –0.61 kg; 95% confidence interval [CI]: –1.28 to 0.06), and an effect on BMI was no longer observed (MD –0.01 kg/m^2; 95% CI: –0.38 to 0.35). The results of subgroup analyses also suggest that the effects observed on body weight may be greater in overweight or obese individuals and in those actively trying to lose weight – that is, trials in which weight loss was a primary aim and participants were instructed to both use NSS and reduce energy intake. However, results were not statistically significant, and the differences were small in the comparison by body weight status and highly heterogeneous in the comparison by weight loss status.

Results from a small number of RCTs and observational studies that could not be meta-analysed were largely consistent with results obtained from the meta-analyses described above.

NCDs and mortality

Meta-analyses of prospective cohort studies showed that higher intakes of NSS were associated with a 23% increase in risk of type 2 diabetes when consumed in NSS-sweetened beverages and a 34% increase in risk when consumed as a tabletop item (i.e. added to foods and beverages by the consumer), as well as a 21% increase in risk of elevated fasting glucose. Results from meta-analyses of RCTs suggested no significant effect of NSS on biomarkers used in the assessment and diagnosis of diabetes and insulin resistance, including fasting glucose, fasting insulin and haemoglobin A1c (HbA1c). The majority of several RCTs that could not be included in the meta-analyses also reported no significant effect of NSS on biomarkers relevant to diabetes.

Higher intakes of NSS were also associated with a 32% increased risk of CVDs, including stroke (19% increase) and its precursor hypertension (13% increase), but not with coronary heart disease, cancer diagnoses or chronic kidney disease, as assessed by meta-analyses of prospective cohort studies. Results from RCTs suggested no significant effect of NSS on biomarkers used in the assessment and diagnosis of CVDs, including blood pressure, low-density lipoprotein (LDL) cholesterol and other blood lipids. Higher intakes of NSS (primarily saccharin) were associated with increased risk of bladder cancer as assessed in case–control studies, but were not associated with overall risk of cancer as assessed by meta-analysis of prospective cohort studies.

Higher intakes of NSS were associated with a 10% increase in risk of death from any cause (i.e. all-cause mortality) and a 19% increase in risk of death from CVDs, but were not associated with death from cancer.

Eating behaviour

Results from meta-analyses of RCTs found that, at the end of the trials, those consuming NSS had significantly reduced daily energy intake (–569 kJ) and daily sugars intake (–38.4 g). In subgroup analyses, a reduction in energy intake was only observed when NSS were compared with sugars; energy intake was not reduced when NSS were compared with placebo or water.

The overall certainty in the available evidence for an effect of NSS intake on outcomes in adults was assessed as *low*.[1] GRADE assessments for each outcome can be found in **Annex 6**, GRADE evidence profiles 1 and 2.

Children

Evidence for health effects of NSS use in children was much more limited than that identified for adults. One well-conducted RCT reported small but significant reductions in several measures of body fatness. However, results of meta-analyses of RCTs and prospective cohort studies found no significant relationships between NSS use and measures of body fatness, including risk of being overweight (**Table 2**).

Additionally, although two RCTs found that use of stevia reduced indicators of dental caries, the interventions varied greatly: one trial assessed effects of stevia-containing snacks, the other the effects of a stevia mouth

Table 2. Summary of results from meta-analyses of RCTs and observational studies for higher compared with lower intake of NSS in children

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty
Body weight (kg)				
RCT	MD –1.01 (–1.54 to –0.48)	1	641	Moderate
Observational (cont)	MD 0.03 (–0.14 to 0.21)	2	1 633	Low
BMI (kg/m²)				
Observational (cont)	MD 0.08 (–0.01 to 0.17)	5	11 907	Very low
Observational (H/L)	MD 0.04 (–0.32 to 0.40)	2	2 426	Very low
BMI *z*-score				
RCT	MD –0.07 (–0.26 to 0.11)	2	1 264	Moderate
Observational (cont)	MD –0.23 (–0.70 to 0.25)	3	610	Very low
Observational (H/L)	MD 0.00 (–0.30 to 0.30)	1	98	Very low
Waist circumference				
RCT	MD –0.66 (–1.23 to –0.09)	1	641	Moderate
Body fat mass (kg)				
RCT	MD –0.57 (–1.02 to –0.12)	1	641	Moderate
Observational	MD –1.00 (–2.52 to 0.52)	1	98	Very low
Body fat mass (%)				
RCT	MD –1.07 (–1.99 to –0.15)	1	641	Moderate
Observational	MD –1.53 (–5.73 to 2.66)	2	720	Very low
Overweight				
Observational	OR 1.25 (0.43 to 3.66)	2	3 064	Very low

BMI: body mass index; CI: confidence interval; cont: continuous; H/L: highest versus lowest; MD: mean difference; OR: odds ratio; RCT: randomized controlled trial.

[1] Based on the grades of evidence set by the GRADE Working Group. *High* certainty means that we are very confident that the true effect lies close to that of the estimate of the effect; *moderate* certainty means that 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 means that our confidence in the effect estimate is limited – the true effect may be substantially different from the estimate of the effect; and *very low* certainty means that we have very little confidence in the effect estimate – the true effect is likely to be substantially different from the estimate of the effect *(37)*.

rinse. No significant relationships were found for other outcomes of interest, including biomarkers used in the assessment and diagnosis of type 2 diabetes, CVDs, cancer, neurocognition, or energy and sugars intake, although the number of studies contributing to the evidence base for these outcomes was limited.

The overall certainty in the available evidence for an effect of NSS intake on outcomes assessed directly in children was assessed as *moderate*. GRADE assessments for each outcome can be found in **Annex 6**, GRADE evidence profile 3. In formulating the recommendation, because both adult data and child data were considered for children, the overall certainty in the available evidence across both groups was assessed as *low*.

Pregnant women

Evidence for health effects of NSS use in pregnant women was also limited. Higher intakes of NSS were associated with a 25% increase in risk of preterm birth, as assessed by meta-analyses of three prospective cohort studies (odds ratio [OR] 1.25; 95% CI: 1.07 to 1.46; 129 009 pregnant women). A dose–response relationship was observed in the two studies that reported a significant association. Additional analyses suggested that the association was primarily for late preterm delivery (34–37 weeks), not early preterm delivery (<32 weeks), and that the observed risk was similar for lean and overweight women.

Results from prospective cohort studies on potential impact of NSS use during pregnancy on birth weight and body weight of offspring later in life were not amenable to meta-analyses and were inconsistent. Results from two prospective cohort studies suggested no association between NSS use during pregnancy and birth weight, whereas results from a third suggested an increase in birth weight. In addition, results from two separate prospective cohort studies suggested an association between NSS use during pregnancy and increased body fatness in offspring in early or mid-childhood, whereas results from a third suggested no association.

Results for other outcomes were generally limited to single studies. Results from one prospective cohort study suggested an association between NSS use during pregnancy and increased risk of asthma and allergies in offspring in early and mid-childhood, and results from another suggested an association between NSS use during pregnancy and early and mid-childhood cognition scores. No associations were observed between NSS use and risk of gestational diabetes.

The certainty in the available evidence for an effect of NSS intake on outcomes in pregnant women was assessed as *very low* overall. GRADE assessments for each outcome can be found in **Annex 6**, GRADE evidence profile 4. In formulating the recommendation, because both adult data and data from pregnant women were considered for pregnant women, the certainty in the available evidence across both groups was assessed as *low*.

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 helps to establish the context for the recommendation *(37)*. They are summarized below.

Varied interventions in RCTs. The design of the interventions in RCTs included in the systematic review varied considerably, which reduced confidence that the overall results observed were highly relevant for the primary, intended purpose of NSS, which is to replace free sugars in the diet, particularly in the diet of individuals habituated to high levels of sweetness. Most trials provided NSS or free sugars (in beverage form) as an addition to the regular diet, often to assess whether individuals compensated energy intake when provided with additional free sugars, with NSS serving as a control. Although such studies can assess whether adding NSS to the diet affects energy intake or other relevant outcomes compared with adding free sugars, they do not assess the behavioural component of switching from free sugars to NSS, and thus are an indirect measure of the effects of replacing free sugars with NSS. Only four trials specifically assessed the effects on habitual consumers of sugar-sweetened beverages of replacing these beverages with NSS-sweetened alternatives, and while effects on body weight remained, an effect on BMI was no longer observed. In the three studies that also assessed water as a replacement in a separate arm, water was found to be as effective as, or more effective than, NSS-sweetened beverages with respect to lowering body weight. In addition to these trials, a small number of trials provided NSS with water or nothing (placebo)

as the comparator (with or without accompanying instructions to restrict energy intake), provided NSS in capsule form, or assessed the effects of asking habitual consumers of NSS-sweetened beverages to switch to water. Therefore, although it was possible to compare how individuals responded to NSS compared with free sugars across a fairly large number of trials, the evidence for effects of specifically replacing free sugars with NSS is somewhat limited.

Potential mechanisms of NSS action on body weight. The wide variety of interventions in the included RCTs did allow assessment of the effects of NSS regardless of potential mechanism of action – that is, whether the effects observed for NSS use were a result of inherent pharmacological properties of NSS or changes in behaviour, such as modifying energy intake. Additional subgroup analyses allowed further assessment of effects of NSS by delivery mode, comparator, type of NSS and other parameters. Results of these analyses showed that a significant difference in body weight and BMI was only observed in trials that reported a reduction in energy intake, and energy intake was only significantly different in the arms of trials that compared NSS with free sugars. This suggests that the lower body weight and BMI observed in the RCTs is mediated at least in part by lower energy intake as a result of decreased free sugars intake, rather than primarily by an inherent property of NSS that can modulate body weight (independently of energy intake).

Duration of RCTs. Because weight loss or maintenance of a healthy weight must be sustained over the long term[1] in order to realize associated health benefits, any intervention being investigated for effects on body weight should provide evidence of sustained weight loss or maintenance. The majority of RCTs assessing NSS lasted 3 months or less, and the small number that lasted more than 3 months gave inconsistent results. Of these, only one trial lasted longer than 18 months *(40)*. However, this trial mainly assessed the outcome of asking habitual users of NSS to stop using NSS, and therefore did not directly assess the effects of replacing free sugars with NSS. In addition, both individuals who were instructed to continue using NSS and those who were instructed not to use NSS lost an equivalent amount of weight during the active weight loss phase of the trial (first 16 weeks). Only during the subsequent weight maintenance and follow-up phases did those not using NSS regain more weight, although, at 1 year after the weight loss phase, energy intakes were equivalent between the two groups and, at 3 years, the difference in aspartame intakes between the two groups narrowed considerably (although less than 50% of the original participants provided data).

Because results from the longer-term trials were inconsistent and difficult to interpret, and evidence from long-term observational studies suggested increased BMI and risk of obesity with NSS use, the NUGAG Subgroup on Diet and Health did not consider the observed weight loss in RCTs – driven primarily by trials lasting 3 months or less – to be indicative of health benefit.

Possible differences in manner of NSS use between RCTs and prospective cohort studies. The manner in which individuals consumed NSS and free sugars in the RCTs was carefully planned and controlled. In many trials, participants were provided with foods and beverages to be consumed according to a schedule, and otherwise were given explicit instructions on what to do. In some trials, participants also received additional or follow-up support from those conducting the trials (e.g. nutrition guidance, further instruction). Participants understood that they were taking part in a scientific study and generally, but not always, knew which intervention they were receiving (i.e. whether they were consuming NSS, free sugars, water, something else or nothing), although the actual aims of many of the trials were purposefully obscured so as to not influence the participants. The manner in which individuals consume NSS in the "real world" likely differs significantly from how they were consumed in the trials and is more accurately reflected in the prospective cohort studies. In free-living populations, NSS are likely consumed in complex ways *(41–44)*, often not as a conscious replacement for free sugars, but together with foods and beverages containing free sugars, or in a compensatory manner in which a food or beverage containing NSS is consumed so that another, often energy-dense, food can be consumed. Some may add foods and beverages containing NSS to existing diets with the general belief that NSS-containing foods are simply "healthier" *(45)*. Rather than consuming fewer calories, as observed in many of the RCTs included in the systematic review, some evidence suggests that those using NSS in free-living populations may consume more calories than those who do not use NSS *(43)*. There is also limited evidence to suggest that health effects may differ when certain NSS are consumed together with sugars compared with when they are consumed alone *(46, 47)*, though more research is needed to understand whether this is broadly applicable and what the implications may be.

[1] Ideally, healthy weight is maintained throughout the life course.

Therefore, although NSS use has been shown to lower body weight in RCTs when a reduction in energy intake is achieved, the applicability of these results to free-living populations in which NSS are likely consumed in a number of different ways is uncertain.

Potential role of reverse causation in the results from prospective cohort studies. Reverse causation was noted as a possible explanatory factor for the associations observed between NSS and health outcomes in the observational studies included in the systematic review. Reverse causation suggests that those already at elevated risk of disease initiated or increased use of NSS because of their risk status, rather than NSS leading to increased risk in otherwise healthy or low-risk individuals. In some studies, those using NSS had a higher prevalence of relevant risk factors. Pre-existing overweight and obesity – risk factors for many of the outcomes for which associations were observed – was also noted as an important potential confounder and in several studies included in the systematic review, those with higher intakes of NSS had higher average BMI at baseline.

Most authors of the included studies appreciated the potential role of reverse causation and/or confounding by body weight, and made efforts to minimize the contribution these factors may have made to the results of their studies, including:

- controlling for relevant confounders (including BMI);
- stratifying results by body weight; and
- conducting various sensitivity analyses, such as limiting analyses to individuals of normal body weight, removing from analyses those at risk for disease at baseline or who had intentionally lost weight prior to baseline, and excluding results from the first several years of follow-up to minimize the contribution to relevant health outcomes by individuals at high risk of disease at baseline who were subsequently diagnosed with the disease or experienced a relevant event shortly thereafter.

The impact of the various sensitivity analyses on results varied: some results were attenuated, some were strengthened, some were only observed at highest intakes, some remained when analyses were restricted to individuals of healthy weight, and some were more or less pronounced in overweight or obese individuals. However, in the majority of studies, particularly for type 2 diabetes, associations persisted in some way in fully adjusted models after sensitivity and other exploratory analyses. Since associations largely persist when body weight is controlled for, and there is limited evidence for an effect of NSS on incident obesity *(48, 49)*, it is possible that increased body weight (resulting from chronic NSS use) may be an intermediary step in the development of disease rather than a confounding factor.

Overall dietary quality has also been cited as a potential confounder. However, there was no consistent difference between levels of NSS use and diet quality at baseline in the studies included in the systematic review (i.e. diet quality was not consistently lower, higher or equivalent in individuals using more NSS compared with those using less), and many studies controlled for dietary quality without a significant impact on the observed associations.

It was concluded that, although reverse causation and residual confounding may be contributing factors, the available evidence suggests that the associations observed between NSS use and health outcomes in observational studies cannot be dismissed as being solely a result of reverse causation or residual confounding.

Sources of NSS exposure in studies. Most RTCs included in the systematic review assessed the effects of NSS-containing beverages. Associations observed between NSS use and priority health outcomes in prospective cohort studies of adults, children and pregnant women were also almost exclusively based on consumption of NSS-containing beverages. A small number of studies assessed the effects of tabletop NSS use (i.e. NSS added to foods or beverages by the consumer), consumption of NSS-containing foods, or some combination of beverage, food and tabletop sources. As described elsewhere in this section, the underlying mechanisms for the observed associations – particularly in observational studies – are unclear, are likely complex, and may or may not be modulated by whether NSS are primarily consumed in foods or beverages. Therefore, although most of the evidence is based on consumption of NSS-containing beverages, it was considered appropriate to evaluate the evidence with a focus on the exposure to NSS regardless of how it was consumed, and formulate recommendations accordingly.

Potential mechanisms for associations with cardiometabolic health in prospective cohort studies. Putative mechanisms have been proposed that may help to explain the associations observed between NSS use and increased risk of poor cardiometabolic health, some of which may be attributed to the expression of sweet taste receptors outside the oral cavity, including in glucose-sensing cells of tissues such as the gastrointestinal tract and pancreas *(17)*. A detailed discussion of the proposed mechanisms (and the data compiled in exploring these mechanisms) is beyond the scope of this guideline, and this topic has been reviewed extensively elsewhere *(18–22)*. In brief, potential mechanisms include effects on taste perception (e.g. sweet taste preference, thresholds of sweet-taste sensitivity), eating behaviour (e.g. hunger, appetite) and other neural responses (e.g. hedonic response to sweet taste, memory and reward pathways in the brain); pathways that link the sensing of sweet taste in the oral cavity with the expectation of subsequent energy delivery to the digestive tract; release of metabolic hormones and other biological molecules; and alterations to the bacteria colonizing the small and large intestines (i.e. gut microbiota). Proposed mechanisms are not mutually exclusive and may ultimately differ between individual NSS.

Much of the research into biological mechanisms has been carried out in in vitro and rodent models, and further research is needed to determine whether observations in non-human models translate to humans. Although there are as yet no conclusive mechanistic links between NSS use and many of the associations observed in prospective cohort studies, that plausible mechanisms have been identified, tested and in some cases validated (albeit mostly in non-human models) reinforces the seriousness with which the associations observed in prospective cohort studies should be considered and highlights the need for further exploration of possible mechanisms with additional research.

Individual versus "class" effects of NSS. Although different NSS interact with the same sweet-taste receptor to elicit sweet taste and likely result in shared physiological effects to some extent, they are not a homogeneous class of compounds: each has a unique chemical structure, which is reflected in different sweetness intensities, organoleptic properties and routes of processing by the body *(15)*. As a result of these differences, individual NSS may have different physiological effects in humans *(19)*. However, further research is necessary to allow for definitive conclusions.

Sources of potential differences in effects of NSS use. Evidence from studies included in the systematic review and elsewhere suggests that there may be important differences in the response to NSS based on sex, ethnicity and body weight status. Although evidence is currently insufficient to reach any firm conclusions regarding such differences, they may be an important consideration when assessing future evidence and should be explored further with appropriately designed studies. In addition, some outcomes (e.g. those assessing glucose metabolism) commonly assessed in RCTs of NSS use may be influenced by history of NSS use of participants at enrolment – that is, regular users of NSS may already be affected by, or desensitized to, the effects of NSS compared with non-users or infrequent users; this may explain some of the differences observed in such studies. Similarly, patterns of NSS use prior to baseline exposure assessment in prospective cohort studies may affect results. Therefore, additional research is needed to further explore the potential moderating effect of prior NSS consumption patterns on empirically obtained data.

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 that the intervention would address, values and preferences related to the effects of the intervention in different settings, the feasibility and acceptability of implementing the intervention in different settings, the potential impact on equity and human rights, and the cost of the options available to public health officials and programme managers in different settings.

Because the recommended "intervention" in this guideline is a suggestion to not include NSS in the diet, it can be viewed as a dietary goal, rather than a specific intervention, and can therefore be translated into policies and actions in a number of ways. These include various behaviour change interventions, fiscal policies, regulation of the marketing of foods and beverages, product labelling schemes, and reformulation of manufactured products, among others. Because each of these interventions has its own evidence base (which was not reviewed by the NUGAG Subgroup on Diet and Health) and requires individual consideration of the additional evidence to recommendation factors, a detailed discussion of these factors for each of the possible means of achieving the recommendation is beyond the scope of this guideline. However, forthcoming WHO guidelines will provide specific guidance on nutrition labelling policies, policies to restrict the marketing of food and non-alcoholic beverages to children, fiscal policies, and school food and nutrition policies, which will enable policy-makers to translate dietary goals into evidence-informed policy actions.[1] Therefore, in assessing the factors relevant to translating the evidence into recommendations for this guideline, the NUGAG Subgroup on Diet and Health primarily considered each in the context of achieving the recommended dietary goal.

Evidence for this process was gathered via comprehensive searches of relevant scientific databases and identification of high-quality studies, including recent systematic reviews, where available. An evidence to recommendations table can be found in **Annex 7**.

Overall certainty in the evidence

The overall certainty in the evidence was as assessed as *low* and is based on undesirable effects of NSS use on prioritized health outcomes observed in prospective cohort studies, which were individually assessed as having *very low* to *low* certainty of evidence.

Balance of desirable and undesirable effects

Although short-term benefit of NSS use on measures of body fatness was observed in controlled experimental settings, the NUGAG Subgroup on Diet and Health concluded that the lack of evidence to suggest that NSS use is beneficial for body weight and other measures of body fatness over the long term together with possible long-term adverse effects in the form of increased risk of death and disease, offset any potential short-term health benefit resulting from the relatively small reduction in body weight and BMI observed in randomized controlled trials. In addition, limited evidence for beneficial effects of NSS use on dental caries was observed in studies of children. However, this was generally only observed in studies where intake of NSS was compared with intake of free sugars, suggesting that NSS do not have any inherent properties that impact risk of dental caries; rather, the effect is a result of displacing free sugars.

[1] https://www.who.int/groups/nutrition-guidance-expert-advisory-group-(nugag)/policy-actions

In the case of NSS, the potential undesirable effects carry a greater weight when assessing desirable vs undesirable effects because a reduction in free sugars intake can be achieved and corresponding desirable health benefits realized without the use of NSS. In addition, unlike the potential effects observed from long-term exposure in adults, the evidence from prospective studies of pregnant women suggests that potential adverse effects from NSS use occur over the relatively short period of gestation.

Evidence from RCTs suggests that the effects of NSS in these studies primarily occur via a reduction in energy intake. Therefore, any potential benefit of NSS use would largely be for those who are trying to lose or maintain body weight via restriction of energy intake (resulting from replacing free sugars with NSS). NSS use may not produce desirable effects for those who are not regular consumers of free sugars or who are otherwise not at risk of excess energy intake resulting from free sugars intake. This segment of the general population would therefore likely only be subjected to the potential undesirable effects of NSS use.

NSS are not essential dietary components and provide no nutritional value themselves, and are frequently a component of highly processed foods. Therefore, a possible undesirable effect of NSS use in the context of reducing free sugars intake is the inclusion of a greater number of highly processed foods and beverages in the diet than would be included if free sugars were reduced without NSS use *(50)*.

The recommendation to not use NSS could result in potential undesirable effects, not inherent to NSS, if some individuals currently using NSS discontinue use and increase free sugars intake in order to maintain the level of sweetness in their diet. However, the undesirable effects of free sugars intake are well documented, and awareness of these effects among the general public is fairly high. Together with the fact that the recommendation in this guideline should be considered in the context of the WHO recommendations to reduce free sugars intake (14), this suggests that individuals switching from NSS to free sugars would not be a widespread occurrence.

Overall, the NUGAG Subgroup on Diet and Health concluded that the desirable effects of not using NSS outweighed the undesirable effects.

Priority of the problem, and values and preferences

Although NSS as a replacement for free sugars is generally discussed in the context of their potential impact on overweight and obesity, the evidence reviewed for the development of this guideline suggests that NSS use may also be relevant to other important health outcomes, including type 2 diabetes, CVDs and mortality, impacts on which may partly be mediated by changes in body weight.

Escalating rates of obesity threaten the health and lives of hundreds of millions individuals worldwide *(3, 4)*, and NCDs are the leading causes of death globally *(5)*. Therefore, interventions and programmes targeting reduction in risk of these outcomes are valuable in all contexts and a high priority for many countries. Despite the global burden of these outcomes, the priority placed on this problem by authorities at different levels may vary depending on the real or perceived magnitude of the problem within a particular country or region. The spotlight on prevention and management of obesity has intensified recently as a result of the COVID-19 pandemic, as there is increasing recognition that individuals with certain NCDs or obesity may be at increased risk of adverse outcomes associated with COVID-19 *(6–10)*.

The recommendation in this guideline places a high value on reducing the risk of mortality, overweight, obesity and NCDs. Although individuals almost universally value the prevention of premature mortality, those that may be impacted by the recommendation may place different values on the benefit of reducing the risk of obesity and associated disease, based on personal preferences, beliefs and customs. For example, because CVDs are a high-profile public health topic, including in many LMICs where they represent a growing threat *(51),* it is expected that most individuals would value efforts to reduce risk. However, in real-world settings, perception of the risk varies considerably *(52–56)*, and outreach and communication efforts may therefore be needed to improve understanding. Similarly, although many people in LMICs are increasingly aware of negative health effects associated with being overweight or obese, some cultures still consider overweight to be a desirable or **negative** attribute *(57–59)*. Others believe body weight to be hereditary and therefore not amenable to management via lifestyle changes *(56, 60)*. And many, regardless of personal beliefs, incorrectly perceive their own body weight in the context of overweight and obesity – that is, they believe that they are at a healthy body weight when in fact they are overweight or obese according to accepted standards for assessing body weight outcomes *(56, 60, 61)*.

Feasibility

The recommendation in this guideline can be implemented in numerous ways, including through behaviour change interventions, fiscal policies, regulation of marketing of foods and beverages, product labelling schemes, and reformulation of manufactured products. Feasibility of these interventions will depend on the country context. Regardless of specific modes of implementation, the recommendation can be incorporated into existing measures designed to promote healthy diets and would naturally complement existing efforts to reduce intake of free sugars. For example, appropriate messaging on NSS use can readily be added to existing food-based dietary guidelines and the increasing number of actions being taken to address free sugars intake, such as behaviour change and education campaigns, fiscal policies, marketing and labelling policies, and reformulation. A number of countries and municipalities already include beverages sweetened with NSS in existing food and beverage tax legislation *(62)*, and several national food-based dietary guidelines already provide guidance on NSS use *(63)*. This suggests that implementing the recommendation to not use NSS is feasible, particularly in settings that already have robust dietary guidelines and established health messaging infrastructure. However, existing efforts to reduce free sugars intake also have the potential to make implementation of the NSS recommendation more challenging: recent evidence suggests that sales of NSS-containing beverages (but not NSS-containing foods) are increasing in regions that have implemented multiple policy actions targeting free sugars intake, relative to regions that have implemented fewer or no actions *(23)*. Because NSS, and foods and beverages containing NSS are already widely available and used by large segments of the global population, implementing the recommendation will have its challenges, particularly in settings without robust infrastructure for implementing public health measures, including behaviour change communications and messaging, or where "piggy backing" on efforts to address free sugars intake is not possible.

Regardless of which interventions and policy actions are used to implement the recommendation, some amount of behaviour change at the individual level will likely be required; the extent to which this can be achieved will depend on the willingness of individuals who have become habituated to a certain level of sweetness in foods and beverages to reduce the overall sweetness in their diets. For those not habituated to high levels of sweetness in the diet (including infants and young children), avoiding NSS (and excess free sugars) – particularly in beverage form – should be very feasible. However, as noted below, because of the way in which NSS-containing foods and beverages are labelled, avoiding NSS may require vigilance on the part of consumers.

The level to which NSS use can be reduced will depend not only on the success of public health efforts and individual choice, but the extent to which consumers are aware of the NSS content in products they purchase. Evidence suggests that some consumers may not be aware that many of the food and beverages they are purchasing contain NSS *(45, 64)*, and generally may have difficulties interpreting nutrient declaration labels, health claims and other relevant labelling *(65–69)*.

Acceptability

Although the recommendation in this guideline is already in line with existing national guidance in a number of countries, acceptability may vary across different countries, and socioeconomic and cultural contexts.

Acceptability may be influenced by:

- how the recommendation is translated into policies and actions – some means of implementation may be more acceptable than others;
- the level of awareness of the potential health problems associated with NSS use – interventions may be less acceptable in settings where awareness is low;
- the potential impact on national economies; and
- compatibility with existing policies.

At an individual level, because adhering to the recommendation to not use NSS together with WHO recommendations to reduce free sugars might require a reduction in the overall sweetness of the diet, acceptability of the recommendation may be low, particularly for those accustomed to sweetness in certain types of food and beverages. Popular perceptions about NSS may also feed into acceptability

to consumers. These encompass both positive and negative feelings about sweeteners, which might be affected by whether sweeteners are categorized and marketed as "artificial" or "natural". However, for those who acknowledge the potential health risks of consuming NSS over the long term and value reducing this risk, acceptability should be high, because obesity, CVDs and type 2 diabetes are significant, recognized global health problems.

Acceptability of this recommendation can be improved through appropriate public health measures, including behaviour change communication and messaging. This should encompass not only NSS use and free sugars intake, but more broadly an overall healthy diet, including the message that whole fruits can provide a healthy source of sweetness in the diet, along with beneficial nutrients.

Equity and human rights

The impact of the recommendation on equity and human rights is not conclusively known, given the uncertainty around long-term health effects of NSS use. Assuming that the long-term associations between NSS use and increased risk of unhealthy weight gain and NCDs are valid, the recommendation in this guideline has the potential to reduce health inequity by improving the long-term health of people of lower socioeconomic status, as they are generally disproportionately affected by overweight, obesity and NCDs *(70–73)*. However, in some LMIC settings, people of higher socioeconomic status may be more at risk than those of lower socioeconomic status and may benefit more from relevant interventions *(74, 75)*. Regardless, the effect on equity and human rights would likely be affected by how the recommendation is translated into policies and actions. For example, a small number of studies suggest that fiscal policies targeting foods and beverages, front-of-pack labelling and restrictions on marketing unhealthy foods may increase health equity *(76)*. However, if such measures affect all individuals in a population equally, relevant inequalities may not be addressed *(77)*. Overall, evidence is extremely limited and inconclusive.

Resource implications

Absolute costs of translating the recommendation in this guideline into policy actions and interventions will vary widely depending on which approaches are taken. Costs may be minimized by coupling measures taken with existing efforts to reduce free sugars intake and promote healthy diets. For example, as noted under *Feasibility* above, it may be possible to incorporate the recommendation into existing policy actions and interventions, such as food-based dietary guidelines and fiscal policies targeting sugar-sweetened beverages, which might limit the resources required to implement the recommendation. Implementation of the recommendation will likely require consumer education and public health communications. These can also be incorporated into existing public health nutrition education campaigns and other existing nutrition programmes at the global, regional, national and subnational levels.

Whether or not implementing the recommendation is cost-effective (i.e. the savings in health-care costs offset or exceed the cost of implementation) is not conclusively known, given the uncertainty of long-term health effects of NSS use. However, assuming that the long-term associations between NSS use and increased risk of unhealthy weight gain and NCDs are valid, implementing the recommendation may be associated with long-term savings in costs of health care, though the extent of the savings depends on strategies chosen for implementation and the timescale for evaluation. For example, although very few (if any) cost-effectiveness analyses have been conducted for NSS use, a number of cost-effectiveness studies on taxation of sugar-sweetened beverages have been published, with most finding that taxes have the potential to result in substantial cost savings and health impact with respect to obesity and diet-related NCDs *(78–82)*. Similarly, limited evidence suggests that other policies and interventions that would be relevant to NSS, such as restrictions on marketing of unhealthy foods and beverages to children, may be cost-effective *(76)*.

In general, not using NSS should lead to a decrease in both the purchase of NSS themselves (for use by the consumer) and the purchase of foods and beverages containing NSS. In the case of NSS and certain foods and beverages with no caloric value, further adjustments to the diet would not be needed, and money could be saved by simply forgoing these purchases. Adhering to the recommendation could therefore have a positive or negative impact on disposable income, which might be amplified in people of lower socioeconomic status – particularly in LMICs – as they tend to spend a higher proportion of their income on foods and beverages *(83–85)*.

Recommendation and supporting information

This recommendation should be considered in the context of WHO recommendations to reduce free sugars intake *(14)* and other guidance promoting healthy diets, including WHO guidelines on carbohydrates *(86)*, total fat *(87)*, saturated and trans-fatty acids *(88)*, polyunsaturated fatty acids *(36),*[1] sodium (89) and potassium *(90)*. An explanation of the strength of WHO recommendations can be found in **Box 1**.

WHO recommendation

WHO suggests that non-sugar sweeteners not be used as a means of achieving weight control or reducing the risk of noncommunicable diseases (*conditional recommendation*).

Rationale and remarks

The following provides the reasoning (rationale) behind the formulation of the recommendation, as well as remarks designed to provide context for the recommendation and facilitate its interpretation and implementation.

Rationale

- The recommendation is based on evidence of *low* certainty overall, from a systematic review that assessed the health effects of higher compared with lower intake of NSS *(39)*.[2] The systematic review found no evidence of long-term benefit on measures of body fatness in adults or children, and potential undesirable effects from long-term use in the form of increased risk of type 2 diabetes, CVDs and mortality in adults. Limited evidence suggests potential undesirable effects in the form of increased risk of preterm birth with NSS use during pregnancy.
- Specific findings from the systematic review supporting this recommendation are as follows.

Adults

Evidence from randomized controlled trials (RCTs) was as follows.

- NSS use in any manner[3] resulted in reduced sugars and energy intake, lower body weight and lower BMI in short-term RCTs (all *low* certainty evidence), the majority of which lasted 3 months or less. NSS use did not significantly affect other measures of body fatness or intermediate markers of cardiometabolic health, including glucose, insulin or blood lipids (*very low* to *moderate* certainty evidence). Evidence from a small number of longer-term trials lasting 6–18 months did not suggest an effect on body weight but was difficult to interpret because of many differences in how these trials were conducted and results reported.

[1] WHO guidance on polyunsaturated fatty acids is currently being updated.
[2] Many RCTs compared use of NSS with no use of NSS, whereas prospective observational studies compared different levels of NSS use. To maintain consistency in comparing results across study designs, results are therefore generally reported for effects of higher compared with lower intake, noting that, in most trials, "lower intake" may in fact be no intake.
[3] NSS were consumed by the participants in the RCTs in a variety of ways, including in pre-mixed beverages, powders or drops to be added to beverages by the participants themselves, solid foods, and capsules. To test for inherent properties of NSS, all forms of NSS were combined in the main analysis regardless of how they were consumed. Additional analyses assessed the individual ways of consuming NSS separately.

Box 1. Strength of WHO recommendations

WHO recommendations can either be *strong* or *conditional*, based on a number of factors including overall certainty in the supporting scientific evidence, balance of desirable and undesirable consequences, and others as described in the *Evidence to recommendations* section of the guideline.

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.

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 or when the anticipated net benefits are very small. Therefore, substantive discussion amongst policy-makers may be required before a *conditional* recommendation can be adopted as policy.

The reasoning behind the strength of the recommendation in this guideline is provided in the rationale for the recommendation. Additional information on assessing the strength of WHO recommendations can be found in the *WHO handbook for guideline development (54)*.

- When intake of NSS was directly compared with intake of free sugars (i.e. one group in a trial received NSS, and another group received free sugars), those receiving NSS had lower body weight and BMI, similar in magnitude to the results when NSS was used in any manner. However, most of these trials provided foods and beverages containing NSS or free sugars in addition to existing diets and therefore did not directly measure the effects of replacing free sugars with NSS. When NSS were compared with nothing/placebo or water (i.e. one group in a trial received NSS, and another group received nothing/placebo or water), no effects on body weight or BMI were observed.
- When NSS were assessed specifically as replacements for free sugars in a small number of RCTs (i.e. habitual consumers of foods or beverages containing free sugars were asked to switch to versions containing NSS in place of free sugars), the effect on body weight was significantly weakened relative to that observed for NSS used in any manner, and an effect on BMI was no longer observed.

Evidence from prospective observational studies, with up to 10 years of follow-up, was as follows.

- Higher intakes of NSS were associated with higher BMI and increased risk of incident obesity, but not other measures of body fatness (*very low* to *low* certainty evidence).
- Higher intakes of NSS were associated with increased risk of type 2 diabetes, CVDs and CVD mortality, and all-cause mortality in long-term prospective observational studies with average follow-up of 13 years (*very low* to *low* certainty evidence), but were not associated with differences in overall cancer incidence or mortality (*very low* certainty evidence).
- Use of NSS (predominantly saccharin) was associated with increased risk of bladder cancer as assessed in case–control studies (*very low* certainty evidence).

Children

One RCT conducted in children reported a reduction in several measures of body fatness when sugar-sweetened beverages were replaced with those containing NSS *(91)* (*moderate* certainty evidence). However, when results for BMI *z*-score[1] were combined with those from a second trial *(92)*, no effect was observed (*moderate* certainty evidence), and results from prospective observational studies did not suggest any significant associations between NSS use and measures of body fatness (*very low* certainty evidence). All other identified studies reported no significant associations between NSS use and prioritized health outcomes in children.

[1] BMI *z*-scores are adjusted for sex and age relative to standardized reference values.

Pregnant women

Meta-analysis of three prospective observational studies found an increased risk of preterm birth with higher NSS use during pregnancy (*low* certainty evidence), but associations between birth weight or weight of offspring later in life and NSS use during pregnancy were inconsistent (*very low* certainty evidence). Other individual prospective observational studies reported associations between NSS use during pregnancy and outcomes in offspring, including increased risk of asthma and allergies, and poorer cognitive function (*very low* certainty evidence). No associations were observed between NSS use and risk of gestational diabetes.

- The lack of evidence for long-term benefit of NSS use on measures of body fatness assessed in RCTs and potential long-term effects of NSS use observed for adults in prospective observational studies were considered to be relevant for women during pregnancy, and were reasonably expected to be relevant for children and adolescents as well. Therefore, in addition to the limited direct evidence for children and pregnant women, the evidence from RCTs and observational studies in adults was extrapolated to children, adolescents and pregnant women without downgrading for indirectness.
- In reviewing the evidence and formulating the recommendation, the NUGAG Subgroup on Diet and Health noted the following.
    - Because the primary role of NSS use is presumably to reduce free sugars intake (and consequently risk of unhealthy weight gain and disease associated with excess free sugars intake), the currently available evidence on which to base a recommendation on NSS is largely indirect – that is, most RCTs comparing intake of NSS with intake of free sugars did not explicitly assess the replacement of free sugars with NSS.
    - Because weight loss and maintenance of a healthy weight must be sustained over the long term[1] to have a meaningful impact on health, evidence of minor weight loss or reduced BMI over several months or less, as observed in the RCTs, without additional evidence of long-term impact, does not represent a health benefit.
    - The discordant results between the RCTs and prospective cohort studies suggest that the small amount of weight loss resulting from NSS use in short-term experimental settings may not be relevant to the effects of long-term NSS use in the general population.

    In addition, the NUGAG Subgroup on Diet and Health noted that:

    - there were no identified undesirable effects or other mitigating factors[2] that would argue against not using NSS;
    - NSS are not essential dietary factors and have no nutritional value; and
    - use of NSS is not the only way to achieve a reduction in free sugars intake; viable alternatives exist that are compatible with features of a healthy diet including consumption of foods with naturally occurring sugars, such as fruit, and unsweetened foods and beverages.

    Based on the evidence and other considerations noted above, the NUGAG Subgroup on Diet and Health concluded that the lack of evidence to suggest that NSS use is beneficial for body weight or other measures of body fatness over the long term, together with possible long-term undesirable effects in the form of increased risk of NCDs and death, outweighed any potential short-term health effects resulting from the small reductions in body weight and BMI observed in RCTs.
- Because of lack of certainty about the overall balance of desirable and undesirable effects associated with long-term NSS use for reducing NCD risk, including the possibility that reverse causation[3] may have contributed to one or more of the associations observed between long-term NSS use and risk of disease in prospective observational studies, a conservative approach was taken, leading to a *conditional* recommendation.

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[1] Ideally, healthy body weight is maintained throughout the life course.
[2] See the section *Evidence to recommendations*.
[3] A phenomenon sometimes observed in prospective cohort studies whereby those already in a pre-disease state or with increased risk of disease increase their exposure to the risk factor of interest, erroneously leading to the conclusion that increased exposure to the risk factor of interest leads to increased risk of disease.

Remarks

- With the exception of individuals with diabetes (as noted below), this recommendation is relevant for everyone: children and adults of any age, including pregnant and lactating women.
- The objective of this guideline is to provide guidance on the use of NSS in efforts to prevent unhealthy weight gain and diet-related NCDs, in the context of reducing free sugars intake. Assessing the health effects of NSS on individuals with pre-existing diabetes with the aim of providing guidance on disease management was beyond the scope of the guideline. Consequently, in the evidence reviewed, studies conducted exclusively in individuals with pre-existing diabetes were excluded, and in studies with mixed populations, diabetes was often controlled for as a potential confounding characteristic. Therefore, although individuals with diabetes can also reduce free sugars intake without the need for NSS, the recommendation does not apply to individuals with existing diabetes.
- The recommendation is relevant for all NSS, which are defined in this guideline as all synthetic and naturally occurring or modified non-nutritive sweeteners that are not classified as sugars. Common NSS include acesulfame K, aspartame, advantame, cyclamates, neotame, saccharin, sucralose, stevia and stevia derivatives. Because low-calorie sugars and sugar alcohols (polyols) are sugars or sugar derivatives containing calories, they are not considered NSS, and therefore the recommendation does not apply to these sweeteners.
- In this recommendation, "use" of NSS means consumption of foods or beverages that contain NSS, or the addition of NSS to food or beverages by the consumer.
- Many medications, and personal care and hygiene products contain NSS in small amounts to make them more palatable. The recommendation in this guideline does not apply to such products.
- "Weight control" in this recommendation refers to weight loss in cases of existing overweight or obesity, and preventing unhealthy weight gain by maintaining a healthy weight.
- The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has set acceptable daily intakes (ADIs) for most commercially used NSS. Evidence supporting this WHO recommendation comes from a systematic review of studies in which NSS were consumed in amounts within the ADI set by JECFA, either because this was explicitly stated in the study or it was reasonably inferred that the ADI was not being exceeded.[1]
- The recommendation in this guideline was made based on evidence that suggests that there may be health effects associated with NSS use irrespective of which NSS is being used – that is, NSS as a class of compounds, despite individual NSS having different chemical structures, may have an impact on health. It is recognized that NSS are not a homogeneous class of compounds: each has a unique chemical structure. As a result, individual NSS have different sweetness intensities and organoleptic properties, and are processed differently by the body. Although limited evidence suggests that individual NSS may also differ in some of their physiological effects in humans, the evidence is currently insufficient to make recommendations for individual NSS.
- Efforts to reduce free sugars intake should be implemented in the context of achieving and maintaining a healthy diet. Because free sugars are often found in highly processed foods and beverages with undesirable nutritional profiles, simply replacing free sugars with NSS results means that the overall quality of the diet is largely unaffected. Replacing free sugars in the diet with sources of naturally occurring sweetness, such as fruits, as well as minimally processed unsweetened foods and beverages, will help to improve dietary quality, and should be the preferred alternatives to foods and beverages containing free sugars.

[1] For prospective cohort studies, it was generally not possible to determine the absolute highest intakes because the highest quantile was generally a specified amount or more (e.g. ≥2 servings per day). Although it is possible that some adults may have exceeded the ADI in some of these studies, the number doing so would probably have been an extremely small percentage of the entire group *(23, 24, 29)*. The likelihood that children exceed the ADI is greater given their lower body weight; however, it is still expected to be a small percentage in most populations *(24)*.

Uptake of the guideline and future work

Dissemination

The guideline will be disseminated through:

- the WHO e-Library of Evidence for Nutrition Actions (eLENA),[1] 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 relevant WHO meetings, as well as at global and regional scientific meetings.

Translation and implementation

The recommendation in this guideline should be considered in conjunction with other WHO guidance on healthy diets – in particular, guidelines relating to free sugars *(14)*, as well as carbohydrates *(86)*, total fat *(87)*, saturated and *trans*-fatty acids *(88)*, polyunsaturated fatty acids *(36),*[2] sodium *(89)* and potassium *(90)*, to guide effective policy actions and intervention programmes to promote healthy diets and nutrition, and prevent unhealthy weight gain and diet-related NCDs.

A detailed discussion of how the recommendation on NSS use might be implemented is beyond the scope of this guideline, however they can be considered by policy-makers and programme managers when discussing possible measures, including:

- monitoring of NSS intake and its use in food and beverage production;
- regulation of marketing of foods and beverages;
- restrictions on the promotion and sales of food and beverages containing NSS in public institutions, including schools;
- fiscal policies targeting foods and beverages that contain NSS;
- nutrition labelling;
- consumer education; and
- translation of the recommendation at the country level into culturally and contextually specific food-based dietary guidelines that take into account locally available food and dietary customs.

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[1] https://www.who.int/tools/elena
[2] WHO guidance on polyunsaturated fatty acids is currently being updated.

Efforts should be targeted to the general population, with a particular focus on infants and young children who have not yet been directly exposed to foods and beverages containing free sugars and/or NSS, as well as their caregivers, as evidence suggests that early taste exposures shape taste preferences and eating behaviour later in life *(93–95)*.

Because a significant percentage of NSS consumed globally comes in the form of NSS-sweetened beverages and much of the global effort to reduce the intake of free sugars is focused on sugar-sweetened beverages, messaging about potable water as a preferred replacement for sugar-sweetened beverages and as a mode of hydration generally can be incorporated into public health communications and food-based dietary guidelines. Similar messaging regarding tabletop addition of NSS to beverages can be developed, with a focus on unsweetened beverages.

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 Nutrition Action (GINA)[1] – a centralized platform developed by the WHO Department of Nutrition and Food Safety for sharing information on nutrition actions in public health practice implemented around the world. GINA currently contains information on thousands of policies (including laws and legislation), nutrition actions and programmes in more than 190 countries. GINA includes data and information from many sources, including the first and second WHO global nutrition policy reviews conducted in 2010–2011 and 2016–2017, respectively *(96, 97)*. By providing programmatic implementation details, specific country adaptations and lessons learned, GINA serves as a platform for monitoring and evaluating how guidelines are being translated into policy actions and intervention programmes to address the issues related to fat intake in various countries.

Research gaps and future initiatives

Based on the results of the systematic reviews 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:

- potential long-term effects of NSS use on relevant outcomes in all target populations (including children, and pregnant and lactating women), including NSS exposures other than NSS-containing beverages; this will require elaboration and refinement of prospective cohort studies assessing health effects of NSS, including
  - more robust exposure assessment (e.g. multiple, sequential assessments of exposure)
  - more precise evaluations of NSS intake (e.g. different sources of NSS exposure, types of NSS consumed, exposure of NSS in mg/day), including the development of objective biomarkers of NSS intake to allow more accurate exposure assessments
  - addressing how patterns of NSS use (i.e. how long, how much, for what reasons) prior to baseline assessment of exposure might impact associations
  - assessments in LMIC settings
  - further efforts to address reverse causation;
- effects of NSS intake from foods and beverages on oral health, including dental caries, across all age groups, from young children to adults;
- effects of NSS intake on gastrointestinal health;
- differential health effects of individual NSS in humans, assessed via RCTs and prospective cohort studies, where possible;

[1] https://extranet.who.int/nutrition/gina/en

- potential differences in short-term and long-term responses to NSS based on sex, age, ethnicity, genotype, body weight status and risk for relevant NCDs, with sensitive methods to detect short-term changes, particularly in assessing insulin resistance;
- how patterns and history of NSS use by participants in RCTs may affect relevant outcomes (e.g. glucose metabolism);
- health effects of consuming mixtures of NSS, and NSS concurrently with other nutrients and components of foods, including sugars and other carbohydrates, compared with NSS alone, and whether this contributes to observed differences in health effects across studies;
- how post-ingestive sensing of sugars and NSS functions in humans, and to what extent this affects preferences, cravings and responses to NSS;
- biological mechanisms for physiological effects of NSS, as assessed in humans;
- how early exposure to NSS in children (including in utero exposure) might affect sweet preference, and other neural, metabolic and behavioural responses to sweetness later in life;
- how NSS are consumed in real-world settings and how this might affect sugars intake and dietary quality, as well as modulate any health effects of NSS;
- differences in NSS use by age, sex, ethnicity and socioeconomic status; and
- effective interventions to reduce reliance on, or habituation to, high levels of sweetness in the diet.

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 NSS 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 it would need to be re-evaluated. 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 (37)*. 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 3
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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) ▸ Pan American Health Organization (PAHO): Chair, PAHO Technical Advisory Group to Mobilize Cardiovascular Disease Prevention through Dietary Salt/Sodium Control Policies and Interventions (2015–2021) ▸ PAHO: member/Chair of 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-fatty acids (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 Codex Committee on Nutrition and Foods for Special Dietary Uses, and to Codex Committee on Food Labelling (2018–2021) ▸ National Nutrient Databank Conference: 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 determined that they would not impact the ability of this expert to serve as a member of the NUGAG Subgroup

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 on "what to eat" (2016–2021) ▸ Received research funding from various agencies: Canadian Institute of Health Research, 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 Collaborative 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)	on Diet and Health in an objective manner, and the expert was allowed to participate fully as a member of the NUGAG Subgroup on Diet and Health throughout the guideline development process.
Barbara Schneeman	▸ US Agency for International Development (USAID): 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 (FDA): employed through 2012 (retired in 2013) ▸ Head of the US delegate to the Codex Committee on Nutrition and Foods for Special Dietary Uses, and Codex Committee on Food Labelling; she presented the positions of the United States 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 to 2017) ▸ McCormick Science Institute: member of advisory committee reviewing research proposals on spices and herbs (2014 to 2021) ▸ Ocean Spray: temporary adviser on health claim petitions that are submitted to US FDA related to cranberries (2014 to 2015) ▸ General Mills: temporary adviser on labelling requirements in the United States for nutrition declarations (2014 to 2016, and 2018) ▸ DSM: temporary adviser on Codex Alimentarius processes (2014 to 2015) ▸ Hampton Creek: temporary adviser on labelling standards for mayonnaise (2014 to 2015) ▸ Washington DC law firm: temporary adviser on labelling of genetically modified foods (2014 to 2015) ▸ NASEM: member of the National Academies and member/ Chair of the Dietary Guidelines Advisory Committee, involved in reviewing the evidence for developing the Dietary Guidelines for Americans	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 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*. Regarding her membership on the US Dietary Guidelines Advisory Committee, although the nature of the work was similar to the work being carried out for this guideline, the work was done for

Member	Interests declared/identified	Action taken
	— Nominated to the Dietary Guidelines Advisory Committee of the USA by representatives from the North American Branch of the International Life Sciences Institute; American Beverage Association; American Bakers Association, Grain Chain; Grocery Manufacturers Association USA Dry Pea & Lentil Council, American Pulse Association — Received honorariums for presentations on the process to develop the Dietary Guidelines for Americans and policies for food labelling in the United States at various scientific meetings organized by PMK Associates (Institute of Food Technologists and American Oil Chemists' Society), McCormick Science Institute, Fibre Association 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 organization (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)	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. Because none of the interests were directly relevant to the objective of this guideline or were otherwise determined not to represent a conflict of interest, it was concluded that the interests would not impact the ability of this expert to serve as a member of the NUGAG Subgroup on Diet and Health in an objective manner. The expert was allowed to participate fully as a member of the NUGAG Subgroup on Diet and Health throughout the guideline development process.

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).

Members of the external peer review group

Member	Interests declared/identified	Action taken
Amos Laar	▸ International Development Research Center, Canada: research support to study the food environments of Ghanaian children to prevent obesity and NCDs (MEALS4NCDs)	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.
Allison Sylvetsky	▸ Speaking engagement in 2019 for Siggi's sessions, an education portal designed to support the needs of the nutrition and wellness community hosted by Siggi's Icelandic Yogurt Company. Title of the presentation was "Sweeteners, weight, and health: the state of the science"	Given the nature of the engagement and small honorariums, it was not considered to represent a conflict of interest for serving as an external reviewer of this guideline.

Member	Interests declared/identified	Action taken
Mathilde Touvier	▸ Funding (research support) received for research projects on food additives (including artificial sweeteners) and health from public institutions (European Research Council, French National Cancer Institute, French Ministry of Health)	Given the source of the funding, 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, nor were any interests independently identified (see **Annex 3** for the full list of external peer reviewers).

Members of the systematic review teams

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

Annex 5

Key questions in PICO format (population, intervention, control and outcomes)

PICO questions

- What is the effect on prioritized health outcomes in adults, children and pregnant women of higher intake of NSS compared with lower intake?
- What is the effect on prioritized health outcomes in adults, children and pregnant women of replacing free sugars with NSS?

Population	Apparently healthy adults and children in low-, middle- and high-income countries, including those with elevated BMI. ▸ In each, consider population characteristics, such as age, gender, ethnicity, country/region (urban/rural), socioeconomic status, demographic factors, sanitation, health background and health status, including baseline risk of CVDs
Intervention/exposure	The interventions of interest include intake of any type of NSS, either alone or in combination with one or more additional NSS. NSS may include aspartame, acesulfame K, saccharin, sucralose, advantame, neotame, cyclamate, stevia, thaumatin, brazzein and others. ▸ NSS versus sugar (quantity/frequency) ▸ High versus low intake of NSS (quantity/frequency) ▸ NSS-sweetened beverages versus water ▸ Possible subgroup analyses include: — discretionary use (i.e. consumer added versus pre-packaged foods) — solids and liquids — type of NSS — level of sweetness — “artificial” and “natural” NSS
Comparator	Sugars, no intervention, “placebo”, water (in the case of NSS-sweetened beverages), other type of NSS (when sugars or nothing/placebo/water also included)
Outcome	*Adults and children* ▸ Overweight/obesity ▸ Dental caries ▸ Prediabetes/type 2 diabetes[a] ▸ Eating behaviour (appetite, satiety) ▸ Sweet preference ▸ Cancer ▸ CVDs[a] ▸ Mood ▸ Behaviour (hyperactivity and aggression) ▸ Neurocognition ▸ Chronic kidney disease ▸ Asthma (children only) ▸ Allergies (children only)

[a] Includes intermediate/surrogate markers of disease (i.e. markers of glycaemic control for diabetes, blood lipids for CVDs)

Annex 6

GRADE evidence profiles

GRADE evidence profile 1

Question: What is the effect of higher compared with lower NSS intake in adults?

Population: General adult population

Assessment							No. of events/participants (study event rate)		Effect		Certainty[6]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Body weight (kg)											
29	RCT	Serious[7]	Serious[8]	Not serious	Not serious	None	1 252	1 181	**MD –0.71** (–1.13 to –0.28)	--	⨁⨁◯◯ Low
4	Observational (continuous)	Not serious[9]	Serious[8]	Not serious	Not serious[10]	None	118 457		**MD –0.12** (–0.40 to 0.15)	--	⨁◯◯◯ Very low
5	Observational (high vs low)	Serious[11]	Not serious	Not serious	Not serious[10]	None	11 874		**MD –0.01** (–0.67 to 0.64)	--	⨁◯◯◯ Very low
BMI (kg/m²)											
23	RCT	Serious[7]	Serious[8]	Not serious	Not serious[12]	None	940	917	**MD –0.14** (–0.30 to 0.02)	--	⨁⨁◯◯ Low
5	Observational (high vs low)	Not serious[9]	Serious[8]	Not serious	Not serious	None	80 583		**MD 0.14** (0.03 to 0.25)	--	⨁◯◯◯ Very low
Incident obesity											
2	Observational	Not serious[9]	Not serious	Not serious	Not serious [13]	None	603/1 668 (36.2%)		**HR 1.76** (1.25 to 2.49)	**275 more** (from 91 more to 539 more)	⨁⨁◯◯ Low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[6]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Abdominal obesity											
4	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	5 381/10 895 (49.4%)		**HR 1.33** (0.91 to 1.96)	**163 more** (from 44 fewer to 474 more)	⨁◯◯◯ Very low
Waist-to-hip ratio											
3	RCT	Serious[15]	Not serious	Not serious	Serious[16]	None	121	79	**MD 0.00** (–0.01 to 0.01)	--	⨁⨁◯◯ Low
Waist circumference (cm)											
10	RCT	Not serious[17]	Serious[8]	Not serious	Not serious[10]	None	688	564	**MD –0.24** (–1.06 to 0.58)	--	⨁⨁⨁◯ Moderate
3	Observational (high vs low)	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	12 886		**MD 0.92** (–1.73 to 3.56)	--	⨁◯◯◯ Very low
Fat mass (kg)											
6	RCT	Not serious[18]	Serious[8]	Not serious	Serious[14]	None	332	286	**MD –0.54** (–1.56 to 0.49)	--	⨁⨁◯◯ Low
Fat mass (%)											
10	RCT	Not serious[18]	Serious[8]	Not serious	Serious[14]	None	343	414	**MD –0.11** (–0.78 to 0.56)	--	⨁⨁◯◯ Low
Lean mass (kg)											
6	RCT	Not serious[18]	Not serious	Not serious	Not serious[10]	None	255	284	**MD –0.29** (–0.70 to 0.11)	--	⨁⨁⨁⨁ High
Diabetes											
13	Observational (beverages)	Not serious[9]	Not serious	Not serious	Not serious	None[19]	28 222/408 609 (6.9%)		**HR 1.23** (1.14 to 1.32)	**16 more** (from 10 more to 22 more)	⨁⨁◯◯ Low
2	Observational (tabletop)	Not serious[9]	Not serious	Not serious	Not serious	None	2 250/62 582 (3.6%)		**HR 1.34** (1.21 to 1.48)	**12 more** (from 8 more to 17 more)	⨁⨁◯◯ Low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[6]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Fasting glucose (mmol/L)											
16	RCT	Serious[20]	Not serious	Not serious	Not serious[10]	None	844	650	**MD –0.01** (–0.05 to 0.04)	--	⨁⨁⨁◯ Moderate
Fasting insulin (pmol/L)											
10	RCT	Not serious[21]	Serious[8]	Not serious	Serious[14]	None	444	315	**MD –0.49** (–4.99 to 4.02)	--	⨁⨁◯◯ Low
HbA1c (%)											
6	RCT	Not serious[22]	Not serious	Not serious	Serious[16]	None	212	199	**MD 0.02** (–0.03 to 0.07)	--	⨁⨁⨁◯ Moderate
HOMA-IR											
11	RCT	Serious[23]	Serious[8]	Not serious	Not serious[10]	None	457	329	**MD 0.03** (–0.32 to 0.38)	--	⨁⨁◯◯ Low
High fasting glucose											
3	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	6 086/11 213 (54.3%)		**HR 1.21** (1.01 to 1.45)	**114 more** (from 5 more to 245 more)	⨁⨁◯◯ Low
Dental caries											
1	RCT	Serious[24]	Serious[25]	Not serious	Very serious[26]	None	14	15	In a 6-month RCT among adults *(1)*,[27] the participants who were assigned to consume sugar-sweetened or NSS-sweetened soft drinks did not develop caries or acid erosion of the enamel during the intervention.		⨁◯◯◯ Very low
All-cause mortality											
8	Observational	Not serious[9]	Serious[8]	Not serious	Not serious	None	102 677/860 873 (11.9%)		**HR 1.12** (1.05 to 1.19)	**14 more** (from 6 more to 23 more)	⨁◯◯◯ Very low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[6]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Cardiovascular disease mortality											
5	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	13 089/598 951 (2.2%)		**HR 1.19** (1.07 to 1.32)	**4 more** (from 2 more to 7 more)	⨁⨁◯◯ Low
Cardiovascular diseases											
3	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	6 384/166 938 (3.8%)		**HR 1.32** (1.17 to 1.50)	**12 more** (from 6 more to 19 more)	⨁⨁◯◯ Low
Coronary heart disease											
4	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	10 104/205 455 (4.9%)		**HR 1.16** (0.97 to 1.39)	**8 more** (from 1 fewer to 19 more)	⨁◯◯◯ Very low
Stroke											
6	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	8 346/655 953 (1.3%)		**HR 1.19** (1.09 to 1.29)	**2 more** (from 1 more to 4 more)	⨁⨁◯◯ Low
Hypertension											
6	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	81 965/234 137 (35%)		**HR 1.13** (1.09 to 1.17)	**46 more** (from 32 more to 60 more)	⨁⨁◯◯ Low
Systolic blood pressure (mmHg)											
14	RCT	Serious[28]	Not serious	Not serious	Not serious[10]	None	838	602	**MD –1.33** (–2.71 to 0.06)	--	⨁⨁⨁◯ Moderate
Diastolic blood pressure (mmHg)											
13	RCT	Serious[28]	Not serious	Not serious	Not serious[10]	None	689	448	**MD –0.51** (–1.68 to 0.65)	--	⨁⨁⨁◯ Moderate
LDL cholesterol (mmol/L)											
12	RCT	Serious[28]	Not serious	Not serious	Serious[14]	None	653	540	**MD 0.03** (–0.03 to 0.09)	--	⨁⨁◯◯ Low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[6]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Total cholesterol (mmol/L)											
14	RCT	Serious[28]	Serious[8]	Not serious	Not serious[10]	None	567	511	**MD 0.01** (–0.09 to 0.11)	--	⨁⨁◯◯ Low
HDL cholesterol (mmol/L)											
13	RCT	Serious[28]	Not serious	Not serious	Not serious[10]	None	659	546	**MD 0.00** (–0.03 to 0.03)	--	⨁⨁⨁◯ Moderate
Total cholesterol to HDL cholesterol ratio											
4	RCT	Not serious[29]	Not serious	Not serious	Serious[16]	None	166	160	**MD 0.09** (0.02 to 0.16)	--	⨁⨁⨁◯ Moderate
Low HDL cholesterol											
4	Observational	Not serious[9]	Not serious	Not serious	Serious[14]	None	5 823/11 916 (48.9%)		**HR 1.03** (0.92 to 1.16)	**15 more** (from 39 fewer to 78 more)	⨁◯◯◯ Very low
Triglycerides (mmol/L)											
14	RCT	Serious[28]	Serious[8]	Not serious	Serious[14]	None	684	559	**MD –0.04** (–0.11 to 0.04)	--	⨁◯◯◯ Very low
High triglycerides											
4	Observational	Not serious[9]	Not serious	Not serious	Serious[14]	None	6 673/12 728 (52.4%)		**HR 1.03** (0.88 to 1.21)	**16 more** (from 63 fewer to 110 more)	⨁◯◯◯ Very low
Cancer mortality											
4	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	25 494/568 175 (4.5%)		**HR 1.02** (0.92 to 1.13)	**1 more** (from 4 fewer to 6 more)	⨁◯◯◯ Very low
Cancer (any type)											
7	Observational	Not serious[9]	Not serious	Not serious	Serious[14]	None	27 573/942 600 (2.9%)		**HR 1.02** (0.95 to 1.09)	**1 more** (from 1 fewer to 3 more)	⨁◯◯◯ Very low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[6]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Cancer (bladder)											
26	Observational (case-control)	Serious[11]	Serious[8]	Not serious	Not serious	None	11 071 cases 17 518 controls		**OR 1.31** (1.06 to 1.62)	--	⨁◯◯◯ Very low
Chronic kidney disease											
2	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	3 161/18 372 (17.2%)		**HR 1.41** (0.89 to 2.24)	**71 more** (from 19 fewer to 213 more)	⨁◯◯◯ Very low
Creatinine (µmol/L)											
2	RCT	Serious[30]	Serious[8]	Not serious	Very serious[31]	None	93	52	**MD 8.80** (–14.65 to 32.25)	--	⨁◯◯◯ Very low
Albumin (g/L)											
2	RCT	Serious[30]	Not serious	Not serious	Serious[16]	None	93	52	**MD 0.00** (–0.56 to 0.56)	--	⨁⨁◯◯ Low
Energy intake (kJ/day)											
25	RCT	Serious[32]	Serious[8]	Not serious	Not serious	None	1 131	1 077	**MD –569** (–859 to –278)	--	⨁⨁◯◯ Low
Sugars intake (g/day)											
12	RCT	Serious[33]	Serious[8]	Not serious	Not serious	None	652	587	**MD –38.4** (–57.8 to –19.1)	--	⨁⨁◯◯ Low

-- : not applicable; BMI: body mass index; CI: confidence interval; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; HR: hazard ratio; LDL: low-density lipoprotein; MD: mean difference; NSS: non-sugar sweeteners; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk.

[1] Unless otherwise noted, observational studies are prospective cohort studies that assessed outcomes by comparing the highest quantile of intake with the lowest. Some cohort studies assessed outcomes continuously, as noted in the evidence profile.

[2] All studies were conducted in the population of interest (i.e. general adult population). Although most studies were conducted in North America and Europe, and very few were conducted in LMICs, physiological responses to NSS are not expected to differ significantly across different populations. Behavioural responses may differ between those who are habituated to sweet-tasting foods and beverages and those whose diets contain little to no sweet foods or beverages. However, in populations with limited exposure to NSS (which may be found more widely in LMICs), the effects observed on the consumption of NSS in this review may be largely irrelevant unless NSS are introduced to these populations. With the exception of LDL cholesterol, blood lipids, glycaemic markers and blood pressure are largely unvalidated intermediate markers of disease and, although informative, are not a surrogate for disease. However, the WHO NUGAG Subgroup on Diet and Health prioritized intermediate markers in the outcomes of interest and, therefore, none of these outcomes were downgraded for indirectness.

[3] Funnel plot analyses conducted for outcomes with 10 studies or more. Unless otherwise noted, funnel plot analysis did not suggest significant risk of publication bias.

[4] For observational studies, relative effects are most-adjusted multivariate estimates (i.e. the multivariate association measure with the highest number of covariates as reported in individual studies).

[5] Based on the event rate in the studies – that is, the number of people with events divided by the total number of people. The absolute effect (per 1000 people) is calculated using the following equation: absolute effect = 1000 × [event rate × (1 – RR)]. The magnitude of absolute effect in "real world" settings depends on baseline risk, which can vary across different populations.

[6] Critical outcomes in this evidence profile are shown in blue and important outcomes in black, as prioritized by the WHO NUGAG Subgroup on Diet and Health. Outcomes can be assessed as either not important, important or critical for decision-making in the WHO guideline development process *(2)*.

[7] Most RCTs included in the meta-analyses for measures of body fatness were assessed as having unclear risk of bias overall as a result of lack of necessary detail in reporting the methods that were used. Less than half the trials for body weight and slightly more than half for BMI appeared to use appropriate methods of random sequence generation (one or two employed inadequate randomization methods). Less than a quarter of the trials reported adequate allocation concealment for body weight and a third for BMI (except for one trial with inadequate allocation concealment for body weight; details in remaining trials were not reported and thus assessed as unclear). Blinding of participants was only possible in one or two studies; it was not possible in half the remaining trials (studies comparing NSS with water or nothing) and unclear in the other half (NSS compared with sugars, because it is unknown to what extent the participants could taste the difference between foods and beverages sweetened with NSS and those sweetened with sugars). Only a very small number of trials provided sufficient information to enable an assessment regarding blinding of outcome assessment. A little fewer than half the trials did not report significant participant dropout or imbalance in dropout rates across arms, and about half the remaining trials reported significant dropout rates (>15%), which represent a serious concern. However, most trials did not provide sufficient detail regarding reasons for participant dropout, so it is difficult to determine whether attrition might have affected results. Selective reporting of outcomes was clearly evident in only a very small number of trials; of the remaining trials, about half were assessed as having low risk of bias and half unclear risk of bias. No other significant sources of bias were identified. Although most trials appeared to be well conducted, the widespread lack of detail in the reporting of methods creates significant uncertainty regarding risk of bias. Downgraded once as a conservative measure.

[8] $I^2 \geq 50\%$, indicating a significant level of heterogeneity. Where the number of studies was sufficient to explore heterogeneity via subgroup and sensitivity analyses, results of the analysis did not significantly explain the observed heterogeneity. Downgraded once.

[9] Mean Newcastle–Ottawa Score of >5 with very conservative application of ratings. Not downgraded.

[10] A small mean effect, likely of little to no clinical significance, and neither bound of the 95% CI includes a potentially important benefit or harm. Therefore, considered a sufficiently precise estimate of no effect. Not downgraded.

[11] Mean Newcastle–Ottawa Score of ≤5 with very conservative application of ratings. Downgraded once.

[12] One bound of the 95% CI includes potentially important benefit or harm, and the other bound crosses the null in the opposite direction, but only very slightly and as a result of the outlying effect in one study *(3)*. In sensitivity analysis in which the study is removed, the upper bound no longer crosses the null. Not downgraded.

[13] The sample size is relatively small for prospective cohort studies, but sufficiently large and with a high event rate. Not downgraded.

[14] One bound of the 95% CI includes potentially important benefit or harm, and the other bound crosses the null in the opposite direction, and/or the sample size is small. Downgraded once.

[15] Only one trial was assessed as having adequately randomized and maintained allocation concealment (others unclear). One trial was an abstract only, with overall high risk of bias. Remaining domains for the other two trials were assessed as half with low risk of bias and half with unclear risk. Downgraded once.

[16] A small mean effect, likely of little to no clinical significance, and neither bound of the 95% CI includes a potentially important benefit or harm. However, the sample size is small. Downgraded once.

[17] All but one trial had adequate randomization, and nearly half had adequate allocation concealment (the remainder were unclear). One trial had incomplete data, and another concerns about selective reporting. Six trials could not blind participants, and it was unclear whether participants were blinded in the other two. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[18] The majority of trials had adequate randomization, but only one or two had adequate allocation concealment (the remainder were unclear). Two trials had incomplete data. Two trials could not blind participants, and it was unclear whether participants were blinded in the remaining trials. For fat mass (%), there were concerns in one trial about selective reporting. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[19] Six of the 10 comparisons that reported a P_{trend} reported a P_{trend} of <0.05, suggesting a dose–response relationship within these individual studies. However, as a conservative measure, it was not upgraded. Funnel plot analysis suggested a slight possibility of publication bias, but not of significant concern. Not downgraded.

[20] Slightly more than half the trials had adequate randomization, and one had inadequate randomization. Only four of the trials had adequate allocation concealment (the remainder were unclear). More than half the trials could not blind participants to treatment. Two trials had incomplete data, and there were concerns about selective reporting in two trials (one trial had both). One trial was an abstract only with overall high risk of bias. The remaining domains were approximately half with low risk of bias and half unclear. Downgraded once.

[21] In these trials, the majority had adequate randomization, and one had inadequate randomization. Half had adequate allocation concealment (the remainder were unclear). Slightly more than half the trials could not blind participants to treatment. One trial had incomplete data. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[22] In these trials, the majority had adequate randomization, and half had adequate allocation concealment (the remainder were unclear). Half the trials could not blind participants to treatment. One trial had incomplete data, and one had concerns about selective reporting. One trial was an abstract only with overall high risk of bias. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[23] Fewer than half the trials had adequate randomization, and one had inadequate randomization. Only four of the trials had adequate allocation concealment (the remainder were unclear). More than half the trials could not blind participants to treatment. Two trials had incomplete data. The remaining domains were approximately half with low risk of bias and half unclear. Downgraded once.

[24] This single study had adequate randomization but insufficient information to assess allocation concealment, blinding of outcome assessment or selective reporting. It was at high risk of bias for blinding of participants and incomplete data. Downgraded once.

[25] Unable to assess inconsistency in a single study. Downgraded once.

[26] Extremely small sample size. Downgraded twice.

[27] The data for dental caries were reported in the original publication of this trial (Maersk et al. 2012) *(4)*.

[28] The majority of trials had adequate randomization, but fewer than half had adequate allocation concealment (the remainder were unclear). A significant number of trials could not blind participants, and it was unclear whether participants were blinded in the remaining trials. One or two trials trial had incomplete data, and there were concerns in 1–3 trials about selective reporting. One or two of the trials for most outcomes were abstracts only and of high risk of bias overall. The remaining domains were approximately half with low risk of bias and half unclear. Downgraded once.

[29] The majority of trials had adequate randomization, but only one had adequate allocation concealment (the remainder were unclear). Only one trial could not blind participants. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[30] One trial was fairly well reported, and the other was mostly unclear, with concerns about selective reporting of outcomes. Downgraded once.

[31] The 95% CI crosses the null and includes both significant benefit and harm. Downgraded twice.

[32] A little fewer than half the trials had adequate randomization, and about a quarter had adequate allocation concealment (the remainder were unclear). One trial was at high risk of bias for both inadequate randomization and allocation concealment. Half the trials could not blind participants, and it was unclear whether participants were blinded in all but two of the remaining trials. Eight trials had incomplete data, and there were concerns in one trial about selective reporting. The remaining domains were approximately half with low risk of bias and half unclear. Downgraded once.

[33] A third of the trials had adequate randomization, and one had adequate allocation concealment (the remainder were unclear). One trial was at high risk of bias for both inadequate randomization and allocation concealment. More than half the trials could not blind participants, and it was unclear whether participants were blinded in all but one of the remaining trials. Three trials trial had incomplete data. The remaining domains were more low risk of bias than unclear, but not by a significant margin. Downgraded once.

GRADE evidence profile 2

Question: What is the effect of replacing sugars with NSS in adults?

Population: General adult population

Assessment							No. of events/participants (study event rate)		Effect		Certainty[3]
No. of studies/ cohorts	Study design	Risk of bias	Inconsistency	Indirectness[1]	Imprecision	Other[2]	Lower/no NSS intake	Higher NSS intake	MD (95% CI)	Absolute – per 1000 (95% CI)	
Body weight (kg)											
4	RCT	Not serious[4]	Not serious	Not serious	Serious[5]	None	361	236	**MD –0.61** (–1.28 to 0.06)	--	⨁⨁⨁◯ Moderate
BMI (kg/m²)											
4	RCT	Not serious[4]	Not serious	Not serious	Serious[5]	None	286	180	**MD –0.01** (–0.38 to 0.35)	--	⨁⨁⨁◯ Moderate

-- : not applicable; BMI: body mass index; CI: confidence interval; MD: mean difference; NSS: non-sugar sweeteners; RCT: randomized controlled trial.

[1] All studies were conducted in the population of interest (i.e. general adult population). Although most studies were conducted in North America and Europe, and very few were conducted in LMICs, physiological responses to NSS are not expected to differ significantly across different populations. Behavioural responses may differ between those who are habituated to sweet-tasting foods and beverages and those whose diets contain little to no sweet foods or beverages. However, in populations with limited exposure to NSS (which may be found more widely in LMICs), the effects observed on the consumption of NSS in this review may be largely irrelevant unless NSS are introduced to these populations. With the exception of LDL cholesterol, blood lipids, glycaemic markers and blood pressure are largely unvalidated intermediate markers of disease and, although informative, are not a surrogate for disease. However, the WHO NUGAG Subgroup on Diet and Health prioritized intermediate markers in the outcomes of interest, and, therefore, none of these outcomes were downgraded for indirectness.

[2] Too few studies to conduct funnel plot analyses.

[3] Both outcomes are critical outcomes as prioritized by the WHO NUGAG Subgroup on Diet and Health. Outcomes can be assessed as either not important, important or critical for decision-making in the WHO guideline development process *(2)*.

[4] Half the trials had adequate randomization, but most lacked sufficient detail to assess whether allocation concealment was adequate (unclear risk of bias). Three of the four trials could not blind participants to treatment. There were no other significant sources of bias. Not downgraded.

[5] One bound of the 95% CI includes potentially important benefit or harm, and the other bound crosses the null in the opposite direction, and/or the sample size is small. Downgraded once.

GRADE evidence profile 3

Question: What is the effect of higher compared with lower NSS intake in children?[1]

Population: General child population

Assessment							No. of events/participants (study event rate)		Effect		Certainty[4]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD (95% CI)	Absolute – per 1000 (95% CI)	
Body weight (kg)											
1	RCT	Not serious[5]	Serious[6]	Not serious	Not serious	None	319	322	**MD –1.01** (–1.54 to –0.48)	--	⨁⨁⨁◯ Moderate
2	Observational (continuous)	Not serious[7]	Not serious	Not serious	Not serious[8]	None	1 633		**MD 0.03** (–0.14 to 0.21)	--	⨁⨁◯◯ Low
BMI (kg/m²)											
5	Observational (continuous)	Not serious[7]	Serious[9]	Not serious	Not serious[8]	None	11 907		**MD 0.08** (–0.01 to 0.17)	--	⨁◯◯◯ Very low
2	Observational (high vs low)	Not serious[7]	Not serious	Not serious	Serious[10]	None	2 426		**MD 0.04** (–0.32 to 0.40)	--	⨁◯◯◯ Very low
BMI *z*-score											
2	RCT	Not serious[11]	Not serious	Not serious	Serious[10]	None	424	840	**MD –0.07** (–0.26 to 0.11)	--	⨁⨁⨁◯ Moderate
3	Observational (continuous)	Not serious[7]	Serious[9]	Not serious	Serious[10]	None	610		**MD –0.23** (–0.70 to 0.25)	--	⨁◯◯◯ Very low
1	Observational (high vs low)	Serious[12]	Serious[6]	Serious[13]	Serious[10]	None	98		**MD 0.00** (–0.30 to 0.30)	--	⨁◯◯◯ Very low
Waist circumference (cm)											
1	RCT	Not serious[5]	Serious[6]	Not serious	Not serious	None	319	322	**MD –0.66** (–1.23 to –0.09)	--	⨁⨁⨁◯ Moderate

Assessment							No. of events/participants (study event rate)		Effect		Certainty[4]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD (95% CI)	Absolute – per 1000 (95% CI)	
Fat mass (kg)											
1	RCT	Not serious[5]	Serious[6]	Not serious	Not serious	None	319	322	**MD –0.57** (–1.02 to –0.12)	--	⨁⨁⨁◯ Moderate
1	Observational	Serious[12]	Serious[6]	Serious[13]	Serious[10]	None	98		**MD –1.00** (–2.52 to 0.52)	--	⨁◯◯◯ Very low
Fat mass (%)											
1	RCT	Not serious[5]	Serious[6]	Not serious	Not serious	None	319	322	**MD –1.07** (–1.99 to –0.15)	--	⨁⨁⨁◯ Moderate
2	Observational	Not serious[7]	Serious[9]	Not serious	Serious[10]	None	720		**MD –1.53** (–5.73 to 2.66)	--	⨁◯◯◯ Very low
Incident overweight											
2	Observational	Not serious[7]	Not serious	Not serious	Very serious[14]	None	235/3 064 (7.7%)		**OR 1.25** (0.43 to 3.66)	**19 more** (from 44 fewer to 205 more)	⨁◯◯◯ Very low
Diabetes (intermediate markers)											
1	Observational	Serious[12]	Serious[6]	Serious[14]	Serious[10]	None	98		In this cohort of 12–18-year-old overweight children followed up for 1 year, chronic consumers of NSS-sweetened beverages had no difference in intermediate markers of diabetes when compared with those initiating consumption ("initiators") of NSS-sweetened beverages and non-consumers, except for HbA1c, which increased more in chronic consumers of NSS-sweetened beverages ($P = 0.01$) *(5)*.		⨁◯◯◯ Very low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[4]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD (95% CI)	Absolute – per 1000 (95% CI)	
Dental caries											
2	RCT	Not serious[15]	Serious[16]	Not serious	Serious[10]	None	115	116	*Unable to meta-analyse* In one trial, snacks containing stevia or sugars were given twice daily to children for 6 weeks. At the end of the trial, in the stevia arm, the concentrations of cariogenic bacteria Streptococcus mutans and lactobacilli ($\chi^2 = 8.01$; $P < 0.01$) and the probability of developing caries (measured by a cariogram) decreased compared with baseline, whereas there were no statistically significant changes in the sugars arm *(6)*. In another trial, mouth rinse containing stevia or placebo was used daily by children for 6 months. At the end of the trial, there was a significant improvement in the stevia arm compared with the placebo group in plaque scores ($P = 0.03$) and gingival scores ($P = 0.01$). There were no changes in the number of cavitated lesions in the stevia arm, but there was an increase in cavitated lesions in the placebo arm (from 5.6% to 5.8%) *(7)*.		⨁⨁◯◯ Low
1	Observational	Serious[12]	Serious[6]	Not serious	Serious[17]	None	642		This prospective cohort study found that low intakes of NSS-sweetened beverages were associated with fewer teeth surfaces having caries compared with no intake ($P < 0.025$). However, the association with high intakes of NSS-sweetened beverages was not reported *(8)*.		⨁◯◯◯ Very low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[4]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD (95% CI)	Absolute – per 1000 (95% CI)	
Cardiovascular diseases (blood lipids)											
1	Observational	Serious[12]	Serious[6]	Serious[14]	Serious[10]	None	98		In this cohort of 12–18-year-old overweight children followed up for 1 year, chronic consumers of NSS-sweetened beverages had no difference in total, HDL or LDL cholesterol, or triglycerides when compared with initiators of NSS-sweetened beverages and non-consumers *(5)*.		⨁◯◯◯ Very low
Brain cancer											
2	Observational (case–control)	Serious[12]	Not serious	Not serious	Serious[10]	None	371 cases 780 controls		**OR 1.14** (0.80 to 1.63)	**2 more** (from 2 fewer to 7 more)	⨁◯◯◯ Very low
Energy intake (kJ/day)											
1	RCT	Not serious[18]	Serious[6]	Not serious	Serious[10]	None	199	187	In this trial, the energy intake of children receiving drinks with sugars was 419 kJ/day higher than in those receiving drinks with NSS *(9)*.		⨁⨁⨁◯ Moderate
2	Observational	Serious[12]	Serious[17]	Not serious	Serious[17]	None	173 (cohort 1) 2371 (cohort 2)		*Unable to meta-analyse* In one cohort study, energy intake in initiators of NSS-sweetened beverages was 432 kJ/day higher and in chronic/existing consumers of NSS-sweetened beverages was 2462 kJ/day higher than in those who did not consume NSS-sweetened beverages after 1 year of follow-up *(5)*. In the second cohort study, energy intake was 122 kJ/day higher per 100 g/day increase in consumption of NSS-sweetened beverages *(10)*.		⨁◯◯◯ Very low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[4]
No. of studies/ cohorts	Study design[1]	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other[3]	Lower/no NSS intake	Higher NSS intake	Relative/MD (95% CI)	Absolute – per 1000 (95% CI)	
Sugars intake (g/day)											
2	Observational	Serious[12]	Serious[17]	Not serious	Serious[17]	None	173 (cohort 1) 2371 (cohort 2)		*Unable to meta-analyse* In one cohort study, chronic users of NSS-sweetened beverages had a 40.2 g/day (SE 11.6) higher sugars intake than never users, whereas initiators of NSS-sweetened beverages had a –23.9 g/day (SE 17.9) lower sugars intake than never users *(5)*. In a second cohort study, sugars intake was not associated with consumption of NSS-sweetened beverages *(10)*.		⨁◯◯◯ Very low
Neurocognition											
1	RCT	Not serious[18]	Serious[6]	Not serious	Serious[10]	None	200	199	In an RCT, children were given drinks with sucralose or sucrose for 8.5 months. There were no significant differences between the two arms in cognition measures (tested using the Kaufman Assessment Battery for Children version II [KABC-II] subtests and the Hopkins Verbal Learning Test [HVLT]) *(9)*.		⨁⨁◯◯ Low
1	Observational	Not serious[7]	Serious[6]	Not serious	Serious[17]	None	1234		In a cohort study following children in utero up to 7 years of age, early- and mid-childhood cognition scores were not associated with childhood intake of NSS-sweetened beverages at 3 years *(11)*.		⨁◯◯◯ Very low

--: not applicable; BMI: body mass index; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MD: mean difference; NSS: non-sugar sweeteners; OR: odds ratio; RCT: randomized controlled trial; SE: standard error.

[1] Unless otherwise noted, observational studies are prospective cohort studies that assessed outcomes by comparing the highest quantile of intake with the lowest. Some cohort studies assessed outcomes continuously, as noted in the evidence profile.

[2] Unless otherwise noted, all studies were conducted in the population of interest (i.e. general child population). Although most studies were conducted in North America and Europe, and very few were conducted in LMICs, physiological responses to NSS are not expected to differ significantly across different populations. Behavioural responses may differ between those who are habituated to sweet-tasting foods and beverages and those whose diets contain little to no sweet foods or beverages. However, in populations with limited exposure to NSS (which may be found more widely in LMICs), the effects observed on the consumption of NSS in this review may be largely irrelevant unless NSS are introduced to these populations.

[3] Too few studies to conduct funnel plot analyses.

[4] Critical outcomes in this evidence profile are shown in blue and important outcomes in black, as prioritized by the WHO NUGAG Subgroup on Diet and Health. Outcomes can be assessed as either not important, important or critical for decision-making in the WHO guideline development process *(2)*.

[5] This single RCT was well conducted, with adequate randomization and allocation concealment. There was a high attrition rate, with more than 20% of participants dropping out; however, imputation of missing values suggested no imbalance in arms with or without missing participants. Not downgraded.

[6] Unable to assess inconsistency as there is only a single study. Downgraded once.

[7] Mean Newcastle–Ottawa Score of >5 with very conservative application of ratings. Not downgraded.

[8] A small mean effect, likely of little to no clinical significance, and neither bound of the 95% CI includes a potentially important benefit or harm. Therefore, considered a sufficiently precise estimate of no effect. Not downgraded.

[9] $I^2 \geq 50\%$, indicating a significant level of heterogeneity. Downgraded once.

[10] One bound of the 95% CI includes potentially important benefit or harm, and the other bound crosses the null in the opposite direction, and/or the sample size is small. Downgraded once.

[11] These RCTs were well conducted, although for one it was unclear whether it was adequately randomized. Both had adequate allocation concealment. There was a high attrition rate, with more than 20% of participants dropping out of one trial; however, imputation of missing values suggested no imbalance in arms with or without missing participants. No other sources of significant bias were noted. Not downgraded.

[12] Mean Newcastle–Ottawa Score of ≤5 with very conservative application of ratings. Downgraded once.

[13] This single, very small cohort was conducted exclusively in overweight Hispanic adolescents. As evidence from this review suggested that people with overweight and/or obesity may respond differently to the use of NSS from people of normal weight, this cohort may not be an adequate representation of the general child population. Downgraded once, together with inconsistency.

[14] The 95% CI crosses the null and includes both significant benefit and harm. Downgraded twice.

[15] Neither trial included sufficient information to assess whether randomization was adequate, but both had adequate allocation concealment, and other domains were mostly assessed as having low risk of bias. Not downgraded.

[16] Unable to assess inconsistency as there are only two studies, which could not be meta-analysed, although both report lower risk of caries with NSS. Downgraded once as a conservative measure.

[17] Unable to assess. Downgraded once.

[18] It was unclear whether this single, well-conducted trial was adequately randomized, but other domains – save for blinding of participants (unclear) – were assessed as having low risk of bias. Not downgraded.

GRADE evidence profile 4

Question: What is the effect of higher compared with lower NSS intake in pregnant women?

Population: Pregnant women

Assessment							No. of events/participants (study event rate)		Effect		Certainty[3]
No. of studies/ cohorts	Study design	Risk of bias	Inconsistency	Indirectness[1]	Imprecision	Other[2]	Lower/no NSS intake	Higher NSS intake	Relative/MD (95% CI)	Absolute – per 1000 (95% CI)	
Gestational diabetes											
1	Observational	Not serious[4]	Serious[5]	Not serious	Serious[6]	None	860/13 475 (6.4%)		**RR 0.92** (0.81 to 1.04)	**5 fewer** (from 12 fewer to 0 more)	⨁◯◯◯ Very low
Preterm birth											
3	Observational	Not serious[4]	Not serious	Not serious	Not serious	None	6 381/129 009 (4.9%)		**OR 1.25** (1.07 to 1.46)	**12 more** (from 3 more to 23 more)	⨁⨁◯◯ Low
Birth weight											
3	Observational	Serious[7]	Serious[5]	Not serious	Serious [8]	None	3 716		*Unable to meta-analyse* In a cohort analysis of the German GeliS trial, the daily intake of light drinks during pregnancy was associated non-significantly with growth measures in the child at birth (birth weight – adjusted regression coefficient –5; 95% CI: –18 to 6; BMI at birth – adjusted regression coefficient 0.005; 95% CI: –0.020 to 0.035; low birth weight – adjusted OR 0.99; 95% CI: 0.91 to 1.08; small for gestational age – adjusted OR 1.03; 95% CI: 0.98 to 1.09; and large for gestational age – adjusted OR 1.01; 95% CI: 0.85 to 1.07) *(12)*. In a Dutch cohort of pregnant women, intake of NSS-sweetened products before conception was associated with increased birthweight (adjusted *z*-score coefficient per 10 g per 1000 kcal/day 0.001; 95% CI: 0.000 to 0.001; *P* = 0.002) *(13)*. In a cohort study with women with gestational diabetes in Slovenia, intake of low-calorie beverages[9] was not associated with large for gestational age (Spearman correlation coefficient 0.118; *P* non-significant) *(14)*.		⨁◯◯◯ Very low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[3]
No. of studies/ cohorts	Study design	Risk of bias	Inconsistency	Indirectness[1]	Imprecision	Other[2]	Lower/no NSS intake	Higher NSS intake	Relative/MD (95% CI)	Absolute – per 1000 (95% CI)	
Offspring body fatness											
3	Cohort	Not serious[4]	Serious[5]	Not serious	Serious[8]	None	5 029		*Unable to meta-analyse* In a prospective cohort study of pregnant women conducted in Canada, the daily intake of NSS-sweetened beverages during pregnancy (compared with less than 1 serving per month) was associated with a 0.2 increase in infant BMI *z*-score (95% CI: 0.02 to 0.38) and a more than twofold increase in risk of overweight at 1 year of age (adjusted OR 2.19; 95% CI: 1.23 to 3.88). Adjustment was made for maternal BMI, diet quality, total energy intake and other obesity risk factors *(15)*. In a prospective cohort study conducted in the USA, consumption of NSS-sweetened beverages during pregnancy was not associated with BMI *z*-score or waist circumference in offspring at mid-childhood (median 7.7 years of age) *(16)*. In a prospective cohort study conducted in Denmark, the children of women with gestational diabetes who consumed NSS-sweetened beverages at ≥1/day (compared with never) had a higher BMI *z*-score (β 0.59; 95% CI: 0.23 to 0.96) and risk of overweight or obesity (RR 1.93; 95% CI: 1.24 to 3.01) at 7 years of age *(17)*.		⨁◯◯◯ Very low
Offspring asthma											
1	Cohort	Not serious[4]	Serious[5]	Not serious	Not serious	None	1 536/31 849 (4.8%)		**OR 1.20** (1.07 to 1.35)	**10 more** (from 3 more to 17 more)	⨁◯◯◯ Very low
Offspring allergies											
1	Cohort	Not serious[4]	Serious[5]	Not serious	Serious[6]	None	1 855/37 971 (4.9%)		**OR 1.11** (0.86 to 1.43)	**5 more** (from 7 fewer to 21 more)	⨁◯◯◯ Very low

Assessment							No. of events/participants (study event rate)		Effect		Certainty[3]
No. of studies/ cohorts	Study design	Risk of bias	Inconsistency	Indirectness[1]	Imprecision	Other[2]	Lower/no NSS intake	Higher NSS intake	Relative/MD (95% CI)	Absolute – per 1000 (95% CI)	
Offspring neurocognition											
1	Observational	Not serious[4]	Serious[5]	Not serious	Serious[8]	None	1 234		In a prospective cohort study following children in utero up to 7 years of age, early- and mid-childhood cognition scores were inversely associated with maternal intake of NSS-sweetened beverages during pregnancy (PPVT-III, early childhood –1.2; 95% CI: –2.9 to 0.5; total WRAVMA, early childhood –1.5; 95% CI: –2.9 to –0.1; KBIT-II verbal, mid-childhood –3.2; 95% CI: –5.0 to –1.5; KBIT-II non-verbal, mid-childhood –2.0; 95% CI: –4.3 to 0.2; WRAVMA drawing, mid-childhood –1.7; 95% CI: –4.1 to 0.6; WRAML visual memory, mid-childhood –0.1; 95% CI: –0.7 to 0.5), but not with childhood intake of NSS-sweetened beverages at 3 years *(11)*.		⨁◯◯◯ Very low

BMI: body mass index; CI: confidence interval; KBIT-II, Kaufman Brief Intelligence Test 2nd edition; MD: mean difference; NSS: non-sugar sweeteners; OR: odds ratio; PPVT-III: Peabody Picture Vocabulary Test-III; RR: relative risk; WRAML: Wide Range Assessment of Memory and Learning; WRAVMA: Wide Range Assessment of Visual Motor Ability.

[1] All studies were conducted in the population of interest (i.e. general population of pregnant women). Although most studies were conducted in North America and Europe, and very few were conducted in LMICs, physiological responses to NSS are not expected to differ significantly across different populations. Behavioural responses may differ between those who are habituated to sweet-tasting foods and beverages and those whose diets contain little to no sweet foods or beverages. However, in populations with limited exposure to NSS (which may be found more widely in LMICs), the effects observed on the consumption of NSS in this review may be largely irrelevant unless NSS are introduced to these populations.

[2] Too few studies to conduct funnel plot analyses.

[3] Outcomes specific to pregnancy were not prioritized by the WHO NUGAG Subgroup on Diet and Health, and therefore there is no designation as critical or important.

[4] Mean Newcastle–Ottawa Score of >5 with very conservative application of ratings. Not downgraded.

[5] Unable to assess inconsistency as there is only a single study, or a small number of studies that could not be meta-analysed. Downgraded once.

[6] One bound of the 95% CI includes potentially important benefit or harm, and the other bound crosses the null in the opposite direction, and/or the sample size is small. Downgraded once.

[7] Mean Newcastle–Ottawa Score of ≤5 with very conservative application of ratings. Downgraded once.

[8] Unable to assess. Downgraded once.

[9] Based on the reporting of other beverage types in this study, it was determined that “low-calorie beverages” consisted primarily, if not entirely, of NSS-sweetened beverages.

Annex 6 references

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Annex 7

Evidence to recommendations table

Background

Intervention: not using NSS
Comparison: lower/no compared with higher NSS intake; replacement of sugars with NSS
Main outcomes: body weight, energy and sugars intake, NCDs
Setting: healthy individuals; RCTs and observational studies

Assessment

	Judgement	Research evidence	Additional considerations
Problem	**Is the problem a priority?** ☐ No ☐ Probably no ☐ Probably yes ■ **Yes** ☐ Varies ☐ Don't know	In 2016, more than 1.9 billion adults aged 18 years and older were overweight *(1)*. Of these, more than 600 million were obese. In 2020, more than 38 million children under 5 years of age were overweight – an increase of about 6 million over the past 20 years *(2)*. High BMI was responsible for an estimated 4 million deaths in 2017 *(3)*, and increases in BMI in the overweight and obesity range led to a greater risk of mortality *(4)*. Overweight and obesity are also risk factors for many NCDs, including CVDs, type 2 diabetes and certain types of cancer. NCDs are the leading causes of death globally and were responsible for an estimated 41 million (71%) of the 55 million deaths in 2019 *(5)*.	Rates of obesity and diet-related NCDs are growing rapidly in LMICs.
Desirable effects	**How substantial are the desirable anticipated effects?** **Adults** ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ■ **Don't know**	**Adults** The NUGAG Subgroup on Diet and Health did not consider the short-term weight loss observed in RCTs of varied design to be a health benefit (desirable effect). Because the evidence for reduced energy and sugars intake also came from the same short-term trials (and is only relevant to the extent that it contributes to weight loss or healthy weight maintenance), these were also not considered desirable effects. Therefore, the NUGAG Subgroup on Diet and Health does not know whether there are desirable effects on body weight with NSS use. The effects observed are summarized below; they were considered to be small (body weight, BMI) to moderate (energy intake, sugars intake). *Higher compared with lower NSS intake* Body weight: MD –0.71 kg (95% CI: –1.13 to –0.28) BMI: MD –0.14 kg/m^2 (95% CI: –0.30 to 0.02) Energy intake: –569 kJ/day (95% CI: –859 to –278) Sugars intake: –38.4 g/day (95% CI: –57.8 to –19.1) *Replacement of sugars with NSS* Body weight: MD –0.61 kg (95% CI: –1.28 to 0.06) Desirable effects were not observed for other outcomes with NSS use.	Design of intervention in RCTs in adults is heterogeneous, and overall trial duration is relatively short – in some cases, too short to be able to reliably assess effects on body weight.

	Judgement	Research evidence	Additional considerations
Desirable effects	**Children** ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ■ **Don't know** **Pregnant women** ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ■ **Don't know**	**Children** For similar reasons as for adults, the NUGAG Subgroup on Diet and Health does not know whether there are desirable effects on body weight with NSS use. The main effects observed are summarized below; they were considered to be small to moderate (energy intake, sugars intake). *Replacement of sugars with NSS* Body weight: MD –1.01 kg (95% CI: –1.54 to –0.48) Fat mass: MD –1.07% (95% CI: –1.99 to –0.15) Other measures of body fatness, when present, were also considered to be small to moderate. Two RCTs reported desirable effects for dental caries; however, the size of the effects was unclear. **Pregnant women** No desirable effects specific to pregnant women were identified.	
Undesirable effects	**How substantial are the undesirable anticipated effects?** **Adults** ☐ Trivial ☐ Small ■ **Moderate** ☐ Large ☐ Varies ☐ Don't know **Children** ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ■ **Don't know** **Pregnant women** ☐ Trivial ☐ Small ■ **Moderate** ☐ Large ☐ Varies ☐ Don't know	Assuming that the associations observed in prospective cohort studies are valid, the following assessments were made. **Adults** Undesirable effects for adults were observed primarily in prospective cohort studies.[a] They varied from small to moderate, and were considered overall to be moderate, based on the outcomes below. *Higher compared with lower NSS intake* BMI: MD 0.14 kg/m2 (95% CI: 0.03 to 0.25) Incident obesity: hazard ratio (HR) 1.76 (95% CI: 1.25 to 2.49) Type 2 diabetes (NSS in beverages): HR 1.23 (95% CI: 1.14 to 1.32) Type 2 diabetes (tabletop NSS): HR 1.34 (95% CI: 1.21 to 1.48) All-cause mortality: HR 1.10 (95% CI: 1.03 to 1.18) CVD mortality: HR 1.19 (95% CI: 1.07 to 1.32) CVD events: HR 1.32 (95% CI: 1.17 to 1.50) Stroke: HR 1.19 (95% CI: 1.09 to 1.29) Hypertension: HR 1.13 (95% CI: 1.09 to 1.17) **Children** No undesirable effects specific to children were identified; however, effects observed for adults are expected to also be relevant for children. Given the lack of direct evidence, "Don't know" was conservatively selected. **Pregnant women** An undesirable effect for pregnant women was observed in prospective cohort studies and was considered to be moderate: *Higher compared with lower NSS intake* Preterm birth: OR 1.25 (95% CI: 1.07 to 1.46)	It is possible that reverse causation and confounding by body weight or other residual confounding contributes significantly to the associations observed in prospective cohort studies for adults and pregnant women. However, efforts taken by the authors to address reverse causation and confounding in most studies suggest that these phenomena are not the sole causes of observed associations and may not even play a significant role in many of the studies.

[a] An increase in the total cholesterol:HDL cholesterol ratio was also observed in RCTs and was considered to be small, and an increased risk of bladder cancer in case–control studies was considered to be moderate.

	Judgement	Research evidence	Additional considerations
Certainty of evidence	**What is the overall certainty in the evidence of effects?** **Adults** ☐ Very low ■ **Low** ☐ Moderate ☐ High ☐ No included studies **Children** ☐ Very low ■ **Low** ☐ Moderate ☐ High ☐ No included studies **Pregnant women** ☐ Very low ■ **Low** ☐ Moderate ☐ High ☐ No included studies	**Adults** The overall certainty in the evidence for effects in adults of higher intakes of NSS compared with lower (or no) intake is low, and for NSS as a replacement for sugars is moderate. Because the associations with possible increased risk of death and disease observed in prospective cohort studies would be sufficient on their own to make recommendations, and are *very low* to *low* certainty, the overall certainty in the evidence for adults is *low*. Certainty in the evidence for key outcomes is listed below. Body weight: *low* (RCT) BMI: *low* (RCT) Energy intake: *low* (RCT) Sugars intake: *low* (RCT) Incident obesity: *low* (observational) Type 2 diabetes (NSS in beverages): *low* (observational) Type 2 diabetes (tabletop NSS): *low* (observational) All-cause mortality: *very low* (observational) CVD mortality: *low* (observational) CVD events: *low* (observational) Coronary heart disease: *very low* (observational) Stroke: *low* (observational) Hypertension: *low* (observational) **Children** The associations with possible increased risk of death and disease observed in prospective cohort studies for adults would be sufficient on their own to make recommendations and have been extrapolated to children. Therefore, the overall certainty in the evidence for children is low. Certainty in the evidence for key outcomes assessed directly in children is listed below. Body weight: *moderate* (RCT) BMI *z*-score: *moderate* (RCT) Energy intake: *moderate* (RCT) Dental caries: *low* (RCT) All outcomes assessed in observational studies were assessed as *very low* certainty evidence, except for body weight, which was assessed as *low* certainty evidence. Because the NUGAG Subgroup on Diet and Health concluded that the potential long-term undesirable effects outweighed any effects of short-term weight loss, the overall certainty in the evidence was based on that assigned to adults. **Pregnant women** The associations with possible increased risk of death and disease observed in prospective cohort studies for adults would be sufficient on their own to make recommendations and are relevant for pregnant women. Therefore, the overall certainty in the evidence for pregnant women is *low*. Certainty in the evidence for key outcomes assessed directly in pregnant women is listed below. Preterm birth: *low* (observational) Other outcomes from observational studies: all *very low*	See GRADE evidence profiles for certainty of evidence for all outcomes (**Annex 6**).

	Judgement	Research evidence	Additional considerations
Values	**Is there important uncertainty about, or variability in, how much people value the main outcomes?** ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ■ **Probably no important uncertainty or variability** ☐ No important uncertainty or variability	The recommendation in this guideline places a high value on reducing the risk of mortality, overweight, obesity and NCDs. Although individuals almost universally value the prevention of premature mortality, those that may be impacted by the recommendation may place different values on the benefit of reducing the risk of obesity and associated disease, based on personal preferences, beliefs and customs. For example, because CVDs are a high-profile public health topic, including in many LMICs where they represent a growing threat *(6)*, it is expected that most individuals would value efforts to reduce risk. However, in real-world settings, perception of the risk varies considerably *(7–11)*, and outreach and communication efforts may therefore be needed to improve understanding. Similarly, although many people in LMICs are increasingly aware of negative health effects associated with being overweight or obese, some cultures still consider overweight to be a desirable or positive attribute *(12–14)*. Others believe body weight to be hereditary and therefore not amenable to management via lifestyle changes *(11, 15)*. And many, regardless of personal beliefs, incorrectly perceive their own body weight in the context of overweight and obesity – that is, they believe that they are at a healthy body weight when in fact they are overweight or obese according to accepted standards for assessing body weight outcomes *(11, 15, 16)*.	
Balance of effects	**Does the balance between desirable and undesirable effects favour using NSS or not using NSS?** ☐ Favours using NSS ☐ Probably favours using NSS ☐ Does not favour either ■ **Probably favours not using NSS** ☐ Favours not using NSS ☐ Varies ☐ Don't know	Although short-term benefit of NSS use on measures of body fatness was observed in controlled experimental settings, the NUGAG Subgroup on Diet and Health concluded that the lack of evidence to suggest that NSS use is beneficial for body weight and other measures of body fatness over the long term together with possible long-term adverse effects in the form of increased risk of death and disease, offset any potential short-term health benefit resulting from the relatively small reduction in body weight and BMI observed in randomized controlled trials. In addition, limited evidence for beneficial effects of NSS use on dental caries was observed in studies of children. However, this was generally only observed in studies where intake of NSS was compared with intake of free sugars, suggesting that NSS do not have any inherent properties that impact risk of dental caries; rather, the effect is a result of displacing free sugars. In the case of NSS, the potential undesirable effects carry a greater weight when assessing desirable vs undesirable effects because a reduction in free sugars intake can be achieved and corresponding desirable health benefits realized without the use of NSS. In addition, unlike the potential effects observed from long-term exposure in adults, the evidence from prospective studies of pregnant women suggests that potential adverse effects from NSS use occur over the relatively short period of gestation. Evidence from RCTs suggests that the effects of NSS in these studies primarily occur via a reduction in energy intake. Therefore, any potential benefit of NSS use would largely be for those who are trying to lose or maintain body weight via restriction of energy intake (resulting from replacing free sugars with NSS). NSS use may not produce desirable effects for those who are not regular consumers of free sugars or who are otherwise not at risk of excess energy intake resulting from free sugars intake. This segment of the general population would therefore likely only be subjected to the potential undesirable effects of NSS use.	The assessment that the balance between desirable and undesirable effects probably favours not using NSS was made taking into account the uncertainty in the results of the prospective observational studies. If there were greater certainty in these results, an assessment of "Favours not using NSS" would likely have been made.

	Judgement	Research evidence	Additional considerations
Balance of effects		NSS are not essential dietary components and provide no nutritional value themselves, and are frequently a component of highly processed foods. Therefore, a possible undesirable effect of NSS use in the context of reducing free sugars intake is the inclusion of a greater number of highly processed foods and beverages in the diet than would be included if free sugars were reduced without NSS use *(17)*. The recommendation to not use NSS could result in potential undesirable effects, not inherent to NSS, if some individuals currently using NSS discontinue use and increase free sugars intake in order to maintain the level of sweetness in their diet. However, the undesirable effects of free sugars intake are well documented, and awareness of these effects among the general public is fairly high. Together with the fact that the recommendation in this guideline should be considered in the context of the WHO recommendations to reduce free sugars intake *(18)*, this suggests that individuals switching from NSS to free sugars would not be a widespread occurrence. Overall, the NUGAG Subgroup on Diet and Health concluded that the desirable effects of not using NSS outweighed the undesirable effects.	
Resources required	**How large are the resource requirements (costs) of not using NSS?** ☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ■ **Varies** ☐ Don't know	Absolute costs of translating the recommendation in this guideline into policy actions and interventions will vary widely depending on which approaches are taken. Costs may be minimized by coupling measures taken with existing efforts to reduce free sugars intake and promote healthy diets. For example, as noted under "Feasibility" above, it may be possible to incorporate the recommendation into existing policy actions and interventions, such as food-based dietary guidelines and fiscal policies targeting sugar-sweetened beverages, which might limit the resources required to implement the recommendation. Implementation of the recommendation will likely require consumer education and public health communications. These can also be incorporated into existing public health nutrition education campaigns and other existing nutrition programmes at the global, regional, national and subnational levels. In general, not using NSS should lead to a decrease in both the purchase of NSS themselves (for use by the consumer) and the purchase of foods and beverages containing NSS. In the case of NSS and certain foods and beverages with no caloric value, further adjustments to the diet would not be needed, and money could be saved by simply forgoing these purchases. Adhering to the recommendation could therefore have a positive or negative impact on disposable income, which might be amplified in people of lower socioeconomic status – particularly in LMICs – as they tend to spend a higher proportion of their income on foods and beverages *(19–21)*.	An assessment of the costs of all possible ways of implementing the recommendation is beyond the scope of this guideline. In any case, there is very little published evidence for costs of possible actions specifically targeting NSS. Therefore, proxy studies targeting sugar-sweetened beverages have been used as examples given that the majority of NSS in most settings are consumed in pre-packaged beverage form (i.e. "diet" sodas and drinks). Because NSS use is already widespread, not doing anything would be maintaining the status quo and would therefore likely cost little to nothing in terms of public health expenditure –

	Judgement	Research evidence	Additional considerations
			and therefore more than implementing the recommendation to not use NSS. However, health-care costs of the status quo could end up being much higher if the long-term risks observed with NSS use are valid.
Certainty of evidence for required resources	**What is the certainty in the evidence of resource requirements (costs)?** ☐ Very low ☐ Low ☐ Moderate ☐ High ■ **Don't know**	Because the costs will vary widely depending on which approaches are taken and detailed discussion of all possible approaches is beyond the scope of this guideline, assigning a certainty to the evidence of resource requirements is not applicable.	
Cost-effectiveness	**Does the cost-effectiveness of not using NSS favour using NSS or not using NSS?** ☐ Favours using NSS ☐ Probably favours using NSS ☐ Does not favour either ☐ Probably favours not using NSS ☐ Favours not using NSS ☐ Varies ■ **No included studies**	Whether or not implementing the recommendation is cost-effective (i.e. the savings in health-care costs offset or exceed the cost of implementation) is not conclusively known, given the uncertainty of long-term health effects of NSS use. However, assuming that the long-term associations between NSS use and increased risk of unhealthy weight gain and NCDs are valid, implementing the recommendation may be associated with long-term savings in costs of health care, though the extent of the savings depends on strategies chosen for implementation and the timescale for evaluation. For example, although very few (if any) cost-effectiveness analyses have been conducted for NSS use, a number of cost-effectiveness studies on taxation of sugar-sweetened beverages have been published, with most finding that taxes have the potential to result in substantial cost savings and health impact with respect to obesity and diet-related NCDs *(22–26)*. Similarly, limited evidence suggests that other policies and interventions that would be relevant to NSS, such as restrictions on marketing of unhealthy foods and beverages to children, may be cost-effective *(27)*. Overall, the cost-effectiveness of different approaches will likely vary and cannot be determined with certainty.	This question cannot be answered with certainty because it requires: ▸ an assessment of the different, individual modes of implementing the recommendation (beyond the scope of this guideline); ▸ proxy data from studies of sugar-sweetened beverages (given that no studies for NSS were identified); and ▸ assumptions to be made for the proxy data (as most studies are modelling studies).

	Judgement	Research evidence	Additional considerations
Equity	**What would be the impact on health inequity?** ☐ Reduced ■ **Probably reduced** ☐ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☐ Don't know	The impact of the recommendation on equity and human rights is not conclusively known, given the uncertainty around long-term health effects of NSS use. Assuming that the long-term associations between NSS use and increased risk of unhealthy weight gain and NCDs are valid, the recommendation in this guideline has the potential to reduce health inequity by improving the long-term health of people of lower socioeconomic status, as they are generally disproportionately affected by overweight, obesity and NCDs *(28–31)*. However, in some LMIC settings, people of higher socioeconomic status may be more at risk than those of lower socioeconomic status and may benefit more from relevant interventions *(32, 33)*. Regardless, the effect on equity and human rights would likely be affected by how the recommendation is translated into policies and actions. For example, a small number of studies suggest that fiscal policies targeting foods and beverages, front-of-pack labelling and restrictions on marketing unhealthy foods may increase health equity *(34)*. However, if such measures affect all individuals in a population equally, relevant inequalities may not be addressed *(35)*. Overall, evidence is extremely limited and inconclusive. Although there is a suggestion that implementing the recommendation might reduce health inequity, it is ultimately unknown.	Little to no published data are available on which to base assessments. The assessment was based on two related observations. ▸ Obesity and diet-related NCDs disproportionately affect people of lower socioeconomic status. If effective, the recommendation therefore would likely reduce health inequity, regardless of the approach taken ("probably reduced"). ▸ Limited data are available for a small number of specific interventions that may preferentially help those of lower socioeconomic status, but in theory could also help everyone equally or preferentially help those of higher socioeconomic status ("don't know").

	Judgement	Research evidence	Additional considerations
Acceptability	**Is not using NSS acceptable to key stakeholders?** ☐ No ☐ Probably no ☐ Probably yes ☐ Yes ■ **Varies** ☐ Don't know	Although the recommendation in this guideline is in line with existing national guidance in a number of countries, institutional acceptability may vary across different countries and cultural contexts. Acceptability may be influenced by: ▸ how the recommendation is translated into policies and actions – some means of implementation may be more acceptable than others; ▸ the level of awareness of the potential health problems associated with NSS use – interventions may be less acceptable in settings where awareness is low; ▸ the potential impact on national economies; and ▸ compatibility with existing policies. At an individual level, because adhering to the recommendation to not use NSS and WHO recommendations to limit free sugars might require a reduction in the overall sweetness of the diet, acceptability of the recommendation may be low, particularly for those accustomed to sweetness in certain types of foods and beverages. Popular perceptions about NSS may also feed into acceptability to consumers. These encompass both positive and negative feelings about sweeteners, which might be affected by whether sweeteners are categorized and marketed as "artificial" or "natural". However, for people who acknowledge the potential health risks of consuming NSS over the long term and value reducing this risk, acceptability should be high, because obesity, CVDs and type 2 diabetes are significant, recognized global health problems. Acceptability of this recommendation can be improved through appropriate public health messaging, not only on NSS and free sugars, but more broadly on an overall healthy diet, including the message that whole fruits can provide a healthy source of sweetness in the diet.	Published data on which assessments could be based were not identified.
Feasibility	**Is not using NSS feasible to implement?** ☐ No ☐ Probably no ■ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	The recommendation in this guideline can be implemented in numerous ways, including through behaviour change interventions, fiscal policies, regulation of marketing of foods and beverages, product labelling schemes, and reformulation of manufactured products. Feasibility of these interventions will depend on the country context. Regardless of specific modes of implementation, the recommendation can be incorporated into existing measures designed to promote healthy diets and would naturally complement existing efforts to reduce intake of free sugars. For example, appropriate messaging on NSS use can readily be added to existing food-based dietary guidelines and the increasing number of actions being taken to address free sugars intake, such as behaviour change and education campaigns, fiscal policies, marketing and labelling policies, and reformulation. A number of countries and municipalities already include beverages sweetened with NSS in existing food and beverage tax legislation *(36)*, and several national food-based dietary guidelines already provide guidance on NSS use *(37)*. This suggests that implementing the recommendation to not use NSS is feasible, particularly in settings that already have robust dietary guidelines and established health messaging infrastructure. However, existing efforts to reduce free	

	Judgement	Research evidence	Additional considerations
Feasibility		sugars intake also have the potential to make implementation of the NSS recommendation more challenging: recent evidence suggests that sales of NSS-containing beverages (but not NSS-containing foods) are increasing in regions that have implemented multiple policy actions targeting free sugars intake, relative to regions that have implemented fewer or no actions *(38)*. Because NSS, and foods and beverages containing NSS are already widely available and used by large segments of the global population, implementing the recommendation will have its challenges, particularly in settings without robust infrastructure for implementing public health measures, including behaviour change communications and messaging, or where "piggy backing" on efforts to address free sugars intake is not possible. Regardless of which interventions and policy actions are used to implement the recommendation, some amount of behaviour change at the individual level will likely be required; the extent to which this can be achieved will depend on the willingness of individuals who have become habituated to a certain level of sweetness in foods and beverages to reduce the overall sweetness in their diets. For those not habituated to high levels of sweetness in the diet (including infants and young children), avoiding NSS (and excess free sugars) – particularly in beverage form – should be very feasible. However, as noted below, because of the way in which NSS-containing foods and beverages are labelled, avoiding NSS may require vigilance on the part of consumers. The level to which NSS use can be reduced will depend not only on the success of public health efforts and individual choice, but the extent to which consumers are aware of the NSS content in products they purchase. Evidence suggests that some consumers may not be aware that many of the food and beverages they are purchasing contain NSS *(39, 40)*, and generally may have difficulties interpreting nutrient declaration labels, health claims and other relevant labelling *(41–45)*.	

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