International Sweeteners Association

5th edition

Low/no Calorie Sweeteners: Role and Benefits

A guide to the science of low/no calorie sweeteners

This booklet has been developed by the International Sweeteners Association (ISA) for healthcare professionals and is designed to provide factual scientific information about low/no calorie sweeteners: their approval and use in foods and drinks, their benefits and role in the diet and in sugar reduction. It is based on publicly available science, with references and contribution from internationally recognised experts.

This is the fifth edition of the ISA booklet. Updated in September 2023, it presents an overview of the latest scientific information on low/no calorie sweeteners in a web-friendly way.

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Summary

People innately enjoy sweet taste. Research indicates, however, that excess consumption of sugars may increase the risk of weight gain, which, in turn, is a risk factor for developing adverse health conditions, such as diabetes. Low/no calorie sweeteners provide a simple way of reducing the amount of calories and sugars in our diet without affecting the enjoyment of sweet-tasting foods and drinks.

The safety of low/no calorie sweeteners has been thoroughly evaluated and consistently confirmed by a strong body of scientific evidence and regulatory bodies worldwide. For a low/no calorie sweetener to be approved for use on the market, as any food additive, it must first undergo a thorough safety assessment by the competent food safety authority. Based on the wealth of scientific studies, food safety bodies around the world, such as the Joint Food and Agriculture Organization (FAO)/ World Health Organization (WHO) Expert Committee on Food Additives (JECFA), the US Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), have consistently confirmed the safety of all approved low/no calorie sweeteners.

By having a very high sweetening power compared to sugars, low/no calorie sweeteners are used in minute amounts to confer the desired level of sweet taste, while contributing very little or no energy at all to the final product. As such, low/no calorie sweeteners can play a helpful role in reducing total energy (calorie) intake and, thus, in weight control, when used in place of sugars and as part of a balanced diet and healthy lifestyle. Furthermore, low/no calorie sweeteners are valued by, and can be a significant aid to, people living with diabetes who need to manage their carbohydrate intake, as low/no calorie sweeteners do not affect blood glucose control. Also, by being non-cariogenic ingredients, low/no calorie sweeteners can contribute to good dental health.

In recent years, there has been a steady and significant increase in consumer demand for low-calorie, low-sugar products. As a result, there is growing interest among healthcare professionals and the general public to learn more about low/no calorie sweeteners and how they may help in nutritional strategies aiming to reduce overall calorie intake and improve weight management and overall health.

Low/no Calorie Sweeteners: Role and Benefits, a guide to the science of low/no calorie sweeteners, is supported by contributions from a group of eminent scientists and doctors who have undertaken a significant amount of research around low/no calorie sweeteners in the areas of epidemiology, public health nutrition, appetite, eating behaviour and weight management, diet and health. We hope you find this booklet useful and that it will serve as a valuable reference tool in your daily work.

1.
An introduction to low/no calorie sweeteners

What is a low/no calorie sweetener?

Low/no calorie sweeteners (LNCS) are sweet-tasting food ingredients with no, or virtually no, calories that are used to confer the desired sweetness to foods and drinks, while contributing very little or no energy at all to the final product *(Fitch et al, 2012; Gibson et al, 2014).*

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Commonly used low/no calorie sweeteners

The most known and commonly used LNCS worldwide are acesulfame potassium (or acesulfame-K), aspartame, cyclamate, saccharin, sucralose and steviol glycosides. Other LNCS that have been approved for use in Europe and around the world include: thaumatin, neotame, neohesperidine DC and advantame.

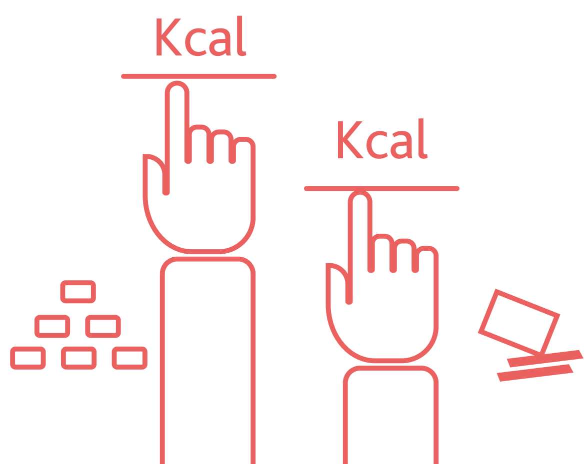
The history behind the discovery of low/no calorie sweeteners

Low/no calorie sweeteners have been safely used and enjoyed by consumers all over the world for more than a century. The first commonly used LNCS, saccharin, was discovered at Johns Hopkins University in 1879. Since then, a number of other LNCS have been discovered and are now in use in foods and drinks around the world (Figure 1).

Before approval, all LNCS used in foods and drinks today are subject to a rigorous safety evaluation process *(Serra-Majem et al, 2018; Ashwell et al, 2020)*. This is discussed in detail in the next chapter (Chapter 2).

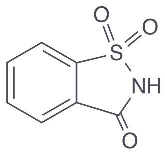
Different terms are frequently used to describe LNCS in the scientific literature. The term *low/no calorie sweeteners (LNCS)* is used throughout this booklet, while other common terms include: intense sweeteners, high intensity sweeteners, high potency sweeteners, low-calorie sweeteners, non-nutritive sweeteners and non-sugar sweeteners.

Low/no calorie sweeteners impart no, or virtually no, calories to our foods and drinks, so they can be a helpful tool in reducing individuals' total energy intake.



History of the most commonly used low/no calorie sweeteners.

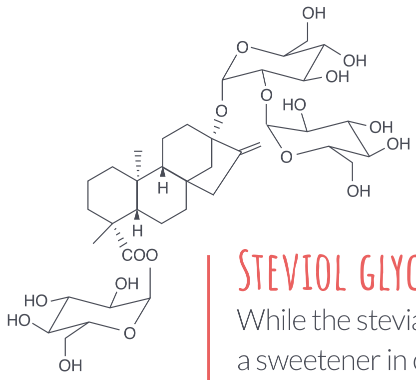
1879



Saccharin

was discovered in 1879 by Remsen and Fahlberg; saccharin is the “oldest” low calorie sweetener, used for more than a century in foods and drinks.

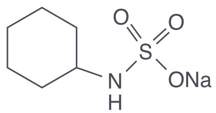
1931



Steviol glycosides

While the stevia plant has been used as a sweetener in certain South American countries for centuries, it was around the 1900s that Dr. Moises Santiago Bertoni, a Swiss botanist, started studying the plant. In 1931, two chemists in France isolated the first steviol glycosides, which are purified extracts of the sweet components of the stevia leaf that are approved for use today.

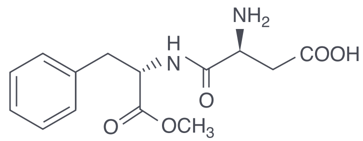
1937



Cyclamate

was discovered in 1937 at the University of Illinois and it is the term given to the low calorie sweetener cyclamic acid and its calcium or sodium salts.

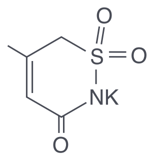
1965



Aspartame

was discovered in 1965 by the chemist James Schlatter.

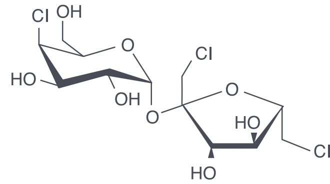
1967



Acesulfame-K

was discovered in 1967 by Dr Karl Clauss, a researcher at Hoechst AG in Germany.

1976



Sucralose

was discovered in 1976 during a research program on sugar by researchers at Queen Elizabeth College, University of London.

Figure 1: History of the most commonly used low/no calorie sweeteners.

Source: In book: Encyclopedia of Food Sciences and Nutrition, Edition: 2nd, 2003. Publisher: Academic Press Ltd., Editors: B. Caballero, L. Trugo, P. Finglas.

Commonalities and differences

While all LNCS used in food and drink production confer sweet taste with no, or practically no, calories and they all have a much higher sweetening power compared to sugar, each one of the different LNCS has a unique structure and metabolic fate, technical characteristics and taste profile (Magnuson et al, 2016). Some key characteristics of the most commonly used LNCS are presented in Table 1.

Click here for Table 1

LOW/NO CALORIE SWEETENERS SHARE A LOT IN COMMON,
BUT THEY HAVE DIFFERENCES AS WELL, SUCH AS...

- Taste profile
- Sweetening potency
- Metabolism
- Technical properties

Table 1: Key characteristics of the most common low/no calorie sweeteners

	Acesulfame-K	Aspartame	Cyclamate	Saccharin	Sucralose	Steviol glycosides
Year of discovery	1967	1965	1937	1879	1976	1931
Sweetening power (compared to sucrose)	Approx. 200 times sweeter than sucrose*	Approx. 200 times sweeter than sucrose*	Approx. 30-40 times sweeter than sucrose*	Approx. 300-500 times sweeter than sucrose*	Approx. 600-650 times sweeter than sucrose**	Approx. 200 to 300 times sweeter than sucrose (depending on the glycoside)*
Metabolic and biological properties	Not metabolised and excreted unchanged.	Metabolised to its constituent amino acids (protein building blocks) and a very small amount of methanol, in quantities commonly found in many foods.	Generally not metabolised and excreted unchanged.	Not metabolised and excreted unchanged.	Minimally metabolised and excreted unchanged.	Steviol glycosides are broken down to steviol in the gut. Steviol is excreted in the urine as steviol glucuronide.
Caloric value	Calorie-free	4kcal/g (used in very small amounts thus providing practically no calories)	Calorie-free	Calorie-free	Calorie-free	Calorie-free

*Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council; **Opinion of the Scientific Committee on Food on sucralose, September 2000

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2.

Safety and regulation of low/no calorie sweeteners

Low/no calorie sweeteners (LNCS) are amongst the most thoroughly researched ingredients worldwide. Based on a strong body of scientific evidence, regulatory food safety bodies around the world confirm their safety.

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The regulatory bodies involved in safety assessment

As with all food additives, for an LNCS to be approved for use on the market, it must first undergo a thorough safety assessment by the competent food safety authority. At an international level, the responsibility of evaluating the safety of all additives, including LNCS, rests with the Joint Expert Scientific Committee on Food Additives (JECFA) of the United Nations Food & Agriculture Organization (FAO) and the World Health Organization (WHO). JECFA serves as an independent scientific committee which performs safety assessments and provides advice to the Codex Alimentarius, a body of the FAO-WHO, and the member countries of these organisations.

Throughout the world, nations rely on regional or international governing bodies and expert scientific committees, such as JECFA, to evaluate the safety of food additives, or have their own regulatory bodies for food safety oversight. For example, many countries in Latin America approve the use of LNCS based on JECFA's safety assessment and the Codex Alimentarius provisions. In the US and in Europe, the safety assessment of all food additives is the responsibility of the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), respectively. These regulatory bodies have consistently confirmed the safety of approved LNCS at current levels of use *(Fitch et al, 2012; Magnuson et al, 2016; Serra-Majem et al, 2018)*.

Safety evaluation

All LNCS have undergone a thorough and very strict premarket safety evaluation and approval process.

As with all food additives, for an LNCS to be approved, the applicants must present to the food safety body a comprehensive safety database relevant to the proposed use of the ingredient and in accordance with the requirements published by the relevant food safety authority *(EFSA 2012; FDA, 2018)*. To determine the safety of an additive, the authorities thoroughly review and assess data on the chemistry, kinetics and metabolism of the substance, the proposed uses and exposure assessment, as well as extensive toxicological studies *(Barlow, 2009)*. The safety assessment process is based on independent expert review of the collective research. **Only when there is strong evidence of no safety concern is a food additive permitted for use in foods.**

In the approval process, the risk assessment experts of the food safety agencies establish an Acceptable Daily Intake (ADI) for each approved LNCS.

Worldwide, low/no calorie sweeteners are among the most thoroughly tested food ingredients. Numerous regulatory bodies around the world have confirmed their safety.

What is the Acceptable Daily Intake (ADI)?

The Acceptable Daily Intake (ADI) is defined as the amount of an approved food additive that can be consumed daily in the diet, over a lifetime, without appreciable health risk. The ADI is expressed on a body weight basis: in milligrams (mg) per kilogram (kg) of body weight (bw) per day *(Barlow, 2009)*.

How the Acceptable Daily Intake is Established

Regulatory authorities derive the ADI based on the daily maximum intake that can be given to test animals throughout life without producing any adverse biological effects, known as the No-Observed Adverse Effect Level (NOAEL). The NOAEL is then divided by a 100-fold safety factor to establish the ADI. The 100-fold safety factor is to cover for possible differences between species and also within species, for example special population groups, such as children and pregnant women *(Renwick, 2006; Barlow 2009)*. The use of the ADI principle for toxicological evaluation and safety assessment of food additives is accepted by all regulatory bodies worldwide.

Usage levels are set, and use is monitored by national and regional authorities so that consumption does not reach ADI levels *(Renwick, 2006; Martyn et al, 2018)*. As the ADI relates to lifetime use, it provides a safety margin large enough for scientists not to be concerned if an individual's short-term intake exceeds the ADI, as long as the average intake over long periods of time does not exceed it *(Renwick, 1999)*. The ADI is the most important practical tool for scientists in ensuring the appropriate and safe use of LNCS *(Renwick, 2006)*. The ADIs of individual sweeteners as established internationally by JECFA are provided in Table 1.

Low/no calorie sweetener	Acceptable Daily Intake (ADI) (mg/ kg BW/ day)
Acesulfame-K (INS 950)	0-15 mg/kg
Aspartame (INS 951)	0-40 mg/kg
Cyclamate (INS 952)	0-11 mg/kg
Saccharin (INS 954)	0-5 mg/kg
Sucralose (INS 955)	0-15 mg/kg
Thaumatin (INS 957)	Not specified (An ADI of "not specified" means that thaumatin can be used according to Good Manufacturing Practice (GMP))
Steviol glycosides (INS 960)	0-4 mg/kg (expressed as Steviol)

Table 1: Acceptable Daily Intake (ADI) for commonly used low/no calorie sweeteners, as established by the Joint Expert Scientific Committee on Food Additives (JECFA) of the United Nations Food & Agriculture Organization (FAO) and the World Health Organization (WHO). *Note: The 'INS' reference for each additive refers to the International Numbering System of the Codex Alimentarius.*

An example comparing aspartame consumption to the sweetener's ADI and NOAEL is presented in Figure 1.

Aspartame consumption compared with the ADI

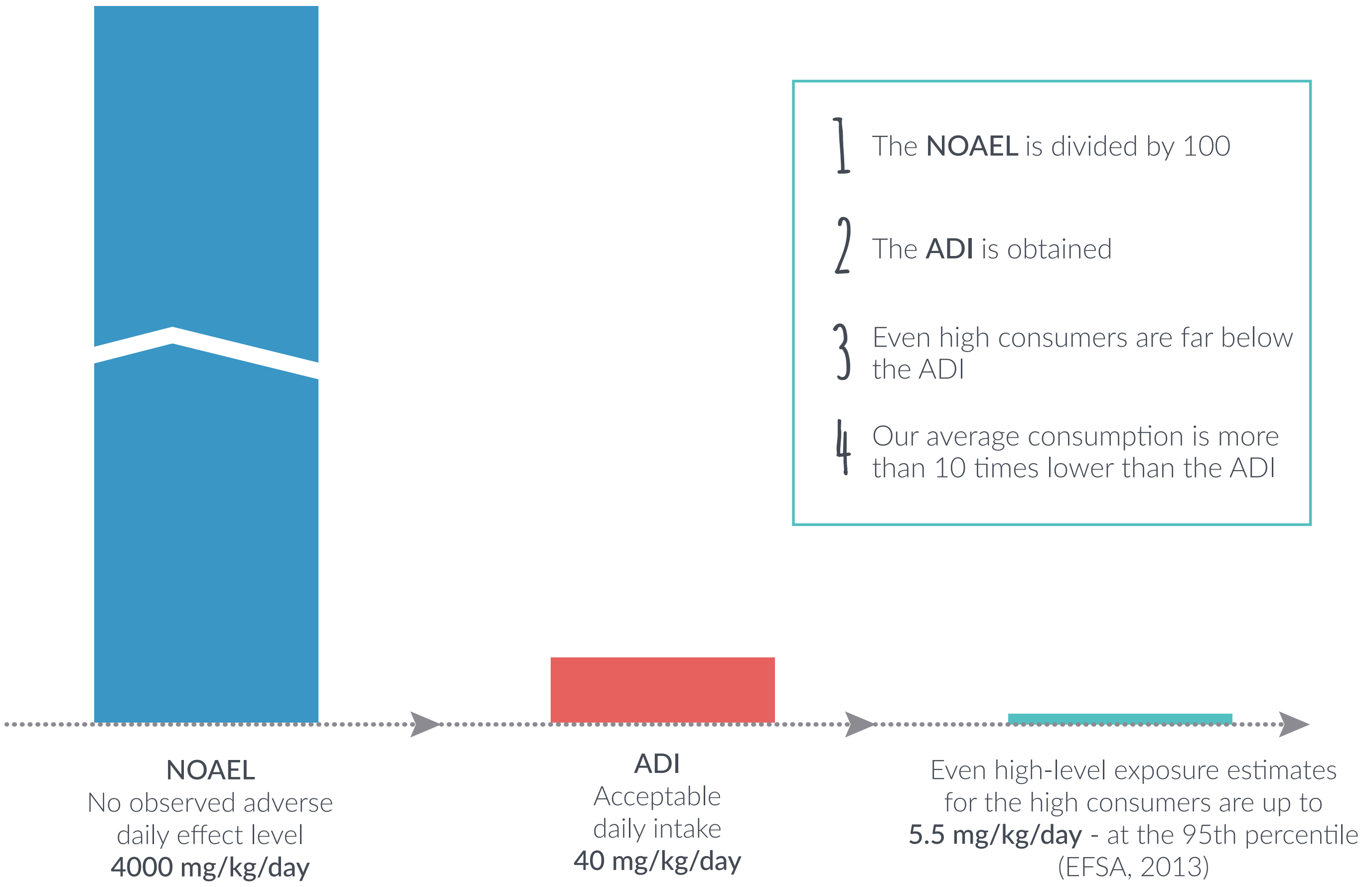

Figure 1: Aspartame consumption (EFSA, 2013) compared to the sweetener's Acceptable Daily Intake (ADI) and No Observed Adverse Effect Level (NOAEL).

Consumption of low/no calorie sweeteners globally

In 2018, a published review of the global literature regarding the intake of the most commonly used LNCS concluded that, overall, the studies conducted to determine the exposures of LNCS over the last decade raise no concerns with respect to exceedance of the individual sweetener ADIs among the general population globally (*Martyn et al, 2018*). The current data also do not suggest a significant shift in exposure over time, with several studies indicating a reduction in intakes *(Renwick, 2006; Renwick, 2008; Martyn et al, 2018)*. Thus, this review provides a significant degree of confidence that there does not appear to be a significant shift in patterns of LNCS intake and that levels of exposure are generally within the ADI limits for the individual sweeteners.

Consumption of sweeteners in Europe

The most refined and analytical exposure assessments of LNCS to date have been conducted in Europe. A total of 19 European peer-reviewed studies on LNCS intake and, further, seven studies from authoritative sources have been published over the last decade, with most studies using a standardized approach *(Martyn et al, 2018)*.

The majority of the studies in Europe were conducted for the general population, with intakes calculated for the mean and high-level consumers (the high-level intake percentile has been most commonly established at the 95th percentile). Generally, **there was no issue with exceeding the ADIs for the individual sweeteners among the evaluated European population groups, even for high consumers.** Furthermore, several studies examined intakes in specific subgroups, including young children and people with diabetes.

Current evidence shows that the intakes of approved low/no calorie sweeteners are well below the Acceptable Daily Intake (ADI) values.

In a series of analytical studies conducted in different European populations in Belgium *(Huvaere et al, 2012)*, Ireland *(Buffini et al, 2018)* and Italy *(Le Donne et al, 2017)*, which were led by the Belgian Scientific Institute for Public Health in collaboration with local organisations in each country, data showed that LNCS intake is well below the ADI for each sweetener and does not pose a risk even for high consumers of low calorie sweetened products. These studies examined exposure to LNCS both at the level of the more conservative approach and when actual concentration levels in foods were taken into account, and found that the studied Belgian, Irish and Italian populations are not at risk of exceeding the corresponding ADI of each sweetener. In fact, even for the very high consumers of low/no calorie sweetened products (the top 1% of the population) the levels of consumption remain well below the ADI.

Recent studies have also focused on children because of their higher intakes of foods and drinks on a body weight basis, and on both children and adults with diabetes, because of their higher potential intakes of LNCS *(Devitt et al, 2004; Husøy et al, 2008; Leth et al, 2008; EFSA, 2013; Vin et al, 2013; EFSA, 2015a; EFSA, 2015b; Mancini et al, 2015; Van Loco et al, 2015; Martyn et al, 2016)*. Overall, these studies also confirm that average intake of LNCS is generally below the relevant ADI values for the individual sweeteners.

EU Legislation on Sweeteners

In the EU, sweeteners are regulated under the EU framework regulation on food additives, Regulation 1333/2008 *(Regulation (EC), 2008)*. Annex II of this legislation, established by Commission Regulation 1129/2011, provides a Community list of sweeteners approved for use in foods, beverages and table-top sweeteners and their conditions of use. Where appropriate, maximum use levels are specified *(Commission Regulation (EU) No 1129/2011)*. Sweeteners must also meet EU purity criteria specifications *(Commission Regulation (EU) No 231/2012)*.

Within the EU, the eleven LNCS currently authorised for use are acesulfame-K (E950), aspartame (E951), aspartame-acesulfame salt (E962), cyclamate (E952), neohesperidine DC (E959), saccharin (E954), sucralose (E955) thaumatin (E957), neotame (E961), steviol glycosides (E960) and advantame (E969). The 'E' reference for each sweetener refers to Europe and shows that the ingredient is authorised and regarded as safe in Europe. In effect, the E-classification system is a robust food safety system introduced in 1962 and intended to protect consumers from possible food-related risks. Food additives must be included either by name or by an E number in the ingredients list.

At the request of the European Commission, EFSA is currently carrying out an ambitious re-evaluation of the safety of all food additives, which were approved on the EU market before 20th January 2009. Aspartame is the first sweetener to have undergone this re-evaluation process, which reconfirmed its safety.

The Regulatory Bodies involved in Europe

Regulatory approval of LNCS in the EU is granted by the European Commission on the basis of the scientific advice of EFSA. The EFSA panel dealing with the safety of sweeteners is the FAF Panel (Food Additives and Flavourings), an independent panel composed of scientific experts appointed on the basis of proven scientific excellence. Previously, the EU relied on the Scientific Committee on Food (SCF). Since April 2003, this has been the responsibility of EFSA.

How a Low/no Calorie Sweetener is Approved for use in Foods and Drinks in the EU

The authorisation and conditions of use of an LNCS, like any other food additive, is harmonised at EU level. EFSA is responsible for the provision of scientific advice and scientific technical support for European Union legislation and policies in all fields that have a direct or indirect impact on food and food safety. Applicants (e.g. ingredient manufacturers) can only apply for approval of an LNCS after extensive safety tests have been completed and evidence provided of the product's safety and utility. The design and nature of studies to be conducted are expected to follow specific guidelines (OECD Test Guidelines and Principles of Good Laboratory Practice (GLP)). The petition provides technical details about the product and comprehensive data obtained from safety studies.

The safety data are then examined by EFSA. At any time, questions raised by EFSA must be answered by the applicant. Sometimes this may require additional studies. Completing and analysing the safety studies may take up to 10 years. In the approval process, an ADI is set for each LNCS by EFSA. Following the publication of a scientific opinion by EFSA, the European Commission drafts a proposal for authorisation of use of the LNCS in foods and drinks available in European Union countries.

After following the required procedure and only if the regulators are fully satisfied that the ingredient is safe, will approval be given. This means that all of the LNCS available on the EU market are safe for human consumption.

The Acceptable Daily Intake (ADI) is a guarantee of safety, representing the average amount of a low/no calorie sweetener that can be safely consumed on a daily basis throughout a person's lifetime.

EFSA opinion on aspartame

In December 2013, as part of the re-evaluation process and following one of the most comprehensive scientific risk assessments undertaken on a food additive, EFSA published its opinion on aspartame, re-confirming that aspartame is safe for consumers at levels currently permitted *(EFSA, 2013)*.

Highlighting the publication of the opinion on its website, EFSA pointed out, **Experts of ANS Panel have considered all available information and, following a detailed analysis, have concluded that the current Acceptable Daily Intake (ADI) of 40mg/kg bw/day is protective for the general population".** EFSA also highlighted that the breakdown products of aspartame (phenylalanine, methanol and aspartic acid) are also naturally present in other foods. For instance, methanol is found in fruit and vegetables and is even generated in the human body by endogenous metabolism *(EFSA, 2013)*.

What is the case with the use of aspartame in phenylketonuria (PKU)?
Phenylketonuria (PKU) is a rare inherited condition affecting about 1 in 10,000 people. Throughout most of Europe, PKU is screened for shortly after birth. Those who have it lack the enzyme that converts phenylalanine into the amino acid tyrosine. Phenylalanine is an essential amino acid required for protein biosynthesis. It is also a component of aspartame. For those with PKU, consuming protein-containing food leads to a build-up of phenylalanine in the body. People with PKU must avoid the intake of phenylalanine in the diet. This means that high protein foods such as meat, cheese, poultry, eggs, milk/ dairy products and nuts are not permitted. The amount of phenylalanine contributed to foods from aspartame, as compared to that provided by common protein sources, like meat, eggs and cheese, is very small.

For the benefit of persons with PKU, foods, drinks and healthcare products that contain the LNCS aspartame must legally carry a label statement indicating that the product contains phenylalanine: "Contains a source of phenylalanine".

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Labelling of low/no calorie sweeteners

LNCS are clearly labelled on the packaging of all food and beverage products that contain them. In Europe, according to EU labelling regulation *(Regulation (EU) No 1169/2011)*, the presence of an LNCS in foods and beverages must be labelled twice on food products. The name of the LNCS (e.g. saccharin) or the E-number (e.g. E954) must be included in the list of ingredients. In addition, the term 'with sweetener(s)' must be clearly stated on the label together with the name of the food or beverage product.

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Low/no calorie sweeteners do not increase the risk of developing cancer

Dr Carlo La Vecchia: There is no consistent scientific evidence that links the consumption of LNCS to cancer. Several toxicological and epidemiological studies were published during the last five decades on this topic.

A recent review (*Pavanello et al, 2023*) provided a comprehensive quantitative revision of the toxicological and epidemiological evidence on the possible relation between LNCS and cancer. The toxicological section included the evaluation of genotoxicity and carcinogenicity data for several LNCS, including acesulfame K, advantame, aspartame, cyclamates, saccharin, steviol glycosides and sucralose, while the epidemiological section included the results of a systematic search of 22 cohort and 46 case-control studies.

The large majority of the studies showed no association of LNCS with cancer risk. Some risks for bladder, pancreas and hematopoietic cancers found in a few studies were not confirmed in other studies. An issue on liver cancer was recently raised, but subsequently not supported by data from the Women's Health Initiative (*Zhao et al, 2023*), which found no association between LNCS, cirrhosis and liver cancer.

Based on both the experimental data on genotoxicity or carcinogenicity of the specific LNCS evaluated, and the epidemiological studies, there is therefore now no evidence of cancer risk associated to LNCS consumption..

Are low/no calorie sweeteners safe for children and pregnant women?
Dr Carlo La Vecchia: Consumption of LNCS, within the ADI set by the regulatory authorities, is safe during pregnancy, because all low/no calorie sweeteners have been subject to appropriate testing. No risk difference, as compared to sweetened beverages, has consistently been reported. The variety of foods and drinks sweetened with LNCS can help satisfy a pregnant woman's taste for sweetness while adding few or no calories. Pregnant and breastfeeding women, however, do need to consume adequate calories to nourish the foetus or infant and should consult with a physician about their nutritional needs. It is important to remember that weight control remains a priority, particularly in pregnancy.

LNCS are also safe for children. It is also important, however, to keep in mind that children, particularly young children, need ample calories for rapid growth and development. LNCS are not approved for use in foods for infants (defined as children under the age of 12 months) and young children (defined as children between 1-3 years).

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3.

Low/no calorie sweeteners' use and role in sugar reduction and a healthy diet

At a time when the rates of obesity and non-communicable diseases (NCDs) continue to increase worldwide, and amid strong recommendations to limit free sugars intake, low/no calorie sweetened products can help individuals reduce the consumption of dietary sugars as part of a healthy eating plan.

Low/no calorie sweeteners (LNCS) are used in food and drink products in place of sugar to confer the desired level of sweetness while contributing very little or no energy at all to the final product. Therefore, LNCS represent a helpful tool in food reformulation and public health efforts aiming at sugar reduction.

The use of low/no calorie sweeteners

All approved LNCS are used in food and beverages as well as in table-top sweeteners in place of sugar and other caloric sweeteners to provide the desired sweetness with fewer or zero calories *(Gibson et al, 2014)*. LNCS have a much greater sweetening power compared to sugar, meaning that they are hundreds of times sweeter than sugar by weight (Figure 1), and therefore, LNCS are used in very small quantities in food and drink products *(Magnuson et al, 2016)*.

A variety of food and drink products, including soft drinks, table-top sweeteners, chewing gum, confectionery, yogurts, and desserts, can be sweetened with LNCS, in line with local regulatory requirements. LNCS are also used in healthcare products such as in mouthwashes, chewable multivitamins, and cough syrups, thus making these products more palatable. LNCS are clearly labelled on the packaging of food, drink and healthcare products that contain them, as discussed in Chapter 2.

Figure 1: EU references to sweetness potency of low/no calorie sweeteners

Acesulfame K
Approx. **200 times** sweeter than sugar by weight

Aspartame
Approx. **200 times** sweeter than sugar by weight

Cyclamate
Approx. **30-40 times** sweeter than sugar by weight

Saccharin
Approx. **300-500 times** sweeter than sugar by weight

Sucralose
Approx. **600-650 times** sweeter than sugar by weight

Thaumatin
Approx. **2000-3000 times** sweeter than sugar by weight

Neohesperidine DC
Approx. **1000-1800 times** sweeter than sugar by weight

Steviol glycosides
Approx. **200-300 times** sweeter than sugar by weight

Neotame
Approx. **7000-13000 times** sweeter than sugar by weight

Advantame
Approx. **37000 times** sweeter than sugar by weight

Sources:

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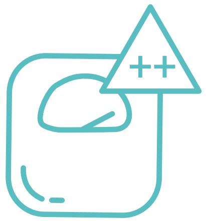
Food reformulation and sugar reduction: the key role of low/no calorie sweeteners

As the rates of obesity and accompanying NCDs continue to increase globally, public health authorities are encouraging food manufacturers to replace sugars and reduce calories in their products as part of their reformulation goals. LNCS represent a helpful tool for developing such products *(Gallagher et al, 2021)*. They can facilitate substantial reductions in sugars and help to reduce calories when used in place of higher energy ingredients *(Gibson et al, 2017)*.

By having a very high sweetening power compared to sugars, LNCS are used in minute amounts to confer the desired level of sweetness to foods and drinks, while contributing very little or no energy at all to the final product. This offers one major advantage to food and drink as well as to table-top sweetener manufacturers and ultimately consumers – sweet taste whilst eliminating or substantially reducing the calories in a food or drink when replacing sugars.



the rates of obesity and non-communicable diseases continue to increase worldwide

LNCS can facilitate substantial sugar reduction in foods and drinks

Opportunities and challenges in food reformulation

Removing significant amounts of sugars from a food or drink has a noticeable effect on the sensory profile of the product, which can impact on overall consumer liking for the product. With few options available for giving food and beverages a palatable sweet taste without the calories of sugars, LNCS are important ingredients for the food industry *(Gibson et al, 2017; Miele et al, 2017; McCain et al, 2018)*. Other than sweetness, sugar has more functional properties in foods providing, for example, bulk and/or textural qualities. As a result, sugar reduction in food formulation is sometimes more complicated that just removing sugar from the food. Thus, innovation and advances in recipe development from the food and drink industry have made possible a wide variety of great-tasting food and beverage products sweetened with LNCS.

The increased range of available LNCS, and the fact that these can be used either alone or in blends, is a useful tool in food reformulation efforts. LNCS can be used synergistically in blends to achieve the desired sensory profile at lower levels of use *(Ashwell et al, 2020)*. By combining two or more LNCS, food and drink manufacturers can tailor the taste and characteristics of sweetness to the demands of a product and to consumers' tastes *(Miele et al, 2017; McCain et al, 2018)*.

In Europe, the use of LNCS is strictly regulated in the legislation on permitted use of additives under European Union (EU) Regulation 1333/2008 and therefore permitted use depends on the food category or categories into which the product falls *(Regulation (EC), 2008)*.

Low/no calorie sweeteners provide an effective way of reducing sugars content of food products helping the food industry in reformulation efforts

Effective prevention and control of non-communicable diseases (NCDs) require a 'whole-of-society effort'

At the United Nations (UN) General Assembly meeting in September 2011, global leaders committed to responding to the challenge of NCDs with a political declaration which recognised that effective NCDs prevention and control requires a 'whole-of-society effort' through an integrated multi-sectoral approach including the engagement of industry. At subsequent UN High-level Meetings on NCDs in 2014 and 2018, governments took stock of the progress made and re-confirmed their commitment to a coherent, inclusive, multi-stakeholder effort to stem the rise of NCDs. The next High-level Meeting of the United Nations General Assembly will be held in 2025 when the World Health Assembly has settled on a deadline for a set of nine voluntary global targets for the prevention and control of NCDs.

Industry was called upon to contribute to reducing NCDs risk factors and creating health-promoting environments by **"reformulating products to provide healthier options"**. **In seeking to support this global public health objective through product reformulation, LNCS are critical ingredients to help achieve products with less sugars and fewer/zero calories, while still being palatable to consumers.** This has allowed the food industry to respond with innovation and product development and to bring to the market less energy-dense foods and drinks. To sustain and scale up these efforts, LNCS have a key role to play in providing the consumer with wider choice and in creating healthier food environments.

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The role of low/no calorie sweeteners in reducing the intake of free sugars

Low/no calorie sweetened products can help individuals replace sugar-sweetened foods and drinks in their diet and, hence, reduce free sugars intake in line with public health recommendations (*SACN, 2015; WHO, 2015; EFSA, 2022*). Research confirms the beneficial role of LNCS use in sugars intake reduction. A systematic review by the World Health Organization (WHO) found that, as assessed in meta-analyses of randomised controlled trials (RCTs), LNCS intake resulted in a reduction in sugars intake of approximately 39 grams per day (*Rios-Leyvraz and Montez, 2022*). The same study showed that LNCS use led to a significant reduction of total energy intake by almost 134 kcal per day.

Several observational studies have also reported that LNCS consumption is associated with lower dietary sugars intake (*Drewnowski and Rehm, 2014; Hedrick et al, 2015; Gibson et al, 2016; Hedrick et al, 2017; Leahy et al, 2017; Patel et al, 2018; Silva-Monteiro et al, 2018; Barraj et al, 2019; Fulgoni and Drewnowski, 2022*). These findings confirm that low/no calorie sweetened foods and drinks can play a useful role in helping individuals to reduce their free sugars intake in the context of public health recommendations and nutritional guidelines.

Furthermore, in Europe, the use of LNCS in a food or beverage, in almost all cases, must also result in a product that has a total energy reduction of at least 30% according to European Union (EU) Regulation 1333/2008 on food additives (Regulation (EC), 2008). For consumers, this can mean a significant calorie saving, which may be especially helpful in managing overall energy balance.

Low/no calorie sweeteners can help us reduce sugars and energy (calorie) intakes, in line with public health recommendations

LNCS CAN HELP IN REDUCING TOTAL DAILY SUGARS AND ENERGY INTAKES

(REDUCTION OF ~39G SUGARS AND ~134 KCAL PER DAY)

Source: As assessed in meta-analyses of RCTs in the WHO systematic review by Rios-Leyvraz and Montez, 2022

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Sugar-swaps and calorie savings

By using LNCS in place of caloric sweeteners and by swapping a sugar-sweetened food or drink with its low/no calorie sweetened equivalent, we can remove both sugars and energy (calories) from a variety of foods and drinks. For example, by adding table-top sweeteners instead of sugars in beverages, we can "save" approximately 4 g of sugars and 16 kcal for each teaspoon of added sugars. Similarly, by switching to a diet/light/zero sugar soft drink, which contains less than 1 kcal, we can reduce energy intake by around 100 kcal per glass (or 140 kcal per can of 330ml) as compared to the regular (sugar-sweetened) product. More examples of calorie- and sugar-saving swaps are provided in Table 1.

Click here for Table 1

By **adding table-top sweeteners** instead of table sugar in our coffee or tea, we can "save" approximately 16-20 calories and 4-5g of sugar for each teaspoon of added sugar.

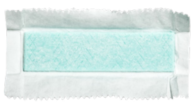
By **switching to a diet/light/zero soft drink** from the sugar-sweetened version, we can "save" approximately 100 calories per glass (250ml) and about 25g of sugar.

By **choosing a low-fat fruit yogurt** with low calorie sweeteners instead of the sugar-sweetened version, we can "save" about 50 calories and about 10g of sugar per portion (200g).

Table 1: Calorie and sugars content in sugar-sweetened versus comparable low/no calorie sweetened products (on average or range of values).







Sugar-sweetened products			Low/no calorie sweetened products		
Type of product	Energy (kcal)	Sugars (g)	Type of product	Energy (kcal)	Sugars (g)
1 teaspoon (4 g) of sugar (white, brown)	16	4	Table-top sweeteners	1	0
1 glass (250 ml) of sugar-sweetened cola-type soft drink	100	25	1 glass (250 ml) of diet/ light/ zero cola-type soft drink	<1	0
1 glass (250 ml) of iced tea drink with sugar	60	15	1 glass (250 ml) of iced tea drink with sugar	<5	0-1
1 portion (200 g) of low fat (1%) fruit yogurt with sugar	160	25	1 portion of low fat fruit yogurt with LNCS (200 g)	110	15
1 large scoop (100 g) of vanilla ice cream with sugar (full fat)	170	22	1 large scoop (100 g) of vanilla ice cream with LNCS (full fat)	120	8
A serving of raspberry jelly with sugar	80	20	A serving of raspberry jelly with LNCS	10	2
1 tablespoon (20 g) of jam with sugar	40-50	10-12	1 tablespoon of jam with LNCS	10-20	2-5
1 tablespoon (17 g) of ketchup with sugar	16	4	1 tablespoon of ketchup with LNCS	7	1
1 piece of chewing gum with sugar	10	2,5	1 piece of chewing gum with LNCS	<5	0
1 piece of hard candy with sugar	25	4	1 piece of hard candy with LNCS	10	0





Source: U.S. Department of Agriculture, Agricultural Research Service. FoodData Central, 2019. fdc.nal.usda.gov.

Experts' views

Low/no calorie sweeteners in sugar reduction: A public health perspective...

Prof Alison Gallagher: Current public health recommendations are that we limit our dietary intakes of free sugars. Free sugars are those added to food or those naturally present in honey, syrups and unsweetened fruit juices, but do not include naturally occurring sugars in milk and milk products. The potential negative impact of high consumption of free sugars on health, particularly from sugar-sweetened beverages, is well recognised being associated with increased weight gain (and thus contributing to obesity), increased risk of developing type 2 diabetes and increased incidence of tooth decay. The World Health Organization (WHO) recommends that we reduce our intakes of free sugars across the life course, recommending that adults and children limited their intake of free sugars to 10% of total energy intake (*WHO, 2015*). In the UK, the Scientific Advisory Committee on Nutrition (SACN) recommends intakes of free sugars should not exceed 5% of total energy intake (*SACN, 2015*). Given the current high consumption of free sugars within the population (in the UK average intakes are estimated to be over double the recommended), achieving such reductions in sugar intakes is challenging and requires targeted approaches including the promotion of healthier choices, reductions in portion size and product reformulations.

LNCS provide a desired sweet taste without the addition of appreciable energy and can help maintain the palatability of reformulated products. All LNCS undergo rigorous safety evaluations prior to their approval for use, usually resulting in the assignment of an acceptable daily intake (ADI) and we can be confident about the safety of LNCS currently approved for use in foods and beverages; indeed, recent global intake data highlight no cause for concern in relation to current LNCS intakes (Martyn et al, 2018). When used to replace sugar-sweetened products with LNCS alternatives, LNCS represent an easy way to reduce dietary intake of sugars. For example, replacing a regular (sugar-sweetened) product with a LNCS equivalent results in a reduction in sugar and energy intake. When used in this way, LNCS have the advantage of reducing energy intake without reducing the palatability (or sweetness) of the diet. Reformulating a beverage to reduce its sugars content is a relatively straight-forward. However, reformulating a food product can be more challenging since the sugars may be present in the food matrix not only for sweetness and palatability, but also for its functional properties. LNCS continue to represent a useful part of efforts to reduce overall intakes of sugars and help with body weight management.

Sugar reduction policies: The UK example

In the United Kingdom, a structured and monitored sugar reduction programme was launched in 2016 with an objective for all sectors of the food industry to voluntarily reduce sugar by 20% by 2020 across the top categories of food that contribute most to intakes of children up to the age of 18 years.

The role of LNCS use in food and beverage reformulation efforts to help the industry achieve sugar reductions was pointed out in evidence reviews and technical reports by Public Health England (PHE) (*PHE, 2017*). The PHE technical report "Sugar Reduction: Achieving the 20%" outlined guidelines for the industry endorsing the European Food Safety Authority's (EFSA) scientific opinion on LNCS and stated that: "Sweeteners that have been approved through EFSA's processes are a safe and acceptable alternative to using sugar and it is up to businesses if and how they wish to use them" (*PHE, 2017*). In reviewing the scientific evidence for sugar reduction, PHE also recognised that replacing foods and drinks sweetened with sugars with those containing LNCS could be useful in helping people to manage their weight as they reduce the calorie content of foods and drinks while maintaining a sweet taste (*PHE, 2015*).

A final progress report between 2015 and 2020 showed mixed progress across different sectors and food categories indicating significant reductions in sugar content in drinks and in specific food categories in retailers and manufacturer branded products (e.g., yogurts, fromage frais, breakfast cereals, ice cream, lollies and sorbets, sweet spreads and sauces), while less progress was reported for the out of home sector (*OHIC, 2022*). Compared with a baseline year of 2015 or 2017, larger sugar content reductions (reductions in sales weighted average sugar per 100ml) were reported for various drink categories, especially for soft drinks (-46%), pre-packed milk based drinks (-29,7%), milkshake powders, syrups and pods as consumed (-34.2%), coffee and tea powders, syrups and pods as consumed (-20.3%), fermented yogurt drinks (-7.1%), and flavoured milk substitute drinks (-6.9%), while reductions for pre-packed juice categories were smaller.

In 2022, WHO Europe launched a new, voluntary, Member State led Sugar and Calorie Reduction Network to promote healthier diets as well as reduce overweight and obesity levels across the WHO European Region, which will be led by the UK Department of Health and Social Care (DHSC) and its Office for Health Improvement and Disparities (OHID) for the first 3-year term, bringing forward the UK's extensive experience in addressing sugar intake at the national level (*WHO/Europe, 2022*).

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Role of low/no calorie sweeteners in a healthy diet

Healthy dietary patterns encourage the consumption of a variety of vegetables and fruits, nuts and pulses, whole grains, lean protein foods with emphasis on plant-based sources, and vegetable oils, while emphasising the importance of limiting intakes of foods high in saturated fats, salt, and sugars. Limiting intake of free sugars to less than 10% of total energy intake is part of a healthy diet, as indicated by strong scientific evidence *(WHO, 2015)*. **LNCS and products containing them can support individuals in meeting recommendations to reduce excessive sugars consumption, as part of an overall healthy diet and lifestyle.**

The consumption of LNCS has been linked to improved diet quality in several observational studies examining the dietary habits of different populations around the world *(Duffey and Popkin, 2006; Sánchez-Villegas et al, 2009; Naja et al, 2011; Drewnowski and Rehm, 2014; Hedrick et al, 2015; Gibson et al, 2016; Hedrick et al, 2017; Leahy et al, 2017; Patel et al, 2018; Silva-Monteiro et al, 2018; Barraj et al, 2019; Fulgoni and Drewnowski, 2022)*.

In the first study that examined the health habits of LNCS consumers, Drewnowski and Rehm used data from the National Health and Nutrition Examination Survey (NHANES) collected between 1999 and 2008 from more than 22,000 US citizens *(Drewnowski and Rehm, 2014)*. The researchers reviewed the participants' diets using the Healthy Eating Index, a USDA tool to compare an individual's diet to the Dietary Guidelines for Americans, and found that LNCS consumers had much higher scores on the index than those who did not consume LNCS. Consumers of LNCS reported similar energy intakes but higher intakes of fruits, vegetables, calcium and magnesium, as well as lower intakes of fat, added sugars, and saturated fats, compared to non-consumers. So, overall, LNCS consumers had a better diet quality as illustrated in Figure 2. The same study also showed that individuals who consumed LNCS were less likely to smoke and tended to be more physically active. In all, this was the first study indicating that LNCS consumption was correlated with an overall healthier diet and lifestyle.

LNCS consumers had better diets

Figure 2: Healthy Eating Index in consumers of low/no calorie sweeteners (LNCS) vs. non-consumers. *(Drewnowski and Rehm, 2014)*
Source: Center for Public Health Nutrition, University of Washington

Source: Center for Public Health Nutrition, University of Washington (*Drewnowski and Rehm, 2014*)

These findings were later confirmed in US studies by Leahy et al (2017), Barraj et al (2019) and Fulgoni and Drewnowski (2022) who used data from more recent NHANES cycles. Leahy and colleagues found that higher consumption of low/no calorie sweetened drinks was associated with significantly lower intakes of total and added sugars (*NHANES 2001–2012; n=25,817*) (*Leahy et al, 2017*). Barraj and colleagues showed that, across all life stages, consumers of low/no calorie sweetened beverages had higher diet quality and lower intakes of total and added sugars when compared to consumers of sugar-sweetened beverages (SSBs) (*NHANES 2009-2016; n=32,959*) (*Barraj et al, 2019*). More recently, Fulgoni and Drewnowski (2022) also reported that LNCS consumers had higher diet quality and were less likely to smoke, indicating an overall healthier lifestyle (*NHANES 1999-2018; n=48,754*). Interestingly, a study of randomised controlled design in a US sample of rural Virginian adults found similar results: LNCS consumers had significantly higher overall dietary quality than non-consumers, as assessed via the Healthy Eating Index (*Hedrick et al, 2017*).

Similarly, two UK studies that examined data from the UK National Diet and Nutrition Survey (NDNS) found that consumers of LNCS beverages had a better diet quality compared to consumers of SSBs *(Gibson et al, 2016; Patel et al, 2018)*. Gibson and colleagues found that the LNCS group had higher fish, fruits and vegetables intake, and lower meat, fat and saturated fat as well as lower sugar and energy intake, compared to SSBs consumers *(Gibson et al, 2016)*. These findings were confirmed in a subsequent analysis of NDNS data (data collected 2008-2012 and 2013-2014) in a larger sample of 5,521 British adults *(Patel et al, 2018)*. Patel and colleagues found that consumers of low/no calorie sweetened beverages had lower total and free sugars intake and an overall better diet quality, compared to consumers of SSBs *(Patel et al, 2018)*. The study also found that consumers of LNCS beverages were more likely to meet UK recommendations for free sugars' intake, compared to consumers of SSBs *(Patel et al, 2018)*.

Similar findings have also been reported in population studies from other countries *(Sánchez-Villegas et al, 2009; Naja et al, 2011; Hedrick et al, 2015; Silva-Monteiro et al, 2018)*. For example, in a study analysing data of 32,749 individuals participating in the nationally representative Brazilian National Dietary Survey (data collected 2008–2009), it was shown that the mean daily energy intake of participants using table-top sugar (sucrose) was approximately 16% higher compared with those who used LNCS-containing table-top LNCS (Silva-Monteiro et al, 2018). On average, the use of table-top sugar to sweeten foods and beverages was accompanied by an increase of 186 kcal daily compared with the use of table-top LNCS, which corresponded to a 10% increase in total energy intake. Furthermore, individuals who reported exclusive use of sweeteners to sweeten their foods and drinks had also lower consumption of SSBs, sweets and desserts, and higher consumption of vegetables and fruits, compared to those who used sugar, indicating a dietary pattern of higher quality for LNCS users.

Consumers of low/no calorie sweetened foods and drinks tend to have higher quality diets with less sugar-containing food products

Recommendations about the use of low/no calorie sweeteners as part of a healthy diet

The recommendation to limit the excess intake of free or added sugars in the diet is based on strong evidence and therefore supported by health organisations and public health authorities worldwide *(SACN, 2015; WHO, 2015; EFSA, 2022)*. **LNCS can be safely used to replace and help reduce dietary sugars as part of a healthy eating plan, as confirmed by food safety bodies globally** (See Chapter 2). This is also reflected in Food-Based Dietary Guidelines (FBDG) and position statements of health and nutrition organisations around the world.

The benefit of replacing added sugars with LNCS in reducing energy intake in the short-term and aiding in weight management was supported by the US Dietary Guidelines for Americans, 2020-2025 (*USDA, 2020*) based on the results of a systematic review and the recommendation by the US Dietary Guidelines Advisory Committee (*DGAC, 2020*). Similarly, the UK dietary guidelines "The Eatwell Guide" recognised that by replacing sugary foods and beverages with LNCS options, people can reduce sugar intake while still keep enjoying the desired sweet taste in their diet. As such, LNCS can play a helpful role in individuals' efforts to keep their daily free sugars intake below the recommended level of 5-10% of total energy intake (*PHE, 2016*).

The role of LNCS in dietary sugars and energy reduction and, hence, their potential benefit in weight control and the nutritional management of diabetes has also been acknowledged by numerous health and nutrition organisations, including the Academy of Nutrition and Dietetics in the United States *(Fitch et al, 2012; Franz et al, 2017)*; the American Diabetes Association *(Gardner et al, 2012; Evert et al, 2019; ElSayed et al, 2023)*, and the American Heart Association *(Gardner et al, 2012; Johnson et al, 2018)*, the British Dietetic Association (BDA, 2016) and Diabetes UK *(Diabetes UK, 2018; Dyson et al, 2018)*, the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) (DNSG-EASD, 2023), the Latin-American Association of Diabetes *(Laviada-Molina et al, 2018)*, the Mexican Societies of Cardiology and of Nutrition and Endocrinology *(Alexanderson-Rosas et al, 2017; Laviada-Molina et al, 2017)*, and Obesity Canada *(Brown et al, 2022)*, among others.

Contrary to these recommendations of clinical practice guidelines for the nutritional management of obesity and diabetes by multiple organisations around the world, a recent WHO guideline on the use on non-sugar sweeteners suggested that they should not be used as a means of achieving weight control or reducing risk of noncommunicable diseases issuing a **conditional** (or else "weak") recommendation (*WHO, 2023*). Conclusions were largely based on low certainty evidence from observational studies which are at high risk of reverse causation and are discussed in detail in the next Chapter (see Chapter 4). Importantly, the recommendation is not supported by the results of the WHO systematic review and meta-analyses of RCTs, which showed that the use of LNCS leads to reduced sugars and energy intakes, and in turn to modest weight loss without affecting cardiometabolic risk factors *(Rios-Leyvraz and Montez, 2022)*. Finally, WHO has not examined whether implementing this conditional recommendation suggesting against LCNS use could lead to undesirable effects, such as to increased sugars intake and associated health outcomes.

The evidence supporting the benefits of LNCS is discussed in detail in the next chapters of this booklet (Chapter 4 – Low/no calorie sweeteners and weight control; Chapter 5 – Low/no calorie sweeteners, diabetes and cardiometabolic health; Chapter 6 – Low/no calorie sweeteners and oral health).

i

"Conditional recommendations are those recommendations for which the WHO guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very small. Therefore, substantive discussion amongst policy-makers may be required before a conditional recommendation can be adopted as policy." (WHO, 2023)

Conclusion

Enjoying the food we eat while aiming for a healthier diet is key for sustainable, long-term dietary changes. Strategies aimed at improving diet quality should also consider the sensory pleasure response to foods. However, reducing sugars intake may sometimes go against the latter. In this context, **LNCS can help reduce excess intake of dietary sugars while still keeping the enjoyment of sweet taste in the diet as part of an overall healthy dietary pattern.**

LNCS can provide a means to help reduce energy and sugars intake and be a useful dietary tool to people with weight management LNCS can provide a means to help reduce energy and sugars intake and be a useful dietary tool for dental health, and to people with weight management problems or those living with diabetes, as discussed in the next three Chapters.

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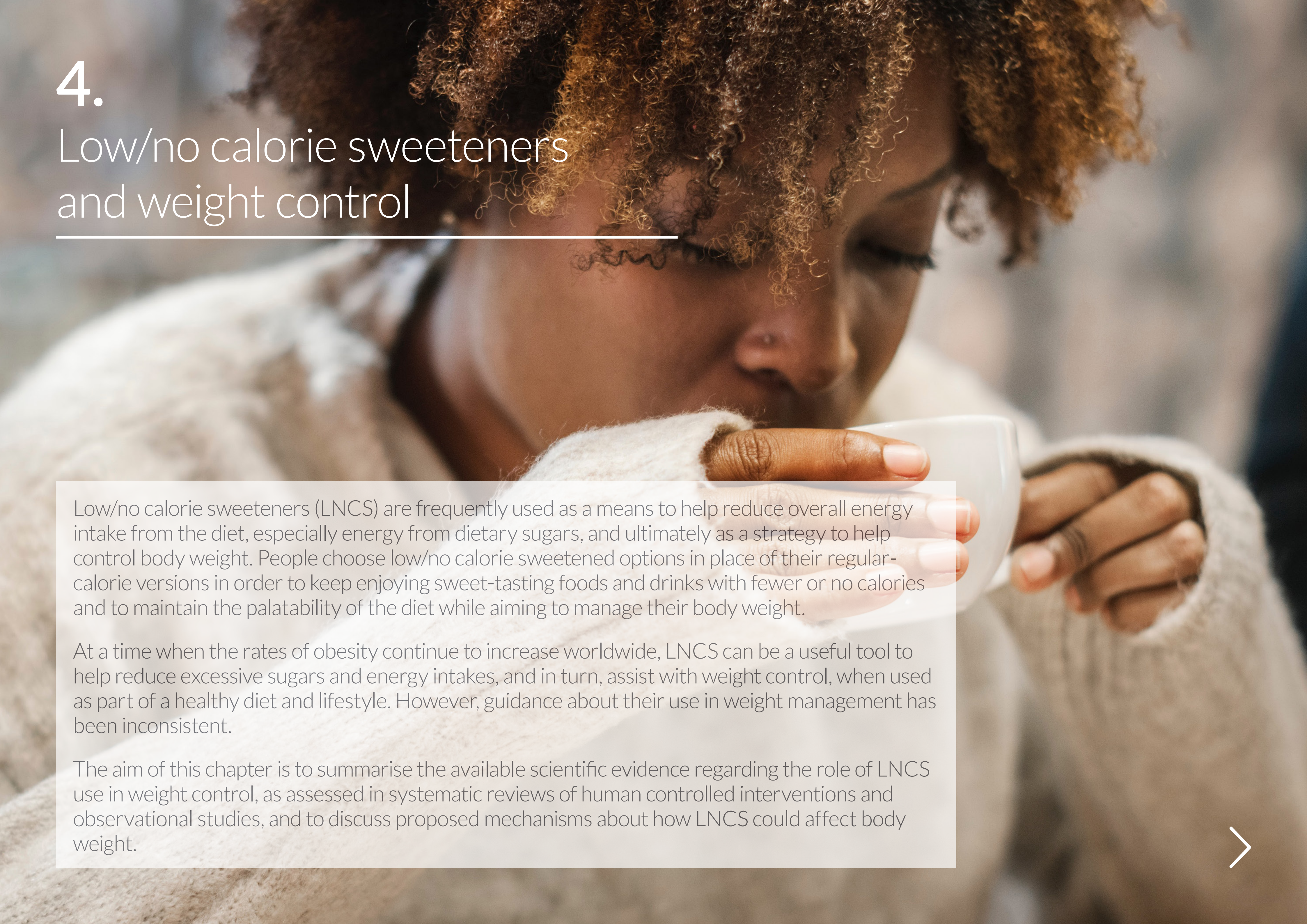

4.

Low/no calorie sweeteners and weight control

Low/no calorie sweeteners (LNCS) are frequently used as a means to help reduce overall energy intake from the diet, especially energy from dietary sugars, and ultimately as a strategy to help control body weight. People choose low/no calorie sweetened options in place of their regular-calorie versions in order to keep enjoying sweet-tasting foods and drinks with fewer or no calories and to maintain the palatability of the diet while aiming to manage their body weight.

At a time when the rates of obesity continue to increase worldwide, LNCS can be a useful tool to help reduce excessive sugars and energy intakes, and in turn, assist with weight control, when used as part of a healthy diet and lifestyle. However, guidance about their use in weight management has been inconsistent.

The aim of this chapter is to summarise the available scientific evidence regarding the role of LNCS use in weight control, as assessed in systematic reviews of human controlled interventions and observational studies, and to discuss proposed mechanisms about how LNCS could affect body weight.

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Introduction

Obesity poses an increasing public health challenge worldwide. More than two billion people globally are living with overweight or obesity with the prevalence nearly tripled from 1975 to 2016 *(NCD-RisC, 2017)*. Alarmingly, recent studies from several countries suggest that the COVID-19 pandemic has accelerated the rising rates of obesity, especially among children and adolescents *(WHO Europe, 2022)*.

Obesity is a complex and multifactorial disease caused by an interplay of genetic, metabolic, behavioural and environmental factors *(WHO, 2021)*. Living with overweight and obesity affects both physical and psychological health. People living with obesity experience weight bias and stigma *(Wharton et al, 2020)*. Importantly, they are at increased risk of developing noncommunicable diseases (NCDs) including cardiovascular diseases, type 2 diabetes, and some types of cancer, and more likely to be hospitalized for COVID-19 *(WHO Europe, 2022)*.

Facts about overweight and obesity

More than 2 billion people globally are living with overweight or obesity[1]

In Europe, overweight and obesity affect almost **60% of the adult population** and nearly **one in three children**[2]

Sources:
(1) World Health Organization (WHO). Factsheet. Obesity and overweight. 9 June 2021. Accessed 21 October 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight;
(2) WHO European Regional Obesity Report 2022. Copenhagen: WHO Regional Office for Europe; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Body weight is affected by many factors including unhealthy diets and physical inactivity which can lead to energy imbalance between energy (calories) consumed and energy (calories) expended (Figure 1) *(Bray et al, 2018)*. At an individual level, a number of strategies that can help people increase their energy expenditure and/or limit their daily energy intake, especially from excessive dietary fat and sugars consumption, have a role to play in weight management efforts *(WHO, 2021)*. **By replacing caloric sweeteners in foods and beverages, LNCS are one among a pool of dietary tools that can help bring down total energy intake, and in turn assist in weight control** *(Ashwell et al, 2020)*.

The energy our body needs to function normally is measured in kilojoules or kilocalories, commonly called calories.

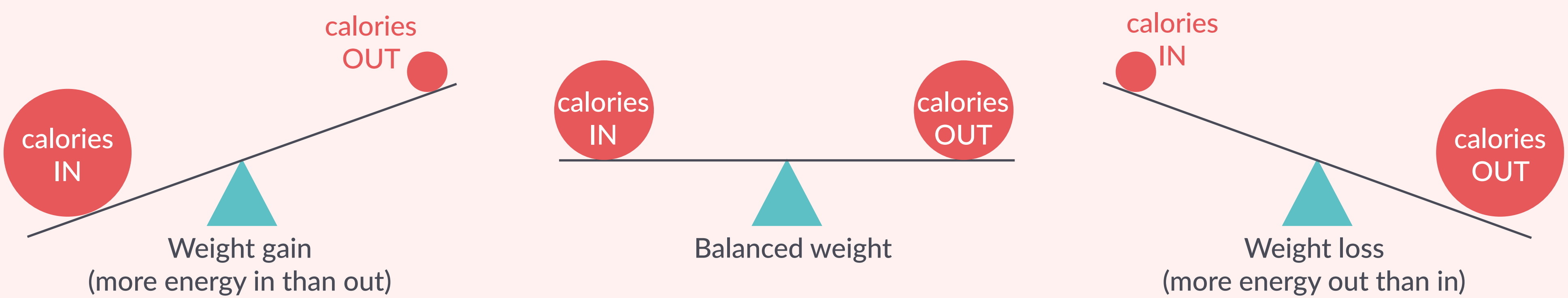

Figure 1: The impact of energy balance (calories in – calories out) on body weight.

Low/no calorie sweeteners and body weight: Evidence from human studies

The impact of LNCS on body weight has been studied in numerous well-designed randomised controlled trials (RCTs), which represent the most reliable study design for drawing causal inferences. The collective evidence from these studies, as assessed in systematic reviews and meta-analyses of RCTs, indicates a modest but robust and significant beneficial effect of LNCS use on weight loss when they are used in place of dietary sugars and in the context of an overall healthy diet and lifestyle *(Miller and Perez, 2014; Rogers et al, 2016; Laviada-Molina et al, 2020; Rogers and Appleton, 2021; McGlynn et al, 2022; Rios Leyvraz and Montez, 2022)*.

Despite the consistently supportive evidence from RCTs, the role of LNCS in weight control is frequently questioned. The controversy arises primarily from the divergent results reported between RCTs and observational studies, which can be explained by the variability and the nature of the study design *(Normand et al, 2021)*. In contrast to RCTs, observational studies frequently suggest a positive association between higher LNCS intake and increased body weight or obesity *(Azad et al, 2017; Rios Leyvraz and Montez, 2022)*, however, correlation in observational research does not imply causation *(Andrade et al, 2014)*.

Each study design has its strengths and limitations, however the associations reported in observational studies are prone to residual confounding and reverse causality, meaning that people living with overweight or obesity frequently turn to LNCS to manage their weight and not the other way round *(Mela et al, 2020; Lee et al, 2022)*. A body of evidence based on RCTs is rated as being of higher quality and is regarded the gold standard in the hierarchy of research designs (Figure 2) *(Richardson et al, 2017)*.

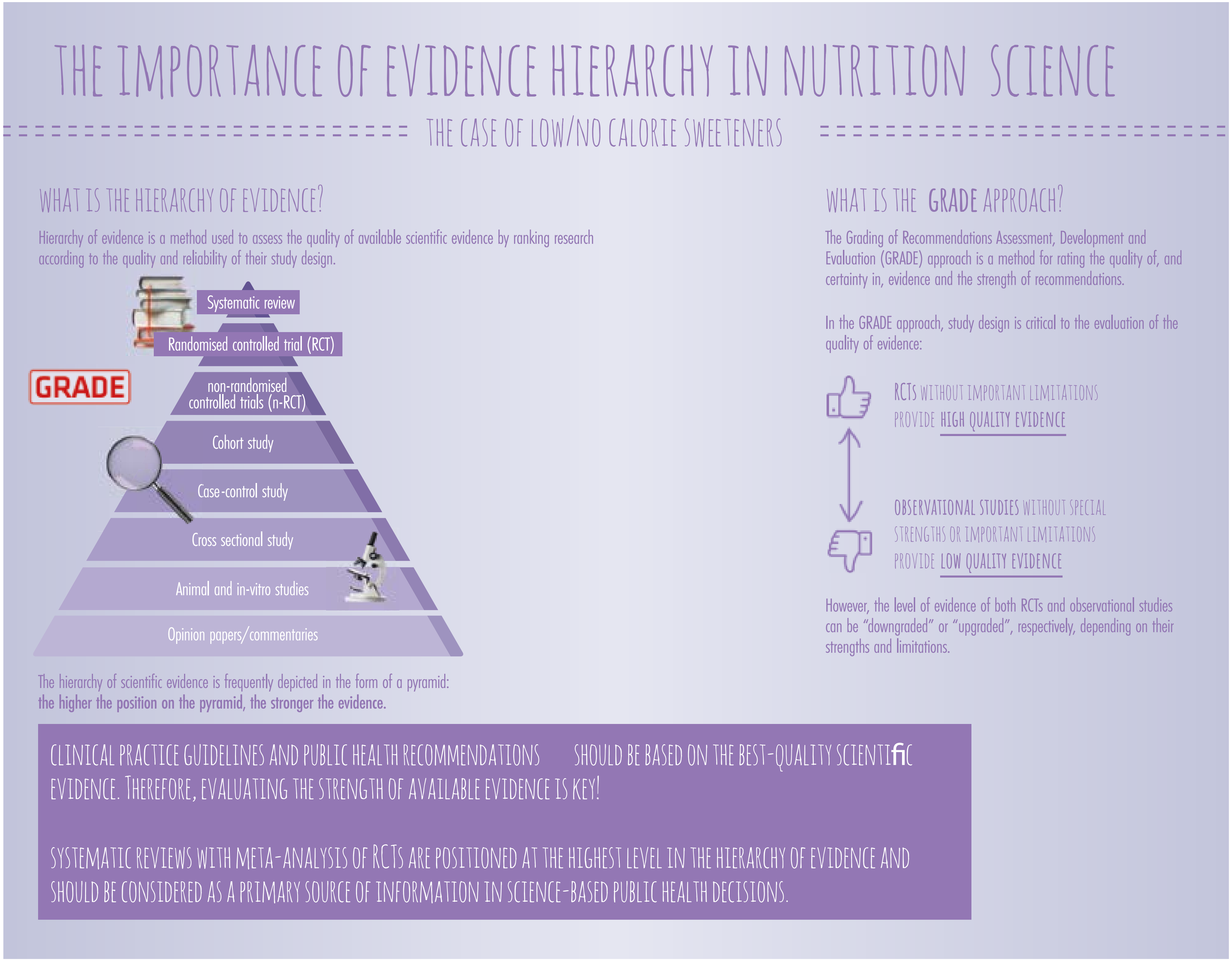

Figure 2: The importance of evidence hierarchy in nutrition science (Source: ISA Infographic).

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Evidence from systematic reviews of randomized controlled trials (RCTs)
Over the last decade, there have been several publications of comprehensive systematic reviews and meta-analyses of RCTs investigating the impact of LNCS on body weight. **Overall, these studies support the assertion that LNCS can help people reduce overall energy intake** *(Lee et al, 2021; Rogers and Appleton, 2021; Rios-Leyvraz and Montez, 2022)* **and thus be a useful tool in weight control, when used to replace dietary sugars and as part of an energy-controlled diet and a healthy lifestyle** *(Miller and Perez, 2014; Rogers et al, 2016; Dietary Guidelines Advisory Committee, 2020; Laviada-Molina et al, 2020; Rogers and Appleton, 2021; McGlynn et al, 2022; Rios-Leyvraz and Montez, 2022)*. The conclusions of key systematic reviews and meta-analyses of RCTs studying LNCS impact on weight control are summarised in Table 1.

In 2022, a systematic review assessing the health effects of LNCS was published by the World Health Organization (WHO) *(Rios-Leyvraz and Montez, 2022)*. The results of this meta-analyses of 29 RCTs (2433 participants) showed that LNCS use resulted in reduced sugars and energy intake, modest weight loss, and lower body mass index (BMI), without affecting other measures of adiposity. The effects were more pronounced when LNCS were compared with sugars, mediated by a reduction in energy intake *(Rios-Leyvraz and Montez, 2022)*. The benefit of replacing added sugars with LNCS in reducing energy intake in the short-term and aiding in weight management is also supported by a systematic review by the US Dietary Guideline Advisory Committee (2020) of the Dietary Guidelines for Americans, 2020-2025.

Similarly, a systematic review and network meta-analysis of 17 RCTs (1444 participants) examining the cardiometabolic effects of beverages sweetened with LNCS found that substituting sugar-sweetened beverages (SSBs) with LNCS beverages was associated with reductions in adiposity and cardiometabolic risk factors in adult participants with overweight or obesity who were at risk of developing or had type 2 diabetes *(McGlynn et al, 2022)*. The results showed that substituting SSBs with LNCS beverages was associated with small but significant reductions in body weight, BMI, percentage of body fat and intrahepatocellular lipid, with moderate certainty of evidence *(McGlynn et al, 2022)*. These improvements were similar in direction and effect size to those associated with water substitution.

The largest systematic review and meta-analyses of RCTs to date also concluded that the evidence from human intervention studies supported the use of LNCS in weight management, when they were consumed in place of sugars in the diet *(Rogers and Appleton, 2021)*. The study analysed data from 60 studies including 88 RCTs according to whether they compared LNCS with sugars (involving 2267 participants), LNCS with water or nothing (1068 participants), or LNCS capsules with placebo capsules (521 participants). Results showed a favourable effect of LNCS on body weight, BMI and energy intake, when LNCS were compared with sugars. The study also found that the more sugar is removed from the diet, the greater the impact was: for every 240 calories replaced by LNCS, body weight decreased by approx. 1 kg in adults. Furthermore, when LNCS were compared to water or placebo, and hence no energy displacement occurred, there was no difference in weight outcomes *(Rogers and Appleton, 2021)*.

A few years earlier, Laviada-Molina and colleagues published a systematic review and meta-analysis of 20 RCTs involving 2914 children and adult participants that assessed the effects of LNCS on body weight under several clinical scenarios *(Laviada-Molina et al, 2020)*. The study found that replacing dietary sugars with LNCS led to weight reduction, whereas when LNCS were compared with water or placebo there was no significant difference on body weight. Laviada et al. concluded that the use of LNCS resulted in clinically appreciable lower body weight/ BMI, especially in people with overweight or obesity, a result that was also reported in a WHO-supported review by Toews et al, which however included only a limited subset of the available literature *(Toews et al, 2019)*.

Earlier systematic reviews and meta-analyses of RCTs that have examined LNCS effects taking into consideration the nature of the comparator (i.e., LNCS versus sugar, or water, or placebo) consistently indicated a modest decrease in body weight with LNCS use compared with sugars *(Miller and Perez, 2014; Rogers et al, 2016)*, while meta-analyses that have not made a distinction between comparators indicated a neutral effect on body weight *(Azad et al, 2017)*. It should be expected that the intended effect of LNCS would differ depending on the amount of energy that is available to be displaced from the comparator, e.g., sugars *(Sievenpiper et al, 2017)*. Therefore, when LNCS are compared to water or placebo with no caloric displacement (isocaloric comparators), no meaningful weight loss is found.

In all, evidence from human intervention studies supports the assertion that LNCS use can assist in weight control, with the overall beneficial effect depending on the amount of dietary sugars, and hence energy (calories) that LNCS can displace in the diet.

Table 1: Systematic reviews and meta-analyses of randomised controlled trials (RCTs) examining the impact of low/no calorie sweeteners (LNCS) on body weight, published in the last decade

Publication (author, year)	Number of included studies	Study characteristics (PICO) *Population*	*Intervention*	*Comparators*	*Outcome*	Conclusions
Miller and Perez, 2014	15 RCTs with ≥2-wk duration	Healthy population of any age, gender, weight status	Any type of LNCS and food/drink products with LNCS	SSBs and/or beverages, or placebo capsules, or energy-reduced diet without LNCS	Body weight, BMI, fat mass, waist circumference	LNCS modestly but significantly reduced body weight, BMI, fat mass, and waist circumference.
Rogers et al, 2016	12 RCTs with ≥4-wk duration	Healthy population of any age, gender, weight status	Foods or beverages with any type of LNCS	Sugar-sweetened products, or water or habitual diet	Body weight, BMI	Consumption of LNCS versus sugars led to reduced body weight, and similar relative reduction versus water.
Azad et al, 2017	7 RCTs with ≥6-month duration	Adults and adolescents over 12y, of any gender and weight status	Any type of LNCS	Comparators grouped together without considering their nature (sugars, water, placebo)	BMI, body weight, fat mass, waist circumference	No significant effect of LNCS on BMI and other measures of body composition.
Toews et al, 2019	5 RCTs in adults and 2 in children with ≥7-day duration	Healthy population of any age, gender, weight status	Any type of LNCS; the type of LNCS should be clearly named in the study	Any control (sugars, water, placebo) without considering comparator's nature	BMI, body weight, body fat	In adults, no significant differences in weight change, but a beneficial effect of LNCS on BMI was found for people with overweight and obesity. In children, a smaller increase in BMI z-score was observed with LNCS intake compared with sugars intake.
Laviada-Molina et al, 2020	20 RCTs with ≥4-wk duration	Healthy population of any age, gender, and weight status	Any type of LNCS	Caloric comparators (sucrose, HFCS or non-caloric comparators (water, placebo, nothing)	Body weight, BMI	LNCS use results in lower body weight/ BMI when used in place of sugars, especially in the adult population and in people with overweight/ obesity. No difference when compared to water/ placebo.
Rogers and Appleton, 2021	60 RCTs with ≥1-wk duration	Population of any age, gender, weight, and health status	Any type of LNCS	Sugars or water/ nothing or placebo in capsules	Body weight, BMI	Consumption of LNCS vs sugars decreases body weight by reducing daily energy intake. No differences in body weight for LNCS vs water/ nothing or placebo (non-caloric comparators).

Publication (author, year)	Number of included studies	Study characteristics (PICO) *Population*	*Intervention*	*Comparators*	*Outcome*	Conclusions
McGlynn et al, 2022*	17 RCTs with ≥2-wk duration with 24 trial comparisons (direct and network estimate)	Adults with and without diabetes	Beverages with LNCS	LNCS beverages vs SSBs, or SSBs vs water, or LNCS beverages vs water	Body weight, BMI, body fat, intrahe-patocellular lipid	Substitution of SSBs with LNCS beverages was associated with reductions in body weight, BMI, percentage of body fat, and intrahepatocellular lipid. No difference compared with water.
Rios-Leyvraz & Montez, 2022	32 RCTs in adults and 2 RCTs in children with ≥7-day duration	Healthy populations of adults, children or pregnant women	Any type of LNCS	No or lower doses of LNCS or any type of sugars, or placebo, or water or no intervention	Body weight, BMI, fat mass, lean mass	In adults, higher intakes of LNCS resulted in a reduction in body weight and BMI. Non-significant weight change in children.

*Systematic review with network meta-analysis

Evidence from systematic reviews of observational studies

Contrary to evidence from RCTs, systematic reviews of observational studies provide inconsistent evidence about the association between LNCS intake and body weight *(Miller and Perez, 2014; Rogers et al, 2016; Azad et al, 2017; Toews et al, 2019; Lee et al, 2022; Rios-Leyvraz and Montez, 2022)*. Observational research and reviews in this field frequently report a link between higher LNCS intake and increased body weight or risk of obesity, however the observed associations are susceptible to reverse causation *(Normand et al, 2021)*. This is recognised in WHO-supported reviews *(Lohner et al, 2017; Towes et al, 2019; Rios-Leyvraz & Montez, 2022)*: for example, the WHO-supported scoping review by Lohner and colleagues recognised that: **"a positive association between NNS [non-nutritive sweeteners] consumption and weight gain in observational studies may be the consequence of and not the reason for overweight and obesity"** *(Lohner et al, 2017)*. The case of reverse causation is also backed by data from the US National Health and Nutrition Examination Survey (NHANES) showing that LNCS use is associated with the prior intent to lose weight *(Drewnowski and Rehm, 2016)*.

By design, observational studies cannot establish a cause-and-effect relationship and as such they provide low certainty evidence due to their inability to exclude both unmeasured and measured residual confounding, demonstrate any causal relationships, or attenuate the effects of reverse causality *(Lee et al, 2022)*. To partly overcome the influence of reverse causality, some prospective observational studies have used change or substitution analyses to provide more robust and biologically plausible associations *(Keller et al, 2020)*.

Using low/no calorie sweetened foods and beverages in place of sugar-sweetened products can help in weight control, with the overall benefit depending on the amount of sugars and energy that are displaced in the diet

Aiming to mitigate the impact of reverse causation, a recent systematic review and meta-analysis of 14 prospective cohort studies restricted the analyses to cohort comparisons where investigators modelled the exposure as either change in LNCS intake over time (with repeated intake assessments) or substitution of SSBs with LNCS beverages (i.e., the "intended substitution"), LNCS beverages with water, or SSBs with water. The study results showed that the substitution of SSBs with LNCS beverages was associated with lower weight and reduced risk of obesity, as well as lower cardiometabolic disease risk and total mortality *(Lee et al, 2022)*. The authors stressed that the assessment of changes in exposure over time rather than baseline or prevalent exposure, and further modelling of the intended substitution of SSBs with LNCS alternatives appear to provide more consistent results. Importantly, the results by Lee et al (2022) are also in line with findings of systematic reviews and meta-analyses of RCTs *(McGlynn et al, 2022)*, which are positioned at the highest level in the hierarchy of clinical evidence (Figure 2) *(Burns et al, 2011)*. Indeed, experts raise concerns about the weight that should be placed on observational data when data from controlled clinical studies are available *(Mela et al, 2020)*

Contrary to observational studies that cannot establish a cause-and-effect relationship, randomised controlled trials (RCTs) represent the most reliable study design for drawing causal inferences

Examining proposed mechanisms linking low/no calorie sweeteners to body weight regulation

LNCS impart no or virtually no calories, so they cannot be a cause of body weight gain by virtue of their (lack of) energy content. However, for many years there has been a debate about whether LNCS can affect appetite and food/ energy intake or disrupt metabolic functions and thus cause overeating and weight gain *(Burke and Small, 2015)*. Potential mechanisms have been explored mostly in cell lines and animal models in an attempt to explain the positive association found in observational studies, but to date none of the proposed mechanisms examined in in vitro or animal experiments have been confirmed in human studies *(Peters and Beck, 2016; Rogers, 2018; O'Connor et al, 2021; Lee et al, 2021; Zhang et al, 2023)*.

Energy intake and food reward

By replacing sugars in common foods and beverages, LNCS help to decrease the energy density of these foods, i.e., the amount of calories per unit weight (gram of food), which, in turn, can mean significant calorie savings *(Drewnowski, 1999)* (see Chapter 3). Because low energy-density foods provide fewer calories in the same food weight, they can, in theory, help to reduce our total energy intake, and hence, assist in weight loss *(Rogers, 2018)*. Despite consistent evidence from RCTs supporting that LNCS can lead to energy intake reduction *(Lee et al, 2021; Rogers and Appleton, 2021; Rios-Leyvraz et al, 2022)*, it has been suggested that consumers of LNCS may compensate, consciously or not, for the "missing" calories at the next meal or later during the day, so that their use results in no positive benefit *(Mattes, 1990)*.

In a review of the literature, Rogers (2018) examined three of the most widely proposed mechanisms linking LNCS consumption to weight gain including: (1) the potential for LNCS to disrupt the learned control of energy intake; (2) the potential increased desire for sweet taste by exposure to sweetness and; (3) the conscious overcompensation for 'calories saved'. The author concluded that none of these proposed mechanisms stands up to close examination or has been proven in humans *(Rogers, 2018)*. In fact, in many studies, the use of LNCS is associated with a lower intake of sweet tasting substances *(de Ruyter et al, 2013; Piernas et al, 2013; Fantino et al, 2018)*. This suggests that LNCS may help to satisfy a desire for sweetness and do not encourage a "sweet tooth" *(Bellisle 2015; Rogers 2018)*. The literature regarding potential changes in food reward after LNCS consumption is discussed in Chapter 7.

The benefit of reduced total energy intake with LNCS use in place of dietary sugars has been repeatedly confirmed in more than 60 acute/ short- and long-term RCTs in humans, and assessed collectively in systematic reviews and meta-analyses of RCTs *(Rogers et al, 2016; Lee et al, 2021; Rogers and Appleton, 2021; Rios-Leyvraz and Montez, 2022)*. Numerous short-term RCTs of different study designs have tested the impact of the consumption of low/no calorie sweetened preloads on the subsequent energy intake in an ad libitum meal and compared it to the impact of different comparators including sugars or unsweetened products like water, placebo or nothing (controls) *(Rogers et al, 2016; Lee et al, 2021)*. While studies have shown that there can be some compensation for the "missing" calories when LNCS are used to replace sugars, this compensation is only partial, meaning that there is a net significant caloric decrease (and benefit) with LNCS use when compared to sugars, and thus, a decrease in overall calories consumed over the day *(Rogers et al, 2016)*.

Regarding longer-term effects, the WHO systematic review and meta-analysis of 25 RCTs with a duration from 7 days to two years showed that LNCS use resulted in reduced daily energy intake by approximately 130 calories, with the effect being larger when LNCS were compared with sugars *(Rios-Leyvraz and Montez, 2022)*. This finding is in line with the results of the systematic review and meta-analysis of 34 RCTs by Rogers and Appleton (2021). Moreover, in meta-regression analyses, this study showed an association between sugar dose replaced by LNCS and difference in body weight: the magnitude of this effect is such that for every 1 MJ (approx. 240 kcal) of energy replaced by LNCS, body weight decreases by ~1.06 kg in adults.

Appetite

Suggested biological mechanisms by which an LNCS might impact appetite include, among others, the potential interaction with oral and gut sweet taste receptors affecting appetite-related hormones as well as glucose homeostasis. However, human data to date do not support the hypotheses that LNCS may affect appetite by eliciting a cephalic phase insulin response (CPIR) or by stimulating the gut sweet taste receptors *(O'Connor et al, 2021; Pang et al, 2021)*. These hypotheses are also discussed in greater detail in Chapter 5.

CPIR is an early low-level increase in blood insulin associated with only oral exposure, i.e., occurring prior to increasing plasma glucose levels typically seen with intake of foods containing carbohydrate. Eliciting CPIR has sometimes been hypothesized as a possible way for some LNCS to cause hunger *(Mattes and Popkin, 2009)*. While a few studies have suggested that exposure to LNCS may elicit a CPIR *(Just et al. 2008; Dhillon et al. 2017)*, most clinical trials to date do not confirm such an impact *(Teff et al, 1995; Abdallah et al, 1997; Morricone et al, 2000; Ford et al, 2011; Pullicin et al, 2021)*. Additionally, other research has suggested that CPIR is generally not a meaningful determinant of hunger or glucose response *(Morey et al, 2016)*. Recently, a systematic review on endocrine cephalic phase responses to food cues concluded that there was weak evidence for human CPIR and, importantly, the evidence for the existence of a physiologically relevant CPIR appeared to be minimal *(Lasschuijt et al, 2020)*.

In addition, research in humans has disproved hypothesis arising from early studies of gastrointestinal sweet taste receptors which suggested that LNCS could affect appetite either by causing an increase in the absorption of glucose from the intestinal lumen or by altering the secretion of incretins that play a role in satiety (to ultimately cause increased hunger/food intake) *(Bryant and McLaughlin, 2016)*. While these hypotheses gained much research interest, it must be remembered that they arose mainly from in vitro studies *(Fujita et al, 2009)*. Because many of these studies also exposed cells to an exceptionally high concentration of an LNCS outside of the human body, the testing conditions could have caused reactions that would not be observed with real-life exposure conditions. Therefore, findings from in vitro experiments may not translate to humans, and in any case, results of in vitro testing must not supersede the results of in vivo testing.

In vivo studies, including many RCTs in humans, provide strong evidence that LNCS do not cause an increased uptake of glucose following a meal and otherwise do not adversely affect glycaemic control *(Grotz et al, 2017; Zhang et al, 2023)*, as discussed in detail in the next chapter (see Chapter 5). There is also a lack of evidence from in vivo studies for any clinically meaningful effect of LNCS on the secretion of incretins *(Zhang et al, 2023)* and on gastric emptying *(Bryant and McLaughlin, 2016)* (Figure 3).

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Gut microbiota

It has also been assumed that LNCS could potentially lead to weight gain via causing gut microbiota dysbiosis. The impact of the different LNCS on gut microbiota composition and function are discussed in detail in the next chapter (see Chapter 5), but overall, there is no clear evidence that LNCS may adversely impact body weight, or health in general, via effects on the gut microbiota when consumed by humans at approved levels *(Lobach et al, 2019)*. Also, claims are often based on studies that attribute results of single LNCS to the whole class, despite LNCS being metabolically distinct compounds *(Magnuson et al, 2016)*. Importantly, the clinical significance of reported gut microbiota changes by some LNCS is questioned since, collectively, evidence from RCTs do not confirm adverse effects of LNCS on host physiology *(Hughes et al, 2021)*.

Taken together, there is no causal nor established mechanistic evidence to support the hypothesis that LNCS, or products containing them, can lead to weight gain in humans. In contrast, the collective evidence from RCTs consistently shows that the consumption of LNCS in place of dietary sugars can help reduce overall energy intake, and hence body weight, and that, contrary to the concern that LNCS might increase appetite and food intake, energy intake does not differ for LNCS versus water or versus unsweetened product, both after acute and longer-term consumption.

Evidence suggests low/no calorie sweeteners don't affect hormones involved in appetite control

- The gut brain axis has a key role in the regulation of food intake.
  Brain: Controls appetite, hunger cues, desire to eat.
  Gut: Releases hormones that help regulate nutrient metabolism and signalling to the brain for appetite response.
- Research supports low/no calorie sweeteners have no effect on gut function or hormones to affect the gut-brain axis in controlling food intake in humans.

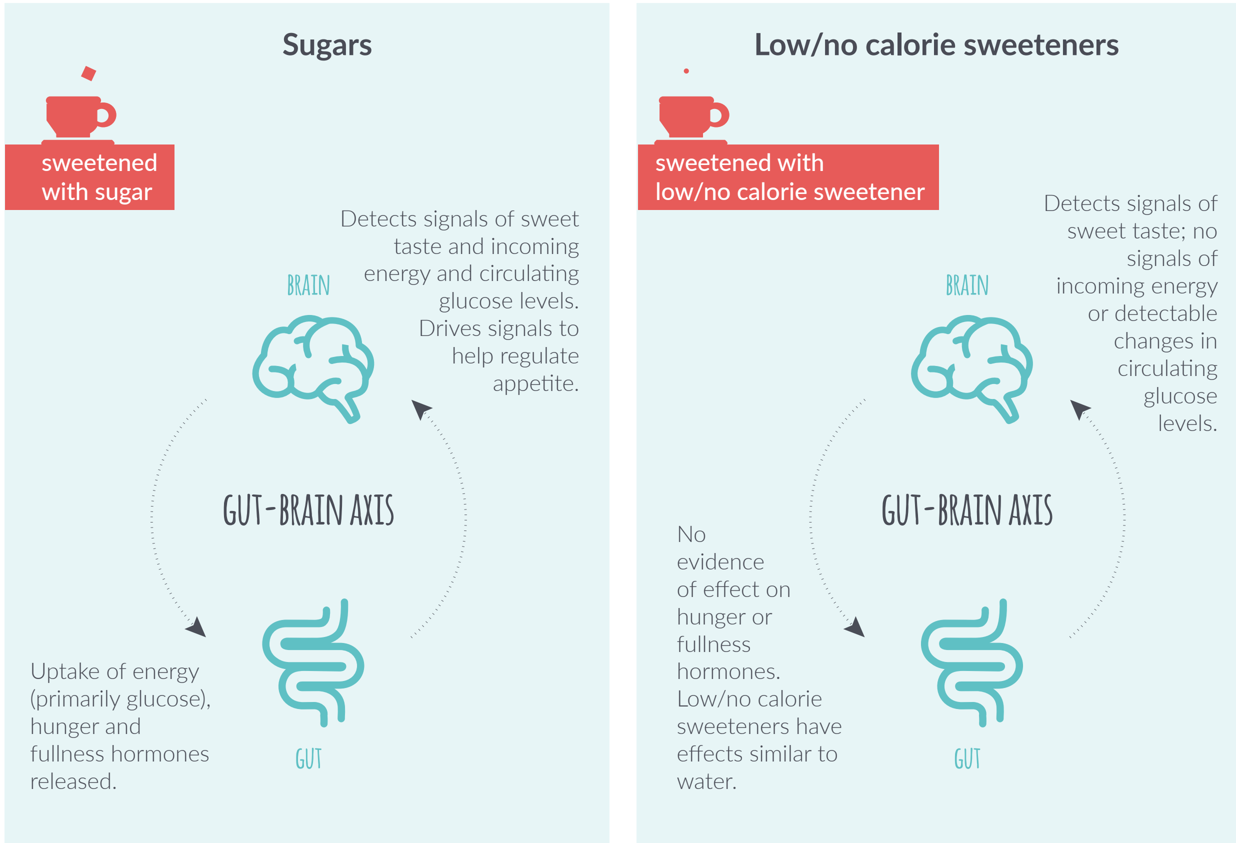

Figure 3: Different effects of sugars and of low/no calorie sweeteners on gut hormones involved in appetite control (Bryant and McLaughlin, 2016).

Do low/no calorie sweeteners affect appetite, hunger and food intake? Evidence from randomised controlled trials (RCTs).

Dr Marc Fantino: Although the ability of LNCS to reduce overall caloric intake has been largely demonstrated by numerous RCTs, some epidemiological observations have reported an association between obesity and LNCS consumption. Ignoring the fact that such an association is more likely reflecting an inverse causality (overweight/ obese people consume LNCS in their effort to limit weight gain), some researchers have cast doubt on the usefulness of LNCS for long-term weight management, claiming that LNCS could increase caloric intake and thus body weight. Two of the most plausible mechanisms of action that could explain how LNCS could hypothetically stimulate food intake have been specifically investigated in a large RCT *(Fantino et al, 2018)*, and ultimately have been refuted.

The first hypothesis postulates that sweet taste provided by LNCS could directly stimulate food intake, by increasing and/ or maintaining the preference for sweet products. However, this hypothesis misses to consider that, among the fundamental taste perceptions, the attractiveness for sweet taste is innate. The second mechanism suggested involves the disruption of learning that governs the physiological control of food intake and energy homeostasis. The uncoupling between the sweet flavour provided by LNCS and the absence of calories could hypothetically distort the learning of the caloric content of other sweet products.

Both hypotheses have not been confirmed experimentally in a published clinical study conducted in 166 healthy, male and female adults, who were initially not habitual consumers of food and drinks containing LNCS *(Fantino et al, 2018)*. The sweet taste provided to the participants by the "acute" consumption of a non-caloric beverage, sweetened with LNCS (3 servings each day x 2 days), did not increase their appetite, hunger and energy intake at subsequent meals (over the next 48 hours), compared to water intake, and even resulted in a significant reduction in the number of sweet food items selected and consumed.

Furthermore, in the second, longer-term arm of this RCT, half of the 166 participants, non-habitual users of LNCS, were "turned" into habitual consumers by a daily administration of 660 mL of the calorie-free drink sweetened with LNCS (2 daily servings) over 5 weeks. The other half remained to water consumption only. After this period, all the participants' ad libitum feeding behaviour was measured again under rigorous experimental conditions, either with water or with the consumption of a significant amount of the same LNCS-sweetened drink. It was found that the participants' food intake was the same under both conditions. Similar results were obtained in both LNCS-naïve and LNCS-habituated individuals. Thus, it was concluded that the longer-term consumption of a high amount of LNCS in beverages by previously non-consumers did not lead to an increase in food and energy intake, disproving the above claims.

In conclusion, the hypotheses that the consumption of foods and beverages sweetened with LNCS could increase subsequent food intake in the following meals or lead to increased overall energy intake in the longer-term do not stand up to close examination and have not been confirmed by the findings of this and other recently published RCTs and systematic review of RCTs *(Lee et al, 2021; Rogers and Appleton, 2021)*.

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The role of low/no calorie sweeteners in long-term weight control and obesity management

At a time when the rates of obesity continue to increase worldwide, LNCS have been proposed as a useful dietary tool to help reduce excessive sugars and energy intakes, and in turn, assist with weight loss and maintenance, when used as part of a healthy diet and lifestyle *(Peters and Beck, 2016)*. Contrary to a WHO recommendation suggesting against the use of non-sugar sweeteners for achieving weight control *(WHO, 2023)*, based on a lack of evidence for LNCS benefits in long-term weight management as assessed in observational studies, clinical practice guidelines for obesity and diabetes management are supportive of a beneficial role of LNCS in weight control *(Fitch et al, 2012; Gardner et al, 2012; Franz et al, 2017; Laviada-Molina et al, 2017; Laviada-Molina et al, 2018; Johnson et al, 2018; British Dietetic Association, 2019; Brown et al, 2022; ElSayed et al, 2023)*, in line with evidence from systematic reviews of RCTs (Table 1) including the WHO study *(Rios-Leyvraz and Montez, 2022)*.

Several organisations globally recognise that LNCS can be safely used in place of sugars to help reduce total energy intake and assist in weight control, as long as no full compensation of energy reduction by intake of other food sources occurs. These include the American Heart Association (AHA) *(Gardner et al, 2012; Johnson et al, 2018)*, the American Diabetes Association (ADA) *(Gardner et al, 2012; ElSayed et al, 2023)*, the Academy of Nutrition and Dietetics (AND) in the United States *(Fitch et al, 2012; Franz et al, 2017)*, the British Dietetics Association (2019), the Latin-American Association of Diabetes *(Laviada-Molina et al, 2018)*, the Mexican Society of Nutrition and Endocrinology *(Laviada-Molina et al, 2017)*, and Obesity Canada *(Brown et al, 2022)*, among others. For example, the 2022 update of the nutritional recommendations of the Canadian Adult Obesity Clinical Practice Guidelines concluded that: "Taken together, these different lines of evidence indicate that low-calorie sweeteners in substitution for sugars or other caloric sweeteners, especially in the form of sugar-sweetened beverages, may have advantages like those of water or other strategies intended to displace excess calories from added sugars" *(Brown et al, 2022)*.

In addition, the US Dietary Guidelines Advisory Committee (2020) recommended LNCS to be considered as an option for managing body weight while the benefit of replacing added sugars with LNCS in reducing energy intake in the short-term and aiding in weight management was supported by the US Dietary Guidelines for Americans, 2020-2025 *(USDA, 2020)*.

Of note, long-term RCTs with a follow-up up to 3 years studying the impact of LNCS on weight control support their useful role in long-term weight management for both adults and children *(Blackburn et al, 1997; de Ruyter et al, 2012; Peters et al, 2016)*. Also, participants from the US National Weight Control Registry who have successfully lost and maintained the reduced weight stated that LNCS helped them manage their energy intake by using them to replace products containing caloric sweeteners *(Catenacci et al, 2014)*. Research suggests that substituting sugar-sweetened foods and beverages with their LNCS sweetened alternatives may be a useful dietary tool to improve compliance with weight loss or weight maintenance plans *(Peters et al, 2016)*.

In an RCT with the longest duration to date, Blackburn and colleagues conducted an outpatient clinical trial investigating whether the addition of the LNCS aspartame to a multidisciplinary weight control programme would improve weight loss and long-term control of body weight over a 3-year follow-up in 163 obese women *(Blackburn et al, 1997)*. The women were randomly assigned to groups that either consumed or abstained from foods sweetened with aspartame. The results indicated that both groups lost an average of 10% of their initial body weight during the 19-week weight loss phase of the study, with those who consumed LNCS being more successful in keeping the lost weight off in the long term during a 1-year maintenance and a 2-year follow-up period. After 3 years, the group that abstained from foods sweetened with aspartame had, on average, regained almost all of the weight, while the group that consumed food sweetened with aspartame maintained a clinically significant average weight loss of 5% of their initial bodyweight (Figure 4) *(Blackburn et al, 1997)*.

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for Figure 4

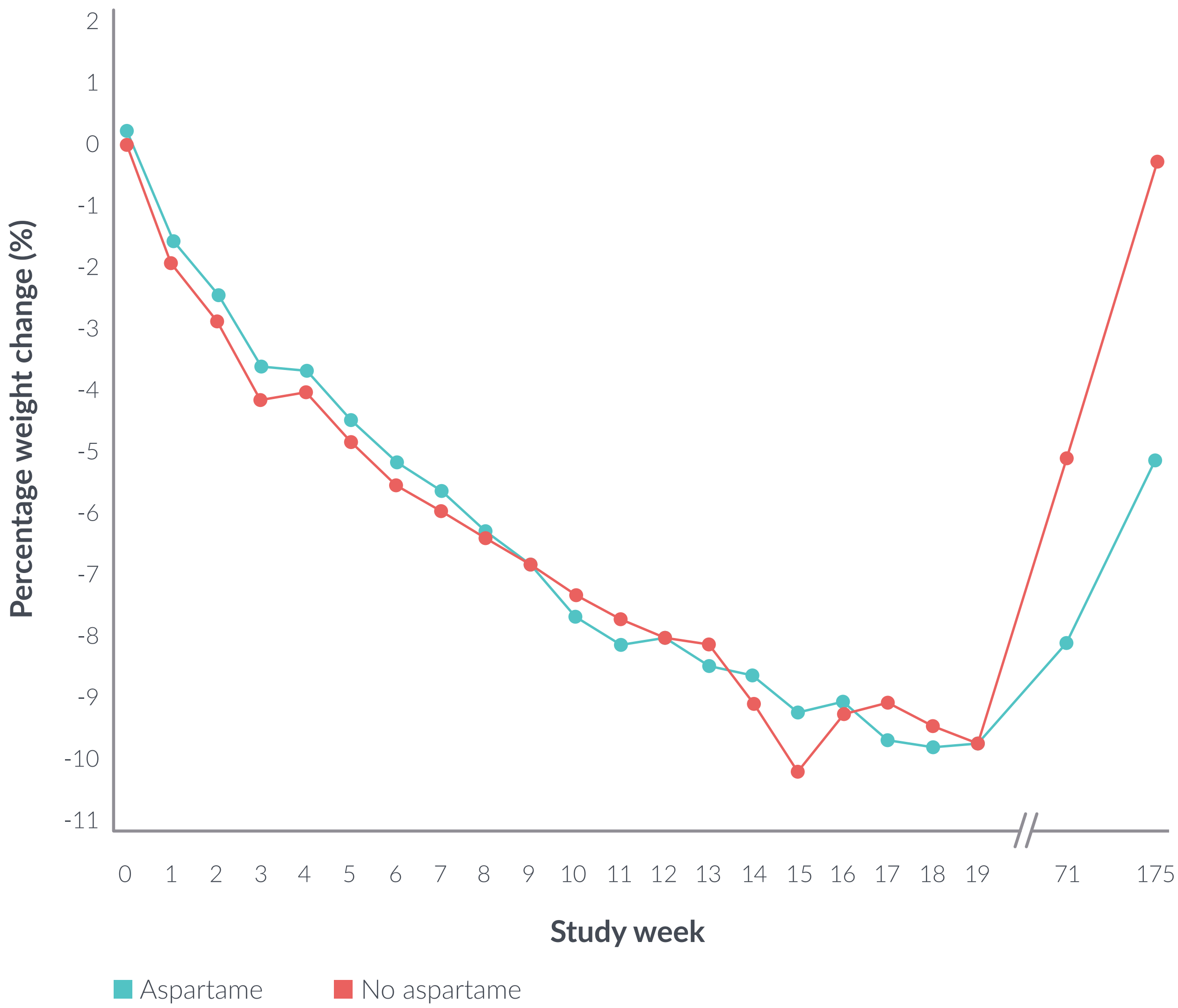


Figure 4: Percentage change in body weight over 175 wk for women (N=163) participating in a comprehensive weight-control programme with and without aspartame-containing products upon 19 weeks of active weight loss followed by a 36-month weight loss maintenance and follow-up period. (Blackburn et al, 1997)

Another large RCT by Peters and colleagues (2016) also indicated that LNCS beverages can help people to successfully lose body weight and further maintain weight loss in the longer-term. The study evaluated the effects of water versus LNCS beverages on body weight in a sample of 303 overweight and obese adults over a 12-week behavioural weight loss programme *(Peters et al, 2014)*, followed by a year-long weight maintenance period *(Peters et al, 2016)*. The participants were randomly assigned to one of two groups: those who were allowed to consume LNCS beverages (710 ml/daily) and those who were in a control group allowed to drink only water. Results from the one-year follow-up study, showed that the LNCS beverage group had greater maintenance of weight loss and higher reduction in waist circumference, compared to the water group. In terms of effects on body weight, participants drinking LNCS beverages had a mean weight loss of 6.21±7.65 kg versus 2.45±5.59 kg for the water group. In percentage terms, 44% of participants in the diet beverage group lost at least 5% of their body weight from baseline to the end of the first year of follow-up, compared to 25% in the water (control) group (Figure 5) *(Peters et al, 2016)*.

There should be no expectation that LNCS, by themselves, would cause weight loss, as they are not substances that can exert such pharmacologic-like effects *(Ashwell et al, 2020)*. However, as failure to achieve or to maintain weight loss in many individuals is caused by poor adherence to a reduced-calorie diet *(Gibson and Sainsbury, 2017)*, greater dietary compliance by improving the palatability of a diet with LNCS use may be a helpful factor in weight management efforts *(Peters et al, 2016)*.

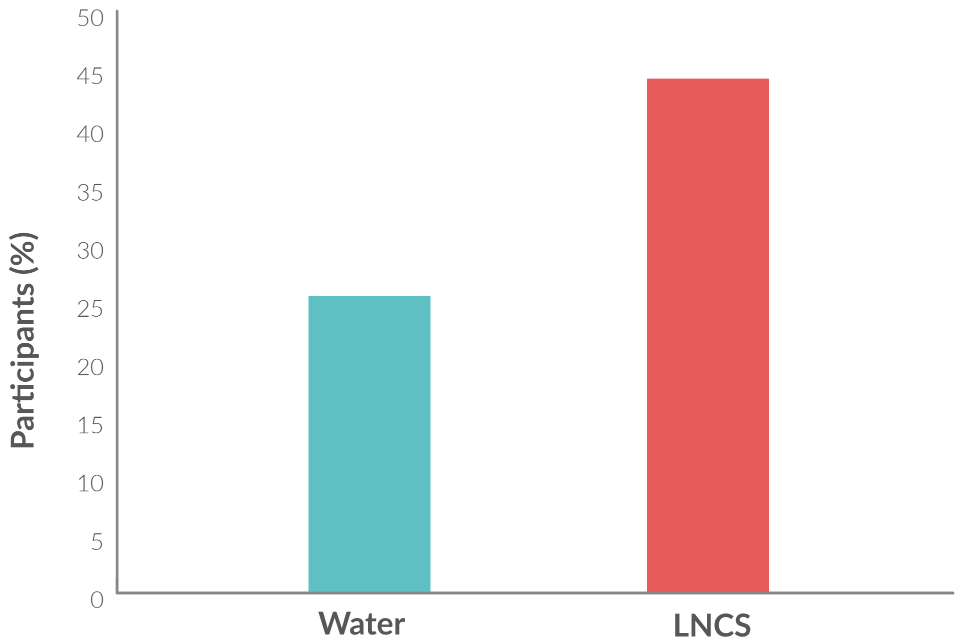


Figure 5: Percentage of participants who achieved at least 5% weight loss. Results based on X2 analysis. N=154 for LNCS, n=149 for water. *P < 0.001 (Peters et al, 2016).

What are the benefits of LNCS use in terms of appetite and weight management?

Dr France Bellisle: As confirmed in many recent RCTs and systematic reviews of the literature, the use of LNCS has been shown to facilitate weight loss in dieters, to help with the maintenance of the weight loss following a diet, and to enhance sensory-specific satiety for sweet-tasting foods and beverages *(Rogers & Appleton 2021; Rios-Leyvraz & Montez 2022)*. In addition, evidence exists that LNCS use could help in prevention of weight gain over time, at least in young people *(de Ruyter et al, 2012; de Ruyter et al, 2013)*. The benefits in terms of weight loss are modest, although significant. It should be remembered however that there is no magic associated with LNCS use: they will only be useful if they allow a reduction of energy intake over sufficient long periods of time to affect the body energy balance.

In this respect many factors have to be considered. The motivation of the user is of importance. It should also be acknowledged that LNCS will only reduce energy intake if they reduce the energy density of the foods in which they replace sugars. This is not true of all foods. Consumers should therefore make sure that replacement of sugars by LNCS does decrease the energy density of the product.

The modest weight benefits reported in the literature are in line with what can be expected from nutritional (versus pharmacological or surgical) factors. Although LNCS can help in weight control, they are not by themselves sufficient to reverse obesity. They can be viewed as one tool that a person may want to use in order to limit energy intake, in the context of a whole diet and lifestyle. LNCS can be painlessly used over extended periods of time, facilitate compliance with dietary programs, and contribute to satiating a person's appetite for sweet tasting foods and beverages. All these effects represent considerable long-term benefits in one's struggle against the powerful influences operating in the "obesogenic world".

Weight control and obesity in children: The role of sugars and low/no calorie sweeteners

Globally, the prevalence of overweight and obesity has increased dramatically among children and adolescents with more than 340 million individuals aged 5–19 years estimated to be overweight or obese *(WHO, 2021)*. Recommendations for the management of overweight and obesity in children and adolescents call for dietary strategies that can help reduce total energy intake and the consumption of energy-dense, nutrient-poor foods and beverages that are high in fats and sugars *(Hassapidou et al, 2023)*. Also, WHO recommends a reduced intake of free sugars in both adults and children *(WHO, 2015)*. However, children have a marked preference for sweet taste *(Bellisle, 2015)* and therefore managing sweetness in children's diet could be a challenge (see Chapter 7). Using LNCS in place of sugars has been considered as a tool to help reduce the intake of sugar-sweetened products while still preserving the sweet taste, but questions about their use in children remain *(Baker-Smith et al, 2019)*.

In early studies published in the 1970s investigating the effects of LNCS added in the form of capsules in the diets of children and adolescents, it was shown that LNCS themselves have no adverse effect on body weight and other health outcomes examined in these studies *(Frey, 1976; Knopp et al, 1976)*. Subsequent trials studying the impact of replacing SSBs with LNCS alternatives have shown beneficial effects of such replacement in children adiposity *(Ebbeling et al, 2006; Rodearmel et al, 2007; Ebbeling et al, 2012; de Ruyter et al, 2012)*. Results of these studies are presented in Table 2.

In one of the largest RCTs to date, conducted in 641 normal-weight children 5-11 years old in the Netherlands, the consumption of LNCS beverages versus SSBs over 18 months reduced weight gain and fat accumulation associated to growth at this age *(de Ruyter et al, 2012)*. This effect was found to be greater in children with a higher initial BMI due to a reduced tendency to compensate for the "saved" calories from the beverage swap in these children *(Katan et al, 2016)*. Specifically, the children with a higher BMI who were randomised to receive sugar-free beverages appeared to recover only 13% of the calories removed from their drink, leading to the more pronounced weight and fat reductions in children with the higher initial BMI. This secondary analysis of the data of the de Ruyter et al (2012) study shows that reducing the intake of SSBs through replacement with low calorie options may benefit a large proportion of children, especially those who show a tendency to become overweight, but also those for which overweight is not yet evident *(Katan et al, 2016)*. Similarly, in a study in teenagers, the beneficial effect of replacing SSBs with LNCS beverages on reduction of weight gain was most prominent in adolescents in the upper level of BMI (aged 13-18 years) *(Ebbeling et al, 2006)*. A recent systematic review and meta-analysis of RCTs also indicated that LNCS versus sugars intake resulted in less BMI gain in adolescents and children/ adolescents with obesity *(Espinosa et al, 2023)*.

Table 2: Summary of outcomes of randomised controlled trials (RCTs) in children and adolescents studying the effects of replacing sugar-sweetened beverages (SSBs) with low/no calorie sweetened beverages (LNCSBs) on body weight.

Publication (author; year)	Description of the study	Conclusions
RCTs in children and adolescents		
Ebbeling et al, 2006	RCT of parallel design; 103 adolescents,13-18y, who regularly consumed SSBs were assigned to either replace SSBs with LNCSBs (intervention group) or to no change (control group) for 25 weeks.	Consumption of SSBs decreased in the intervention (LNCSBs) group; Among participants with higher body weight, BMI was reduced significantly more in the intervention compared to the control group, with a net effect of -0.75 kg/m2.
Rodearmel et al, 2007	RCT of parallel design; A 6-month intervention in families with at least 1 overweight or at risk of overweight child, 7-14y. Intervention group, n=116, replaced SSBs with LNCSB and walked additional 2000 steps per day; control group, n=102, were asked not to change their diet and physical activity habits.	During the 6-month intervention period, both groups showed a reduction in BMI-for-age, however, the intervention (LNCSBs) group had a significantly higher percentage of children who maintained or reduced their BMI-for-age, compared to the control group.
Ebbeling et al, 2012	RCT of parallel design; 224 overweight and obese adolescents, 13-18y, who regularly consumed SSBs were assigned to either replace SSBs with water and LNCSBs (intervention group) or to no change (control group) for 1 year, with a follow-up for another 1 year.	Consumption of SSBs decreased in the intervention group; Replacement of SSBs with LNCSBs reduced weight gain in adolescents at year 1: there were significant between-group differences for changes in BMI (−0.57 kg/m2) and body weight (−1.9 kg) at year 1, which was not retained at the 2-year follow-up.
De Ruyter et al, 2012; Katan et al, 2016	RCT of parallel design; 641 normal-weight children, 5-11 years, were assigned to 250 ml per day of a LNCSB (sugar-free group) or to 250 ml per day of SSB (sugars group) for 18 months.	Consumption of LNCSBs vs SSBs reduced weight gain and fat accumulation; Weight increased by 6.35 kg in the LNCSB group compared with 7.37 kg in the sugars group. The increase in skinfold-thickness measurements, waist-to-height ratio, and fat mass was also significantly less in the LNCS group; the observed effect was greater in children with a higher BMI.

A policy statement from the American Academy of Pediatrics (AAP) concluded that, "When substituted for caloric- sweetened foods or beverages, NNSs [non-nutritive sweeteners] can reduce weight gain or promote small amounts of weight loss (~1 kg) in children (and adults)" (Baker-Smith et al, 2019). While the AAP report noted that the use of LNCS should not be expected to lead to substantial weight loss, it also stated that children living with certain diseases, such as obesity and type 2 diabetes may benefit from the use of LNCS if they are used to replace caloric sweeteners in the diet.

Similarly, an extensive review of the literature by a group of Mexican experts concluded that the use of LNCS can help reduce energy and sugars intake in children *(Wakida-Kuzunoki et al, 2017)*. Also, evidence reviewed in this work supported the assertion that replacing dietary sugars with LNCS could lead to lower weight gain in children. The group of experts noted that, in general, caloric restriction should not be promoted for healthy children during periods of growth and development, however, in children who require caloric restriction or sugar reduction, such as children living with overweight or obesity, LNCS can be safely used.

Generally, children need adequate energy and a variety of foods and nutrients as part of an overall balanced diet to support growth and development, and in order to reach or maintain a healthy weight for height *(Gidding et al, 2006)*. Caloric restriction should not be promoted during growth unless a child or adolescent needs to control excess weight gain. In managing overweight and obesity in children and adolescents, lifestyle modifications including dietary changes aimed at decreasing total caloric intake, increasing physical activity and reducing sedentary time are critical for weight control. In children with conditions that require sugar and/or energy intake reduction, such as obesity, metabolic syndrome or type 1 and 2 diabetes, LNCS can be an additional dietary tool to be included in a healthy lifestyle that integrates a balanced diet and physical activity *(Wakida-Kuzunoki et al, 2017)*.

Do low/no calorie sweeteners have a role in the obesity epidemic?

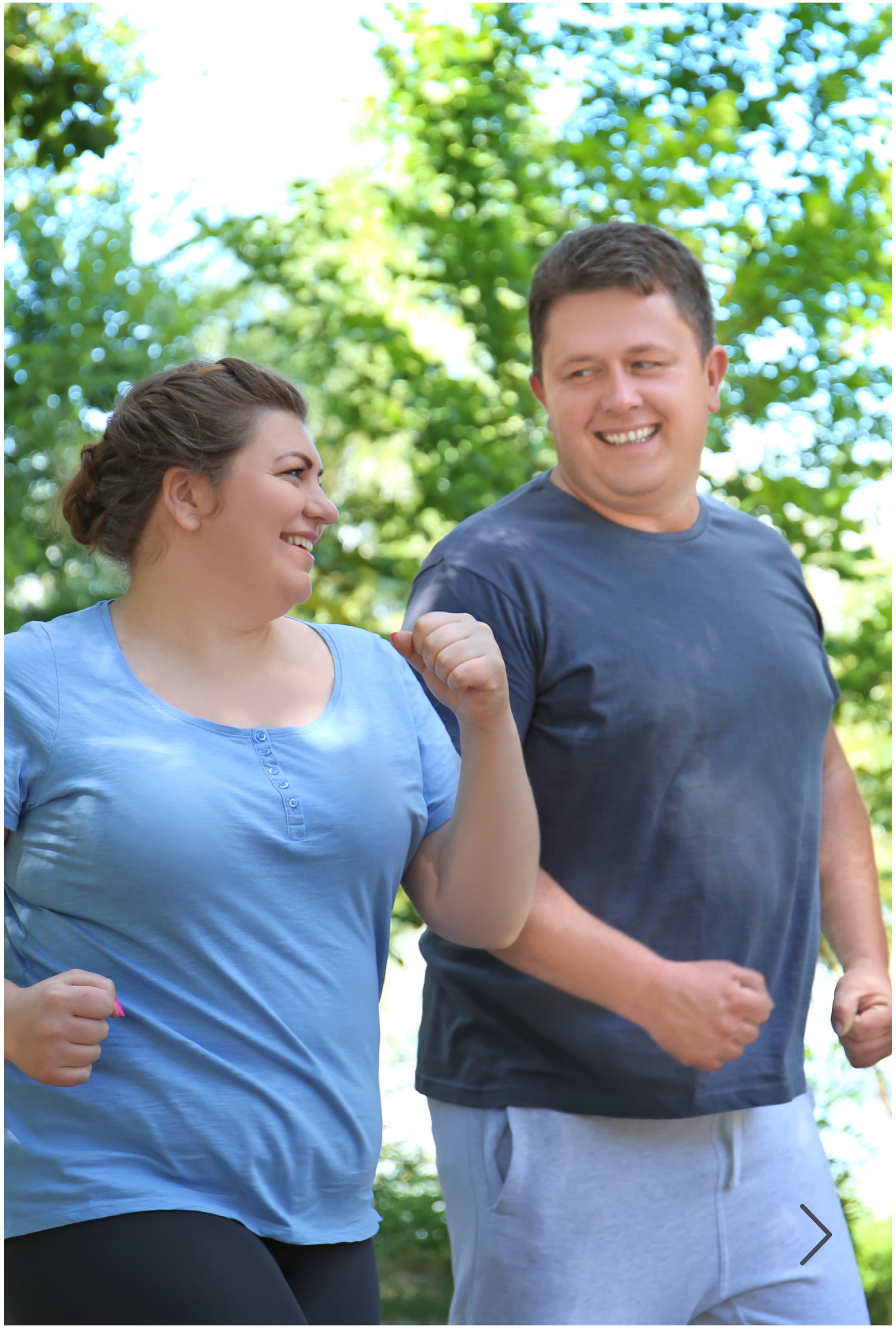
Prof Alison Gallagher: Where substitution of sugar-sweetened products for LNCS-sweetened equivalents are made there is clear evidence that an overall reduction in energy intake can be achieved. Furthermore, because such energy reductions are achieved without a reduction in overall dietary sweetness or palatability, it is likely that such 'sugar-swaps' will effectively ensure greater dietary compliance and better weight management outcomes in the longer-term for individuals. To properly curb the obesity epidemic, no one strategy alone will ever be sufficient. LNCS represent one way in which individuals can take control of the energy density of their diet but are not a panacea. Whilst replacement of sugar in beverage products is relatively straightforward, this is more challenging for food products where aside from sweetness added sugars act as a preservative, flavouring and colouring agent, bulking agent, fermentation substrate and as a texture modifier.

The causes of obesity are multifactorial and require a variety of strategies focused on the individual through to the population level. However, as with any public health strategy, more work is needed to educate the consumer on the benefits of LNCS as part of a healthy and energy balanced diet so that the potential benefits of LNCS use can be maximised. LNCS are not the 'magic bullet' answer to the obesity epidemic, but they do have a useful role to play in body weight management and as such have a real part to play in tackling the obesity epidemic.

Conclusion

By virtue of reducing the energy density of the foods and drinks in which sugar substitutes are used, LNCS can help decrease overall energy intake and thereby be a useful tool in weight control. Of course, LNCS cannot be expected to act as a "silver bullet" and to cause weight loss by themselves, so the overall impact will depend on the amount of sugars and calories replaced in the diet by the use of LNCS.

At a time when the rates of overweight and obesity continue to increase worldwide, the option of consuming an LNCS food or beverage instead of the sugar-sweetened version can be helpful by reducing overall dietary sugars and energy intakes and thus in weight control, when used as part of a balanced diet and healthy lifestyle.



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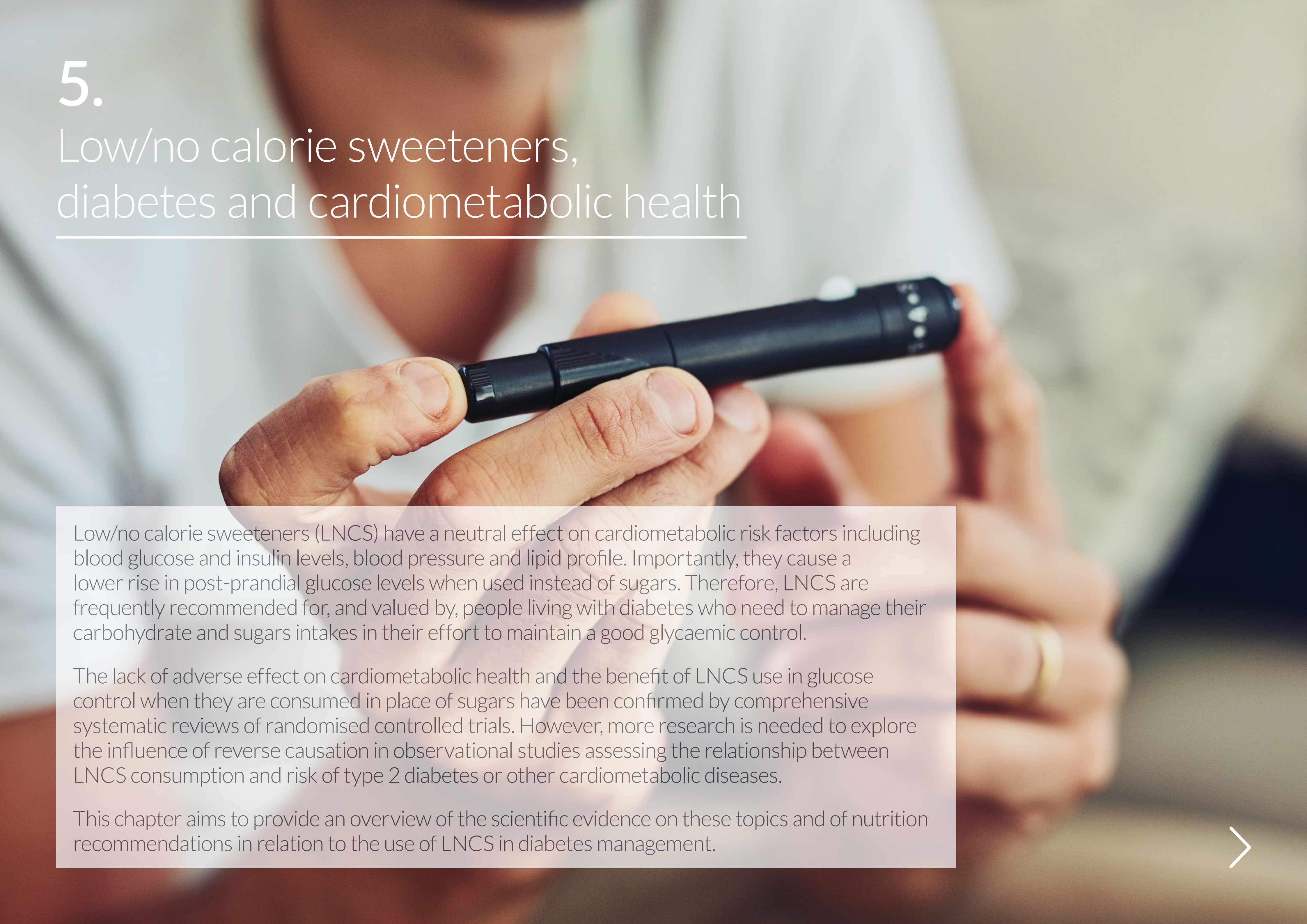


5.

Low/no calorie sweeteners, diabetes and cardiometabolic health

Low/no calorie sweeteners (LNCS) have a neutral effect on cardiometabolic risk factors including blood glucose and insulin levels, blood pressure and lipid profile. Importantly, they cause a lower rise in post-prandial glucose levels when used instead of sugars. Therefore, LNCS are frequently recommended for, and valued by, people living with diabetes who need to manage their carbohydrate and sugars intakes in their effort to maintain a good glycaemic control.

The lack of adverse effect on cardiometabolic health and the benefit of LNCS use in glucose control when they are consumed in place of sugars have been confirmed by comprehensive systematic reviews of randomised controlled trials. However, more research is needed to explore the influence of reverse causation in observational studies assessing the relationship between LNCS consumption and risk of type 2 diabetes or other cardiometabolic diseases.

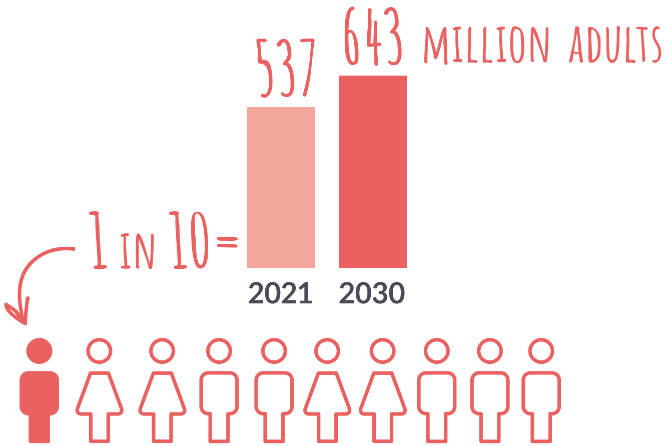
This chapter aims to provide an overview of the scientific evidence on these topics and of nutrition recommendations in relation to the use of LNCS in diabetes management.

Introduction

Cardiometabolic health is a term that refers to a combination of conditions and related risk factors, including insulin resistance, type 2 diabetes, non-alcoholic fatty liver disease, and cardiovascular disease (CVD). Common risk factors involve poor glucose control, hypertension, raised blood lipid levels and increased body weight, as well as following an unhealthy lifestyle including smoking, lack of physical activity, inadequate sleep and eating an unhealthy diet *(Vincent et al, 2017)*.

Optimal cardiometabolic health rates are falling as indicated by the increasing prevalence of CVD, including heart disease and stroke, type 2 diabetes, and other cardiometabolic diseases *(World Heart Federation, 2019; International Diabetes Federation, 2021)*. A recent study found that less than 7% of the US adult population had good cardiometabolic health in 2018, declining significantly compared to 2000 *(O'Hearn et al, 2022)*. It is believed that the COVID-19 pandemic has further affected cardiometabolic health, as there is evidence that physical activity decreased and unhealthy habits increased during the lockdown periods *(Freiberg et al, 2021)*.

Diabetes and cardiovascular disease (CVD): Facts and figures



In 2021, **537 million adults** were living with diabetes - 1 in 10 adults globally. By 2030, this number is predicted to further rise to 643 million.

In 2019, **CVD caused 18.6 million deaths worldwide**. This marks a **24% increase** in the global CVD burden compared to 2000.

Following a healthy diet, exercising regularly, maintaining a normal body weight, and avoiding tobacco use are ways to **prevent or delay the onset of cardiometabolic diseases**.

Sources:
International Diabetes Federation (IDF). IDF Diabetes Atlas, 10th edition, 2021. Available at: https://diabetesatlas.org/
World Heart Federation (WHF). World Heart Observatory. Trends in cardiovascular disease. 2019. Available at: https://worldheartobservatory.org/trends/

A healthy diet is key to protecting cardiometabolic health. Eating a balanced diet low in dietary fat, salt and sugars that includes a variety of fruits and vegetables, legumes, nuts, and whole grains, can help prevent or manage cardiometabolic diseases including CVD and type 2 diabetes *(WHO, 2020)*. Limiting excess intake of free sugars is globally recommended as part of a healthy diet *(WHO, 2015; USDA, 2020; EFSA, 2022)*. **LNCS can help individuals reduce excessive sugars intake and be part of an overall healthy diet and lifestyle, including for people with, or at risk of, cardiometabolic diseases.**

Low/no calorie sweeteners and glycaemic control

Evidence from randomised controlled trials

Several systematic reviews including meta-analyses of a large battery of available randomised controlled trials (RCTs) have examined the impact of LNCS on glycaemic control (Table 1). These comprehensive studies that consider the totality of published controlled clinical trials confirm that, as food ingredients, LNCS have no effect on blood glucose levels post-prandially, i.e., after food ingestion *(Romo-Romo et al, 2016; Tucker and Tan, 2017; Nichol et al, 2018; Greyling et al, 2020; Zhang et al, 2023)*, or after longer-term consumption *(Lohner et al, 2020; McGlynn et al, 2022; Rios-Leyvraz and Montez, 2022)*. Similarly, LNCS do not affect insulin secretion and blood insulin levels *(Greyling et al, 2020; Lohner et al, 2020; McGlynn et al, 2022; Rios-Leyvraz and Montez, 2022; Zhang et al, 2023)*. The absence of glycaemic or insulinemic effect of LNCS has been shown for healthy individuals as well as for people living with diabetes *(Greyling et al, 2020; Lohner et al, 2020)*.

In 2022, a systematic review by the World Health Organization (WHO) including a meta-analysis of 21 medium- to long-term RCTs reporting on intermediate markers of type 2 diabetes concluded that LNCS had no significant effects on any measures of glycaemic control (fasting glucose, fasting insulin, HbA1c (glycosylated haemoglobin), HOMA-IR (homeostatic model assessment of insulin resistance) in healthy adults or children *(Rios-Leyvraz and Montez, 2022)*. Similarly, a Cochrane and WHO-supported systematic review and meta-analysis of 9 long-term RTCs also indicated a neutral effect of LNCS on glycaemic control and other health outcomes in people living with type 1 or type 2 diabetes *(Lohner et al, 2020)*. Similar findings were reported for people living with overweight or obesity in a systematic review and network meta-analysis of 17 RCTs with a median duration of 12 weeks, involving 1733 participants *(McGlynn et al, 2022)*. McGlynn and colleagues examined the impact of LNCS beverages on several cardiometabolic risk factors and found no long-term effect on glycaemia or other outcomes.

With the aim to examine the acute effect of LNCS consumption, Greyling and colleagues (2020) conducted a systematic review and meta-analysis of RCTs showing that the ingestion of LNCS, consumed either alone or together with a caloric preload, had no acute effects on postprandial glycaemic (34 trials involving 452 participants) or insulinemic responses (29 trials involving 394 participants) compared with a control intervention. The results did not appreciably differ by the type or dose of LNCS consumed. Interestingly, in patients with type 2 diabetes, results showed a small beneficial effect of LNCS on postprandial glucose response, versus control *(Greyling et al, 2020)*.

Zhang and colleagues (2023) concluded to similar results in a systematic review and network meta-analysis of data from 36 acute feeding trials (involving 472 participants) examining the short-term effect of LNCS beverage consumption on glycaemic and endocrine responses, versus water or sugar-sweetened beverages (SSBs). The study found that, like water, beverages with either single or blends of LNCS had no effect on postprandial glucose or insulin levels, or on endocrine responses (i.e., glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide (GIP), peptide YY (PYY), ghrelin, leptin, and glucagon), whereas SSBs increased postprandial glucose, insulin, and incretin levels. The results were similar in all tested patterns of intake, i.e., when LNCS beverages were consumed alone, or together with additional energy (calories) from carbohydrates, or when given as a preload, prior to added energy/ carbohydrates *(Zhang et al, 2023)*.

What is glycaemic control?

Glycaemic control is a term referring to the regulation of blood glucose levels. In people with diabetes, many of the long-term complications of diabetes result from many years of elevated levels of glucose in the bloodstream, which is also referred to as hyperglycaemia. Therefore, good glycaemic control is an important goal in diabetes care *(IDF, 2021)*.

Earlier reviews reported similar findings. In their systematic review and meta-analysis of 29 RCTs involving 741 participants, Nichol and colleagues found that the intake of LNCS did not increase glycaemia post-prandially (Figure 1), and that the glycaemic impact did not differ by type of LNCS (Nichol et al, 2018). A year earlier, Tucker and Tan concluded that under acute conditions, when administered without a carbohydrate load, LNCS consumption led to reduced blood glucose levels compared to caloric sweeteners such as sugars *(Tucker and Tan, 2017)*. This was not attributed to a direct effect of the LNCS consumption, but rather to an absence of an effect and a total lower carbohydrate load that led to a lower blood glucose response. The review also found that LNCS did not differ from water in their effects on blood glucose. Romo-Romo and colleagues also suggested that the majority of RCTs reported neutral effects on blood glucose and insulin levels, but a meta-analysis was not conducted in this study *(Romo-Romo et al, 2016)*.

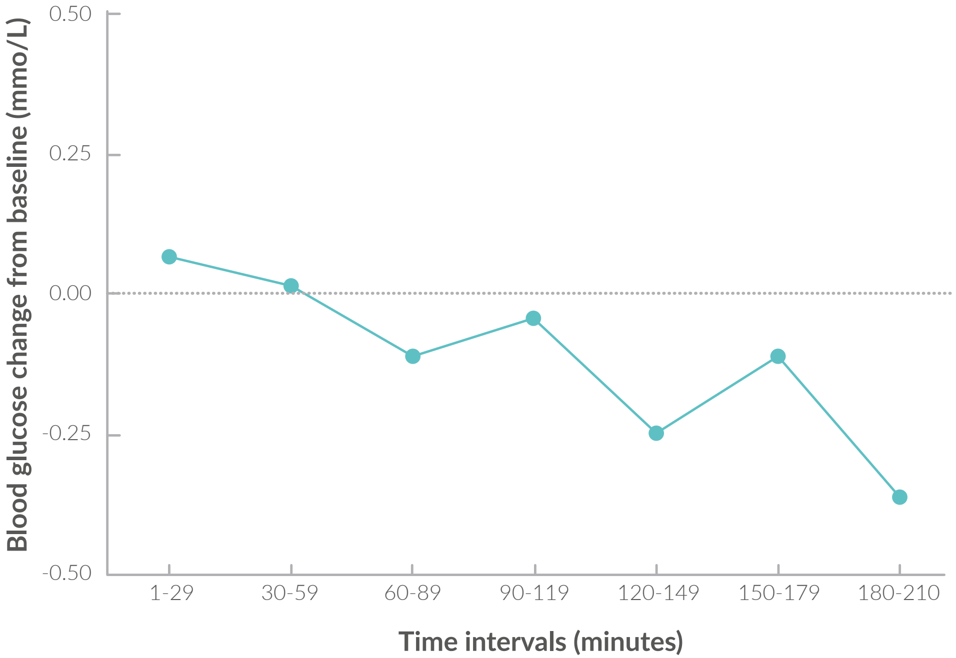


Figure 1: Estimated trajectory for glycaemic impact of low/no calorie sweeteners consumption over 210 minutes following ingestion, as estimated in the meta-analysis by Nichol et al. (2018).

The benefit of LNCS on glucose control when used in place of sugars has been recognised more than a decade ago. Reviewing the collective evidence, the European Food Safety Authority (EFSA) concluded in a scientific opinion that: **"Consumption of foods containing intense sweeteners instead of sugar induces a lower blood glucose rise after their consumption compared to sugar-containing foods"** *(EFSA, 2011)*. This is an authorised health claim in the EU as stated in the Commission Regulation (EU) No 432/2012.

Low/no calorie sweeteners cause a lower spike in post-prandial blood glucose levels when used instead of sugars, without otherwise affecting overall glycaemic control.

Table 1: Systematic reviews and meta-analyses of randomised controlled trials (RCTs) examining the impact of low/no calorie sweeteners on glycaemic control.

Systematic review (first author, year)	Number of included studies	Study characteristics (PICO)				Conclusions
		Population	*Intervention*	*Comparison*	*Outcome*	
Romo-Romo et al, 2016*	28 acute and long-term studies (including non-RCTs)	Adult population of any gender, weight and diabetes status	Any type of LNCS, ingested alone, or with a meal, or as preloads	Water or caloric sweeteners	Glucose, Insulin, HbA1c, GLP-1, GIP, C-peptide	Majority of RCTs reported neutral effects on blood glucose and insulin levels. No possible comparison between trials due to heterogeneity. No meta-analysis.
Tucker & Tan, 2017*	41 RCTs, acute studies	Adult population of any gender, weight and diabetes status	Any type of LNCS, ingested alone, or with a meal, or as preloads	Water or caloric sweeteners or placebo	Fasting blood glucose, Fasting blood insulin, Glucagon, GLP-1, GIP, Glucose absorption rates	No acute effects on measures of glycaemic control when LNCS are administered alone. LNCS lead to reduced blood glucose when compared with caloric sweeteners. No meta-analysis.
Nichol et al, 2018	29 RCTs, acute studies	Population of any age, gender, weight and diabetes status	LNCS under examination included aspartame, saccharin, steviosides, & sucralose	Comparison with baseline (Trajectory over time, from baseline to 210 min after consumption)	Change in blood glucose levels	LNCS consumption did not increase blood glucose level, and its concentration gradually declined following LNCS intake. No difference by type of LNCS.
Greyling et al, 2020	34 RCTs for postprandial blood glucose & 29 RCTs for postprandial insulin response, acute studies	Population of any age >3y, gender, weight and diabetes status	Acute exposure to LNCS alone; in water, diet beverage, or intragastric infusion; or with meal or other nutrient-containing preloads	Same intervention without LNCS	Glucose iAUC, Insulin iAUC	LNCS intake, administered alone or in combination with a nutrient-containing preload, has no effect on mean change in postprandial glycemic or insulinemic responses. No difference by type and dose of LNCS.

LNCS, low/no calorie sweeteners; LNCSB, low/no calorie sweetened beverage; SSB, sugar-sweetened beverage; HbA1c, glycosylated haemoglobin A1c; GLP-1, glucagon-like peptide 1; GIP, gastric inhibitory peptide; PYY, peptide YY; iAUC, incremental area under the curve; HOMA-IR, homeostatic model assessment of insulin resistance.
*Systematic review without meta-analysis
**Systematic review with network meta-analysis

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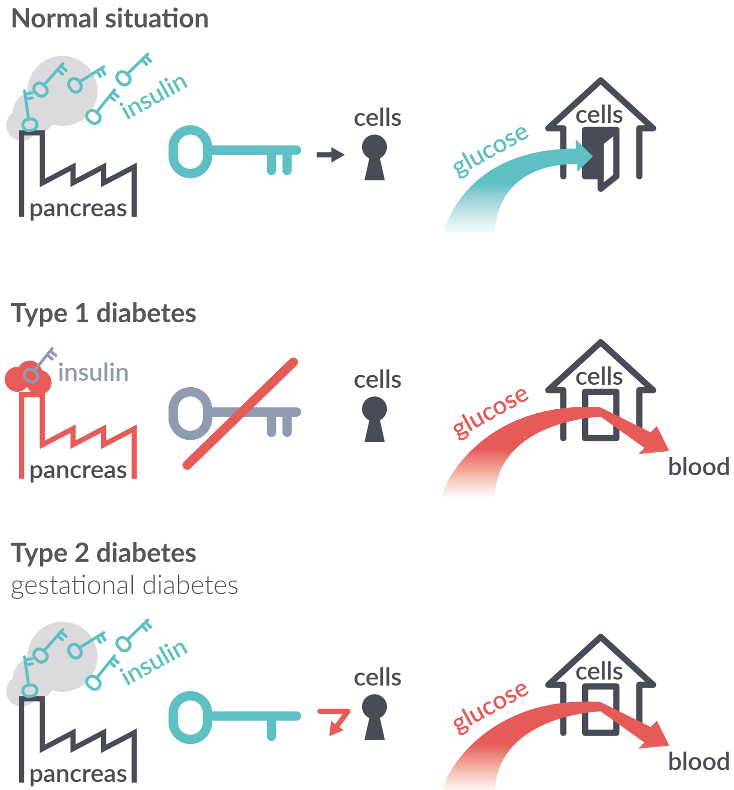
Systematic review (first author, year)	Number of included studies	Study characteristics (PICO)				Conclusions
		Population	*Intervention*	*Comparison*	*Outcome*	
Lohner et al, 2020	9 RCTs with ≥4-wk duration	Individuals with type 1 and type 2 diabetes	Any type of LNCS	Usual diet, or no intervention, or placebo, or water, or a different LNCS, or a caloric sweetener	HbA1c	Results showed no difference between LNCS and sugars, or placebo
McGlynn et al, 2022**	19 RCTs with ≥2-wk duration	Adult population of any gender, with or at risk of obesity and type 2 diabetes	LNCSBs or SSBs or water	LNCSBs vs SSBs, or SSBs vs water, or LNCSBs vs water	Fasting blood glucose, Fasting blood insulin, 2-hour post-prandial glucose, HbA1c, HOMA-IR	LNCSBs did not differ on their effects on any measures of glycaemic control, except for a greater decrease in HbA1c with water vs LNCSBs.
Rios-Leyvraz & Montez, 2022	21 RCTs in adults and 1 RCT in children with ≥7-day duration	Healthy populations of adults, children or pregnant women	Any type of LNCS	No or lower doses of LNCS or any type of sugars, or placebo, or water or no intervention	Fasting blood glucose, Fasting blood insulin, HbA1c, HOMA-IR	No significant effects were observed for any measure of glycaemic control
Zhang et al, 2023**	36 acute feeding trials	Population of any age, gender, weight and health status	LNCSBs with single of LNCS blends or SSBs or water	LNCSBs vs SSBs or vs water	Glucose iAUC, Insulin iAUC, GLP-1 iAUC, PYY iAUC, GIP iAUC, Ghrelin iAUC, Glucagon iAUC	No effect of LNCSBs on glycaemic and endocrine responses, like water. SSBs increased postprandial glucose, insulin, and incretins

LNCS, low/no calorie sweeteners; LNCSB, low/no calorie sweetened beverage; SSB, sugar-sweetened beverage; HbA1c, glycosylated haemoglobin A1c; GLP-1, glucagon-like peptide 1; GIP, gastric inhibitory peptide; PYY, peptide YY; iAUC, incremental area under the curve; HOMA-IR, homeostatic model assessment of insulin resistance.
*Systematic review without meta-analysis
**Systematic review with network meta-analysis

The role of low/no calorie sweeteners in the diet of people living with diabetes

The absence of glycaemic effect, and the lower spike in postprandial blood glucose LNCS cause when used instead of dietary sugars, makes them a useful dietary aid for people living with diabetes who need to manage their carbohydrate and sugars intake.

Living with diabetes often means being constantly concerned about what and how much to eat and feeling deprived, especially when it comes to sweet taste. However, having diabetes shouldn't keep people from enjoying a variety of foods including some favourites in moderation.



Diabetes is a serious, chronic condition that occurs either when the pancreas cannot produce enough insulin or when the body cannot effectively use the insulin it produces. Source: IDF Diabetes Atlas, 10th edition, 2021.

In persons living with diabetes, blood glucose levels are affected by how much carbohydrate is being consumed within each meal *(Evert et al, 2019)*. Therefore, managing carbohydrate intake and reducing excess sugars' consumption are important aspects of glycaemic control in diabetes management *(ElSayed et al, 2023)*. Using LNCS instead of sugars can make meal planning for diabetes management easier. Furthermore, because humans have an innate preference for sweet taste (see Chapter 7), having palatable, good-tasting foods can help improve the compliance in meal planning for diabetes. In addition, a variety of LNCS products can help people with diabetes feel less deprived *(ElSayed et al, 2023)*. There should be no expectation that LNCS, by themselves, would decrease blood glucose levels as they are not substances that can exert pharmacologic-like effects, however, **LNCS can help provide people with diabetes with wider food choices and satisfy their cravings for sweet taste without contributing to raised blood glucose levels or increased insulin needs** *(Fitch et al, 2012)*. In addition, using LNCS in place of sugars in the context of an overall healthy diet can help reduce energy intake and be a useful tool in nutritional strategies for weight management, which is especially important for people living with type 2 diabetes or pre-diabetes who need to lose weight or prevent additional excess weight gain *(Diabetes UK, 2018)*. This strategy may be particularly helpful for people who regularly consume sweet foods and especially SSBs. The role of LNCS in weight control is discussed in Chapter 4.

For individuals with type 1 diabetes, a key element in the nutritional management of their diabetes is carbohydrate-counting meal planning adjustments to insulin doses based on carbohydrate intake. The American Diabetes Association's consensus recommendations on nutrition therapy support that intensive insulin therapy using the carbohydrate counting approach can result in improved glycaemia *(Evert et al, 2019)*. In this context, using LNCS in place of sugars in foods and drinks has the potential to reduce the carbohydrate content in a meal or snack, and thus to reduce the insulin dose required for this eating occasion.

Experts' views

"Any dietary measure that has the potential to limit an excessive rise in blood glucose levels can assist with overall glycaemic control and is therefore likely to promote the maintenance of optimal health. A considerable amount of scientific evidence demonstrates that the substitution of sugars with low/no caloric sweeteners is one of the available means to help achieve this goal as, by themselves, low/no caloric sweeteners do not induce any glycaemic excursion."

Dr Marc Fantino, Emeritus Professor

Diabetes- and nutrition-related organisations support the use of low/no calorie sweeteners in diabetes management

Several health organisations around the world have issued clinical guidelines for the nutritional management of diabetes. Nutritional recommendations aim to serve as a guide for health professionals in educating their patients, and ultimately, to help individuals living with diabetes make more balanced and healthier choices in order to improve their glycaemic control.

Diabetes-related organisations globally, including the American Diabetes Association (ADA), the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes (EASD), Diabetes UK, Diabetes Canada, and the Latin-American Association of Diabetes (Asociación Latinoamericana de Diabetes – ALAD) recognise that **LNCS can be safely used to replace dietary sugars and be a useful tool in the nutritional management of diabetes**.

In its 2023 update of Medical Nutrition Therapy recommendations, ADA supported that: "The use of nonnutritive sweeteners as a replacement for sugar-sweetened products may reduce overall calorie and carbohydrate intake as long as there is not a compensatory increase in energy intake from other sources. There is evidence that low- and no-calorie sweetened beverages are a viable alternative to water." *(ElSayed et al, 2023)*

In the same year, the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) published updated European recommendations for the nutritional management of diabetes with the aim to provide health professionals with evidence-based guidelines *(Reynolds et al, 2023)*.

The European guidelines recommend the use of LNCS to replace sugars in foods and beverages, while the intake of free or added sugars should be below 10% of total energy intake. The latest European recommendations on sweeteners are based on a series of systematic reviews and meta-analyses of RCTs *(McGlynn et al, 2022)* and prospective cohort studies *(Lee et al, 2022)* assessing the impact of LNCS beverages on cardiometabolic health in people with or at risk of developing diabetes. The two studies concluded that LNCS beverages, when replacing SSBs, reduce body weight and cardiometabolic risk factors in people with or at risk for diabetes and are associated with reductions in the risk of obesity and cardiovascular outcomes in participants inclusive of people with diabetes, with reductions similar to those seen with water *(McGlynn et al, 2022; Lee et al, 2022)*.

Similarly, the Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes supported that LNCS may be recommended for diabetes as they are safe and have no effect on glycaemia *(Dyson et al, 2018)*. In its Position Statement about the use of LNCS, Diabetes UK concluded that replacing free sugars with LNCS can be a helpful strategy to aid glucose management and weight control *(Diabetes UK, 2018)*.

In line with the above conclusions, a consensus of the Latin-American Association of Diabetes (ALAD) also acknowledged that LNCS use can have benefits in energy intake reduction, weight loss and glucose control, when used to replace sugars in the context of a structured dietary plan *(Laviada-Molina et al, 2018)*.

Also, in its 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, Diabetes Canada Clinical Practice Guidelines Expert Committee pointed out that the evidence from systematic reviews and meta-analyses of RCTs, which give a better protection against bias, have shown a weight loss benefit when LNCS are used to displace excess calories from added sugars *(Sievenpiper et al, 2018)*.

Diabetes-related organisations globally recognise that, when used in place of sugars, low/no calorie sweeteners can be a useful dietary strategy in the nutritional management of diabetes

Nutrition-related organisations have reached similar conclusions. For example, the US Academy of Nutrition and Dietetics (AND) recommended that registered dietitians and nutritionists (RDNs) should educate adults living with diabetes that the use of approved LNCS does not significantly affect glucose or insulin levels and has the potential to reduce overall energy and carbohydrate intake if they are used in place of caloric sweeteners, without compensation by intake of additional calories from other food sources *(Franz et al, 2017; MacLeod et al, 2017)*. Likewise, the British Dietetic Association (2016) supported that opting for LNCS may assist in the management of weight and other health conditions such as diabetes mellitus adding that a tailored individualised approach is required.

People living with diabetes consider low/no calorie sweeteners as a useful dietary tool…

- "They help me feel less deprived while still enjoying sweet taste in my diet"
- "Low/no calorie sweeteners can be a quick and easy replacement for sugar"

Source: Patients' focus group as part of ISA activities for World Diabetes Day 2017

Low/no calorie sweeteners and cardiometabolic risk factors beyond diabetes markers

Evidence from randomised controlled trials
Human clinical research shows that, beyond a lack of effect on glycaemic control, LNCS ingestion has a neutral, or even beneficial, impact on other cardiometabolic intermediate markers such as blood pressure and blood lipids, liver enzymes, uric acid and intrahepatocellular lipid *(Onakpoya and Heneghan, 2015; Pham et al, 2019; Toews et al, 2019; Movahedian et al, 2021; McGlynn et al, 2022; Rios-Leyvraz and Montez, 2022; Golzan et al, 2023)*.

The WHO systematic review reported that higher intakes of LNCS did not have a significant effect on systolic or diastolic blood pressure *(meta-analysis of 14 RCTs)*, though a trend to lower systolic blood pressure was observed with LNCS intake *(Rios-Leyvraz and Montez, 2022)*. Furthermore, this study found no significant effects for any blood lipid measure in RCTs (meta-analysis of 14 RCTs), including LDL cholesterol or triglycerides, with the exception of a small, clinically insignificant, increase in total cholesterol:HDL cholesterol.

In their systematic review and network meta-analysis, McGlynn and colleagues reported a neutral effect of LNCS beverages on glycaemia, blood lipid levels, uric acid and liver enzymes, and a beneficial effect of LNCS beverages as an intended substitute for SSBs in Body Mass Index (BMI), percentage of body fat, and intrahepatocellular lipid, which was a result of displacement of calories from SSBs *(McGlynn et al, 2022)*. The study also found that LNCS beverages compared with water were associated with a greater decrease in systolic blood pressure.

Other systematic reviews are in line with these conclusions *(Pham et al, 2019; Toews et al, 2019; Movahedian et al, 2021; Golzan et al, 2023)*. A systematic review and meta-analysis of 10 RCTs, involving 854 participants, showed that LNCS intake had no significant effect on liver enzyme levels in adults *(Golzan et al, 2023)*. Also, Movahedian and colleagues systematically reviewed and meta-analysed data from 14 RCTs, involving 1407 participants, that examined the impact of LNCS on blood triglyceride levels, total cholesterol, LDL- and HDL cholesterol. The results showed non-significant effects of LNCS on lipid profile *(Movahedian et al, 2021)*. Also, Pham et al (2019) concluded that LNCS have demonstrated minimal or no effect on postprandial blood pressure, while Toews et al (2019) reported that data from three RCTs showed that systolic and diastolic blood pressure were lower in people receiving LNCS than in those receiving sugars or placebo, and two other RCTs reported a neutral effect.

Collectively, **evidence from systematic reviews of RCTs, including from the WHO review by Rios-Leyvraz and Montez (2022), does not support a WHO recommendation suggesting against the use of non-sugar sweeteners as a means for reducing the risk of non-communicable diseases** (WHO, 2023). This recommendation was largely based on low certainty evidence from observational studies with important methodological issues, while clinical studies in humans consistently show a neutral or even beneficial impact, and no adverse effect, of LNCS on cardiometabolic intermediate markers and risk factors of non-communicable diseases (NCDs).

Low/no calorie sweeteners and risk of diabetes and cardiovascular disease

Evidence from observational studies

Contrary to evidence from RCTs, which consistently indicates a lack of adverse effect of LNCS on cardiometabolic risk factors, observational research reports inconsistent outcomes. As a result, while some systematic reviews and meta-analyses of observational studies have reported a positive association between higher LNCS intake and risk of diabetes or CVD *(Romo-Romo et al, 2016; Azad et al, 2017; Meng et al, 2021; Rios-Leyvraz and Montez, 2022)*, this was not confirmed in a recent review including meta-analysis of prospective cohort studies that used repeated measures of LNCS intake and substitution analyses to mitigate the influence of reverse causation *(Lee et al, 2022)*. Importantly, systematic reviews of observational studies mainly provide low certainty evidence as a result of the limitations of observational research. **By design, observational studies cannot establish a cause-and-effect relationship due to their inability to exclude residual confounding or attenuate the effects of reverse causality**, as discussed in Chapter 4.

Reverse causation is a major risk of bias in observational research. The term implies that individuals who are already at high risk for disease at baseline (e.g., have elevated risk factors) may have in response turned to, or increased, LNCS intake, thus leading to a spurious association between LNCS intake and increased cardiometabolic risk *(Rios-Leyvraz and Montez, 2022)*. In addition, inaccuracies resulting from the methods used to assess dietary intake of LNCS, usually evaluated only at baseline, raise concerns regarding the reliability and interpretation of associations reported in observational studies *(Gallagher and Logue, 2019)*. Baseline analyses of LNCS intake cannot capture change over time or the intended replacement strategy of the substitution of SSBs with LNCS beverages and are susceptible to reverse causation, resulting in an underestimation of the intended cardiometabolic benefits *(Lee et al, 2022)*.

Prospective observational studies that have used substitution analyses that model the intended replacement strategy for LNCS sweetened beverages (i.e., substitution of SSBs with LNCS beverages) can partly overcome these methodological limitations and provide more consistent results. For example, results from the Harvard Pooling Project of Diet and Coronary Disease Substitution analyses suggested that replacing SSBs with LNCS beverages might be associated with a lower risk of developing coronary events *(Keller et al, 2020)*.

A systematic review and meta-analysis by EASD's Diabetes and Nutrition Study Group included only prospective observational studies that used change analyses of repeated measures of intake and substitution analyses in order to minimize the impact of reverse causality and residual confounding from incomplete adjustment of confounders *(Lee et al, 2022)*. The results of this meta-analysis of 14 prospective cohort studies (416,830 participants) showed that the intended substitution of SSBs with LNCS beverages was associated with lower body weight and lower risk of incident obesity, coronary heart disease, CVD and total mortality, with no adverse associations across other outcomes such as type 2 diabetes. The findings by Lee et al (2022) confirm that LNCS are not associated with higher, but rather, with a lower risk in important cardiometabolic outcomes in the intended substitution for SSBs, comparable with outcomes for water, and are in line with the evidence from systematic reviews and meta-analyses of RCTs of intermediate cardiometabolic risk factors *(McGlynn et al, 2022; Rios-Leyvraz and Montez, 2022)*.

Indeed, the association between the consumption of LNCS and the risk of diabetes that is reported in observational studies is usually attenuated or lost after adjustment for variables, including age, physical activity, family history of diseases, diet quality, energy intake and mainly measures of adiposity such as BMI and waist circumference *(Romo-Romo et al, 2017)*. In a meta-analysis of ten observational studies estimating the risk of type 2 diabetes by consuming LNCS beverages, Imamura et al. found that after adjustment for BMI and the calibration for information and publication bias, the association between LNCS drinks and the development of type 2 diabetes was no longer statistically significant *(Imamura et al, 2015)*. Similarly, links between LNCS intake and CVD reported in some studies *(Mossavar-Rahmani et al, 2019; Debras et al, 2022)* are subject to the same criticism: limitations of observational studies including selection bias, reverse causation and residual confounding may partly or largely explain the reported associations *(Khan et al, 2019; Pyrogianni & La Vecchia, 2019)*.

By design, observational studies cannot establish a causal relationship due to their inability to exclude residual confounding or attenuate the effects of reverse causality

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How can we interpret contradictory findings between randomised controlled trials and observational research studying low/no calorie sweeteners' cardiometabolic health effects?

Prof Carlo La Vecchia: Randomised controlled trials (RCTs) provide a more valid and reliable evidence than observational (cohort and case-control) studies essentially since they are not affected by selection bias. Information and other sources of bias can also severely distort the findings of observational studies but are of little or no relevance for RCTs where allocation is randomised. Thus, the evidence from RCTs that LNCS have a favourable – though moderate – effect on cardio-metabolic, and more in general cardiovascular risk factors has to be considered the valid and relevant one on the issue.

Since most RCTs have a limited duration, they cannot provide adequate information on long-term effects of LNCS on the risk of cardiovascular disease and cardiometabolic factors. The apparently inconsistent findings of several observational studies are largely or totally attributable to reverse causation, i.e., in the long term LNCS tend to be more frequently used by subjects with overweight and obesity, hyperglycemia, diabetes or – more in general – an unfavourable cardiometabolic profile. There is no way to overcome such inherent bias of observational studies, and it is also not possible to reliably estimate its possible impact on the outcomes of interest. Other sources of bias and confounding of observational studies may also distort the findings. As a general rule, a change in relative risk estimates of the order of 20% (i.e. RRs 0.80 to 1.20) do not allow inference on causation since bias and confounding cannot be excluded.

In short, LNCS are associated to favourable cardiometabolic patterns in the short term. Assuming adequate compliance, these should be maintained in the long term too, but data on long term effects from RCTs are inadequate for the moment.

Examining proposed mechanisms linking low/no calorie sweeteners to cardiometabolic effects

Several potential mechanisms have been suggested and explored mostly in in-vitro and animal studies in an attempt to explain the positive association reported in some observational studies. Proposed mechanisms include alterations in intestinal glucose absorption, changes in insulin secretory capacity, insulin resistance, and sweetener-induced gut microbiota dysbiosis *(Pang et al, 2021)*. However, a 2018 science advisory from the American Heart Association (AHA) on LNCS beverages and cardiometabolic health warned that caution is required before drawing conclusions about whether these findings, primarily conducted in rodents, are applicable to humans *(Johnson et al, 2018)*. To date none of the proposed mechanisms of how LNCS could affect glucose homeostasis or otherwise increase the risk of cardiometabolic diseases has been confirmed in humans *(O'Connor et al, 2021; McGlynn et al, 2022)*.

Importantly, evidence from RCTs does not confirm these hypotheses and consistently shows no adverse effect on risk factors linked to cardiometabolic health, including blood pressure, blood lipids levels, glucose homeostasis, or body weight *(Nichol et al, 2018; Pham et al, 2019; Toews et al, 2019; Greyling et al, 2020; Movahedian et al, 2021; Rogers and Appleton, 2021; McGlynn et al, 2022; Rios-Leyvraz and Montez, 2022; Golzan et al, 2023; Zhang et al, 2023)*.

Intestinal Glucose Absorption

It has been suggested that LNCS may enhance intestinal glucose absorption by activating sweet taste receptors in the gut, which, in turn stimulates the secretion of incretin hormones, glucagon-like protein-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), known to have a role in regulating glucose absorption and promoting insulin release. Nevertheless, to date no differences in intestinal glucose absorption in humans have been reported *(O'Connor et al, 2021; Pang et al, 2021; Zhang et al, 2023)*

The present hypothesis stems largely from isolated cell or tissue (in vitro) experiments that typically utilised LNCS concentrations that were extraordinarily high *(Fujita et al, 2009)*. Because effects are seen under these testing conditions, however, does not mean they are reliable for interpreting what happens with exposure in the whole human body. Contrary to the findings of these in vitro studies, most clinical human trials have found no effects of LNCS on circulating incretin hormones levels *(Gregersen et al, 2004; Ma et al, 2009; Ma et al, 2010; Ford et al, 2011; Steinert et al, 2011; Maersk et al, 2012a; Wu et al, 2012; Wu et al, 2013; Sylvetsky et al, 2016; Higgins et al, 2018; Ahmad et al, 2020a; Romo-Romo et al, 2020; Orku et al, 2022; Zhang et al, 2023)*.

In a few studies testing the effects of LNCS-containing beverages, results reported a significant increase in GLP-1 in healthy adults with overweight and obesity *(Brown et al, 2009; Temizkan et al, 2015; Sylvetsky et al, 2016; Lertrit et al, 2018)* or in healthy youth with and without type 1 diabetes *(Brown et al, 2012)*, however, these effects have not been found in patients with type 2 diabetes participating in the same studies *(Brown et al, 2012; Temizkan et al, 2015)*. It is unknown whether levels of changes in endogenous GLP-1 secretion as observed in these studies have any clinically relevant consequences *(Brown et al, 2012)*. Importantly, the collective evidence as assessed in a systematic review and network meta-analysis of 36 acute feeding studies showed that LNCS beverages with single or blends of LNCS had no significant effect on endocrine responses including GLP-1 and GIP, similar to water controls, when consumed alone, or together with, or prior to the consumption of a carbohydrate load *(Zhang et al, 2023)*.

Taken together, current evidence from human studies doesn't support a clinically meaningful stimulatory effect of LNCS on the secretion of gut hormones in humans *(Bryant and McLaughlin, 2016; Grotz et al, 2017; Ahmad et al, 2020b; Zhang et al, 2023)*.

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Insulin secretion

A large body of evidence, as comprehensively assessed in systematic reviews and meta-analyses of RCTs, confirms that LNCS do not significantly affect blood insulin levels *(Greyling et al, 2020; Zhang et al, 2023)*. Moreover, human data collectively do not confirm proposed mechanisms suggesting that LNCS may affect insulin secretion via eliciting a cephalic phase insulin response (CPIR) or by stimulating the gut sweet taste receptors *(O'Connor et al, 2021; Pang et al, 2021)*.

CPIR is an early low-level increase in blood insulin associated with only oral exposure, i.e., occurring prior to increasing plasma glucose levels typically seen with intake of foods containing carbohydrate. Eliciting CPIR has sometimes been hypothesized as a possible way for LNCS to cause hunger (see Chapter 4) or a later increase in blood glucose levels that is abnormal *(Mattes and Popkin, 2009)*. While a few studies have suggested that exposure to LNCS may elicit a CPIR *(Just et al. 2008; Dhillon et al. 2017)*, most clinical trials did not confirm such an impact *(Teff et al, 1995; Abdallah et al, 1997; Morricone et al, 2000; Ford et al, 2011; Pullicin et al, 2021)*. Additionally, other research has suggested that CPIR is generally not a meaningful determinant in hunger or glucose response *(Morey et al, 2016)*. Recently, a systematic review on endocrine cephalic phase responses to food cues concluded that there was weak evidence for human CPIR and, importantly, the evidence for the existence of a physiologically relevant CPIR seemed minimal *(Lasschuijt et al, 2020)*. Taken together, human data collectively do not support the assertion that LNCS may significantly affect insulin secretion and blood insulin levels, nor confirm an adverse effect of LNCS on either appetite regulation or glucose metabolism *(Tucker and Tan, 2017; Greyling et al, 2020; O'Connor et al, 2021; Pang et al, 2021; Zhang et al, 2023)*.

Insulin sensitivity

The potential effect of LNCS on insulin sensitivity garnered attention primarily following the publication in 2014 of an animal experiment and a small, non-randomised human trial in 7 subjects by Suez and colleagues suggesting that high doses of saccharin at the ADI level might contribute to insulin resistance via effects on the gut microbiota *(Suez et al, 2014)*. Several controlled human clinical studies have been conducted since then. A few RCTs have suggested a potential adverse effect of sucralose on insulin sensitivity *(Lertrit et al, 2018; Romo-Romo et al, 2018; Bueno-Hernández et al, 2020; Romo-Romo et al, 2020)*. However, in one study the effect was not consistent with dose *(Bueno-Hernández et al, 2020)*, and a second study reported an increase in the homeostasis model assessment of insulin resistance only at 1 week postdosing, but not during or after the end of the intervention, which is of unknown clinical significance, if any *(Romo-Romo et al, 2020)*. In contrast, the majority of published RCTs have shown no impact of different doses of LNCS including aspartame alone *(Maersk et al, 2012b; Engel et al, 2018; Higgins and Mattes, 2019; Ahmad et al, 2020a)* or in blend with acesulfame-K *(Bonnet et al, 2018; Kim et al, 2020; Orku et al, 2022)*, saccharin *(Higgins and Mattes, 2019; Serrano et al, 2021; Orku et al, 2022)*, steviol glycosides *(Higgins and Mattes, 2019)*, and sucralose *(Higgins and Mattes, 2019; Thomson et al, 2019; Ahmad et al, 2020a; Orku et al, 2022)* on insulin sensitivity. A meta-analysis of 11 RCTs in the WHO systematic review also confirmed a neutral effect of LNCS on HOMA-IR, a method for assessing insulin resistance *(Rios-Leyvraz and Montez, 2022)*.

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Gut microbiota

Some LNCS compounds have been assumed to affect glucose homeostasis and/or insulin sensitivity by modulating the gut microbiota *(Suez et al, 2014; Richardson and Frese, 2022; Suez et al, 2022)*. Most research to date has been studies involving in-vitro and animal experiments, and often, testing has utilized very high doses of LNCS *(Lobach et al, 2019; Ruiz-Ojeda et al, 2020; Plaza-Diaz et al, 2020)*, limiting biological relevance due to differences in the rodent gut microbiome and limitations in extrapolating tested concentrations in vitro to human exposure levels from the diet *(Hughes et al, 2021)*. A few RCTs have investigated potential gut microbiota changes following exposure to different types and doses of LNCS in humans reporting mixed and inconsistent findings *(Thomson et al, 2019; Ahmad et al, 2020c; Serrano et al, 2021; Méndez-García et al, 2022; Suez et al, 2022)*.

Three controlled clinical trials found no impact of aspartame *(Ahmad et al, 2020c)*, saccharin *(Serrano et al, 2021)* or sucralose *(Thomson et al, 2019; Ahmad et al, 2020c)* on gut microbiota, and ultimately on glucose homeostasis or insulin sensitivity. A randomized, double-blind controlled trial in 34 subjects using a parallel study design concluded that consumption of high doses of sucralose for 7 days did not alter glycaemic control, insulin resistance, or gut microbiome in healthy individuals *(Thomson et al, 2019)*. Another RCT of cross-over design in 17 participants found that daily repeated consumption of pure aspartame or sucralose for 14 days in doses reflective of typical high consumption had no impact on gut microbiota composition or the production of short-chain fatty acids (SCFAs), a subset of fatty acids that are produced by the gut microbiota *(Ahmad et al, 2020c)*. Interestingly, a double-blind, placebo-controlled, parallel arm RCT in 23 adults also showed that the consumption of pure saccharin at maximum acceptable levels for 2 weeks did not alter microbial diversity or composition in humans and mice alike, nor caused any changes in fecal metabolites or SCFAs *(Serrano et al, 2021)*. Results also showed no impact of saccharin consumption on glucose tolerance. These findings by Serrano et al, who used a well-controlled trial design, contradicted the results of a small study by Suez et al, which lacked a control group, and suggested that in 4 out of 7 participants saccharin administration at ADI levels for 1 week induced glucose intolerance by altering the gut microbiota *(Suez et al, 2014)*.

In contrast, two human studies reported potential adverse effects of LNCS on gut microbiota *(Méndez-García et al, 2022; Suez et al, 2022)*. An open-label, parallel-design RCT in 40 young adults reported that consumption of 48mg of sucralose for 10 weeks induced gut dysbiosis associated with altered insulin and glucose levels during an oral glucose tolerance test *(Méndez-García et al, 2022)*. However, in the present study, habitual diet was neither controlled nor well-characterised, so any reported changes in the gut microbiota could very likely be due to unreported dietary differences between the sucralose and water groups. Also, an unblinded, parallel-arm RCT testing the impact of four different LNCS, water (control) or glucose, consumed for 2 weeks in doses lower than the ADI (n=20 participants per group) suggested that some LNCS might induce person-specific, microbiome-dependent glycaemic alterations *(Suez et al, 2022)*. The latest study by Suez and colleagues reported a significant effect on the microbiome composition and function linked to elevated glycaemic response in the sucralose and saccharin groups, while aspartame and stevia had no impact on glycaemia despite inducing distinct alterations in microbiome function.

However, participants' diet in this study, while recorded, was also not fully controlled. Indeed, it is well established that, not only energy and nutrients intake, but also differences in the type of food consumed can rapidly alter the human gut microbiome *(David et al, 2014)*. Therefore, it cannot be ruled out that dietary intake aspects, which are known to affect the gut microbiota but have not been recorded in this trial, had an impact on the study results. When conducting dietary intervention studies to assess the effects of ingredients that are added to the diet in small amounts, such as LNCS, the habitual diet of the subjects should be well-characterized and the intervention diets should be carefully controlled *(Lobach et al, 2019)*. Contrary to these findings by Suez et al (2022), numerous clinical trials, and systematic reviews of RCTs, have consistently confirmed that LNCS have no impact on glycaemic response *(Grotz et al, 2017; Tucker and Tan, 2017; Nichol et al, 2018; Greyling et al, 2020; Lohner et al, 2020; Rios-Leyvraz and Montez, 2022; Zhang et al, 2023)*.

Important considerations in evaluating and interpreting research about LNCS and gut microbiota is the different absorption, distribution, metabolism, and excretion (ADME) profiles of each individual sweetener, and the biological plausibility of how the different LNCS could potentially affect the gut microbiota composition or function *(Plaza-Diaz et al, 2020)*. Importantly, extrapolation of the effect of one LNCS on the gut microflora to all LNCS is not appropriate, on the basis of well-documented differences in their chemistry, movement through the body, and the amount of LNCS or their metabolites that reach the gut microbiota *(Magnuson et al, 2016)*.

Aspartame is rapidly hydrolysed and absorbed in the small intestine and neither aspartame as an intact molecule nor its metabolites ever reach the colon or contact gut bacteria *(EFSA, 2013)*. Therefore, a direct effect of aspartame on gut microbiota synthesis or function is not biologically plausible. Similarly, it is extremely unlikely that acesulfame-K could have a direct effect on the colonic microbiota as the concentration that reaches the gut microbiota is negligible. Once ingested, acesulfame-K is absorbed almost completely in the small intestine as an intact molecule and distributed by the blood to different tissues without undergoing any metabolization, with 99% of acesulfame-K excreted in urine and less than 1% being eliminated in the feces *(Magnuson et al, 2016)*. On the other hand, sucralose has a very low level of absorption and is practically not metabolized *(Roberts et al, 2000)*. However, although more than 85% of the ingested sucralose reaches the gut microbiota, between 94% and 99% of this sweetener is recovered in the feces without any structural change, indicating practically no metabolism by the intestinal bacteria. Thus, sucralose does not appear to be a substrate for the colonic microbiota. With regard to saccharin, after its intake, more than 85% is absorbed as an intact molecule and does not undergo gastrointestinal metabolism *(Renwick, 1985; Magnuson et al, 2016)*. Hence, only a small percentage of non-absorbed saccharin is excreted into the feces, indicating that only high doses of this sweetener could lead to changes in the composition of the intestinal microbial population. Finally, steviol glycosides enter the colon as intact molecules and need bacteria for their metabolisation into steviol *(Magnuson et al, 2016)*. However, the resulting steviol is not a substrate for the intestinal microbiota, since it is resistant to bacterial degradation, and is further completely absorbed. So, while steviol glycosides interact with the colonic microbiota, there is no indication that these sweeteners could adversely affect the gut microbiota.

While certain diseases have been associated with abnormal microbiota (ie, dysbiosis), it is unclear what constitutes a "healthy" gut microbiome *(Fan and Pedersen, 2021)*. The role of the gut microbiota in affecting human health is currently an area of extensive research. There are hypotheses that certain types of changes could translate into increased risk of certain health outcomes, however, in general, the meaningfulness of most changes are unknown. There are also no changes known to be reliable biomarkers for increased risk of either becoming overweight or developing diabetes or CVD. There is commonly also a wide variability in the normal gut microbiome profile between one human subject and another, further complicating interpretation of data outcomes even from RCTs *(Lobach et al, 2019)*. Additionally, the gut microbiome profile can change daily just with normal changes in daily food intake *(David et al, 2014)*.

Taken together, there is no clear evidence that LNCS may adversely impact health via effects on the gut microbiota when consumed by humans at approved levels. The clinical significance of reported gut microbiota changes by some LNCS is questioned since, collectively, evidence from RCTs do not confirm adverse effects of LNCS on host physiology.

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Considerations in interpreting research on low/no calorie sweeteners and gut microbiota. The role of study design.

Prof Wendy Russell: Dietary change such as replacing sugars with LNCS is likely to have an impact on shaping our gastrointestinal microbiota. To date, these changes are mostly substantiated from feeding trials with animal models and there are still only a handful of studies in humans where the results are contradictory *(Harrington et al, 2022)*. One study has shown that bacterial diversity (but not abundance) differed between consumers and non-consumers of aspartame and/or Acesulfame K *(Frankenfeld et al, 2015)* and another demonstrated positive correlations between high LNCS consumption and several taxonomic entities *(Suez et al, 2014)*. In contrast, three more recent interventional studies have shown no effect of sucralose and/or aspartame, or saccharin, respectively, on the gut microbiome *(Thomson et al, 2019; Ahmad et al, 2020c and Serrano et al, 2021)*. There is also evidence that inter-individual heterogeneity could be an important factor *(Suez et al, 2022)*.

While these outcomes are difficult to interpret, it is important to appreciate that changes in the microbiome do not necessarily indicate an impact on human health. If we are to begin to understand the impact of LNCS on the gut microbiota and more importantly what this means for health outcomes, several factors need to be considered. While there is a need for more well-designed randomized controlled trials, we also need information on the microbiome beyond the genus level, as most studies to date have profiled the microbiota using only 16S rRNA sequencing. Studies exploring microbiome function, which is almost completely unknown for LNCS, will be extremally informative. Intervention studies providing information at a species level, as well functional output will allow for a greater understanding of personalised effects, and this is likely key to recognising the impact of LNCS on human health.

Conclusion

In all, LNCS and foods and drinks containing them can be safely used by people living with, or at risk of developing diabetes or other cardiometabolic diseases since they have a neutral effect on cardiometabolic risk factors including blood glucose and insulin levels, blood pressure and lipid profile. Using LNCS in place of caloric sweeteners can help reduce excess sugars intake and curb cravings for something sweet without risking a spike in blood glucose levels, provided that other ingredients of the food/ drink don't influence blood glucose either. Certainly, there should be no expectation that LNCS, by themselves, would have a glucose lowering effect, but they can be part of an overall healthy diet aiming to help reduce the excess intake of calories and sugars in the diet.

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6.
Low/no calorie sweeteners and oral health

Low/no calorie sweeteners (LNCS) are non-cariogenic ingredients and therefore, contrary to sugars and other fermentable carbohydrates, LNCS do not contribute to the development of dental caries. Untreated dental caries is the single most common health condition globally, affecting more than 2 billion people worldwide.

This chapter aims to provide information about oral health, the effect of diet on dental caries and the role that LNCS and sugar-free chewing gum can play in good dental health.

Introduction

Untreated oral diseases affect almost half of the world's population, making them the most widespread conditions among the more than 300 diseases and conditions that affect humanity *(WHO, 2022)*. In 2019, almost 3.5 billion people globally suffered from different forms of oral diseases including untreated caries of deciduous (primary) and permanent teeth, severe periodontal disease (gum disease), edentulism (total tooth loss) and cancer of the lip and oral cavity *(Global Burden of Disease, 2019)*.

Oral diseases can impact many different aspects of life, from overall health to personal relationships and self-confidence, to even enjoying food. In fact, oral health affects general health by causing considerable pain and by changing what people eat, their overall quality of life and well-being. According to the FDI World Dental Federation's definition of oral health, "Oral health is multi-faceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow and convey a range of emotions through facial expressions with confidence and without pain, discomfort and disease of the craniofacial complex (head, face, and oral cavity)."

Oral diseases are also linked to other chronic non-communicable diseases (NCDs), sharing common causal pathways, and affecting each other in a bi-directional way *(Seitz et al, 2019)*. For example, research shows that periodontitis (gum disease) can result in patients changing their dietary habits to include less fruit and vegetables *(Tonetti et al, 2017)*. Tooth pain or tooth loss can lead people to opt for softer, easier-to-chew foods that can be higher in calories, fat and sugar. As a result, poor oral health can itself contribute to unhealthy dietary patterns that are associated with increased risk of chronic NCDs such as obesity and type 2 diabetes.

Our oral health impacts our general health and well-being!

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Facts about oral diseases

Oral diseases affect nearly **3,5 billion people worldwide**.

Between 1990 and 2019, estimated case numbers grew by more than 1 billion – a **50% increase**.

Oral diseases take many shapes and forms, with **the most common being dental caries** (also known as tooth decay) **and gum disease**.

Risk factors for oral diseases include poor oral hygiene, diets high in sugar, tobacco use and excess alcohol consumption.

Sources:
(1) World Health Organization (WHO). Global oral health status report: towards universal health coverage for oral health by 2030. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO
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About dental caries

Dental caries, which is also known as tooth decay or cavities, is the most widespread chronic disease worldwide and constitutes a major global public health challenge affecting people of all ages across the lifespan *(WHO, 2022)*. Tooth decay forms over time, when bacteria in the mouth break down sugars and other fermentable carbohydrates, producing acids that damage the hard tissues of the tooth leading to the formation of cavities.

The negative health effects of dental caries are cumulative because the disease is the result of lifelong exposure to dietary risk factors. Being free of cavities in childhood does not mean being caries-free for life, and most dental caries is now occurring in adults *(Moynihan and Kelly, 2014)*. Importantly, dental caries is largely preventable and avoidable and can be treated in their early stages *(FDI, 2015a)*.

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Prevalence of dental carries

According to the Global Burden of Disease (GBD) Study (2019), untreated dental caries in permanent teeth is the most prevalent condition among all diseases, affecting more than 2 billion people worldwide – more than one third of the world's population. In deciduous (primary) teeth, untreated caries is the single most common chronic childhood disease, affecting 514 million children worldwide *(Bernabe et al, 2020)*. The estimated prevalence of dental caries of deciduous and permanent teeth worldwide is presented in Figures 1 and 2, respectively.

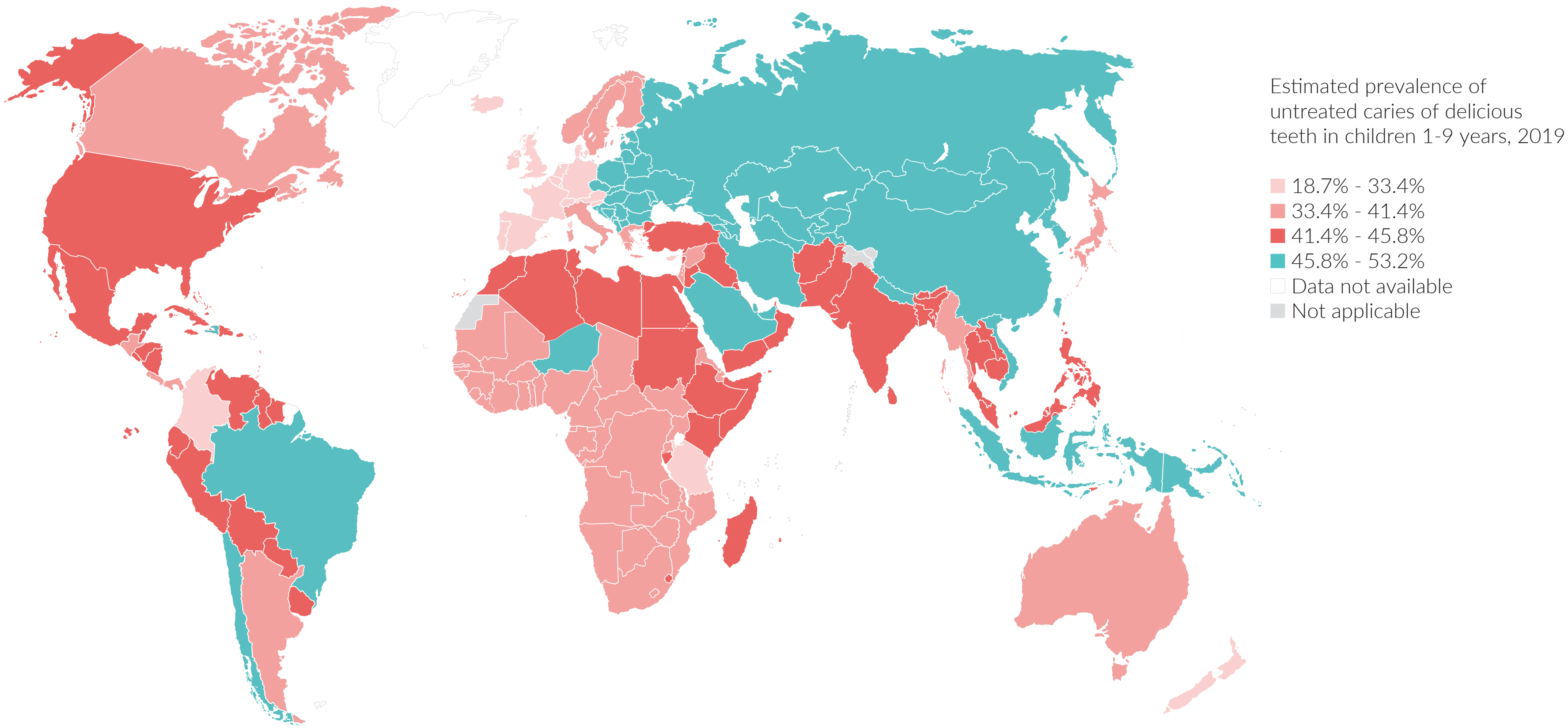

Figure 1: Estimated prevalence of dental caries of deciduous teeth in children 1-9 years globally
Data source: Global Burden of Disease Collaborative Network. GBD 2019. Seattle: IHME; 2020. Map Production: WHO NCD/MND unit. Map Creation Date: 30 August 2022. Note. N = 194 countries; data are for children aged 1–9 years, both sexes, from GBD 2019

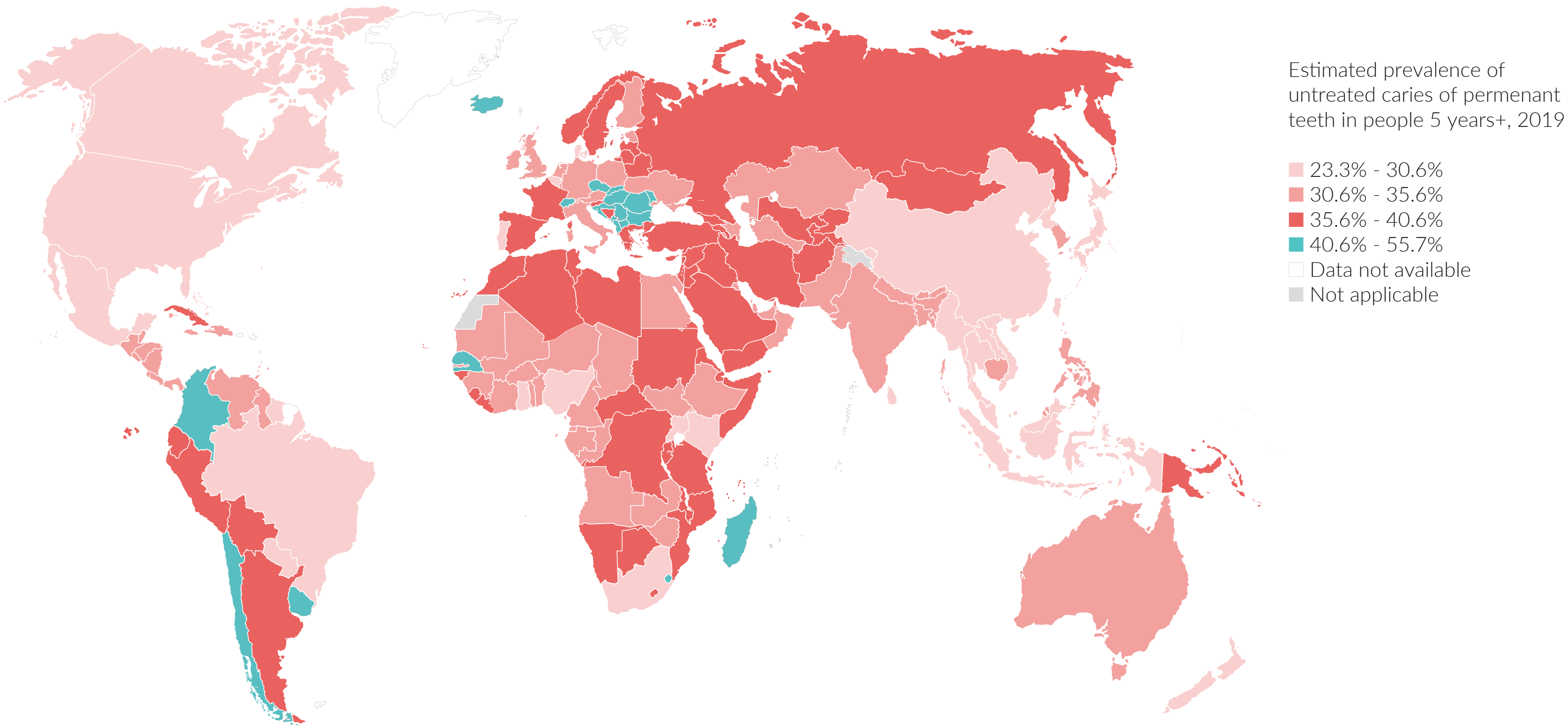

Figure 2: Estimated prevalence of dental caries of permanent teeth globally
Data source: Global Burden of Disease Collaborative Network. GBD 2019. Seattle: IHME; 2020. Map Production: WHO NCD/MND unit. Map Creation Date: 30 August 2022. Note. N = 194 countries; data are age standardized, for ages greater than 5 years, both sexes, from GBD 2019

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Diet and dental caries

Oral health and diet are connected. Nutrition affects the teeth during development and malnutrition may exacerbate periodontal and oral infectious diseases. However, the most significant effect of nutrition on teeth is the impact of diet in the mouth on the development of dental caries and enamel erosion.

Tooth decay is caused by acids produced when sugars and other fermentable carbohydrates present in our foods or drinks are broken down by oral bacteria of the dental plaque on the tooth surface. The acid produced leads to a loss of calcium and phosphate from the enamel, a process that is called demineralisation *(Gupta et al, 2013).*

Following a healthy diet together with practicing good oral hygiene practices from an early age are key priorities for the prevention and early treatment of dental caries *(WHO, 2022)*. When it comes to a diet for optimal dental health, excess intake of sugars and other fermentable carbohydrates should be limited.

Maintaining a good oral health is possible by practicing good oral hygiene including:

- Brushing our teeth for two minutes, twice a day, with a fluoride toothpaste
- Visiting the dentist for regular check-ups and dental cleanings
- Eating a well-balanced diet that is low in sugar and high in fruit and vegetables
- Avoiding all forms of tobacco and limiting alcohol consumption
- Chewing sugar-free gum after eating and drinking

Sources:
(1) FDI World Dental Federation. The Challenge of Oral Disease – A call for global action. The Oral Health Atlas. 2nd ed. Geneva. 2015a. Available at: https://www.fdiworlddental.org/oral-health-atlas (Accessed 9 March 2023)
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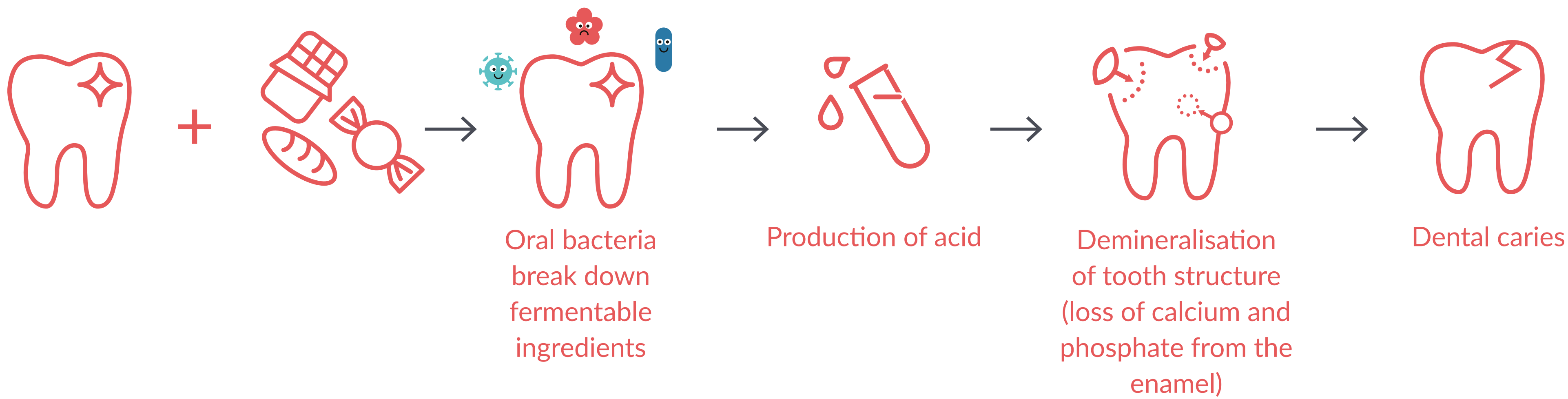
Sugar and dental caries

Frequent sugars' consumption is a significant dietary factor in the development of dental caries. A systematic review that was conducted aiming to inform the World Health Organization's (WHO) guideline on free sugars intake found that there is consistent evidence supporting a relationship between the amount of free sugars intake and the development of dental caries across age groups *(Moynihan and Kelly, 2014)*. The review process has also shown evidence of moderate quality to support that limiting intake of free sugars to <10% of daily energy intake minimises the risk of dental caries throughout the life course *(WHO, 2015)*.

Recently, in its Scientific Opinion on the Tolerable Upper intake level for dietary sugars, the European Food Safety Authority (EFSA) confirmed a positive linear dose-response relationship between total sugars intake and risk of dental caries in permanent and primary dentition *(EFSA, 2022)*. The mechanisms by which sugars increase the risk of dental caries are well established: they are metabolised by plaque microorganisms to organic acids which demineralise enamel and dentine, subsequently causing caries. Furthermore, caries risk has been found to be greater if sugars are consumed at high frequency and are in a form that is retained in the mouth for long periods *(Anderson et al, 2009)*.



No cariogenic effect of low/no calorie sweeteners

Contrary to sugars, LNCS have no cariogenic effect, meaning that they do not cause dental caries, as they are not substrates for oral microorganisms. **All approved LNCS are sweet-tasting food ingredients with no, or practically no calories that cannot be fermented by oral bacteria, and therefore, they do not contribute to tooth decay** *(Roberts and Wright, 2012; van Loveren et al, 2012).*

The first scientific evidence regarding the dental health benefits of LNCS dates to the 1970s *(Olson, 1977).* Since then, a number of studies and reviews have examined and confirmed the non-cariogenic nature of LNCS *(Grenby et al, 1986; Mandel and Grotz, 2002; Matsukubo and Takazoe, 2006; EFSA, 2011; Giacaman et al, 2013; Gupta et al, 2013; Brambilla et al, 2014; Ferrazzano et al, 2015; Vandana et al, 2017; Cocco et al, 2019; Shinde et al, 2020; Zhu et al, 2021).*

When evaluating a non-sugar sweetener in relation to dental caries, it is important to consider the potential for metabolism by oral microorganisms and dental plaque, the influence of consumption on cariogenic microorganisms, and the risk of microbial adaptation to the sweetener. Examining the impact of sugars and LNCS on dental health, a review concluded that LNCS such as aspartame, acesulfame-K, cyclamate, saccharin, sucralose and steviol glycosides, among others, are not metabolized to acids by oral microorganisms and they cannot cause dental caries *(Gupta et al, 2013).*

In its policy statement published in 2008, the FDI World Dental Federation supported that when sugars are replaced with non-cariogenic sugar substitutes in products such as confectionary, chewing gum and drinks, the risk of dental caries is reduced *(FDI Policy Statement 2008).*

Scientific evidence into EU regulation

Reviewing the available evidence, the European Food Safety Authority (EFSA) supports in the respective scientific opinions that "there is sufficient scientific information to support the claims that intense sweeteners, as all sugar replacers, maintain tooth mineralisation by decreasing tooth demineralisation if consumed instead of sugars" *(EFSA, 2011).*

Based on this scientific opinion by EFSA, the European Commission authorised the health claim: "Frequent consumption of sugars contributes to tooth demineralisation. Consumption of foods/drinks containing low calorie sweeteners instead of sugar may help maintain tooth mineralisation by decreasing tooth demineralisation" *(Commission Regulation (EU) No 432/2012, 16 May 2012).*

How do low/no calorie sweeteners influence the cariogenic potential of oral microbiome?

Dr Wendy Russell: While there is an increasing understanding of the impact of diet on the gut microbiome, the oral microbiome is less well studied. It is known that oral bacteria generate acidic products from sucrose that lead to demineralization and that sugar substitutes can contribute to caries prevention *(Matsukubo et al, 2006)*, but the role of the oral microbiome has only recently been explored.

In a recent human study, it was shown that LNCS significantly impacted on the oral bacteria *(Suez et al, 2022)*. Changes were observed in the relative abundance of six Streptococcus species with sucralose and there was reduced relative abundance of Fusobacterium with saccharin and reduced abundance of Porphyromonas and Prevotella nanceiensis with aspartame. Apart from an impact of stevia on the metabolism-related KEGG pathway (which informs on biological high-level function), the impact of the changes in these microbial profiles on oral health is not known. However, changes in the Streptococcus abundance may be important as Streptococcus mutans, Streptococcus sanguinis and Streptococcus gordonii have been associated with the development of dental caries *(Takahashi and Nyvad, 2011)*. Recent work has also shown that acesulfame-K, aspartame, saccharin, and sucralose can suppress the growth and biofilm formation of both Streptococcus mutans and Streptococcus sanguinis *(Zhu et al, 2021)*. Although this work is early stage, it suggests potential of LNCS to beneficially impact oral health by modulating the cariogenic potential of oral microbiome.

The role of sugar-free chewing gum in oral health

Chewing sugar-free gum, sweetened with non-fermentable LNCS, stimulates the production of saliva and has been shown to have important dental health benefits.

Reviewing the available evidence, EFSA concluded in its Scientific Opinions that a cause-and-effect relationship has been established between the consumption of sugar-free chewing gum and reduction of oral dryness, maintenance of tooth mineralisation, and neutralisation of plaque acids *(EFSA, 2009; EFSA, 2010a; EFSA, 2010b)*, all of which are beneficial to oral health by helping reduce the incidence of caries. Based on these Scientific Opinions by EFSA, the European Commission has authorised respective health claims.

A recent systematic review and meta-analysis of 12 studies also confirmed that chewing sugar-free gum may reduce the further development of dental caries *(Newton et al, 2020)*. Sugar-free chewing gums were found to significantly reduce caries increment giving a preventative fraction of 28%.

Finally, **the FDI World Dental Federation also supports the assertion that the regular use of chewing gum containing non-cariogenic sweeteners has a role to play in preventing dental caries because of its non-cariogenic nature and its salivary stimulatory effect** *(FDI Policy Statement, 2008)*.

The oral care benefits of chewing sugar-free gum are widely recognized, including by the European Union *(Commission Regulation (EU) No 432/2012, 16 May 2012)*, federal health departments and bodies in Canada *(Health Canada, 2014)*, and Australia *(Australia's National Oral Health Plan 2015-2024)*, the FDI World Dental Federation *(FDI, 2015b)* and more than 20 national oral or dental health associations around the world.

How does sugar free chewing gum protect our teeth?

Chewing sugar-free gum stimulates the production of saliva – our mouth's defense system against tooth decay

Saliva neutralises plaque acids protecting enamel

Increasing saliva flow helps reduce dryness in our mouth

It also aids our teeth retain the minerals they need to maintain hardness and strength

Brushing our teeth twice a day and chewing sugar-free gum after meals and snack can help keep our teeth healthy

Conclusion

By being not fermentable and thus non-cariogenic ingredients, LNCS are tooth friendly ingredients providing dental benefits when used instead of sugars in foods and beverages, sugar-free chewing gums, toothpaste and medications, provided that other constituents are also non-cariogenic and non-erosive (other ingredients in some low/no calorie sweetened food products such as starch and/or naturally occurring sugars may still cause caries) *(Gibson et al, 2014)*.

Overall, and from a public health perspective, reducing the amount and frequency of dietary exposure to sugars is an important adjunct in preventing caries and, in this context, LNCS can help people reduce overall sugar intake and still keep enjoying sweet taste in the context of a tooth-friendly diet without bearing a cariogenic effect.

Low/no calorie sweeteners are tooth friendly ingredients

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7.
Sweet taste in the human diet

Sweetness is an integral part of the human diet. Our appetite for sweet taste is innate, expressed even before birth, and spans across all ages and cultures around the world. However, our food environment has changed considerably over the last decades and high-calorie, palatable foods, which are usually high in fat and sugar content, are now widely available and easily accessible. In times when health organisations worldwide recommend that free sugars intake should be reduced to less than 10%, or even 5% of total daily energy intake, managing dietary sweetness is critical from a nutritional and a public health perspective.

This chapter aims to present scientific information about the role of sweet taste in the human diet and to discuss the role of low/no calorie sweeteners (LNCS) in managing our innate appetite for sweetness.

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Why do we like sweet taste?

Taste plays a key role in food choice and food intake *(de Graaf and Boesveldt, 2017)*. In conjunction with other senses, taste drives our decisions about whether a potential food will be accepted or rejected, while ensuring the intake of sufficient nutrients. In humans, as well as in many animal species, taste has the additional value of contributing to the overall pleasure and enjoyment of a food or drink *(Drewnowski 1997; Steiner et al, 2001)*. The generally recognised five "basic tastes" include: sweet, sour, bitter, salt and umami (Figure 1), while emerging evidence suggests that there may be a sixth basic taste: fat *(Running et al, 2015; Jaime-Lara et al, 2023)*.

Figure 1: Basic tastes

Sweet taste always was and remains an integral part of the human diet. The affective response to sweetness is also evident in the fact that the word "sweet" is used widely to describe not only this basic taste quality but also something that is pleasurable, e.g., "la dolce vita" [sweet life] *(Reed and McDaniel, 2006)*.

The sensory pleasure derived from tasting sweet substances has an innate basis. Experts believe that the inborn acceptance of sweet stimuli and rejection of bitter ones have developed through natural evolution and constitute an adaptive advantage, preparing the new-born to spontaneously accept sources of energy and to reject potentially toxic bitter substances *(Mennella and Bobowski, 2015)*. As a result, infants' appetite for sweetness facilitates the acceptance of breast milk which tastes sweet due to its content of lactose, the sugar found in maternal milk. Therefore, it has been suggested that it is basic biology that dictates a liking for sweetness *(Drewnowski et al, 2012)*.

"Liking" and "wanting" are two distinct components of food reward *(Morales and Berridge, 2020)*. "Liking" underpins the subjective pleasure elicited by tasting a particular food, while "wanting" refers to the desire to actually ingest a food *(Berridge, 1996; Blundell et al, 2010)*. On the other hand, "preference" involves a comparison between two or more stimuli, where one is preferred over others, and a hierarchy of attractiveness can be established *(Zellner, 2007)*. Different levels of "liking" or "wanting" can determine preferences between various stimuli.

How does our body "recognise" sweetness?

Sweetness is one of the basic tastes that humans recognise. A sweet tasting stimulus is detected by sweet taste receptors located in the oral cavity. Various sweet tasting molecules can bind to and stimulate the sweet taste receptor including sugars, polyols, and a broad variety of LNCS *(Renwick and Molinary, 2010)*.

Sweetness perception involves two G-protein coupled transmembrane receptor proteins, T1R2 and T1R3, which dimerise to form the sweet-taste receptor. The G-protein associated with the sweet-taste receptor is alpha-gustducin. Binding of a sweet compound to the receptor activates the release of alpha-gustducin, which triggers intracellular signalling events such as the opening of ion channels or the generation of other biochemical signals, leading to a release of intracellular calcium (Ca2+). Stimulation of the T1R2 + T1R3 taste receptor activates peripheral gustatory nerves transmitting sensory information to the brain and, in turn, brain gustatory pathways *(Renwick and Molinary, 2010)*.

Identical receptors have also been found in other parts of the digestive tract, from the stomach and pancreas to the colon and enteroendocrine cells *(Mehat and Corpe, 2018)*. Such receptors respond to the presence of sugars by inducing a number of metabolic responses usually associated with satiety and glucose metabolism (e.g. secretion of gut hormones and insulin, reduction of ghrelin, slowing of gastric emptying). Contrary to the metabolic responses evoked by sugars, evidence from human studies suggests that LNCS do not significantly affect gut hormones, gastric motility, appetite or glucose metabolism in humans *(Renwick and Molinary, 2010; Steinert et al, 2011; Bryant and McLaughlin, 2016; Mehat and Corpe, 2018; Zhang et al, 2023)*.

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Sweetness preference: From early life to adulthood

The acceptance of sweetness and the rejection of bitterness are innate traits *(Mennella and Bobowski, 2015)*. This is evident, for example, from the characteristic "gusto-facial reflexes", the stereotyped reactions elicited in human new-borns a few hours after birth by placing a small amount of sapid solutions into their mouths. Sugar elicits a characteristic acceptance response, which is in sharp contrast to the rejection caused by bitter- and sour-tasting substances *(Steiner, 1977)* (Figure 2). When a sweet solution is placed in the infant's oral cavity, face relaxation, tongue protrusion and lip searching, and sometimes a smile are observed *(Steiner et al, 2001)*.

Early research on the developmental trajectory of sweet taste preferences suggests that such preferences are even expressed before birth *(Mennella and Beauchamp, 1998)*. A recent study using 4D ultrasound scans showed that foetuses aged 32 to 36 weeks react to flavours of foods ingested by their pregnant mother in a similar way as postnatally *(Ustun et al, 2022)*. In this study, foetuses expressed different types and frequencies of facial movements in relation to the type of flavour that they were exposed to, namely, more laughter-face expressions when exposed to a carrot (sweet) flavour and more cry-face expressions when experiencing a kale (bitter) flavour.

Infant facial expressions

Image courtesy of John Wiley and Sons

Figure 2: Infant facial expressions in response to sweet, sour, bitter and salt taste stimuli (After Steiner, 1977)

Humans are born with a liking for sweetness, which decreases from childhood to adolescence and into adulthood.

Our natural appetite for sweetness remains until old age, however, there is clear evidence that it decreases from childhood to adulthood *(Desor et al, 1975; Desor and Beauchamp, 1987; de Graaf and Zandstra, 1999; Mennella et al, 2011)*. Children prefer higher sucrose concentrations than adults with the changeover occurring during adolescence *(de Graaf and Zandstra, 1999; Petty et al, 2020)*.

A study in 485 individuals showed that children had higher sucrose taste detection thresholds compared with adolescents, who in turn required higher concentrations than adults, meaning they required higher concentrations of sucrose to detect a taste different from water *(Petty et al, 2020)*. However, no significant relationship between sweet taste detection thresholds and preferences across age groups was found, indicating that sweet preference is not readily explained by differences in the ability to detect sweetness. It has been suggested that the heightened preference for sweetness during childhood and adolescence may in part reflect the higher caloric and nutritional needs during periods of maximal physical growth, as shown in studies linking the most preferred level of sweetness with children's height and levels of a biomarker for bone resorption and growth *(Coldwell et al, 2009; Mennella et al, 2014)*.

Finally, research suggests that, in general, taste perception declines during the healthy ageing process, although the extent of decline – including for sweetness – varies between studies *(Methven et al, 2012)*.

Determinants of sweetness preference beyond age

While all humans express the same response to sweetness immediately after birth, preference for sweet taste changes over time and becomes highly idiosyncratic in adults *(Reed and McDaniel, 2006)*. An appetite for sweetness is present in most adults but large inter-individual differences exist in the preferred level of sweetness intensity. It is not yet clear why individuals exhibit so different hedonic responses to sweet tastes *(Armitage et al, 2021)*.

Some research suggests that humans fall into three phenotypic sweetness response patterns: those whose liking increases with sweetness intensity (sweet likers), those who show increasing dislike as sweetness increases (sweet dislikers), and a third group who show preference for moderate levels of sweetness *(Iatridi et al, 2019)*.

Recent reviews have examined the potential role of several determinants of sweetness preference and liking in humans *(Venditti et al, 2020; Armitage et al, 2021)*. The impact of age, genetics, dietary and lifestyle factors, reproductive hormonal factors, body weight status and weight loss, personality and cultural factors, previous exposure and disease status was reviewed.

There is evidence that genetic differences among people may partly account for individual variations in sweetness perception and preference *(Reed and McDaniel, 2006; Keskitalo et al, 2007; Fushan et al, 2010; Reed and Knaapila, 2010; Bachmanov et al, 2011; Joseph et al, 2016)*. However, how these genetic differences might translate into food intake and food preference at each age is still unclear.

The associations between sweetness preferences and reproductive hormonal factors are overall inconsistent, as assessed in the scoping review by Venditti and colleagues *(Venditti et al, 2020)*. Similarly, there is limited and heterogeneous evidence regarding the links between various personality traits with sweetness preference, with no clear or consistent associations. Also, no clear pattern for sweetness preference based on dietary macronutrient composition or meal composition has been reported. However, there is some consistency in the literature regarding a general increase in sweetness preference in the fasted versus satiated state, as well as some suggestion, albeit from a very limited number of studies, that increased physical activity may be associated with a reduction in sweetness preference *(Venditti et al, 2020)*

Other potential determinants of sweetness preference and/or liking, including body weight status and previous exposure to sweet taste, are discussed in the following paragraphs.

Is there a link between sweetness and obesity?

The attraction of humans to sweet tasting foods has given rise to the notion that a strong appetite for sweet taste may be a key driver of obesity. It has been suggested that an individual's appetite for sweet-tasting foods and drinks could facilitate overconsumption and, in a society where palatable and convenient food products are widely available, potentially override the physiological energy-regulation mechanisms *(Bellisle, 2015)*.

There is no doubt that overconsumption of energy-dense products, some of which are sweet-tasting, may lead to an imbalance between energy intake and expenditure, and consequently, to weight gain. However, current evidence shows no clear support for the wide assumption that a strong attraction to sweetness is associated with overeating and obesity *(Venditti et al, 2020; Armitage et al, 2021)*. In fact, a recent review pointed to many studies reporting the opposite, i.e. that individuals with obesity express a lower overall liking for sweetness, and that sweet dislikers, rather than sweet likers, may have slightly higher body fat *(Armitage et al, 2021)*. Also, current evidence does not clearly support the assertion that people with obesity have altered sweet taste sensitivity and perception, compared to normal-weight people *(Ribeiro and Oliveira-Maia, 2021)*. In all, available data do not support the notion that sweet liking is linked to higher body weight and obesity in adults, and if anything, provides evidence to the contrary *(Armitage et al, 2021)*. However, potential effects of weight loss, including after bariatric surgery, on sweetness preferences and perception need to be examined in future studies *(Ribeiro and Oliveira-Maia, 2021)*.


Credit © World Obesity Federation

Studies in children and adolescents also show no differences in sweetness preference, or sweet food intake, based on weight status *(Venditti et al, 2020)*. For example, in a study of 366 children, aged 7-9 years, no association was found between adiposity and liking for sweet-tasting sugary foods *(Hill et al, 2009)*. Similarly, a study in 574 children and adolescents, aged 10-17 years, indicated no different sensory preferences or taste sensitivity among the different body weight categories *(Alexy et al, 2011)*. In adolescents, results from the Finnish Health in Teens cohort study in 4237 girls and boys suggested that a higher consumption of sweet-tasting treats was unrelated to being overweight or to weight change over a 2-year follow-up period *(Lommi et al, 2021)*. Finally, a study in both children and adults found that, regardless of age, sweet preference and liking for both caloric sweeteners and LNCS did not differ between individuals with or without obesity (Figure 3) *(Bobowski et al, 2017)*. Altogether, these findings suggest that stronger liking or preference for sweetness is not related to body weight status in children, adolescents, or adults.

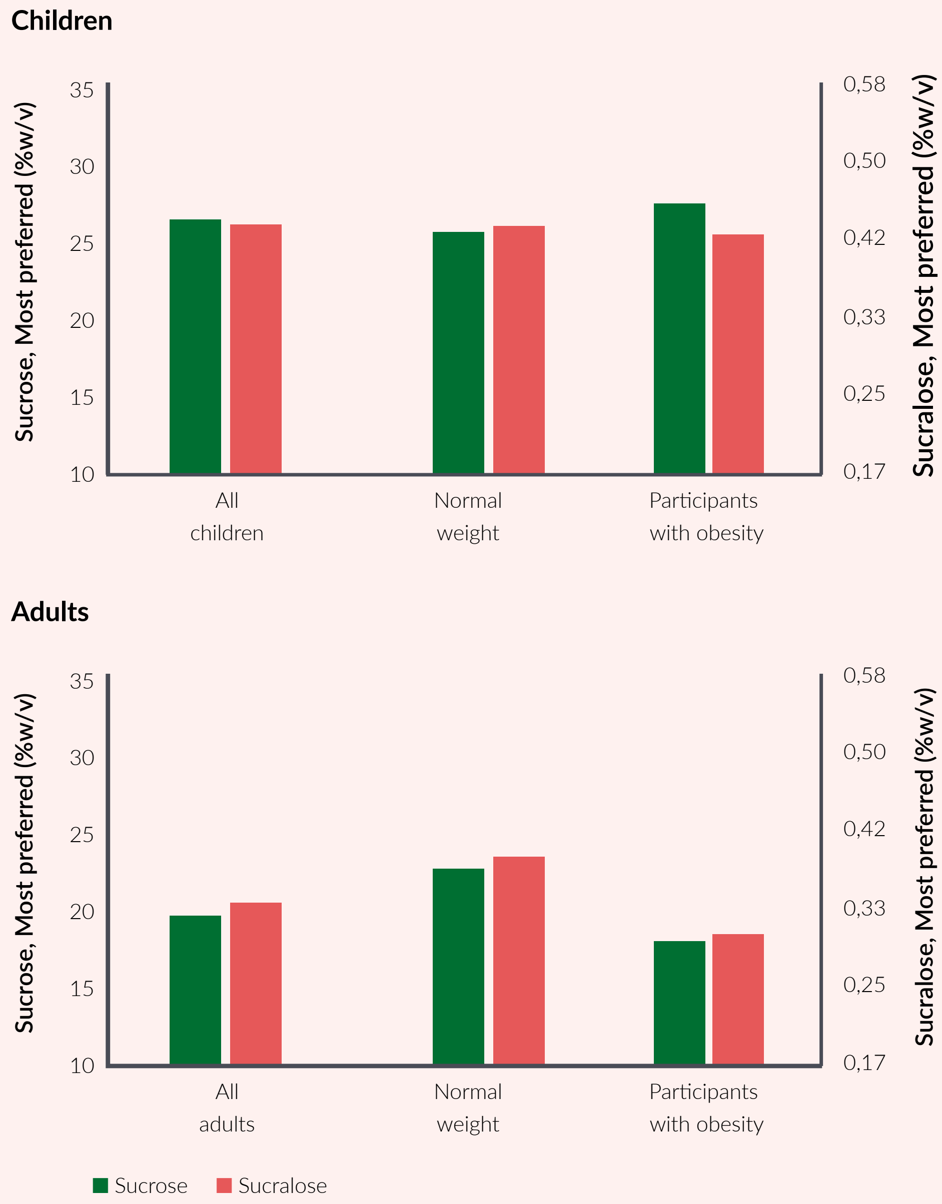

Figure 3: Most preferred levels of sucrose and sucralose among all children (a) and adults (b), or according to weight status: There were no significant relationships between BMI and most preferred level of sucrose or sucralose, regardless of age. Data are means ± standard error. (Bobowski et al, 2017)

Exposure to sweet taste and sweetness preference

There is a common belief that repeated exposure to sweet taste through the diet may stimulate our appetite for sweetness, lead to overeating, and hence, weight gain, despite a lack of clear evidence to support this notion *(Bellisle, 2015; Public Health England, 2015; Rogers, 2018; Appleton et al, 2018; Wittenkind et al, 2018; Venditti et al, 2020; Armitage et al, 2021; Higgins et al, 2022).*

A systematic review that examined the outcomes from 21 studies in both children and adults concluded that current evidence from human controlled trials do not support the assertion that dietary exposure to sweetness affects the subsequent generalized acceptance, preference, or choice of sweet-tasting foods or beverages in the diet *(Appleton et al, 2018)*. In fact, a higher sweet taste exposure rather tends to lead to reduced preferences for sweetness in the shorter term, a phenomenon known as sensory-specific satiety (exposure to a particular sensory attribute, for example sweetness, can lead to reductions in the apparent pleasantness and choice of foods and beverages with that same attribute).

In a 3-month RCT, a low-sugar, low-sweetness exposure diet did not change sweet preference compared to a habitual diet, despite heightened ratings of sweetness intensity perception *(Wise et al, 2016)*. However, if sweet intensity perception does not result in a shift in the preferred sweetness of foods, it is unclear how food choice would be altered. Results from seven available studies assessing the impact of exposure to different levels of dietary sweetness do not support the assertion that exposure to a high versus low dietary sweetness affects calorie and sweet food consumption, or that it results in overeating *(Higgins et al, 2022)*. A longer-term RCT is currently under way with the aim to assess the effect of low, regular, and high dietary sweetness exposure over 6 months on sweetness preference and perception, food choice and intake, among other health outcomes *(Čad et al, 2023).*

Sweetness without calories: the role of low/no calorie sweeteners

In times of an obesity epidemic, with increased sugar and fat intakes contributing to excess energy intake and ultimately to weight gain, different strategies for managing our innate appetite for sweetness, such as the use of LNCS in place of caloric sweeteners, have been proposed as useful tools in reducing sugars and thus overall energy intake.

In traditional food products, sweetness is brought primarily by sugars. Sugars are carbohydrates with a distinctive sweet taste and an energy content of 4 kcal per gram. In order to allow consumers to enjoy the palatable sweet taste of their favourite foods and beverages without the energy load of sugar, a number of LNCS have been developed in the last decades *(Bellisle, 2015)*. LNCS have a much higher sweetening power compared to sugars, so that they can be used in very small amounts (mg in place of grams of sugars) to create the desired level of sweetness of a food or drink, while contributing very little or no energy at all to the final product. By reducing the energy content of foods and beverages, LNCS may potentially be a helpful tool for satiating our desire for sweet taste with fewer or zero calories.

However, over the years, concerns have been expressed about potential adverse effects of LNCS on appetite for sweet taste *(Yunker et al, 2020)*. More specifically, it has been suggested that LNCS might enhance the natural appetite for sweet taste, and therefore increase intake of sweet foods and beverages, preventing consumers from managing their response to sweetness. Likewise, a review that examined the related evidence rejected this claim and concluded that consumption of LNCS does not increase food or energy intake compared with water and may have the advantage of to some extent satisfying desire for sweetness when consumed shortly before or with a meal *(Rogers, 2018)*.

Several controlled clinical studies have shown that the use of LNCS is associated with a lower intake of sweet tasting substances in children *(de Ruyter et al, 2013)* and adults *(Piernas et al, 2013; Fantino et al, 2018; Higgins et al, 2018; Maloney et al, 2019)*. For example, a large RCT in children found that the consumption of beverages with LNCS for 18 months did not exacerbate liking or desire of sweet tasting products, and in contrast, LNCS use was associated with a lower intake of sweet foods *(de Ruyter et al, 2013)*. The CHOICE study, a 6-month RCT in 104 adults with obesity, showed a broader suppression of appetite for sweetness in participants with a high daily intake of LNCS drinks than in the control group allowed only water *(Piernas et al, 2013)*. Similarly, the study by Fantino and colleagues showed that acute or longer-term consumption of low/no calorie sweetened beverages with meals does not affect appetite and hunger or overall calorie and food intake, when compared to water *(Fantino et al, 2018)* (see also Chapter 4). More recently, a study by Maloney and colleagues found that low/no calorie sweetened beverages may help some individuals to better control food cravings possibly by satisfying their desire for sweetness *(Maloney et al, 2019)*. Further recently published studies addressing these concerns found no support for an exacerbation of the appetite for sweetness with the use of LNCS *(Rogers et al, 2020; Appleton, 2021; Appleton et al, 2021)*.

In conclusion, **current evidence does not support the notion that LNCS use can lead to a heightened appetite for sweetness, sugar, or sweet products, or that there is an association between exposure to sweetness and a change in taste preferences.** In many instances, LNCS contribute to satisfy a desire for sweetness *(Bellisle, 2015)*.

There is no evidence of an association between low/no calorie sweeteners' use and a heightened appetite for sugar or sweet products in children or adults.

Can exposure to sweet taste enhance the "sweet tooth"?

Dr France Bellisle: The term "sweet tooth" refers to a person's strong preference for sweet-tasting foods. It is not a scientific concept with any rigorous definition. However, it is legitimate to ask whether repeated exposure to sweetness, with or without calories, could enhance the liking of and appetite for sweet tasting products, which could in turn lead to increased consumption. An increased use of LNCS in many foods and beverages could create such a situation.

Current evidence does not support the notion that repeated exposure to sweet taste in general, or to sweetness without calories in particular, leads to a heightened appetite and/or consumption of sugar-sweetened foods and drinks *(Rogers, 2018; Appleton et al, 2018)*. What laboratory and field studies have shown, however, is that consumption of products with a particular sensory attribute (e.g. sweetness) leads to reductions in the momentary pleasantness and attractiveness of foods and beverages with that same attribute, a robust phenomenon known as "sensory-specific satiety" *(Rolls, 1986; Hetherington et al, 2000; Liem and de Graaf, 2004)*. Therefore, exposure to the sweet taste of foods and beverages with low amounts of sugars, sweetened with LNCS, may not only decrease the consumption of free sugars but could also satiate the desire for sweetness from other sources *(Appleton et al, 2018)*.

Conversely, the potential effects of reducing sweetness in the diet (from caloric and non-caloric sources) on appetite remain to be investigated in randomised controlled trials *(Wittenkind et al, 2018)*. One study *(Wise et al, 2016)* showed that a low-sugar diet maintained for three months did not change the preference for sweetness, even if the participants rated sweet foods as tasting sweeter after the end of the intervention period. However, once the low-sugar diet ended, people quickly increased their ad libitum sugar intake to baseline levels and their judgments of sweet taste intensity reverted to pre-diet levels. It seems that preference and appetite for sweetness do not change according to the higher or lower exposure to sweet tasting foods, at least in adults.

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Can use of low/no calorie sweeteners disrupt the control of energy intake?

Dr France Bellisle: The notion that LNCS might paradoxically enhance appetite and intake is not a new one *(Bellisle, 2015)*. It was formulated in the 1980's by John Blundell and his team *(Blundell and Hill, 1986)*, who made the important point that LNCS uncouple sweet taste and energy content. When a sweet-tasting and energy-containing product is ingested, the sensory stimulation is followed by post-ingestive effects that act to limit intake; such effects include satiation signals from the gastro-intestinal tract that inform the brain that energy and nutrients have been obtained. By contrast, according to Blundell's early hypothesis, LNCS stimulate appetite via their sweet taste, but exert no post-ingestive inhibitory influence since they provide no energy. Thus, the experience of sweetness in the absence of calories might possibly weaken the learned "sweetness = energy" association and consequently disrupt appetite control mechanisms.

Numerous studies using very different methodological approaches (observational, RCTs, and Magnetic Resonance Imaging) in various types of participants (men, women, lean, obese, never obese, formerly obese) have examined the impact of LNCS on appetite for sweet taste and ultimately on intake of sweet tasting products *(Anton et al, 2010; de Ruyter et al, 2013; Piernas et al, 2013; Fantino et al, 2018; Higgins et al, 2018)*. Furthermore, several systematic reviews and meta-analyses have evaluated the available data. Overall, the existing studies reach largely consistent conclusions: the short- or long-term use of LNCS shows no association with a heightened appetite in general, or specific appetite for sugar or sweet products. In fact, in many instances, the use of LNCS is associated with a decreased intake of sweet tasting substances *(Rogers et al, 2016; Rogers, 2018)*. Likewise, a report by Public Health England (2015) concluded that there is no evidence to suggest that maintaining the sweet taste through the use of LNCS increases the selection of higher calorie foods and drinks.

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Contributors

Leading academics and researchers working in the areas of food science and nutrition, epidemiology, nutrition psychology and eating behaviour have reviewed the content of this booklet and provided answers to the most frequently asked questions about low/no calorie sweeteners.

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Following her Bachelor Degree (McGill University, Montreal) and a Masters Degree (Concordia University, Montreal) in experimental psychology, France Bellisle worked at the College de France in Paris in the laboratory of Jacques Le Magnen. She obtained Doctorate Degrees from the University of Paris. From 1982 until 2010, in the context of French National Research Institutes (CNRS, INRA), she developed original research in the field of human ingestive behaviours. Her research interests cover all types of determinants of food and fluid intake in human consumers, including psychological, sensory and metabolic factors as well as environmental influences. She has published over 250 articles in peer reviewed journals and contributed chapters to several books. She is now an independent consultant for scientific projects in the field of human appetite.

Dr Marc Fantino, Honorary Professor of the University of Burgundy, France

Marc Fantino is a Medical Doctor (MD) and Doctor of Sciences. Appointed as full professor at the Medical School of the University of Burgundy (1982), he was head of the Department of Human Physiology and Nutrition from 1987 to 2013 and also head of a medical department at University- Hospital of Dijon-France. At the same time, he was Director of the Doctoral School of Life Sciences of the University of Burgundy (1993 to 2001), expert at the French National Agency for Food Safety (1996-2006) and also Chairman of the National Nutrition and Health Program logo award committee (2004-2011).

Being now retired from the University of Burgundy since 2013, as an honorary Professor he co-founded, and managed from 2013 to 2018, a clinical research organization, CREABio Rhône-Alpes®, where applied research were implemented in the fields of the sensorial and metabolic processes which control feeding behaviours and body weight regulation in humans.

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Wendy Russell is a chemist specialised in molecular nutrition researching the complex interplay between diet and health. Her research aims to establish the effect of our diet on several population groups and through dietary interventions, to understand the role of food in preventing disorders such as cardiovascular disease, type 2 diabetes and cancer. Wendy has funding from the Scottish Government to investigate the potential of novel crops, particularly in protein provision for the future and the exploitation of underutilised plant species to improve nutrition and agrobiodiversity. As well as researching new opportunities for the UK Food and Drink industry, Global Challenges funding is allowing translation of this work to benefit smallscale rural farmers and co-operatives in sub-Saharan Africa. Wendy is an associate editor for Microbiome and chairs International Life Science Institute expert groups on 'nutritional management of postprandial glycaemia' and 'efficacy of intervention in those with metabolic syndrome'.

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Alison Gallagher is Professor of Public Health Nutrition at Ulster University, where she contributes to the research conducted within the Nutrition Innovation Centre for Food and Health (NICHE). Her research interests resonate within the area of obesity and include low energy/non-nutritive sweeteners and their potential impact on health, development of risk factors for disease and lifestyle interventions at key stages across the lifecycle particularly to enhance physical activity and health.

A Registered Nutritionist (Public Health) and Fellow of the Association for Nutrition (FAfN) on the island of Ireland. She is an active member of the Nutrition Society and is currently Editor-in-Chief of the Proceedings of the Nutrition Society. In addition to being an expert member on the Scientific Advisory Panel on Sweeteners supported by the ISA, she is also a member/Vice-chair of Northern Ireland Chest Heart Stroke Scientific (NICHS) Research Committee, member/Chair of the Editorial Advisory Board of the Nutrition Bulletin and a member of the UK Nutrition and Health Claims Committee. She is a passionate advocate for the European Nutrition Leadership Platform (ENLP), having participated in the ENLP seminar in 1997 and being involved with this international leadership programme ever since, now as Chair/ President of the ENLP Board (www.enlp.eu.com).

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Dr. Carlo La Vecchia received his MD from the University of Milan and a Master of Science degree in Clinical Medicine (epidemiology) from Oxford University. Presently, he is Professor of Medical Statistics and Epidemiology at the Faculty of Medicine at the University of Milan.

Dr. La Vecchia serves as an editor for numerous clinical and epidemiologic journals. He is among the most renowned and productive epidemiologists in the field with over 2260 peer-reviewed papers in the literature and is among the most highly cited medical researchers in the world, according to ISI HighlyCited.com, the developer and publisher of the Science Citation Index (2003, 2017-2020, H index 182, H10 index 1800). Dr. La Vecchia was an Adjunct Associate Professor of Epidemiology, Harvard School of Public Health, Boston, Ma (1996-2001) and .Adjunct Professor of Medicine at Vanderbilt Medical Centre and the Vanderbilt-Ingram Cancer Centre (2002-18).

About the ISA

The International Sweeteners Association AISBL is an international non-profit organisation with scientific aims representing suppliers and users of low/no calorie sweeteners, including tabletop sweetener manufacturers. Established over 40 years ago, the ISA is recognised by the European Commission, national and international regulatory and public health authorities, and the World Health Organisation, and has Non-Government Observer status with the Codex Alimentarius Commission which establishes international food standards.

The ISA informs and educates on the most up-to-date nutritional and scientific information in relation to the role and benefits of low/no calorie sweeteners, and the foods and beverages that contain them. The ISA also encourages research into and enhances understanding of the role that low/no calorie sweeteners can play in achieving a balanced diet, including in the context of current health challenges globally and of the efforts from public health authorities in encouraging food manufacturers to replace sugar and reduce calories as part of their reformulation goals.

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