

WHAT IS ASPARTAME?

Aspartame is a low-calorie sweetener that has been used for decades as a way to lower one's intake of added sugars while still providing satisfaction from enjoying something sweet. Aspartame is about 200 times sweeter than sugar, and as such only a small amount of the sweetener is needed to match the sweetener is needed to match the sweetenes provided by sugar. In tabletop packets and prepared foods and beverages, aspartame is often blended with other sweeteners or food components to minimize bitter flavors and enhance overall taste.

Aspartame consists of two amino acids—aspartic acid and phenylalanine. When ingested, aspartame is broken down into these amino acids for use in protein synthesis and metabolism. In addition to aspartic acid and phenylalanine, aspartame digestion also yields a small amount of methanol, a compound that is naturally found in foods like fruits and vegetables and their juices. The amount of methanol resulting from consuming an aspartame-sweetened beverage is about five to six times less than that resulting from the same volume of tomato juice.¹

Aspartame can be used as an ingredient in beverages (such as diet sodas, light or low-sugar juices and flavored waters), dairy products (such as light yogurt and low-fat flavored milk), nutrition bars, desserts (such as sugar-free puddings and gelatins, light ice cream and popsicles), chewing gum, sauces, syrups and condiments. Aspartame is also found in several types of low-calorie tabletop sweeteners. The most common brand of aspartame tabletop sweetener in the U.S. is Equal[®]. Brands outside the U.S. include Canderel® (found in Europe) and Pal Sweet® (found in Asia). In addition, some prescription and over-the-counter medications and chewable vitamins may contain aspartame to increase their palatability. Aspartame is not well-suited for use

in foods that require baking for a long time because prolonged exposure to high temperatures can cause it to lose its sweetness.

BY THE INTERNATIONAL FOOD INFORMATION COUNCIL



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IS ASPARTAME SAFE TO CONSUME?

YES. Aspartame is one of the most exhaustively studied ingredients in the human food supply, with more than 200 studies supporting its safety. The U.S. Food and Drug Administration (FDA) approved its use in dry foods in 1981, in carbonated beverages in 1983 and as a general-purpose sweetener in 1996. Leading global health authorities such as the European Food Safety Authority (EFSA) and the Joint FAO/ WHO Expert Committee on Food Additives (JECFA) conduct scientific risk assessments and safety evaluations of food additives and have concluded that aspartame is safe for its intended uses.^{2,3} Based on these conclusions and other independent reviews, government regulators around the world, including Japan's Ministry of Health, Labor, and Welfare: Food Standards Australia New Zealand; Health Canada; and the U.S. FDA permit the use of aspartame.

The FDA has established an acceptable daily intake (ADI) for aspartame of 50 milligrams per kilogram of body weight (mg/kg) per day. The EFSA has established a slightly lower ADI of 40 mg/kg per day. The ADI represents an amount 100 times less than the quantity of aspartame found to achieve a no-observed-adverseeffect-level (NOAEL) in toxicology studies. The ADI is a conservative number that the vast majority of people will not reach. Using the ADI established by the FDA, a person weighing 150 pounds (68 kg) would exceed the ADI (3,400 mg of aspartame) if consuming more than an average of 19 cans of diet soda or more than 85 individual packets of aspartame every day over the course of their lifetime. In people who report consuming aspartame, the estimated average intake is 4.9 mg/kg per day, which is less than 10 percent of the FDA's ADI.⁴ For those in the 95th percentile of aspartame consumption, intake is estimated at 13.3 mg/kg per day-still far below the FDA ADI. Globally, aspartame intake also remains well below the FDA and EFSA ADIs. A 2018 study noted that only in rare instances did individuals exceed more than 20 percent of the ADI, even in the highest-consuming groups.⁵ For more on how ADIs are set, see the "What is an ADI?" sidebar.

Although the safety of aspartame is established for intakes not exceeding the ADI, aspartame intake should be limited by people with phenylketonuria (PKU). PKU is a rare genetic disease that makes an affected person unable to properly metabolize phenylalanine, one of the amino acids found in

WHAT IS AN ADI?

The acceptable daily intake, or ADI, is the average daily intake over a lifetime that is expected to be safe for human consumption based on significant research.⁶ It is derived by determining the no-observed-adverse-effect-level, or NOAEL, which is the highest intake level found to have no adverse effects in lifetime studies in animal models, divided by 100.⁷ Setting the ADI 100 times lower than the upper level found to have no adverse effects studies helps ensure that human intakes will be safe.

aspartame and many common foods like milk, cheese, nuts and meat. Individuals with PKU need to avoid or restrict their intake of phenylalanine from all sources. All packaged foods and beverages with aspartame as an ingredient are required by the FDA to have a statement on the label informing consumers of phenylalanine's presence.

CAN CHILDREN CONSUME ASPARTAME?

YES. Aspartame metabolism is the same in healthy children as it is in healthy adults. The EFSA, FDA and JECFA have concluded that aspartame is safe for adults and children to consume within the ADI. Just like with adults, the only exception is for children with PKU who need to avoid or restrict their intake of phenylalanine.

Foods and beverages sweetened with aspartame can add sweetness without contributing to increased calorie intake, added sugars intake or risk of dental caries. With a focus on reducing consumption of added sugars in recent decades, the prevalence of daily consumption of low-calorie sweeteners among children and adults has increased since 2000.⁸ Just like intake among adults, absolute amounts of low-calorie sweeteners consumed by children is considered to be well within acceptable levels.

The American Heart Association (AHA) advises against children regularly consuming beverages containing low-calorie sweeteners, instead recommending water and other unsweetened beverages such as plain milk.9 One notable exception in the 2018 AHA science advisory is made for children with diabetes, whose blood glucose management may benefit by consuming low-calorie-sweetened beverages in place of sugar-sweetened varieties. Citing an absence of data, the 2019 policy statement from the American Academy of Pediatrics does not provide advice on children under two years of age consuming foods or beverages that contain low-calorie sweeteners.¹⁰

CAN PREGNANT AND BREASTFEEDING WOMEN CONSUME ASPARTAME?

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YES. The consumption of low-calorie sweeteners, including aspartame, within the ADI is safe for women who are pregnant or breastfeeding, according to the EFSA, FDA and JECFA. Research has shown that aspartame has no adverse effects on expecting or nursing mothers or on the fetus. Aspartame is rapidly metabolized to the amino acids phenylalanine and aspartic acid and a small amount of methanol following indestion, so it is not present in breast milk.^{11,12} All women who are pregnant or nursing need the necessary nutrients and calories for their baby's optimal growth and development, while taking care not to exceed their needs.

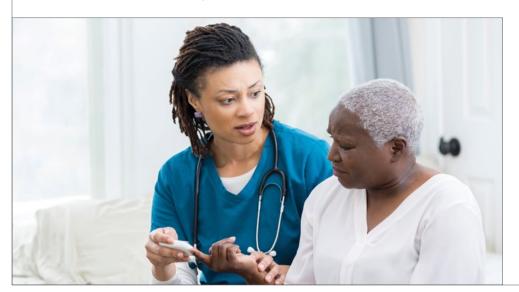
CAN PEOPLE WITH DIABETES CONSUME ASPARTAME?

YES. Foods and beverages made with aspartame are frequently recommended to people with diabetes as an alternative to sugar-sweetened foods and beverages and as a way to help them satisfy their desire for sweet taste. Extensive research shows that aspartame does not raise blood glucose levels or otherwise affect blood glucose management in humans.¹³⁻¹⁵ In a 2018 randomized controlled trial, aspartame ingestion had no effect on blood glucose or insulin levels over the 12-week intervention as compared



with a placebo.¹⁶ Recent consensus statements by experts in nutrition, medicine, physical activity and public health cite the neutral effects of lowcalorie sweeteners on hemoglobin A1C, insulin and fasting and post-prandial glucose when concluding that the use of low-calorie sweeteners in diabetes management may contribute to better glycemic control.¹⁷⁻¹⁹

Global health professional organizations have published their own conclusions on the safety and role of low-calorie sweeteners for people with diabetes. The <u>2020 American Diabetes</u> <u>Association Standards of Medical Care</u> <u>in Diabetes</u> state that "For some people with diabetes who are accustomed to sugar-sweetened products, nonnutritive



sweeteners (containing few or no calories) may be an acceptable substitute for nutritive sweeteners (those containing calories, such as sugar, honey, and agave syrup) when consumed in moderation. While use of nonnutritive sweeteners does not appear to have a significant effect on glycemic management, they can reduce overall calorie and carbohydrate intake."²⁰ Similar statements addressing the safety and potential use of low-calorie sweeteners such as aspartame for people with diabetes are supported by <u>Diabetes UK</u> and <u>Diabetes Canada</u>.²¹²²

Despite these conclusions, some studies have periodically raised questions about aspartame and blood glucose management. A few observational studies have demonstrated an association between low-calorie sweetener consumption and risk for type 2 diabetes²³⁻²⁵ but are not able to directly link cause and effect, and as with the studies on body weight and obesity, they are at risk of confounding and reverse causality. For instance, many studies do not adjust for obesity status, a direct contributor to developing prediabetes and type 2 diabetes. Given that overweight and obese individuals tend to consume more low-calorie-sweetened beverages as compared with lean individuals,²⁶ this is a critical omission.

CAN ASPARTAME HELP WITH WEIGHT LOSS OR WEIGHT MAINTENANCE?

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Substituting foods and beverages sweetened with aspartame for their full-sugar counterparts can play a role in weight loss or weight management. In a survey of members of the National Weight Control Registry, the largest longitudinal study of successful weight loss maintainers who had lost at least 30 pounds and kept if off for more than one year, over 50 percent of all respondents stated that they regularly consume low-calorie beverages, 78 percent of whom felt that doing so helped control their calorie intake.²⁷

Some observational studies have reported an association between lowcalorie sweeteners and increased body weight and waist circumference in adults.²⁸ A 2017 systematic review and meta-analysis of observational studies found that consumption of low-calorie sweeteners was also associated with increases in BMI and higher incidence of obesity and several diet-related disease conditions in adults.²⁹ In children and adolescents. observational studies have shown an association between consumption of low-caloriesweetened beverages and increased body weight, while evidence from randomized trials have not.³⁰ Many other recent systematic reviews and metaanalyses have concluded that findings from observational studies showed no association between low-calorie sweetener intake and body weight and a small positive association with higher body mass index (BMI).³¹⁻³³

It is important to note the limitations of observational studies, which examine the association between an exposure (such as aspartame intake) and an outcome (such as body weight or a health condition), and their inability to provide evidence of cause and effect. Observational studies are also at risk for demonstrating reverse causality, in which the direction of cause and effect runs counter to what one might expect. A common example of this is a person changing their diet after being



diagnosed with a health condition: The disease led to their dietary choices; the dietary choices did not lead to the disease. Additionally, observational studies are not randomized, so they cannot control for all of the other exposures or factors that may be causing or influencing results.

For example, one hypothesis is that people may compensate for "caloriefree" choices by eating or drinking more calories in other food choices or future meals.^{34,35} Think of a person who may justify ordering dessert at a restaurant because they had a diet soda with their meal: the extra calories from the dessert will be greater than the calories saved by ordering the diet beverage. These additional calories may contribute to weight gain or prevent further weight loss. This behavior is called the "licensing effect" or "self-licensing," in which an individual justifies giving into indulgences by finding reasons to make a behavior that is inconsistent with their goals more acceptable.³⁶ Although it may occur in some instances, there is little evidence from scientific studies that people consistently and consciously overconsume calories as a result of consuming low-caloriesweeteners or foods and beverages that contain them.37

It has also been suggested that people who are already overweight or obese may begin to choose low-caloriesweetened foods and beverages as one method for losing weight.³⁸⁻⁴¹ This makes it difficult to assume that the use of a low-calorie sweetener can be the cause of weight gain, since reverse causality may be a factor.

Data from randomized controlled trials, considered to be the gold

standard for assessing causal effects, support that substituting low-caloriesweetener options for regular-calorie versions leads to modest weight loss.31-^{33,42-44} In a 2016 randomized clinical trial, over 300 participants were assigned to consume either water or low-caloriesweetened beverages for one year as part of a program that included 12 weeks of weight loss followed by 40 weeks of weight maintenance interventions. Those who were assigned to the low-caloriesweetened beverage group lost 6.21 kg on average as compared with those in the water group, who lost 2.45 kg.45 And vet, other studies have concluded that low-calorie-sweetener consumption does not lead to appreciable weight loss or weight gain: a 2017 systematic review and meta-analysis of randomized controlled trials found no effect of lowand no-calorie sweeteners on body mass index (BMI) and other measures of body composition.²⁹ One key difference between these seeminaly conflicting research findings is the comparison used: as stated by Mela, et al.,⁴¹ some study designs³² allow for the analysis of

The Scientific Report of the 2020 Dietary Guidelines Advisory Committee (DGAC) included a systematic review of 37 studies (six of which were randomized controlled trials) published between January 2000 and June 2019 on the role of low- and no-caloriesweetened beverages on adiposity. The DGAC report concluded that lowand no-calorie sweeteners should be considered as an option for managing body weight.⁴⁶

outcomes between caloric and non-

caloric alternatives, while others²⁹ do not.

It is important to note that losing and maintaining body weight requires multiple simultaneous approaches. Making a single change, such as substituting low-calorie sweeteners for full-calorie, sugar-containing products is just one component. Lifestyle and behavioral practices like eating healthfully, exercising regularly, getting enough sleep, and maintaining social support networks are all important factors in achieving weight loss and weight maintenance goals.

CAN ASPARTAME MAKE ME HUNGRIER?

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Highly palatable foods activate brain regions of reward and pleasure. This positive association can enhance appetite, and if left unchecked, the resulting increase in food intake can lead to overweight and obesity.⁴⁷ Substituting full-calorie and addedsugars-containing foods with their counterparts made with low-calorie sweeteners has exhibited a similar effect on reward pathways, but without contributing additional calories.

Some have expressed concern that activating reward pathways without delivering calories to the body may have unintended consequences, and the role that low-calorie sweeteners have on appetite and food cravings is a developing area of research. As noted in recent reviews,^{28,42} some research in animal models has demonstrated changes in food intake and appetiterelated hormones after consuming low-calorie sweeteners. And yet, similar effects have not been seen in humans. To date there is no strong evidence that low-calorie sweeteners. including aspartame, enhance appetite or cravings in humans,48 and some randomized trials have demonstrated the opposite effect—including a decrease in hunger⁴⁵ and reduced dessert intake compared with those who drank water.49





These discrepancies underscore an area in which animals and humans are inherently different as research subjects. In humans, the link between physiology, psychology, personal experiences and food is unmistakably complex, and the translation of animal research to this area of study should be viewed with caution.

WHAT ABOUT THE GUT MICROBIOME?

Although research on the gut microbiome is still in its infancy, the microbes living in our intestinal tract have become recognized as potentially significant contributors to our health. Studies on aspartame's effect on the gut microbiome are lacking, and its route and location of digestion may be a factor in the lack of research. Because aspartame is digested to its component amino acids and a small amount of methanol in the small intestine, it is unlikely that intact aspartame reaches gut microbes, which predominantly cluster at the end of the intestinal tract. One animal study published in 2014 showed an interaction between type of eating pattern and aspartame consumption, in which there was an increased number of total bacteria and change in abundance of several bacterial species in rats consuming both aspartame-sweetened water and

a high-fat eating pattern compared with rats consuming a high-fat diet with plain water, standard chow diet with aspartame-sweetened water or standard chow diet with plain water.⁵⁰ One very small study in humans published in 2015 compared the microbial profiles of aspartame consumers and non-consumers.⁵¹ There were no differences in the abundance of gut bacteria, although bacterial diversity differed between groups. There are significant differences between the microbiome profiles from one person to another and research has shown that the gut microbiome changes in response to normal changes in food choices.52 A great deal of research is still needed to identify a microbiome profile and degree of diversity considered to be "optimal" in populations and in individuals. A 2019 literature review found no conclusive evidence that low-calorie sweeteners negatively impact gut microbiota.53 In 2020, a panel of experts on low-calorie sweeteners came to a similar conclusion that, at this time, data on the effects of low-calorie sweeteners on the human gut microbiota are limited and do not provide adequate evidence that they impact gut health at doses that are relevant to human consumption.¹⁹

IS IT POSSIBLE TO BE SENSITIVE TO ASPARTAME?

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Despite aspartame's safety approvals by many international regulatory authorities, anecdotal reports detailing symptoms presumed to be related to aspartame intake (most commonly, headaches) continue to surface. Only a few studies have been conducted on this possible connection, all of which are hampered by small sample sizes and methodological difficulties. In a 2016 narrative review, two of four studies found that aspartame exposure was associated with increased headache frequency, but the other two found no difference between aspartame and control groups.⁵⁴ Each of these studies used doses of aspartame that are higher than the amount normally consumed. Additionally, a 2015 United Kingdom Food Standards Agency randomized controlled trial did not find differences in physical, biochemical or psychological symptoms after consuming aspartame in self-reported "aspartame-sensitive" participants.⁵⁵ It is important to remember that aspartame is broken down in the intestinal tract to aspartic acid, phenylalanine and methanol, all of which are naturally present in other foods and beverages and in much higher quantities. This makes a biological mechanism for aspartame-specific symptoms and/or sensitivities difficult to hypothesize.

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ASPARTAME AT A GLANCE

SCIENTIFIC NAME: Aspartame

BRAND NAME: Equal®(U.S.), Canderel® (Europe), Pal Sweet® (Asia) and other store brands

DATE APPROVED BY FDA: 1981 for dry foods 1983 for carbonated beverages 1996 for all foods

WHAT'S THE BOTTOM LINE?

All types of foods and beverages can have a place in healthy eating patterns, including those made with aspartame. Aspartame has been FDA-approved since 1981, and its safety has been acknowledged by many international health authorities. However, people with phenylketonuria (PKU) should avoid or restrict their intake of aspartame (along with other sources of phenylalanine).

Aspartame's impact on and association with chronic metabolic conditions like obesity and diabetes has been extensively studied. Observational studies linking lowcalorie sweeteners to weight gain inherently cannot demonstrate a causal relationship and suffer from methodological issues like confounding and reverse causality. In addition, randomized controlled trials consistently support that lowcalorie sweeteners like aspartame can be useful in nutritional strategies to assist with weight-loss and weightmaintenance goals. Aspartame has no impact on glucose or insulin levels in randomized trials and no effect on appetite. Evidence of sensitivity to aspartame is slim, and there is no biological mechanism for aspartame-specific symptoms. Studies of aspartame's effects on the gut

microbiome have been conducted although because it is consumed in small amounts and absorbed in the small intestine, it is unlikely that intact aspartame reaches gut microbes.

Adopting a healthful, active lifestyle that is tailored to personal goals and priorities is vital to supporting one's well-being. Choosing foods and beverages sweetened with low-calorie sweeteners such as aspartame is one way to reduce consumption of added sugars and keep calories in check important components in maintaining health and reducing the risk for diet-, weight-, and lifestyle-related diseases.

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REFERENCES

International

 <u>Butchko HH</u>, Kotsonis FN. Acceptable daily intake vs actual intake: the aspartame example. *J Am Coll Nutr.* 1991 Jun;10(3):258-66.

Food Information

- 2. <u>EFSA ANS Panel</u> (EFSA Panel on Food Additives and Nutrient Sources added to Food), Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive. *EFSA Journal.* 2013 Dec;11(12):3496.
- Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and contaminants: Fifty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, Switzerland. 2001.
- Magnuson BA, Burdock GA, Doull J, Kroes RM, Marsh GM, Pariza MW, Spencer PS, Waddell WJ, Walker R, Williams GM. Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. *Crit Rev Toxicol.* 2007;37(8):629-727.
- Martyn D, Darch M, Roberts A, Lee HY, Yaqiong Tian T, Kaburagi N, Belmar P. Low-/No-Calorie Sweeteners: A Review of Global Intakes. *Nutrients.* 2018 Mar 15;10(3):357.
- World Health Organization, Food and Agriculture Organization of the United Nations. Principles and Methods for the Risk Assessment of Chemicals in Food. Chapter 5. 2009.
- <u>Renwick AG</u>. Safety factors and establishment of acceptable daily intakes. *Food Addit Contam.* 1991 Mar-Apr;8(2):135-49.
- Sylvetsky AC, Jin Y, Clark EJ, Welsh JA, Rother KI, Talegawkar SA. Consumption of Low-Calorie Sweeteners among Children and Adults in the United States. *J Acad Nutr Diet*. 2017 Mar;117(3):441-448.e2.
- Johnson RK, Lichtenstein AH, Anderson CAM, Carson JA, Després JP, Hu FB, Kris-Etherton PM, Otten JJ, Towfighi A, Wylie-Rosett J; American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Quality of Care and Outcomes Research; and Stroke Council. Low-Calorie Sweetened Beverages and Cardiometabolic Health: A Science Advisory From the American Heart Association. *Circulation.* 2018 Aug 28;138(9):e126-e140.
- Baker-Smith CM, de Ferranti SD, Cochran WJ; COMMITTEE ON NUTRITION, SECTION ON GASTROENTEROLOGY, HEPATOLOGY, AND NUTRITION. The Use of Nonnutritive Sweeteners in Children. *Pediatrics.* 2019 Nov;144(5):e20192765.
- <u>Sylvetsky AC</u>, Gardner AL, Bauman V, Blau JE, Garraffo HM, Walter PJ, Rother KI. Nonnutritive sweeteners in breast milk. *J Toxicol Environ Health A*. 2015; 78(16):1029–32.
- Magnuson BA, Carakostas MC, Moore NH, Poulos SP, Renwick, AG. Biological fate of low-calorie sweeteners. *Nutr Rev.* 2016 Nov;74(11):670-689.
- Romo-Romo A, Aguilar-Salinas CA, Brito-Cordova GX, Gomez Diaz RA, Vilchis Valentin D, Almeda-Valdes P. Effects of non-nutritive sweeteners on glucose metabolism and appetite regulating hormones: systematic review of observational prospective studies and clinical trials. *PLoS One.* 2016 Aug 18;11(8):e0161264.
- Santos NC, de Araujo LM, De Luca Canto G, Guerra ENS, Coelho MS, Borin MF. Metabolic effects of aspartame in adulthood: A systematic review and meta-analysis of randomized clinical trials. *Crit Rev Food Sci Nutr.* 2017 Apr 10:1-14.
- Nichol AD, Holle MJ, An R. Glycemic impact of non-nutritive sweeteners: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr.* 2018 Jun;72(6):796-804.
- <u>Higgins KA</u>, Considine RV, Mattes RD. Aspartame Consumption for 12 Weeks Does Not Affect Glycemia, Appetite, or Body Weight of Healthy, Lean Adults in a Randomized Controlled Trial. *J Nutr.* 2018 Apr 1;148(4):650-657.

- Serra-Majem L, et al. Ibero-American Consensus on Low- and No-Calorie Sweeteners: Safety, Nutritional Aspects and Benefits in Food and Beverages. *Nutrients*. 2018 Jun 25;10(7):818.
- Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, Mitri J, Pereira RF, Rawlings K, Robinson S, Saslow L, Uelmen S, Urbanski PB, Yancy WS Jr. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. *Diabetes Care.* 2019 May;42(5):731-754.
- Ashwell M, Gibson S, Bellisle F, Buttriss J, Drewnowski A, Fantino M, Gallagher AM, de Graaf K, Goscinny S, Hardman CA, Laviada-Molina H, López-García R, Magnuson B, Mellor D, Rogers PJ, Rowland I, Russell W, Sievenpiper JL, la Vecchia C. Expert consensus on low-calorie sweeteners: facts, research gaps and suggested actions. *Nutr Res Rev.* 2020 Jun;33(1):145-154.
- American Diabetes Association.
 Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020 Jan;43(Suppl 1):S48-S65.
- Dyson PA, Twenefour D, Breen C, Duncan A, Elvin E, Goff L, Hill A, Kalsi P, Marsland N, McArdle P, Mellor D, Oliver L, Watson K. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. *Diabet Med.* 2018 May;35(5):541-547.
- 22. <u>Diabetes Canada Clinical Practice Guidelines Expert Committee</u>, Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. Nutrition Therapy. Can *J Diabetes*. 2018 Apr;42 Suppl 1:S64-S79.
- Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K, Nagasawa SY, Morikawa Y, Ishizaki M, Kido T, Naruse Y, Suwazono Y, Sasaki S, Nakagawa H. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men. *Eur J Nutr.* 2014 Feb;53(1):251-8.
- 24. <u>Imamura F</u>, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, Forouhi NG. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *BMJ.* 2015 Jul 21;351:h3576.
- <u>Kuk JL</u>, Brown RE. Aspartame intake is associated with greater glucose intolerance in individuals with obesity. *Appl Physiol Nutr Metab.* 2016 Jul;41(7):795-8.
- 26. <u>Bleich SN</u>, Wolfson JA, Vine S, Wang YC. Diet-beverage consumption and caloric intake among US adults, overall and by body weight. *Am J Public Health*. 2014 Mar;104(3):e72-8.
- <u>Catenacci VA</u>, Pan Z, Thomas JG, Ogden LG, Roberts SA, Wyatt HR, Wing RR, Hill JO. Low/no calorie sweetened beverage consumption in the National Weight Control Registry. *Obesity* (Silver Spring). 2014 Oct;22(10):2244-51.
- Fowler SPG. Low-calorie sweetener use and energy balance: Results from experimental studies in animals, and large-scale prospective studies in humans. *Physiol Behav.* 2016 Oct 1;164(Pt B):517-523.
- 29. <u>Azad MB</u>, Abou-Setta AM, Chauhan BF, Rabbani R, Lys J, Copstein L, Mann A, Jeyaraman MM, Reid AE, Fiander M, MacKay DS, McGavock J, Wicklow B, Zarychanski R. Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. *CMAJ*. 2017 Jul 17;189(28):E929-E939.
- Young J, Conway EM, Rother KI, Sylvetsky AC. Low-calorie sweetener use, weight, and metabolic health among children: A mini-review. *Pediatr Obes.* 2019 Aug;14(8):e12521.
- Miller PE, Perez V. Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies. Am J Clin Nutr. 2014 Sep;100(3):765-77.
- 32. <u>Rogers PJ</u>. Hogenkamp PS, de Graaf C, Higgs S, Lluch A, Ness AR, Penfold C, Perry R, Putz P, Yeomans MR, Mela DJ. Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies. *Int J Obes* (Lond). 2016 Mar;40(3):381-94.

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- 33. <u>Laviada-Molina H</u>, Molina-Segui F, Pérez-Gaxiola G, Cuello-García C, Arjona-Villicaña R, Espinosa-Marrón A, Martinez-Portilla RJ. Effects of nonnutritive sweeteners on body weight and BMI in diverse clinical contexts: Systematic review and meta-analysis. *Obes Rev.* 2020 Jul;21(7):e13020.
- 34. <u>Mattes RD</u>, Popkin BM. Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms. *Am J Clin Nutr.* 2009 Jan;89(1):1-14.

Food Information

International

- 35. <u>Peters JC</u>, Beck J. Low Calorie Sweetener (LCS) use and energy balance. *Physiol Behav.* 2016 Oct 1;164(Pt B):524-528.
- 36. <u>De Witt Huberts JC</u>, Evers C, De Ridder DT. "Because I am worth it": a theoretical framework and empirical review of a justificationbased account of self-regulation failure. *Pers Soc Psychol Rev.* 2014 May;18(2):119-38.
- <u>Rogers PJ.</u> The role of low-calorie sweeteners in the prevention and management of overweight and obesity: evidence v. conjecture. *Proc Nutr Soc.* 2018 Aug;77(3):230-238.
- 38. <u>Drewnowski A</u>, Rehm CD. The use of low-calorie sweeteners is associated with self-reported prior intent to lose weight in a representative sample of US adults. *Nutr Diabetes*. 2016 Mar 7;6:e202.
- Sievenpiper JL, Khan TA, Ha V, Viguiliouk E, Auyeung R. The importance of study design in the assessment of nonnutritive sweeteners and cardiometabolic health. *CMAJ*. 2017 Nov 20;189(46):E1424-E1425.
- 40.<u>Malik VS</u>. Non-sugar sweeteners and health. *BMJ*. 2019 Jan 3;364:k5005.
- Mela DJ, McLaughlin J, Rogers PJ. Perspective: Standards for Research and Reporting on Low-Energy ("Artificial") Sweeteners. *Adv Nutr.* 2020 May 1;11(3):484-491.
- Sylvetsky AC, Rother KI. Nonnutritive sweeteners in weight management and chronic disease: a review. *Obesity* (Silver Spring). 2018 Apr;26(4):635-640.
- 43. <u>Toews I</u>, Lohner S, Küllenberg de Gaudry D, Sommer H, Meerpohl JJ. Association between intake of non-sugar sweeteners and health outcomes: systematic review and meta-analyses of randomised and non-randomised controlled trials and observational studies. *BMJ*. 2019 Jan 2;364:k4718.
- 44. <u>Ebbeling CB</u>, Feldman HA, Steltz SK, Quinn NL, Robinson LM, Ludwig DS. Effects of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Beverages on Cardiometabolic Risk Factors, Body Composition, and Sweet Taste Preference: A Randomized Controlled Trial. *J Am Heart Assoc.* 2020 Aug 4;9(15):e015668.
- 45. <u>Peters JC</u>, Beck J, Cardel M, Wyatt HR, Foster GD, Pan Z, Wojtanowski AC, Vander Veur SS, Herring SJ, Brill C, Hill JO. The effects of water and non-nutritive sweetened beverages on weight loss and weight maintenance: A randomized clinical trial. *Obesity* (Silver Spring). 2016 Feb;24(2):297-304.
- 46. <u>Dietary Guidelines Advisory Committee</u>. Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC. 2020.
- 47. Singh M. Mood, food, and obesity. Front Psychol. 2014 Sep 1;5:925.
- 48. <u>Rogers PJ</u>. The role of low-calorie sweeteners in the prevention and management of overweight and obesity: evidence v. conjecture. *Proc Nutr Soc.* 2017 Nov 23:1-9.
- 49. <u>Piernas C</u>, Tate DF, Wang X, Popkin BM. Does diet-beverage intake affect dietary consumption patterns? Results from the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial. *Am J Clin Nutr.* 2013 Mar;97(3):604-11.
- 50. <u>Palmnäs MS</u>, Cowan TE, Bomhof MR, Su J, Reimer RA, Vogel HJ, Hittel DS, Shearer J. Low-dose aspartame consumption differentially affects gut microbiota-host metabolic interactions in the diet-induced obese rat. *PLoS One.* 2014 Oct 14;9(10):e109841.

- Frankenfeld C, Sikaroodi M, Lamb E, Shoemaker S, Gillevet P. High-Intensity sweetener consumption and gut microbiome content and predicted gene function in a cross-sectional study of adults in the United States. Ann Epidemiology. 2015 Oct;25(10):736-42.e4.
- 52. <u>David LA</u>, Maurice CF, Carmody RN, Gootenburg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014 Jan 23;505(7484):559-63.
- Lobach AR, Roberts A, Rowland IR. Assessing the in vivo data on low/ no-calorie sweeteners and the gut microbiota. *Food Chem Toxicol.* 2019 Feb;124:385-399.
- 54. <u>Martin VT</u>, Vij B. Diet and Headache: Part 1. *Headache*. 2016 Oct;56(9):1543-1552.
- 55. <u>Sathyapalan T</u>, Thatcher NJ, Hammersley R, Rigby AS, Courts FL, Pechlivanis A, Gooderham NJ, Holmes E, le Roux CW, Atkin SL. Aspartame sensitivity? A double blind randomised crossover study. *PLoS One.* 2015 Mar 18;10(3):e0116212.