International
Sweeteners
Association

Low Calorie Sweeteners: Role and Benefits

A guide to the science of low 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 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 fourth edition of the ISA booklet. Updated in September 2018, it presents an overview of the latest scientific information on low 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. Lifestyle changes to help decrease the risk of overweight are an important goal for a great proportion of the world's population at this time. High obesity rates show that more people need to focus on active, healthy lifestyles and energy balance – that is, balancing the calories consumed with the calories burned through physical activity.

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

The safety of low calorie sweeteners has been thoroughly evaluated and consistently confirmed by a strong body of scientific evidence and regulatory bodies worldwide. For a low 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 calorie sweeteners.

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 calorie sweeteners, the lower-calorie foods and drinks in which they are found, and how they may be able to help in nutritional strategies aiming to reduce overall calorie intake and improve weight management and overall health.

Low Calorie Sweeteners: Role and Benefits is supported by contributions from a group of eminent scientists and doctors who have undertaken a significant amount of research around low calorie sweeteners, in the areas of toxicology, 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 calorie sweeteners

What is a low calorie sweetener?
Low calorie sweeteners (LCS) 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).*

Commonly used low calorie sweeteners

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

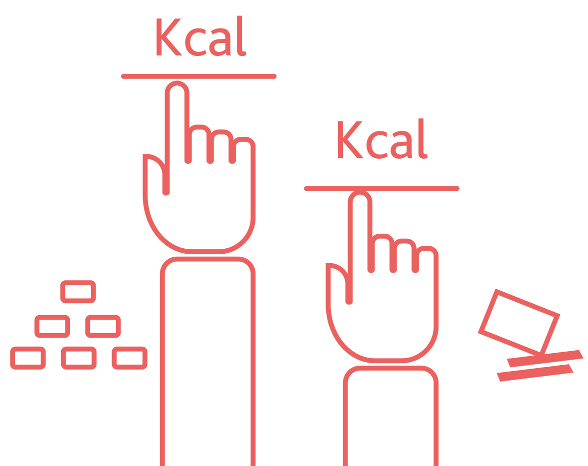
The history behind the discovery of low calorie sweeteners

Low calorie sweeteners have been safely used and enjoyed by consumers all over the world for more than a century. The first commonly used LCS, saccharin, was discovered at Johns Hopkins University in 1879. Since then, a number of other LCS have been discovered and are now in use in foods and drinks around the world (Figure 1).

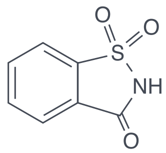
Before approval, all LCS used in foods and drinks today are subject to a rigorous safety evaluation process *(Serra-Majem et al, 2018)*. This is discussed in detail in the next chapter (Chapter 2).

Different terms are frequently used to describe LCS in the scientific literature. The most common include: intense sweeteners, high intensity sweeteners, high potency sweeteners, non-nutritive sweeteners and non-sugar sweeteners. While there is no consensus in the literature, the term that reasonably captures the functional property of the compounds and may be the most easily understood by consumers is **low calorie sweeteners (LCS)** *(Mattes, 2016)*; therefore, this term is used throughout this booklet.

Low 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.



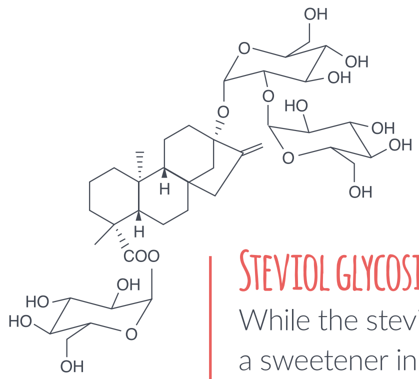
History of the most commonly used low calorie sweeteners.



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

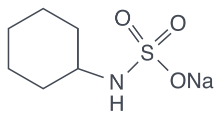
Steviol glycosides

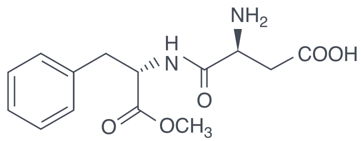
While the stevia plant has been used as a sweetener in certain South American countries for centuries, it was around the 1900s that Dr. Moises Santiago Bertoni, a Swiss botanist, started studying the plant. In 1931, two chemists in France isolated the first steviol glycosides, which are purified extracts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

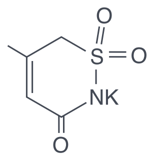
Aspartame

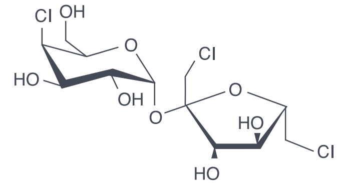
was discovered in 1965 by the chemist James Schlatter.

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 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.

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Commonalities and differences

While all LCS 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 LCS has a unique structure and metabolic fate, technical characteristics and taste profile *(Magnuson et al, 2016)*. Some key characteristics of the most commonly used LCS are presented in Table 1.

Click here for table 1

LOW CALORIE SWEETENERS HAVE 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 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 calorie sweeteners

Low calorie sweeteners (LCS) 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.

The regulatory bodies involved in safety assessment

As with all food additives, for a LCS 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 LCS, 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 LCS 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 LCS at current levels of use *(Fitch et al, 2012; Magnuson et al, 2016; Serra-Majem et al, 2018)*.

Safety evaluation

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

As with all food additives, for an LCS 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 LCS.

Worldwide, low 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. 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 LCS *(Renwick, 2006)*. The ADIs of individual sweeteners as established internationally by JECFA are provided in Table 1.

Low 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 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

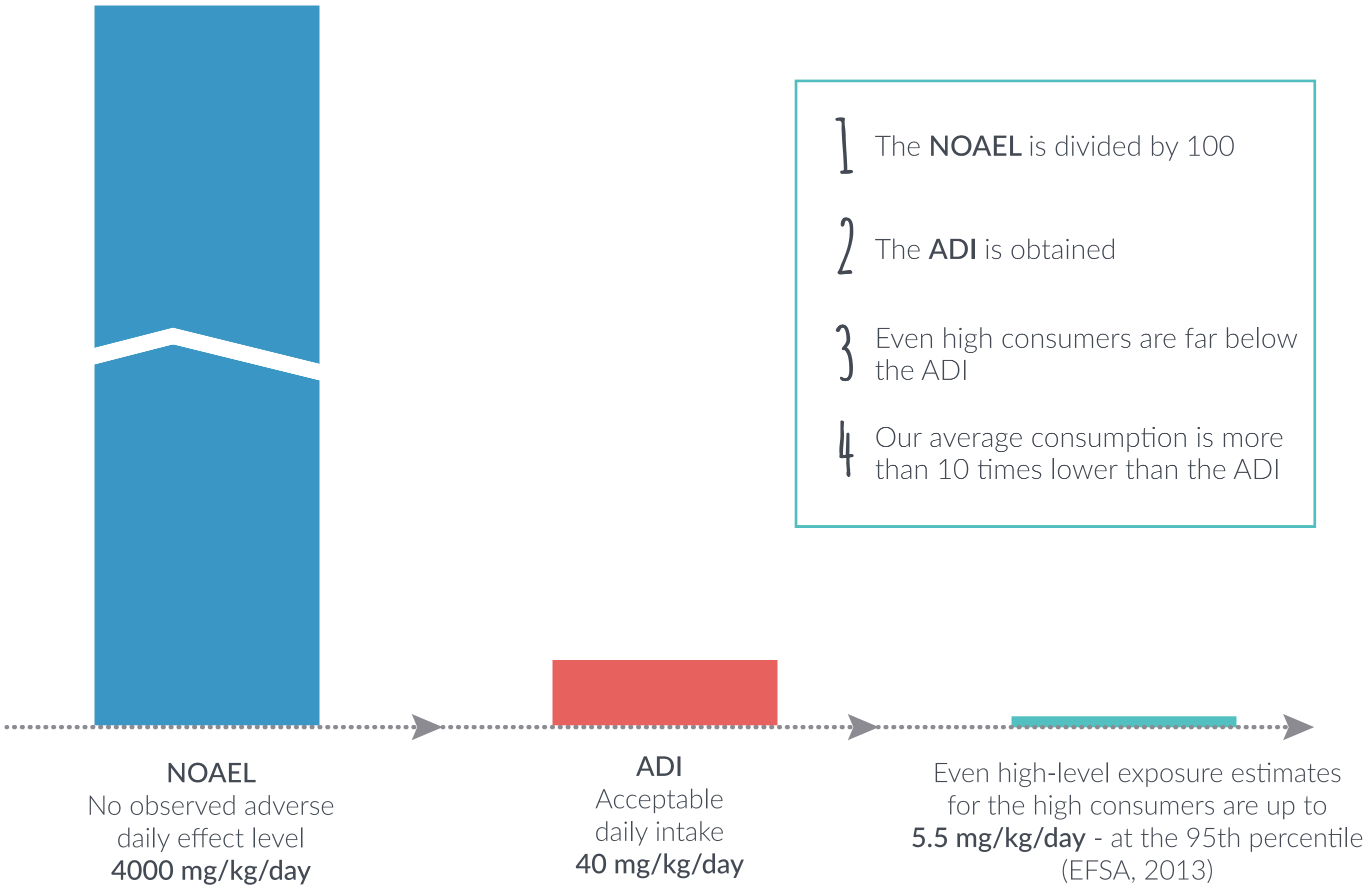

Figure 1: Aspartame consumption (EFSA, 2013) compared to the sweetener's Acceptable Daily Intake (ADI) and No Observed Adverse Effect Level (NOAEL).

Experts' views

Why is the ADI important?

Dr Gerhard Eisenbrand: The ADI is accepted worldwide as the pivotal tool for scientists and health authorities to ascertain the safe use of a given food additive, such as a low calorie sweetener. Since its introduction by JECFA in 1961, it has been very successful in protecting consumers' health. It provides reassurance that a given additive including a low calorie sweetener can be consumed safely through lifetime without any adverse health effects.

Its establishment is based on the daily maximum dosage applied to test animals without intake-related adverse biological effects, defined as the Non-Observed Adverse Effect Level or NOAEL. To derive the ADI, the NOAEL is divided by a 100-fold safety factor. This ensures a margin of safety covering differences between test animals and humans, also taking into account sensitive subpopulations such as children or pregnant women.

What if someone exceeds the ADI on any given day?

Dr Gerhard Eisenbrand: The ADI is not intended to set a maximum safe level on a given day. Instead, it confers a guideline for daily consumption up to a maximum intake level that is safe. Food safety agencies additionally set usage levels of LCS in foods and beverages to further help ensure that consumption stays within safe levels.

Since the ADI covers lifetime consumption of low calorie sweeteners, its margin of safety is sufficiently large not to cause concern in case a consumer's short-term intake, e.g. on a given day, is exceeding it. Concern may be raised if the average long-term intake would be in substantial excess of the ADI.

Consumption of low calorie sweeteners globally

In 2018, a published review of the global literature regarding the intake of the most commonly used LCS concluded that, overall, the studies conducted to determine the exposures of LCS 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 LCS 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 LCS to date have been conducted in Europe. A total of 19 European peer-reviewed studies on LCS 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 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 LCS 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 LCS 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 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 LCS *(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 LCS 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. 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 LCS 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 LCS 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 Calorie Sweetener is Approved for use in Foods and Drinks in the EU

The authorisation and conditions of use of an LCS, 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 LCS 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 LCS by EFSA. Following the publication of a scientific opinion by EFSA, the European Commission drafts a proposal for authorisation of use of the LCS 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 LCS 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 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 LCS 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 calorie sweeteners

Low calorie sweeteners 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 LCS in foods and beverages must be labelled twice on food products. The name of the LCS (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.

Experts' views

Are low calorie sweeteners safe?

Dr Gerhard Eisenbrand: All approved low calorie sweeteners have undergone a rigorous safety evaluation before their admittance to the market. They are amongst the most comprehensively studied food additives worldwide and they have a long history of safe use in humans. Sporadically, anecdotal reports have claimed various adverse health effects, such as associations with neurological or mental problems or various malignant diseases, including leukemias, lymphomas or brain tumours. Such reports have been scrutinized by EFSA and other health authorities worldwide and were found unsubstantiated and devoid of credible scientific evidence.

Low 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 low calorie sweeteners to cancer. Silvano Gallus and colleagues from the Institute of Pharmacological Research Mario Negri in Italy, published a study that further supports the claim that there is no indication that low calorie sweeteners cause any of the major cancer sites, including digestive-tract and hormone-related cancers *(Gallus et al, 2007)*.

We studied the intakes of low calorie sweeteners in patients with a range of different cancers. Data were collected over a 13-year period on over 11,000 cases after taking into account various confounding factors (such as smoking, alcohol consumption and total energy intake), and it was determined that consumers of low calorie sweeteners were not at an increased risk of any of the cancers. Furthermore, when we divided low calorie sweetener use into saccharin, aspartame and other sweeteners, none of the results suggested a significant increase in any of the cancer forms.

A subsequent report in 2009 found no association between low calorie sweeteners and gastric, pancreatic and endometrial cancer *(Bosetti et al, 2009)*. Indeed, low calorie sweeteners may have a more favourable impact compared to sugar on gastric and colorectal cancer risk *(La Vecchia et al, 1998, Galeone et al, 2018)* as well as on colorectal cancer prognosis *(Guercio et al, 2018)*.

Are low calorie sweeteners safe for children and pregnant women?

Dr Carlo La Vecchia: Consumption of low calorie sweeteners, within the ADI set by the regulatory authorities, is safe during pregnancy, because all low 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 low calorie sweeteners 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.

Low calorie sweeteners 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. Low calorie sweeteners 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).

Why is there still concern over the safety of low calorie sweeteners?

Dr Carlo La Vecchia: Over the past decades, various reports have claimed that low calorie sweeteners are associated with a range of adverse health effects. However, when the evidence for these claims has been reviewed by international agencies, such as EFSA, they have concluded that such claims are without substance. Much of the potentially frightening misinformation about low calorie sweeteners is based on misinterpretation of selected data, data dredging and inappropriate extrapolation from rodent experiments open to criticisms, or selective use of information, rather than a comprehensive, critical and balanced view of all the available evidence. The claimed adverse effects have not been found in subsequent studies. Nonetheless, unsubstantiated anecdotal reports have been widely covered in the media and online, leaving some consumers unsure as to whether low calorie sweeteners are safe. Providing evidence-based reassurance is therefore a priority.

Regulatory agencies, such as EFSA, continue to advise the European Commission that the use of low calorie sweeteners in foods and drinks, consumed within acceptable daily intake allowances, pose no threat to human health. Thus, concern on low calorie sweeteners is unjustified by the available evidence.

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Low calorie sweeteners' use and role in sugar reduction

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The use of low calorie sweeteners

All approved low calorie sweeteners (LCS) are used in foods 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 no calories *(Fitch et al, 2012; Gibson et al, 2014)*. LCS have a much greater sweetening power compared to sugar (sucrose), meaning that they are hundreds of times sweeter than sugar by weight, and therefore, LCS 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, yoghurts and desserts, can be sweetened with LCS, in line with local regulatory requirements. LCS are also used in healthcare products such as in mouthwashes, chewable multivitamins and cough syrups, thus making these products more palatable. LCS are clearly labelled on the packaging of food, drink and healthcare products that contain them, as discussed in Chapter 2.

Low calorie sweeteners can help us reduce calorie and sugars intake, in line with public health recommendations



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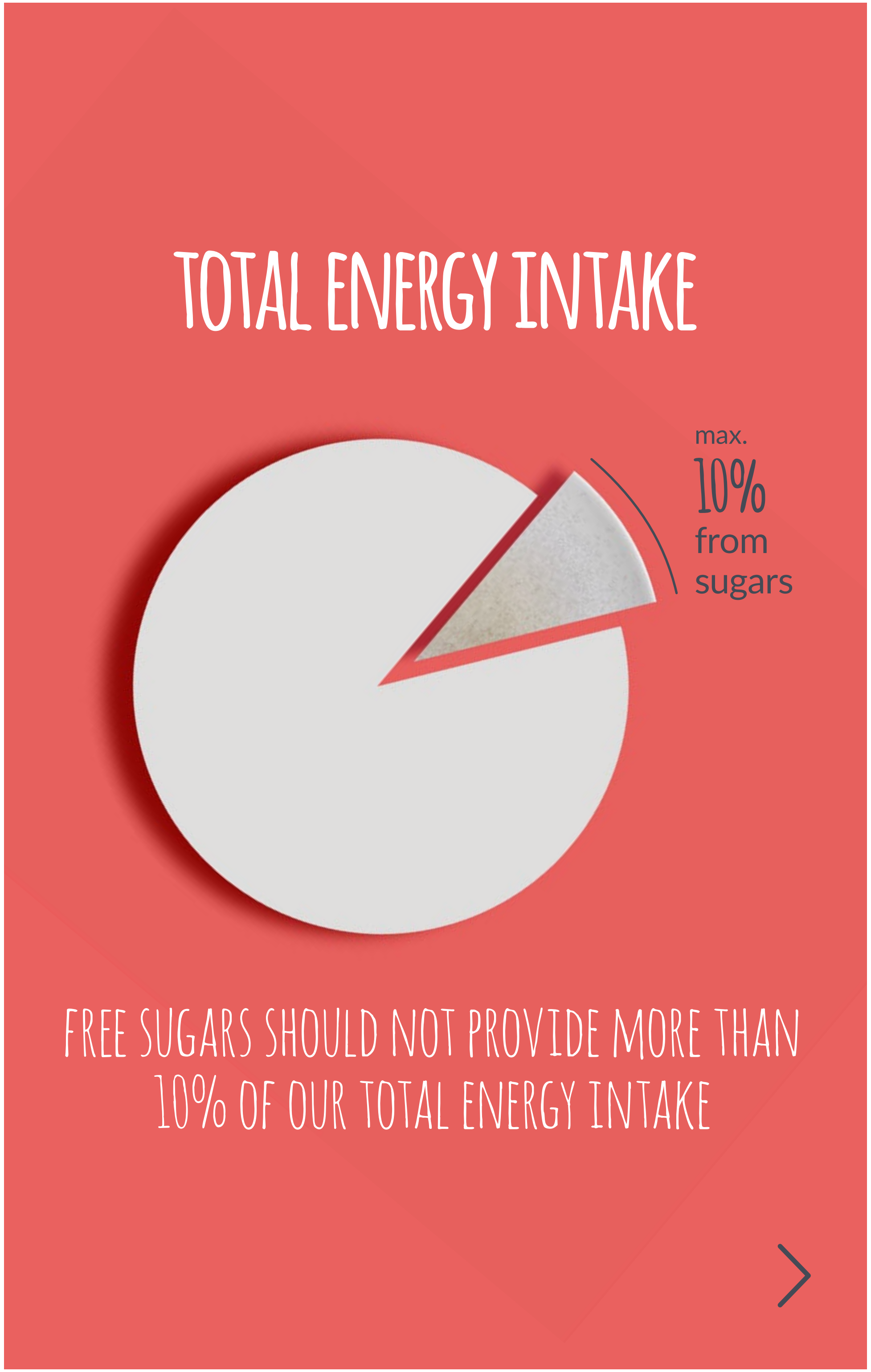
The role of low calorie sweeteners in sugar reduction and food reformulation

In 2015, the World Health Organization (WHO) issued a recommendation that free sugars should not provide more than 10% of our total energy intake *(WHO, 2015)*. In light of this recommendation, a number of policies aiming to help reduce free sugars' intake have been proposed, including food reformulation as one of the most prominent strategies *(PHE, 2015)*.

By having a very high sweetening power compared to sugars, in practice, LCS 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.

Therefore, low calorie sweeteners can help us reduce overall free sugars intake, in line with public health recommendations. In a recently published study analysing data from 5,521 adults participating in the United Kingdom's National Diet and Nutrition Survey *(NDNS; 2008-2012 and 2013-2014)*, Patel et al. found that consumers of low calorie sweetened beverages had a better diet quality, lower free sugars' consumption and higher chances of meeting the UK recommendation for free sugars' intake, compared to consumers of sugar-sweetened beverages (SSB) *(Patel et al, 2018)*. This finding confirms that low calorie sweetened foods and drinks can play a useful role in helping individuals to reduce their free sugars' intake in the context of recent nutrition recommendations.

Furthermore, in Europe, the use of LCS 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. For consumers, this can mean a significant calorie saving, which may be especially helpful in managing overall energy balance.



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Sugar reduction policies: The UK example

In March 2017, Public Health England (PHE) published a technical report entitled 'Sugar Reduction: Achieving the 20%' outlining guidelines for industry, in which it states, *"We endorse the European Food Safety Authority's (EFSA) scientific opinion on low calorie/non-caloric sweeteners. 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 the 2015 PHE evidence report 'Sugar reduction: The evidence for action', it was concluded that replacing foods and drinks sweetened with sugars with those containing LCS 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)*.

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Opportunities and challenges in food reformulation

At a time when the rates of obesity and related diseases continue to increase worldwide, and public health authorities are encouraging food manufacturers to replace sugars and reduce calories as part of their reformulation goals, LCS represent a helpful tool for creating such products. In fact, LCS can facilitate substantial reductions in sugars intake and help to reduce energy when used in place of higher energy ingredients *(McCain et al, 2018)*.

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 foods and beverages a palatable sweet taste without the calories of sugars, LCS 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 are a necessary part of providing a wide variety of great-tasting food and beverage products sweetened with LCS.

The increased range of available LCS, and the fact that these can be either used either alone or in blends, is a useful tool in food reformulation efforts. By combining two or more LCS, it is possible for food and drink manufacturers to 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)*.

However, some regulatory constrains regarding the use of sweeteners may limit the opportunities of food reformulation *(Gibson et al, 2017)*. A recent WHO Europe report has highlighted "current regulations on nutrition claims and use of sweeteners" as "disincentives to reduce sugar in manufactured foods" *(WHO, 2017)*. For example, in Europe, the use of LCS 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.

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

LCS can facilitate substantial sugar reduction in foods and drinks

Low calorie sweeteners provide an effective way of reducing sugars content of food products helping the food industry in reformulation efforts

Sugar-swaps

By using LCS in place of caloric sweeteners and by swapping a sugar-sweetened food or drink with its low calorie sweetened equivalent we can remove both sugars and calories from a variety of foods and drinks. For example, by adding table-top sweeteners instead of sugar in beverages, we can "save" approximately 4 g of sugar and 16 kcal for each teaspoon of added sugar. Similarly, by switching to a diet or light soft drink, which contains less than 1 kcal, we can reduce calorie 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

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).

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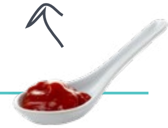



	Sugar-sweetened products	Low calorie sweetened products
1 teaspoon (4 g) of sugar vs table-top sweetener	16 kcal and 4 gr of sugars	<1 kcal and 0 gr of sugars
1 glass (250 ml) of cola-type soft drink	100 kcal and 25 gr of sugars	<1 kcal and 0 gr of sugars
1 glass (250 ml) of iced tea drink	60 kcal and 15 gr of sugars	<5 kcal and 0-1 gr of sugars
1 portion (200 g) of low fat (1%) fruit yogurt	160 kcal and 25 gr of sugars	110 kcal and 15 gr of sugars
1 large scoop (100 g) of vanilla ice cream (full fat)	170 kcal and 22 gr of sugars	120 kcal and 8 gr of sugars
A serving of raspberry jelly	80 kcal and 20 gr of sugars	10 kcal and 2 gr of sugars
1 tablespoon (20 g) of jam	40-50 kcal and 10-12 gr of sugars	10-20 kcal and 2-5 gr of sugars
1 tablespoon (17 g) of ketchup	16 kcal and 4 gr of sugars	7 kcal and 1 gr of sugars
1 piece of chewing gum	10 kcal and 2,5 gr of sugars	<5 kcal and 0 gr of sugars
1 piece of hard candy	25 kcal and 4 gr of sugars	10 kcal and 0 gr of sugars

Table 1: Calorie and sugars content in sugar-sweetened versus comparable low calorie sweetened products (on average or range of values).
Source: USDA Food Composition Databases. Available at: https://ndb.nal.usda.gov/ndb/

Benefits of low calorie sweeteners' use

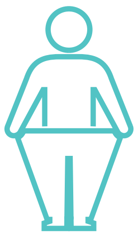
When used as part of a balanced diet and healthy lifestyle, LCS can help individuals achieve reduced total energy (calorie) intake and thus be a helpful tool in lowering excess body weight *(Miller and Perez, 2014; Rogers et al, 2016)*. Furthermore, LCS are valued by, and can be a significant aid to, people with diabetes who need to manage their carbohydrate intake, an important aspect of diabetes management *(EFSA, 2011; Timpe Behnen et al, 2013; Nichol et al, 2018)*. Additionally, LCS can be beneficial to oral health due to their non-cariogenic properties *(EFSA, 2011)*.

The evidence supporting the benefits of LCS is discussed in detail in the next chapters of this booklet:

Chapter 4 – Low calorie sweeteners, energy intake and weight management

Chapter 5 – Low calorie sweeteners, glucose control and diabetes management

Chapter 6 – Low calorie sweeteners and oral health



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LCS can be beneficial to oral health due to their non-cariogenic properties

Experts' views

Low 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.

LCS provide a desired sweet taste without the addition of appreciable energy and can help maintain the palatability of reformulated products. We can be confident about the safety of LCS currently approved for use in foods and beverages with all LCS undergoing rigorous safety evaluations prior to their approval for use, usually resulting in the assignment of an acceptable daily intake (ADI); indeed, recent global intake data highlight no cause for concern in relation to current LCS intakes *(Martyn et al, 2018)*. When used to replace sugar-sweetened products with low calorie sweetened alternatives, LCS represent an easy way to reduce sugar intake in the diet. For example, replacing a regular (sugar-sweetened) product with a low-calorie sweetened equivalent results in a reduction in sugar and energy intake. When used in this way, LCS have the advantage of reducing energy intake without reducing the palatability (or sweetness) of the diet. LCS represent a useful part of efforts to reduce overall intakes of sugars and help with body weight management.

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4.
Low calorie sweeteners, energy intake and weight management

Low calorie sweeteners (LCS) are frequently used as a means to help reduce overall energy (calorie) intake from the diet, especially calories from sugars, and ultimately as a strategy to help control body weight. Practically, people choose low 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. However, the role of LCS in weight management has been a controversial topic recently, despite the balance of evidence indicating a beneficial effect in weight control when LCS are used in place of sugars and in the context of an overall healthy diet and lifestyle.

In this context, the aim of this chapter is to present a review of the scientific evidence about how LCS affect energy intake and body weight, focusing on available data from human studies.

Low calorie sweeteners and energy intake

By replacing sugars in common foods and beverages, LCS help to decrease the energy density of these foods, which, in turn, can mean significant calorie savings. Despite this benefit, it has been suggested that users of LCS may compensate for the "missing" calories to result in no positive benefit. The beneficial effect of LCS consumption on energy intake, however, has been confirmed in a large number of clinical trials in humans, both of short- and of longer-term duration. *(Rogers et al, 2016)*

Energy density is defined as the amount of energy (calories) per unit weight (gram of food) and has been suggested as a key determinant of energy intake *(Poppitt & Prentice, 1996)*. Higher dietary energy density has been linked to higher energy intakes and weight gain *(Drewnowski et al, 2004)*.

LCS offer an effective method of reducing energy density of selected foods while maintaining their palatability, a frequent issue in the formulation of low energy-density foods *(Drewnowski, 1999)*. Because low energy-density foods provide fewer calories in the same food weight, they can, in theory, help to reduce energy intake and therefore weight loss. While it has been argued that LCS-sweetened products may not lead to energy savings, due to compensatory eating at the next meal or later during the day, this has not been confirmed by evidence from randomised controlled trials (RCTs).

What is a randomised controlled trial (RCT)?

A randomised control trial (RCT) is a study in which subjects are randomly assigned to one of two groups: the experimental group receiving the intervention or the substance to be tested, and the control group receiving an alternative (conventional or placebo) treatment *(Kendall, 2003)*. The two groups are then followed up to investigate what effect the testing has on a specific endpoint of interest. Thus, RCTs are a direct test for possible effects in a human population. RCTs are the most stringent way of determining whether a cause-effect relation exists between the intervention and the outcome. Indeed, the RCT is considered the strongest study design for drawing causal inferences regarding relations between exposures, including dietary exposures, and health outcomes for the human population *(Maki et al, 2014)*. That said, even the results of RCTs must be carefully evaluated and all data should be considered when evaluating outcomes from RCTs.

Scientific evidence from randomised controlled trials

A wealth of acute, short-term RCTs of different study designs have tested the impact of the consumption of low calorie sweetened preloads on the subsequent energy intake in an ad libitum meal and compared it to the impact of different comparators including versus sugar or unsweetened products, water, placebo or nothing (controls). While studies have shown that there can be some compensation for the "missing" calories when LCS are used to replace sugar, this compensation is only small. Hence, it is partial and not in full, meaning that there is a net significant caloric decrease (benefit) with LCS use when compared to sugar, and thus, a decrease in overall calories consumed in the subsequent meal(s) and overall within the day *(Anton et al, 2010; Bellisle, 2015; Rogers et al, 2016; Rogers, 2017)*. Furthermore, there is no increased energy intake following consumption of low calorie sweetened beverages compared to energy intake following consumption of water or other unsweetened drinks *(Mattes and Popkin, 2009; Rogers et al, 2016)*.

In the most thorough review work to date by a group of experts who reviewed in a systematic way the results of animal, human observational and intervention studies providing information on the impact of LCS consumption on energy intake and/ or body weight, Rogers et al found that the weight of the evidence from 56 acute preload studies (including 129 comparisons) and from 10 longer-term studies (including 12 comparisons) indicates decreased energy intake with consumption of LCS relative to sugar *(Rogers et al, 2016)*. Notably, in all long-term studies, the LCS group had the lowest absolute values for total energy intake, compared with the control group (either sugar or water), but with varying magnitude of the difference in intakes, as shown in Table 1.

Type and number of studies (or number of comparisons)	Results
Short-term RCTs (≤1day) (56 studies; 129 comparisons)	Energy Intake from preload plus ad libitum meal when preload was LCS versus sugar, unsweetened control, water, nothing or placebo (in capsules): • Lower energy intake with LCS versus sugar (in both children and adults) • Not statistically different energy intake with LCS versus unsweetened control, water, nothing, placebo (in capsules)
Sustained RCTs (>1 day); *Studying Energy Intake as an outcome* (10 comparisons)	In all cases the absolute value for total or change in Energy Intake was lower for LCS: • LCS versus sugar: −75 to −514 kcal per day (9 comparisons) • LCS versus water: −126 kcal per day (1 comparison)

Table 1: Summary of the results of the meta-analysis of short-term and sustained randomised controlled trials (RCTs) studying the effect on energy intake of low calorie sweeteners (LCS) versus different comparators (sugar, unsweetened, water, nothing, placebo) [adaptation from the publication by Rogers et al, 2016].

While it is reasonable that most studies would compare the impact on eating behaviour of LCS in foods and drinks to sugar and sugary products, in line with their intended use as sugar substitutes, there have been questions about their impact on energy and food intake when compared to water. This has been addressed in a recently published RCTs that compared the longer-term effect of low calorie sweetened drinks on energy and food intake versus water *(Fantino et al, 2018)*. This RCT examined the short- and longer-term effects of low calorie sweetened drinks versus water on appetite, energy and food intake in a sample of 166 "naïve" consumers, i.e. people who were not used to consuming LCS. The study found that low calorie sweetened beverages and water do not differ in their impact on calorie, sugar and sweet food intakes, after acute consumption or after a longer-term habituation period. After a 5-week habituation period to LCS, total calorie and food intakes did not change in the LCS group versus the control (water) group and there was no increase in the consumption of sweet foods.

Taken together, the collective evidence from RCTs consistently shows that the consumption of LCS in place of sugars can help reduce overall energy intake and that, contrary to the concern that LCS might increase appetite and food intake, energy intake does not differ for LCS versus water or versus unsweetened product, both after acute or longer-term consumption. **Therefore, when used in place of sugars, LCS can be a useful dietary tool, among a pool of other strategies, in helping us reduce our daily calorie intake and manage overall energy balance** *(Peters and Beck, 2016)*.

Low calorie sweetened beverages and water do not differ in their impact on calorie, sugar and sweet food intake

Fantino et al, 2018

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Role of low calorie sweeteners in weight loss and maintenance

Energy density of foods is an important determinant of energy intake in a meal or of the total calorie intake over the course of the day. As discussed earlier in this chapter, by substituting sugars with LCS, it is possible to lower the energy density of foods and drinks and thus help in total daily energy intake reduction and, as a result, contribute to weight loss when consumed in the context of a calorie-controlled diet. Of course, their ultimate effect will depend on their integration within a reduced energy diet since one should not expect that LCS alone would cause weight loss by themselves.

The effect of LCS on body weight has been studied in a large number of well-designed controlled human trials which are presented in Table 2 and are discussed in the following paragraphs.

Scientific evidence from randomised controlled trials (RCTs)…

…in adults

More than ten long-term RCTs have studied the effects of LCS on body weight in adults, either as part of a weight loss programme *(Kanders et al, 1988; Blackburn et al, 1997; Peters et al, 2014; Koyuncu and Balci, 2014; Madjd et al, 2015; Peters et al, 2016)* or in the context of a free, ad libitum diet *(Raben et al, 2002; Reid et al, 2007; Reid et al, 2010; Maersk et al, 2012; Tate et al, 2012; Sorensen et al, 2014)*. These RCTs compared the effects of LCS to sugar, or to water, or to a control group where no sweeteners were permitted in the diet (nothing). Although these intervention studies vary in design, the results show a favourable effect of using LCS in place of sugar in weight loss *(Raben et al, 2002; Maersk et al, 2012; Tate et al, 2012; Sorensen et al, 2014)*.

Results from the Choose Healthy Options Consciously Everyday (CHOICE) RCT, where 318 overweight or obese adult participants were asked to replace sugar-sweetened beverages with either a low calorie sweetened alternative or with water, showed that both the diet beverage group and the water group resulted in significant weight loss (mean weight loss of 2.5 kg and of 2.03 kg for the diet beverage and the water group, respectively) and that the chance of achieving a 5% weight loss at 6 months was significantly greater in the low calorie beverage group than in the control group that made their own dietary changes *(Tate et al, 2012)*. Based on their findings, Tate et al. *(2012)* conclude that, **on a population level, replacement of caloric beverages with noncaloric alternatives could be an important public health message.**

When compared to water or to a control, some studies have shown a favourable effect of LCS on overall weight control, and especially in longer-term weight loss maintenance when used as part of a behavioural weight loss programme *(Blackburn et al, 1997; Peters et al, 2014; Peters et al, 2016)*, with some other studies showing similar effects of both low calorie sweetened beverages and water on body weight *(Maersk et al, 2012; Tate et al, 2012)*.

click here for figure 1

In an RCT with the longest duration to date, Blackburn et al. *(1997)* conducted an outpatient clinical trial investigating whether the addition of the LCS 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. 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 at the first phase of the study with those who consumed LCS being more successful in keeping the lost weight off in the long term. After 3 years, the group that abstained from foods sweetened with aspartame had, on average, regained almost all the weight lost, while the group that consumed food sweetened with aspartame maintained a clinically significant average weight loss of 5% of their initial bodyweight (Figure 1). This was the first study showing a beneficial role of long-term LCS use in weight loss maintenance, a finding with important clinical implications given the poor long-term success rates of weight loss efforts *(Blackburn et al, 1997)*.

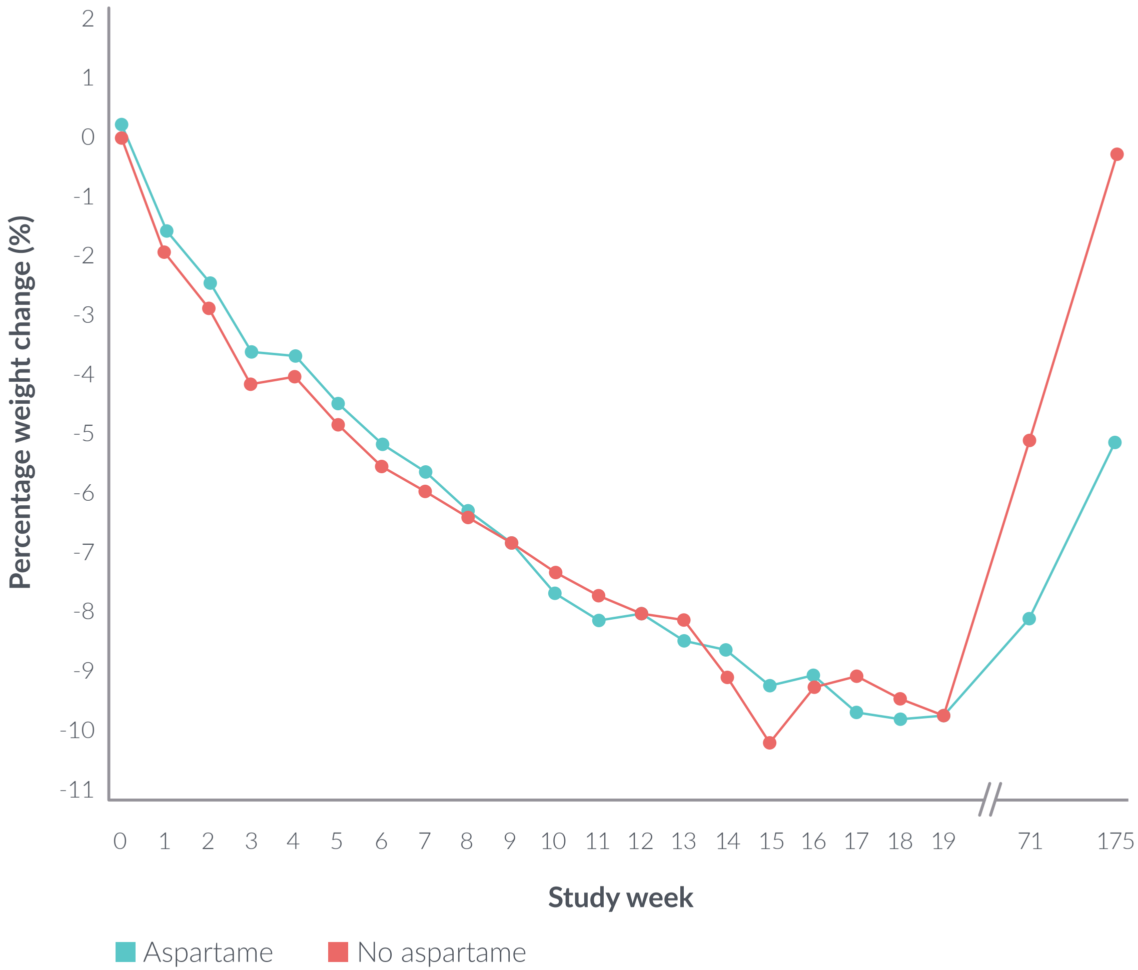

Figure 1: Percentage change in body weight over 175 wk for women (N=163) participating in a comprehensive weight-control programme with and without aspartame-containing products upon 19 weeks of active weight loss followed by a 36-month weight loss maintenance and follow-up period. (Blackburn et al, 1997)

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More recently, another large RCT by Peters et al. also indicated that low calorie sweetened beverages can help people to successfully lose body weight and further maintain body weight loss in the longer-term *(Peters et al, 2016)*. The study evaluated the effects of water versus low calorie sweetened (diet) drinks 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 diet 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 diet 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 diet beverages had a mean weight loss of 6.21±7.65 kg versus 2.45±5.59 kg $p<0.01$) 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 group (Figure 2) *(Peters et al, 2016)*. This effect was not observed in a smaller study of 65 patients with diabetes who completed a study asking them to replace, or not (control group), their usual diet beverage with water while in a weight loss programme of 24 weeks *(Madjd et al, 2015)*. In this trial, the water group had a small but statistically significant greater reduction in body weight. However, both groups lost statistically significant body weight during the intervention period. Contrary to the study by Peters et al. *(2016)*, the participants in the study by Madjd et al. were not followed after the weight loss phase.

No published RCT study has to date observed weight gain with LCS use. **Taken together, results from RCTs are consistent in showing a benefit of LCS, especially when used in place of sugar, which suggests that LCS can be a useful tool for people actively engaged in managing their body weight for weight loss and maintenance** *(Peters and Beck, 2016)*.

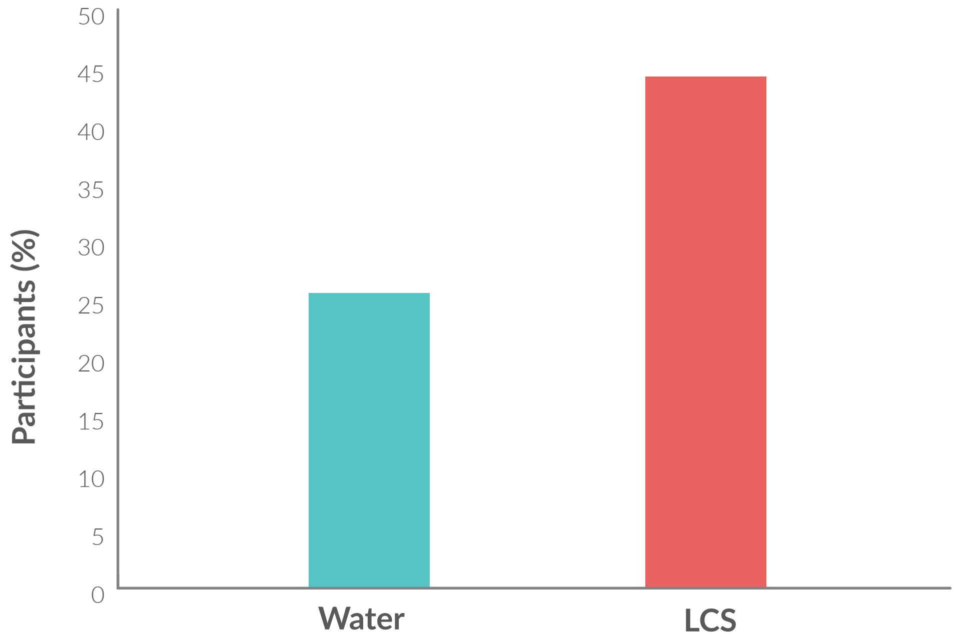

Figure 2: Percentage of participants who achieved at least 5% weight loss. Results based on $\chi 2$ analysis. n=154 for LCS, n=149 for water. *P < 0.001 (Peters et al, 2016).

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...in children and adolescents

In early studies published in the 1970s investigating the effects of LCS added in the form of capsules in the diets of children and adolescents, it was shown that LCS themselves have no adverse effect on body weight and other health outcomes examined in these studies *(Frey et al, 1976; Knopp et al, 1976)*. More recent trials studying the impact of replacing sugar-sweetened beverages (SSBs) with low calorie sweetened 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; Katan et al, 2016)*.

In an RCT in 641 normal-weight children 5-11 years old in the Netherlands, the consumption of low calorie sweetened beverages versus sugar-sweetened beverages (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 reduced tendency to compensate for the "saved" calories from the beverage swap in these children. 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 study shows that reducing the intake of sugar-sweetened drinks 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, the beneficial effect of replacing sugar-sweetened with low calorie sweetened drinks on reduction of weight gain was most prominent in adolescents in the upper level of BMI (aged 13-18 years) *(Ebbeling et al, 2006)*.

Study (first author; year of publication)	Description of the study	Findings
RCTs in adults		
Kanders et al, 1988	Parallel design; 55 obese men and women followed a weight-loss, low-calorie diet with (intervention group) or without (control group) the addition of aspartame-containing foods and drinks for 12 weeks.	All participants lost weight: men more than women; women lost on average 3.7 kg more weight with the addition of aspartame-containing products compared to control; no difference for men between the intervention and the control groups; better compliance and increased satisfaction from the diet with LCS use.
Blackburn et al, 1997	Parallel design; 163 obese women were assigned to consume or to abstain from aspartame-sweetened foods and beverages during a 19-wk weight-reduction program (active weight loss), followed by a 1-y maintenance program, and a 2-y follow-up period.	Women in both treatment groups lost approximately 10% of initial body weight during active weight loss phase; the aspartame group lost significantly more weight overall and regained significantly less weight during maintenance and follow-up than did the no-aspartame group: during maintenance and follow-up, participants in the aspartame group experienced a 2.6% and 4.6% regain of initial body weight after 71 and 175 wk, respectively, whereas those in the no-aspartame group gained an average of 5.4% and 9.4%, respectively.
Raben et al, 2002	Parallel design; 41 overweight men and women added either sugar-sweetened beverages (SSBs) or LCS-sweetened drinks in an ad-libitum diet on a daily basis for 6 months.	The SSBs group gained 1.6 kg body weight whereas the LCS beverages group lost 1 kg body weight over the 6-month period.
Reid et al, 2007; Reid et al, 2010	Parallel design; 133 normal-weight women *(Reid et al, 2007)* and 53 overweight men and women *(Reid et al, 2010)* added either SSBs or aspartame-sweetened drinks in an ad-libitum diet on a daily basis for 4 weeks.	No statistically significant difference in body weight.

Table 2: Summary of outcomes of the published long-term randomised controlled trials (RCTs) in adults and children studying the effects of low calorie sweeteners (LCS) on body weight in comparison to sugar or water or nothing.

Study (first author; year of publication)	Description of the study	Findings
Maersk et al, 2012	Parallel design; 47 overweight men and women were asked to drink either SSBs or aspartame-sweetened beverages or milk or water on a daily basis in an ad-libitum diet for 6 months.	The SSBs group increased mean body weight by 1,28 kg while no weight change was recorder for the LCS or the water group; the relative changes between baseline and the end of 6-mo intervention were significantly higher in the SSBs group than in the 3 other groups for liver fat, skeletal muscle fat, visceral fat; LCS beverages had effects similar to those of water.
Tate et al, 2012	Parallel design; 210 overweight and obese men and women were asked to replace SSBs with either LCS-sweetened drinks or with water for 6 months, or by making dietary changes of the participants' choosing.	Mean weight losses were 2.5 kg in the LCS beverage group and 2.03 kg in the water group (no significant differences between groups) at 6 months. The chance of achieving a 5% weight loss at 6 months was greater in the LCS beverage group than in the group that made their own dietary changes.
Koyuncu and Balci, 2014	Cross-over design; 54 pre-diabetic patients were assigned to either diet alone for the first 3 months followed by diet + aspartame for another 3 months (group 1) or to diet + aspartame for the first 3 months followed by diet alone for another 3 months (group 2).	Aspartame seems to have some beneficial effect on weight loss in prediabetic patients. In the first group, diet alone was effective on losing weight at the end of the third month, and after aspartame was added, weight loss continued till the end of the 6 month. In the second group, weight loss was detected with aspartame and diet during the first three months, however, in the second three months with diet alone, weight gain occurred after aspartame was discontinued.
Sørensen et al, 2014	Parallel design; 22 adults were asked to consume supplements of sucrose-sweetened drinks and foods or similar amounts containing LCS in an ad libitum diet over a 10-wk study.	In the sucrose group, mean body weight (+1.46 kg) and fat mass (+1.2 kg) increased and in the LCS group body weight (-1.2 kg) and fat mass (-0.9 kg) decreased during the 10-wk intervention, which resulted in between group differences amounting to 2.7 kg body weight and 2.0 kg body fat.

Study (first author; year of publication)	Description of the study	Findings
Madjd et al, 2015	Parallel design; 65 overweight and obese women with type 2 diabetes, who usually consumed diet beverages in their diet, were assigned to either substitute water for diet beverages or continue drinking LCS beverages five times per week after lunch for 24 weeks during a weight loss program.	Both groups have lost significant body weight; compared with the diet beverage group, the water group had a slightly greater decrease in weight (−6.40 kg versus −5.25 kg). While the "time x group" interaction has been found to be statistically significant, the difference in weight reduction between the two groups did not differ significantly.
Peters et al, 2014; Peters et al, 2016	Parallel design; 303 obese men and women were assigned to either LCS beverage or water on a daily basis for a 12-week weight loss phase followed by a 9-month weight maintenance phase while attending a behavioral weight loss treatment program.	The LCS beverage treatment group lost significantly more weight compared to the water group (5.9 kg versus 4.09 kg) after 12 weeks *(Peters et al, 2014)*; At year 1 (weight maintenance phase) participants receiving water had maintained a 2.45±5.59 kg weight loss while people at the LCS beverage group maintained a higher body weight loss of 6.21±7.65 kg *(Peters et al, 2016)*.

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Study (first author; year of publication)	Description of the study	Findings
RCTs in children and adolescents		
Ebbeling et al, 2006	Parallel design; 103 adolescents,13-18y, who regularly consumed SSBs were assigned to either replace SSBs with LCS beverages (intervention group) or to no change (control group) for 25 weeks.	Consumption of SSBs decreased in the intervention group, where SSBs were replaced with LCS beverages; Among participants with higher BMI, BMI was reduced significantly more in the intervention compared to the control group, with a net effect of -0.75 kg/m^2.
Rodearmel et al, 2007	A 6-month behavioural family-intervention study in families with at least 1 overweight or at risk of overweight child, 7-14y. Intervention group, n=116, (America on the Move): replaced SSBs with LCS beverage and walked additional 2000 steps per day; control group, n=102, were not asked to change their diet and physical activity habits, but were asked to monitor physical activity levels with a pedometer.	During the 6-month intervention period, both groups showed a reduction in BMI-for-age, however, the intervention 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	Parallel design; 224 overweight and obese adolescents, 13-18y, who regularly consumed SSBs were assigned to either replace SSBs with water and LCS beverages (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 LCS beverages 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 after the end of the intervention at the 2-year follow-up.
De Ruyter et al, 2012; Katan et al, 2016	Parallel design; 641 normal-weight children, 5-11 years, were assigned to 250 ml per day of a LCS beverage (sugar-free group) or to 250 ml per day of SSB (sugar group) for 18 months.	Replacement of SSBs with LCS beverages reduced weight gain and fat accumulation in children; Weight increased by 6.35 kg in the sugar-free group as compared with 7.37 kg in the sugar group. The increase in skinfold-thickness measurements, waist-to-height ratio, and fat mass was also significantly less in the LCS group; *(de Ruyter et al, 2016)*; the observed effect was greater in children with a higher BMI *(Katan et al, 2016)*.

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Summarising the evidence: Conclusions from systematic reviews
Synthesising the outcomes of the available randomised controlled trials (RCTs), published systematic reviews and meta-analysis of RCTs, **the balance of evidence indicates that the use of LCS in place of sugar, in children and adults, leads to reduced energy intake and body weight,** and possibly also when compared with water (outcomes summarised in Table 3). Substituting low calorie sweetened options for their regular-calorie versions may be a useful dietary tool to improve compliance with weight loss or weight maintenance plans *(de la Hunty et al, 2006; Miller and Perez, 2014; Rogers et al, 2016).*

Type and number of studies (or number of comparisons)	Results
RCTs with a duration of ≥ 4 weeks studying the effects of LCS on body weight outcomes (10 studies with 12 comparisons)	**Difference in weight change favoured LCS:** *LCS versus sugar in adults:* −1.41 kg *(8 comparisons: Kanders et al, 1988; Blackburn et al, 1997; Raben et al, 2002; Reid et al, 2007; Njike et al, 2011; Reid et al, 2010; Tate et al, 2012; Maersk et al, 2012b)*
	LCS versus sugar in children: −1.02 kg *(1 comparison: de Ruyter et al, 2012)*
	LCS versus water in adults: −1.24 kg *(3 comparisons: Tate et al, 2012; Maersk et al, 2012b; Peters et al, 2014)*

Table 3: Summary of the results of sustained randomised controlled trials (RCTs) studying effect of low calorie sweeteners (LCS) on body weight [adaptation from the systematic review and meta-analysis by Rogers et al, 2016]

Observational studies vs RCTs: the role of study design

While findings from RCTs consistently show that the consumption of LCS in place of sugars can help reduce energy intake and thus body weight, results from observational studies evaluating whether LCS use is associated with increased BMI and obesity risk have been mixed and inconsistent *(Azad et al, 2017; Sylvetsky & Rother 2018)*.

Some observational data suggest that the consumption of LCS may be associated with a long-term increase in BMI and obesity risk *(Azad et al, 2017)*. However, observational studies are subject to several sources of bias, including in this specific situation, of reverse causation, and cannot prove cause and effect *(Andrade 2014; Sievenpiper et al, 2017)*. Caution should be applied when interpreting results of observational studies which correlate body weight data to LCS intake due to the possibility that the results can be explained by reverse causality (i.e., overweight "caused" the observed higher LCS intake vs. the observed intake "caused" overweight) *(Sylvetsky and Rother, 2018)*. Other limitations of observational studies include the presence of possible unmeasured confounding factors, - even after adjustment for relevant covariates, findings may still be biased by residual confounding-, and potentially biased measures of dietary exposures due to self-reported dietary intake tools associated with substantial error *(Maki et al, 2014)*.

What is an observational study?

Observational studies play an important role in nutritional epidemiological research. They can also help generate questions and hypothesis for future RCTs. In an observational study, certain dietary patterns and behaviours of a group of individuals are observed and their potential association with health outcomes is evaluated. However, observational studies include no intervention as in clinical trials. There are different types of observational studies, such as cross-sectional, case-control and cohort studies, with prospective cohort studies generally having the most advantages and stronger study design compared to the other observational study designs *(Boushey et al, 2006)*. However, observational studies are subject to several sources of bias, which must be carefully considered when discussing causality for diet-disease relations *(Maki et al, 2014)*. Nevertheless, in evaluating research, the totality of the evidence, the quality of the research and the type of study design have to be carefully considered and evaluated.

Aiming to assess the possibility that reverse causation might be influencing the associations found in some observational studies, Drewnowski and Rehm analysed data from the US National Health and Nutrition Examination Survey (NHANES) in a representative sample of U.S. adults *(Drewnowski and Rehm 2016)*. They found that the use of LCS is associated with prior intent to lose weight, that makes clear that observational studies based on nutrition survey data carries the possibility of reverse causality, i.e., the higher use of foods/ beverages containing LCS by persons who are overweight may be explained by a desire to control body weight and in an attempt to lose weight or reduce weight gain. This is also noted in a recent scoping review of literature reporting on health outcomes of non-nutritive sweeteners (NNS), sponsored by the World Health Organization, *"a positive association between NNS consumption and weight gain in observational studies may be the consequence of and not the reason for overweight and obesity" (Lohner et al. 2017)*.

Unlike observational studies, the general design of RCTs allows for a direct measure of effects in humans under controlled conditions that includes elements generally agreed upon to be important for minimizing the risk of obtaining false positive results. For example, such studies require that study volunteers be randomly assigned to treatment groups to avoid potential investigator bias in the make-up of participants within any treatment group, as well as to help ensure that treatment groups are reasonably similar in attributes that could be important to interpretation of study outcomes. While outcomes from RCTs still need to be considered in the context of all available data, they are required for demonstration of cause-and-effect relationship, particularly when the primary outcome of interest (e.g. body weight change) can be directly measured.

Examining proposed mechanisms linking low calorie sweeteners to weight gain

For many years there has been a debate about whether LCS can affect appetite and food intake and thus cause overeating and weight gain. Numerous potential mechanisms have been explored mostly in cell lines and in animal models, in an attempt to explain the positive association found in some observational studies, but to date none of the proposed mechanisms have been confirmed in human studies *(Peters and Beck, 2016)*.

Suggested biological mechanisms by which an LCS might impact energy balance and metabolic function include, among others, the potential interaction with oral and gut sweet taste receptors affecting appetite-related hormone secretion, potential impact on gastric emptying, gut microbiota (see Chapter 5), brain responses and cognitive processes (e.g. reward learning) and post-ingestive consequences of uncoupling of sweet taste from nutrient intake (see Chapter 7) *(Burke and Small, 2015)*. However, as noted previously, **none of the proposed mechanisms has ever been confirmed in human studies.** Also, it is important to consider that findings from in-vitro experiments may not translate to humans; similarly, outcomes from rodent models investigating the relationship between sweet taste and preference may not apply to humans, as rodents appear to differ in their attraction to, and preference for, certain caloric and non-caloric sweeteners *(Johnson et al, 2018)*.

In a recent review of the literature, Rogers *(2017)* examined three of the most widely proposed mechanisms including:

(1) the potential for LCS to disrupt the learned control of energy intake (sweet taste confusion hypothesis);

(2) the potential increased desire for sweet taste by exposure to sweetness (sweet tooth hypothesis) and;

(3) the conscious overcompensation for 'calories saved' (conscious overcompensation hypothesis).

None of these proposed mechanisms stands up to close examination or has been proven in humans *(Rogers, 2017)*. In fact, human studies suggest that LCS neither promote nor suppress appetite *(Bellisle 2015; Fantino et al 2018)*. Furthermore, in many instances, the use of LCS was associated with a lower intake of sweet tasting substances *(de Ruyter et al, 2013; Piernas et al, 2013)*. This suggests that LCS may help to satisfy a desire for sweetness and do not encourage a "sweet tooth" *(Bellisle 2015; Rogers 2017)*. These mechanisms are discussed in more detail in Chapter 7.

Additionally, research has disproved hypotheses that suggest LCS disrupt normal metabolism and/or nutrient processing, by activation of gastrointestinal sweet taste receptors, proposed by some investigators as possible explanations for how a sweetener could cause weight gain *(Bryant and McLaughlin, 2016)*. Specifically, the two major hypotheses that resulted from the early studies of gastrointestinal sweet taste receptors, were that LCS could either (1) cause an increase in the absorption of glucose from the intestinal lumen, such that more energy altogether is absorbed from usual daily food intake and (2) alter the secretion of incretins, including insulin, that play a role in satiety (to ultimately cause increased hunger/food intake). While these hypotheses gained much research interest, it must be

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remembered that they arose from *in vitro* studies *(Fujita et al, 2009)*. Because many of these studies also exposed cells to an exceptionally high concentration of an LCS, the testing conditions could have caused reactions that would not be seen with real-life exposure conditions. 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 LCS do not cause an increased uptake of glucose following a meal and otherwise do not adversely affect glycemic control, as discussed in detail in the next chapter (see Chapter 5). *(Romo-Romo et al, 2016; Grotz et al. 2017; Tucker and Tan, 2017; Nichol et al, 2018)* There is also a lack of evidence from *in vivo* studies for any clinically meaningful effect of LCS on the secretion of incretins and on gastric emptying. *(Bryant and McLaughlin 2016)* (Figure 3).

Evidence suggests low calorie sweeteners don't affect hormones involved in appetite control

- The gut-brain axis is a continuous cycle that helps regulate our desire for food
  Brain: Controls appetite, hunger cues, desire to eat
  Gut: Releases hormonal triggers that help to regulate nutrient metabolism and signaling to the brain for appetite response.
- Research supports low calorie sweeteners have no effect on gut function or hormones to affect the gut-brain axis in controlling food intake.

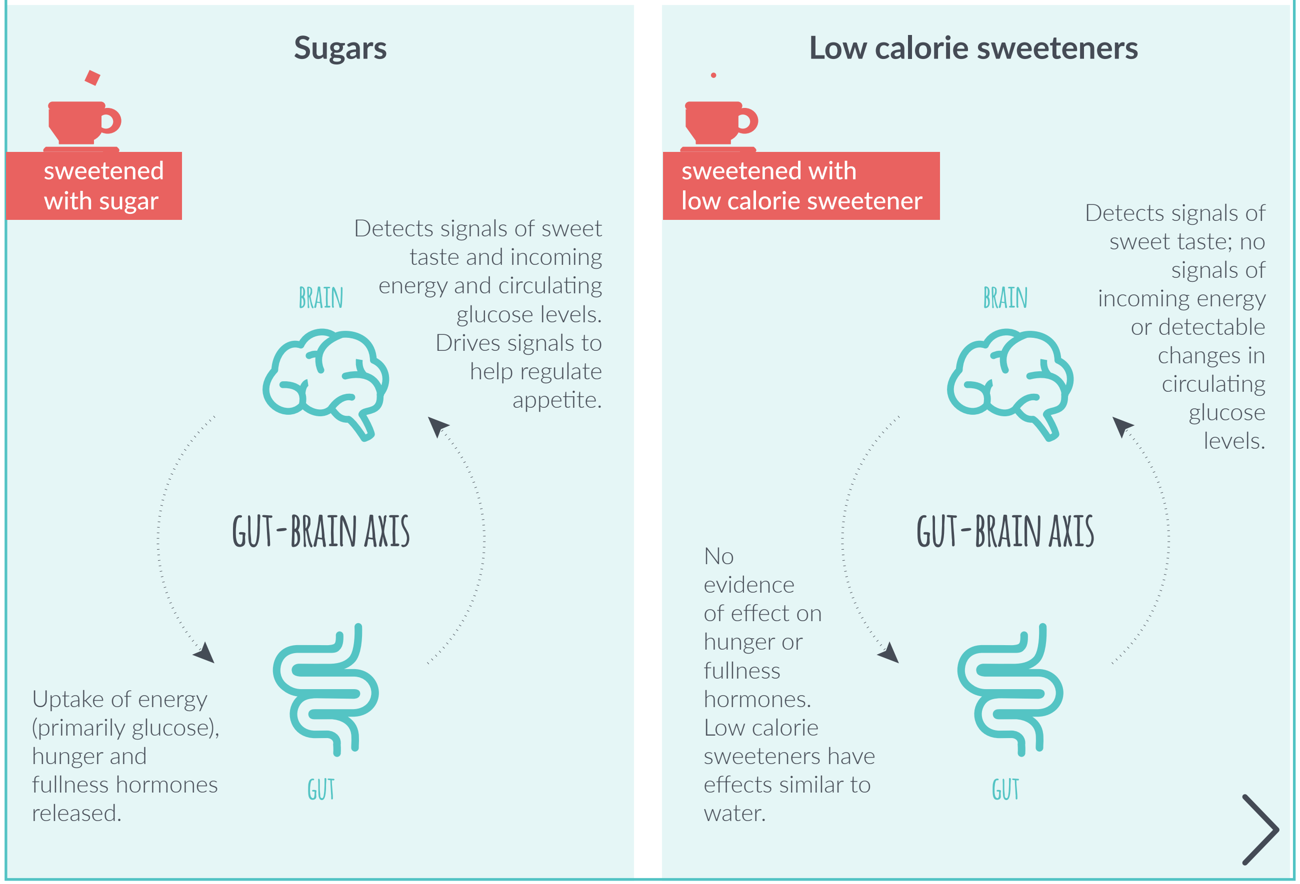

Figure 3: Different effects of sugars and of low calorie sweeteners on gut hormones involved in appetite control. *(Bryant C and McLaughlin J. Low calorie sweeteners: Evidence remains lacking for effects on human gut function. Physiology and Behaviour 2016; 164(Pt B): 482-5.)*

Notably, **there is no example of a controlled human intervention study that has indicated increased energy intake or body weight gain with LCS use, and thus no such study supports the claimed hypothetical adverse effect of LCS on body weight** *(Rogers et al, 2016)*. On the other hand, there should be no expectation that LCS, by themselves, can cause weight loss, as they are not substances that can exert such pharmacologic-like effects. However, based on the outcomes of RCTs (or systematic reviews and meta-analyses based on these), the most reliable types of human research, the collective evidence supports that LCS can be a helpful tool in reasonable nutritional strategies for weight management, when used as a replacement for sugars, and where sugars replaced represents a reasonable part of a person's daily caloric intake.

Do low calorie sweeteners affect appetite, hunger and food intake? Evidence from a randomised controlled trial (RCT).

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

The first hypothesis postulates that sweet taste provided by LCS 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 LCS 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 recently published clinical study conducted in 166 healthy, male and female adults, who were initially not habitual consumers of food and drinks containing LCS *(Fantino et al, 2018)*. The sweet taste provided to the participants by the "acute" consumption of a non-caloric beverage, sweetened with LCS, did not increase their appetite, hunger and caloric intake at subsequent meals (over the next 48 hours), compared to water intake. LCS beverage intake 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, the 166 participants, non-habitual users of LCS, were “turned” into habitual consumers by a daily administration of 660 mL of the calorie-free drink sweetened with LCS (2 daily servings) over 5 weeks. After this period, 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 LCS-sweetened drink (3 serving each day x 2 days) and it was found that the participants’ food intake was the same under both conditions. Thus, it was concluded that the longer-term consumption of a high amount of LCS 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 LCS 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 recently published RCT.

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The use of low calorie sweeteners in the context of the obesity epidemic

Strategies to halt the obesity epidemic need to focus on both reducing energy intake and increasing energy expenditure *(Bray et al, 2018; Stanhope et al, 2018)*. While a variety of healthy dietary and physical activity plans can be followed by individuals who wish to lose or maintain their body weight, on all occasions achieving the right energy balance is essential in weight management. The provision of low or reduced calorie foods is one way of helping people to reduce caloric intake and thereby to assist in weight loss.

Furthermore, considering the challenge of increasing rates of obesity and diabetes LCS can provide an important alternative to caloric sweeteners *(Raben and Richelsen, 2012)*. Lowering caloric intake from excess sugars consumption has been recommended for weight management and obesity prevention. The World Health Organization's guideline on free sugars intake for adults and children recommends the reduction of free sugars to less than 10% of daily energy intake across the life course *(WHO, 2015)*.

Therefore, at a time when the rates of obesity and accompanied non-communicable diseases continue to increase worldwide, the option of consuming a low-calorie sweetened food or beverage instead of the sugar-sweetened version can be helpful by reducing overall daily sugar and energy intakes and thus in weight control, when used as part of a balanced diet and healthy lifestyle.

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Can low calorie sweeteners be a helpful dietary strategy in managing our body weight?

Dr France Bellisle: As confirmed in many recent RCTs and systematic reviews of the literature, the use of LCS has been shown to facilitate weight loss in dieters, to help with the maintenance of the weight loss following a diet, and to contribute to the sensory specific satiety for sweet-tasting foods and beverages (*Rogers et al 2016, Miller & Perez 2014*). In addition, some evidence exists that LCS could help in prevention of weight gain over time, at least in young people (*de Ruyter et al, 2012, 2013*). The benefits in terms of weight are modest, although significant. It should be remembered however that there is no magic associated with LCS 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 LCS 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 LCS does decrease the energy density of the product. Finally, the modest weight benefits reported in the literature suggest that although LCS can help in weight control, they are not by themselves sufficient to address obesity.

Do low calorie sweeteners have a role in managing the obesity epidemic?

Prof Alison Gallagher: Where substitution of sugar-sweetened products for LCS-sweetened equivalents are made there is now 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. The causes of obesity are multifactorial and require a variety of strategies focused on the individual through to the population level. To properly curb the obesity epidemic, no one strategy alone will ever be sufficient. LCS represent one way in which individuals can take control of the energy density of their diet. However, as with any public health strategy, more work is needed to educate the consumer on the benefits of LCS as part of a healthy and energy balanced diet so that the potential benefits of LCS use can be maximised.

LCS 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.

Obesity facts

Overweight and obesity are important public health issues worldwide affecting more than 1.9 billion adults globally; of these, over 650 million adults are obese. The problem is particularly of concern in younger populations, evidenced by the dramatic increase in the prevalence of overweight and obesity among children over 5 years and adolescents, risen from 4% in 1975 to over 18% in 2016 *(WHO, 2017)*.

Recent trends suggest that we are making some progress in the prevention and control of the obesity epidemic *(Bray et al, 2018)*. For example, in the US, the prevalence of obesity among 2- to 5-year-old children has decreased significantly since 2003/2004 *(Dietz et al, 2015)* and additionally, since 2005 it has plateaued among 6- to 11-year-olds and within the adult male population, but not in adult women *(Flegal et al, 2016)*. Similarly, some European countries report positive progress in reducing overweight and obesity rates among children over the last years *(COSI, 2018)*.

Obesity is associated with, and contributes to, a number of noncommunicable diseases including type 2 diabetes mellitus, cardiovascular disease, some cancers, kidney disease, obstructive sleep apnoea, and osteoarthritis, among others *(WHO, 2017)*. However, weight loss can help reduce the risk of developing all of these diseases *(Bray et al, 2018)*.

Achieving body weight reductions requires lifestyle interventions that includes a healthy, calorie-controlled diet in combination with increased physical activity in order to achieve a sustained negative energy balance (calories in < calories out; Figure 4) *(Stanhope et al, 2018)*. Every single strategy that can help individuals manage their calorie intake and increase their energy expenditure has a role to play in weight management efforts. And of course, when choosing a diet, it is important to select foods that you enjoy and to eat lower calorie healthy foods that can improve the overall quality of your diet *(Bray et al, 2018)*.

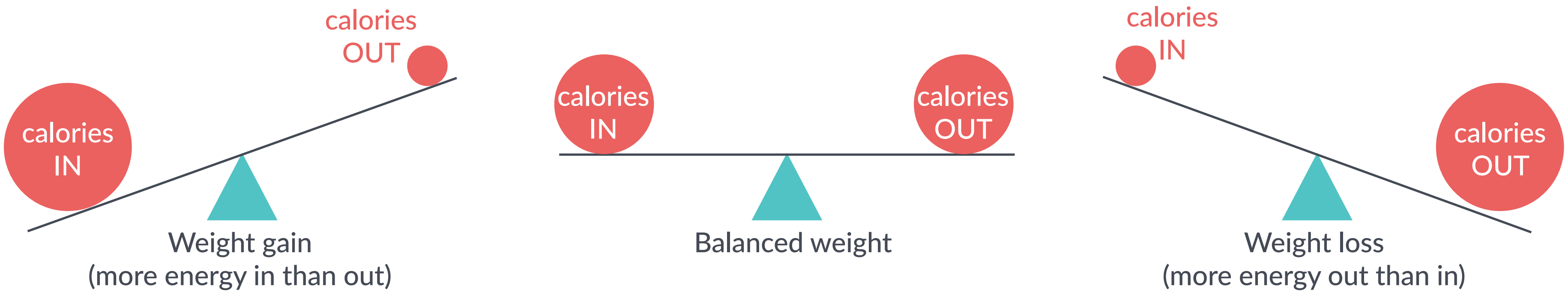

Figure 4: How energy balance affects body weight.

Conclusion

By virtue of reducing the energy density of the foods and drinks in which LCS are used, LCS can help decrease overall energy intake and thereby be a useful tool in weight loss and overall management. Of course, LCS 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 LCS *(Bellisle and Drewnowski, 2007)*.

In this context, health-related organisations such as the American Heart Association (AHA) and American Diabetes Association (ADA) *(Gardner et al, 2012)* as well as the US Academy of Nutrition and Dietetics (AND) *(Fitch et al, 2012)* support that LCS may be used in a structured diet to replace sources of added sugars. This substitution may result in modest energy intake reductions and weight loss where no full compensation of energy reduction by intake of other food sources occurs *(Gardner et al, 2012; Fitch et al, 2012)*. More recently, in a science advisory on low calorie sweetened beverages and cardiometabolic health from the American Heart Association (AHA) published in 2018, a group of AHA experts concluded that evidence from clinical studies suggests that replacement of sugar-sweetened beverages with LCS beverages could help in the management of overweight and obesity, particularly among high-risk overweight or obese individuals with harmful levels of visceral or ectopic fat *(Johnson et al, 2018)*.

These conclusions are supported by controlled clinical trials showing that LCS can facilitate weight loss or weight loss maintenance under real-life conditions when used as part of a behavioural weight control programme, possibly by improving compliance to the dietary plan *(Gibson et al, 2014; Miller and Perez, 2014; Rogers et al, 2016)*. 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 low calorie sweeteners' use may be a helpful factor in weight management efforts.

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Low calorie sweeteners, glucose control and diabetes management

Low calorie sweeteners (LCS) are frequently recommended for, and valued by, people with diabetes who need to manage their carbohydrate and sugars intakes in their effort to maintain a good glycaemic control. The impact that LCS have on blood glucose levels and the role they can play in the diet of persons with diabetes have been studied extensively over the last decades and evidence consistently supports that LCS do not affect blood glucose or insulin levels post-prandially. However, there has recently been a renewed research interest in the effects that LCS might have on insulin sensitivity and longer-term glucose control.

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

Reviewing the evidence: Low calorie sweeteners and glucose control

Short term RCTs investigating the effect of LCS on glycaemic control
Unlike carbohydrates that raise glycaemia – glucose levels in the blood –, LCS do not affect acute blood glucose homeostasis *(Russell et al, 2016; Tucker and Tan, 2017; Nichol et al, 2018)*. Recent publications, through systematic reviews and/or meta-analyses of the published randomised controlled trials (RCTs) **have confirmed a lack of adverse effect, and a benefit of LCS use, on glucose control when LCS are used in place of sugars** *(Tucker and Tan, 2017; Nichol et al, 2018)*. These reviews summarize findings from a large number of studies (Table 1). Amongst all of these, only a single study reported findings that were considered a possible effect on blood glucose control *(Pepino et al. 2013)*. This study, however, was a small, single-dose study, in which there was no negative control for comparison, and while a statistically significant increase in peak blood glucose levels was reported, versus that seen with water, the peak levels were within normal range and the blood glucose Area Under the Curve (AUC) was not significantly different for the intervention and water groups. No clinical significance can be assigned to these findings.

In the most recently published systematic review, Nichol et al. found that the intake of LCS alone does not increase glycaemia post-prandially, following their consumption (Figure 1), and that the glycaemic impact does not differ by type of LCS *(Nichol et al, 2018)*. The absence of glycaemic effect of LCS consumption makes them a potentially useful dietary aid for people with diabetes. Similarly, Tucker and Tan concluded that under acute conditions, when administered without a carbohydrate load, LCS consumption leads to reduced blood glucose levels compared to caloric sweeteners such as sugar *(Tucker and Tan, 2017)*. This is not attributed to a direct effect of the

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, 2017)*.

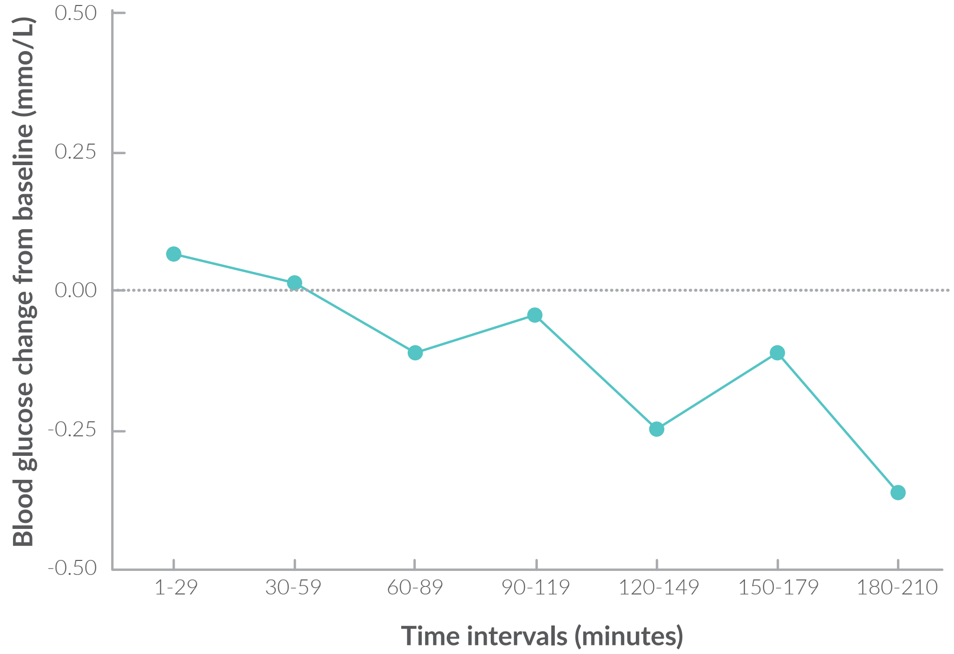

Figure 1: Estimated trajectory for glycaemic impact of low calorie sweetener consumption over 210 minutes following ingestion, as estimated in the meta-analysis by Nichol et al. (2018).

LCS consumption, but rather to an absence of an effect and a total lower carbohydrate load that leads to a lower blood glucose response. The review also found that LCS do not differ from water in their effects on blood glucose.

Reviewing the collective evidence, the European Food Safety Authority (EFSA) has also confirmed 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 Register of nutrition and health claims *(Commission Regulation (EU) No 432/2012)*.

Long-term RCTs investigating the effect of LCS on glycaemic control

Recent publications have reviewed the longer-term RCTs which investigated the potential for LCS to affect glucose control, and covers a range of population subtypes, including healthy individuals and people with diabetes *(Timpe Behnen et al, 2013; Grotz et al, 2017)*. Focusing particularly on LCS impact on glycaemic control in patients with diabetes, **the systematic review by Timpe Behnen et al. concluded that, overall, it appears that LCS may be used by patients with diabetes without affecting glycaemic control** *(Timpe Behnen et al, 2013)*.

Table 1 also presents the longer-term studies that have evaluated the impact of individual LCS on blood glucose, and also on insulin levels and glycated haemoglobin (HbA1c), the latter being an index of glycaemic control during the past 2-3 months. As discussed above, these collectively confirm that LCS consumption has no adverse long-term effect on overall glycaemic control in people with diabetes *(Stern et al, 1976; Nehrling et al, 1985; Okuno et al, 1986; Cooper et al, 1988; Colagiuri et al, 1989; Grotz et al, 2003; Reyna et al, 2003; Barriocanal et al, 2008; Maki et al, 2008; Argianna et al, 2015)*, or in normoglycemic persons *(Baird et al, 2000; Maersk et al, 2012b; Grotz et al, 2017; Engel et al, 2018; Higgins et al, 2018)*.

Click here for table 1

Studies	Summary of outcomes
Acute, short-term, single-dose studies	
Healthy individuals (22 studies) *(Okuno et al, 1986; Horwitz et al, 1988; Rodin et al, 1990; Härtel et al, 1993; Geuns et al, 2007; Ma et al, 2009; Brown et al, 2009; Anton et al, 2010; Ma et al, 2010; Ford et al, 2011; Steinert et al, 2011; Brown et al, 2011; Maersk et al, 2012a; Brown et al, 2012; Wu et al, 2012; Pepino et al, 2013; Bryant et al, 2014; Hazali et al, 2014; Temizkan et al, 2015; Sylvetsky et al, 2016; Tey et al, 2017; Higgins et al, 2018)*	**Studies comparing LCS to placebo or water:** No different effect on blood glucose and insulin levels between the LCS tested and placebo or water in all but one study that was not blinded and was in a morbidly obese population with evidence of glucose intolerance **Studies comparing LCS to standardized meal or sugar/ carbohydrate load:** Lower blood glucose and insulin levels post-prandially compared to sugar in all studies
People with type 1 and type 2 diabetes (9 studies) *(Shigeta et al, 1985; Okuno et al, 1986; Horwitz et al, 1988; Cooper et al, 1988; Mezitis et al, 1996; Gregensen et al, 2004; Brown et al, 2012; Olalde-Mendoza et al, 2013; Tezmikan et al, 2015)*	**Studies comparing LCS to placebo or water:** No different effect on blood glucose and insulin levels between the LCS tested and placebo or water in most studies; favourable effects for LCS versus control in 2 studies **Studies comparing LCS to standardized meal or sugar/ carbohydrate load:** Lower blood glucose and insulin levels post-prandially compared to sugar in all studies
Longer-term studies (2-week until 6-month duration)	
Healthy individuals (5 studies) *(Baird et al, 2000; Maersk et al, 2012b; Engel et al, 2018; Grotz et al, 2017; Higgins et al, 2018)*	No effect of LCS use on long-term glycaemia (fasting glucose and insulin, HbA1c) or on insulin sensitivity
People with type 1 and type 2 diabetes (10 studies) *(Stern et al, 1976; Nehrling et al, 1985; Okuno et al, 1986; Cooper et al, 1988; Colagiuri et al, 1989; Grotz et al, 2003; Reyna et al, 2003; Barriocanal et al, 2008; Maki et al, 2008; Argianna et al, 2015)*	No effect of LCS use on long-term glycaemic control (fasting blood glucose and insulin levels, c-peptide, HbA1c) in most studies; slightly improved HbA1c with the use of LCS in the diet in 2 studies

Table 1: Summary of outcomes of published acute and longer-term randomised controlled trials (RCTs) studying the effects of low calorie sweeteners (LCS) on glycaemic control in healthy individuals and in people with diabetes (N=40 studies).

Observational studies

Despite the consistent findings from RCTs, indicating a lack of adverse effect of LCS on blood glucose levels, some observational studies have reported a positive association between higher LCS intake and risk of diabetes or metabolic syndrome *(Romo-Romo et al, 2016)*. It is widely acknowledged that this association might be due to residual confounders such as adiposity, which is a confounder frequently found in these observational studies, and to reverse causation, meaning that people who are already at risk of obesity and metabolic syndrome or have diabetes, turn to LCS in their efforts to reduce sugar intake *(Romo-Romo et al, 2017)*.

More than ten observational studies have evaluated the association between the consumption of LCS, especially in beverages, and the development of diabetes or metabolic syndrome with mixed outcomes. A positive association between the consumption of LCS and the risk of diabetes has been shown in some of these studies, however, most of these associations are attenuated or even lost after adjustment for variables, including age, physical activity, family history of diseases, diet quality, energy intake and measures of adiposity such as body mass index (BMI) and waist circumference *(Romo-Romo et al, 2016; Romo-Romo et al, 2017)*.

Notably, when an adjustment for variables related to adiposity is performed in observational studies, the association between LCS intake and diabetes does not remain statistically significant. This finding strongly enhances the possibility that the observed association is a case of reverse causation.

Simply explained, the link between LCS use and diabetes can be attributed to the fact that people with higher BMI, already at risk to develop diabetes, consume low calorie sweetened foods and drinks more often in their effort to control their body weight. In a meta-analysis of ten observational studies estimating the risk of type 2 diabetes by consuming low calorie sweetened beverages, Imamura et al. found that after adjustment for BMI and the calibration for information and publication bias, the association between low calorie sweetened drinks and the development of type 2 diabetes was no longer statistically significant *(Imamura et al, 2015)*.

For example, the Nurses' Health Study I (NHS I) that studied more than 70,000 women with an average follow-up of 24 years *(Bhupathiraju et al, 2013)*, the Health Professionals Follow-Up Study with approximately 40,000 male health professionals followed over 20 years *(de Koning et al, 2011)* and the European Prospective Investigation into Cancer and Nutrition (EPIC) Study performed in eight European countries including 340,234 men and women *(InterAct 2013)*, found a significant association between LCS consumption and the development of type 2 diabetes, which however was lost in all cases after the adjustment for adiposity (for BMI) or for other co-variates. Similarly, the association between table-top sweetener consumption and risk of diabetes was found to be partially mediated by adiposity in a study analysing data of 61,440 women participating in the E3N-EPIC study, conducted between 1993 and 2011 *(Fagherazzi et al, 2017)*.

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On the other hand, other studies, such as the Nurses' Health Study II (NHS II) that included more than 90,000 women with a follow-up of 8 years found no association between LCS intake and risk of diabetes *(Schulze et al, 2004)*. Furthermore, in the Framingham Offspring cohort, a prospective observational study that tested the relationship between long-term low calorie beverage consumption, insulin resistance and prediabetes, no association was found linking the long-term intake of diet drinks with insulin resistance, as assessed by homeostatic model assessment of insulin resistance (HOMA-IR - an index of insulin resistance) and incidence of prediabetes *(Ma et al, 2016)*. Similarly, analysing data from the US National Health and Nutrition Examination Survey (NHANES) 2001-2012 in 25,817 adults that were free of diabetes, Leahy et al. found that higher intake of low calorie sweetened beverages was significantly associated with lower insulin levels, lower haemoglobin A1c (HbA1c) and lower HOMA-IR *(Leahy et al, 2017)*.

In any case, such positive associations observed in observational studies are not unexpected given that the populations studied were people prone to develop diabetes, who might have turned to LCS as a dietary strategy to reduce their calorie intake or to replace sugar in their diets. In explaining this positive association found in some of these studies it is important to take into consideration the fact that observational studies can only assess if there is a relationship between two factors, but they cannot study the direction of this relationship, in other words which factor causes the other. Most importantly, in the face of a strong evidence from RCTs that show no effect of LCS on blood glucose control, it is not prudent to draw conclusions only from the observational studies *(Greenwood et al, 2014)*.

No effect of low calorie sweeteners on insulin secretion

Studies of the last decade using human cell lines and animal subjects have raised questions about whether consumption of LCS might enhance insulin secretion and thus affect glucose metabolism. Proposed mechanisms include the enhancement of the cephalic phase of insulin secretion or the stimulation of the gut sweet taste receptors and subsequently the increase of gut hormones secretion. However, none of these suggested mechanisms has been confirmed in humans and, importantly, the collective evidence from RCTs in both normoglycemic individuals and in persons with diabetes show that LCS do not have any of the adverse effects on insulin secretion (Table 1).

The hypothesis of eliciting a cephalic phase insulin response

Exposure to LCS has sometimes been associated with evidence of a cephalic phase insulin response or CPIR *(Liang et al. 1987; Just et al. 2008; Dhillon et al. 2017)*. 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 LCS to cause hunger or to cause a later increase in blood glucose levels that is abnormal *(Mattes and Popkin, 2009)*. An adverse effect of LCS on either appetite regulation or glucose metabolism, however, is not confirmed in clinical trials *(Mattes and Popkin, 2009; Renwick and Molinary, 2010; Bellisle, 2015; Grotz et al, 2017)*. Additionally, other research has shown that CPIR is generally not a meaningful determinant in food desire, hunger or glucose response *(Morey et al, 2016)*. In addition, there are clinical studies that do not show an effect of LCS on CPIR *(Teff et al, 1995; Abdallah et al, 1997; Morricone et al, 2000; Ford et al, 2011; Boyle et al, 2016)*. Research also indicates that CPIR differences can be caused by differences in stress *(Dušková et al, 2013)*. Importantly, the sum of the evidence does not support that LCS will cause increases in appetite or blood glucose levels.

The hypothesis of stimulating the gut sweet taste receptors and incretin release

The gut incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP), known to have a role in insulin secretion and thus in glucose control, are released from the gut in response to the intake of food and nutrients and, in turn, stimulate insulin secretion from pancreatic cells. The role of carbohydrate ingestion in stimulating the release of incretins has been extensively studied and well established, but unlike carbohydrates, current evidence doesn't support a clinically meaningful stimulatory effect of LCS on the secretion of gut hormones in humans *(Bryant and McLaughlin, 2016)*.

It has been proposed that through activation of sweet taste receptors in the gut, which are know to play a role in regulating glucose absorption and promoting insulin release, LCS may adversely affect glycaemic control. This hypothesis, however, stems largely from isolated cell or tissue *(in vitro)* experiments that also typically utilised LCS concentrations that were extraordinary 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 body. Contrary to the findings of these *in vitro* studies, most clinical human trials have found no effects of LCS on circulating incretin 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)*.

GLP-1 was increased in a few studies with beverages containing acesulfame-K and sucralose or only sucralose in healthy overweight and obese adults *(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, 2015)*. It is unknown whether changes in endogenous GLP-1 secretion as observed in these studies have any clinically relevant consequences *(Brown et al, 2012)*. Changes observed may also be a consequence of normal variation. Interestingly, in one study where these sweeteners were also tested alone (sucralose), or in combination (acesulfame-K with sucralose) in non-commercial drinks, no increase in GLP-1 was found *(Sylvetsky et al, 2016)*.

Collectively, the evidence from *in vivo* animal and human studies do not support the notion that LCS induce the release of clinically meaningful quantities of gut hormones. In a review of the literature by Bryant and McLaughlin, the authors concluded that: **"activation of the sweet taste receptors by LCS in the human gut fails to replicate any of the effects on gastric motility, gut hormones or appetitive responses evoked by caloric sugars."** *(Bryant and McLaughlin, 2016)*. Similarly, Meyer-Gerspach et al infer from the evidence reviewed in their work that LCS have little, if any, effect on gastric emptying and incretin release in humans *(Meyer-Gerspach et al, 2016)*. Furthermore, in general, caution is necessary in the extrapolation of *in vitro* effects to the *in vivo* situation and the extrapolation of data from studies in animals to humans *(Renwick and Molinary, 2010)*.

Emerging research

Low calorie sweeteners and insulin sensitivity

The potential effect of LCS on insulin sensitivity garnered attention primarily following the publication of an animal experiment and a very small human trial in 7 subjects by Suez et al., published in 2014, suggesting that high doses of saccharin at the level of the Acceptable Daily Intake (ADI) might contribute to insulin resistance via effects on the gut microbiota *(Suez et al, 2014)*. The findings of this study have not been replicated nor confirmed in humans. In contrast, larger RCTs examining the effects of LCS or of products containing them on indexes of insulin sensitivity have showed no effect of LCS on insulin sensitivity *(Maersk et al, 2012b; Engel et al, 2018; Bonnet et al, 2018)*.

In a study by Engel et al. *(2018)*, the results support that the consumption of low calorie sweetened drinks does not affect insulin sensitivity differently than water after 6 months' intake. The main finding of this 6-month RCT is that a long-term daily consumption of 1L of milk, sugar-sweetened beverage, LCS drink and water had no effects on insulin sensitivity or risk markers of type 2 diabetes in 60 overweight or obese adults *(Engel et al, 2018)*.

Similarly, in an RCT in 50 healthy, non-diabetic, normal- and overweight individuals, where participants consumed 2 cans (330 mL each) of a carbonated beverage containing aspartame and acesulfame-K on a daily basis for 12 weeks, no effect was found on insulin sensitivity or insulin secretion, when compared to an unsweetened control beverage *(Bonnet et al, 2018)*. This study adds further evidence to previous findings supporting that LCS consumption does not negatively affect insulin sensitivity.

Furthermore, observational studies such as the Framingham Offspring cohort, a prospective observational study that tested the relationship between long-term low calorie beverage consumption and insulin resistance as well as prediabetes, found no association between the long-term intake of diet drinks sweetened with LCS and insulin resistance or prediabetes *(Ma et al, 2016)*. Similarly, analysing data from the US National Health and Nutrition Examination Survey (NHANES) 2001-2012 in 25,817 adults that were free of diabetes, Leahy et al. found that higher intake of low calorie sweetened beverages was significantly associated with lower insulin levels, lower haemoglobin A1c (HbA1c) and lower HOMA-IR *(Leahy et al, 2017)*.

Low calorie sweeteners and gut microbiota

The role of the gut microbiome, or microbiota or microflora, in affecting human health is currently an area of extensive research. The intestinal microbiome is part of the overall human physiology that is important to regulating our health, including our gastrointestinal health and function *(Pascale et al, 2018)*. While many experiments are now on-going, and a few studies investigating changes following exposure to LCS have been reported, it's important to know that this field of research is basically in its infancy, insofar as understanding what impact particular nutrients may have on the gut microbiota profile and/or function. 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. Moreover, there are large differences between the gut microbiome profile in laboratory animals and people, so translating data from these studies is very suspect *(Johnson et al, 2018)*. 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. Additionally, the gut microbiome profile can change daily just with normal changes in daily food intake.

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Most research on LCS has been studies involving animal experiments. Often, testing has also utilized very high doses of LCS. There have been mixed outcomes with this research, however, there is no evidence that changes reported are changes that would cause an adverse health effect. *(Magnuson et al, 2016)*

In the future, it will be important for human studies on the potential for LCS to impact the gut microbiome to be very carefully conducted. Well-designed studies should examine potential effects in the context of human realistic consumption levels *(Sylvetsky et al, 2018)*. Careful control of other factors known to affect gut microflora, such as changes in food consumption and diet composition, are also necessary to avoid confounding effects *(Magnuson et al, 2016)*. Finally, extrapolation of the effect of one LCS on the gut microflora to all LCSs is not appropriate, on the basis of well-documented differences in their chemistry, their movement through the body, and the amount of LCS or LCS metabolites that reach the gut microflora.

The impact of diet on gut microbiota. What does evidence show about low calorie sweeteners?

Prof Wendy Russell: Increasing evidence demonstrates that the intestinal microbiome may have a significant role in the prevention and development of non-communicable diseases. This includes metabolic, as well as gastrointestinal disorders *(Pascale et al, 2018)*. Arguably, although lifestyle choices to increase physical activity and lose weight will impact on health outcomes, dietary composition is likely to have the strongest impact on directly shaping the gut microbiome, with changes occurring within 24 hours *(David et al, 2014)*. Carbohydrates are the most widely studied, with non-digestible fibre supplying the microbiota with energy, a carbon source and major precursors to short chain fatty acids, important for maintaining gut health *(Chen et al, 2013)*. Digestible carbohydrate includes fibre and starch, which can be degraded in the small intestine, as well as mono- and disaccharides including sucrose (sugar), which have been shown to modulate the gut microbiota and microbial crosstalk *(Eid et al, 2014, Lambertz et al, 2017)*.

It is clear that modulating carbohydrate intakes can impact on the gut microbiota and assessing the effect of low calorie sweeteners will require carefully controlled human studies that include an understanding of the carbohydrate forms replaced. Although some animal studies have shown that low calorie sweeteners, usually tested at high levels not typically consumed by humans, could have negative effects on the gut microbiota, by shifting the balance and diversity *(Nettleton et al, 2016)*, there is as yet no conclusive evidence from observational or interventional studies in humans. In light of the very low intakes of low calorie sweeteners in the typical human diet, it is questionable as to whether any impact there may be would result in clinically meaningful changes.

The role of diet in diabetes management

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces (Figure 2). Insulin is a key hormone that regulates blood glucose. There are different types of diabetes, but the most common are type 1, type 2 and gestational diabetes, with type 2 diabetes being the most rapidly increasing *(WHO, 2017)*.

Normal situation

Type 1 diabetes

Type 2 diabetes
gestational diabetes

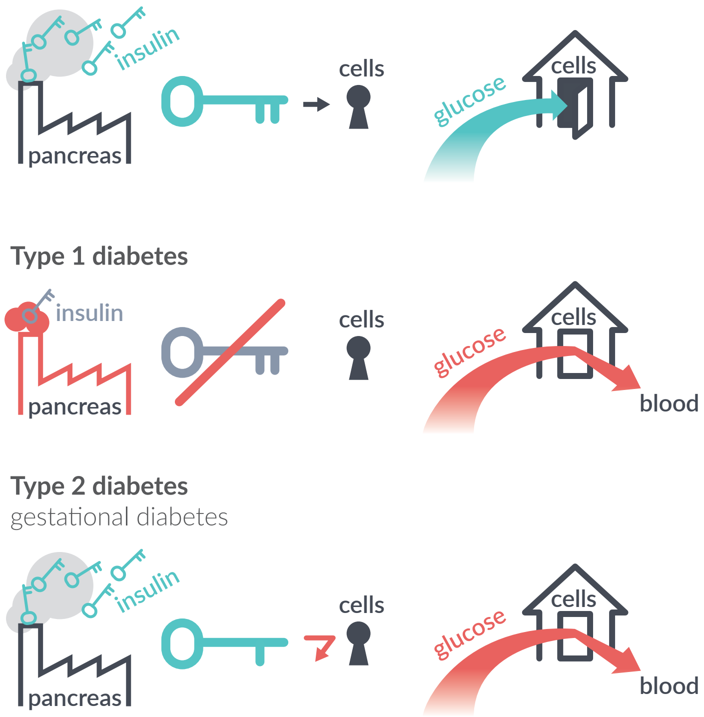
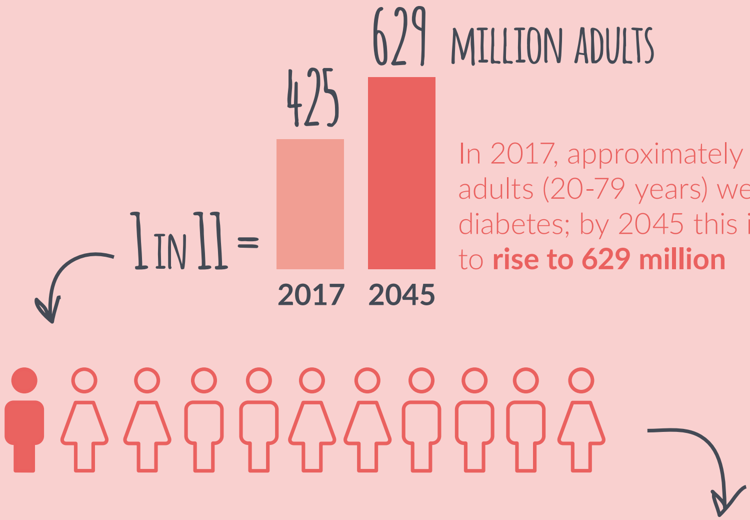


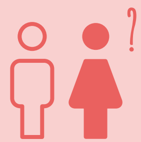
Figure 2: Diabetes occurs either when the pancreas does not produce enough insulin (type 1 diabetes) or when the body cannot effectively use the insulin it produces (type 2 diabetes). Source: IDF Diabetes Atlas – 6th edition, 2013.

Diabetes in numbers

(IDF, 2017)

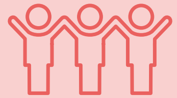


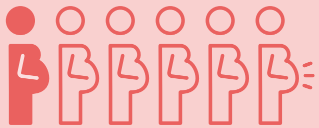
In 2017, approximately 425 million adults (20-79 years) were living with diabetes; by 2045 this is expected to **rise to 629 million**



1 IN 2 people with diabetes are **undiagnosed**

> 1 MILLION children and adolescents have type 1 diabetes





About 1 IN 6 births is affected by **hyperglycaemia in pregnancy**

Nutrition therapy plays a critical role in managing both types of diabetes, reducing the potential complications related to poor glycaemic, lipid, and blood pressure control, and improving quality of life. Thus, today, nutrition therapy and nutrition education are recommended for all people with diabetes including those at risk of developing type 2 diabetes (pre-diabetes) *(Evert et al, 2014)*.

Goals of nutrition therapy are to promote and support healthy eating patterns with a variety of nutrient-dense foods in appropriate portion size to achieve individualised glycaemic, blood pressure, and lipid goals; attain and maintain body weight goals; and delay or prevent complications of diabetes. A further goal is to maintain the pleasure of eating by providing positive messages about food choices and practical tools for day-to-day meal planning. Indeed, for many individuals with diabetes, the most challenging part of the treatment plan is determining what to eat *(Evert et al, 2014)*.

Nutrition therapy plays a critical role in managing both types of diabetes.

Use of low calorie sweeteners in the diet for diabetes - A practical perspective

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.

In persons with diabetes, blood glucose levels are affected by how much carbohydrate is being consumed within each meal. Therefore, managing carbohydrate intake and reducing excess sugars' consumption are important aspects of glycaemic control in diabetes management. Using LCS instead of sugars can make meal planning for diabetes management easier. Furthermore, because humans have an innate preference for sweet taste, having palatable, good-tasting foods can help improve the compliance in meal planning for diabetes. There should be no expectation that LCS, by themselves, would decrease blood glucose levels as they are not substances that can exert pharmacologic-like effects. However, LCS 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)*.

For individuals with type 1 diabetes, since one key element in the nutritional management of their diabetes is carbohydrate-counting meal planning and adjustments to insulin doses based on carbohydrate intake in order to maintain blood glucose levels within the normal range, using LCS 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.

Nutrition guidelines for diabetes prevention and management

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

In addressing the role of LCS in diabetes management, **several organizations globally recognise that LCS can be safely used to replace sugars in the nutritional management of diabetes as LCS have no effect on glycaemia.** For example, both the American Diabetes Association *(ADA 2018)* and the US Academy of Nutrition and Dietetics in their Medical Nutrition Therapy (MNT) recommendations for type 1 and type 2 diabetes *(Franz et al, 2017)* conclude that LCS use has the potential to reduce overall calorie and carbohydrate intake if substituted for caloric sweeteners and without compensation by intake of additional calories from other food sources. Similarly, the latest Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes, published in March 2018, concludes that LCS may be recommended as they have no effect on glycaemia and that they can be a useful strategy for those individuals trying to reduce calorie intake *(Dyson et al, 2018)*. Table 2 presents these recommendations regarding the use of LCS in diabetes.

Organisation (year of publication)	Recommendations about the role of low calorie sweeteners (LCS) in diabetes management
Diabetes UK (2018)	• LCS are safe and may be recommended • LCS have the potential to reduce overall energy and carbohydrate intake and may be preferred to sugar when consumed in moderation • LCS can be a useful strategy for those individuals seeking to control their calorie intake and manage their weight • LCS may help reduce HbA1c [glycated haemoglobin] when used as part of a low-calorie diet
American Diabetes Association (2018)	• LCS are generally safe to use within the defined acceptable daily intake levels • The use of LCS may have the potential to reduce overall calorie and carbohydrate intake if substituted for caloric (sugar) sweeteners and without compensation by intake of additional calories from other food sources.
US Academy of Nutrition and Dietetics (2017)	• Registered dietitians and nutritionists (RDNs) should educate adults with diabetes that intake of approved LCS will not have a significant influence on glycemic control. • Research reports no significant influence of consuming LCS (such as aspartame, steviol glycosides, and sucralose), independent of weight loss, on HbA1c [glycated haemoglobin], fasting glucose levels, or insulin levels

Table 2: Nutrition guidelines for diabetes management: recommendations regarding the use of low calorie sweeteners in the diet for diabetes

Weight management in diabetes

Excess body weight is a known risk factor for both the development and exacerbation of type 2 diabetes. Being overweight or obese may worsen glycaemic control and increase cardiometabolic risk. Therefore, it is critical to prevent weight gain in individuals with diabetes or pre-diabetes. For overweight or obese adults with type 2 diabetes, modest weight loss (5% to 10% of body weight) has been shown to provide significant clinical benefits including, importantly, improved glucose control *(Franz et al, 2017)*. To achieve modest weight loss, lifestyle interventions including a calorie-reduced, healthy eating plan, physical activity, and behaviour change are required. Dietary changes can help in modest and sustained weight loss, and they may produce clinically meaningful reductions in glycosylated haemoglobin A1c (HbA1c) *(Evert et al, 2014)*.

A variety of eating patterns are acceptable and can be effective in the management of diabetes aiming also in weight control *(Dyson et al, 2018)*. LCS can be part of a calorie-controlled healthy diet and may also help persons with diabetes in efforts to lose weight *(Rogers et al, 2016; Dyson et al, 2018)*. Especially for those who typically overconsume sugars, LCS may be a useful tool in helping to reduce both sugars and calorie intake. More scientific information about the role of LCS in weight management is provided in the previous chapter (see chapter 4).

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Conclusion

In all, LCS and foods and drinks containing them can be safely used by people with diabetes to help 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. Using LCS in place of sugars can also help reduce overall calorie intake and be a helpful tool in nutritional strategies for weight management, which is especially important for people with type 2 diabetes or pre-diabetes who need to lose weight or prevent additional excess weight gain. By making lifestyle changes that can help towards a healthier body weight, such as improving diet quality and increasing physical exercise, the risk of developing type 2 diabetes can be markedly diminished. Of course, there should be no expectation that LCS, by themselves, would cause weight loss or decrease blood glucose levels, but they can certainly be part of an overall high-quality diet aiming to improve overall glycaemic control in diabetes.

> Using low calorie sweeteners in place of sugars can help reduce overall calorie intake and be a helpful tool in nutritional strategies for weight management.

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6.
Low calorie sweeteners and oral health

Low calorie sweeteners (LCS) are non-cariogenic ingredients and therefore, contrary to sugars and other fermentable carbohydrates, LCS do not contribute to the development of dental caries.

This chapter aims to provide information about oral health, the effect of diet on dental caries and the role LCS can play in good dental health.

Why is good oral health important?

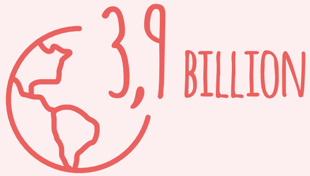
According to the FDI World Dental Federation, *"Oral health is multi-faceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow and convey a range of emotions through facial expressions with confidence and without pain, discomfort and disease of the craniofacial complex."* *(FDI, 2015).*

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. Oral health also has an effect on other chronic diseases *(Sheiham, 2005).*

Our mouth is a mirror to our body and reflects our general health and well-being!

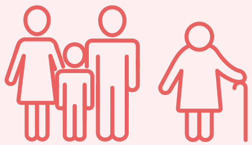
Facts about oral diseases (FDI, 2015)

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



Overall, oral diseases affect **3,9 billion people worldwide.**

Dental caries is a major public health challenge worldwide. **Over 40% of the global population** is dealing with untreated decay of permanent teeth.



Tooth decay is the **most common childhood disease**, but it affects people of all ages.

If not properly managed, oral diseases can negatively impact overall health and well-being.

Tooth decay is largely preventable! Good oral hygiene and a healthy diet are key in dental caries prevention.

About dental caries

Dental caries, which is also referred to as tooth decay or cavities, is amongst the most widespread chronic disease worldwide and constitutes a major global public health challenge. It is the most common childhood disease, but it affects people of all ages across the lifespan *(FDI, 2015).*

When you eat certain foods, the bacteria in your mouth breaks them down and produces acids that have the ability to seriously damage the hard tissues of your tooth. The result is the formation of dental caries (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. Therefore, even a small reduction in risk of dental caries in childhood is of significance in later life *(Moynihan and Kelly, 2014).*

Importantly, dental caries is largely preventable and avoidable – in most cases there is nothing inevitable about them *(FDI, 2015).*

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Prevalence of dental carries

Tooth decay is the most prevalent of oral health conditions, affecting more than 40% of the world population in 2010. More than 3 billion people worldwide are affected by untreated decay of primary and permanent teeth and it has been estimated to be the most prevalent condition out of 291 diseases included in the Global Burden of Disease Study *(FDI, 2015)*. The prevalence of tooth decay worldwide is presented in Figure 1.

Tooth decay worldwide

CLICK BULLETS TO COLOUR THE MAP

- high (more than 3.5)
- moderate (2.6-3.5)
- low (1.2-2.5)
- very low (0.0-1.1)
- no data

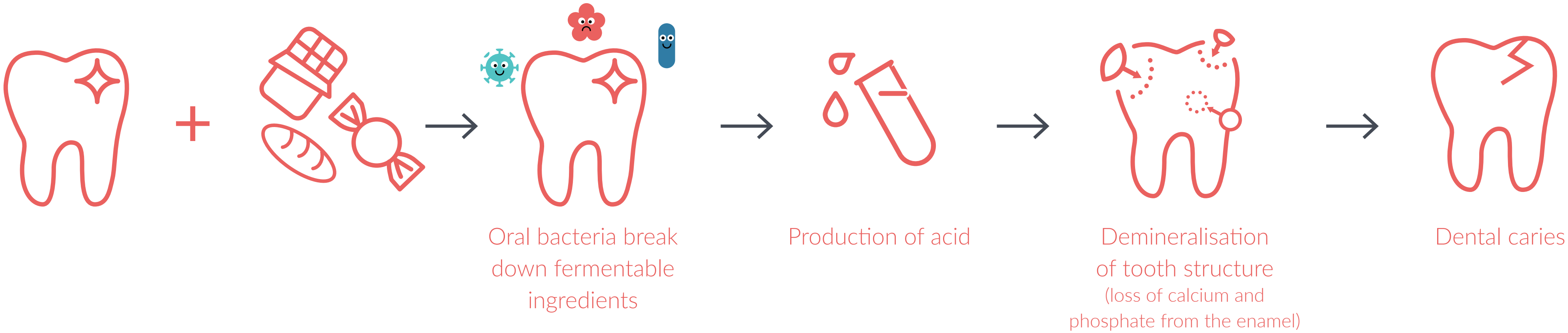
Figure 1: Tooth decay worldwide. Average number of decayed (D), missing (M), and filled (F) teeth (T) in12-year-olds latest available data 1994–2014. From: The Challenge of Oral Disease – A call for global action by FDI World Dental Federation. Maps and graphics © Myriad Editions 2015

Diet and dental caries

Oral health is related to diet in many ways. 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 local action of diet in the mouth on the development of dental caries and enamel erosion.

Of the many factors that contribute to the development of dental caries, diet plays an important role. 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. When it comes to a diet for optimal dental health, excess intake of sugars and other fermentable carbohydrates should be limited.



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 (WHO) guidelines on 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)*. 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)*.

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).

No cariogenic effect of low calorie sweeteners

Contrary to sugars, LCS have no cariogenic effect as they are not substrates for oral microorganisms. All approved LCS 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 LCS dates back to the 1970s *(Olson, 1977)*, and since then, a number of studies and reviews have examined and confirmed the non-cariogenic nature of LCS *(Grenby et al, 1986; Mandel and Grotz, 2002; Matsukubo et al, 2006; Gupta et al, 2013; Ferrazzano et al, 2016)*.

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 of LCS on dental health, a 2013 literature review concluded that **LCS 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)*.

Conclusion

By being not fermentable and thus non-cariogenic ingredients, LCS are tooth friendly ingredients providing dental benefits when used instead of sugars in foods and beverages, toothpaste and medications, provided that other constituents are also non-cariogenic and non-erosive (other ingredients in some low calorie sweetened food products such as starch and/ or naturally occurring sugars may still cause caries) *(Gibson et al, 2014)*. **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)*.

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, LCS 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 calorie sweeteners are tooth friendly ingredients

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7. Sweetness in the human diet

Sweet taste is universally liked. Human appetite for sweetness is innate, expressed even before birth, and spans across all ages and cultures around the world, which makes sweetness an integral part of the human diet. However, in times when health organisations worldwide recommend that free sugars intake should be reduced to less than 10% of total daily energy intake for people of all ages, managing sweetness is critical from a nutritional and a public health perspective.

This chapter aims to present scientific information about the role of sweet taste overall in the human diet and to discuss the role of low calorie sweeteners (LCS) in managing our innate preference for sweetness.

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Why do we like sweet taste?

Taste plays a key role in food choice and dietary intake. In conjunction with other senses, taste plays a crucial role in 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)*. The five basic tastes include: sweet, sour, bitter, salt and umami (Figure 1).

Sweetness is classically recognized as one of the "basic tastes" detected by the sensory receptors present in the oral cavity. Experts believe that the innate acceptance of sweet stimuli and rejection of bitter ones have developed through natural Evolution and constitute an adaptive advantage, preparing the young to spontaneously accept sources of energy and to reject potentially toxic bitter substances *(Mennella et al, 2014; Mennella and Bobowski, 2015)*.

The infant's appetite for sweetness facilitates the acceptance of breast milk with its sweet taste due to its content of lactose, the sugar found in maternal milk *(Reed and Knaapila, 2010)*. Therefore, it has been suggested that biology dictates a liking for sweetness across the lifespan and makes sweetness an important part of the human diet *(Drewnowski et al, 2012)*.

Figure 1: Five basic tastes

How does our body "recognise" sweetness?

Sweet taste receptors are located in the oral cavity and are responsible for the initial detection of a sweet tasting stimulus. They respond to various sweet tasting molecules including sugars, polyols, and a broad variety of LCS *(Renwick and Molinary, 2010).*

For sweetness perception, two G-protein coupled transmembrane receptor proteins, T1R2 and T1R3, 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 events such as the opening of ion channels or the generation of other biochemical signals. Stimulation of the T1R2 + T1R3 taste receptor activates peripheral gustatory nerves and, in turn, brain gustatory pathways *(Renwick and Molinary, 2010).*

Identical receptors have recently been found in other parts of the digestive tract, from the stomach and pancreas to the colon and enteroendocrine cells. 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), whereas LCS appear metabolically inactive in humans and/ or without significant and clinically relevant effects *(Steinert et al, 2011; Bryant and McLaughlin, 2016; Mehat and Corpe, 2018).*

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Sweetness preference: From early life to adulthood

The acceptance of sweetness and the rejection of bitterness are innate traits. This is evident, for example, from the characteristic "gusto-facial reflexes", the positive affective reactions elicited in human new-borns a few hours after birth by placing a small amount of sweet solution into their mouths, which is in sharp contrast to the rejection caused by bitter- and sour-tasting substances (Figure 2). In fact, when a sweet solution is placed in the oral cavity, infants relax the face and sometimes smile *(Steiner 1977; Rosenstein and Olster 1988; Steiner et al, 2001).*

Our natural liking for sweetness remains until old age, however, there is evidence that it decreases from childhood to adolescence and into adulthood. Liking for sweetness is intense during childhood, which may reflect the nutritional need for attracting young organisms to foods that are high in energy during periods of maximal growth *(Desor and Beauchamp, 1987; Mennella et al, 2011; Mennella et al, 2014)*. In adolescents, the preferred intensity of sweetness is lower than in younger children, and it is lower in adults than in adolescents *(de Graaf and Zandstra, 1999).*

While all humans express the same response to sweetness immediately after birth, the liking for sweet products changes over time and becomes highly idiosyncratic in adults *(Schwartz et al, 2009)*. An appetite for sweetness is present in most adults, although large inter-individual differences exist in both the preferred level of sweetness in familiar products and in the range of foods and drinks that are consumed sweet *(Reed and McDaniel, 2006; Bachmanov et al, 2011).*

There is evidence that genetic differences among people may partly account for individual differences in sweetness preference and in the consumption of sweet foods and drinks *(Reed and McDaniel, 2006; Keskitalo et al, 2007; Joseph et al, 2016)*. However, how these genetic differences in sweet perception or liking might translate into food intake and food preference is still unclear.

Infant facial expressions

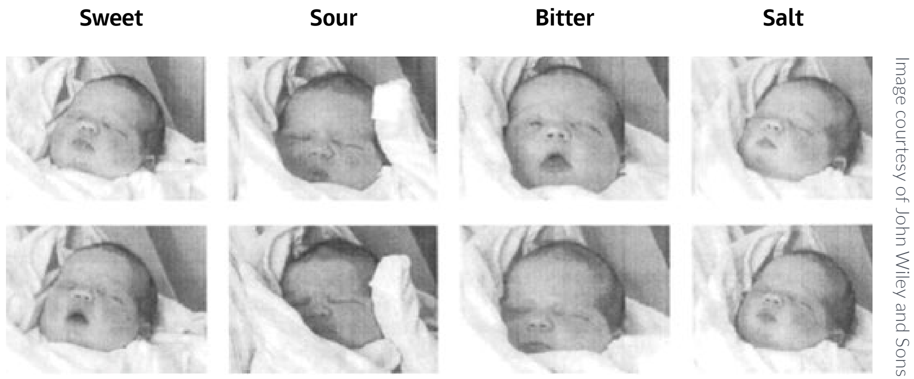

Figure 2: Infant facial expressions in response to sweet, sour, bitter and salt taste stimuli (Steiner, 1977).

Acceptance of sweetness is innate and universal. Humans are born with a liking for sweetness, which decreases from childhood to adolescence and into adulthood.

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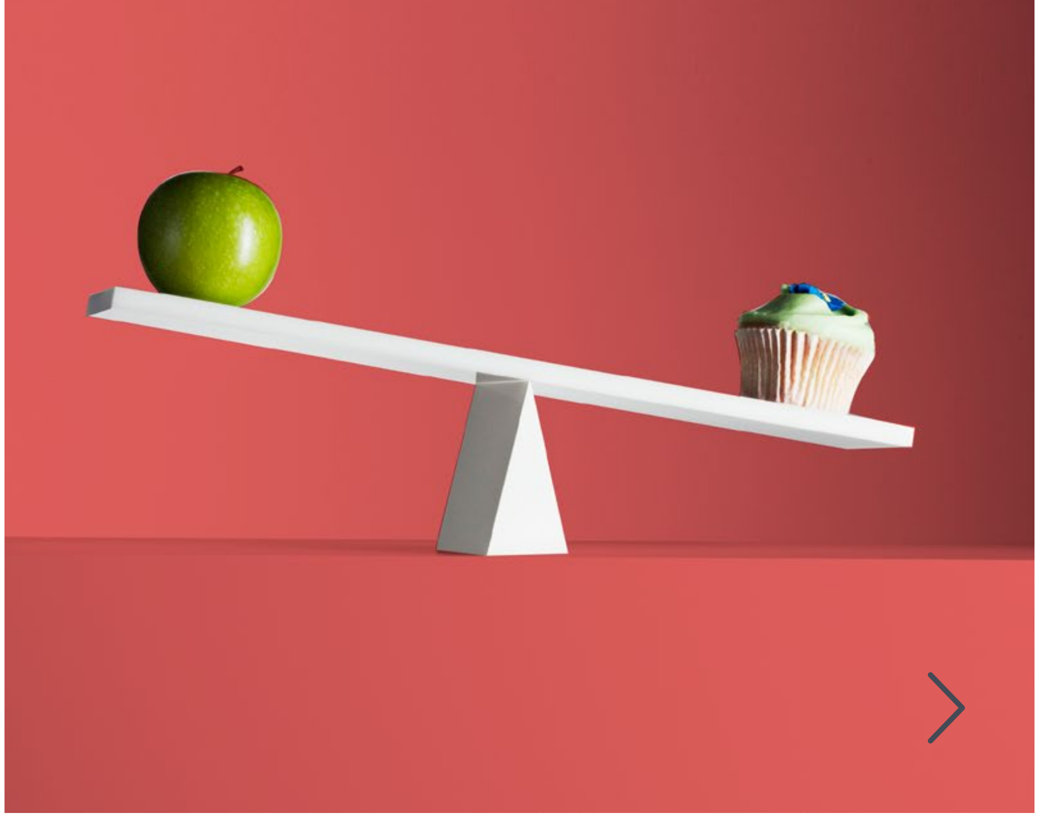
The role of sweetness in the diet

Acceptance of sweetness is innate and universal, thus, it's not a surprise that sweetness always was and still remains an integral part of the human diet. The liking of sweetness is also evident by the fact that the word "sweet" is used to describe not only this basic taste quality but also something that is desirable or pleasurable, e.g., "la dolce vita" [sweet life] *(Reed and McDaniel, 2006)*.

Our diets and food production have changed significantly since early humans hunted for and gathered food. Over the last decades, our food environment has changed considerably and high-calorie, palatable foods, which are usually higher in fat and sugar content, are now widely available and easily accessible. So, 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 liking for sweetness such as by using LCS in place of caloric sweeteners may be helpful in reducing sugars and thus overall energy intakes.

Excess sugar intake can contribute to excess energy intake and therefore to weight gain and obesity



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Is there a link between sweetness and obesity?

The attraction of humans to sweet tasting foods and beverages has given rise to the notion that the appetite for sweet products may stimulate overeating and induce weight gain over the long term *(Deglaire et al, 2015)*. An individual's appetite for energy-rich 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)*. However, existing evidence doesn't clearly support that liking for sweetness differs by weight status or that it is associated with obesity *(McDaniel and Reed, 2004)*.

Most studies that have examined the potential association between taste preferences and obesity have found no difference in liking for sweetness across different body mass index (BMI) categories in children and adults *(Cox et al, 1999; Hill et al, 2009; Bobowski et al, 2017)*. For example, a recent study in both children and adults found that, regardless of age, sweet preference and liking, both for caloric sweeteners and LCS, did not differ between obese and non-obese individuals (Figure 3) *(Bobowski et al, 2017)*. Similarly, in a study of 366 children, aged 7-9 years, no association was found between adiposity and liking for sugary or fatty foods, fruits or vegetables *(Hill et al, 2009)*. This suggests that overweight in children is not reflective of differences in liking for selected common foods and shows that liking for sweetness is not related to body weight status in children.

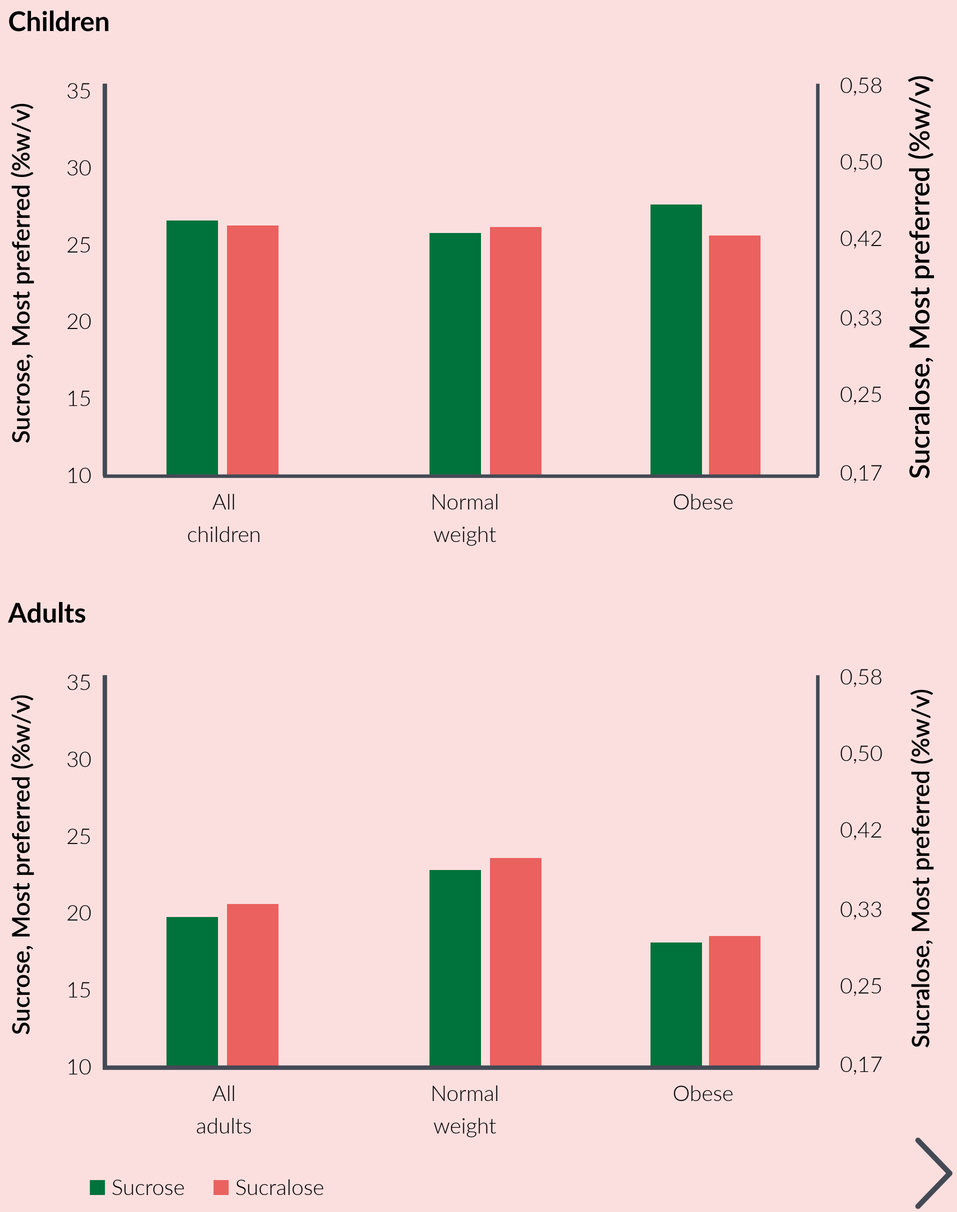

Figure 3: Most preferred levels of sucrose and sucralose among all and among obese vs. nonobese children (a) and adults (b): There were no statistically significant relationships between BMI and most preferred level of sucrose or sucralose, regardless of age. Data are means ± standard error. *(Bobowski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

Furthermore, a recently published study found lower liking ratings and intakes of sweet foods for obese compared to lean individuals *(van Langeveld et al, 2018)*. In particular, the study combined data from two population studies in the Netherlands, the Dutch National Food Consumption Survey (DNFCS 2007–2010; n 1351) and the Nutrition Questionnaires plus (NQplus) study (2011–2013; n 944) with a taste database containing 476 foods' taste values, and found that obese men and women consumed significantly less energy from foods tasting 'sweet and fat' than normal-weight men and women, although the difference was only statistically significant in men *(van Langeveld et al, 2018)*.

Sweetness without calories

In traditional food products, sweetness is brought primarily by sugars, carbohydrates with a distinctive sweet taste, which also bring calories: 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 intense sweetening agents have been developed in the last decades. LCS have a much higher sweetening power compared to sugars, so that they can be 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. Thus, sweetness per se provides little information about the energy value of a food. By reducing the energy content of foods and beverages, LCS may potentially be a helpful tool in satiating our desire for sweet taste.

However, over the years, concerns have been expressed about potential effects of LCS on hunger or on appetite for further sweetness. More specifically, it has been suggested that LCS might enhance the natural appetite for sweetness, exacerbate the liking for sweet products of all kinds, and prevent consumers from managing their response to sweetness. **A plethora of scientific studies have addressed these concerns over the last 40 years and found no support for an exacerbation of the appetite for sweetness with the use of LCS** *(Bellisle, 2015)*.

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.

The "sweet tooth" hypothesis: Can exposure to sweet taste increase the appetite for sweetness?

Dr France Bellisle: The term "sweet tooth" refers to strong preferences 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 and the appetite for sweet tasting products, leading to increased consumption. An increased use of LCS in many foods and beverages could lead to such a situation. Again, much recent research has addressed this hypothesis.

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, 2017; Appleton et al, 2018)*. What laboratory and field studies have shown is that exposure to a particular sensory attribute (e.g., sweetness) leads to reductions in the momentary pleasantness and choice 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 sweet taste from dietary sources with low amounts of sugars, for example sweetened with LCS, 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)*. To address this research question, a recent study showed that reducing sweetness in a diet by following a low-sugar diet for three months did not change the preference for sweetness, even if the subjects rated the foods as tasting sweeter after the end of the intervention period. However, once the low-sugar diet ended, people quickly increased their sugar intake to baseline levels and their judgments of sweet taste intensity reverted to pre-diet levels. It seems that preference and liking of sweetness does not change within each individual according to the higher or lower exposure to sweet tasting foods *(Wise et al, 2016)*.

Low calorie sweeteners' intake neither promotes nor suppresses appetite in humans.

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The sweet taste confusion hypothesis: Can low calorie sweeteners disrupt the learned control of energy intake?

Dr France Bellisle: The notion that LCS 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)*. According to this early hypothesis, LCS 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, LCS might stimulate appetite via their sweet taste, but exert no post-ingestive inhibitory influence as they provide no energy. Thus, the experience of sweetness in the absence of calories might weaken the natural sweetness-energy relationship and consequently disrupt appetite control mechanisms.

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

Numerous scientific studies using very different methodological approaches (observational studies, RCTs, experimental studies carried out in laboratory settings and studies using functional Magnetic Resonance Imaging (fMRI)) in various types of consumers (men, women, lean, obese, never obese, formerly obese) have examined the impact of LCS 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 recent reviews of the literature have evaluated the available data in humans about LCS effects on appetite and energy intake. **Overall, the existing studies reach largely consistent conclusions: the short- or long-term use of LCS shows no consistent association with a heightened appetite in general, or specific appetite for sugar or sweet products. In fact, in many instances, the use of LCS is associated with a decreased intake of sweet tasting substances** *(Bellisle, 2015; Rogers et al, 2016; Rogers, 2017)*. This is also the conclusion of a report by Public Health England (PHE), noting that there is no evidence to suggest that by maintaining the sweet taste through the use of non-caloric sweeteners individuals are subsequently more likely to make higher calorie food and drink choices *(PHE, 2015)*.

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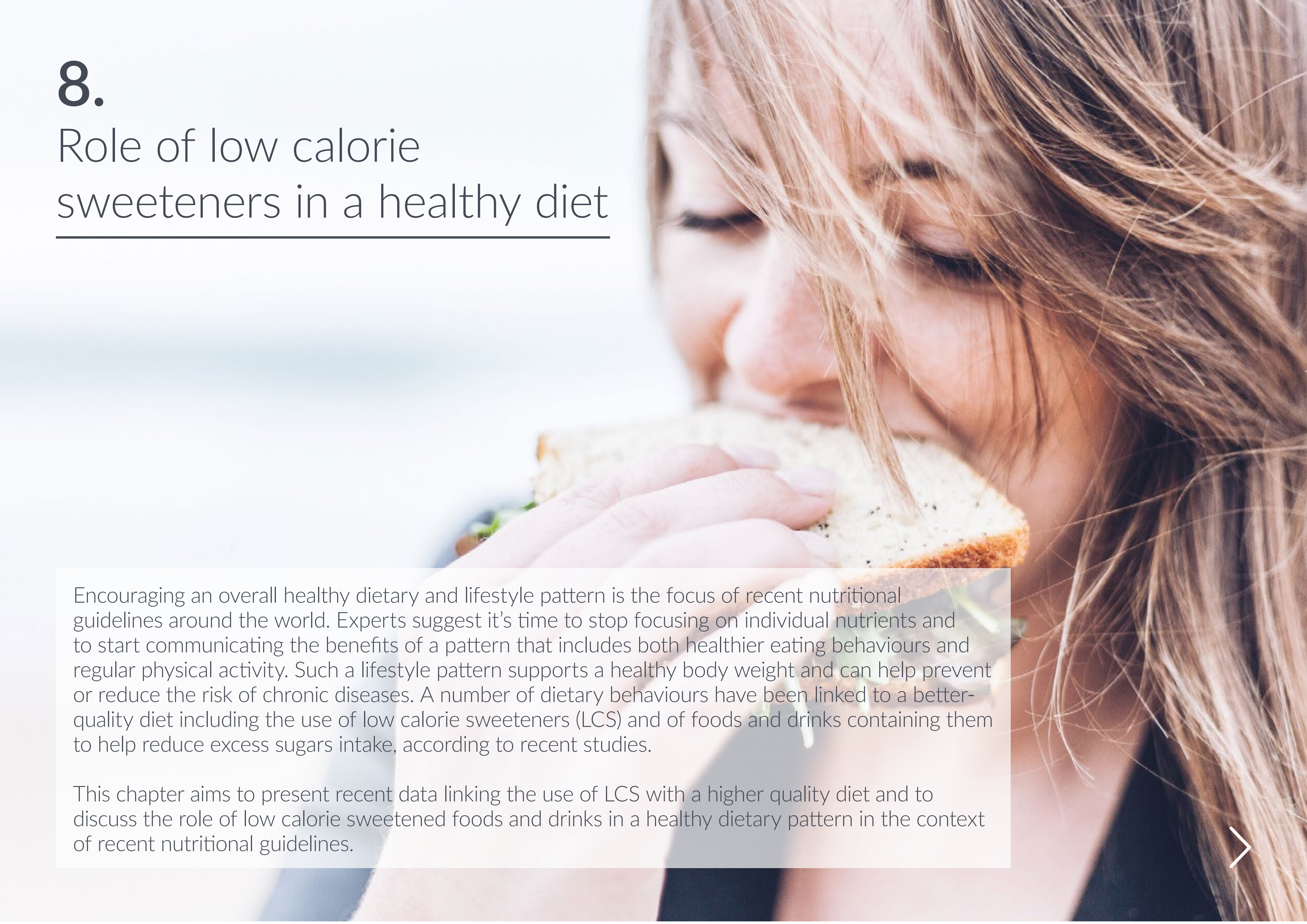

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Role of low calorie sweeteners in a healthy diet

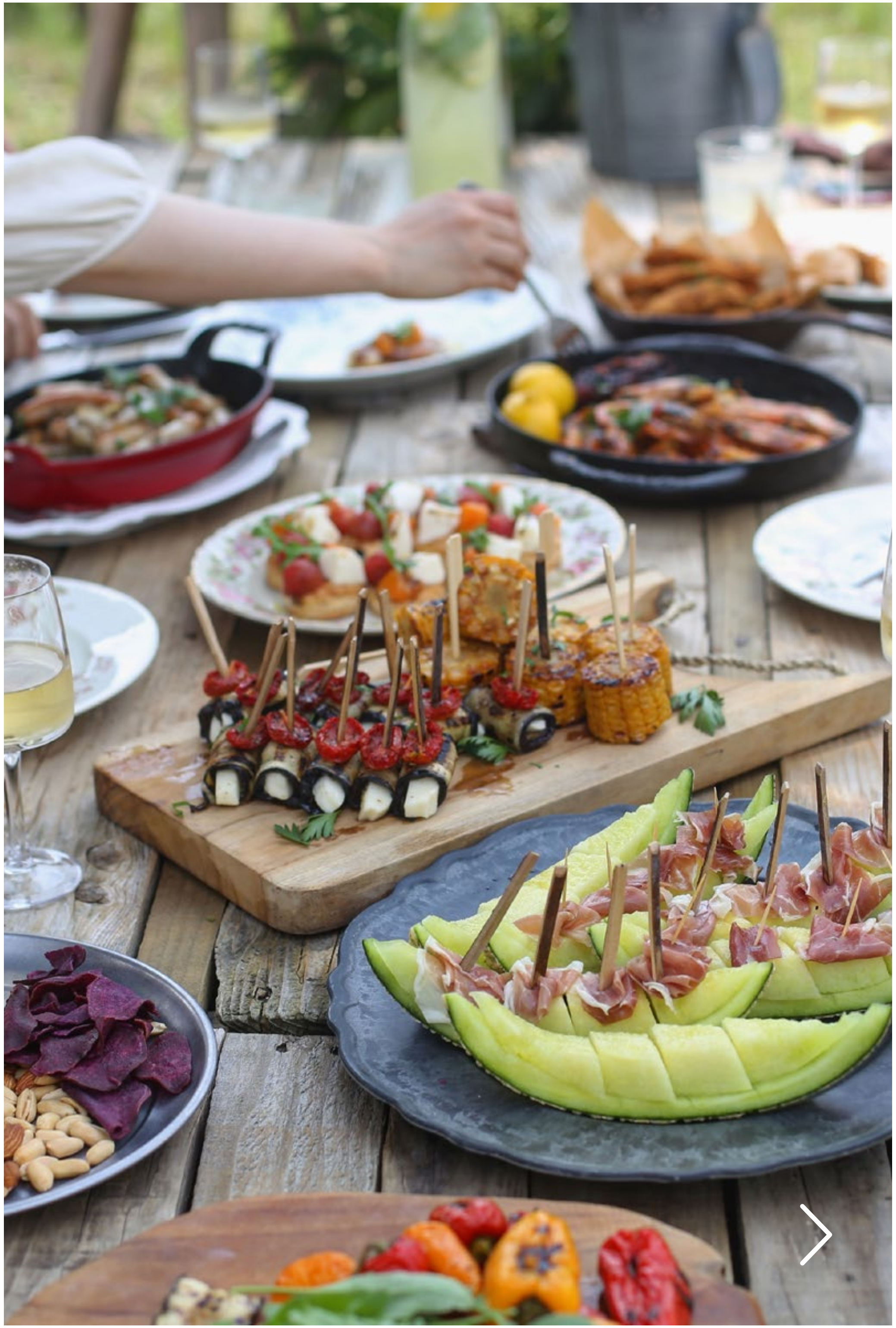
Encouraging an overall healthy dietary and lifestyle pattern is the focus of recent nutritional guidelines around the world. Experts suggest it's time to stop focusing on individual nutrients and to start communicating the benefits of a pattern that includes both healthier eating behaviours and regular physical activity. Such a lifestyle pattern supports a healthy body weight and can help prevent or reduce the risk of chronic diseases. A number of dietary behaviours have been linked to a better-quality diet including the use of low calorie sweeteners (LCS) and of foods and drinks containing them to help reduce excess sugars intake, according to recent studies.

This chapter aims to present recent data linking the use of LCS with a higher quality diet and to discuss the role of low calorie sweetened foods and drinks in a healthy dietary pattern in the context of recent nutritional guidelines.

Low calorie sweeteners linked to higher quality diet

The link between LCS intake and improved diet quality has been shown in a growing number of observational studies in 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)*. Some of these studies have also found a positive association with an overall healthier lifestyle including, for example, higher levels of physical activity *(Drewnowski and Rehm, 2014)*.

Aiming to examine the health habits of LCS 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 LCS consumers had much higher scores on the Index than those who did not consume LCS. **Consumers of LCS 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, LCS users had a better diet quality as illustrated in Figure 1. The same study also showed that individuals who consume LCS were less likely to smoke and tended to be more physically active. In all, this study suggests that LCS consumption correlates with an overall better and healthier diet and lifestyle.



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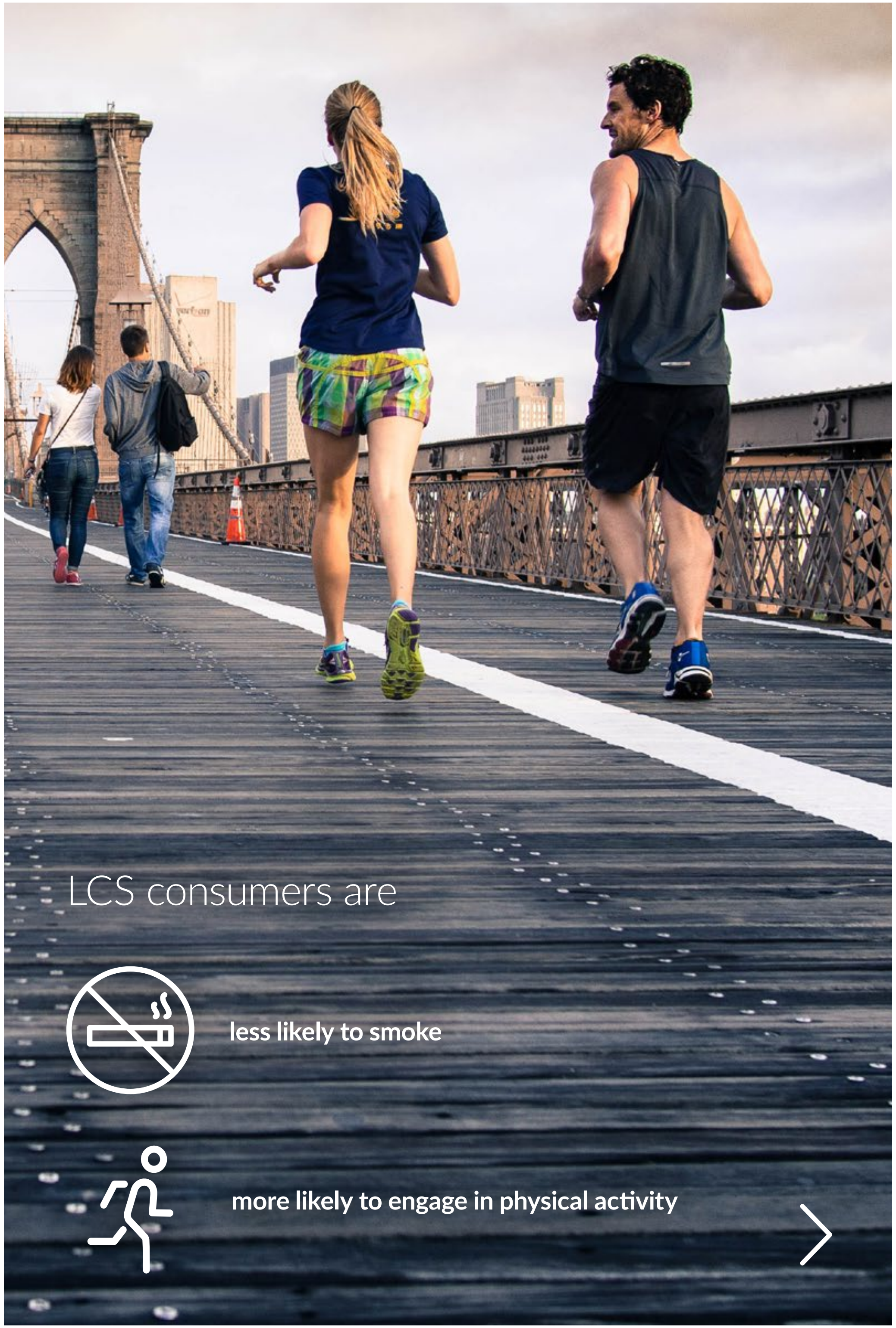
LCS consumers have better diets

Figure 1: Higher Healthy Eating Index in consumers of low calorie sweeteners vs. non-consumers.
Source: Center for Public Health Nutrition, University of Washington



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These findings were confirmed in a later study by Leahy et al., who used data from the National Health and Nutrition Examination Survey (NHANES) 2001–2012 in 25,817 adults and found that **higher consumption of low calorie sweetened drinks was associated with significantly lower intakes of carbohydrates, total and added sugars** *(Leahy et al, 2017)*. Also, in a smaller US sample of rural Virginian adults, a randomised controlled trial (RCT) found that LCS consumers had significantly higher overall dietary quality than non-consumers, as assessed via the Healthy Eating Index *(Hedrick et al, 2017)*. In this RCT, healthier dietary behaviours for LCS consumers versus non-consumers included significantly lower intakes of total daily energy, total beverage energy, sugary beverages, total and added sugar and energy density (kcal/g).

Similarly, a UK study published in early 2016, which examined data from 1590 participants of the UK National Diet and Nutrition Survey (NDNS), found that consumers of low calorie sweetened drinks had a better diet quality compared to consumers of sugar sweetened beverages (SSBs) and similar to non-consumers of SSBs *(Gibson et al, 2016)*. **The LCS group had higher fish, fruits and vegetables intake, and lower meat, fat and saturated fat as well as lower sugar intake, compared to SSBs consumers.** Furthermore, diet drink consumers had an identical mean total energy intake (1719 kcal/ day) as non-consumers (1718 kcal/day) and a significantly lower energy intake compared to SSBs consumers (1958 kcal/day) and consumers of both type of beverages (1986 kcal/day). These findings were confirmed in a subsequent analysis of recent NDNS data (NDNS 2008-2012 and 2013-2014) in 5,521 British adults, which found that consumers of low calorie sweetened beverages had lower total and free sugars intake and an overall better diet quality, compared to consumers of sugar-sweetened beverages (SSB) *(Patel et al, 2018)*.

In another study analysing data from the Brazilian National Dietary Survey (2008–2009) in order to examine the dietary habits of consumers of sugar and of table-top sweeteners containing LCS in a representative sample of 32,749 individuals over 10 years old, it was shown that the mean daily energy intake of individuals using only sugar was approximately 16% higher than those who used table-top sweeteners exclusively *(Silva-Monteiro et al, 2018)*. On average, the use of sugar to sweeten foods and beverages was accompanied by an increase of 186 kcal daily, corresponding to a 10% increase in total energy intake. Furthermore, **individuals who reported exclusive use of LCS to sweeten their foods and drinks had also lower consumption of sugar-sweetened beverages, sweets and desserts, and higher consumption of vegetables and fruits, compared to those who used sugar, indicating a dietary pattern of higher quality for LCS users.**

The above findings are also in line with outcomes of earlier studies in different population groups *(Hedrick et al, 2015)*. In the Lebanese National Nutrition and Non-Communicable Disease Risk Factor Survey (2009), a study examining data of a nationally representative sample of 2,048 Lebanese adults aged 20-55 years, the consumption of diet sodas was associated with a prudent-type dietary pattern, characterised by higher consumption of fruits, vegetables, whole grains, and fish *(Naja et al, 2011)*. Similarly, in the SUN (Seguimiento Universidad de Navarra) study in Spain, in a sample of 15,073 university graduates, increased consumption of diet beverages was associated with a Mediterranean dietary pattern, while decreased consumption was associated with a Western dietary pattern *(Sánchez-Villegas et al, 2009)*.

Low calorie sweeteners and higher diet quality go hand-in-hand: Consumers of low calorie sweetened foods and drinks tend to have better quality diets with less sugar-containing food products

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Low calorie sweeteners frequently used in weight management efforts as part of a healthy diet

The observation that LCS are more frequently consumed by overweight and obese individuals or by people with diabetes has been shown in several studies; as also discussed in chapter 4, this is a rather reasonable finding given that these groups of individuals usually turn to LCS in their efforts to manage their body weight and/ or their blood glucose levels *(Lohner et al, 2017)*. In fact, recent studies have provided evidence supporting that, indeed, people being in a weight-loss effort or who overall are mindful of and wish to manage their body weight or their glucose control are using low calorie sweetened foods and drinks more often *(Drewnowski and Rehm, 2016; Grech et al, 2018)*.

In a study published in 2016, Drewnowski and Rehm concluded that the intent to lose or maintain body weight was one likely predictor of current LCS use and that their use was tied directly to dieting behaviors, regardless of whether the participants were overweight or obese. This study merged National Health and Nutrition Examination Survey (NHANES) dietary intake data with retrospective weight control histories, a rarely exploited resource within NHANES (data from five NHANES cycles in a representative US sample of 22,231 adults) *(Drewnowski and Rehm, 2016)*. The findings confirm the main hypothesis that **trying to lose or maintain body weight was associated with higher LCS use, independent of body weight.** Specifically, it was found that individuals who tried to lose weight during the past year were 64% more likely to consume any type of LCS product. Similar results were obtained with the 'trying to not gain weight' variable. Furthermore, LCS use was much more common among individuals who experienced significant weight change in the preceding 10 years as compared with those who did not. This new finding confirms what has been assumed for years, that **people troubled by weight management issues integrate LCS in their diets as a strategy for weight control.**

The link has also been shown in a recent analysis of dietary and physical activity data from the National Nutrition and Physical Activity Survey (NNPAS), 2011–12, in 12,153 Australian individuals, which found that **LCS consumption in adults was associated with being on a weight-loss diet and with self-reported diabetes status** *(Grech et al, 2018)*.

Other studies have suggested that **LCS are used as a strategy to manage sweet tooth and to successfully reduce energy intake when in a state of craving, as well as by successful "weight loss maintainers".** In a 2014 online survey by Catenacci et al., the consumption of LCS was higher among individuals who have not only lost weight but who also kept it successfully off. Weight loss maintainers stated that they try to manage their energy intake by choosing foods and drinks containing LCS instead of caloric sweeteners. These consumers have also been found to follow higher-quality, more balanced diets and to get more physical activity *(Catenacci et al, 2014)*.

Furthermore, in an ongoing study being conducted by the University of Liverpool, UK, which examines the "psychology of dieting" and how LCS beverages may help dieters in achieving their goals, preliminary data that have been presented at the European Congress on Obesity in Porto, Portugal, suggest that the consumption of diet drinks sweetened with LCS may help dieters to control food intake when in a state of craving, and also to align potentially conflicting goals of dieters, i.e. pleasurable eating and weight control *(Maloney et al, unpublished data presented at ECO 2017)*.

When combined with a healthy diet, being physically active and adopting a healthy lifestyle, using low calorie sweeteners to reduce calories can be a winning strategy for improved weight management and better health.

Recommendations about the use of low calorie sweeteners as part of a healthy diet

Health organisations globally recognise that LCS can be safely used to replace sugars as part of a healthy eating plan.

In a position statement issued in 2012, **the US Academy of Nutrition and Dietetics states that LCS, when used in place of nutritive sweeteners, may help consumers limit carbohydrate and energy intake as a strategy to manage blood glucose or body weight** *(Fitch et al, 2012)*. Overall, the Academy concludes that *"consumers can safely enjoy a range of nutritive and non-nutritive sweeteners when consumed within an eating plan that is guided by current federal nutrition recommendations, such as the Dietary Guidelines for Americans and the Dietary Reference Intakes, as well as individual health goals and personal preference"*.

More recently, **the British Dietetic Association (BDA) concluded in a policy statement that opting for an LCS may assist in weight control and in the management of other health conditions such as diabetes mellitus in some individuals in the context of a dietetic intervention and a tailored individualised approach** *(BDA, 2016)*.

Similarly, in a scientific statement from the American Heart Association and the American Diabetes Association it was concluded that, limiting added sugars is an important strategy for supporting optimal nutrition and healthy weights, and that, **when used judiciously, LCS could facilitate reductions in added sugars intake, thereby resulting in decreased total energy and weight loss/weight control, and promoting beneficial effects on related metabolic parameters, as long as there is no compensatory increase in energy intake from other sources** *(Gardner et al, 2012)*.

In line with health organisations in the US and the UK, the position statements of the Mexican Society of Cardiology and the Mexican Society of Nutrition and Endocrinology support that the use of LCS in situations that affect cardiovascular health, such as obesity, diabetes, metabolic syndrome and dyslipidemias can be an alternative to reduce simple carbohydrates in the context of an overall treatment *(Alexanderson-Rosas et al, 2017; Laviada-Molina et al, 2017)*.

With regard to nutritional guidelines, in the publication of a recent Ibero-American Consensus paper, a group of experts concluded that foods and beverages with LCS could be included in dietary guidelines as alternatives to products sweetened with free sugars, and that this could encourage product reformulation by the food industry and help in achieving sugar reduction at a population basis *(Serra-Majem et al, 2018)*. For example, dietary recommendations from several countries refer to foods and beverages containing LCS as possible alternatives to products sweetened with caloric sweeteners to promote the reduction of free sugars' consumption.

In Food-Based Dietary Guidelines: Recommendations about consumption of low calorie sweetened foods and drinks

Food-based dietary guidelines recognise that a healthy and balanced diet is more than just nutrient requirements and aim to encourage a holistically healthy eating pattern which should be based on fruits, vegetables and wholegrains, nuts and pulses, fish and low-fat dairy products and urges people to cut down on the amount of foods high in saturated fat, salt and sugar. The role of low calorie sweetened foods and drinks in helping to meet these guidelines has been acknowledged in the recommendations of different European countries including of Belgium, Germany, Spain and the United Kingdom.

United Kingdom

The latest UK dietary guidelines launched by Public Health England (2016) and called *"The Eatwell Guide"*, state that by replacing sugary foods and drinks with low calorie sweetened options, people can reduce sugar intake while still keep enjoying the desired sweet taste in their diet. As such, LCS 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.

Germany

In the German recommendations issued by the German Nutrition Society (Deutche Gesellschaft für Ernährung (DGE), 2013), it is stated that LCS are safe and that for people who want to lose weight, they can be a good alternative in the context of a balanced diet.

Belgium

In 2017, the Belgian National Health and Nutrition Plan recognises LCS as an option to reduce calories and recommends opting for low calorie sweetened beverages instead of sugar-sweetened drinks as an alternative source of hydration, with water being the preferred hydration mean (Plan National Nutrition Santé, 2017).

Spain

In Spain, dietary guidelines and food guides developed by national and regional nutrition associations have been adopted by the Ministry of Health. In the latest nutritional guidelines for the Spanish population issued by the Spanish Society of Community Nutrition, low calorie sweetened beverages are suggested as a solution that allows people to consume less sugar while offering sweet taste, without bringing in calories *(Grupo Colaborativo de la Sociedad Española de Nutrición Comunitaria (SENC) 2016).*

In conclusion...

When it comes to nutrition, looking at the diet quality as a whole rather than focusing on individual ingredients or single foods is the right approach. Also, dietary intervention strategies aimed at improving diet quality should also consider the sensory pleasure response to foods. Dietitians and nutritionists always emphasise the importance of enjoying the food we eat while aiming for a healthier diet at the same time; however, reducing sugar intake may sometimes go against the first. In this context, low calorie sweeteners can help replace some of the sugars while still keeping the enjoyment of sweet taste in the diet. But as goes with every single food ingredient, LCS should be consumed alongside an overall healthy diet.

As part of an overall healthy dietary pattern, low calorie sweeteners can provide a means to help reduce energy and sugar intake and can be a useful tool to people with weight management problems and to persons living with diabetes.

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Contributors

Renowned scientific experts participating in the Scientific Advisory Panel on Sweeteners supported by the International Sweeteners Association (ISA) have reviewed and assisted in editing the content of this booklet and provided answers to the most frequently asked questions about low calorie sweeteners. The Panel provides independent scientific advice to the ISA on the science related to low calorie sweeteners and is comprised of academic experts and researchers working in the areas of food science and nutrition, toxicology, epidemiology and public health, nutrition psychology and eating behaviour, obesity and metabolic diseases.

Scientific Advisory Panel on Sweeteners supported by the International Sweeteners Association (ISA), 2018:

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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 Gerhard Eisenbrand, University of Kaiserslautern, Germany (honorary Professor)

Gerhard Eisenbrand graduated from the Pharmacy and Food Chemistry department of the University of Freiburg/Breisgau in 1967. His PhD Thesis was obtained at DFG Res Group Preventive Medicine, Max-Planck-Institute for Immune Biology Freiburg in 1971. From 1972 until 1981, he has been Senior Scientist at the Institute of Toxicology and Chemotherapy, at the German Cancer Research Centre, in Heidelberg, Germany. Gerhard Eisenbrand has been a Full Professor (1982-2009) and Head of the Division of Food Chemistry and Toxicology at the Department of Chemistry of the University of Kaiserslautern, and a Senior Research Professor from 2009 until his retirement in 2013.

His main research interests include: Molecular Toxicology; Mechanisms of Genotoxicity and Carcinogenicity; Risk Assessment; Food Chemistry and functional effects of Food Constituents, Biomarkers; Action mechanisms of genotoxic agents; Experimental chemotherapy and anticancer drug research.

Dr Marc Fantino, CREABio Rhône-Alpes, 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 a clinical research organization, CREABio Rhône-Alpes®. In this centre, applied research is implemented in the fields of the sensorial and metabolic processes which control feeding behaviours and body weight regulation in humans. Different behavioural, neurophysiologic and pharmacological approaches are developed.

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Prof Alison Gallagher, Professor of Public Health Nutrition, Ulster University, Northern Ireland, UK

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), she was the first Fellow of the Association for Nutrition (FAfN) on the island of Ireland. An active member of the Nutrition Society, she currently co-Chairs the Science Committee for the next FENS European Nutrition Conference (www.fens2019.org). 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 medical degree from the University of Milan and a Master of Science degree in 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 2050 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, H index 155, H10 index 1577, second Italian in Clinical Medicine). Currently, Dr. La Vecchia is an Adjunct Professor of Medicine at Vanderbilt Medical Centre and the Vanderbilt-Ingram Cancer Centre (2002-18).

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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 small-scale 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'.

About the ISA

The International Sweeteners Association (ISA) is an international non-profit organisation with scientific aims representing suppliers and users of low calorie sweeteners. Established over 35 years ago, the ISA is recognised by the European Commission, national and international regulatory authorities, and the World Health Organization, and has Non-Government Observer status with the Codex Alimentarius Commission which establishes international food standards.

The ISA aims to inform and to educate on the most up-to-date nutritional and scientific information in relation to the role and benefits of low calorie sweeteners, and the foods and beverages that contain them. The ISA also encourages research into, and enhances understanding of the role that low calorie sweeteners can play in achieving a balanced diet.

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www.sweeteners.org