Scientific Advisory Committee on Nutrition

SACN statement on the WHO guideline on non-sugar sweeteners

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1. Introduction

In the UK, non-sugar sweeteners (NSS) are used to replace free sugars in a wide range of products. They can be used in products such as drinks, sweets and chocolate confectionery, as well as savoury products such as pasta sauces and baked beans. They can also be used in the home in baking or in hot drinks such as tea and coffee.

NSS offer a sweeter taste for fewer, or no calories compared to free sugars and enable manufacturers and individuals to reduce the free sugars and calorie content of foods while maintaining the sweet taste (EFSA, 2011).

The Scientific Advisory Committee on Nutrition (SACN) has previously noted that NSS intake in the UK may have increased as a result of the government's interventions to reduce population free sugars intakes (see minutes of the SACN 2022 horizon scan meeting available on the SACN webpage). Some businesses use NSS to lower the free sugars content of their products. NSS are understood to be much less commonly used in food products than in drinks.

In May 2023, the World Health Organization (WHO) published its guideline on the use of NSS. This guideline includes the following conditional recommendation:

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

WHO states that conditional recommendations are those:

> "for which the WHO guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very small. Therefore, substantive discussion amongst policy-makers may be required before a conditional recommendation can be adopted as policy."

This position statement summarises and reviews the WHO guideline and the supporting systematic review (SR) with meta-analysis (MA) (Rios-Leyvraz and Montez, 2022) on NSS, with a view to assisting SACN in considering NSS in a UK context. NSS are of policy relevance to the UK in relation to reduction of free sugars and energy intake and maintenance of a healthy weight. Also of interest is the potential role of NSS to reduce dental caries, when used in place of free sugars.

The purpose of this position statement is to consider only the WHO guideline and the supporting SR with MA, which focus on NSS. It seeks to summarise and consider whether NSS are effective for reducing overweight and obesity, preventing weight-related

noncommunicable diseases (NCDs) and promoting dental health within a UK context. This position statement does not:

- consider the impact of NSS on all NCDs such as cancer
- consider toxicological issues, which are under the remit of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)
- seek to replicate the assessment of the evidence carried out within the SR with MA

Foods that contain NSS would be considered 'ultra processed foods' (UPFs) by the NOVA classification. This statement should be read alongside SACN's 2025 evidence update on processed foods and health (SACN, 2025).

Of specific relevance to this review, SACN:

- concluded that on balance, most people are likely to benefit from reducing their consumption of processed foods which are high in energy, saturated fat, salt and free sugars and low in fibre
- reiterated its existing advice in relation to minimising intake of sugar-sweetened drinks

SACN recommended that government:

- compels industry to make data publicly available on the amounts of individual additives such as NSS within food products to enable monitoring and further research on associations with health outcomes
- monitors the consumption of individual additives such as emulsifiers and NSS in the UK diet, particularly among high consuming and vulnerable groups

2. Background

SACN discussed the issue of NSS at its horizon scan meeting in June 2022 (the minutes are available on the SACN webpage). In light of the mixed evidence base and the potential increase in intakes as a result of the soft drinks industry levy (SDIL), SACN agreed to add NSS to its watching brief and to consider the evidence base as it develops and any available information on trends and use.

WHO published its guideline on use of NSS in May 2023. SACN agreed to review the evidence supporting the WHO guideline and to consider the appropriateness of the WHO conditional recommendation for the UK (see minutes of the June 2023 SACN meeting available on the SACN webpage).

2.1 Definition of non-sugar sweeteners

The WHO guideline uses the term NSS to describe low or no calorie alternatives to sugars. This term is therefore used in this position statement. WHO defines NSS as "all synthetic and naturally occurring or modified non-nutritive sweeteners that are not classified as sugars". The guideline states that NSS can also be referred to as "high-intensity sweeteners, low or no-calorie sweeteners, non-nutritive sweeteners, non-caloric sweeteners and sugar substitutes". This definition did not include caloric or bulk NSS such as polyols. It is of note that SACN's preferred term is "low or no calorie sweeteners" as it was considered to best describe the range of sweeteners of interest, see minutes from June 2023 SACN meeting available from the SACN webpage.

2.2 Assessment of non-sugar sweeteners in the UK

All NSS used in food and drink products in the UK have undergone a rigorous safety assessment by the European Food Safety Authority (EFSA), considering "all the data available on the chemical and biological properties, potential toxicity and dietary exposure estimates of food additives".

Following exit from the EU, a significant amount of EU legislation became part of the law in Great Britain (and is known as assimilated legislation) as a result of the Retained EU Law (Revocation and Reform) Act 2023. UK legislation dictates the amount of NSS that can be used and in which products, along with any specific conditions of use; compliance is monitored by the Food Standards Agency (FSA). The FSA's COT is now responsible for assessing the safety of additives before they can be used in food as well as ensuring that the science on additives is strictly reviewed. Since the UK left the EU Ministers have authorised 2 new steviol glycosides. The FSA and Office for Health Improvement and Disparities (OHID) continue to endorse EFSA scientific opinions on the safety and use of NSS that the UK fed into while it was an EU member state.

The FSA lists 22 sweeteners approved for use in Great Britian on the FSA Approved additives and E numbers webpage, 11 of which provide no calories or are low in calories. These include acesulfame potassium (acesulfame-K), aspartame, cyclamate, saccharin, sucralose, thaumatin, neohesperidin dihydrochalcone, steviol glycosides, neotame, aspartame-acesulfame salt and advantame. SACN's 2015 report on Carbohydrates and Health (SACN, 2015) provides a definition of free sugars.

2.3 UK dietary advice on free sugars and non-sugar sweeteners

SACN has been considering the expression of dietary recommendations during 2024 and 2025 (see the SACN meeting papers available on the SACN webpage). Throughout this

position statement, energy intake from free sugars and other macronutrients is expressed as a percentage of energy excluding the energy provided by any ethanol (alcohol).

SACN has not previously undertaken a specific risk assessment on NSS.

UK recommendations on reducing free sugars are based on findings from the SACN report on Carbohydrates and Health (SACN, 2015). SACN did not consider NSS specifically but noted randomised controlled trials (RCTs) conducted in children and adolescents indicate that consumption of sugars-sweetened drinks, as compared with non-calorically sweetened drinks, results in greater weight gain and increases in body mass index (BMI). SACN concluded in its report that if people consume fewer free sugars they would lower the risks of tooth decay, eating too many calories and obesity. SACN recommended that population intakes of free sugars should be reduced to no more than 5% energy. For further details of SACN's conclusions on carbohydrates and health, see annex 1.

UK government advice on a healthy, balanced diet, based on SACN recommendations, is encapsulated in the UK's national food guide, the Eatwell Guide. The guide does not include recommendations in relation to NSS. Accompanying advice states that if consuming foods and drinks high in free sugars (such as sugar-sweetened soft drinks), to have these less often and in small amounts. The Eatwell Guide recommends that people should aim to drink 6 to 8 cups or glasses of fluid a day and notes that water, lower-fat milk and sugar-free drinks, including tea and coffee, all count.

2.4 Estimates of non-sugar sweetener intakes

2.4.1 UK

The National Diet and Nutrition Survey (NDNS) is the primary and nationally representative tool for monitoring dietary intake in the UK. The NDNS rolling programme was established in 2008 to collect continuous data on the diet and nutritional status of the UK population.

There are challenges in monitoring intakes of NSS. The NDNS is not currently designed to quantify exposure to NSS in that it generally does not distinguish between products containing NSS and those containing free sugars or products that are unsweetened. Manufacturers are obliged to list NSS in the ingredients of pre-packaged food and drink, but not the amount of NSS.

For some product categories within the NDNS it can be surmised that they will generally contain NSS, for example no added sugar soft drinks. However, within the NDNS databank it would not currently be possible to distinguish soft drinks containing free sugars only, from those containing a mixture of free sugars and NSS. A study by Patel and others (2018) provides an example of how studies assess NSS intake by measuring consumption

of NSS-sweetened drinks and using this as a proxy measure for NSS. For other categories such as yoghurt, it would be difficult to infer the presence of NSS in product categories in the current NDNS coding frame. Assumptions would need to be made and modelling carried out to estimate the amount of each NSS consumed in order to monitor intakes of NSS in the UK.

The NDNS does however collect information about use of tabletop NSS (for example adding sweeteners in tea or coffee) as part of the 24-hour recalls (using the online dietary assessment tool Intake24) and previously as part of the paper food diary. These are coded in the same way as foods. It is possible to look at the number of consumers of various types of NSS (for example polydextrose, inulin and oligofructose, sorbitol, stevia based, and non-stevia based NSS). Questions about frequency of NSS use were added to the survey in 2024.

An FSA survey of the intake of intense sweeteners by young children from soft drinks was carried out in 2003 (FSA, 2003). The FSA concluded that young children were unlikely to exceed the acceptable daily intakes (ADIs) for aspartame, acesulfame K and saccharin at that time. However, high-level consumers of cyclamate (intake at the 97.5 percentile was 14.07mg per kg bodyweight) had an estimated intake twice the ADI of 7mg per kg bodyweight. To note this survey was carried out more than 20 years ago and intakes of NSS are likely to have changed in the intervening period.

2.4.2 International

For the 2023 aspartame hazard and risk assessment, the International Agency for Research on Cancer and the WHO and the Food and Agriculture Organization Joint Expert Committee on Food Additives provided an example that, for “a can of diet soft drink containing 200 or 300mg of aspartame, an adult weighing 70kg would need to consume more than 9 to 14 cans per day to exceed the acceptable daily intake, assuming no other intake from other food sources”. This provides an indication of the level of consumption required to reach maximum recommended daily intakes.

A study published in 2016 (Martyn and others, 2016) examined the intakes of 4 NSS (acesulfame K, aspartame, saccharin, sucralose) in the diets of children aged 1 to 4 years using food consumption and NSS presence data from the Irish National Pre-School Nutrition Survey (2010 to 2011) and analytical data for NSS concentration in foods obtained from a national testing programme. Exposure assessment scenarios were conducted. Mean daily intakes for all 4 NSS were found to be below the ADI.

In 2018, Martyn and others (2018) published a review of global NSS intakes and concluded that "overall, the studies conducted since 2008 raised no concerns with respect to exceedance of individual NSS ADIs among the general population globally. The data identified do not suggest a shift in exposure over time, with several studies indicating a

reduction in intake. However, some data suggest there may have been an increase in the numbers of consumers of low-/no-calorie-sweetened products".

2.5 Sugar reduction policies and non-sugar sweeteners

While outside of SACN's remit, SACN notes that a range of policies have an impact on NSS intakes in the UK and internationally.

2.5.1 UK

Following SACN's report on Carbohydrates and Health (2015), the UK initiated a range of policies to reduce population free sugars intakes (PHE, 2015; OHID, 2024).

This included the UK's SDIL which applies to manufacturers and importers of added sugar soft drinks with a total sugar content of 5g sugar per 100ml or more (OHID, 2022). In many cases, the sugars taken out of drinks subject to SDIL have been replaced with NSS (Luick and others, 2024), and a variety of NSS are used. However, there is a paucity of contemporary data on the levels of NSS present within foods and drinks in the UK.

A sugar reduction monitoring report published by OHID in December 2022 stated that between 2015 to 2020, overall the percentage change in sales weighted average sugar was down 46% from 2015 and decreases were similar across all socioeconomic groups (reductions of between 44% to 47%) (OHID, 2022). NDNS time trend data for 2008 and 2009 to 2016 and 2017 (years 1 to 9 of the rolling programme) show that free sugars intakes have fallen for some age groups (PHE, 2019). In older children and adolescents, this appears to be partly driven by soft drinks contributing less to free sugars intakes (Rogers and others, 2024).

In 2016, Public Health England (PHE) launched a voluntary sugar reduction programme (PHE, 2017). Reformulation is not entirely dependent on the use of NSS to replace the free sugars taken out of food and drink products and businesses manufacturing the same products can take very different approaches.

2.5.2 International

International dietary recommendations largely focus on reducing free sugars consumption and often do not mention NSS, including the:

- Australian dietary guidelines
- Dietary Guidelines for Americans
- Nordic Nutrition Recommendations 2023

However, some countries' sugar reduction policies do include NSS. Examples include the following.

Some countries in Europe (including France, Belgium, Norway, Portugal and Latvia), South America (including Chile), and parts of the USA and Canada (including British Colombia and Philadelphia) include NSS in drinks taxes (as noted in Thow and others (2022), the Global Food Research Program (2022) at the University of North Carolina and the World Bank Group's Global Sugar-Sweetened Beverages Tax Database (2023))

Some countries have policies to exclude NSS within schools (Greece, Hungary, Latvia, Malta, Spain, Australia, Brazil) (as noted by the European Commission's Health Promotion and Disease Prevention Knowledge Gateway).

Some countries account for NSS within national food labelling schemes. The Pan American Health Organization Nutrient Profile Model identified products containing NSS, and some countries have used this to inform their labelling regulations. These include the 2023 update to the French front-of-pack labelling system Nutri-Score and the Nordic keyhole labelling scheme (as outlined on the Swedish Food Agency website).

3. The World Health Organization guideline on use of non-sugar sweeteners

The objective of the WHO guideline was to:

> "provide guidance on the use of NSS to be used by policy-makers, programme managers, health professionals and other stakeholders in efforts to reduce free sugars intake, promote healthy diets, and prevent unhealthy weight gain and diet-related NCDs."

The recommendation from WHO in the guideline is:

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

The guideline states the recommendation is "conditional". It is noted within the guideline that:

> "conditional WHO recommendations are those recommendations for which the WHO guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very

small. Therefore, substantive discussion amongst policy-makers may be required before a conditional recommendation can be adopted as policy."

It is also stated that:

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

The guideline states that it was developed following the WHO guideline development process, as outlined in the WHO handbook for guideline development. The handbook includes:

> "a review of systematically gathered evidence by an international, multidisciplinary group of experts; assessment of the certainty in (that is, quality of) that evidence via the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework; and consideration of additional, potentially mitigating factors when translating the evidence into recommendations."

3.1 Summary of evidence behind the guideline

The WHO guideline was supported by evidence from an SR with MA by Rios-Leyvraz and Montez (2022) that assessed the health effects of higher compared with lower intakes of NSS.

The figure included in the executive summary on page 1 of the Rios-Leyvraz and Montez (2022) SR summarises the results of this SR with MA for the key outcomes in adults and pregnant women, further details of the SR are provided in chapter 4.

The WHO guideline describes the evidence behind the recommendation as follows:

> "higher NSS consumption by adults led to lower body weight and BMI, compared with not consuming NSS or consuming lower amounts of NSS, when assessed in short-term RCTs, but was associated with increased BMI and risk of incident obesity in long-term prospective observational studies"

> "effects on body weight and BMI from RCTs are observed only when intake of NSS is compared with intake of free sugars" and is likely to be "mediated at least in part by a reduction in energy intake"

> “no other significant effects or associations on measures of body fatness were observed in either RCTs or prospective cohort studies”

> “from observational studies “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 (CVDs) and mortality in adults”

> “limited evidence suggesting potential undesirable effects in the form of increased risk of preterm birth with NSS use during pregnancy.”

The WHO guideline states:

> “the discordant results between the RCTs and prospective cohort studies suggest that the small amount of weight loss resulting from NSS use in short-term experimental settings may not be relevant to the effects of long-term NSS use in the general population.”

It therefore prioritises the longer-term evidence from prospective cohort studies (PCS) over the short-term evidence from RCTs. The rationale given for this decision is that the majority of RCTs assessing NSS lasted 3 months or less, with inconsistent results from those lasting more than 3 months. The observed weight loss in RCTs was not considered to be indicative of a long-term health benefit.

The guideline states:

> “the lack of evidence for long-term benefit of NSS use on measures of body fatness [including weight and BMI] assessed in RCTs and potential long-term effects of NSS use observed for adults in prospective observational studies were considered to be relevant for women during pregnancy, and were reasonably expected to be relevant for children and adolescents as well.”

The guideline interprets the SR findings as:

> “no evidence of long-term benefit on measures of body fatness in adults or children, and, from observational evidence, potential undesirable effects from long-term use in the form of increased risk of type 2 diabetes, CVDs and mortality in adults. Limited evidence suggests potential undesirable effects in the form of increased risk of preterm birth with NSS use during pregnancy.”

3.2 Research recommendations identified in the systematic review with meta-analysis

The SR with MA underpinning the WHO guideline reports areas in which further research is needed. These include:

- effects of regularly consuming NSS and free sugars together, as research on this is very limited
- evidence to determine whether the observed associations are genuine or a result of reverse causation and/or residual confounding
- research in children and pregnant women, the latter group for which PCS currently suggest possible unfavourable effects of NSS consumption on birthweight and adiposity (body fat) in offspring later in life
- to confirm the findings for pregnant women, given that NSS use may be increasing among pregnant women (Sylvetsky and others, 2019)

4. Rios-Leyvraz and Montez (2022) systematic review with meta-analysis

This chapter summarises in detail the SR with MA by Rios-Leyvraz and Montez (2022), which was commissioned by the WHO to inform the development of the WHO guidance on NSS intake. It updates a previous SR by Toews and others (2019) with new studies published since the search for the original review was conducted. The updated SR also includes studies excluded from the original review in which NSS were not specified by name, as well as studies assessing the effects of NSS intake in pregnant women. This SACN position statement focuses on the updated SR only, as this is the evidence which directly underpins the WHO guideline.

4.1 Methods

Inclusion criteria for the SR were RCTs (including parallel, cluster and crossover trials), non-RCTs, PCS, case-control studies and cross-sectional studies. Studies investigated the effect of or the association between any type of NSS and a range of health outcomes. Health outcomes included measures of adiposity, NCDs, (such as CVD, type 2 diabetes, cancers, and dental caries), mortality, maternal and child outcomes and behaviours and preferences.

As discussed in chapter 1, NSS are of policy relevance to the UK in relation to free sugars reduction, energy reduction resulting weight loss and potential prevention of dental caries

through reduced free sugars intake. The focus of this position statement is to consider the evidence assessed by the SR on body weight health outcomes related to body weight (including type 2 diabetes and CVDs), and dental health. Therefore, only RCT and PCS evidence on body fatness, type 2 diabetes, CVDs and dental caries is presented here.

The SR covered a wide range of outcomes, most of which are not the focus of this position statement. Most of the wider outcomes were not found to have a significant association with NSS; exceptions were low or very low certainty observational evidence for all-cause mortality, bladder cancer and pre-term birth in adults (see the figure included in the executive summary on page 1 of the Rios-Leyvraz and Montez (2022) SR).

The SR included studies with a minimum intervention duration or follow-up of 13 days for blood lipid outcomes, one year for disease incidence outcomes (incident cancer, CVDs, type 2 diabetes), and 7 days for all other outcomes conducted in adults and children. Assessment of NSS exposure during pregnancy was required for studies with pregnancy or offspring outcomes.

The quality of the SR with MA by Rios-Leyvraz and Montez (2022) was assessed independently by 2 members of the SACN secretariat using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews, version 2) (Shea and others, 2017). There was no disagreement between the reviewers' assessments. Overall confidence in the findings of the Rios-Leyvraz and Montez (2022) SR with MA was rated as "moderate". The main reason not to give a higher rating was that the authors had not extracted primary study data in duplicate and did not report on any potential sources of conflict of interest. A summary of the AMSTAR 2 assessment is provided in annex 2.

4.2 Characteristics of studies included in the systematic review

Studies included in the SR by Rios-Leyvraz and Montez (2022) were conducted in adults, children and pregnant women. Studies specifically assessing the effects on individuals with pre-existing diabetes or including only such individuals were excluded.

A total of 370 records, representing 283 unique studies were included in the review; 50 RCTs, 97 PCS, 47 case-control studies assessing cancer outcomes, 5 non-RCTs, 69 cross-sectional studies, 15 ongoing or registered trials (for which published results were not identified).

The studies included in the SR that were considered in this position statement were published from 1976 onwards. With respect to RCTs, one study was published in the 1970s (1976), one study was published in the 1980s (1988), one study was published in the 1990s (1997), 3 studies were published in the 2000s, 32 studies were published in the 2010s and 9 studies were published between 2020 and the date of the SR search (26 July 2021). With respect to PCS, one study was published in the 1980s (1986), one study was

published in the 1990s (1997), 14 studies were published in the 2000s, 52 studies were published in the 2010s and 11 studies were published between 2020 and the date of the SR search (26 July 2021).

In the SR, results of the MAs are provided for a range of health outcomes for adults, children and pregnant women separately. Studies were included that compared NSS consumption with no or lower NSS consumption. RCTs were included that compared the intervention with any type of sugar, placebo, plain water or no intervention.

4.2.1 Randomised controlled trials

The SR included 45 RCTs conducted in adults, 4 in children, one including both adults and children and one in pregnant women.

Of the 50 RCTs included in the SR, 47 evaluated adiposity, intermediate markers of type 2 diabetes and CVD, or dental health outcomes. These were therefore considered in this position statement and were:

- measures of adiposity (n = 39 (36 in adults, 2 in children, one in adults and children)) (to note 32 were included in the MA)
- type 2 diabetes and pre-diabetes (intermediate markers of glycaemic control) (n = 31 (30 in adults, one in adults and children))
- CVDs (intermediate markers, such as blood pressure and lipids) (n = 25 (24 in adults, one in adults and children))
- dental health outcomes (n = 2, both in children)

One RCT identified in pregnant women evaluated gestational weight gain and risk for excessive gestational weight. This outcome was not specified in advance of data collection.

Interventions used in these RCTs were aspartame in 12 studies, sucralose in 7 studies, stevia in 5 studies, saccharin in one study and advantame in one study. Four studies used a mix of more than one NSS, 3 studies tested multiple NSS separately and 14 studies used an unspecified NSS as the intervention.

The comparators used in the RCTs considered in this position statement are listed below. The majority of RCTs (27/47) used a form of sugar as the comparator. Overall, the comparators were:

- a form of sugar, comprised of:

    - sucrose (11 studies)
    - “sugars” (6 studies)
    - mix of glucose and fructose (one study)
    - mix of “sugars” or sugars-sweetened beverages (SSB) with water (2 studies)
    - mix of sugar or “sugars” with a form of oligosaccharide (maltodextrin or fructooligoaccharide) (3 studies)
    - fructose (one study)
    - lactose (one study)
    - D-allulose (one study)
    - sugars-sweetened snack (one study)
- water, comprised of:
    - water (6 studies)
    - unsweetened water (study describes as ‘placebo’) (one study)
- other, comprised of:
    - “placebo” in 5 studies: empty capsules in 3 studies, capsules containing cellulose in 1 study and “daily mouth rinse placebo” in 1 study)
    - avoiding aspartame (control participants told to avoid all NSS products) (2 studies)
    - no intervention (2 studies)
    - SSB, water and milk (1 study)
    - placebo, lactisole (an inhibitor of the sweet taste receptor), saccharin with lactisole (1 study)
    - unsweetened drinks and SSB (1 study)
    - 0 unspecified soft drink per day (versus one or more) (1 study)

Forty RCTs that evaluated either adiposity, intermediate markers of type 2 diabetes, CVDs or dental caries outcomes used a single mode of delivery for the intervention. These

included “soft drink” as the most common mode of delivery (in 18 trials), followed by “drink” in 9 trials, “capsule” in 5 trials, “table-top” in 3 trials, “food” in 2 trials, and “water”, “hot drink” or “mouth rinse”, each in one trial. Seven trials used 2 or more modes of delivering the intervention. These included food and drink in 3 trials, food, drink and tabletop in 2 trials, and food, drink and capsule or drink and capsule each in one trial. Details for each RCT that evaluated either adiposity, type 2 diabetes, CVDs or dental caries outcomes are presented in annex 3.

Trial duration in adults (including follow-up post-intervention) ranged from 7 days to more than 3 years. Eight of the 45 trials were longer than 3 months and one of those was longer than 2 years. Trials in adults were conducted in Australia (n = 2), Denmark (n = 2), France (n = 2), Greece (n = 1), the Islamic Republic of Iran (n = 1), the Republic of Korea (n = 4), Latvia (n = 1), Mexico (n = 6), New Zealand (n = 2), Switzerland (n = 1), Thailand (n = 1), the UK (n = 7), the USA (n = 14) and multiple countries (n = 1). In terms of health status, adult populations were lean (n = 10), mixed-weight (n = 20) or exclusively overweight (n = 15). Participant numbers ranged from 10 to 641.

Trial duration in children ranged from 6 weeks to 18 months. Three of the 4 trials in children were longer than 3 months and none were over 2 years. Trials were conducted in India (n = 1), Italy (n = 1), the Netherlands (n = 1), and South Africa (n = 1). Details of the health status of child populations and study sample sizes were not provided in the systematic review. Participant numbers ranged from 108 to 641.

One trial was identified in pregnant women. Dietary intake data was collected at baseline (gestational week 11 to 14) and endpoint (gestational week 36 to 37). The trial was conducted in Denmark and included 342 participants. Details of the health status of participants were not provided in the systematic review.

4.2.2 Prospective cohort studies

The SR included 64 PCS conducted in adults (representing approximately 35 unique cohorts), 15 PCS in children (representing 13 unique cohorts), one PCS in children and adults (representing one unique cohort) and 17 PCS in pregnant women (representing 12 unique cohorts).

Of the 97 PCS included in the SR, 79 studies were considered for this position statement (due to the health outcomes considered as specified above). These evaluated:

- measures of adiposity (n = 43 (20 in adults, 15 in children, 8 in pregnant women))
- type 2 diabetes and pre-diabetes (incidence and intermediate markers of glycaemic control) (n = 20 (17 in adults, one in children, 2 in pregnant women))

- CVDs (incidence and intermediate markers, such as blood pressure and lipids) (n = 24 (21 in adults, one in children, 2 in pregnant women))

- dental caries (n = one, in children)

To note, some studies evaluated more than one health outcome.

In PCS that evaluated adiposity outcomes in pregnant women, outcomes were reported as adiposity in offspring (n = 3), gestational weight gain (n = 2), birthweight (n = 2), obesity, BMI and waist circumference (n = 1) and large for gestational age (n = 1). Type 2 diabetes outcomes in pregnant women were reported as glycated haemoglobin (HbA1c), fasting glucose, fasting insulin, insulin resistance and type 2 diabetes (n = 1) and gestational diabetes (n = 1). CVD outcomes in pregnant women were reported as congenital heart disease in offspring (n = 2) and triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol (n = 1).

In all PCS the exposure to NSS was unspecified, except one PCS in adults where the exposure reported was saccharin.

Comparison of NSS consumption was reported in a variety of ways across PCS that evaluated either adiposity, type 2 diabetes, CVDs or dental caries outcomes. Daily serving of NSS was compared in 16 studies and users versus non-users of NSS were compared in 6 studies. The highest number of daily, weekly or monthly servings versus the lowest number (for example greater than or equal to (≥) once a day versus less than (<) once a week or ≥ once a day versus none) was compared in 44 studies. Increase in number of servings per day or week versus no change was compared in 4 studies. “Dose-response” was compared in 2 studies. Decreased SSB with increased NSS consumption, per serving, per 10g of artificially sweetened beverages (ASBs) standardised to 1,000kcal per day, per 100mL per day, low versus no intake, chronic user versus never, always or almost always versus never or rarely and “linear” were compared in one study each. One study compared NSS-sweetened drink consumption between pregnant women with “excessive”, “optimal” and “suboptimal” gestational weight gain.

Sixty-four PCS that evaluated either adiposity, type 2 diabetes, CVDs or dental caries outcomes assessed a single mode of delivery of the exposure of NSS. These included “soft drink” as the most common mode of delivery (in 43 studies), followed by “drink” in 20 studies, and “table top” in one study. Fourteen studies used 2 or more modes of delivering the exposure. These included soft drink and fruit drink in 5 studies, food and drink in 4 studies, soft drink and tabletop, or soft drink and hot drink each in 2 studies, and drink and tabletop in one study. In one study the mode of delivery for the exposure was unclear. Details for each PCS that evaluated either adiposity, type 2 diabetes, CVDs or dental caries outcomes are presented in annex 3.

Follow-up in cohort studies in adults ranged from 2 years to more than 30 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 UK (n = 1), the USA (n = 44) and multiple countries (n = 5). The cohort study conducted in children and adults was conducted in Australia. Participant numbers ranged from 101 to 487,922.

Follow-up in cohort studies in children ranged from 8 months to 10 years. Cohort studies in children were conducted in Australia (n = 1), Denmark (n = 1), the UK (n = 1) and the USA (n = 12). Participant numbers ranged from 49 to 16,771.

Follow-up in cohort studies in the offspring of pregnant women ranged from 8 months to 16 years. 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 UK (n = 1) and the USA (n = 3). Participant numbers ranged from 57 to 88,514.

4.2.3 Risk of bias

Rios-Leyvraz and Montez (2022) assessed risk of bias (ROB) for RCTs using the Cochrane ROB tool. In assessing ROB in RCTs, emphasis was placed on adequate randomisation, limited loss to follow-up (incomplete outcome data) and selective reporting. The authors noted that “blinding of participants would have been difficult in many studies, given different behavioural advice, and the obvious taste differences between sugars, water and NSS”. ROB for PCS was assessed using the Newcastle-Ottawa Scale.

Rios-Leyvraz and Montez (2022) assessed ROB for both RCTs and PCS by study not outcome therefore it was not possible to report ROB by the outcomes addressed in this position statement (adiposity, type 2 diabetes, CVD and dental caries). For further details of the ROB assessment, see annex 4. ROB was also considered for each health outcome in GRADE assessments and is detailed throughout the summary of results below.

4.3 Results of meta-analysis in adults: for adiposity

GRADE profiles as assessed by Rios-Leyvraz and Montez (2022), including a summary of each study, are provided in 'Annex 7. GRADE evidence profiles' (page 98 onwards) in Health effects of the use of non-sugar sweeteners: a systematic review and meta-analysis.

For each study, the summary tables include the:

- outcome
- study design
- findings (effect)

- author graded certainty of evidence

A total of 32 RCTs and 13 PCS reporting NSS intakes and measures of adiposity were included in MAs. Separate MAs were conducted for different anthropometric measures which included body weight (kg), BMI, obesity, waist circumference, abdominal obesity, waist-to-hip ratio, fat mass (kg), fat mass (percentage) and lean mass (kg).

4.3.1 Body weight (kg)

Randomised controlled trial evidence
An MA of 29 RCTs (1,252 participants in lower or no NSS group and 1,181 participants in higher NSS group, follow-up time frame of RCTs ranged from 7 days to 3.5 years) reported that higher consumption of NSS was associated with a 0.71kg reduction in body weight (mean difference (MD) -0.71; 95% confidence interval (CI) -1.13 to -0.28, I squared statistic (I^2) = 83%).

The SR notes that sensitivity analyses using a fixed effects model, removing studies of shorter duration (less than 8 weeks) did not significantly change the effect observed for body weight. One trial (n = 163) was longer than 2 years, which reported that that higher consumption of NSS was associated with a 5.11kg reduction in body weight (MD -5.10; 95% CI -7.15 to -3.05).

The certainty of the evidence was “low” as graded by the SR authors. The evidence was graded as low due to serious ROB (downgraded once) and serious inconsistency (downgraded once). In terms of ROB, although most trials appeared to be well conducted, there was a widespread lack of detail in the reporting of methods. Less than half appeared to use appropriate methods of random sequence generation. Less than a quarter reported adequate allocation concealment. Blinding was either not possible or unclear in most trials and dropout rates were considered significant in half (cut off used greater than (>) 15%). Heterogeneity was considered significant based on a cut off of $I^2 \geq 50\%$. Where the number of studies was sufficient to explore heterogeneity via subgroup and sensitivity analyses, results of these analyses did not significantly explain the observed heterogeneity.

Prospective cohort study evidence
An MA of 4 PCS (continuous consumption) and another MA of 5 PCS (high versus low consumption) found no significant association between NSS intakes and body weight (kg).

4.3.2 BMI

Randomised controlled trial evidence
An MA of 23 RCTs was conducted to assess the relationship between NSS consumption and BMI. The overall combined effect was non-significant. To note, in the figure on page 1

of the SR, the green arrow indicating an effect of NSS on decreased BMI may relate to the subgroup analysis of studies that replaced “sugars” with NSS (see section 4.3.5 below).

Prospective cohort study evidence
An MA of 5 PCS (80,583 adults, follow-up ranged from 6 months to 10 years) reported that higher baseline intakes of NSS were associated with an increase in BMI of 0.14 kg/m2 at follow-up (MD 0.14; 95% CI 0.03 to 0.02, I^2 = 79%).

Information on key adjustments for potential confounders was provided for 4 out of 5 PCS. All 4 PCS adjusted for age, sex and smoking, 3 out of 4 adjusted for “disease risk” (that is, identified risk factors for disease), 2 out of 4 adjusted for BMI, alcohol and “other diet” factors and one adjusted for total energy. No PCS adjusted for consumption of “sugars/SSBs”.

The certainty of the evidence was “very low”. The evidence was graded as very low due to serious inconsistency (downgraded once). Heterogeneity was considered significant based on $I^2 \geq 50\%$. Where the number of studies was sufficient to explore heterogeneity via subgroup and sensitivity analyses, these did not significantly explain the observed heterogeneity.

4.3.3 Obesity incidence

Randomised controlled trial evidence
No RCT evidence was identified.

Prospective cohort study evidence
An MA of 2 PCS (1,668 adults, follow-up ranged from 9 years to 10 years) reported that higher intakes of NSS at baseline were associated with a 76% greater incidence of obesity at follow-up (MD 1.76; 95% CI 1.25 to 2.49, I^2 = 0%).

Both PCS adjusted for age, smoking and BMI. One out of 2 PCS adjusted for sex and “disease risk” and neither PCS adjusted for consumption of alcohol, “other fat”, total energy, “sugars/SSBs” or “other diet”.

The certainty of the evidence was “low”. The evidence did not have serious ROB, inconsistency, indirectness or imprecision and was therefore not downgraded.

4.3.4 Other measures

No significant associations were observed in MAs of RCTs or PCS for other body fatness measures including waist circumference, abdominal obesity, waist-to-hip ratio, fat mass (kg), fat mass (percentage) or lean mass (kg).

4.3.5 Randomised controlled trial subgroup analysis of effect of non-sugar sweetener intake on body weight (kg) and BMI for trials with explicit replacement of "sugars" with non-sugar sweeteners

Subgroup analyses were conducted on the associations between NSS intakes and body weight and BMI in RCTs. Table 2 below provides a summary of evidence for subgroup analysis of the effect of NSS intake on body weight (kg) and BMI from trials with explicit replacement of "sugars" with NSS. The results showed that:

- no significant differences were observed according to baseline weight status or when comparing weight loss versus non-weight loss studies

- adding NSS to the diet compared with "sugars" (either NSS replacing "sugars", or both NSS and "sugars" being added to the diet, in separate arms of a trial) resulted in decreases in body weight (MD -0.76; 95% CI -1.18 to -0.34, I^2 = 71%) and BMI (MD -0.21; 95% CI -0.36 to -0.06, I^2 = 42%)

- NSS compared with nothing (placebo) or water showed no effect on body weight or BMI (observed changes in body weight noted in the point above were likely to have been mediated by the reduction in energy intake seen when NSS compared to "sugars")

- when studies were limited to those that gave explicit instructions to habitual consumers of SSBs and foods containing sugars to replace these with NSS alternatives, the effect of NSS on reducing body weight became non-significant and the effect on BMI was no longer observed

4.4 Results of meta-analysis in adults: type 2 diabetes and markers

4.4.1 Type 2 diabetes

Randomised controlled trial evidence
No RCT evidence was identified for type 2 diabetes incidence.

Prospective cohort study evidence
An MA of 13 PCS (408,609 adults, follow-up ranged from 4 to 30 years) reported that higher intakes of NSS in drink form at baseline were associated with a 23% increased risk of developing type 2 diabetes at follow-up (hazard ratio (HR) 1.23; 95% CI 1.14 to 1.32, I^2 = 6%).

All studies adjusted for smoking, 11 adjusted for BMI, 9 adjusted for age and/or total energy, 7 adjusted for alcohol consumption, "disease risk", "sugars/SSBs" and/or "other diet", 5 adjusted for sex and 4 adjusted for "other fat".

The certainty of the evidence was “low”. The evidence did not have serious ROB, inconsistency, indirectness or imprecision and was therefore not downgraded.

An MA of 2 PCS (62,582 adults) reported that higher intakes of NSS in tabletop form were associated with a 34% increased risk in developing type 2 diabetes (HR 1.34; 95% CI 1.21 to 1.48, I^2 = 0%).

Both studies adjusted for smoking, BMI, sugar, SSBs and “other diet”. One of the studies adjusted for age, sex, alcohol, “other fat”, “disease risk” or total energy.

The certainty of the evidence was “low”. The evidence did not have serious ROB, inconsistency, indirectness or imprecision and was therefore not downgraded.

4.4.2 Type 2 diabetes intermediate markers

Randomised controlled trial evidence
No significant associations were observed for MAs of RCTs for other type 2 diabetes markers including high fasting glucose, fasting glucose (millimole (mmol) per litre (L)), fasting insulin (picomole (pmol) per L), percentage HbA1c or homeostatic model assessment of insulin resistance (HOMA-IR).

Prospective cohort study evidence
An MA of 3 PCS (11,213 adults) reported that higher intakes of NSS were associated with a 21% increase in risk of high fasting glucose at follow-up (HR 1.21; 95% CI 1.01 to 1.45, I^2 = 47%). High fasting glucose was defined as ≥ 100mg per decilitre (dL). All 3 PCS adjusted for age, sex, smoking and BMI. Two PCS adjusted for total energy and/or “other diet”, one PCS adjusted for “other fat” or “disease risk” and no PCS adjusted for alcohol or “sugars/SSBs”. The certainty of the evidence was “low”. The evidence did not have serious ROB, inconsistency, indirectness or imprecision and was therefore not downgraded.

No significant associations were observed for MAs of PCS for other type 2 diabetes markers including fasting glucose (mmol per L), fasting insulin (pmol per L), percentage HbA1c or homeostatic model assessment of insulin resistance (HOMA-IR).

4.5 Results of meta-analysis in adults: cardiovascular diseases

4.5.1 Cardiovascular disease mortality

Randomised controlled trial evidence
No RCT evidence was identified.

Prospective cohort study evidence
An MA of 4 PCS (comprising 5 cohorts, 598,951 adults) reported that higher intakes of NSS at baseline were associated with a 19% increase in risk of CVD mortality over the follow-up period (HR 1.19; 95% CI 1.07 to 1.32, I^2 = 25%).

All 4 PCS adjusted for alcohol, smoking, BMI, total energy and "other diet". Three PCS adjusted for age, diseases risk and/or "sugars/SSBs", 2 PCS adjusted for sex and no PCS adjusted for "other fat".

The certainty of the evidence was "low". The evidence did not have serious ROB, inconsistency, indirectness or imprecision and was therefore not downgraded.

4.5.2 Cardiovascular disease events

Randomised controlled trial evidence
No RCT evidence was identified.

Prospective cohort study evidence
An MA of 3 PCS (166,938 adults) reported that higher intakes of NSS-containing drinks at baseline were associated with a 32% increase in risk of cardiovascular events at follow-up (HR 1.32; 95% CI 1.17 to 1.50, I^2 = 0%).

All 3 PCS adjusted for age, alcohol, smoking, BMI, "disease risk", total energy, "sugars/SSBs" and "other diet". Two PCS adjusted for sex and none adjusted for "other fat".

The certainty of the evidence was "low". The evidence did not have serious ROB, inconsistency, indirectness or imprecision and was therefore not downgraded.

"Cardiovascular events" in one PCS included stroke, myocardial infarction and vascular death. Another PCS included coronary heart disease, myocardial infarction, heart failure, coronary revascularization procedure, ischaemic stroke, peripheral artery disease and CVD mortality. Specific events were not reported for the third PCS.

4.5.3 Stroke

Randomised controlled trial evidence
No RCT evidence was identified.

Prospective cohort study evidence
An MA of 5 PCS (comprising 6 cohorts, 655,952 adults) reported that higher intakes of NSS-containing drinks were associated with a 19% increase in risk of any type of stroke (HR 1.19; 95% CI 1.09 to 1.29, I^2 = 0%).

Four PCS adjusted for alcohol, smoking and “other diet”, 3 PCS adjusted for age, sex, BMI, “disease risk” and total energy, 2 PCS adjusted for “sugars/SSBs” and one PCS adjusted for “other fat”.

The certainty of the evidence was “low”. The evidence did not have serious ROB, inconsistency, indirectness or imprecision and was therefore not downgraded.

When assessed individually, increases in risk were seen for both haemorrhagic stroke (2 PCS including 3 cohorts, 196,884 adults, HR 1.33; 95% CI 1.03 to 1.72, I^2 = 22%) and ischaemic stroke (3 PCS including 4 cohorts, 200,827 adults, HR 1.22; 95% CI 1.04 to 1.44, I^2 = 44%).

4.5.4 Hypertension

Randomised controlled trial evidence
No RCT evidence was identified.

Prospective cohort study evidence
An MA of 4 PCS (comprising 6 cohorts, 234,137 adults) reported that higher intakes of NSS-containing drinks were associated with a 13% increase in risk of hypertension (HR 1.13; 95% CI 1.09 to 1.17, I^2 = 48%).

Four PCS adjusted for age, smoking and BMI. Three PCS adjusted for sex, total energy and “other diet”, 2 PCS adjusted for “other fat” and “disease risk” and one PCS adjusted for alcohol and “sugars/SSBs”.

The certainty of the evidence was “low”. The evidence did not have serious ROB, inconsistency, indirectness or imprecision and was therefore not downgraded.

4.5.5 Total cholesterol:HDL cholesterol

Randomised controlled trial evidence
An MA of 4 RCTs (participant numbers not reported) found that higher intakes of NSS were associated with a small increase in total cholesterol:HDL cholesterol (MD 0.09; 95% CI 0.02 to 0.16, I^2 = 0%).

The certainty of the evidence was “moderate”. The evidence was graded as “moderate” due to serious imprecision; a small mean effect, likely to be of little to no clinical significance, and neither bound of the 95% CI included a potentially important benefit or harm. However, the sample size was small (downgraded once).

Prospective cohort study evidence
No PCS evidence was identified.

4.5.6 Other cardiovascular disease measures and markers

No significant associations were observed for MA of RCTs or PCS for other CVD measures or markers including coronary heart disease, systolic blood pressure, diastolic blood pressure, total cholesterol, and blood lipids HDL cholesterol, LDL cholesterol, low HDL cholesterol, triacylglycerol (TAG) and high TAG.

4.6 Results of meta-analysis in adults: dental caries

4.6.1 Randomised controlled trial evidence

The SR found no effect of NSS (in a single RCT) on the development of dental caries when comparing consumption of sugars-sweetened soft drinks with NSS-sweetened soft drinks. SACN notes that dental caries was not the primary outcome in that RCT and its 6-month duration is insufficient in length to observe impact on dental caries, which ideally needs a minimum of 2 years.

4.6.2 Prospective cohort study evidence

No PCS evidence was identified.

4.7 Results of meta-analysis in children: adiposity

Table 3a below provides a summary of evidence in the SR with MA for adiposity in children (statistically significant associations only).

Two RCTs and 14 cohort studies reported on NSS intake and measures of adiposity in children. One of the RCTs reported reductions in body weight, waist circumference and body fat mass when SSBs were replaced with NSS-sweetened drinks. For further details see sections 4.7.1, 4.7.2 and 4.7.3 below.

An MA including this RCT and one other RCT also reported BMI z-score (that is, BMI adjusted for child age and sex), however this was non-significant and has not been reported further.

4.7.1 Body weight (kg)

Randomised controlled trial evidence

One RCT (319 children in the lower or no NSS intake group and 322 children in the higher NSS group, follow-up was 18 months) reported a reduction in body weight (kg) (MD -1.01; 95% CI -1.54 to -0.48) when SSBs were replaced with NSS-sweetened drinks.

The certainty of this evidence was “moderate”. The evidence was graded as moderate due to being unable to assess inconsistency of a single study and so was downgraded.

Prospective cohort study evidence
An MA of 2 PCS found no significant association between NSS intakes and body weight (kg).

4.7.2 Waist circumference

Randomised controlled trial evidence
One RCT (319 children in the lower/no NSS intake group and 322 children in the higher NSS group, follow-up was 18 months) reported a reduction in waist circumference (centimetres) (MD -0.66; 95% CI -1.23 to -0.09) when SSBs were replaced with NSS-sweetened drinks.

The certainty of this evidence was “moderate”. The evidence was graded as moderate due to being unable to assess inconsistency from a single study and so was downgraded.

Prospective cohort study evidence
No PCS evidence was identified.

4.7.3 Body fat mass (kg)

Randomised controlled trial evidence
One RCT (319 children in the lower or no NSS intake group and 322 children in the higher NSS group, follow-up was 18 months) reported a reduction in body fat mass (kg) (MD -0.57; 95% CI -1.02 to -0.12) when SSBs were replaced with NSS-sweetened drinks.

The certainty of this evidence was “moderate”. The evidence was graded as moderate due to being unable to assess inconsistency from a single study and so was downgraded.

Prospective cohort study evidence
One PCS found no significant association between NSS intakes and body fat mass.

4.7.4 Body fat mass (percentage)

Randomised controlled trial evidence
One RCT (319 children in the lower or no NSS intake group and 322 children in the higher NSS group, follow-up was 18 months) reported a reduction in body fat mass (percentage) (MD -1.07; 95% CI -1.99 to -0.15) when SSBs were replaced with NSS-sweetened drinks.

The certainty of this evidence was “moderate”. The evidence was graded as moderate due to being unable to assess inconsistency from a single study and so was downgraded.

Prospective cohort study evidence
Two PCS found no association between NSS intakes and body fat mass (percentage).

4.7.5 Other adiposity measures

No significant associations were reported from MA or single RCT or PCS on intakes of NSS and BMI, BMI z-score or overweight in children.

4.8 Results of meta-analysis in children: type 2 diabetes

No studies reported on development of type 2 diabetes in children.

4.9 Results of meta-analysis in children: cardiovascular diseases

No studies reported on development of CVDs in children.

4.10 Results of meta-analysis in children: dental caries

Table 3b below provides a summary of evidence in the SR with MA for dental caries in children (statistically significant associations only).

4.10.1 Randomised controlled trial evidence

In one RCT (264 children, 6 weeks follow-up), snacks containing stevia or sugars were given twice daily to children for 6 weeks. Authors reported:

> "at the end of the trial, the concentrations of cariogenic Streptococcus mutans bacteria and lactobacilli … and the probability of developing caries … in the stevia arm had decreased compared with baseline, whereas there were no statistically significant changes in the sugars arm."

SACN question whether this study was an RCT and noted it used an algorithm to assess "risk" of developing dental caries, rather than directly measuring dental caries and should be treated with caution.

In another oral hygiene RCT (108 children, 6 months follow-up), daily use of mouth rinse containing stevia was assessed for children for 6 months. Authors reported:

> "at the end of the trial, there was a significant improvement in the stevia arm compared with the placebo arm in plaque scores ($p = 0.03$). There were no changes in the number with cavitated lesions in the stevia arm, but there was an increase in number with cavitated lesions in the placebo arm (from 5.6% to 5.8%)."

SACN note that this study has not been accurately reported in the SR and the results should be treated with caution. As this RCT investigated impact of oral hygiene practices, as opposed to use of NSS in the diet SACN do not consider this RCT is relevant.

SR states “unable to meta-analyse” for this evidence.

The certainty of this evidence was classified as “low”. The evidence was downgraded to low due to being unable to assess inconsistency as there were only 2 studies which could not be meta-analysed. The studies could not be meta-analysed due to serious imprecision. Authors reported that:

> “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.”

4.10.2 Prospective cohort study evidence

One PCS (642 children aged 4 to 7 years, 7 years follow-up) found that consumption of NSS-sweetened drinks (low intake) was associated with fewer teeth surfaces having caries compared with no intake of NSS-sweetened drinks ($p < 0.025$). However, the association with high intakes of NSS-sweetened drinks was not reported. This PCS adjusted for age at dental examination, sex, fluoride exposure, dietary variables significant at $p < 0.10$ in univariate analysis (covariates adjusted for in most adjusted model).

The certainty of this evidence was “very low”. The evidence was graded as very low due to serious ROB with a mean Newcastle-Ottawa Scale score of less than or equal to (≤) 5 with very conservative application of ratings (downgraded once), being unable to assess inconsistency as there was only a single study (downgraded once) and unable to assess imprecision (downgraded once).

4.11 Results of meta-analysis in pregnant women (maternal and birth outcomes) and health effects in offspring

Table 4 below provides a summary of evidence in the SR with MA for adiposity and type 2 diabetes in pregnant women (statistically significant associations only).

The SR did not perform an MA on this evidence.

4.11.1 Gestational weight gain

To note, this evidence was not specified in advance of data collection by the SR.

Randomised controlled trial evidence
In one RCT (the “TOP” study, 342 women, 9 months follow-up), gestational weight gain and risk for “excessive gestational weight” were higher in pregnant women consuming one or more NSS-sweetened drinks per day compared with 0 per day (MD 2.0kg; 95% CI –0.2, 4.2; and RR 1.50; 95% CI 1.17, 1.92, respectively).

This evidence was not graded.

Prospective cohort study evidence
In one PCS (the “PREWICE” cohort, 1,326 women, 9 months follow-up), pregnant women with “excessive gestational weight gain” (undefined in the SR) consumed more NSS-sweetened drinks (median: 0.5 times per week at baseline; interquartile range (IQR) 0.1 to 2.0; $p < 0.01$) than those with optimal and suboptimal gestational weight gain (median 0.1; IQR 0.1 to 1.0). This PCS adjusted for maternal pre-pregnancy BMI, age, parity, smoking during pregnancy, educational level, total gestational length and offspring sex (all covariates adjusted for in adjusted model). The study did not mention adjustment for SSB intake.

In another PCS, gestational weight gain was not significantly associated with intake of low-calorie drinks.

This evidence was not graded.

4.11.2 Gestational diabetes

Randomised controlled trial evidence
No RCT evidence was identified.

Prospective cohort study evidence
In a single PCS, intakes of NSS-sweetened drinks was not significantly associated with the risk of developing gestational diabetes.

4.11.3 Birth weight (including large for gestational age)

Randomised controlled trial evidence
No RCT evidence was identified.

Prospective cohort study evidence
In one PCS (1,698 pregnant women, 13 months follow-up), maternal intake of NSS-sweetened products before conception was associated with increased birthweight (adjusted z-score coefficient per 10g per 1000 kcal per day: 0.001; 95% CI 0.000 to 0.001; $p = 0.002$). This PCS adjusted for energy intake, maternal BMI, maternal age, smoking,

alcohol, education level, urbanisation level, parity, sex of newborn, ethnicity and intake of other 21 food groups (all covariates adjusted for in most adjusted model). The study did not mention adjustment for SSB intake.

In another PCS, intake of low-calorie drinks was not associated with large for gestational age.

In a secondary analysis of the cluster-randomised GeliS trial, intake of NSS-sweetened drinks during pregnancy was not associated with birthweight or BMI (at birth), or categorical assessments of low or high birthweight, or small or large for gestational age.

The certainty of this evidence was “very low”. The evidence was graded as very low due to a serious ROB with a mean Newcastle-Ottawa Scale score of ≤ 5 with very conservative application of ratings (downgraded once), being unable to assess inconsistency as there were a small number of studies that could not be meta-analysed (downgraded once) and unable to assess imprecision (downgraded once).

4.11.4 Offspring adiposity

Randomised controlled trial evidence
No RCT evidence was identified.

Prospective cohort study evidence
In one PCS (3,033 infants, one year follow-up), daily intake of NSS-sweetened drinks during pregnancy (compared with < 1 serving per month) was associated with a 0.2 increase in infant BMI z-score (95% CI 0.02 to 0.38) and a more than twofold increase in risk of overweight at one year of age (adjusted odds ratio (OR) 2.19; 95% CI 1.23 to 3.88).

This PCS adjusted for maternal total energy intake, Healthy Eating Index score, maternal postsecondary education, maternal smoking and diabetes during pregnancy, breastfeeding duration, infant sex, introduction of solid foods before 4 months and SSB intake (all covariates adjusted for in most adjusted model). Adjustment for maternal BMI, diet quality, total energy intake or other obesity risk factors did not change the results.

In one PCS (918 children, up to 7 years follow-up) the children of women with gestational diabetes who consumed one or more NSS sweetened drinks per day (compared with never consuming NSS sweetened drinks) had a higher BMI z-score (beta coefficient (β) 0.59; 95% CI 0.23 to 0.96) and risk of overweight or obesity (RR 1.93; 95% CI 1.24 to 3.01) at 7 years of age.

This PCS adjusted for maternal factors: pre-pregnancy BMI, age, socioeconomic status, smoking during pregnancy, intakes of total energy, desserts and sweets, fats (oil, margarine and butter), potato, processed meat, refined grains, whole grains and SSBs

during pregnancy, and physical activity during pregnancy. In offspring adjustments were made for: sex, breastfeeding duration, consumption of ASBs and SSBs at 7 years (only for outcomes at 7 years), physical activity at 7 years (only for outcomes at 7 years) (all covariates adjusted for in the most adjusted model).

In one PCS, consumption of NSS-sweetened drinks during pregnancy was not associated with BMI z-score or waist circumference in offspring at mid-childhood.

The certainty of this evidence was “very low”. The evidence was graded as very low due to being unable to assess inconsistency as there were a small number of studies that could not be meta-analysed (downgraded once) and unable to assess imprecision (downgraded once).

4.12 Summary tables of evidence from the SR with MA for adiposity, type 2 diabetes and CVDs in adults

Tables 1a to 1c summarise the evidence in the SR with MA for adiposity, type 2 diabetes and cardiovascular diseases in adults for statistically significant associations only. Non-significant associations are noted at the bottom of each table.

For detail on the comparators used in each study see annex 3.

Abbreviations used in the tables: BMI: body mass index, CVD: cardiovascular disease, HbA1c: glycated haemoglobin, HDL: high-density lipoprotein, HOMA-IR: homeostatic model assessment of insulin resistance, kg: kilogram, MA: meta-analysis, NSS: non-sugar sweetener, PCS: prospective cohort study, RCT: randomised controlled trial, SR: systematic review, SSB: sugars-sweetened beverage, TAG: triacylglycerol.

Table 1a: summary of evidence in the SR with MA for adiposity in adults

Specific health outcome	Evidence type (number of studies in MA)	Author reported direction of association	Favoured exposure	SR reported adjustments for confounders in PCS	Author graded certainty of the evidence
Body weight (kg)	RCT (29)	Decreased risk	Favours consuming NSS	Not applicable	Low
BMI	PCS (5)	Increased risk	Favours not consuming NSS	Information on key adjustments for potential confounders was provided for 4 out of 5 PCS. Four PCS adjusted for age, sex and smoking. Three out of 4 adjusted for "disease risk". Two out of 4 adjusted for BMI, alcohol and "other diet" factors. One adjusted for total energy and no PCS adjusted for "sugars/SSBs".	Very low
Obesity incidence	PCS (2)	Increased risk	Favours not consuming NSS	Both PCS adjusted for age, smoking and BMI. One PCS adjusted for sex and "disease risk". Neither PCS adjusted for consumption of alcohol, "other fat", total energy, "sugars/SSBs" or "other diet".	Low

No significant associations were observed for:

- body weight (kg) (PCS evidence: one MA including 4 PCS (continuous consumption) and one MA including 5 PCS (highest versus lowest category of intake))
- BMI (RCT evidence: one MA including 23 RCTs)

- other measures of adiposity (any evidence) including waist circumference: one MA including 10 RCTs and one MA including 3 PCS (highest versus lowest category of intake), abdominal obesity: one MA including 4 PCS (highest versus lowest category of intake), waist-to-hip ratio: one MA including 3 RCTs, fat mass (kg): one MA including 6 RCTs, fat mass (percentage): one MA including 10 RCTs or lean mass (kg): one MA including 6 RCTs.

Table 1b: summary of evidence in the SR with MA for type 2 diabetes and markers in adults

Specific health outcome	Evidence type (number of studies in MA)	Author reported direction of association	Favoured exposure	SR reported adjustments for confounders in PCS	Author graded certainty of the evidence
Type 2 diabetes	PCS (13) – beverages	Increased risk	Favours not consuming NSS	All studies adjusted for smoking, 11 adjusted for BMI, 9 adjusted for age and/or total energy, 7 adjusted for alcohol consumption, “disease risk”, “sugars/SSBs” and/or “other diet”, 5 adjusted for sex and 4 adjusted for “other fat”.	Low
Type 2 diabetes	PCS (2) – tabletop	Increased risk	Favours not consuming NSS	Both studies adjusted for smoking, BMI, “sugars/SSBs” and “other diet”. One of the studies adjusted for age, sex, alcohol, “other fat”, “disease risk” or total energy.	Low
High fasting glucose	PCS (3)	Increased risk	Favours not consuming NSS	All 3 PCS adjusted for age, sex, smoking and BMI. Two PCS adjusted for total energy and/or “other diet”. One PCS adjusted for “other fat” or “disease risk” and no PCS adjusted for alcohol or “sugars/SSBs”.	Low

No significant associations were observed for other type 2 diabetes markers (any evidence) including fasting glucose (mmol per L): one MA including 16 RCTs, fasting insulin (pmol per L): one MA including 10 RCTs, percentage HbA1c: one MA including 6 RCTs or HOMA-IR one MA including 11 RCTs.

Table 1c: summary of evidence in SR with MA for CVD in adults

Specific health outcome	Evidence type (number of studies in MA)	Author reported direction of association	Favoured exposure	SR reported adjustments for confounders in PCS	Author graded certainty of the evidence
CVD mortality	PCS (4)	Increased risk	Favours not consuming NSS	All 4 PCS adjusted for alcohol, smoking, BMI, total energy and “other diet”. Three PCS adjusted for age, disease risk and/or “sugars/SSBs”. Two PCS adjusted for sex and no PCS adjusted for “other fat”.	Low
CVD events	PCS (3)	Increased risk	Favours not consuming NSS	All 3 PCS adjusted for age, alcohol, smoking, BMI, “disease risk”, total energy, “sugars/SSBs” and “other diet”. Two PCS adjusted for sex and none adjusted for “other fat”.	Low
Stroke	PCS (5)	Increased risk	Favours not consuming NSS	Four PCS adjusted for alcohol, smoking and “other diet”. Three PCS adjusted for age, sex, BMI, “disease risk” and total energy. Two PCS adjusted for “sugars/SSBs”, and one PCS adjusted for “other fat”.	Low
Hypertension	PCS (4)	Increased risk	Favours not consuming NSS	Four PCS adjusted for age, smoking and BMI. Three PCS adjusted for sex, total energy and “other diet”. Two PCS adjusted for “other fat” and “disease risk” and one PCS adjusted for alcohol and “sugars/SSBs”.	Low

Specific health outcome	Evidence type (number of studies in MA)	Author reported direction of association	Favoured exposure	SR reported adjustments for confounders in PCS	Author graded certainty of the evidence
Total cholesterol:HDL cholesterol	RCT (4)	Increased risk	Favours not consuming NSS	Not applicable	Moderate

No significant associations were observed for other CVD-related outcomes including coronary heart disease: one MA including 4 PCS, systolic blood pressure: one MA including 14 RCTs, diastolic blood pressure: one MA including 13 RCTs, total cholesterol: one MA including 14 RCTs, and blood lipids HDL cholesterol: one MA including 13 RCTs, LDL cholesterol: one MA including 12 RCTs, low HDL cholesterol: one MA including 4 PCS, TAG: one MA including 14 RCTs and high TAG: one MA including 4 PCS.

Table 2: summary of evidence in the SR with MA for subgroup analysis of effect of NSS intake on body weight (kg) and BMI from trials with explicit replacement of sugars with NSS in adults

Adding NSS to the diet compared with “sugars” (either NSS replacing “sugars”, or both NSS and “sugars” being added to the diet, in separate arms of a trial).

Abbreviations used in the table: kg: kilogram, MA: meta-analysis, NSS: non-sugar sweetener, RCT: randomised controlled trial, SR: systematic review, SSB: sugars-sweetened beverage.

Overall health outcome	Specific health outcome	Evidence type (number of studies in MA)	Author reported direction of association	Favoured exposure	Author graded certainty of the evidence
Adiposity	Body weight (kg)	RCT (19)	Decreased risk	Favours consuming NSS	Not graded
Adiposity	BMI	RCT (16)	Decreased risk	Favours consuming NSS	Not graded

When limited to studies giving explicit instructions to habitual consumers of SSBs and “sugars” containing foods to replace these with NSS alternatives, the effect on body weight became non-significant and the effect on BMI was no longer observed.

NSS compared with nothing (placebo) or water showed no effect on body weight or BMI (observed changes likely mediated by the reduction in energy intake seen when NSS compared to “sugars”).

4.13 Summary tables of evidence from the SR with MA for adiposity and dental caries in children

Tables 3a and 3b summarise the evidence in the SR with MA for adiposity and dental caries in children for statistically significant associations only. Non-significant associations are noted at the bottom of each table.

For detail on the comparators used in each study see annex 3.

Abbreviations used in the tables: BMI: body mass index, MA: meta-analysis, NSS: non-sugar sweetener, PCS: prospective cohort study, RCT: randomised controlled trial, SR: systematic review, SSB: sugars-sweetened beverage

Table 3a: summary of evidence in the SR with MA for adiposity in children

Specific health outcome	Evidence type (number of studies in MA)	Author reported direction of association	Favoured exposure	Author graded certainty of the evidence
Body weight (kg)	RCT (1)	Decreased risk	Favours consuming NSS	Moderate
Waist circumference	RCT (1)	Decreased risk	Favours consuming NSS	Moderate
Body fat mass (kg)	RCT (1)	Decreased risk	Favours consuming NSS	Moderate
Body fat mass (percentage)	RCT (1)	Decreased risk	Favours consuming NSS	Moderate

No significant associations were reported for:

- body weight (kg) (PCS evidence: one MA including 2 PCS)
- body fat mass (kg) (PCS evidence: one study)
- body fat mass (percentage) (PCS evidence: one MA including 2 PCS)
- other adiposity measures including BMI: one MA including 5 PCS (continuous consumption) and one MA including 2 PCS (highest versus lowest category of intake), BMI z-score: one MA including 2 RCTs, one MA including 3 PCS (continuous consumption) and one MA including 1 PCS (highest versus lowest category of intake) or overweight: one MA including 2 PCS

Table 3b: summary of evidence in SR with MA dental caries in children

Specific health outcome	Evidence type (number of studies in MA)	Author reported direction of association	Favoured exposure	SR reported adjustments for confounders in PCS	Author graded certainty of the evidence
Dental caries	RCT (2). studies not considered relevant to review	Not applicable	Not applicable	Not applicable	Low
Dental caries	PCS (1)	Decreased risk	Favours consuming NSS	This PCS adjusted for age at dental examination, sex, fluoride exposure and dietary variables significant at $p < 0.10$ in univariate analysis (covariates adjusted for in most adjusted model).	Very low

4.14 Summary table of evidence from the SR with MA for adiposity and type 2 diabetes in pregnant women

Table 4 summarises the evidence in the SR with MA for adiposity and type 2 diabetes in pregnant women for statistically significant associations only. Non-significant associations are noted at the bottom of each table. For detail on the comparators used in each study see annex 3.

Abbreviations used in the table: ASB: artificially-sweetened beverage, BMI: body mass index, NA: not applicable, NSS: non-sugar sweetener, PCS: prospective cohort study, SR: systematic review, SSB: sugars-sweetened beverage.

Table 4: summary of evidence in the SR for adiposity and type 2 diabetes in pregnant women and offspring adiposity measures

Health outcome	Evidence type (number of studies)	Author reported direction of association compared to control	Favoured exposure	SR reported adjustments for confounders in PCS	Author graded certainty of the evidence
Gestational weight gain	RCT (1)	Increased risk	Favours not consuming NSS	Not applicable	Not graded
Gestational weight gain	PCS (1)	Increased risk	Favours not consuming NSS	This PCS adjusted for maternal pre-pregnancy BMI, age, parity, smoking during pregnancy, educational level, total gestational length and offspring sex (all covariates adjusted for in most adjusted model).	Not graded
Birthweight (including large-for-gestational age)	PCS (1)	Increased risk	Favours not consuming NSS	This PCS adjusted for energy intake, maternal BMI, maternal age, smoking, alcohol, education level, urbanisation level, parity, sex of newborn, ethnicity and intake of other 21 food groups (all covariates adjusted for in most adjusted model).	Very low

Health outcome	Evidence type (number of studies)	Author reported direction of association compared to control	Favoured exposure	SR reported adjustments for confounders in PCS	Author graded certainty of the evidence
Offspring adiposity	PCS (1)	Increased risk	Favours not consuming NSS	This PCS adjusted for maternal total energy intake, Healthy Eating Index score, maternal postsecondary education, maternal smoking and diabetes during pregnancy, breastfeeding duration, infant sex, introduction of solid foods before 4 months and SSB intake (all covariates adjusted for in most adjusted model).	Very low
Offspring adiposity	PCS (1)	Increased risk	Favours not consuming NSS	This PCS adjusted for maternal: pre-pregnancy BMI, age, socioeconomic status, smoking during pregnancy, intakes of total energy, desserts and sweets, fats (oil, margarine and butter), potato, processed meat, refined grains, whole grains and SSBs during pregnancy, and physical activity during pregnancy. In offspring adjustments were made for: sex, breastfeeding duration, consumption of ASBs and SSBs at 7 years (only for outcomes at 7 years), physical activity at 7 years (only for outcomes at 7 years) (all covariates adjusted for in the most adjusted model).	Very low

No significant associations were reported for:

- gestational weight gain (PCS evidence: one study)
- birth weight (including large-for-gestational age) (PCS evidence: 2 studies)
- offspring adiposity (PCS evidence: one study)

4.15 Limitations of the evidence within the systematic review

The WHO guideline acknowledges limitations in the design of the primary studies (RCTs and observational studies) included in the Rios-Leyvraz and Montez (2022) SR. Limitations of the SR identified by the authors were:

> "[the] inability to meta-analyse a significant portion of the data, particularly outcomes measured predominantly in subjective terms."
>
> "In addition, because a head-to-head comparison of NSS versus water as replacement for SSB was not prioritized … [it was not possible] …to fully account for the effects of water compared with NSS-sweetened beverages as a replacement for SSBs – that is, the literature search strategy was not designed to identify studies that exclusively assessed water as a replacement, without NSS as a comparator."

It is therefore not possible to assess whether there is any negative effect of NSS compared with water.

> "[the limited] ability to assess potentially differential health effects of individual sweeteners, and while very few of the cohort studies provided detail on specific sweeteners as exposures, it is likely that in most studies, especially those with many years of follow-up, NSS consumed were primarily those that have been on the market for many years, and that newer sweeteners were less well represented."
>
> "because so many different interventions and experimental designs were employed to assess the effects of NSS intake in the included RCTs, it was difficult to relate the pooled effects to the primary interest of NSS as a replacement for sugars in the context of body weight."
>
> "although a small number of studies specifically assessed the effects on habitual users of sugar-sweetened foods and beverages of replacing these foods and beverages with NSS-sweetened alternatives, most trials provided NSS or sugars as an addition to the diet, others provided nothing or water as the comparator, still others provided NSS in capsule form, and a small number assessed the inclusion of NSS in the context of a calorie restricted diet. In addition, two trials assessed the effects of asking habitual users of NSS-sweetened beverages to switch to water. As a result, the majority of the available evidence for effects of NSS used as a replacement for sugars on measures of adiposity is indirect."

Evidence for effects of regularly consuming NSS and “sugars” together is very limited, and further research is needed.

The results for pregnant women require further scrutiny. Although the authors state that the results:

> “are in line with a recent study that provided supporting mechanistic data from animal and in vitro studies regarding a possible association between NSS intake during pregnancy and childhood adiposity (Azad and others, 2020).”

In addition, SACN identified the following limitations.

Studies included in the SR were conducted over the last 50 years and cover a range of countries with likely varying intakes of NSS, potentially limiting the applicability of the conclusions of the WHO guideline to current UK levels of consumption.

Most intervention studies tested NSS-containing drinks. There may be differences in the mechanism of action for NSS in drinks compared to foods or as a tabletop additive meaning that NSS-containing drinks may be poorly satiating compared to NSS-containing foods.

SACN notes that there are 11 NSS approved for use in Europe that provide no calories or are low in calories, however only 5 were specified in the SR. Different NSS may have different effects on health, so it would be helpful to be able to differentiate the health effects of individual NSS.

The majority of RCTs assessing the impact of NSS on weight were 3 months or less and are unable to assess the long-term impact. The SR did not perform subgroup analyses by study duration to confirm the lack of effect in longer-term trials.

The rationale for grading of some outcomes, but not others, was unclear.

WHO notes that observational studies such as PCS are prone to risk of reverse causality and confounding. SACN notes that consumption of some products containing NSS, particularly some brands of “diet” or “zero” drinks, may be associated with particular dietary patterns leading to additional residual confounding. In addition, many of the PCS were conducted in the 1980s and 1990s at which time NSS-containing foods and drinks may have been marketed as “diet” foods and drinks, or foods and drinks to aid weight loss. Consumers of NSS in the 1980s may be different to current consumers of NSS.

The authors of the SR note the adjustments made by cohort studies for key confounders or covariates. SACN has not carried out an assessment of potential confounders or covariates, or adjustments made in primary studies, but noted inconsistency in adjustment

between studies for key covariates such as socioeconomic status. There may therefore be residual confounding and the variation in adjustments across primary studies that impacts on the collation of the findings.

None of the research identified by the SR stated the amount of NSS consumed. There is a lack of data on the quantity of NSS present within foods and drinks. Reporting of NSS consumption within studies is therefore likely to be unreliable making it difficult to estimate any dose response associations of effects.

There is a gap in the evidence from PCS in relation to changes in NSS consumption or trends of total energy and free sugars intake.

A range of exposures and outcomes were assessed making it difficult to draw conclusions.

The decisions made by review authors in applying GRADE may have differed to SACN's assessment. For example, SACN has previously recommended use of $I^2 \geq 75\%$ to indicate possible high heterogeneity whereas the review's authors use $I^2 \geq 50\%$.

An additional limitation is that it was not possible within the timeframe of the position statement for SACN to consider all health outcomes evaluated in the Rios-Leyvraz and Montez (2022) SR with MA and considered by WHO. As stated above, SACN focused on health outcomes of policy relevance to the UK in relation to free sugars reduction, energy reduction resulting weight loss and potential prevention of dental caries through reduced free sugars intake.

5. Commentary

As noted above, the purpose of this statement is to consider whether NSS are effective for reducing overweight and obesity, preventing weight-related NCDs and promoting dental health within a UK context. This position statement does not consider the impact of NSS on all NCDs.

5.1 Interpretation of WHO guideline conclusions

The Rios-Leyvraz and Montez (2022) SR with MA reported on findings from RCTs and PCS on the associations of NSS with adiposity and NCD outcomes.

The SR reports conflicting evidence on the impact of NSS based on the type of evidence assessed. RCT data were available for adiposity outcomes whereas NCD outcomes were largely only considered by PCS. The RCT data indicated that NSS may result in a small reduction in body weight based on low certainty evidence. The PCS data indicated that

NSS may be associated with a broad range of adverse health outcomes based on low to very low certainty evidence.

The SR reports that NSS used in place of “sugars” results in a small reduction in body weight (0.71kg) and BMI in adults, as assessed in RCTs (low certainty evidence), likely mediated by a reduction in energy intake. WHO considered that the shorter-term RCTs (the majority were 3 months or less) included in the SR were of insufficient duration to be able to determine the impact on weight loss. SACN notes that one RCT lasted longer than 2 years and reported a greater reduction in body weight (5.1kg). In addition, the sensitivity analysis found that the association remained when studies of less than 8 weeks were excluded.

A subgroup analysis within the SR suggests that adding NSS to the diet compared with “sugars” (either NSS replacing “sugars” or adding either NSS or “sugars” to the diet) reduces body weight. When studies were limited to those that gave explicit instructions to habitual consumers of SSBs and foods containing sugars to replace these with NSS alternatives, the effect on body weight became non-significant and the effect on BMI was no longer observed. NSS compared with nothing (placebo) or water showed no effect on body weight or BMI.

The SR reported that PCS evidence showed the opposite direction of association, and higher NSS intake was associated with higher measures of body fatness in adults and children (low to very low certainty evidence).

There was limited RCT evidence in relation to NCD outcomes. In adults, RCT evidence indicated that NSS increased the ratio of total to HDL cholesterol by 0.09, based on moderate certainty evidence. SACN notes caution in relation to this result for a number of reasons including limitations of a small cross-over trial that may be driving this result in the MA. In addition, HDL cholesterol may fall during a period of weight loss and rise again when weight loss stabilises, so it is not clear whether this result may be reflecting such changes (Dattilo and Kris-Etherton, 1992). The SR also reported that PCS evidence in adults indicated higher NSS intake was associated with increased risk of type 2 diabetes, CVD and mortality in adults (low to very low certainty evidence). No significant associations were observed for other CVD measures or markers including coronary heart disease, systolic blood pressure, diastolic blood pressure, total cholesterol, and blood lipids HDL cholesterol, LDL cholesterol, low HDL cholesterol, TAG and high TAG.

The SR also reported limited and mixed data on the impact of NSS on dental caries (low and very low certainty evidence).

5.2 Reverse causality

Observational studies such as PCS are at high risk of reverse causality and confounding, which are likely to have contributed to the differences between observational and trial evidence on the impact of NSS use or intake on measures of adiposity and other weight-related NCDs. People who select or report use of NSS may have chosen them for reasons related to their health or weight. Notably people living with overweight or obesity leading to an observed association between NSS consumption and body weight where weight gain has caused increased consumption of NSS rather than the other way around. The consumption of NSS-containing foods may also be indicative of other differences in dietary patterns and behaviours and risk of weight-related NCDs. This may be particularly relevant when considering the PCS evidence from studies conducted in the 1980s and 1990s. At this time NSS-containing foods and drinks may have been marketed as “diet” products or foods and drinks to aid weight loss.

Authors of the SR discussed the issue of reverse causation, but only as a “possible explanatory factor for the observed associations in cohort studies”. Authors of the SR note the adjustments made by cohort studies to reduce the potential for reverse causation: “they undertook extensive adjustments for potential confounders and robust sensitivity analyses to test the impact of removing data that might contribute to reverse causation”.

SACN welcomes the detailed list of confounders or covariates adjusted for in PCS included in the SR. However, the SR authors do not fully acknowledge the possibility of residual and unmeasured confounding that could not be accounted for. The included PCS inconsistently adjusted for key covariates (including age, sex, ethnicity, socioeconomic status, total energy intake, sugars intake, smoking, alcohol consumption and “disease risk”) and other aspects of dietary patterns and lifestyle, which increase the likelihood of residual confounding.

In addition, adjusting for BMI at baseline is unlikely to fully adjust for confounding where NSS use is a marker of dietary concern or restraint (Appleton and Conner, 2001; Lowe and others, 2013; Lowe, 2015; Neumann and others, 2018), as habitual consumers of NSS may be a healthier weight at baseline, and may be at a higher risk of future weight gain than non-consumers of NSS.

Using alternative methodologies, such as change and substitution analysis may better address the issues of confounding in PCS and meta-analyses may reach different conclusions (Lee and others, 2022).

5.3 Discrepancy in findings between prospective cohort studies and randomised controlled trials

SR authors suggest a further explanation for the discrepancy between RCT and PCS findings in relation to adiposity outcomes which "may be found in likely differences in how NSS were consumed between the experimental settings of RCTs and in free-living populations as assessed in prospective cohort studies". In most of the RCTs included in this review, NSS were consumed as an alternative to free sugars, and, in many, NSS were provided directly as a stand-alone item (mostly drinks) for study participants to consume. Although it is not known how the NSS in every trial were actually consumed, given the design of many of the trials, it is reasonable to assume that the NSS were generally treated as an experimental food or drink to be consumed, likely on its own, and in many cases specifically as a replacement for free sugars. In addition, it may be that the inclusion criteria for a trial which replaces SSBs with NSS-sweetened drinks include some level of baseline consumption of SSBs, leading to limited generalisability of study findings.

In contrast, real-world consumption of NSS as assessed in cohort studies is more complex and could follow a variety of patterns. It could include conscious, specific replacement of free sugars resulting in a higher quality diet overall (Gibson and others, 2016). Or intake could arise from consumption of prepared composite foods without specific concern for whether or not they are replacing free sugars, or have low or no calories, and this could result in NSS consumers having a poorer quality diet overall (Sylvetsky and others, 2024). SACN notes that NSS consumption may also be an indication of a greater preference for sweet taste in NSS consumers compared to those who do not consume NSS. NSS consumption could also be used as a justification for consuming other sugary or less healthy foods, that is people who have consumed a food or drink with NSS might feel that it is acceptable to then consume sugar-containing (or otherwise less healthy) foods or drinks (Mosdøl and others, 2018), known as a licencing effect.

SACN notes that RCTs and PCS are designed to answer different questions. The RCTs and PCS included in the SR differed by comparators and therefore the nature of the question tested. RCTs tested the effect of NSS compared with any type of sugar, placebo, plain water or no intervention. Only 4 RCTs specifically replaced SSBs with NSS alternatives. By contrast, PCS assessed the influence of higher versus lower NSS intakes.

As a plausible mechanism for the RCT findings, the SR authors stated that:

> "evidence suggests that the body does not sense calories from SSBs in the same manner as those in solid foods, in terms of satiety (Pan and Hu, 2011) – as a result, they are not compensated for by a reduction in energy intake in the rest of the diet, thus leading to positive energy balance. Because most of the studies included in the review that compared NSS with sugars did so by providing NSS-sweetened drinks or SSBs as a supplement to the existing

> diet, it is likely that those receiving the SSBs did not fully compensate for the extra calories from the added sugars, whereas those receiving NSS-sweetened drinks were not consuming these extra calories."

It may be therefore, that the impact of NSS on adiposity outcomes is influenced by whether an RCT is designed using NSS-containing drinks or foods.

Another discrepancy in the findings was on the subgroup analysis. The subgroup analysis found the effect on adiposity was no longer observed when RCTs were limited to those that gave explicit instructions to habitual consumers of SSBs and foods containing sugars to replace these with NSS alternatives. SACN notes that it is not known whether the findings of the subgroup analysis are due to differences in comparing the 2 types of interventions. The supplemental intervention introduced new drinks on top of usual diet and the behavioural intervention asked study participants to replace what they usually consume. The behavioural intervention may or may not have resulted in dietary change, whereas the supplemental intervention did seem to result in dietary change.

SACN notes the importance of blinding in RCTs of NSS. SR authors note the inconsistency and difficulty in blinding within these RCTs. Less than a quarter of RCTs assessing body weight reported adequate allocation concealment, blinding was either reported as not possible or was unclear in most cases.

5.4 Relative weight placed on prospective cohort studies and randomized controlled trials

In reaching its conclusion that NSS should not be used as a means of achieving weight control or reducing the risk of NCDs, WHO placed greater weight on evidence from observational data over RCT data. The WHO guideline states that:

> "the discordant results between the RCTs and PCS 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… 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 RCTs, without additional evidence of long-term impact, does not represent a health benefit."

SACN notes that there may be a health benefit from short-term weight loss even if there is subsequent weight gain (NICE, 2025; Hartmann-Boyce and others, 2023).

There does not seem to be any indication that WHO or the (Rios-Leyvraz and Montez, 2022) SR planned to place greater weight on PCS data at the outset (see Toews and others (2019) SR protocol).

SACN noted that one trial included in the SR was longer than 2 years. It was an RCT of 163 women aged 43 to 55 years, all participants followed a weight loss program, participants in the aspartame arm were given aspartame-sweetened foods and tabletop NSS. The participants in the no-aspartame arm were told to avoid products sweetened with any low energy NSS. It reported that higher consumption of NSS was associated with a 5.11kg reduction in body weight. The findings are consistent with shorter-term trials (and indicated a stronger effect size as the pooled reduction in body weight from RCTs was 0.71kg), suggesting that weight loss due to NSS use may be sustained over the long-term.

5.5 Methods of evidence evaluation

SACN notes the differences between methods adopted in the SR with MA that underpinned the WHO guideline compared to the SACN Framework for the evaluation of evidence (SACN, 2024).

Notably SACN gives greater weight to good quality RCTs where available because these minimise the potential for selection bias and confounding and facilitate assignment of a causal interpretation. Randomisation is particularly important when looking at weight outcomes given that NSS use is potentially confounded by weight and associations with diet. In this case SACN would give greater weight to the evidence from RCTs, that used NSS in place of free sugars which resulted in a small reduction in body weight and BMI in adults. Although SACN notes that the effect size is small and limited by the length of the trials (most were 3 months or less). In SACN's report on Lower carbohydrate diets for adults with type 2 diabetes (SACN, 2021), trials were considered by study length, and outcomes were assessed in the shorter term (greater than or equal to 3 to 6 months) and longer term (greater than or equal to 12 months). It may have been helpful to take a similar approach in this SR.

With specific reference to the application of the GRADE approach for assessing the certainty of the evidence, SACN notes that the interpretation of factors that can reduce the quality of the evidence and reasons for downgrading (such as drop-out rate, inconsistency and heterogeneity) requires expert judgement. SACN may have used different criteria when establishing a critical or significant level, that could result in up or downgrading. For example, WHO consider $I^2 \geq 50\%$ indicates a significant level of heterogeneity, whereas SACN may consider $I^2 \geq 75\%$ as a significant level. WHO may therefore have downgraded some evidence where SACN may not have.

5.6 Measures of adiposity

There is evidence from longer and shorter-term RCTs to suggest NSS consumption can reduce free sugars and energy intake and therefore prevent weight gain.

There is observational evidence suggesting that NSS may increase weight gain in free living individuals (that is when not taking part in a trial). Given the potential for residual confounding and reverse causality within PCS, SACN conclude that the limited evidence from PCS of NSS and weight gain in the longer-term should be treated with caution.

PCS evidence may provide an insight into how individuals use foods and drinks containing NSS in a real life setting and the impact of the wider environment. RCT's that add a supplementary food or drink to the diet may not be reflective of real-life behaviours. This potentially explains the reason why an effect on weight gain was not seen when RCTs were limited to those that gave explicit instructions to participants to use NSS containing foods and drinks as replacements, rather than when supplementing the diet. That is, people might not find it easy to follow instructions to change their diet, whereas providing supplemental foods can overcome these barriers to dietary change.

5.7 Noncommunicable diseases

The SR identified concerning evidence indicating that NSS may increase NCD risk. Notable associations were observed with total cholesterol:HDL cholesterol ratio from RCTs and for type 2 diabetes and CVD from PCS. However, there is also evidence reporting null effects for outcomes considered through both RCT and PCS. The majority of evidence for NCDs is from PCS. SACN notes the limited RCT evidence in relation to NCDs and the potential for residual confounding and reverse causality within PCS. SACN concludes that while the evidence on NCDs is concerning it should be treated with caution.

5.8 Dental caries

SACN notes the lack of robust evidence on NSS and dental health. Studies reporting the impact of NSS on dental caries were limited and heterogeneous. The only RCT in adults was too short (at 6 months) to identify an impact on dental caries and no PCS were identified in adults. The RCTs in children were limited or not considered relevant to this assessment. One of the RCTs in children lasted only 6 weeks and did not measure dental caries, but instead modelled the risk of dental caries based on presence of bacteria. The other RCT in children investigated the impact of oral hygiene practices, as opposed to the use of NSS in the diet, SACN does not consider this RCT is relevant. The only PCS in children reported "low" intakes of NSS-sweetened drinks were associated with fewer teeth surfaces having caries compared with no intake. Effects of "high" intakes of NSS-sweetened drinks were not reported.

SACN notes that the use of NSS in food and drink may support lowering the intake of free sugars and thereby dental caries. However, drinks which contain acids (for example phosphoric, citric, carbonic) whether they contain free sugars or NSS may increase the risk of dental erosion (Royal College of Surgeons of England, 2021; Inchingolo and others, 2023). This includes sugars-sweetened and sugar-free carbonated soft drinks, cordials, fruit juices, fruit teas and alcoholic drinks. Plain carbonated water has been shown to be minimally erosive (Sang-Kyeom and others, 2015; Reddy and others, 2016; O'Toole and Mullan, 2018; Ryu and others, 2018).

5.9 Data on non-sugar sweetener intakes

RCTs and PCS did not report the amount of NSS consumed. In the UK, manufacturers are obliged to list NSS in the ingredients of pre-packaged food and drink, but not the amount of NSS. Food composition data underpinning the NDNS therefore do not typically include information on the presence of NSS, or their amount in food and drinks, creating challenges in monitoring consumption of NSS. This raises difficulties in reliably estimating a person's consumption of NSS without a laboratory analysis of their diet or appropriate biomarkers. Reporting of NSS within PCS is therefore likely to be limited and studies likely made assumptions about the NSS content of foods and drinks without data on the NSS content of products from manufacturers.

A number of publications suggest the potential for improved monitoring of exposure to NSS through analysis of urinary biomarkers (Myers and others, 2018; Logue and others, 2020; Shi and others, 2022; Diepeveen-de Bruin and others, 2023) and use in validation of methods to collect NSS intake (Buso and others, 2024). Given the difficulties in monitoring NSS and limitations identified in the research to date, SACN very much welcomes further development of these new methods.

6. Conclusions

6.1 Introduction

SACN would like to thank WHO for their thorough review of the evidence and for highlighting this important issue through their guideline.

The WHO guideline was underpinned by a SR with MA by Rios-Leyvras and Montez (2022), which evaluated RCT, PCS and other observational data that tested a range of different questions in relation to NSS use. Only RCT and PCS data were relevant to SACN's consideration of NSS.

SACN has not graded or repeated work undertaken by Rios-Leyvras and Montez (2022). SACN notes the differences between methods described by Rios-Leyvras and Montez (2022) and those used by SACN, as outlined in SACN's Framework for the evaluation of evidence (SACN, 2024). Notably, SACN gives greater weight to RCTs of adequate quality and duration and less weight to PCS evidence, where available because quality RCTs minimise the potential for selection bias and confounding and facilitate assignment of a causal interpretation. WHO gave greater weight to PCS evidence over RCT evidence in reaching conclusions for this guideline. SACN may therefore have drawn different conclusions regarding the certainty of some of the evidence.

SACN notes that WHO issued a conditional recommendation (that NSS should not be used as a means of achieving weight control or reducing risk of NCDs) due to uncertainties of the evidence. WHO states that for conditional recommendations, it "is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very small".

6.2 Measures of adiposity

SACN conclude that evidence from shorter (the majority of trials were 3 months or less) and longer term (one trial was longer than 2 years) RCTs consistently suggest NSS, compared with free sugars, reduce energy intake and therefore body weight, although WHO assess this as low certainty evidence.

The opposite association was found between NSS and measures of body fatness in PCS. Given concerns about potential for confounding and reverse causality in PCS, SACN would give less weight to this evidence. However, SACN notes the potential for PCS evidence to provide an insight into how individuals use foods and drinks containing NSS in a real-life setting and the impact of the wider environment.

There remain significant concerns regarding continued high rates of overweight and obesity in the UK. Free sugars are known to contribute to excess energy intake for which SACN has already made strong recommendations. UK public health policies on overweight and obesity have reduced free sugars in soft drinks and some other products. The resulting reduction in intakes of free sugars may have increased NSS consumption. It remains unclear whether NSS play a useful role in supporting a long-term move to a diet lower in free sugars.

Further research is needed to understand whether there are public health advantages to a gradual reduction in the overall sweetness of the diet. A process of gradual reduction of salt content in processed foods has been successful in reducing population salt intakes (He and others, 2014).

6.3 Weight-related noncommunicable diseases

WHO have raised concerns regarding the risks of NCDs – such as type 2 diabetes and CVD - associated in PCS with consuming NSS. SACN shares these concerns given the range of studies observing such associations. However, reliance on observational data and limited data from RCTs prevents the drawing of robust conclusions. SACN would welcome further, more robust, long-term evidence, particularly from RCTs to explore any association and the possible underlying mechanisms.

6.4 Dental caries

The evidence on the impact of consuming NSS on dental health is poor and more high-quality research of adequate duration (greater than 2 years) is needed to determine long-term impact. Given the current low and very low certainty evidence, SACN determines that it is difficult to draw conclusions regarding NSS and dental health from this review.

SACN concluded in its report on Carbohydrates and Health (SACN, 2015) that if people consume less free sugars they would lower the risks of tooth decay. Replacement with NSS is not essential to reducing free sugars intake, although it may be a useful option for some people.

The authorised EU (and UK) Article 13.1 health claim states that consumption of food and drinks with “sugar replacers”, (which includes NSS) in place of (other) sugars “contributes to the maintenance of tooth mineralisation” (EFSA, 2011). However, soft drinks which contain acids (for example phosphoric, citric, carbonic) (whether sweetened with free sugars or NSS) may also increase the risk of dental erosion.

6.5 Dietary recommendations

Most people in the UK consume excess free sugars which increases the risk of excess weight gain, thus increases the risk of diseases including some cancers, heart disease and type 2 diabetes. Excess consumption of free sugars also increases the risk of dental caries. SACN and WHO agree that a reduction in consumption of free sugars, alongside other positive changes to diet, is likely to be beneficial to health overall. The risk management decision on how to achieve a reduction in intake of free sugars, in the context of risk assessment advice on alternatives to free sugars, is outside of SACN’s remit and is for policy makers.

In relation to the use of NSS as a means to reduce free sugars intake, SACN concludes that the evidence indicates that there may be some value in using NSS to help reduce weight gain in the short to medium term, but it is not essential and is not the only option.

The impact of the acidity of soft drinks on dental health (whether sweetened with free sugars or NSS) is a concern.

The UK population on average consumes too many calories and current intakes do not meet recommendations for saturated fat, salt, free sugars, fibre and fruit and vegetables. Diets high in calories, saturated fat, salt, free sugars, processed meat and low in fibre and fruit and vegetables are associated with an increased risk of obesity and chronic diseases such as heart disease, type 2 diabetes and some cancers. SACN reiterates the importance of following UK government advice on a healthier diet, based on SACN's recommendations, which is encapsulated in the UK's national food guide, the Eatwell Guide.

SACN notes its previously stated concerns about the gap in data on UK population exposure to NSS. An assessment of NSS intakes has not been undertaken in the UK since an FSA survey was carried out in young children in 2003 (FSA, 2003).

There is currently insufficient evidence to carry out a full risk assessment of the evidence on NSS and health. Once better evidence is available, as outlined in the recommendations below, it would be helpful to consider the totality of evidence and carry out a full benefit-risk assessment.

7. Recommendations

The following recommendations are made in the context of existing UK government dietary recommendations. These recommendations should be read alongside SACN's 2025 evidence update on processed foods and health. SACN's recommendations on NSS are precautionary. This is because evidence on NSS and health outcomes is inconsistent.

SACN reiterates its recommendation that average population intake of free sugars should not exceed 5% of energy.

SACN recommends that intake of NSS be minimised.

For younger children, SACN recommends:

- not giving them drinks sweetened with sugar or NSS
- giving them unsweetened food (not sweetened with either sugar or NSS)

For older children and adults, SACN recommends:

- swapping sugars for NSS may help reduce sugar intake from foods and drinks (and so reduce energy intake), at least in the short term - the long-term goal is to limit both sugar and NSS intake

It is recommended that government:

- monitors the NSS content of food and drinks in the UK diet and their consumption, including trends, particularly among high consuming and vulnerable groups
- evaluates the impact of policies to reduce energy and sugar intakes on intakes of NSS, particularly among high consuming and vulnerable groups
- compels industry to make publicly available data on the amounts of individual NSS within foods to enable monitoring and further research on associations with health outcomes

8. Research recommendations

A number of limitations in the available evidence on NSS and health were identified. Further research should consider:

- concerns relating to covariates, confounding and reverse causality for observed associations between NSS and health outcomes
- the most appropriate comparator to NSS (including importance of comparing to water)
- differential effects of different NSS
- differential effects of NSS in foods versus drinks and impacts on wider dietary intake
- length of intervention for studies considering anthropometric outcomes
- innovative ways to reliably monitor exposure to NSS through biomarkers measured by urinary analysis

Further research into the impact of NSS and health should give consideration to:

- vulnerable groups, including high consumers, young children and women who are pregnant or lactating
- further evidence on how people consume NSS including whether they displace free sugars (or other macronutrients) and whether this systematically varies across

different population groups to inform the design of RCTs and PCS (in terms of intervention, exposure and/or comparator)

- further evidence exploring relationships between NSS and health outcomes, including:
    - assessing the design, and quality of data within, existing good quality long-term RCTs to assess the impact of NSS on both anthropometric and all NCD outcomes
    - good quality up-to-date evidence from PCS reflecting current NSS consumption patterns that consistently addresses the weaknesses and uncertainties in existing studies by adjusting for relevant confounders
    - good quality longer-term RCTs and PCS that consider the impact of NSS on the development of dental caries and other oral health conditions including erosive tooth wear, periodontal disease and oral cancer, in relation to and secondary to, the effect of reducing free sugars intake
- understand whether there are any undesirable consequences of advising against use of NSS (for example, increased intake of free sugars)

9. Abbreviations

These are the abbreviations used in this report.

ADIs acceptable daily intakes

ARIC Atherosclerosis Risk in Communities Study

ASBs artificially sweetened beverages

AOAC Association of Analytical Chemists

ATBC Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study

BMI body mass index

CC case-control study

COT Committee on Toxicity of Chemicals in Food Consumer Products and the Environment

CVDs cardiovascular diseases

DBP diastolic blood pressure

DHSC Department of Health and Social Care

EFSA European Food Safety Authority

EU European Union

FSA Food Standards Agency

GRADE Grading of Recommendations Assessment, Development and Evaluation

HbA1c glycated haemoglobin

HDL high-density lipoprotein

HFSS high in saturated fat, salt or free sugars

HOMA-IR homeostatic model assessment of insulin resistance

HPFS Health Professionals Follow-up Study

HR hazard ratio

IQR interquartile range

IWHS Iowa Women's Health Study

LDL low-density lipoprotein

MA meta-analysis

MD mean difference

NCDs noncommunicable diseases

NDB Nutrient Databank

NDNS National Diet and Nutrition Survey

NHS Nurses' Health Study

NSS non-sugar sweeteners

OR odds ratio

OHID Office for Health Improvement and Disparities

PCS prospective cohort study

PHE Public Health England

RCTs randomised controlled trials

ROB risk of bias

ROBINS-I Risk of Bias in Nonrandomized Studies of Interventions

SACN Scientific Advisory Committee on Nutrition

SBP systolic blood pressure

SDIL Soft Drinks Industry Levy

SR systematic review

SSB sugars-sweetened beverages

TAG triacylglycerol

UPF ultra processed foods

WHO World Health Organization

WHS Women’s Health Study

10. SACN's role and membership

The role of SACN is to provide independent scientific advice on and risk assessments of nutrition and related health issues. It advises the 4 UK health departments, and other government departments and agencies.

Membership of SACN and the register of members' interests at the time of publication is provided in the 'SACN annual report 2024'. The SACN annual report and SACN's code of practice is available on the SACN webpage.

11. Suggested citation

The suggested citation is:

Scientific Advisory Committee on Nutrition. Position statement on the World Health Organization guideline on non-sugar sweeteners. 2025.

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Annex 1: conclusions of SACN's report on Carbohydrates and Health

The overall summary and conclusions of the SACN report Carbohydrates and Health (SACN, 2015) are included in chapter 12.

With specific reference to free sugars SACN concluded that:

> "prospective cohort studies indicate that higher consumption of sugars and sugars containing foods and beverages is associated with a greater risk of dental caries."
>
> "prospective cohort studies indicate that greater consumption of sugars-sweetened beverages is associated with increased risk of type 2 diabetes mellitus."
>
> "randomised controlled trials conducted in adults indicate that increasing or decreasing the percentage of total dietary energy as sugars when consuming an ad libitum diet leads to a corresponding increase or decrease in energy intake".
>
> "reduction in the percentage of dietary energy as sugars was achieved in these trials either through the substitution of other macronutrient components or by replacing sugars with non-caloric sweeteners."
>
> "randomised controlled trials conducted in children and adolescents indicate that consumption of sugars-sweetened beverages, as compared with non-calorically sweetened beverages, results in greater weight gain and increases in body mass index."
>
> "with the proposed reduction in the population intake of free sugars, their contribution to recommended total carbohydrate intake should be replaced by starches, sugars contained within the cellular structure of foods and, for those who consume dairy products, by lactose naturally present in milk and milk products. The complete replacement of energy derived from free sugars by these carbohydrate sources would only apply to those people who are a healthy body mass index (BMI) and in energy balance. In those who are overweight, the reduction of free sugars would be part of a strategy to decrease energy intake."
>
> "The definition for 'free sugars' be adopted in the UK and that this comprises all monosaccharides and disaccharides added to foods by the manufacturer, cook or consumer, plus sugars naturally present in honey, syrups and

unsweetened fruit juices. Under this definition, lactose naturally present in milk and milk products and sugars contained within the cellular structure of foods would be excluded."

"The population average intake of free sugars should not exceed 5% of total dietary energy for age groups from 2 years upwards."

"The consumption of sugars-sweetened beverages should be minimised, in both children and adults."

Annex 2: AMSTAR 2 assessment of Rios-Leyvraz and Montez (2022)

Domains	**Answer**
Did the research questions and inclusion criteria for the review include the components of PICO (population, intervention, comparison and outcome)?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? [note1]	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable
Did the review authors use a comprehensive literature search strategy? [note1]	Partial yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	No
Did the review authors provide a list of excluded studies and justify the exclusions? [note1]	Yes
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (ROB) in individual studies that were included in the review? [note1]	Partial yes
Did the review authors report on the sources of funding for the studies included in the review?	Yes

Domains	Answer
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? [note1]	Yes
If meta-analysis was performed, did the review authors assess the potential impact of ROB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for ROB in individual studies when interpreting or discussing the results of the review? [note1]	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? [note1]	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No
Rating	Moderate

Note 1: indicates 'critical' domains of AMSTAR 2.

Annex 3: study details of RCTs or PCS included in the position statement

See Rios-Leyvraz and Montez (2022) systematic review for study references. References given in table footnotes are those provided in the SR with MA by Rios-Leyvraz and Montez (2022).

Study details of RCTs included in the position statement

Tables 5a to 5d summarise study intervention (NSS), comparator, mode of NSS delivery and outcome evaluated in included RCTs that evaluated adiposity, type 2 diabetes, cardiovascular diseases or dental outcomes.

Table 5a: adults

Study	NSS	Mode of delivery	Comparators	Outcome
Al-Dujaili 2017	Stevia	Tabletop	Sugars	Adiposity, CVD (intermediate markers)
Angelopoulos 2015, 2016a, 2016b	Unspecified	Soft drink	Sugars, water	Adiposity [note 1], type 2 diabetes (intermediate marker [note 1]), CVD (intermediate markers [note 1])
Baird 2000	Sucralose	Water	Fructose	Adiposity [note 1], type 2 diabetes (intermediate marker [note 1]), CVD (intermediate markers [note 1])
Ballantyne 2011	Aspartame	Drink	Sucrose	Adiposity [note 1]

Study	NSS	Mode of delivery	Comparators	Outcome
Blackburn 1997	Aspartame	Drink, food, tabletop	Avoiding aspartame	Adiposity
Bonnet 2018	Aspartame, acesulfame K	Soft drink	Water	Adiposity, type 2 diabetes (intermediate marker and insulin sensitivity [note 1])
Bueno-Hernández 2020	Sucralose	Drink	Placebo	Adiposity, type 2 diabetes (intermediate marker and glucose and insulin area under the curve [note 1])
Campos 2015 [note 2]	Unspecified	Soft drink	Sugars	Adiposity, type 2 diabetes (intermediate marker [note 1]), CVD (intermediate markers)
Crutchley 2013	Unspecified	Soft drink	Sugars	Adiposity [note 1], type 2 diabetes (intermediate marker [note 1]), CVD (intermediate markers [note 1])
Dalenberg 2020 [note 3]	Sucralose	Soft drink	Sucrose	Type 2 diabetes (glucose and insulin area under the curve [note 1])
Ebbeling 2020 [note 4]	Unspecified	Soft drink	SSB, water	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)
Engel 2018 [note 5]	Aspartame	Soft drink	SSB, water, milk	Adiposity, type 2 diabetes (intermediate marker and insulin sensitivity [note 1]), CVD (intermediate markers)
Han 2018	Sucralose	Soft drink	D-allulose	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)
Higgins 2018	Aspartame	Drink, capsule	Placebo	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)

Study	NSS	Mode of delivery	Comparators	Outcome
Higgins 2019	Saccharin, aspartame, rebaudioside A, sucralose	Soft drink	Sucrose	Adiposity, type 2 diabetes (intermediate marker [note 1] and glucose and insulin incremental area under the curve [note 1]), CVD (intermediate markers [note 1])
Kanders 1988	Aspartame	Drink, food, tabletop	Avoiding aspartame	Adiposity
Kassi 2016	Stevia	Food	Sugar sweetened snack	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)
Kim 2011	Aspartame	Drink	Sugars, fructooligosaccharide	Adiposity [note 1], type 2 diabetes (intermediate marker [note 1]), CVD (intermediate markers [note 1])
Kim 2020	Acesulfame K and aspartame	Soft drink	Water	Adiposity, type 2 diabetes (intermediate marker)
Kreuch 2020	Acesulfame K and sucralose	Capsule	Placebo	Type 2 diabetes (glycaemic control [note 1])
Kuzma 2015	Aspartame	Drink	Glucose, fructose	Adiposity
Lee 2012	Aspartame	Drink	Sugars, fructooligosaccharide	Type 2 diabetes (intermediate marker)
Lertrit 2018	Sucralose	Capsule	Placebo	Adiposity, type 2 diabetes (intermediate marker and glucagon-like peptide-1 area under the curve [note 1])
Madjd 2018 [note 6]	Unspecified	Drink	Water	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)

Study	NSS	Mode of delivery	Comparators	Outcome
Markey 2016	Unspecified	Drink, food, capsule	Sugars	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)
McLay-Cooke 2016	Acesulfame K and aspartame	Soft drink	Sugar, maltodextrin	Adiposity, CVD (intermediate markers)
Njike 2011	Unspecified	Hot drink	Sugars	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)
Peters 2016 [note 7]	Unspecified	Soft drink	Water	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)
Tate 2012	Unspecified	Soft drink	Water	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)
Raben 2002 [note 8]	Unspecified	Drink, food	Sucrose	Adiposity
Raben 2011	Unspecified	Drink, food	Sucrose	Type 2 diabetes (intermediate marker and glucose incremental area under the curve [note 1]), CVD (intermediate markers)
Reid 2007	Aspartame	Soft drink	Sucrose	Adiposity
Reid 2010	Aspartame	Soft drink	Sucrose	Adiposity
Reid 2014	Aspartame	Soft drink	Sucrose	Adiposity
Romo-Romo 2018 [note 9]	Sucralose	Tabletop	No intervention	Adiposity, type 2 diabetes (intermediate marker)

Study	NSS	Mode of delivery	Comparators	Outcome
Sánchez-Delgado 2021	Sucralose, steviol glycosides	Drink, food	Sucrose	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)
Serrano 2021	Saccharin	Capsule	Placebo, lactisole, or saccharin with lactisole	Adiposity [note 1], type 2 diabetes (glucose area under the curve [note 1])
Stamataki 2020 [note 10]	Stevia	Tabletop	No intervention	Adiposity, type 2 diabetes (intermediate marker [note 1]), CVD (intermediate markers)
Vázquez-Durán 2016 [note 11]	Unspecified	Drink	Unsweetened beverages, SSBs and non-caloric sweetened beverages (no change)	Adiposity, CVD (intermediate markers)
Viveros-Watty 2021	Unspecified	Drink	Water	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers)
Warrington 2011	Advantame	Capsule	Placebo (cellulose)	Type 2 diabetes (intermediate marker), CVD (intermediate markers)

Table 5b: children

Study	NSS	Mode of delivery	Comparators	Outcome
Cocco 2019	Stevia	Food	Sugar	Dental caries
de Ruyter 2013	Sucralose + acesulfame K	Soft drink	Sucrose	Adiposity
Taljaard 2013	Sucralose	Drink	Sucrose	Adiposity

Study	NSS	Mode of delivery	Comparators	Outcome
Vandana 2017	Stevia	Mouth rinse	Placebo	Dental caries

Table 5c: mixed (adults and children)

Study	NSS	Mode of delivery	Comparators	Outcome
Knopp 1976	Aspartame	Capsule	Lactose	Adiposity [note 1], type 2 diabetes (fasting glucose [note 1]), CVD (systolic blood pressure [note 1], diastolic blood pressure [note 1], total cholesterol [note 1], triglycerides [note 1])

Table 5d: pregnant women

Study	NSS	Mode of delivery	Comparators	Outcome
Renault 2015	Unspecified	Soft drink	≥1 per day vs 0 per day	Adiposity (gestational weight gain [note 1])

Note 1: outcomes not included in a meta-analysis.

Note 2: “Campos et al. (2015) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Campos et al. (2015). Campos et al. (2017) is a substudy of Campos et al. (2015).”

Note 3: “Dalenberg et al. (2020) consisted of two separate studies: one in adults and one in adolescents. The study in adolescents was halted prematurely based on results of the study in adults.”

Note 4: “Ebbeling et al. (2020) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Ebbeling et al. (2019).”

Note 5: “Engel et al. (2018) provides data for all participants of a trial originally reported in Maersk et al. (2012), which was missing data from some participants. Therefore, only data from Engel et al. (2018) are included in the meta-analyses in this review. In addition, a correction was issued in 2020, as standard deviations were reported in the original publication instead of standard errors, and the corrected values have been used in this review.”

Note 6: “Madjd et al. (2018) reported data for 12 months of weight maintenance following 6 months of weight loss. Data for the 6-month weight loss period are reported in Madjd et al. (2015).”

Note 7: “Peters et al. (2016) reported data for 40 weeks of weight maintenance following 12 weeks of weight loss. Data for the 12-week weight loss period are reported in Peters et al. (2014).”

Note 8: “Raben et al. (2002) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Raben et al. (2001). Sorenson et al. (2014) is a substudy of Raben et al. (2002) assessing outcomes that are not outcomes of interest.”

Note 9: “A subsequent publication in 2020 reported the same data for a slightly smaller sample size and with less detail. Therefore, data from Romo-Romo et al. (2018) were retained in the systematic review.”

Note 10: “Stamataki et al. (2020) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Stamataki, Crooks & McLaughlin (2020).”

Note 11: “Vázquez-Durán et al. (2016) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Vázquez-Durán et al. (2013).”

Study details of PCS included in the position statement

Tables 6a to 6c summarise exposure (NSS), comparison, mode of NSS delivery and outcome evaluated in included PCS that evaluated adiposity, type 2 diabetes, cardiovascular diseases or dental outcomes.

Table 6a: adults

Study	NSS	Mode of delivery	Comparison (servings-highest vs lowest)	Outcome
Acero 2020	Unspecified	Drink, food	Decreased SSB with increased NSS consumption	Adiposity
Anderson 2020	Unspecified	Drink	>2 per day vs 0 per day	Adiposity
Bernstein 2012	Unspecified	Soft drink	≥1 per day vs none	CVD (stroke)
Bernstein 2012	Unspecified	Soft drink	≥1 per day vs none	CVD (stroke)
Bes-Rastrollo 2006	Unspecified	Soft drink	Per serving	Adiposity [note 1]
Chazelas 2020	Unspecified	Drink	176.7mL per day vs 0 mL per day	Cardiovascular events
Chia 2016	Unspecified	Drink, food	User vs non-user	Adiposity
Chia 2018	Unspecified	Drink, food	User vs non-user	Type 2 diabetes (intermediate marker [note 1])
Cohen 2012 [note 2]	Unspecified	Soft drink, fruit drink	≥1 per day vs <1 per month	CVD (hypertension)
Cohen 2012 [note 2]	Unspecified	Soft drink, fruit drink	≥1 per day vs <1 per month	CVD (hypertension)

Study	NSS	Mode of delivery	Comparison (servings-highest vs lowest)	Outcome
Cohen 2012 [note 2]	Unspecified	Soft drink, fruit drink	≥1 per day vs <1 per month	CVD (hypertension)
de Koning 2012	Unspecified	Drink	4.5 per week to 18 per day vs none	CVD (coronary heart disease)
Drouin-Chartier 2019 [note 3]	Unspecified	Drink	Increase >0.5 serving per day vs no change (and decrease >0.5 serving per day vs no change)	Type 2 diabetes (incident)
Drouin-Chartier 2019 [note 3]	Unspecified	Drink	Increase >0.5 serving per day vs no change (and decrease >0.5 serving per day vs no change)	Type 2 diabetes (incident)
Drouin-Chartier 2019 [note 3]	Unspecified	Drink	Increase >0.5 serving per day vs no change (and decrease >0.5 serving per day vs no change)	Type 2 diabetes (incident)
Duffey 2012	Unspecified	Drink	User vs non-user	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers, hypertension)
Fagherazzi 2013	Unspecified	Soft drink, fruit drink	>603mL per week vs 0 mL per week	Type 2 diabetes (incident)
Fagherazzi 2017	Unspecified	Tabletop	Always or almost always vs never or rarely	Type 2 diabetes (incident)
Ferreira-Pego 2016	Unspecified	Soft drink	>5 per week vs <1 per week	Adiposity, type 2 diabetes (intermediate marker), CVD (intermediate markers, hypertension)

Study	NSS	Mode of delivery	Comparison (servings-highest vs lowest)	Outcome
Fowler 2008	Unspecified	Drink, tabletop	User vs non-user and >21 per week vs none	Adiposity
Fowler 2015	Unspecified	Soft drink	≥1 per day vs none and any vs none	Adiposity
Fung 2009	Unspecified	Soft drink	≥2 per day vs <1 per month	CVD (coronary heart disease)
Gardener 2012 [note 4]	Unspecified	Soft drink	≥1 per day vs <1 per month	CVD (mortality, cardiovascular events, coronary heart disease, stroke)
Gardener 2018	Unspecified	Soft drink	>6 per week vs <1 per month	Type 2 diabetes (incident)
Garduno-Alanis 2020 [note 5]	Unspecified	Soft drink	≥1 per day vs none	Adiposity
Gearon 2014	Unspecified	Soft drink	Dose–response	Adiposity [note 1]
Haslam 2020	Unspecified	Soft drink	>1 per day vs <1 per month	CVD (intermediate markers)
Hirahatake 2019	Unspecified	Soft drink, fruit drink	≥2 per day vs none	Type 2 diabetes (incident)
Huang 2017	Unspecified	Drink	≥2 per day vs <3 per month	Type 2 diabetes (incident)
InterActConsortium 2013	Unspecified	Soft drink	≥1 per day vs <1 per month	Type 2 diabetes (incident)
Jensen 2020	Unspecified, saccharin, sucralose, aspartame	Soft drink, tabletop	≥7 per week vs none (beverages), always vs none (tabletop)	Type 2 diabetes (incident)
Keller 2020 [note 6]	Unspecified	Drink	Per daily serving	CVD (coronary events [note 1])

Study	NSS	Mode of delivery	Comparison (servings-highest vs lowest)	Outcome
Ma 2016	Unspecified	Soft drink	≥1 per day vs <1 per month	Adiposity
Malik 2019	Unspecified	Drink	≥2 per day vs <1 per month	CVD (mortality)
Mossavar-Rahmani 2019	Unspecified	Drink	≥2 per day vs <1 per week	CVD (coronary heart disease, stroke)
Mullee 2019	Unspecified	Soft drink	≥2 per day vs <1 per month	CVD (mortality, stroke)
Nettleton 2009	Unspecified	Soft drink	≥1 per day vs rare or none	Adiposity, type 2 diabetes (incident and intermediate marker), CVD (intermediate markers, hypertension)
O'Connor 2015	Unspecified	Drink	169 to 5848mL per day vs non-user	Type 2 diabetes (incident)
Palmer 2008	Unspecified	Soft drink	≥1 per day vs <1 per month	Type 2 diabetes (incident)
Park 2020 [note 7]	Unspecified	Soft drink	<1 per month vs ≥1 per week	Adiposity [note 1]
Parker 1997	Saccharin	Unclear	0.1 to 28.2g per day vs 0g per day	Adiposity
Pase 2017	Unspecified	Soft drink	≥1 per day vs 0 per week	CVD (stroke)
Sakurai 2014	Unspecified	Soft drink	≥1 per week vs rare or none	Type 2 diabetes (incident)
Smith 2015 [note 8]	Unspecified	Soft drink	Per daily serving	Adiposity
Smith 2015	Unspecified	Soft drink	Per daily serving	Adiposity
Smith 2015	Unspecified	Soft drink	Per daily serving	Adiposity

Study	NSS	Mode of delivery	Comparison (servings-highest vs lowest)	Outcome
Stellman 1986 [note 9]	Unspecified	Soft drink, tabletop	User vs non-user	Adiposity
Stern 2017	Unspecified	Soft drink	Per daily serving Increase of >1 week vs no change	Adiposity
Tucker 2015	Unspecified	Soft drink	User vs non-user	Adiposity
Vyas 2015	Unspecified	Drink	≥2 per day vs 0 to 3 per month	CVD (mortality, cardiovascular events)
Wang 2019	Unspecified	Soft drink	≥1 per day vs none	CVD (common carotid artery intima-media [note 1], thickness, common carotid artery adventitial diameter [note 1], carotid plaque [note 1])
Zhang 2021	Unspecified	Soft drink	≥2 per day vs 0 per day	CVD (coronary heart disease mortality [note 1])

Table 6b: children

Study	NSS	Mode of Delivery	Comparison (servings-highest vs lowest)	Outcome
Berkey 2004	Unspecified	Soft drink	Per daily serving	Adiposity
Blum 2005	Unspecified	Soft drink	Per daily serving	Adiposity
Davis 2018	Unspecified	Drink	Chronic user vs never	Adiposity, type 2 diabetes (intermediate marker [note 1]), CVD (intermediate marker [note 1])
Field 2014	Unspecified	Soft drink	Per daily serving	Adiposity
Haines 2012	Unspecified	Soft drink	≥1 per day vs 0 per week	Adiposity
Kral 2008	Unspecified	Soft drink	Dose–response	Adiposity
Laska 2012	Unspecified	Soft drink	Per daily serving	Adiposity
Ludwig 2001	Unspecified	Soft drink	Per daily serving	Adiposity
Macintyre 2018	Unspecified	Soft drink	≥1 per day vs <1 per week	Adiposity
Marshall 2003	Unspecified	Soft drink	Low vs no intake	Dental caries
Newby 2004	Unspecified	Soft drink	Per daily serving	Adiposity
Striegel-Moore 2006	Unspecified	Soft drink	Per daily serving	Adiposity
Vanselow 2009	Unspecified	Soft drink	≥1 per day vs 0 per week	Adiposity
Zheng 2015a	Unspecified	Drink	Per daily serving	Adiposity

Study	NSS	Mode of Delivery	Comparison (servings-highest vs lowest)	Outcome
Zheng 2015b	Unspecified	Drink	Per daily serving	Adiposity
Zheng 2019	Unspecified	Drink	Per 100mL per day	Adiposity [note 1]

Table 6c: pregnant women

Study	NSS	Mode of delivery	Comparison (servings-highest vs lowest)	Outcome
Azad 2016 [note 10]	Unspecified	Soft drink, hot drink	≥1 per day vs <1 per month	Adiposity in offspring [note 1]
Chen 2009	Unspecified	Soft drink	1 per day vs 0 to 3 per month	Gestational diabetes [note 1]
Dale 2019	Unspecified	Soft drink	≥70mL per day vs ≤25mL per day, ≥4 per day vs none	Congenital heart disease in offspring [note 1]
Gillman 2017	Unspecified	Soft drink	Per daily serving	Adiposity in offspring [note 1]
Gunther 2019	Unspecified	Soft drink	Per daily serving	Birthweight [note 1]
Hinkle 2019	Unspecified	Soft drink, hot drink	≥2 per week in pregnancy and at follow-up vs ≤4 per month in pregnancy and at follow-up	Maternal outcomes (HbA1c [note 1], fasting glucose [note 1], obesity [note 1], fasting insulin [note 1], insulin resistance [note 1], triglycerides [note 1], HDL cholesterol [note 1], LDL cholesterol [note 1], BMI [note 1], waist circumference [note 1], type 2 diabetes [note 1])

Study	NSS	Mode of delivery	Comparison (servings-highest vs lowest)	Outcome
Hrolfsdottir 2019	Unspecified	Drink	Excessive, optimal and suboptimal gestational weight gain	Gestational weight gain [note 1]
Munda 2019	Unspecified	Drink	Linear	Gestational weight gain [note 1], large for gestational age [note 1]
Salavati 2020	Unspecified	Drink, food	Per 10g of ASBs standardized to 1000 kcal per day	Birthweight [note 1]
Schmidt 2020	Unspecified	Drink	≥4 per day vs none	Congenital heart disease in offspring [note 1]
Zhu 2017	Unspecified	Soft drink	≥1 per day vs never	Adiposity in offspring [note 1]

Note 1: outcomes not included in a meta-analysis.

Note 2: “Cohen et al. (2012) updates the results (i.e. reports on additional follow-up from baseline) of a previous report on hypertension in two of these cohorts: Winkelmayer et al. (2005).”

Note 3: “Drouin-Chartier et al. (2019) updates the results (i.e. reports on additional follow-up from baseline) of previous reports on type 2 diabetes in these cohorts: Schulze et al. (2004), de Koning et al. (2011) and Bhupathiraju et al. (2013).”

Note 4: “Gardener et al. (2012) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Gardener et al. (2011).”

Note 5: “Study includes body mass index data from Russia, Poland and Czech Republic, but the data are only provided longitudinally for Russia.”

Note 6: “Pooling study not included in meta-analyses but reported narratively. Includes Atherosclerosis Risk in Communities Study (ARIC), Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study (ATBC), Health

Professionals Follow-up Study (HPFS), Iowa Women’s Health Study (IWHS), Women’s Health Study (WHS) and Nurses’ Health Study (NHS).”

Note 7: “Park et al. (2020) is a prospective cohort study assessing the same population assessed cross-sectionally in Ma et al. (2015).”

Note 8: “Smith et al. (2015) updates the results (i.e. reports on additional follow-up from baseline) of previous reports on body weight in these cohorts: Colditz et al. (1990), Schulze et al. (2004), Mozaffarian et al. (2011) and Pan et al. (2013).”

Note 9: “A subsequent analysis of the dietary quality of the participants in this cohort was conducted but provided no new information on outcomes of interest: Stellman et al. (1988).”

Note 10: “A subsequent publication in 2020 reported the same data but with less detail. Therefore, data from Azad et al. (2016) were retained in the systematic review.”

Annex 4: Rios-Leyvraz and Montez (2022) risk of bias assessment

Risk of bias (ROB) assessment for studies considered in the position statement is outlined below.

ROB in RCTs for the 7 domains were assessed with respect to:

- random sequence generation (selection bias), 34% of studies were rated with a low ROB, 60% unclear and 6% a high ROB
- allocation concealment (selection bias), 32% of studies were rated with a low ROB, 66% unclear and 2% a high ROB
- blinding of participants and personnel (performance bias), 20% of studies were rated with a low ROB, 42% unclear and 38% a high ROB
- blinding of outcome assessment (detection bias), 22% of studies were rated with a low ROB, 76% unclear and 2% a high ROB
- incomplete outcome data (attrition bias), 40% of studies were rated with a low ROB, 38% unclear and 22% a high ROB
- selective reporting (reporting bias), 58% of studies were rated with a low ROB, 34% unclear and 8% a high ROB
- other bias 62% of studies were rated with a low ROB, 34% unclear and 4% a high ROB.

To note, as numeric data on ROB were not explicitly reported for RCTs by Rios-Leyvraz and Montez (2022), low, unclear and high ROB percentages for each domain were calculated by the secretariat. Calculations were done by totalling the number of studies with either low, unclear or high ROB for each domain, dividing by the total number of RCTs (n = 50) and multiplying by 100%.

ROB in prospective cohort studies and case–control studies was assessed by the risk of bias in nonrandomized studies of interventions (ROBINS-I) method and confirmed with the Newcastle-Ottawa Scale. As no case-control studies were identified that reported outcomes of interest to SACN, a summary of the ROB for PCS only is provided here.

Rios-Leyvraz and Montez (2022) present the ROB for the Newcastle-Ottawa Scale scores studies a maximum of up to 9 stars, indicating lower ROB. Of the PCS studies:

- 2 studies were scored all 9 stars
- 13 studies were scored 8 stars
- 29 studies were scored 7 stars
- 24 studies were scored 6 stars
- 13 studies were scored 5 stars
- 13 studies were scored 4 stars
- one study was scored 3 stars
- no studies were scored 2 stars or less.

To note, 96 PCS were included in the ROB whereas 97 PCS are reported as included in the SR. It is unclear why 1 PCS was not included in the ROB assessment.

In terms of each item within the Newcastle-Ottawa Scale tool, the number of studies achieving:

- representativeness of the exposed cohort was 31 (32.3%), 30 studies achieved 1 star and 1 study achieved 2 stars
- selection of the non-exposed cohort was 96 (100%)
- ascertainment of exposure was 84 (87.5%)
- demonstration that outcome of interest was not present at start of study was 57 (59.4%)
- comparability of cohorts on the basis of the design or analysis was 46 (47.9%) achieving 1 star and 37 (38.5%) achieving 2 stars
- assessment of outcome was 68 (70.8%)
- follow-up long enough for outcomes to occur was 95 (99.0%)
- adequacy of follow-up of cohorts was 42 (43.8%).

To note, as numeric data on ROB were not explicitly reported for PCS by (Rios-Leyvraz and Montez, 2022), the number and percentages for each item within the Newcastle-Ottawa Scale tool were calculated by the SACN secretariat. Calculations were done by totalling the number of studies achieving a star rating for each item, dividing by the number of PCS evaluated (n = 96) and multiplying by 100%.