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FOOD FOR THOUGHT 2023

Non-sugar sweeteners: helpful or harmful? The challenge of developing intake recommendations with the available research

Valisa Hedrick and colleagues argue that current evidence on non-sugar sweetener intake is inadequate, and further research is needed to determine the health effects of individual non-sugar sweeteners, especially in specific population subgroups

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Key messages

- Non-sugar sweeteners are widely found in the global food supply and are commonly used to replace added sugars in the diet
- Recommendations surrounding non-sugar sweetener consumption are inconclusive and conflicting, with scarce evidence on long term effects
- Several factors contribute to uncertainty about the health effects of non-sugar sweetener consumption, particularly differences in study design, methods, and interpretation of findings
- Additional research is needed to inform conclusive recommendations for or against the use of non-sugar sweeteners
- Guidelines for non-sugar sweetener use should consider individual types of sweeteners and specific population subgroups such as children, pregnant and breastfeeding women, and people with diabetes

Non-sugar sweeteners are commonly used as replacements for added sugars, both in the general population and among people with obesity and diabetes. Because of ongoing efforts to lower added sugar intake, non-sugar sweeteners have become ubiquitous in the global food supply. The global market for non-sugar sweeteners is expected to grow, with a predicted market value of more than $408bn in 2032—a growth of 7.2% in 10 years.[1] Although their use is widespread and increasing, there is uncertainty about their health effects, which has led to inconclusive recommendations for or against their consumption.

The challenge of developing conclusive intake recommendations for non-sugar sweeteners is particularly timely: in May 2023, the World Health Organization released a guideline for people without diabetes that recommended against using non-sugar sweeteners for weight control and prevention of non-communicable diseases.[2] Notably, the WHO guideline did not provide recommendations for people with diabetes, who make up around 10% of the world's population and commonly use non-sugar sweeteners as a tool for maintaining glycaemic control.[3] Because of the limitations of the available research, however, the WHO guideline is considered conditional and is based on evidence of low certainty. The limitations of the research are not specific to the WHO guideline and pervade existing recommendations. This underscores the need for additional research to inform more conclusive guidance tackling the health effects of individual types of non-sugar sweeteners, and to focus on examining their effects in specific population subgroups.

Considerations for interpreting the WHO guideline

While the guideline took a cautious approach in recommending against non-sugar sweeteners because of the overall contradictory evidence and possible long term unfavourable health effects of their consumption, it acknowledges that shorter term randomised controlled trials showed improvements in body weight and reductions in energy intake with non-sugar sweetener consumption. Meanwhile, observational studies demonstrated long term detrimental impacts of consuming non-sugar sweeteners, including increased risk of obesity, type 2 diabetes, cardiovascular diseases, and mortality. The guideline relies largely on observational studies rather than randomised controlled trials—however, while observational studies provide information on long term health outcomes they are inherently limited by reverse causality and residual confounding and cannot be used to infer causality.

A stated limitation of the WHO guideline was the inability to assess health impacts of different types of non-sugar sweeteners because of a lack of available research. Because non-sugar sweeteners are heterogeneous compounds (for example, sucralose, aspartame, or saccharin) that may affect different metabolic pathways and have diverse impacts on health (fig 1),[4] it is important to consider individual types and specific combinations of sweeteners (such as sucralose and acesulfame potassium together) when developing recommendations. This is not currently feasible, however, because few studies have examined and compared effects of individual types of non-sugar sweeteners. For example, only four randomised controlled trials included in the WHO report examined individual types of non-sugar sweeteners, and subgroup analyses for different types of sweeteners were not conducted for glycaemic control or lipid outcomes. In subgroup analyses for other health outcomes (such as body weight, body mass index, and energy intake) no significant differences were observed across types of non-sugar sweeteners. Studies that compared all types of non-sugar sweeteners were, however, not available.

The WHO guideline noted that although non-sugar sweeteners are different chemical entities, they could have similar impacts on health because of their high intensity sweetness and activation of sweet taste receptors. However, other mechanisms of affecting health could vary.

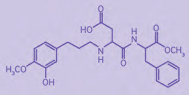
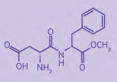
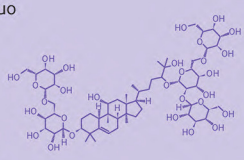
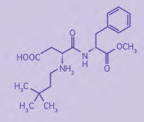
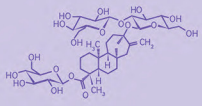
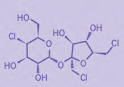
Non-sugar sweeteners	Chemical structure	Method of absorption and circulation‡	Method of excretion‡	Common names or brands	Sweetness compared with sucrose	ADI§ (milligrams per kilogram of body weight a day)
Acesulfame potassium (acesulfame K)		Absorbed acesulfame K is distributed through the blood to tissues throughout the body. Once ingested it is rapidly, and almost completely, absorbed into systemic circulation	Excreted primarily through the kidneys into urine	Sunett Sweet One	200 times	15 (FDA) 0-15 (JECFA)
Advantame		Rapidly but poorly absorbed in the gastrointestinal tract	Main excretion route is faeces (80%) and urine	No brand names	20 000 times	32.8 (FDA) 0-5 (JECFA)
Aspartame		Broken down in gastrointestinal tract to aspartic acid and phenylalanine. Absorption then occurs in the gastrointestinal lumen and in the small intestinal mucosal cells. Phenylalanine in aspartame has been slightly modified by adding a methyl group which gives aspartame its sweet taste. The methyl group from the modified phenylalanine is released in the gut to form methanol. Methanol is also absorbed by the body and most of it used to produce energy. Never found circulating in the blood and the absence of aspartame in the breast milk of lactating women consuming aspartame was recently confirmed	The three digestion products follow their normal metabolic pathways, being broken down further, taken up by tissues in the body, or excreted in urine	Equal NutraSweet Sugar Twin	200 times	50 (FDA) 0-40 (JECFA)
Cyclamate*		Most humans convert only small amounts of cyclamate to cyclohexylamine. Partially absorbed in gastrointestinal tract	Excreted in urine and faeces	Sweet'n Low and Sugar Twin in Canada	30-50 times	0-11 (JECFA)
Luo han guo		Mogrosides reach the colon, gut microbes cleave off the glucose molecules and use them as an energy source. Degraded by enzymes in the gastrointestinal tract, and minor amounts are absorbed into the bloodstream	Excreted in faeces as mogrol (study performed in rats)	Monk fruit	100-250 times	Not specified
Neotame†		Metabolised in the gastrointestinal tract by esterase into de-esterified neotame and methanol	Excreted in the urine and faeces within 72 hours. Smaller amounts in urine	Newtame NutraSweet	7000-13 000 times	0.3 (FDA) 0-2 (JECFA)
Saccharin		Saccharin cannot be metabolised by the body. Slowly and incompletely absorbed from the gastrointestinal tract into systemic circulation	Rapidly eliminated through urine, leading to a reduction in its concentration in plasma	Sweet'N Low	200-700 times	15 (FDA) 0-5 (JECFA)
Steviol glycosides		Hydrolysis in the colon to form steviol, then transported to the liver to form steviol glucuronide, and then enters systemic circulation to reach the kidneys	Excreted in the urine	Stevia	200-400 times	4 (FDA) 0-4 (JECFA)
Sucralose		Around 10-30% is absorbed. Historically regarded as not being metabolised, but this has recently been challenged	Majority of ingested sucralose is not absorbed and is excreted unchanged in faeces. A small percentage of absorbed sucralose is excreted in urine	Splenda	650 times	5 (FDA) 0-15 (JECFA)

Fig 1 | Overview of commonly used non-sugar sweeteners

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Uncertainty because of limited research pervades recommendations

Uncertainty surrounding the role of non-sugar sweeteners in weight management and chronic disease is also highlighted in other recommendations. For example, the dietary guidelines for Americans (DGA) 2020-2025 suggest using non-sugar sweeteners to replace caloric sweeteners, but state that long term use is discouraged, despite minimal research to support this recommendation.[5] The 2020 scientific report of the DGA committee,[6] which informs DGA, included only one study that examined specific types of non-sugar sweeteners.[7] The American Diabetes Association (ADA) 2023 standards of care in diabetes state that products with non-sugar sweeteners may be an acceptable alternative to sugar sweetened products when consumed in moderation, and indicate that non-sugar sweeteners do not seem to significantly affect glycaemic control, although their impact on weight management is unclear.[8] The ADA recommendations are, however, also based on research that did not examine all types of non-sugar sweeteners (for example, there were no studies on acesulfame potassium, which is widely found in foods and beverages).[8]

The American Heart Association and ADA 2012 joint statement said that there is no clear conclusion regarding the effects of non-sugar sweeteners on appetite, energy intake, body weight, cardiometabolic risk factors, or the reduction of added sugars, and highlights the need for research that examines individual types of non-sugar sweeteners and specific population groups.[9] Finally, while the Academy of Nutrition and Dietetics practice guidelines for adults with type 1 and type 2 diabetes (2017) tackled individual types of non-sugar sweeteners for managing glycaemia in adults with diabetes, a stated limitation was the minimal number of long term studies to inform findings.[10] The report concluded that adults with diabetes should be informed that intake of aspartame, sucralose, and steviol glycosides, within the ADI levels, will not have a significant influence on glycaemic control; yet, no studies were included that examined saccharin, acesulfame potassium, and neotame intake on glycaemic outcomes in this population.

Guidance is lacking for key population subgroups

Evidence to inform recommendations is particularly scarce in certain subgroups, such as those who are pregnant or breastfeeding, who widely consume non-sugar sweeteners.[11 12] This is concerning because recent evidence in humans shows that non-sugar sweeteners are transferred through amniotic fluid and breast milk to fetuses and infants.[13 14] While the effects of early life exposure to non-sugar sweeteners on health are not well understood,[15] this represents an important area for future research, especially given the potential for lasting impacts on taste preferences, dietary patterns, and metabolic risk factors.

There is also a dearth of available evidence in children, who may be more susceptible to the effects of non-sugar sweeteners because of greater relative exposure in terms of intake per kilogram of body weight and the fact that they are still developing.[16] Exposure to non-sugar sweeteners early in life is associated with increased body fat and cardiometabolic risk factors in observational studies,[17] although consumption of non-sugar sweetened beverages resulted in less weight gain relative to beverages with added sugar among children in a randomised controlled trial.[18] In the absence of strong scientific evidence, the American Academy of Pediatrics advocated for manufacturers to disclose amounts of non-sugar sweeteners on food packages and reinforced that more data are needed, especially related to long term intake.[19]

Challenges of research into sweeteners

Uncertainty regarding the health effects of non-sugar sweeteners in the general population is attributable to several aspects. Key factors include grouping non-sugar sweeteners as a single entity rather than individual chemical compounds or using low calorie soft drinks as a proxy for non-sugar sweetener intake; limited experimental research conducted in humans; discrepancies in the outcomes and findings of observational and randomised controlled trials; differences in the type, dose, and routes of non-sugar sweetener intake; inherent limitations of observational studies; and the use of study designs that are unable to attribute findings specifically to non-sugar sweetener intake (box 1).

Box 1: Limitations of current non-sugar sweetener research methodology and interpretation

Lack of specificity in studying non-sugar sweeteners

- Non-sugar sweeteners are often studied as a group rather than as individual compounds
- Non-sugar sweeteners are, however, distinct compounds with unique pathways of absorption and metabolism; some are metabolised after ingestion while others are excreted unchanged in urine or faeces. As such, their impacts on metabolic health are likely to differ

Difficulty in accurately estimating amount of non-sugar sweetener intake

- Limitations of dietary databases in terms of specificity, especially regarding individual types of sweeteners, and difficulty keeping up to date with changes in the nutritional composition of products
- Poor ability of consumers to identify non-sugar sweeteners (listed in technical terms and in small print on food and beverage packages) and recall consumption of products with non-sugar sweeteners
- Non-sugar sweeteners are frequently hidden in ultra-processed foods and study participants are often unaware of their consumption and are therefore prone to under-report
- The number of non-sugar sweeteners in products is proprietary and manufacturers are not required to disclose this information
- Acceptable daily intakes vary depending on a person's weight
- Minimal use of validated tools to assess non-sugar sweetener intake (such as food frequency questionnaires or objective dietary biomarkers for non-sugar sweeteners)
- Few experimental studies report on adherence to the intervention or use reliable ways of measuring adherence to instructions to consume or avoid non-sugar sweeteners

Diet beverage intake as a proxy for non-sugar sweetener intake

- Diet beverage intake is often used as a proxy to identify non-sugar sweetener consumers
- This method fails to consider a variety of commonly consumed products with non-sugar sweeteners and leads to misclassification of up to 30% of non-sugar sweetener consumers[20]
- Lack of detail in dietary databases used in observational studies results in many products with non-sugar sweeteners not being captured[21]
- The types, combinations, and numbers of non-sugar sweeteners present in "diet" drinks can vary greatly between brands

Limited non-sugar sweetener research in humans available

- Randomised controlled trials examining metabolic and health effects of specific types of non-sugar sweeteners in humans are lacking
- Most randomised controlled trials on effects of non-sugar sweeteners focus on energy intake and body weight, as opposed to other metabolic risk factors
- Most randomised controlled trials have been conducted in adults, with few trials in children

- Over-reliance on findings of animal studies, which may not be translatable to humans, leads to misinterpretation or over-extrapolation of findings
- Most randomised controlled trials have relatively short follow-up; the effects, therefore, of long term or lifelong non-sugar sweetener intake are unknown

Discrepancies in findings of observational v randomised controlled trials examining non-sugar sweeteners

- Observational studies suggest detrimental impacts of non-sugar sweetener intake, including increased risk of obesity, type 2 diabetes, cardiovascular disease, and mortality
- Many randomised controlled trials and interventions demonstrate positive or neutral effects on health (primarily regarding energy intake and body weight)

Heterogeneity in the type, dose, routes of administration, and comparator in studies examining non-sugar sweetener consumption

Differences in study designs challenge interpretation and comparison of study findings:

- Studies do not include all types of non-sugar sweeteners, or use a combination or unspecified types
- Various dosages, not individualised based on participant's weight—such as ADI of milligrams per kilogram of body weight
- Different routes or sources of intake—for example, non-sugar sweeteners given in beverages, foods, capsules, or intravenously
- Differences in control or comparison group—such as comparing glycaemic response from non-sugar sweeteners with sucrose *v* nothing or water

Difficulties in isolating effects of non-sugar sweeteners

- Non-sugar sweeteners are consumed along with other foods, beverages, and dietary components. It is difficult, therefore, to attribute findings solely to non-sugar sweetener intake because of the potential confound of differences in diet across participants. Many branded food and beverage products contain two or more non-sugar sweeteners along with other added ingredients like maltodextrin—however, potential interactions between different types of sweeteners and between sweeteners and other additive and ingredient combinations is unknown
- Contamination of control groups is likely because of marked increases in the presence of non-sugar sweeteners in packaged foods
- Adherence to the intervention can be hard to achieve and can impact attrition
- Need for controlled feeding studies in multiple population subgroups

Funding considerations

- Interpretation of the existing evidence is challenged by the presence of financial conflicts of interest in studies sponsored by ingredient companies and food and beverage manufacturers, which may introduce bias, as shown for studies on health outcomes related to sugar sweetened beverage consumption

Specific to study designs, there are notable differences in observational and randomised controlled trials on non-sugar sweeteners.

Observational studies are useful as they may include many subpopulation groups, have large sample sizes, include free living participants or real world settings, and have the ability to have long term follow-up. Observational research on non-sugar sweeteners comes with unique challenges, however, such as difficulty ascertaining accurate data on non-sugar sweetener intake; non-sugar sweeteners being typically assessed as a group rather than examined as individual compounds; use of inconsistent methods of identifying and classifying consumers of non-sugar sweeteners; challenges determining causality, with the possibility of reverse causality and residual confounding; and reverse causality occurring because people with obesity tend to consume non-sugar sweeteners and are disposed to an increased risk of developing metabolic disorders.

Randomised controlled trials and interventions, when compared with observational research, are able to isolate effects of non-sugar sweetener intake while controlling for confounding factors, they can determine causality, and they have the ability to examine the impact of specific types of non-sugar sweeteners on various health outcomes. Challenges of randomised controlled trials include small sample sizes; relatively short term follow-up; ability to examine only specific populations; ethical challenges of conducting non-sugar sweetener research in some populations, such as pregnant and lactating women and young children; varying study designs causing difficulty with interpreting findings and developing conclusive recommendations; and the potential for contamination of control groups, increased attrition rate with longer studies, residual effects between interventions with crossover designs, and the high costs of conducting adequately powered, well designed studies.

Is there enough evidence to make conclusive recommendations?

Additional research is needed to inform more conclusive recommendations. We further propose that recommendations should carefully consider, when possible, how individual types of non-sugar sweeteners are, or should be, used among specific population subgroups. Additionally, we argue that the precautionary principle should be applied, which emphasises caution in the absence of conclusive scientific evidence, particularly regarding use in specific populations, such as pregnant and lactating women, young children, and those with diabetes. This is particularly important because evidence of potential harm exists; and, as highlighted in the WHO guideline, non-sugar sweeteners are not essential dietary components.

There are two points of view. At one extreme are those who rely on evidence from randomised controlled trials demonstrating favourable effects of non-sugar sweeteners on energy intake and body weight, while disregarding accumulating evidence demonstrating undesirable effects of non-sugar sweeteners from observational analyses, mechanistic studies, and small trials in humans. At the other extreme are those who rely on findings of animal models, or observational analyses or small mechanistic studies in humans showing potentially adverse effects on health and posit that non-sugar sweeteners should be entirely avoided. Given that both experimental and observational studies have important limitations, we intend to offer a more nuanced approach. We propose that while non-sugar sweeteners may offer a tool for weight management and glycaemic control in some people under certain conditions of use, widespread replacement of added sugars with non-sugar sweeteners may have unintended negative consequences, especially in some subgroups. As different types of non-sugar sweeteners may have divergent impacts on health, however, caution and further research are warranted.

Recommendations and future research directions

Targeted guidelines for specific types of non-sugar sweeteners and various population subgroups will enable clinicians to provide clear intake recommendations. Based on currently available research, people should be counselled to consume an overall healthy dietary pattern tailored to their needs. Simply switching sugar sweetened

beverages for non-sugar sweetened beverages may result in lower energy intake in the short term, but the long term effects of this approach are unclear. Health professionals should caution patients about the possibility of inadvertently compensating for reduced sugar and energy content with other foods and beverages, and they should encourage unsweetened alternatives, such as water and foods with naturally occurring sugar, such as fruit.

In order to reduce heterogeneity among studies and provide guidance on optimal study duration, non-sugar sweetener dosage, and relevant health outcomes (box 2), international health organisations could convene experts to design and critique study protocols for future non-sugar sweetener research and support efforts to develop methods to better capture non-sugar sweetener intake. It is also important that policy makers are aware of the challenges this research might present and greater allocation of resources to undertake research on non-sugar sweeteners should be considered to support more robust and longer term trials. Greater alignment in messaging around non-sugar sweeteners should also be achieved between regulatory agencies, public health organisations, and clinicians to communicate the existing evidence and support consumers in making informed food and beverage choices.

Box 2: Considerations for future non-sugar sweetener research

Types of non-sugar sweeteners

- Research should examine and specify the types of non-sugar sweeteners examined in order to isolate effects of specific sweeteners
- All types of non-sugar sweeteners should be considered, regardless of whether synthetically or naturally derived
- Dosages of non-sugar sweetener should be individualised based on participant's body weight (for example, 50% or 100% of ADI of milligrams per kilogram of body weight)

Accurate measurement of non-sugar sweetener intake

- Validated non-sugar sweetener food frequency questionnaires or dietary biomarkers should be developed and used to facilitate more precise exposure estimates of non-sugar sweetener intake
- All dietary sources of non-sugar sweetener intake (food, beverages, and packets) should be assessed and considered

Study populations

- Findings of human research should be prioritised over animal models
- Impact of specific types of non-sugar sweeteners should be examined across multiple population subgroups, such as women who are pregnant or lactating, children, and those with diabetes

Study design

- Non-sugar sweetener intake and other confounding variables such as diet, weight, and comorbidity status should be controlled or assessed in all types of research
- Both randomised controlled trials and observational research have merit, but findings should be interpreted within the context of their inherent strengths and limitations
- Controlled feeding studies are the gold standard, but are resource intensive and are unlikely to reflect real life consumption patterns
- Long term studies (for example, those greater than 3 months in duration) should be conducted
- Research is lacking on the direct impact of replacing added sugars with non-sugar sweeteners, as well as a lack of studies to assess interactions between non-sugar sweeteners and other food components and other food additives
- Study outcomes should include cardiometabolic outcomes beyond energy intake, body weight, and adiposity (such as gut microbiota, glycaemia, inflammatory cytokines)
- Comparison groups should be carefully considered and unsweetened control groups should be used where possible (for example by comparing glycaemic response from non-sugar sweeteners with sucrose *v* nothing or water)

Other considerations

- Industry funded studies should be clearly distinguished from those that are free from conflicts of interest

Implications for evidence based public policy and practice

Public health strategies to reduce added sugars in the food supply have been implemented, such as sugar sweetened beverage taxes. While they can help reduce population sugar consumption, they can encourage industries to replace sugars with non-sugar sweeteners as observed in other countries.[22] For example, continued uncertainty about the health effects of non-sugar sweeteners has caused some countries in Latin America to implement front-of-package labels to warn about their presence. Mexico was the first, with Argentina and Colombia following with similar labelling. This idea came from Chile, where a new "sugar excess" octagon symbol on the front of a food package led to increases in non-sugar sweeteners in the food supply.[23] Because of the lack of international guidelines, the development of the new front of package label in Mexico (including the non-sugar sweetener disclaimer) was justified by the need to protect the best interest of children, and the petition was based on a scarcity of studies assessing children's health outcomes associated with non-sugar sweetener intake. As a result, the disclaimer warns that the product "contains artificial sweeteners, not recommended for children." This labelling approach could help consumers make informed choices and discourage food companies from inundating the food supply with non-sugar sweeteners until there is more evidence on the consequences of frequent and long term intakes. Currently, the labelling is focused on children, but labels for other population subgroups such as women who are pregnant and those with diabetes should be considered.

Conclusion

Limitations of existing studies examining the health effects of non-sugar sweeteners leave many questions unanswered. Research examining non-sugar sweeteners as a single entity provides unclear findings related to their health effects, especially for obesity, weight management, glycaemic control, and other cardiometabolic disease risk factors. There is a need for additional long term randomised controlled trials examining impacts of individual types of non-sugar sweeteners on metabolic and health outcomes to inform more conclusive intake guidelines in the context of specific health conditions and population subgroups. In the future, a concerted effort should be made, when possible, to develop targeted guidelines for individual types of non-sugar sweeteners and specific population subgroups to provide clear and safe intake recommendations for policy makers, healthcare providers, and consumers.

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