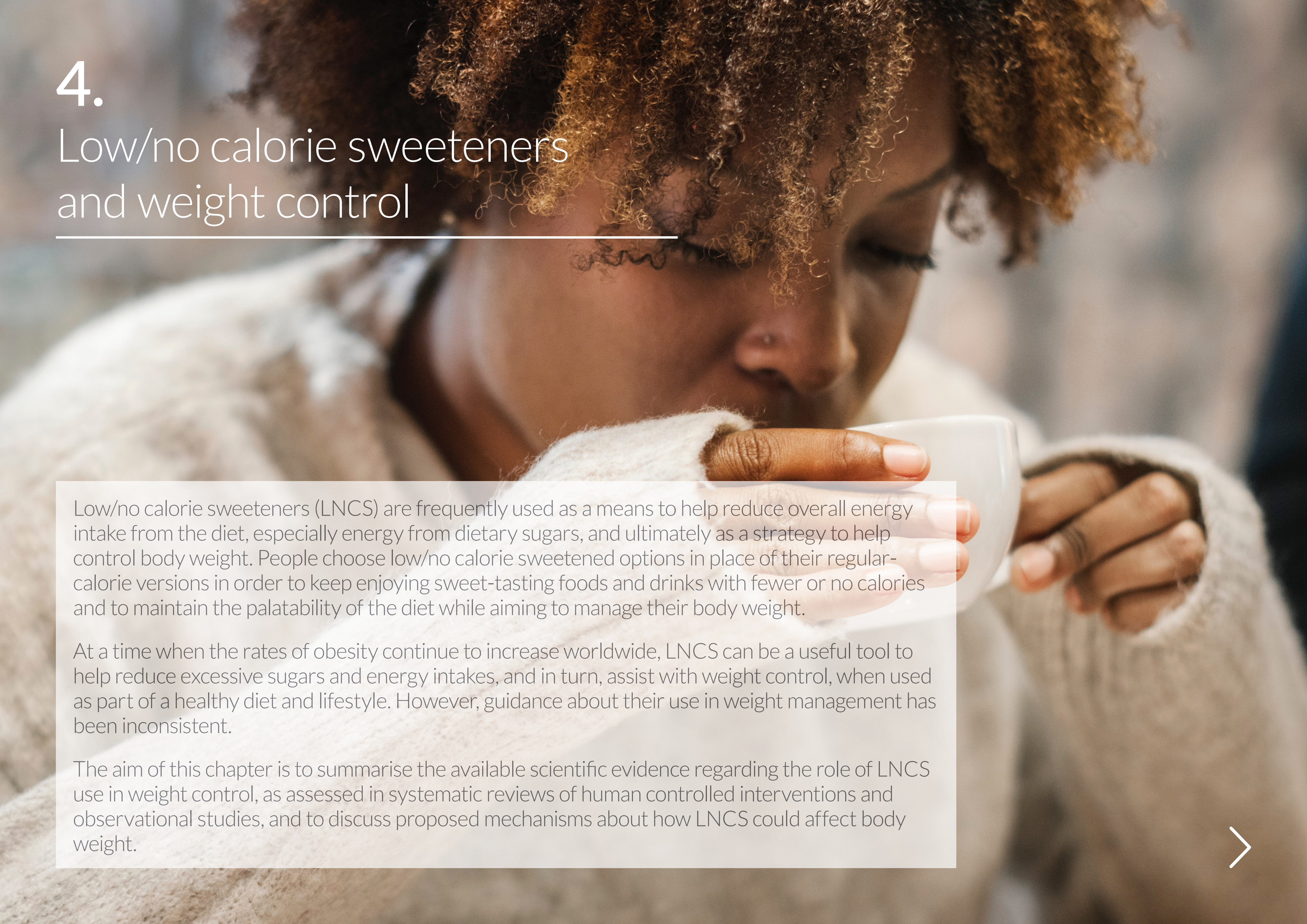


4.
Low/no calorie sweeteners and weight control

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

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

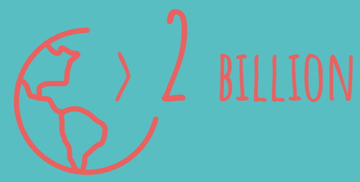
The aim of this chapter is to summarise the available scientific evidence regarding the role of LNCS use in weight control, as assessed in systematic reviews of human controlled interventions and observational studies, and to discuss proposed mechanisms about how LNCS could affect body weight.

Introduction

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

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

Facts about overweight and obesity



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

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

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

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

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

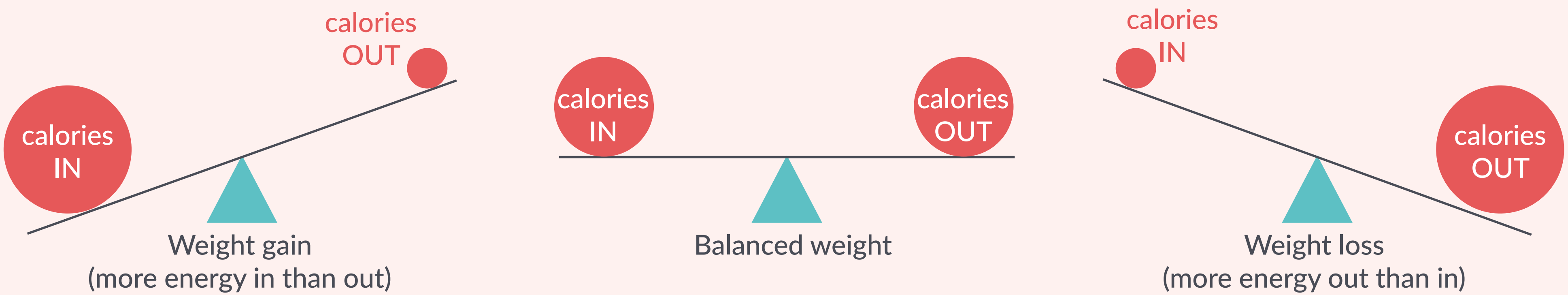

Figure 1: The impact of energy balance (calories in – calories out) on body weight.

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

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

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

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

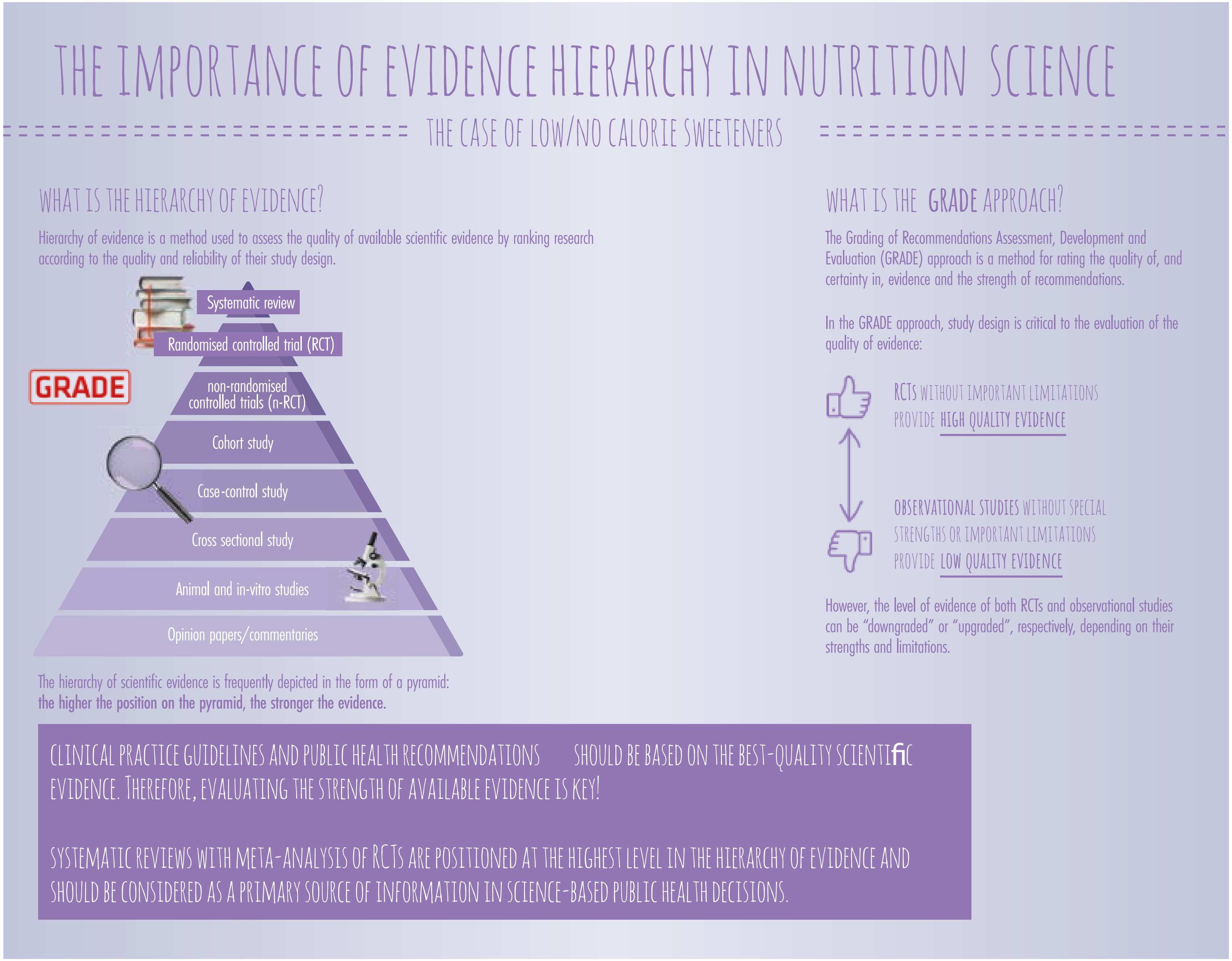

Figure 2: The importance of evidence hierarchy in nutrition science (Source: ISA Infographic).

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

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

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

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

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

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

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

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

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

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

*Systematic review with network meta-analysis

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Evidence from systematic reviews of observational studies

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

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

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

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

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

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

Energy intake and food reward

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

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

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

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

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

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

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

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

Gut microbiota

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

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

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

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

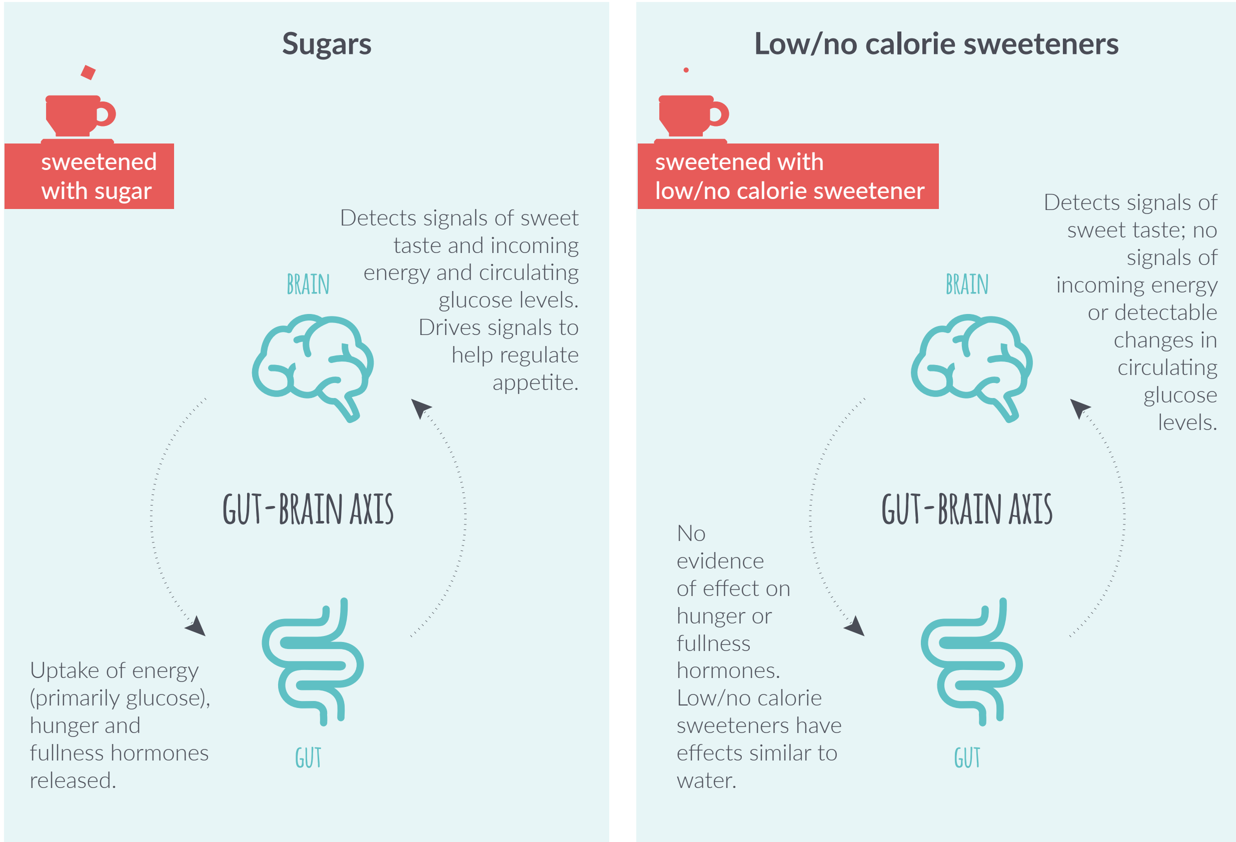

Figure 3: Different effects of sugars and of low/no calorie sweeteners on gut hormones involved in appetite control (Bryant and McLaughlin, 2016).

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

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

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

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

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

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

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

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

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

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

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

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

click here for Figure 4

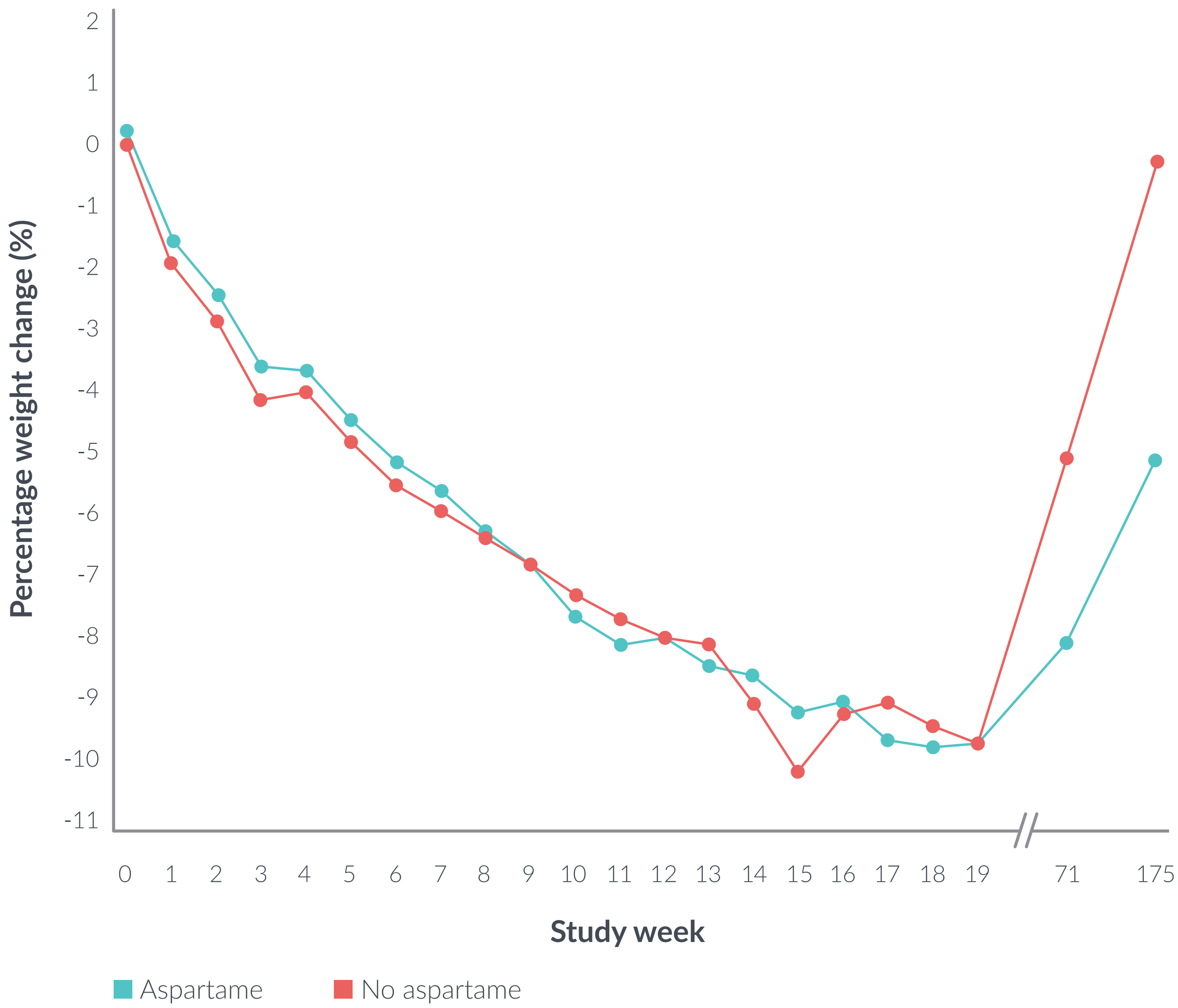

Figure 4: Percentage change in body weight over 175 wk for women (N=163) participating in a comprehensive weight-control programme with and without aspartame-containing products upon 19 weeks of active weight loss followed by a 36-month weight loss maintenance and follow-up period. (Blackburn et al,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

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

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

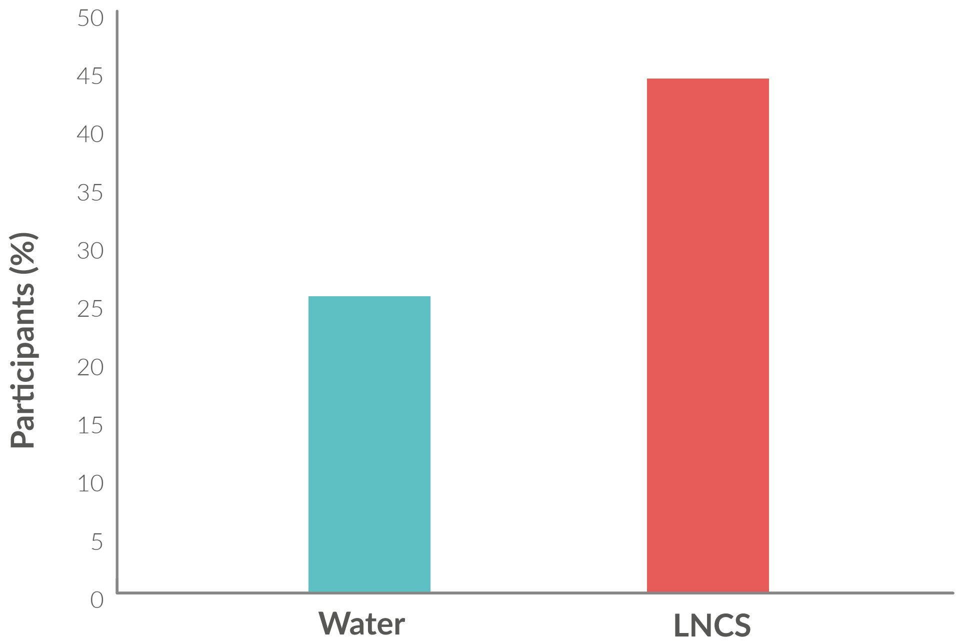

Figure 5: Percentage of participants who achieved at least 5% weight loss. Results based on X2 analysis. N=154 for LNCS, n=149 for water. *P < 0.001 (Peters et al, 2016).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

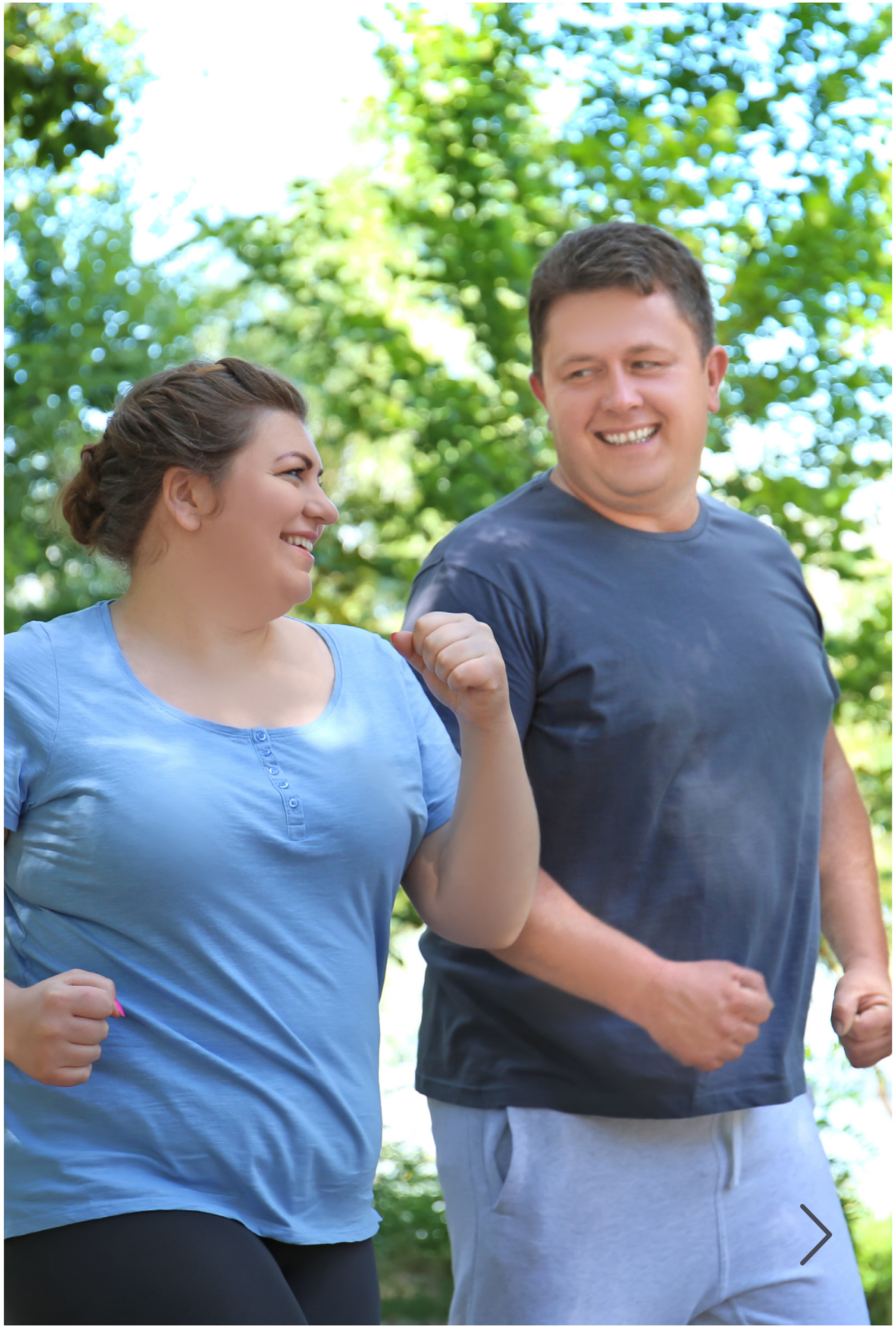
Prof Alison Gallagher: Where substitution of sugar-sweetened products for LNCS-sweetened equivalents are made there is clear evidence that an overall reduction in energy intake can be achieved. Furthermore, because such energy reductions are achieved without a reduction in overall dietary sweetness or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

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

Conclusion

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

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



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