WHO draft guideline: use of non-sugar sweeteners

This document is a draft guideline made available to those participating in the public consultation and is not the final version of the guideline.

World Health Organization

Draft WHO guideline: use of non-sugar sweeteners

Contents

Acknowledgements

(To be added before finalization)

Abbreviations and acronyms

BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
CVD	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
HDL	high-density lipoprotein
HOMA-IR	homeostasis model assessment of insulin resistance
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kcal	kilocalorie
kJ	kilojoules
LDL	low-density lipoprotein
LMICs	low- and middle-income countries
MD	mean difference
NCD	noncommunicable disease
NSS	non-sugar sweeteners
NUGAG	WHO Nutrition Guidance Expert Advisory Group
PICO	population, intervention, comparator and outcome
RCT	randomized controlled trial
RR	risk ratio
SMD	standardized mean difference
WHO	World Health Organization

Executive summary

Background

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

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/ glucose levels/ blood sugar in individuals with diabetes. Individual sweeteners undergo toxicological assessment to establish safe levels of intake (i.e. acceptable daily intake or ADI) but there is no clear consensus on whether NSS are effective for long-term weight loss or if they are linked to other long-term health effects at habitual intakes within the ADI.

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

Objective, scope and methods

The objective of this guideline is to provide guidance on NSS use for the general population, to be used by policymakers, programme managers, health professionals and other stakeholders in efforts to reduce free sugars intake and promote healthy diets. Assessing the health effects of NSS on individuals with pre-existing diabetes was beyond the scope of this 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 the guidance contained within this guideline may not be relevant for individuals with existing diabetes. The guidance contained within this guideline is based on evidence of health effects of NSS use at levels already considered safe (i.e. within the ADI), and is

[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 non-sugar sweeteners.

not intended to provide updated or alternative guidance on safe or maximal levels of intake.[1] This guideline was developed following the WHO guideline development process as outlined in the *WHO handbook for guideline development*, which includes: a review of systematically gathered evidence by an international, multidisciplinary group of experts; assessment of the quality of that evidence via Grading of Recommendations Assessment, Development and Evaluation (GRADE); and consideration of additional, potentially mitigating factors[2] when translating the evidence into recommendations.

The evidence

Evidence from a systematic review and meta-analyses of randomized controlled trials and prospective observational studies found that higher NSS consumption by adults led to lower body weight and BMI (than not consuming NSS or consuming lower amounts of NSS) when assessed in short-term randomized controlled trials, but was associated with increased BMI and risk of incident obesity in long-term prospective observational studies. Effects on body weight and BMI observed in randomized controlled trials are observed only when NSS are compared to 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 randomized controlled trials or prospective cohort studies. Long-term NSS use was also associated with increased risk of type 2 diabetes, cardiovascular diseases, and mortality in prospective cohort studies conducted in adults, but significant effects were not observed on intermediate markers of disease such as fasting glucose, fasting insulin, or blood lipids when assessed in short-term randomized controlled trials.

Evidence from studies conducted in children and pregnant women was more limited than that identified for adults. One randomized controlled trial conducted in children reported a reduction in

[1] Safe levels of intake are based on toxicological assessments of individual NSS and such assessments are completed by authoritative bodies such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) prior to approving individual NSS 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 2020–24 (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 the reviewing of the Acceptable Daily Intake 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.

[2] 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.

several measures of body fatness when sugar-sweetened beverages were replaced with those containing NSS, however when results for BMI *z* score[1] were combined with those from a second trial no effect was observed, and results from prospective observational studies did not suggest any significant associations between NSS use and measures of body fatness. Two randomized controlled trials reported lower indicators of dental caries with stevia use. 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

WHO recommendation
WHO suggests that NSS not be used as a means of achieving weight control or reducing risk of noncommunicable diseases (*conditional recommendation*)[2]
Rationale
• This recommendation is based on evidence of *low* certainty overall, from a systematic review that assessed the health effects of higher compared to lower intake of non-sugar sweeteners (NSS) and 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, cardiovascular diseases, 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: *Adults* In randomized controlled trials:

[1] BMI *z* scores are adjusted for sex and age relative to standardized reference values.
[2] *Conditional* recommendations are those recommendations for which the WHO guideline development group is uncertain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are small. Policymaking related to conditional recommendations therefore may require substantial debate and involvement of various stakeholders.

- NSS use in any manner[1] resulted in reduced energy intake, lower body weight, and lower BMI in short-term randomized controlled trials (all *low* certainty evidence), the majority of which lasted three months or less, and 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). Relevant evidence from a small number of longer term trials lasting from 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 NSS were directly compared to 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 results of when NSS was used in any manner. However, most of these trials provided NSS or free sugars-containing foods and beverages in addition to existing diets and therefore did not directly measure the effects of replacing free sugars with NSS. When NSS were compared to 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 the randomized controlled trials (i.e. habitual consumers of free sugars-containing foods or beverages 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.

In prospective observational studies with up to 10 years of follow-up, 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). In addition, higher intakes of NSS were associated with increased risk of type 2 diabetes, cardiovascular diseases and 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 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 randomized controlled trial 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). When results for BMI *z* score were combined with those from a second trial however, no effect was observed, and results

[1] NSS were consumed by the participants in the randomized controlled trials in a variety of ways including in pre-mixed beverages, powders or drops to be added to beverages by the participants, 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.

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.

- In addition to the limited direct evidence for children and pregnant women, because the potential long-term effects of NSS use observed for adults in prospective observational studies are also relevant for women during pregnancy, and were reasonably expected to be relevant in children and adolescents as well, the evidence from randomized controlled trials 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 risk of disease associated with excess free sugars intake), the currently available evidence on which to base a recommendation on NSS is largely indirect: i.e. most randomized controlled trials comparing NSS to 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 to have a meaningful impact on health, evidence of minor weight loss or reduced BMI over several months or less as observed in the randomized controlled trials without additional evidence of long-term impact, does not represent a health benefit.
    - The discordant results between the randomized controlled trials 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; other viable alternatives exist that are compatible with features of a healthy diet,

including foods with naturally occurring sugars such as fruit, and unsweetened food and beverages.

Based on the evidence and other considerations as 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 death and disease, outweighed any potential short-term health effects resulting from the relatively small reductions in body weight and BMI observed in randomized controlled trials

- Because of lack of certainty about the overall balance of desirable and undesirable effects associated with long-term effects of NSS use for reducing non communicable disease 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, and the recommendation was considered to be *conditional*.

Remarks

- With the possible 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.

- Assessing the health effects of NSS on individuals with pre-existing diabetes was beyond the scope of this 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, while individuals with diabetes can also reduce free sugars intake without the need for NSS, the recommendation may not apply to those with existing diabetes.

- 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. Most studies included in the systematic review assessed the effects of NSS consumed in beverage form. A small number of studies assessed the effects of tabletop use (i.e. added to foods or beverages by the consumer), consumption in foods, or some combination of beverage, food and tabletop.

- “Weight control” in this recommendation refers to weight loss in cases of existing

[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 a subsequent increased risk of disease.

overweight or obesity, and preventing unhealthy weight gain by maintaining a healthy weight.

- This 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. Sugar alcohols and low-calorie sugars are not considered NSS. Common NSS include, but are not limited to, acesulfame K, aspartame, advantame, cyclamates, neotame, saccharin, sucralose, stevia and stevia derivatives.

- 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, either because it 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 which suggests that there are health effects associated with NSS use irrespective of which NSS is being used, i.e. NSS as a class of compounds, despite individual NSS having different chemical structures, have an impact on health. It is recognized that NSS are not a homogenous class of compounds: each has a unique chemical structure and as a result, individual NSS have different sweetness intensities and organoleptic properties, and are processed differently by the body. Limited evidence suggests that individual NSS may also differ in their physiological effects in humans, however, evidence is currently insufficient to make recommendations for individual NSS.

- It is noted that 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 imply that such medications or products should not be used. However, NSS-free versions of these items, when readily obtainable, can be considered.

- This recommendation should be considered in the context of WHO recommendations to reduce free sugars intake and other guidance promoting healthy diets, including WHO guidance on dietary fat, carbohydrates, sodium and potassium.

- 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 in a food or beverage in which any other unhealthy elements are mostly retained, and as a result, the overall quality of the diet remains largely unaffected. Replacing free sugars in the diet with sources of naturally occurring sweetness, such as fruits, as well as

[1] For prospective cohort studies it was generally not possible to determine the absolute highest intakes as the highest quantile was generally a specified amount or more (e.g. ≥ 2 servings per day), and though it is possible that some adults may have exceeded the ADI in some number of these studies, the number doing so would likely 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.

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 2019, more than 38 million children under 5 years of age were overweight – an increase of about 8 million over the past 15 years *(2)*. High body mass index (BMI) was responsible for an estimated 4 million deaths in 2015 *(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, type 2 diabetes and certain types of cancers. 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 *(6-8)*.

A high level of free sugars intake is associated with poor dietary quality *(9)*, obesity *(10)* and risk of NCDs *(11)*, and WHO has issued guidance on limiting free sugars intake to reduce the risk of unhealthy weight gain and dental caries *(12)*. Since the release of the WHO guideline on free sugars intake, interest in the potential utility of non-sugar sweeteners (NSS) in reducing sugars intake at the population level has increased.

Referred to by a variety of names including high-intensity sweeteners, low-/no-calorie sweeteners, nonnutritive sweeteners, noncaloric sweeteners, and sugar-substitutes, NSS[1] have been developed as an alternative to free sugars and are widely used both as an ingredient in pre-packaged foods, beverages and personal care products, as well as added to food 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 and 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 *(13)*. NSS are also frequently recommended as a means of controlling blood glucose/ glucose levels/ blood sugar in individuals

[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 non-sugar sweeteners.

with diabetes. NSS include a wide variety of synthetically derived chemicals and natural extracts that may or may not be chemically modified and are many times sweeter than sugars. Common NSS include acesulfame K, aspartame, advantame, cyclamates, neotame, saccharin, sucralose, stevia and stevia derivatives, though certain d-amino acids and several plant proteins 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 *(14)*. Sweet-taste receptors have more recently been found at sites outside the oral cavity, including the gastrointestinal tract, pancreas, brain, and adipose tissue among others *(15)*, and may be involved in various metabolic effects of NSS observed in a large body of in-vitro, animal and human studies *(16-20)*.

Individual NSS undergo toxicological assessment by various authoritative bodies to establish safe levels of intake (i.e. acceptable daily intake or ADI), and while results of randomized controlled trials have generally suggested 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 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 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 homogenous 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 *(13)*. As a result of these differences, individual NSS may have differential physiological effects in humans *(17)*.

Global trends on NSS use are unclear as NSS have yet to appreciably enter some markets and robust longitudinal intake data is not readily available for most countries outside North America, Europe and Australasia *(21)*. Nevertheless, available data indicate that the number of foods and beverages containing NSS and/or NSS use is significant in diverse settings worldwide *(21-25)*. And although intake rarely appears to exceed the ADI *(26)*, NSS availability and use (predominantly in the form of NSS-sweetened beverage consumption) appear to be increasing in many locations as assessed for example in New Zealand, Norway, Slovenia, and the United States *(27-31)*, and corresponds with a decline in sugar-sweetened beverage consumption as observed in the United States and Norway *(30, 32)*. Because the global trend appears to be a sweetening of the overall diet (largely driven by consumption of sweetened beverages) *(22)*, it may be reasonable to assume that the shift from free sugars to NSS occurring in the United States and elsewhere may also occur in other countries as global efforts to reduce the intake of free sugars intensify.

Rationale

Following the work of the 1989 WHO Study Group on Diet, Nutrition and Prevention of Noncommunicable Diseases *(33)* and the 2002 Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases *(34)*, WHO guidance on free sugars intake was updated and released in 2015 *(12)*. Since the release of the WHO guideline on free sugars intake, interest in whether incorporating NSS into activities aimed at reducing free sugars intake at the population level may be effective and appropriate has increased, as has NSS availability and use by consumers. Therefore, it was considered important to review the evidence in a systematic manner, and issue WHO guidance on NSS use through the current WHO guideline development process.

Scope

This guideline is an extension of the larger effort to update the population nutrient intake goals for the prevention of NCDs established by the 2002 Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases (2) and is intended to complement other WHO guidance on healthy diets, particularly the WHO guideline on free sugars intake *(12)*. The recommendations in this guideline are intended for the general population of children and adults, including pregnant women. The guidance contained within this guideline is based on evidence of health effects of NSS use at levels already considered safe by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[1], and is not intended to provide updated or alternative guidance on safe or maximal levels of intake. Safe levels of intake are based on toxicological assessments of individual NSS, and such assessments are completed by authoritative bodies prior to approving individual NSS for commercial use.[2] Because evidence on the effects of NSS in individuals with pre-existing diabetes was not reviewed, the guidance contained within this guideline may not be relevant for individuals with diabetes.

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

[2] Safe levels of intake are based on toxicological assessments of individual NSS and such assessments are completed by authoritative bodies such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) prior to approving individual NSS 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 2020–24 (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 the reviewing of the Acceptable Daily Intake 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 by consumers. The recommendation in this guideline can be used by policymakers 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 can be an important element of WHO's efforts in implementing the NCD agenda and achieving the 'triple billion' targets set up by the 13th General Programme of Work (2019 – 2023), including one billion more people enjoying better health and well-being. In addition, the recommendations and other elements of this guideline will hopefully support:

- the implementation of the Political Declaration of the UN High-level Meeting on NCDs held in New York in September 2011 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;
- the implementation of the WHO NCD Action Plan for 2013 – 2020 which was adopted by the 66th World Health Assembly held in May 2013;
- implementing the recommendations of 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 and recommended actions in the Framework for Action which recommends a set of policy options and strategies to promote diversified, safe and healthy diets at all stages of life, adopted by the Second International Conference on Nutrition (ICN2) in 2014 and endorsed by the 136th Session of the WHO Executive Board (EB) held in January 2015 and the 68th World Health Assembly held in May 2015, which called on Member States to implement the commitment of the Rome Declaration across multiple sectors;
- achieving the goals of the UN Decade of Action on Nutrition (2016-2025), declared by the UN General Assembly (UNGA) in April 2016, which include increased action at the national, regional and global levels in order to achieve commitment of the Rome Declaration adopted at ICN2, 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 (SDGs), particularly Goal 2 of *Zero Hunger* and Goal 3 of *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:

- regional, national and local policymakers;
- managers and implementers of national and local nutrition and NCD prevention programmes;
- intergovernmental and nongovernmental organizations, including professional societies, involved in managing and implementing nutrition and NCD prevention related programmes;
- health professionals including managers of nutrition and health programmes and public health policymakers in all settings;
- scientists and others involved in nutrition and NCD related research; and
- educators teaching nutrition 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 guideline development process outlined in the *WHO handbook for guideline development (35)*. Because of the complex nature of the guideline topic and rapidly evolving evidence base, the guideline was developed over several, successive meetings of the NUGAG Subgroup on Diet and Health, beginning in 2016. For a complete list of meetings, see https://www.who.int/nutrition-guidance-expert-advisory-group-nugag/diet-and-health.

Contributors to the development of this guideline

Development of this guideline was undertaken 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 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 – entitled the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health – was convened to support the development of this guideline (**Annex 2**). This group included experts who had previously participated in various WHO expert consultations or were members of the WHO expert advisory panels, and others identified through open calls for experts. In forming this group, the WHO Secretariat took into consideration the need for expertise from 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 and 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 and other health professionals involved in the health-care process). The names, institutional affiliations and summary background information of the members of the NUGAG Subgroup on Diet and Health are posted on the WHO website[1], along with information regarding each meeting of the NUGAG Subgroup on Diet and Health.

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 (**Annex 3**). (To be finalized)

Systematic review teams

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

- A team from the University of Freiburg in Germany and 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 prioritised health outcomes commissioned by WHO and published in 2019 *(36)*.
- Magali Rios-Leyvraz, WHO consultant, and Jason Montez of WHO completed the updating and expansion *(37)* of the original 2019 systematic review.

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

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

Stakeholder feedback via public call for comment

Two public calls for comment were held during the development of this guideline: once at the scoping phase of the process and once on the draft guideline. A public online call for comment on the scope of the guideline was held in 2016[1] (feedback was received from a total of 13 individuals and organizational stakeholders) and on the draft guideline in July 2022 (feedback was received from a total of [TBD] 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 call was open to everyone, and 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 as noted in the following section. Comments were summarized, and along with WHO responses to the summary comment, posted on the WHO website.[2] 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 guideline document.

Management of conflicts of interest

According to the rules in the WHO *Basic documents (38)*, whenever an expert or an individual provides independent advice to WHO, including participating in WHO meetings, any financial and intellectual interests must be declared and assessed by the WHO Secretariat. For this guideline, this includes 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. Declared interests were reviewed by members of the WHO steering group in consultation with the WHO Legal Office previously, but since 2014 with the Department of Compliance and Risk Management and Ethics, where necessary. Declared interests of NUGAG Subgroup on Diet and Health members and members of the systematic review teams were reviewed prior to their original engagement in the guideline development and before every meeting. In addition, each NUGAG Subgroup on Diet and Health member (and member of the systematic review team if present) verbally declared his or her interests, if required, at the start of each NUGAG Subgroup on Diet and Health meeting. Declared interests of external reviewers were assessed prior to their invitation 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

[1] A shared, public call for comment was held in which feedback was received on the scope of three guidelines in development: non-sugar sweeteners, carbohydrates, and polyunsaturated fatty acids.
[2] https://www.who.int/nutrition-guidance-expert-advisory-group-nugag/diet-and-health

four years prior to 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, 2nd Edition (35)* were followed.

Interests declared by members of the NUGAG Subgroup on Diet and Health, external reviewers, and members of the systematic review teams, and how any identified conflicts of interest were managed 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. 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.

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. Feedback was received from a total of 13 individuals and organizational stakeholders, and the scope was adapted as necessary.

Priority health outcomes considered for adults were overweight and obesity, dental caries, type 2 diabetes, cardiovascular diseases, cancer, chronic kidney disease, 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 cardiovascular diseases (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.

The key research questions guiding the systematic reviews undertaken are shown below:

What is the effect on risk of prioritised health outcomes in adults, children, and pregnant women of:

- lower intake of NSS compared to higher intake; or
- replacing free sugars with NSS.

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 randomized controlled trials and observational studies that assessed the effects of NSS use in adults and children. This review did not include or assess studies in which NSS were not specified by name or type, and was completed in 2019 *(36)*.
- An update of the 2019 review of randomized controlled trials 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 *(37)*. 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

Grading of Recommendations Assessment, Development and Evaluation (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, the systematic review teams, and the members of the WHO Secretariat present at the meeting, and refined as necessary under the guidance of a methodologist 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, 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, feasibility and acceptability of implementing the intervention in different settings, and the

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

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.

Summary of evidence

Systematic review characteristics

A systematic review of randomized controlled trials and observational studies that assessed the health effects of NSS use in adults, children, and pregnant women identified 283 unique studies, including 50 randomized controlled trials, 97 prospective cohort studies, and 47 case-control studies assessing cancer outcomes *(37)*. Only studies in which NSS were consumed in amounts within the ADI[1], either because it was explicitly stated in the study or it was reasonably inferred that the ADI was not being exceeded, were included in the systematic review.[2] Because assessing the effects of NSS use in individuals with diabetes was beyond the scope of this guideline, studies specifically assessing the effects of or including only individuals with pre-existing diabetes were not included in the review.[3]

Randomized controlled trials

The systematic review included 45 randomized controlled trials conducted in adults, 4 in children, and one including both adults and children. No relevant trials in pregnant women were identified.

Trial duration in adults (including follow-up post-intervention) ranged from seven days to more than three years. Trials in adults were conducted in lean (n=10), mixed weight populations (n=20), or exclusively overweight populations (n=15). 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). Trials in adults were conducted in Australia (n=2), Denmark (n=2), France (n=2), Greece (n=1), the

[1] As assessed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) http://www.fao.org/food-safety/scientific-advice/jecfa/en/

[2] For prospective cohort studies it was generally not possible to determine the absolute highest intakes as the highest quantile was generally a specified amount or more (e.g. ≥ 2 servings per day), and though it is possible that some adults may have exceeded the ADI in some number of these studies, the number doing so would likely have been an extremely small percentage of the entire group *(21, 26)*. 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 *(21)*.

[3] 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.

Republic of Korea (n=4), the Islamic Republic of Iran (n=1), Latvia (n=1), Mexico (n=6), New Zealand (n=2), Switzerland (n=1), Thailand (n=1), the United Kingdom (n=7), the United States (n=14) and multiple countries (n=1).

Randomized controlled trials in children lasted from six 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, the Netherlands 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 affect behaviour change (e.g. replacing sugar-sweetened foods and/or beverages with those containing NSS or that were unsweetened);
- 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 to a placebo.

The focus of the trials wasn't always on assessing the effects of NSS, and 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 approximately 35 unique cohorts), 15 cohort studies in children (representing 13 unique cohorts), 1 cohort study in children and adults (representing 1 unique cohort), 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 which was exclusively girls. Follow up in cohort studies in adults ranged from two years to more than 30, in children from 8 months to 10 years, and in pregnant women from 8 months to 16 years. 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 in 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 conducted 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), the Netherlands (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 data sets) assessing cancer outcomes in adults. All case-control studies were conducted in populations of mixed weight, and two were conducted exclusively in males, three exclusively in females and the rest in mixed sex populations. Twenty-two studies assessed effects of unspecified sweeteners, 11 of multiple sweeteners, seven of saccharin, and two of aspartame. Studies were conducted in Argentina (n=2), Canada (n=4), China (n=2), Denmark (n=3), Egypt (n=1), France (n=2), Italy (n=2), Japan (n=2), Lebanon (n=1), Serbia (n=1), Spain (n=1), Sweden (n=2), the United Kingdom (n=2), the United States (n=15), and one study in multiple countries. 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 randomized controlled trials found that at the end of the trials, those consuming NSS had lower body weight than those consuming less or no NSS (–0.71 kg) and lower BMI (–0.14 kg/m^2), though the latter was not quite statistically significant. No significant effects were observed for other measures of body fatness as assessed in randomized controlled trials. Higher intakes of NSS[2] were associated with a higher BMI (0.14 kg/m2) and a 76% increase in

Table 1. Summary of results from meta-analyses of randomized controlled trials and observational studies for higher compared to lower intake of NSS

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty
Body weight (kg)				
RCT	MD –0.71 (–1.13 to –0.28)	29	2 443	*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/m^2)				
RCT	MD –0.14 (–0.30 to 0.02)	23	1 857	*Low*

[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 as data was available from higher quality randomized controlled trials and/or prospective observational studies.

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

Observational	MD 0.14 (0.03 to 0.25)	5	80 573	*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*
CVD				
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*
Bladder cancer				
Observational (CC)	OR 1.31 (1.06 to 1.62)	26	39 660	*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; CC, case control; cont, continuous; CVD, cardiovascular diseases; CHD, coronary heart disease; H/L, highest versus lowest; HR, hazard ratio; LDL, low-density lipoprotein; MD, mean difference; OR, odds ratio; RCT, randomized controlled trial; TT, tabletop

risk of incident obesity as assessed by meta-analyses of prospective cohort studies. Significant associations between NSS use and other measures of body fatness were not observed in meta-analyses of prospective cohort studies.

Results of subgroup analyses of randomized controlled trials suggest that the effect of NSS on body weight and BMI may differ by comparator: adding NSS to the diet compared to nothing (or placebo) and adding NSS to the diet compared to 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 largest effects when NSS were compared to sugars, while NSS compared to water showed no effect on body weight and a nonsignificant increase in BMI. When randomized controlled trials 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 (MD –0.61 kg; 95%CI: –1.28, 0.06), and an effect on BMI was no longer observed (MD –0.01 kg/m^2; 95%CI: –0.38, 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 (i.e. trials in which weight loss was a primary aim and participants were instructed to both use NSS and reduce energy intake), however results are not statistically significant, and the differences are small in the comparison by body weight status and highly heterogeneous in the comparison by weight loss status.

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

NCDs and mortality

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 as assessed by meta-analyses of prospective cohort studies. Results from meta-analyses of randomized controlled trials suggested no significant effect of NSS on biomarkers used in the assessment and diagnosis of diabetes and insulin resistance, including fasting glucose, fasting insulin, or haemoglobin A1c (HbA1c). The majority of several randomized controlled trials 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 cardiovascular diseases, 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 randomized controlled trials suggested no significant effect

of NSS on biomarkers used in the assessment and diagnosis of cardiovascular diseases, including blood pressure, 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 was 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 cardiovascular diseases, but were not associated with death from cancer.

Eating behaviour

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

The certainty in the available evidence for an effect of NSS intake on outcomes in adults was considered to be *very low* overall. GRADE assessments for each outcome can be found in **Annex 1**; 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 randomized controlled trial reported small but significant reductions in several measures of body fatness, however, results of meta-analyses of randomized controlled trials and prospective cohort studies found no significant relationships between NSS use and measures of body fatness including risk of being overweight (**Table 2**).

Table 2. Summary of results from meta-analyses of randomized controlled trials and observational studies for higher compared to lower intake of NSS

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/m^2)				
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*

cont, continuous; H/L, highest versus lowest; MD, mean difference; OR, odds ratio; RCT, randomized controlled trial

Additionally, two randomized controlled trials found that use of stevia reduced indicators of dental caries, however the interventions varied greatly: one trial assessed effects of stevia-containing snacks, the other the effects of a stevia mouth rinse. No other significant relationships were found for other outcomes of interest including biomarkers used in the assessment and diagnosis of type 2 diabetes and cardiovascular diseases, cancer, neurocognition, or energy and sugars intake, though the number of studies contributing to the evidence base for these outcomes was limited.

The certainty in the available evidence for an effect of NSS intake on outcomes in children was considered to be *very low* overall. GRADE assessments for each outcome can be found in **Annex 1**; GRADE evidence profile 3.

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 (OR 1.25; 95%CI: 1.07, 1.46; 129 009 pregnant women). A dose response relationship was observed in the two studies that reported a significant association and additional analyses suggested that the association was primarily for late preterm delivery (34 ≤ wk <37), not early preterm delivery (< 32 wk), 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 and birthweight 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 birthweight, while those from a third suggested an increase in birthweight, and 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, while those 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 NNS use and risk of gestational diabetes.

The certainty in the available evidence for an effect of NSS intake on outcomes in pregnant women was considered to be *very low* overall. GRADE assessments for each outcome can be found in **Annex 1**; GRADE evidence profile 4.

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 *(35)*. The relevance of the observations for interpreting the results of the systematic review is summarized below.

1. *Varied interventions in randomized controlled trials.* The design of the intervention in randomized controlled trials included in the systematic review varied considerably, which decreased 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 of those habituated to sweetness in the diet, via consumption of foods and beverages containing free sugars. Most trials provided NSS or free sugars (in beverage form) as an addition to the regular diet, often in order to assess whether individuals compensated energy intake when provided with additional free sugars, with NSS serving as a control. While such studies can assess whether when added to the diet, NSS impact energy intake or other relevant outcomes compared to added 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 users 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 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 users of NSS-sweetened beverages to switch to water. Therefore, although it was possible to compare how individuals responded to NSS compared to free sugars across a fairly large number of trials, the evidence for effects of specifically replacing free sugars with NSS is somewhat limited.

2. *Potential mechanisms of NSS action on body weight*. The wide variety of interventions in the included randomized controlled trials did allow for assessment of the effects of NSS regardless of potential mechanism of action, i.e. 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 for the further assessment of effects of NSS by delivery mode, comparator, type of NSS, and other parameters. Results of these analyses show that a significant difference in body weight and BMI is 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 to free sugars. This suggests that the lower body weight and BMI observed in the randomized controlled trials 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).

3. *Duration of randomized controlled trials.* Because weight loss or the maintenance of a healthy weight must be sustained over the long-term in order to realize associated health benefits, there must be evidence for sustained weight loss or maintenance for any intervention being investigated for effects on body weight. The majority of randomized controlled trials assessing NSS lasted three months or less, and the small number that lasted more than three months gave inconsistent results. Of these, only one trial lasted longer than 18 months *(39)*. This trial however, was also effectively an assessment of what happens when habitual users of NSS are asked to stop using NSS and thus not a direct assessment of the effects of replacing free sugars with NSS. In addition, both those that were instructed to continue using NSS and those that were instructed not to use NSS, lost an equivalent amount of weight during the active weight loss phase of the trial (first 16 weeks). It was only during the subsequent weight maintenance and follow-up phases that those not using NSS regained more weight, although at one year post weight-loss energy intakes were equivalent between the two groups, and at three years post-weight-loss phase (though less than 50% of the original participants provided data), the difference in aspartame intakes between the two groups narrowed considerably. 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 randomized controlled trials – driven primarily by those lasting three months or less – to be indicative of health benefit.

4. *Possible differences in manner of NSS use between randomized controlled trials and prospective cohort studies.* The manner in which individuals consumed NSS and free sugars in the randomized

controlled trials 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 in the form of nutrition guidance, further instruction, etc.; and 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) though 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 *(40-43)*, often not as a conscious replacement for free sugars, but alongside free sugars and carbohydrates, in a compensatory manner in which a food or beverage containing NSS is consumed so that another, often energy dense food can be consumed, or with a general belief that NSS containing foods are simply "healthier" *(44)*. Rather than consuming fewer calories as observed in many of the randomized controlled trials included in the systematic review, some evidence suggests that those using NSS in free-living populations may consume more calories than those who don't use NSS *(42)*. There is also limited evidence to suggest that health effects may differ when certain NNS are consumed together with sugars compared to when they are consumed alone *(45, 46)*, though more research is needed to understand if this is broadly applicable and what the implications may be.

Therefore, while NSS have been demonstrated to lower body weight in randomized controlled trials 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.

5. *The potential role of reverse causation in the results from the prospective cohort studies.* Reverse causation, though not unique to the study of NSS in observational studies, was noted as a possible explanatory factor in the associations observed between NSS and health outcomes in the observational studies included in the systematic review (in the case of NSS, reverse causation would suggest 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), and in some studies, those using NSS had 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 of the studies

included in the systematic review those with higher intakes of NSS had higher average BMI at baseline.

Most authors of the included studies also 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 respective studies, including controlling for relevant confounders (including BMI), stratifying results by body weight, and conducting various sensitivity analyses such as limiting analyses to those 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 those at high risk of disease at baseline (i.e. those already at high risk of disease at baseline and who were diagnosed with the disease or experienced a relevant event in the first years of follow-up after exposure assessment, would be among those excluded from the analyses). While the impact of the various sensitivity analyses on results varied (some were attenuated, some were strengthened, some were only observed at highest intakes, some remained when analyses were restricted to healthy weight individuals, some were more or less pronounced in overweight or obese individuals), 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. That associations largely persist when body weight is controlled for, and limited evidence for an effect of NSS on incident obesity *(47, 48)*, suggests the possibility 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 those using more NSS compared to those using less), and many studies controlled for dietary quality without a significant impact on the observations associations.

It was concluded that while reverse causation and residual confounding may be contributing factors, the currently 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.

6. *Potential mechanisms for negative associations with cardiometabolic health in prospective cohort studies.* Putative mechanisms have been proposed that may help to explain the negative associations observed between NSS use and 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 *(15)*. 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 *(16-20)*. 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 colonising the small and large intestine (i.e. gut microbiota). Proposed mechanisms are not mutually exclusive and may ultimately differ between individual NSS.

It is acknowledged that much of the research into biological mechanisms to date has been carried out in in-vitro and rodent models, and that results have often failed to be replicated in humans or are otherwise inconsistent. 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 and tested with some validation (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.

7. *Individual vs "class" effects of NSS*. Although 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 homogenous 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 *(13)*. As a result of these differences, individual NSS may have differential physiological effects in humans *(17)*. However, recent evidence from rodent models demonstrates that unlike oral sensing of sweetness, which is similar between sugars and NSS, post-ingestive sensing of sugars is mediated by a unique gut-brain pathway in mice that is unresponsive to NSS and reinforces a preference for sugars over NSS, regardless of type *(49, 50)*. It is unclear whether this sugars-sensing gut-brain axis functions in humans, but if so, it may provide mechanistic support as to why it can be difficult for some to switch from free sugars to NSS which is not necessarily dependent on type of NSS.

8. *Sources of potential differences in effects of NSS use*. There is evidence from studies included in the systematic review and elsewhere to suggest that there may be important differences in the response to NSS based on sex, ethnicity and body weight status. While evidence is currently

insufficient to make 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 randomized controlled trials of NSS use may be influenced by history of NSS use of participants at enrolment (i.e. regular users of NSS may already be affected by or desensitized to the effects of NSS compared to non- or infrequent users) which 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 impact 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 going from evidence to recommendations, the NUGAG Subgroup 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 cost of the options available to public health officials and programme managers in different settings, feasibility and acceptability of implementing the intervention in different settings, and the potential impact on equity and human rights.

Because the "intervention" covered by the recommendation 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, including various behaviour change interventions, fiscal policies, regulation of marketing 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 on marketing of food and non-alcoholic beverages to children, fiscal and pricing policies, and school food and nutrition policies, which will facilitate the ability of policymakers to translate dietary goals into evidence-informed policies.[1] Therefore, in assessing the evidence to recommendation factors for this guideline, the

[1] https://www.who.int/nutrition/topics/guideline-development/nugag_policyactions/en/

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 recommendation table can be found in **Annex 7**.

Overall certainty in the evidence
The overall certainty in the evidence was considered *low* and is based on undesirable effects of NSS use on prioritized health outcomes observed in prospective cohort studies which were individually considered to be *very low* to *low*.
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. It is further noted that because a reduction in free sugars intake can be achieved and corresponding desirable health benefits realized without the use of NSS, the potential undesirable effects carry a greater weight. It was further noted that, unlike the potential effects observed from long-term exposure in adults, the evidence observed in prospective studies of pregnant women suggest that potential adverse effects from NSS use occur over the relatively short period of gestation. In assessing the balance of desirable and undesirable effects, it is noted that because evidence from randomized controlled trials suggests that NSS work in these studies primarily by reducing energy intake and therefore any potential benefit of NSS 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 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 as suggested by current evidence.

It is further noted in the context of balance of desirable and undesirable effects, that NSS are not essential dietary components and provide no nutritional value themselves, the latter of which is also often the case with the highly processed foods and beverages of which NSS are frequently a component. Therefore one of the implicit, possible undesirable effects 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 *(51)*.

Priority of the problem and values and preferences

While 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 a number of additionally important health outcomes, including type 2 diabetes, cardiovascular diseases, and mortality, impacts on which may possibly be mediated at least in part, 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 *(52)*. Therefore interventions and programmes targeting reduction in risk of these outcomes are valuable in all contexts and are 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 obesity prevention and management has intensified recently as a result of the COVID-19 pandemic, as there is increasing recognition that those with obesity are at increased risk for adverse outcomes associated with COVID-19 *(53)*.

The recommendation in this guideline places a high value on reducing risk of mortality, overweight, obesity and NCDs, and while individuals almost universally value the prevention of premature mortality, those that may be impacted by the recommendation may value the benefit of reducing risk of obesity and associated disease differently based on personal preferences, beliefs and customs. For example, because cardiovascular diseases are a high profile public health topic, including in many LMICs where they represent a growing threat *(54)*, it is expected that most individuals would value efforts to reduce risk, however, in real-world settings, perception of the risk varies considerably *(55-59)* and therefore may require outreach

and communication efforts to improve understanding. Similarly, while many in LMICs are increasingly aware of negative health effects associated with being overweight or obese, some cultures still consider overweight to be a desirable, positive or otherwise "normal" attribute *(60-62)*, others believe body weight to be hereditary and therefore not amenable to management via lifestyle changes *(59, 63)*, and many, regardless of personal beliefs, incorrectly perceive their own body weight in the context of overweight and obesity (i.e. they believe they are at a healthy body weight when in fact they are overweight or obese according to accepted standards for assessing body weight outcomes) *(59, 63, 64)*.

Feasibility

As noted elsewhere in the guideline, implementing the recommendation in this guideline can be achieved in numerous ways, including various behaviour change interventions, fiscal policies, regulation of marketing foods and beverages, product labelling schemes, and reformulation of manufactured products, with feasibility varying depending on approach. Regardless of specific modes of implementation, the recommendation can be incorporated into existing activities designed to promote healthy diets and would naturally complement existing efforts to reduce free sugars. For example, appropriate messaging on NSS 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 *(65)* and several national food-based dietary guidelines already provide guidance on NSS use *(66)*, suggesting 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, 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 public health messaging or where 'piggy backing' on efforts to address free sugars intake is not possible.

Regardless of which interventions are employed to realize the recommendation, and linked to feasibility of the recommendation as discussed below, some amount of behaviour change at the individual level will likely be required, the success of which 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 very young children) avoiding NSS (and excess free sugars) – particularly in beverage form – should be very feasible, though the manner in which NSS-containing foods and beverages are labelled can sometimes create confusion among consumers as to what such foods and beverages actually contain, as noted below.

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 *(21, 44, 67)* and generally may have difficulties interpreting nutrient declaration labels, health claims, and other relevant labelling *(68-72)*. In addition, many consumer products other than foods and beverages contain NSS, such as personal care products, dietary supplements, and over-the-counter medications.

Acceptability

Although the recommendation in this guideline is already in line with existing national guidance in a small 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, as some means of implementation may be more acceptable than others;
- level of awareness of the potential health problems associated with NSS (e.g. it may be less acceptable in settings where awareness is low);
- 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 limit free sugars might for some require a reduction in the overall sweetness of the diet, particularly for those accustomed to sweetness in certain types of food and beverages, acceptability of the recommendation may be low. Popular perceptions about NSS may also feed into acceptability by consumers, which encompass both positive and negative feelings toward sweeteners, sometimes differentiated by whether sweeteners are categorized and marketed as “artificial” or “natural”. However, for those that acknowledge the potential health risks of consuming NSS over the long term and value reducing this risk,

acceptability should be high as obesity, cardiovascular diseases and type 2 diabetes are significant, recognized global health problems.

Acceptability to this recommendation can be improved with appropriate public health messaging not only on NSS and free sugars, but more broadly on an overall healthy diet, including that whole fruits can provide a healthy source of sweetness in the diet.

Equity and human rights

The impact of the recommendation on equity and human rights is not conclusively known given the uncertainty of long-term health effects of NSS. Assuming the long-term risk observed between NSS use and body weight and/or NCDs are valid, the recommendation in this guideline has the potential to reduce health inequity by improving the long-term health of those of lower socioeconomic status as they are generally disproportionately affected by overweight, obesity and NCDs *(73-76)*, although in some LMIC settings, those of higher socioeconomic status may be more at risk than those of lower socioeconomic status and may benefit more from relevant interventions *(77, 78)*. 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 *(79)*, however, if measures affect all individuals in a population equally, relevant inequalities may not be addressed *(80)*. Overall, evidence is extremely limited and inconclusive.

Resource implications

Absolute costs of translating the recommendation in this guideline into polices and actions will vary widely depending on which approaches are taken, but in cases where this can be coupled to existing efforts to reduce free sugars intake and promote healthy diets, costs may be minimized. Implementation of the recommendation will likely require consumer education and public health communications, some or all of which can be incorporated into existing public health nutrition education campaigns and other existing nutrition programmes at the global, regional, national and subnational levels. As noted in the previous section on feasibility, it may be possible to also incorporate this recommendation into existing activities such as food based dietary guidelines and fiscal policies targeting sugar-sweetened beverages, which therefore might limit the resources required to implement this recommendation.

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, however, assuming the long-term risk observed between NSS use and body weight and/or NCDs are valid, implementing the recommendation may be associated with long-term savings in costs of health care, though the extent of the savings depend on strategies chosen for implementation and the timescale for evaluation. For example, while very few if any cost-effectiveness analyses have been conducted for NSS, 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 *(81-85)*. Similarly, limited evidence suggests that other policies and interventions that would be relevant to NSS such as front-of-pack labelling and restrictions on marketing unhealthy foods to children may be cost-effective *(79)*.

Generally speaking, not using NSS would imply that both the purchase of NSS themselves (for use by the consumer) and the purchase of foods and beverages containing them would decrease. 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 not purchasing them. In cases where the NSS-containing foods or beverages have caloric value (which would result in an energy deficit if not replaced) other, preferably more healthy options would be needed as replacements, which, depending on the setting, could cost more, less or the same. Adhering to the recommendation could therefore have a positive or negative impact on disposable income, which might be amplified in those of lower socioeconomic status – particularly in low- and middle-income countries – as they tend to spend a higher proportion of their income on foods and beverages *(86-88)*.

Recommendation and supporting information

Based on a review of the evidence[1] and consideration of additional, potentially mitigating factors[2], WHO generated the following recommendation for non-sugar sweetener use:

WHO recommendation
WHO suggests that NSS not be used as a means of achieving weight control or reducing risk of noncommunicable diseases (*conditional recommendation*)[3]

Rationale and remarks

The following provides the reasoning behind the formulation of the recommendation (i.e. rationale) as well as remarks designed to provide context for the recommendation and facilitate its interpretation and implementation. For further detail on the evidence base and how it was interpreted see the *Summary of evidence* and *Interpreting the evidence* sections on pages 27-32.

Rationale
• This recommendation is based on evidence of *low* certainty overall, from a systematic review that assessed the health effects of higher compared to lower intake of non-sugar sweeteners (NSS) and 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, cardiovascular diseases, 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:

[1] The guidance contained within this guideline is based on evidence of health effects of NSS use at levels already considered safe by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and is not intended to provide updated or alternative guidance on safe or maximal levels of intake (i.e. acceptable daily intake or ADI). Safe levels of intake are based on toxicological assessments of individual NSS, and such assessments are completed by authoritative bodies prior to approving individual NSS for commercial use. For more detail on the evidence used to inform this recommendation in the context of ADIs, see *Remarks*.

[2] Factors 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.

[3] *Conditional* recommendations are those recommendations for which the WHO guideline development group is uncertain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are small *(35)*. Policymaking related to conditional recommendations therefore may require substantial debate and involvement of various stakeholders.

Adults

In randomized controlled trials:

- NSS use in any manner[1] resulted in reduced energy intake, lower body weight, and lower BMI in short-term randomized controlled trials (all *low* certainty evidence), the majority of which lasted three months or less, and 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). Relevant evidence from a small number of longer term trials lasting from 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 NSS were directly compared to 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 results of when NSS was used in any manner. However, most of these trials provided NSS or free sugars-containing foods and beverages in addition to existing diets and therefore did not directly measure the effects of replacing free sugars with NSS. When NSS were compared to 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 the randomized controlled trials (i.e. habitual consumers of free sugars-containing foods or beverages 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.

In prospective observational studies with up to 10 years of follow-up, 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). In addition, higher intakes of NSS were associated with increased risk of type 2 diabetes, cardiovascular diseases and 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 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 randomized controlled trial conducted in children reported a reduction in several

[1] NSS were consumed by the participants in the randomized controlled trials in a variety of ways including in pre-mixed beverages, powders or drops to be added to beverages by the participants, 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.

measures of body fatness when sugar-sweetened beverages were replaced with those containing NSS (*moderate* certainty evidence). When results for BMI z score[1] were combined with those from a second trial however, 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.

- In addition to the limited direct evidence for children and pregnant women, because the potential long-term effects of NSS use observed for adults in prospective observational studies are also relevant for women during pregnancy, and were reasonably expected to be relevant in children and adolescents as well, the evidence from randomized controlled trials 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 risk of disease associated with excess free sugars intake), the currently available evidence on which to base a recommendation on NSS is largely indirect: i.e. most randomized controlled trials comparing NSS to 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 to have a meaningful impact on health, evidence of minor weight loss or reduced BMI over several months or less as observed in the randomized controlled trials without additional evidence of long-term impact, does not represent a health benefit.
    - The discordant results between the randomized controlled trials 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:

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

- 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; other viable alternatives exist that are compatible with features of a healthy diet, including foods with naturally occurring sugars such as fruit, and unsweetened food and beverages.

Based on the evidence and other considerations as 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 death and disease, outweighed any potential short-term health effects resulting from the relatively small reductions in body weight and BMI observed in randomized controlled trials

- Because of lack of certainty about the overall balance of desirable and undesirable effects associated with long-term effects of NSS use for reducing non communicable disease 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, and the recommendation was considered to be *conditional*.

Remarks

- With the possible 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.

- Assessing the health effects of NSS on individuals with pre-existing diabetes was beyond the scope of this 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, while individuals with diabetes can also reduce free sugars intake without the need for NSS, the recommendation may not apply to those with existing diabetes.

- 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. Most studies included in the systematic review assessed the effects of NSS consumed in beverage

[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 a subsequent increased risk of disease.

form. A small number of studies assessed the effects of tabletop use (i.e. added to foods or beverages by the consumer), consumption in foods, or some combination of beverage, food and tabletop.

- "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.

- This 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. Sugar alcohols and low-calorie sugars are not considered NSS. Common NSS include, but are not limited to, acesulfame K, aspartame, advantame, cyclamates, neotame, saccharin, sucralose, stevia and stevia derivatives.

- 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, either because it 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 which suggests that there are health effects associated with NSS use irrespective of which NSS is being used, i.e. NSS as a class of compounds, despite individual NSS having different chemical structures, have an impact on health. It is recognized that NSS are not a homogenous class of compounds: each has a unique chemical structure and as a result, individual NSS have different sweetness intensities and organoleptic properties, and are processed differently by the body. Limited evidence suggests that individual NSS may also differ in their physiological effects in humans, however, evidence is currently insufficient to make recommendations for individual NSS.

- It is noted that 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 imply that such medications or products should not be used. However, NSS-free versions of these items, when readily obtainable, can be considered.

- This recommendation should be considered in the context of WHO recommendations to reduce free sugars intake *(12)* and other guidance promoting healthy diets, including WHO guidelines on dietary fat *(34)*, carbohydrates *(34)*, sodium *(89)* and potassium *(90)*.[2]

[1] For prospective cohort studies it was generally not possible to determine the absolute highest intakes as the highest quantile was generally a specified amount or more (e.g. ≥ 2 servings per day), and though it is possible that some adults may have exceeded the ADI in some number of these studies, the number doing so would likely have been an extremely small percentage of the entire group *(21, 26)*. 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 *(21)*.

[2] Guidance for total fat intake, saturated fatty acid and *trans*-fatty acid intake, and carbohydrate intake are all currently being updated.

- 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 in a food or beverage in which any other unhealthy elements are mostly retained, and as a result, the overall quality of the diet remains 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.

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 policymakers, 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;
- the eLENA mobile phone application, eLENA*mobile,* which provides offline access to eLENA content;
- relevant nutrition webpages on the WHO website,[2] including the Executive summary in all six official WHO languages;
- the electronic mailing lists of the WHO Department of Nutrition and Food Safety and the United Nations Standing Committee on Nutrition;
- the network of the six WHO Regional Offices and Country Offices;
- the WHO Collaborating Centres; and
- the Global Network of Institutions for Scientific Advice on Nutrition.

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

[1] http://www.who.int/elena/en/ **[TEMPORARILY UNAVAILABLE]**
[2] https://www.who.int/health-topics/nutrition

Translation and implementation

The recommendation in this guideline can be used by policymakers and programme managers to develop measures to modify the use of NSS through a range of public health policy actions and intervention programmes.

The recommendations in this guideline should be used in conjunction with other guidance on healthy diets, in particular guidelines related to free sugars *(12)*, sodium *(89)* and potassium *(90)*, as well as total fat, polyunsaturated fatty acids and carbohydrates which are all currently being updated, to guide effective policy actions and intervention programmes to promote healthy diets and nutrition, and prevent diet-related NCDs.

Efforts should be targeted at the general population but with a particular focus on young children who have not yet become accustomed to sweetness in the diet (especially in beverages) as evidence suggests early taste exposures shape taste preferences and eating behaviour later in life *(91-93)*.

The recommendation in this guideline can be:

- used by policymakers and programme managers to:
    - develop or modify policy measures to reduce or prevent use of NSS, through a range of public health interventions, including those that are planned or are already being implemented by countries, such as:
        - regulation of marketing food and non-alcoholic beverages;
        - restricting the sales and promotion of food and beverages containing NSS in schools;
        - fiscal policies targeting foods and beverages that contain NSS;
        - nutrition labelling (i.e. mandatory nutrient declaration), including front-of-pack labelling systems; and
        - consumer education regarding not only NSS, but also in interpreting nutrient declarations, health claims, and other labelling on foods and beverages.
- translated at the country-level into culturally and contextually specific food-based dietary guidelines that take into account locally available food and dietary customs.

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 *(94, 95)*. Through providing programmatic implementation details, specific country adaptations and lessons learnt, GINA serves as a platform for monitoring and evaluating how guidelines are being translated into various policy actions and intervention programmes to address the issues related to 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 pending questions and gaps in the current evidence that should be addressed by future research were identified. Further research is needed to achieve a better understanding of the following :

- potential long-term effects of NSS use on body weight, disease outcomes, and mortality in all target populations including children and pregnant women
    - to this end, elaboration and refinement of prospective cohort studies assessing health effects of NSS, including:
        - more robust exposure assessment (e.g. multiple, sequential assessments of exposure)
        - addressing how patterns of use of NSS (i.e. how long, how much, for what reasons) prior to baseline assessment of exposure night impact associations
        - further efforts to address reverse causation
- effects of NSS intake from foods and beverages on oral health, including dental caries, in a across all age groups, from young children to adults
- differential health effects of individual NSS in humans, assessed via randomized controlled trials and prospective cohort studies where possible
- potential differences in short-term and long-term responses to NSS based on sex, age, ethnicity, genotype, body weight status
- how patterns and history of NSS use by participants in randomized controlled trials may impact relevant outcomes (e.g. glucose metabolism)

[1] http://www.who.int/nutrition/gina/en/index.html

- health effects of consuming NSS concurrently with carbohydrates compared to 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 impacts preferences, cravings and responses to NSS
- biological mechanisms for physiological effects of NSS, as assessed in humans
- how early exposure to NSS in children might impact sweet preference and other neural and behavioural response to sweetness later in life
- how NSS are consumed in real-world settings and how this might modulate any health effects of NSS
- differences in NSS use by age, ethnicity, socioeconomic status
- effective means of reducing reliance on/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; hence, updating of this guideline is 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. It is planned that the recommendation in this guideline will be reviewed when new data and information becomes available. At that time, any new evidence will be evaluated, and formally updated if necessary. 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 (35)*. At the time this 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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Annex 3: External peer-review group

(To be added before finalization)

Annex 4: Summary and management of declarations of interests

(To be added before finalization)

Annex 5: Key questions in PICO format (population, intervention, control and outcomes)

PICO questions

- What is the effect on prioritized health outcomes in adults and children of NSS intake compared to lower or no NSS intake?
- What is the effect on prioritized health outcomes in adults and children 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 cardiovascular diseases
Intervention/exposure	The interventions of interest include intake of any type of non-sugar sweetener, either alone or in combination with one or more additional non-sugar sweeteners. Non-sugar sweeteners may include aspartame, acesulfame potassium, saccharin, sucralose, advantame, neotame, cyclamate, stevia, thaumatin, brazzein, etc. • Non-sugar sweeteners vs sugar (quantity/frequency) • High vs low intake of non-sugar sweeteners (quantity/frequency) • Non-sugar sweetened beverages vs water Possible subgroup analyses include • discretionary use (i.e. consumer added vs. pre-packaged foods) • solids and liquids • type if non-sugar sweetener • level of sweetness • "artificial" and "natural" non-sugar sweeteners
Comparator	Sugars, no intervention, 'placebo', water (in the case of non-sugar sweetened beverages), other type of non-sugar sweetener (when sugars or nothing/placebo/water also included)
Outcome	*Adults and children* • Overweight / Obesity • Dental caries • Prediabetes / type 2 diabetes* • Eating behavior (appetite, satiety) • Sweet preference • Cancer • Cardiovascular disease* • Mood • Behavior (hyperactivity and aggression)

- Neurocognition
- Chronic kidney disease
- Asthma (children only)
- Allergies (children only)

* includes intermediate/surrogate markers of disease (i.e. markers of glycaemic control for diabetes, blood lipids for cardiovascular diseases)

Annex 6: GRADE evidence profiles

GRADE evidence profile 1
Question: What is the effect of higher vs lower non-sugar sweetener 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/mean difference[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Body fatness: body weight (kg)											
29	RCT	Serious[7]	Serious[8]	Not serious	Not serious	None	1252	1181	**MD –0.71** (–1.13 to –0.28)	–	⊕⊕◯◯ LOW
4	Observational (continuous)	Not serious[9]	Serious[8]	Not serious	Not serious[10]	None	118457		**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	11874		**MD –0.01** (–0.67 to 0.64)	–	⊕◯◯◯ VERY LOW
Body fatness: 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	80583		**MD 0.14** (0.03 to 0.25)	–	⊕◯◯◯ VERY LOW
Body fatness: incident obesity											
2	Observational	Not serious[9]	Not serious	Not serious	Not serious[13]	None	603/1668 (36.2%)		**HR 1.76** (1.25, 2.49)	**275 more** (from 91 more to 539 more)	⊕⊕◯◯ LOW
Body fatness: abdominal obesity											
4	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	5381/10895 (49.4%)		**HR 1.33** (0.91 to 1.96)	**163 more** (from 44 fewer to 474 more)	⊕◯◯◯ VERY LOW
Body fatness: 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

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/mean difference[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Body fatness: 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	12886		**MD 0.92** (–1.73 to 3.56)	–	⊕◯◯◯ VERY LOW
Body fatness: 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
Body fatness: 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
Body fatness: 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: incident diabetes											
13	Observational (beverages)	Not serious[9]	Not serious	Not serious	Not serious	None[19]	28222/408609 (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	2250/62582 (3.6%)		**HR 1.34** (1.21 to 1.48)	**12 more** (from 8 more to 17 more)	⊕⊕◯◯ LOW
Diabetes: 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
Diabetes: 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

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/mean difference[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Diabetes: HbA1c (%)											
6	RCT	Not serious[22]	Not serious	Not serious	Serious[16]	None	212	199	**MD 0.02** (–0.03 to 0.07)	–	⊕⊕⊕◯ MODERATE
Diabetes: 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
Diabetes: high fasting glucose											
3	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	6086/11213 (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]	Unable to assess[25]	Not serious	Very serious[26]	None	14	15	In a 6-month RCT among adults *(96)*[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	102677/860873 (11.9%)		**HR 1.12** (1.05 to 1.19)	**14 more** (from 6 more to 23 more)	⊕◯◯◯ VERY LOW
Cardiovascular diseases: cardiovascular disease mortality											
5	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	13089/598951 (2.2%)		**HR 1.19** (1.07 to 1.32)	**4 more** (from 2 more to 7 more)	⊕⊕◯◯ LOW
Cardiovascular diseases: cardiovascular events											
3	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	6384/166938 (3.8%)		**HR 1.32** (1.17 to 1.50)	**12 more** (from 6 more to 19 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/mean difference[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Cardiovascular diseases: coronary heart disease											
4	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	10104/205455 (4.9%)		**HR 1.16** (0.97 to 1.39)	**8 more** (from 1 fewer to 19 more)	⊕◯◯◯ VERY LOW
Cardiovascular diseases: stroke											
6	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	8346/655953 (1.3%)		**HR 1.19** (1.09 to 1.29)	**2 more** (from 1 more to 4 more)	⊕⊕◯◯ LOW
Cardiovascular diseases: hypertension											
6	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	81965/234137 (35%)		**HR 1.13** (1.09 to 1.17)	**46 more** (from 32 more to 60 more)	⊕⊕◯◯ LOW
Cardiovascular diseases: 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
Cardiovascular diseases: 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
Cardiovascular diseases: 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
Cardiovascular diseases: 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
Cardiovascular diseases: 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

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/mean difference[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Cardiovascular diseases: 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
Cardiovascular diseases: low HDL cholesterol											
4	Observational	Not serious[9]	Not serious	Not serious	Serious[14]	None	5823/11916 (48.9%)		**HR 1.03** (0.92 to 1.16)	**15 more** (from 39 fewer to 78 more)	⊕◯◯◯ VERY LOW
Cardiovascular diseases: 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
Cardiovascular diseases: high triglycerides											
4	Observational	Not serious[9]	Not serious	Not serious	Serious[14]	None	6673/12728 (52.4%)		**HR 1.03** (0.88 to 1.21)	**16 more** (from 63 fewer to 110 more)	⊕◯◯◯ VERY LOW
Cancer: cancer mortality											
4	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	25494/568175 (4.5%)		**HR 1.02** (0.92 to 1.13)	**1 more** (from 4 fewer to 6 more)	⊕◯◯◯ VERY LOW
Cancer: incidence (any type)											
7	Observational	Not serious[9]	Not serious	Not serious	Serious[14]	None	27573/942600 (2.9%)		**HR 1.02** (0.95 to 1.09)	**1 more** (from 1 fewer to 3 more)	⊕◯◯◯ VERY LOW
Cancer: incidence (bladder)											
26	Observational (case-control)	Serious[11]	Serious[8]	Not serious	Not serious	None	11071 cases 28589 controls		**OR 1.31** (1.06 to 1.62)	–	⊕◯◯◯ VERY LOW
Chronic kidney disease: incident disease											
2	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	3161/18372 (17.2%)		**HR 1.41** (0.89 to 2.24)	**71 more** (from 19 fewer to 213 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/mean difference[4] (95% CI)	Absolute – per 1000[5] (95% CI)	
Chronic kidney disease: 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
Chronic kidney disease: 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	1131	1077	**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

BMI: body mass index; CI: confidence interval; HDL: high-density lipoprotein; HOMA-IR: Homeostatic 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.

[1] Unless otherwise noted, observational studies are prospective cohort studies that assessed outcomes by comparing the highest quantile of intake to 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 low- and middle-income countries (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 they 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 for 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 *(35)*.

[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 of 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 of 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 provide 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 of 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 low risk of bias and half as 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 *(97)*. 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 if 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 if 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 out of the 10 comparisons that reported a P_{trend} reported a P_{trend} of <0.05, suggestive of a dose–response relationship within those individual studies. However, as a conservative measure, it was not upgraded. Funnel plot analysis suggested 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) *(98)*.

[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 if 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 abstract 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 if 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 if 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 non-sugar sweeteners 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	Relative/mean difference (95% CI)	Absolute – per 1000 (95% CI)	
Body fatness: 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
Body fatness: 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

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 low- and middle-income countries (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 they 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 *(35)*.
[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 vs lower non-sugar sweetener 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/mean difference (95% CI)	Absolute – per 1000 (95% CI)	
Body fatness: body weight (kg)											
1	RCT	Not serious[5]	Unable to assess[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	1633		**MD 0.03** (–0.14 to 0.21)	–	⊕⊕◯◯ LOW
Body fatness: BMI (kg/m²)											
5	Observational (continuous)	Not serious[7]	Serious[9]	Not serious	Not serious[8]	None	11907		**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	2426		**MD 0.04** (–0.32 to 0.40)	–	⊕◯◯◯ VERY LOW
Body fatness: 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]	Unable to assess[6]	Serious[13]	Serious[10]	None	98		**MD 0.00** (–0.30 to 0.30)	–	⊕◯◯◯ VERY LOW
Body fatness: waist circumference (cm)											
1	RCT	Not serious[5]	Unable to assess[6]	Not serious	Not serious	None	319	322	**MD –0.66** (–1.23 to –0.09)	–	⊕⊕⊕◯ MODERATE
Body fatness: fat mass (kg)											
1	RCT	Not serious[5]	Unable to assess[6]	Not serious	Not serious	None	319	322	**MD –0.57** (–1.02 to –0.12)	–	⊕⊕⊕◯ MODERATE
1	Observational	Serious[12]	Unable to assess[6]	Serious[13]	Serious[10]	None	98		**MD –1.00** (–2.52 to 0.52)	–	⊕◯◯◯ 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/mean difference (95% CI)	Absolute – per 1000 (95% CI)	
Body fatness: fat mass (%)											
1	RCT	Not serious[5]	Unable to assess[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
Body fatness: incident overweight											
2	Observational	Not serious[7]	Not serious	Not serious	Very serious[14]	None	235/3064 (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]	Unable to assess[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 NSS-sweetened beverage initiators and non-consumers, except for HbA1c, which increased more in chronic consumers of NSS-sweetened beverages ($P = 0.01$) *(99)*.		⊕◯◯◯ VERY LOW
Dental caries											
2	RCT	Not serious[15]	Unable to assess[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 *(100)*. In another trial, mouth rinse containing stevia		⊕⊕◯◯ 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/mean difference (95% CI)	Absolute – per 1000 (95% CI)	
									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%) *(101)*.		
1	Observational	Serious[12]	Unable to assess[6]	Not serious	Unable to assess[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 *(102)*.		⨁◯◯◯ VERY LOW
Cardiovascular diseases: blood lipids											
1	Observational	Serious[12]	Unable to assess[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 and LDL cholesterol, and triglycerides when compared with NSS-sweetened beverage initiators and non-consumers *(99)*.		⨁◯◯◯ VERY LOW
Cancer: 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]	Unable to assess[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 *(103)*.		⨁⨁⨁◯ 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/mean difference (95% CI)	Absolute – per 1000 (95% CI)	
2	Observational	Serious[12]	Unable to assess[17]	Not serious	Unable to assess[17]	None	173 (cohort 1) 2371 (cohort 2)		*Unable to meta-analyse* In one cohort study, energy intake in those who initiated consuming 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 *(99)*. In the second cohort study, energy intake was 122 kJ/day higher per 100 g/day increase in NSS-sweetened beverage consumption *(104)*.		⨁◯◯◯ VERY LOW
Sugars intake (g/day)											
2	Observational	Serious[12]	Unable to assess[17]	Not serious	Unable to assess[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 *(99)*. In a second cohort study, sugars intake was not associated with NSS-sweetened beverage intake *(104)*.		⨁◯◯◯ VERY LOW
Neurocognition											
1	RCT	Not serious[18]	Unable to assess[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]) *(103)*.		⨁⨁◯◯ LOW
1	Observational	Not serious[7]	Unable to assess[6]	Not serious	Unable to assess[17]	None	1234		In a cohort study following children in utero up to 7 years of age, early- and mid-childhood		⨁◯◯◯ 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/mean difference (95% CI)	Absolute – per 1000 (95% CI)	
									cognition scores were not associated with childhood intake of NSS-sweetened beverages at 3 years *(105)*.		

BMI: body mass index; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MD: mean difference; OR: odds ratio; NSS: non-sugar sweeteners; 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 to 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 low- and middle-income countries (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 they 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 *(35)*.
[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 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 suggests 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 low risk of bias. Not downgraded.

[16] Unable to assess inconsistency as there 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 low risk of bias. Not downgraded.

GRADE evidence profile 4
Question: What is the effect of higher vs lower non-sugar sweetener 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/mean difference (95% CI)	Absolute – per 1 000 (95% CI)	
Gestational diabetes											
1	Observational	Not serious[4]	Unable to assess[5]	Not serious	Serious[6]	None	860/13475 (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	6381/129009 (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]	Unable to assess[5]	Not serious	Unable to assess[8]	None	3716		*Unable to meta-analyse* In a cohort analysis of the German GeliS trial, the daily intake of light drinks during pregnancy was associated nonsignificantly with growth measures in the child at birth (birthweight – adjusted regression coefficient –5; 95% CI -18, 6; BMI at birth – adjusted regression coefficient 0.005; 95% CI –0.020, 0.035; low birthweight – adjusted OR 0.99; 95% CI 0.91, 1.08; small for gestational age – adjusted OR 1.03; 95% CI 0.98, 1.09; and large for gestational age – adjusted OR 1.01; 95% CI 0.85, 1.07) *(106)*. 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, 0.001; *P* = 0.002) *(107)*. In a cohort study with women with gestational diabetes in Slovenia, intake of low-calorie		⊕◯◯◯ 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/mean difference (95% CI)	Absolute – per 1 000 (95% CI)	
									beverages[9] was not associated with large for gestational age (Spearman correlation 0.118; *P* nonsignificant) *(108)*.		
Offspring body fatness											
3	Cohort	Not serious[4]	Unable to assess[5]	Not serious	Unable to assess[8]	None	5029		*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, 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, 3.88). Adjustment was made for maternal BMI, diet quality, total energy intake and other obesity risk factors *(109)*. In a prospective cohort study conducted in the United States, consumption of NSS-sweetened beverages during pregnancy was not associated with BMI z-score or waist circumference in offspring at mid-childhood (median of 7.7 years of age) *(110)*. 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, 0.96) and risk of overweight or obesity (RR 1.93; 95% CI 1.24, 3.01) at 7 years of age *(111)*.		⊕◯◯◯ VERY LOW
Offspring asthma											
1	Cohort	Not serious[4]	Unable to assess[5]	Not serious	Not serious	None	1536/31849		**OR 1.20**	**10 more**	⊕◯◯◯

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/mean difference (95% CI)	Absolute – per 1 000 (95% CI)	
							(4.8%)		(1.07 to 1.35)	(from 3 more to 17 more)	VERY LOW

Offspring allergies

1	Cohort	Not serious[4]	Unable to assess[5]	Not serious	Serious[6]	None	1855/37971 (4.9%)		**OR 1.11** (0.86 to 1.43)	**5 more** (from 7 fewer to 21 more)	⨁◯◯◯ VERY LOW

Offspring neurocognition

1	Observational	Not serious[4]	Unable to assess[5]	Not serious	Unable to assess[8]	None	1234		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, 0.5; total WRAVMA, early childhood: –1.5; 95% CI –2.9, –0.1; KBIT-II verbal, mid-childhood: –3.2; 95% CI –5.0, –1.5; KBIT-II nonverbal, mid-childhood: –2.0; 95% CI –4.3, 0.2; WRAVMA drawing, mid-childhood: –1.7; 95% CI –4.1, 0.6; WRAML visual memory, mid-childhood: –0.1; 95% CI –0.7, 0.5), but not with childhood intake of NSS-sweetened beverages at 3 years *(105)*.	⨁◯◯◯ VERY LOW

BMI: body mass index; CI: confidence interval; KBIT-II, Kaufman Brief Intelligence Test 2nd edition; OR: odds ratio; PPVT-III: Peabody Picture Vocabulary Test-III; NSS: non-sugar sweeteners; OR: odds ratio; 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 low- and middle-income countries (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 they 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 7: Evidence to recommendation table

Background

INTERVENTION: not using NSS

COMPARISON: lower/no vs higher NSS intake; replacement of sugars with NSS

MAIN OUTCOMES: body weight, energy and sugars intake, NCDs

SETTING: healthy individuals; Randomized controlled trials 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 2019, more than 38 million children under 5 years of age were overweight – an increase of about 8 million over the past 15 years *(2)*. High body mass index (BMI) was responsible for an estimated 4 million deaths in 2015 *(3)*, with greater increases in BMI in the overweight and obesity range leading to a greater risk of mortality *(4)*. Overweight and obesity are also risk factors for many noncommunicable diseases (NCDs) including cardiovascular diseases, type 2 diabetes and certain types of cancers. NCDs are the leading causes of death globally and were responsible for an estimated 41 million (73.4%) of the 55.9 million deaths in 2017 *(52)*.	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** ***Children*** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies • **Don't know** ***Pregnant women*** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies • **Don't know**	***Adults*** As noted, the NUGAG Subgroup on Diet and Health did not consider the short-term weight loss observed in randomized controlled trials of a 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 it contributes to weight loss or healthy weight maintenance), this too was not considered a desirable effect. Therefore, the NUGAG Subgroup on Diet and Health does not know if there are desirable effects on body weight with NSS use. The effects observed are summarized below and on their own, are considered to be small (body weight, BMI) to moderate (energy intake, sugars intake). *Higher vs lower NSS intake* Body weight: MD –0.71 kg (–1.13 to –0.28)* BMI: MD –0.14 kg/m^2 (–0.30 to 0.02) Energy intake: –569 kJ/day (–859, –278) Sugars intake: –38.4 g/day (–57.8, –19.1) *NSS replacement of sugars* Body weight: MD –0.61 kg (–1.28 to 0.06) Desirable effects were not observed for other outcomes with NSS use. ***Children*** For similar reasons described above for adults, the NUGAG Subgroup on Diet and Health does not know if there are desirable effects on body weight with NSS use. The main effects observed are summarized below and on their own, are considered to be small to moderate (energy intake, sugars intake). *NSS replacement of sugars* Body weight: MD –1.01 kg (–1.54 to –0.48) Fat mass: MD –1.07% (–1.99 to –0.15) Other measures of body fatness when present, were also considered to be small to moderate. Two randomized controlled trials reported desirable effects for dental caries, however the size of the effects were unclear. ***Pregnant women*** No desirable effects specific to pregnant women were identified.	Design of intervention in randomized controlled trials 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.

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 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*, varied from small to moderate, and were considered overall to be moderate, based on outcomes below: *Higher vs lower NSS intake* BMI: MD 0.14 kg/m^2 (0.03, 0.25) Incident obesity: HR 1.76 (1.25, 2.49) Type 2 diabetes (beverages): HR 1.23 (1.14, 1.32) Type 2 diabetes (tabletop): HR 1.34 (1.21, 1.48) All-cause mortality: HR 1.10 (1.03, 1.18) CVD mortality: HR 1.19 (1.07, 1.32) CVD events: HR 1.32 (1.17, 1.50) Stroke: HR 1.19 (1.09, 1.29) Hypertension: HR 1.13 (1.09, 1.17) * An increase in the total cholesterol:HDL cholesterol ratio was also observed in randomized controlled trials and was considered to be small, and an increased risk of bladder cancer in case-control studies was considered to be moderate. ***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 effects for pregnant women was observed in prospective cohort studies and was considered to be moderate: *Higher vs lower NSS intake* Preterm birth: OR 1.25 (1.07 to 1.46)	Possibility that reverse causation and confounding by bodyweight 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 for observed associations and may not even play a significant role in many of the studies.
CERTAINTY OF EVIDENCE	**What is the overall certainty in the evidence of effects?** ***Adults*** ○ Very low • **Low** ○ Moderate ○ High ○ No included studies ***Children***	***Adults*** The overall certainty of the evidence for effects in adults of higher intakes of NSS compared to 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 of the evidence for key outcomes are listed below: Body weight: low (RCT) BMI: low (RCT)	See GRADE evidence profiles for certainty of evidence for all outcomes (**Annex 1**).

	○ Very low • **Low** ○ Moderate ○ High ○ No included studies ***Pregnant women*** ○ Very low • **Low** ○ Moderate ○ High ○ No included studies	Energy intake: low (RCT) Sugars intake: low (RCT) Incident obesity: low (observational) Type 2 diabetes (beverages): low (observational) Type 2 diabetes (tabletop): low (observational) All-cause mortality: very low (observational) CVD mortality: low (observational) CVD events: low (observational) CHD: 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 are being extrapolated to children. Therefore, the overall certainty in the evidence for children is *low*. Certainty of the evidence for key outcomes assessed directly in children are listed below: Body weight: moderate (RCT) BMI z-score: moderate (RCT) Energy intake: moderate (RCT) Dental caries: low (RCT) Note: 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. All outcomes assessed in observational studies were assessed as *very low*, except for body weight which was assessed as *low*. ***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 of the evidence for key outcomes assessed directly in pregnant women are listed below: Preterm birth: low (observational) Other outcomes from observational studies were all assessed as *very low*.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?**	The recommendation in this guideline places a high value on reducing risk of mortality, overweight, obesity and NCDs, and while individuals almost universally value the prevention of premature mortality, those that may be impacted by the recommendation may value the benefit of reducing risk of obesity and associated disease differently based on personal preferences,	

	○ Important uncertainty or variability ○ Possibly important uncertainty or variability • **Probably no important uncertainty or variability** ○ No important uncertainty or variability	beliefs and customs. For example, because cardiovascular diseases are a high profile public health topic, including in many LMICs where they represent a growing threat *(54)*, it is expected that most individuals would value efforts to reduce risk, however, in real-world settings, perception of the risk varies considerably *(55-59)* and therefore may require outreach and communication efforts to improve understanding. Similarly, while many in LMICs are increasingly aware of negative health effects associated with being overweight or obese, some cultures still consider overweight to be a desirable, positive or otherwise "normal" attribute *(60-62)*, others believe body weight to be hereditary and therefore not amenable to management via lifestyle changes *(59, 63)*, and many, regardless of personal beliefs, incorrectly perceive their own body weight in the context of overweight and obesity (i.e. they believe they are at a healthy body weight when in fact they are overweight or obese according to accepted standards for assessing body weight outcomes) *(59, 63, 64)*.	
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 a difference in body weight 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 the relatively small reduction in body weight and BMI observed in randomized controlled trials. It is further noted that because a reduction in free sugars intake can be achieved and corresponding desirable health benefits realized without the use of NSS, the potential undesirable effects carry a greater weight. It was further noted that, unlike the potential effects observed from long-term exposure in adults, the evidence observed in prospective studies of pregnant women suggest that potential adverse effects from NSS use occur over the relatively short period of gestation. In assessing the balance of desirable and undesirable effects, it is noted that because evidence from randomized controlled trials suggests that NSS work in these studies primarily by reducing energy intake and therefore any potential benefit of NSS 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 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 as suggested by current evidence. It is further noted in the context of balance of desirable and undesirable effects, that NSS are not essential dietary components and provide no nutritional value themselves, the latter of which is also often the case with the highly processed foods and beverages of which NSS are frequently a component. Therefore one of the implicit, possible undesirable effects of NSS use in the context of reducing free sugars intake is the inclusion of a greater number of highly processed foods	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 was greater certainty in these results then an assessment of "favours not using NSS" would have likely been made.

		and beverages in the diet than would be included if free sugars were reduced without NSS use.	
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 polices and actions will vary widely depending on which approaches are taken, but in cases where this can be coupled to existing efforts to reduce free sugars intake and promote healthy diets, costs may be minimized. Implementation of the recommendation will likely require consumer education and public health communications, some or all of which can be incorporated into existing public health nutrition education campaigns and other existing nutrition programmes at the global, regional, national and subnational levels. It may be possible to also incorporate this recommendation into existing activities such as food based dietary guidelines and fiscal policies targeting sugar-sweetened beverages, which therefore might limit the resources required to implement this recommendation. Generally speaking, not using NSS would imply that both the purchase of NSS themselves (for use by the consumer) and the purchase of foods and beverages containing them would decrease. 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 not purchasing them. In cases where the NSS-containing foods or beverages have caloric value (which would result in an energy deficit if not replaced) other, preferably more healthy options would be needed as replacements, which, depending on the setting, could cost more, less or the same. Adhering to the recommendation could therefore have a positive or negative impact on disposable income, which might be amplified in those of lower socioeconomic status – particularly in low- and middle-income countries – as they tend to spend a higher proportion of their income on foods and beverages *(86-88)*.	An assessment of the costs of all possible ways of implementing the recommendation is beyond the scope of this guideline, and in any case, there is very little published evidence for costs of possible actions specifically targeting NSS. As such, 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). It is also noted that because NSS use is already widespread, not doing anything would be maintaining the status quo and would therefore would likely cost little to nothing in terms of public health expenditure 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 between NSS use and body weight and/or NCDs are valid.

CERTAINTY OF EVIDENCE OF	**What is the certainty of the evidence of resource requirements (costs)?** • **Very low** ○ Low ○ Moderate ○ High ○ No included studies	While no studies assessing NSS specifically were identified, studies addressing sugar-sweetened beverages were identified and considered as reasonable proxies as the majority of NSS in most settings are consumed in pre-packaged beverage form (i.e. "diet" sodas and drinks). Because only proxy data could be referenced the certainty in the evidence of resource requirements was considered to be very low.	
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, however, assuming the long-term risks observed between NSS use and body weight and/or NCDs are valid, implementing the recommendation may be associated with long-term savings in costs of health care, though the extent of the savings depend on strategies chosen for implementation and the timescale for evaluation. For example, while very few if any cost-effectiveness analyses have been conducted for NSS, 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 *(81-85)*. Similarly, limited evidence suggests that other policies and interventions that would be relevant to NSS such as front-of-pack labelling and restrictions on marketing unhealthy foods to children may be cost-effective *(79)*. Overall, the cost effectiveness for different approaches will likely vary however it can't be determined with certainty.	This question can't be answered with certainty because it requires the following: - 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 in the proxy data (as most studies are modelling studies).
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 of long-term health effects of NSS. Assuming the long-term risks observed between NSS use and body weight and/or NCDs are valid, the recommendation in this guideline has the potential to reduce health inequity by improving the long-term health of those of lower socioeconomic status as they are generally disproportionately affected by overweight, obesity and NCDs *(73-76)*, although in some LMIC settings, those of higher socioeconomic status may be more at risk than those of lower socioeconomic status and may benefit more from relevant interventions *(77, 78)*. 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 *(79)*, however, if measures affect all individuals in a population equally, relevant inequalities may not be addressed *(80)*.	Little to no direct data for NSS. Assessment made based on two related - the observation that obesity and diet-related NCDs disproportionately affect those of lower socioeconomic status and if treated therefore would likely reduce health inequity regardless of approach if effective ("probably reduced"); and - limited data for a small number of specific interventions which may preferentially help those of lower socioeconomic status,

		Overall, evidence is extremely limited and inconclusive, and while there is a suggestion that implementing the recommendation might reduce health inequity, it is ultimately unknown.	but in theory could also help everyone equally or preferentially help those of higher socioeconomic status ("don't know")
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 already in line with existing national guidance in a small 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, as some means of implementation may be more acceptable than others; • level of awareness of the potential health problems associated with NSS (e.g. it may be less acceptable in settings where awareness is low); • 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 limit free sugars might for some require a reduction in the overall sweetness of the diet, particularly for those accustomed to sweetness in certain types of food and beverages, acceptability of the recommendation may be low. Popular perceptions about NSS may also feed into acceptability by consumers, which encompass both positive and negative feelings toward sweeteners, sometimes differentiated by whether sweeteners are categorized and marketed as "artificial" or "natural". However, for those that acknowledge the potential health risks of consuming NSS over the long term and value reducing this risk, acceptability should be high as obesity, cardiovascular diseases and type 2 diabetes are significant, recognized global health problems. Acceptability to this recommendation can be improved with appropriate public health messaging not only on NSS and free sugars, but more broadly on an overall healthy diet, including that whole fruits can provide a healthy source of sweetness in the diet.	Little to no published evidence from which to draw.
FEASIBILITY	**Is not using NSS feasible to implement?** ○ No ○ Probably no • **Probably yes**	As noted elsewhere in the guideline, implementing the recommendation in this guideline can be achieved in numerous ways, including various behaviour change interventions, fiscal policies, regulation of marketing foods and beverages, product labelling schemes, and reformulation of manufactured products, with feasibility varying depending on approach. Regardless of specific modes of implementation, the recommendation can be incorporated into existing activities designed to promote healthy diets and would naturally	

	○ Yes ○ Varies ○ Don't know	complement existing efforts to reduce free sugars. For example, appropriate messaging on NSS 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 *(65)* and several national food-based dietary guidelines already provide guidance on NSS use *(66)*, suggesting 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, 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 public health messaging or where 'piggy backing' on efforts to address free sugars intake is not possible. Regardless of which interventions are employed to realize the recommendation, and linked to feasibility of the recommendation as discussed below, some amount of behaviour change at the individual level will likely be required, the success of which 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 very young children) avoiding NSS (and excess free sugars) – particularly in beverage form – should be very feasible, though the manner in which NSS-containing foods and beverages are labelled can sometimes create confusion among consumers as to what such foods and beverages actually contain *(44)*. 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 *(21, 44, 67)* and generally may have difficulties interpreting nutrient declaration labels, health claims, and other relevant labelling *(68-72)*. In addition, many consumer products other than foods and beverages contain NSS, such as personal care products, dietary supplements, and over-the-counter medications.	

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