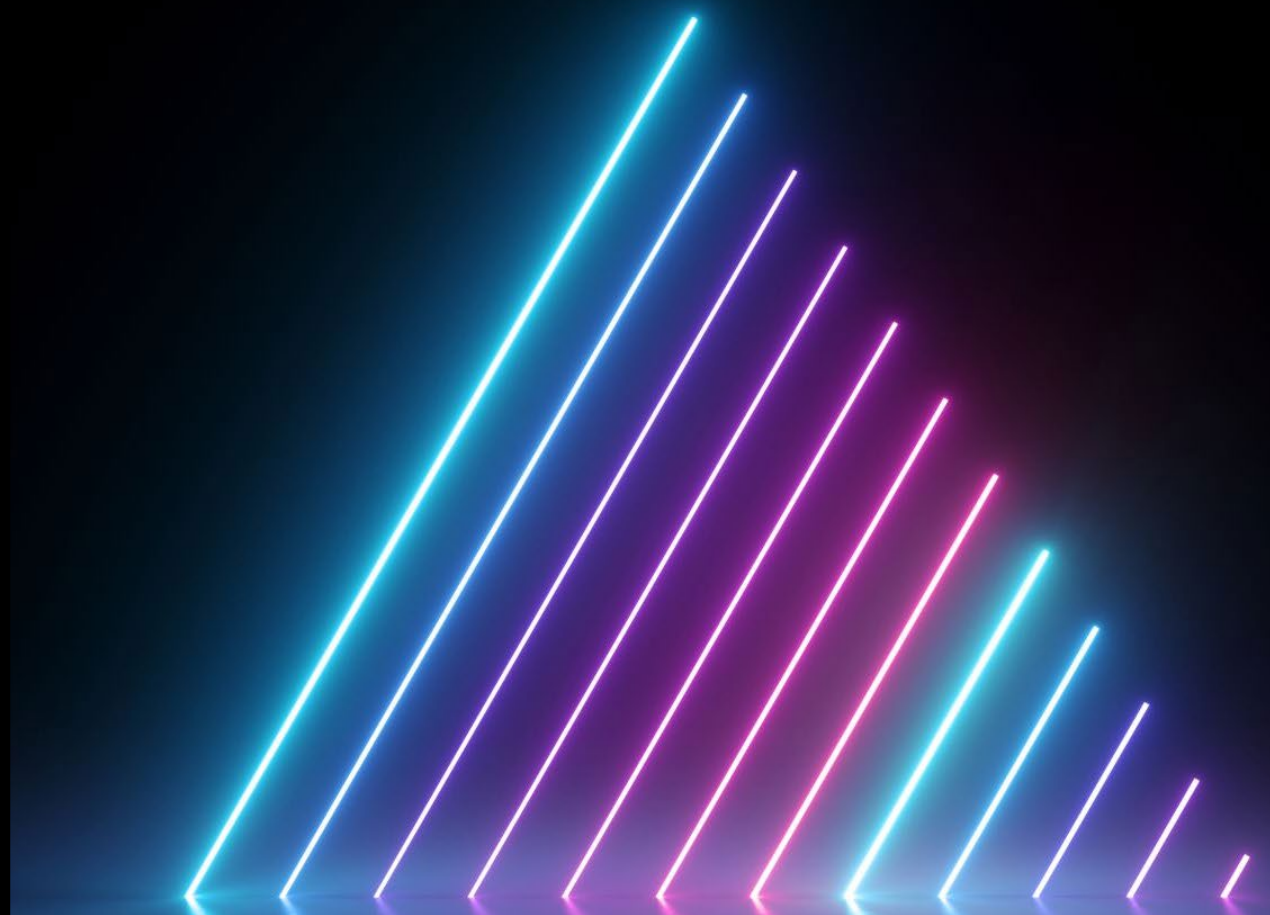
Artificial Sweeteners in Diabetes and Obesity

Alireza Esteghamati



Artificial Sweeteners and Diabetes: A Double-Edged sword

Artificial sweeteners have emerged as a popular alternative to sugar, especially for individuals managing diabetes.

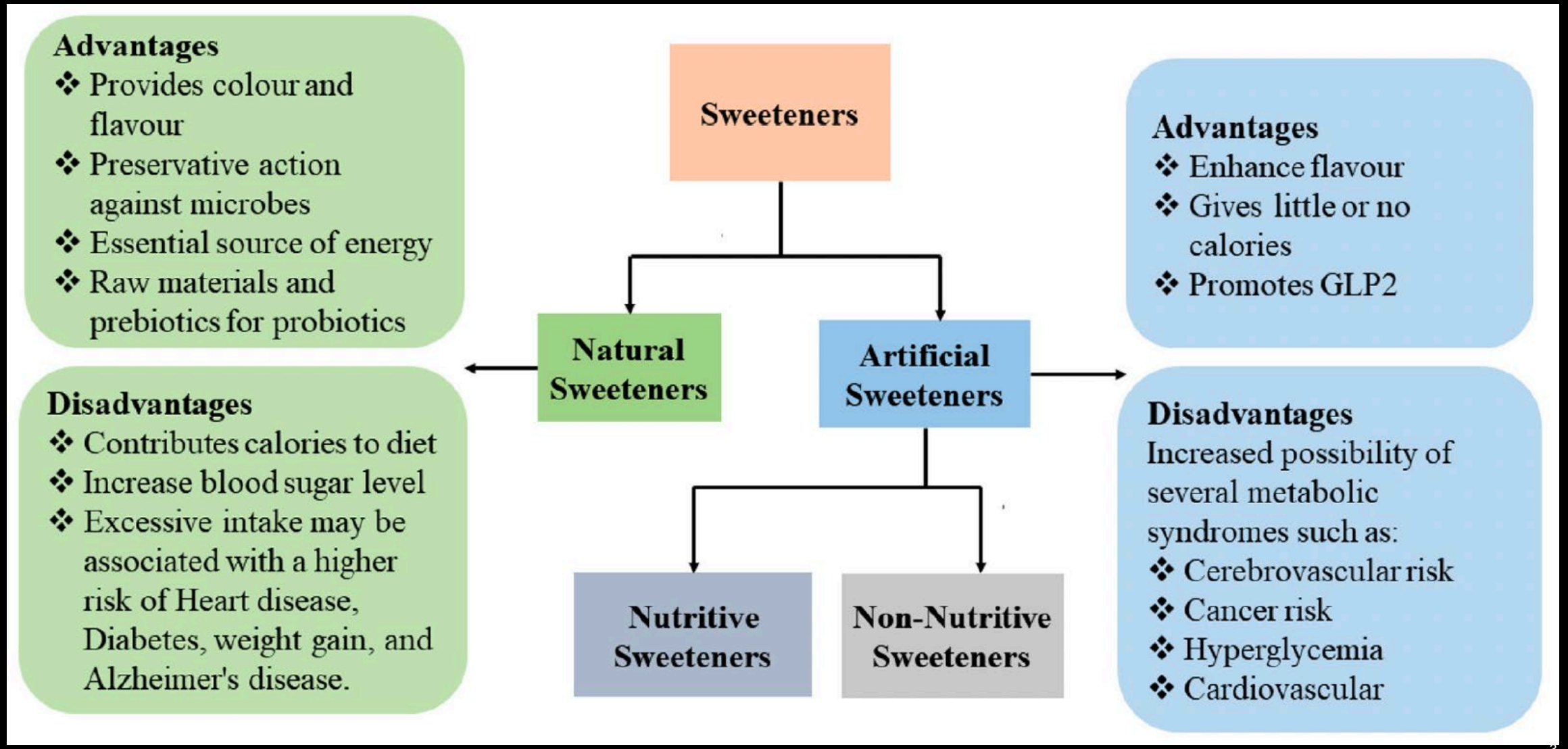
Their impact on health remains a subject of intense scientific scrutiny.

Artificial sweeteners are metabolized differently and have different properties, including sweetness intensity, persistence of sweet taste, coating of the teeth, and aftertaste effects .

This presentation explores the complex relationship between artificial sweeteners and diabetes, examining their benefits, risks, and implications for metabolic health.

Types of sweeteners and their biochemical effects

Sweeteners are classified as natural sweeteners and ASs



Natural Sweeteners

Natural sweeteners can be found or are created by nature without the use of chemicals or sophisticated machinery.

Only naturally occurring sugars and carbohydrates found in live plants such as vegetables, trees, seeds, nuts, and roots are healthy to consume, along with wild, non-hybridized, seeded fruits.

Natural sweeteners consist of the following: Xylitol, coconut sugar, date sugar, coconut nectar, honey, stevia, molasses, and maple syrup

Bulletin of the Transilvania University of Brasov. Series V. (2014) p. 59–64.

Sweeteners

- In the 18th century, the fast expansion of sucrose extraction from sugar beet and sugar cane eclipsed honey, which had previously been the main source of sweetness in human diets.

- The most popular sweetener today is sucrose, also referred to as table sugar and now offered in many refined forms.

- Consumption of sucrose has increased recently, reaching 174 million tons in 2018 and 2019 .

Int J Environ Res Public Health. (2020) 17:6285. doi: 10.3390/ijerph17176285

Sugar risks

The research demonstrates a strong association between consuming too much sugar and an elevated risk of

Cardiovascular disease

Type 2 diabetes

Obesity

Dental caries

Other noncommunicable diseases.

Int J Environ Res Public Health. (2020) 17:6285. doi: 10.3390/ijerph17176285

Artificial Sweeteners: overview

- ASs are further categorized as **nutritive and non-nutritive** sweeteners based on whether or not they include calories.

Examples of natural nutritive sweeteners

- Monosaccharide polyols (xylitol, mannitol, and sorbitol)
- Disaccharide polyols (actitol and maltitol)

- The NNS, known as ASs, include substances from different chemical classes that are 30–13,000 times sweeter than sucrose.

Artificial sweeteners: overview

- NNS with low calorie alternatives that provide little or no energy becoming a common substance of the Western diet.

- Cross-sectional studies have revealed that **25% of children and 41% of adults** regularly include low calorie sweeteners in their diets.

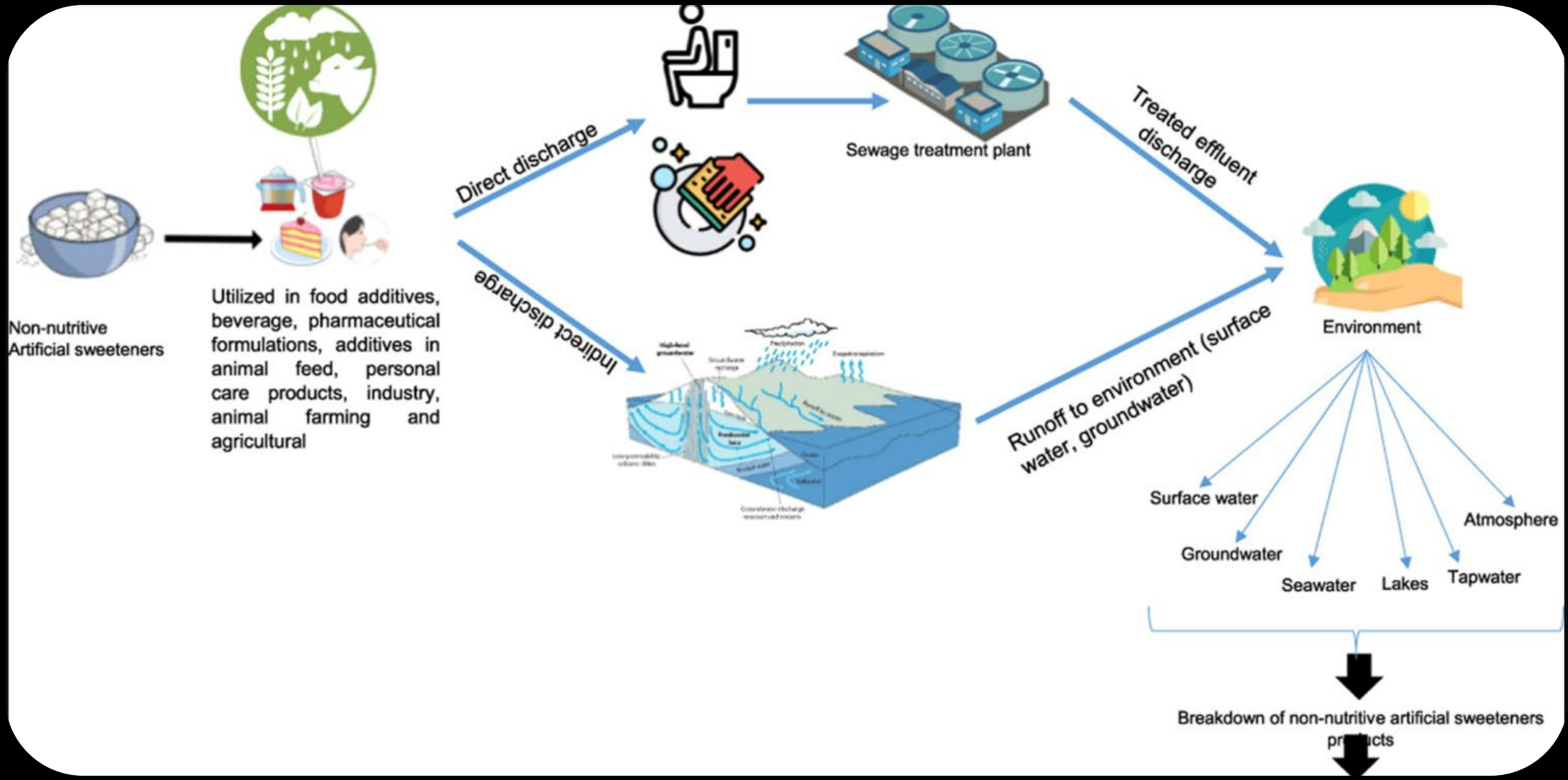
- The consumption of NNS is **higher among females**, individuals who are **obese**, non-Hispanic white individuals, and those with **higher incomes**.

J Acad Nutr Diet. (2012) 112:739– 58. doi: 10.1016/j.jand.2012.03.009

Drug Dev Res. (2013) 74:339–339. doi: 10.1002/ddr.21085

Acad Nutr Diet. (2017) 117:441–8.e2. doi: 10.1016/j.jand.2016.11.004

NNS are detectable in various environmental sources, including surface water, tap water, groundwater, seawater, lakes, and even the atmosphere



Emerging contaminants

Ecotoxicol Environ Saf. (2019) 170:699–707. doi: 10.1016/j.ecoenv.2018.12.048

Artificial sweeteners: overview

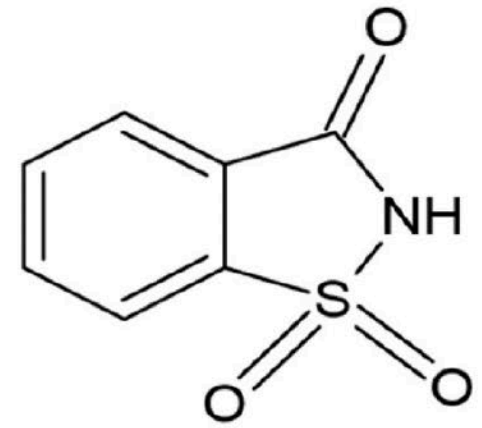
- Presently, FDA has granted approval for the usage of high-intensity sweeteners:

1. Acesulfame-potassium (Ace-K)
2. Aspartame
3. Neotame
4. Saccharin
5. Sucralose
6. purified form of stevia such as rebaudioside A.

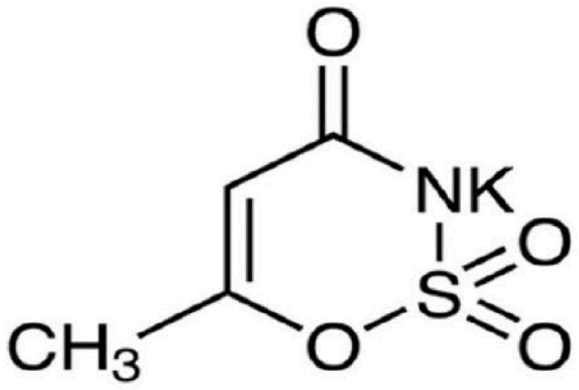
- The European Union has a broader range of approved ASs, including cyclamate

Nutrients. (2019) 11:644. doi: 10.3390/nu11030644

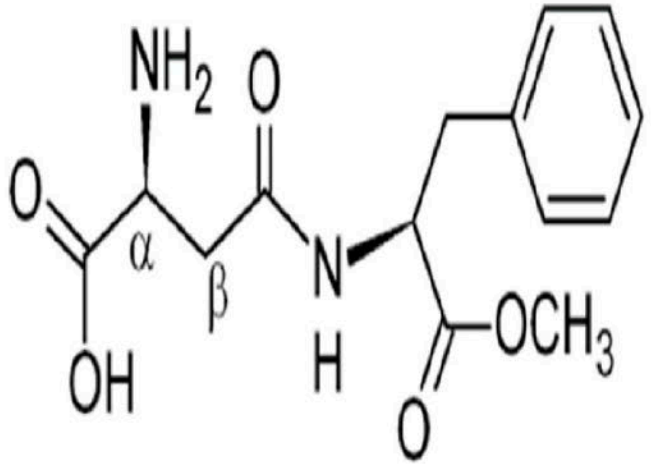
Types and chemical structure of ASs
With FDA approval



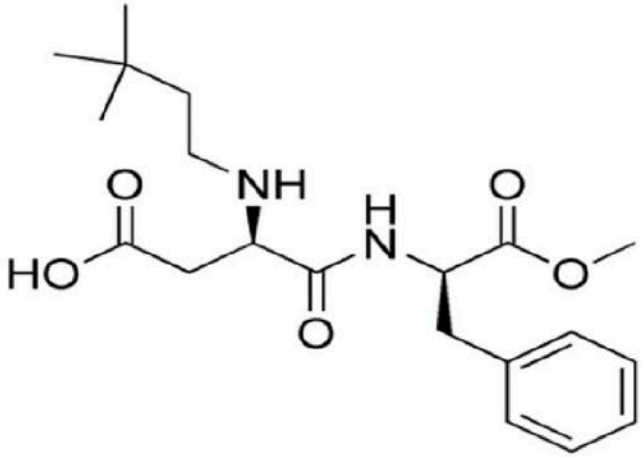
Saccharin



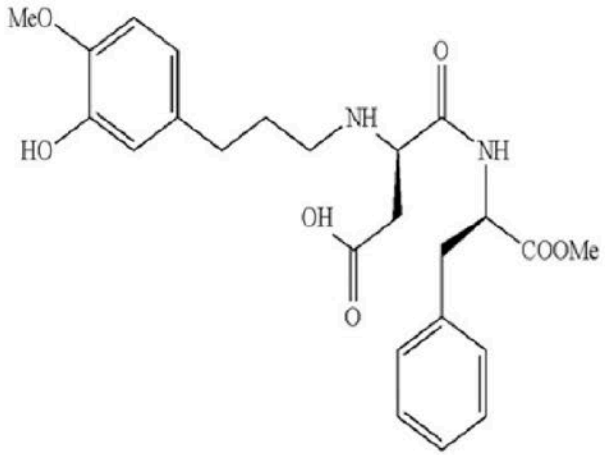
Acesulfame potassium



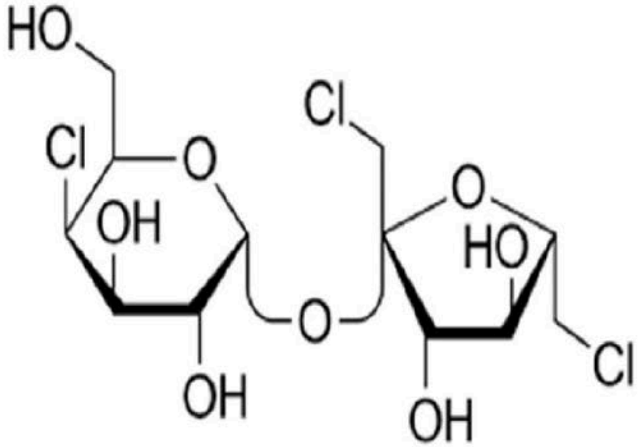
Aspartame



Neotame



Advantame

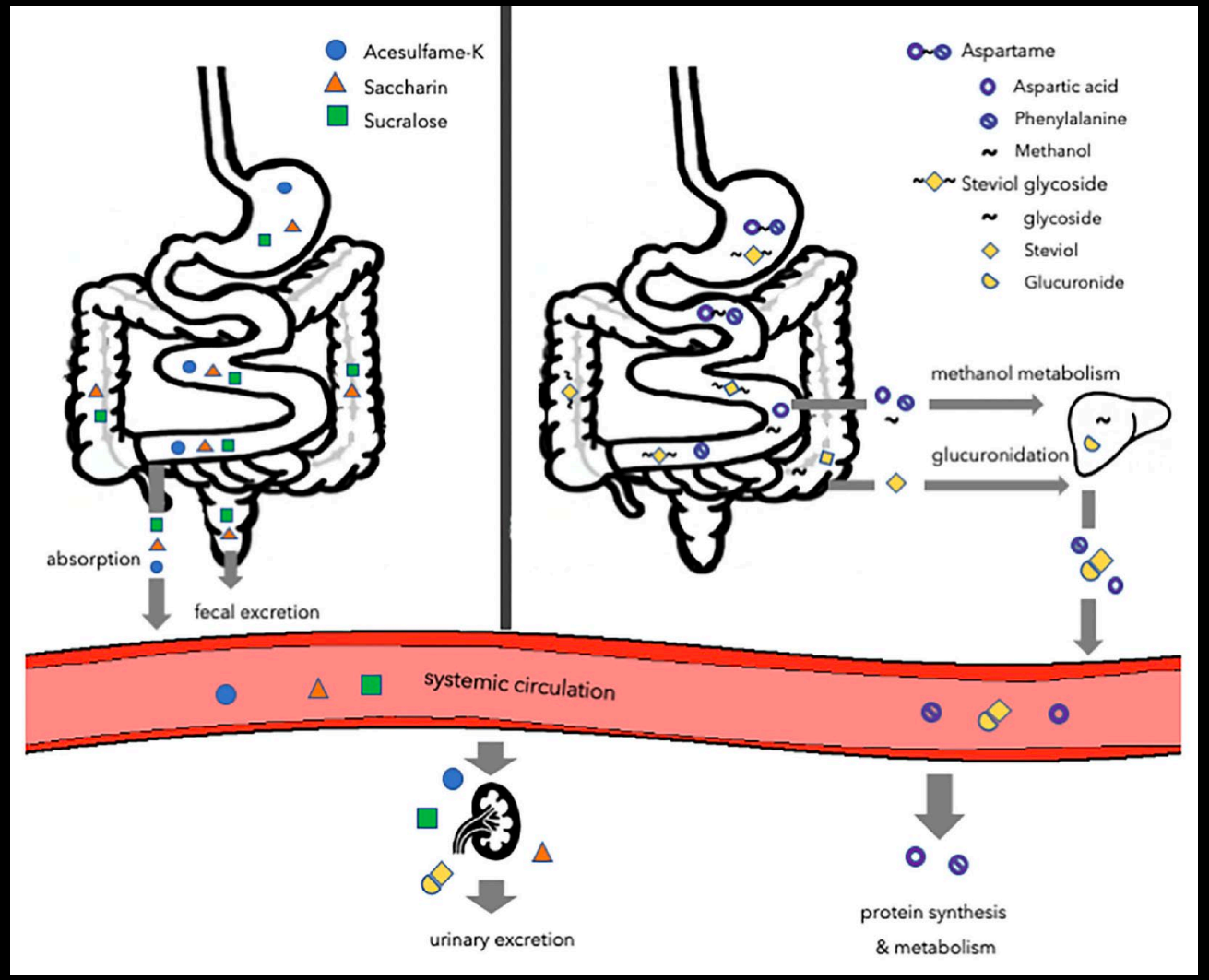


Sucralose

AS	metabolism	Impact on gut microbiota	Urinary excretion	Fecal excretion	metabolites
Acesulfame Potassium	Not metabolized	No impact	99%	<1%	Absorbed in systemic circulation
Saccharin	Not metabolized	Affect on GM	85%	5-15%	85-95% distributed via blood
Aspartame	Rapid digestion Methanol metabolized in liver	No impact		_	Aspartic acid Phenylalanine methanol
Sucralose	No digestion	Affect on GM	20%	80%	
Steviol Glycoside	Absorbed enters liver	Affect on GM	Most of it		

Major routes of absorption, digestion, metabolism, and excretion of different types of artificial sweeteners

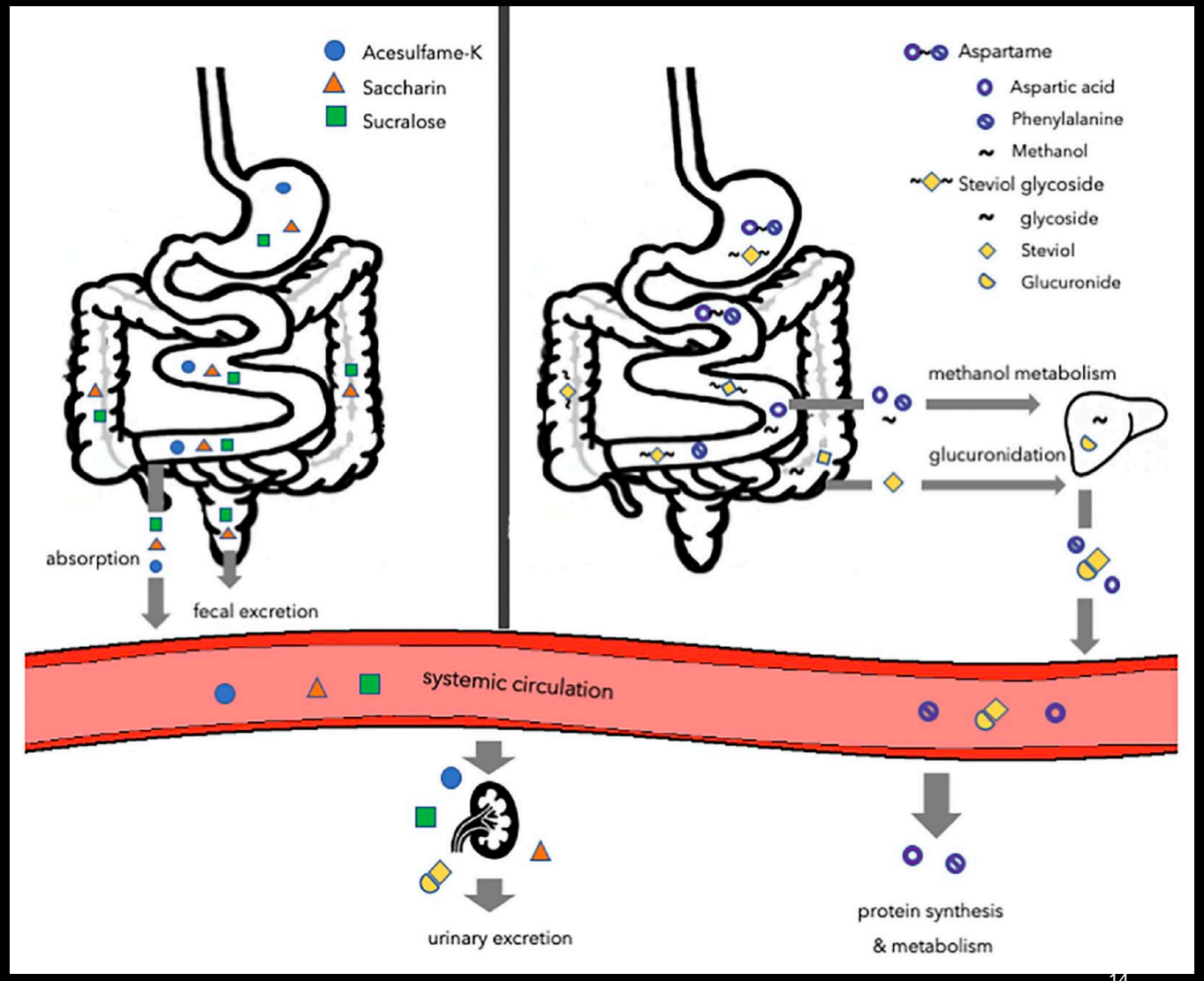
- Acesulfame-K is completely absorbed into the systemic circulation to be excreted in the urine via the kidneys.
- The majority of saccharin is absorbed and distributed, while the remaining amount passes GI tract to be eliminated in the feces.
- Most of the sucralose passes the GI tract to be eliminated in the feces, while a small amount is directed toward the kidneys to be excreted in the urine.



Major routes of absorption, digestion, metabolism, and excretion of different types of artificial sweeteners

- Aspartame is digested in the small intestine and the hydrolyzed components are absorbed and metabolized following their normal metabolic pathways

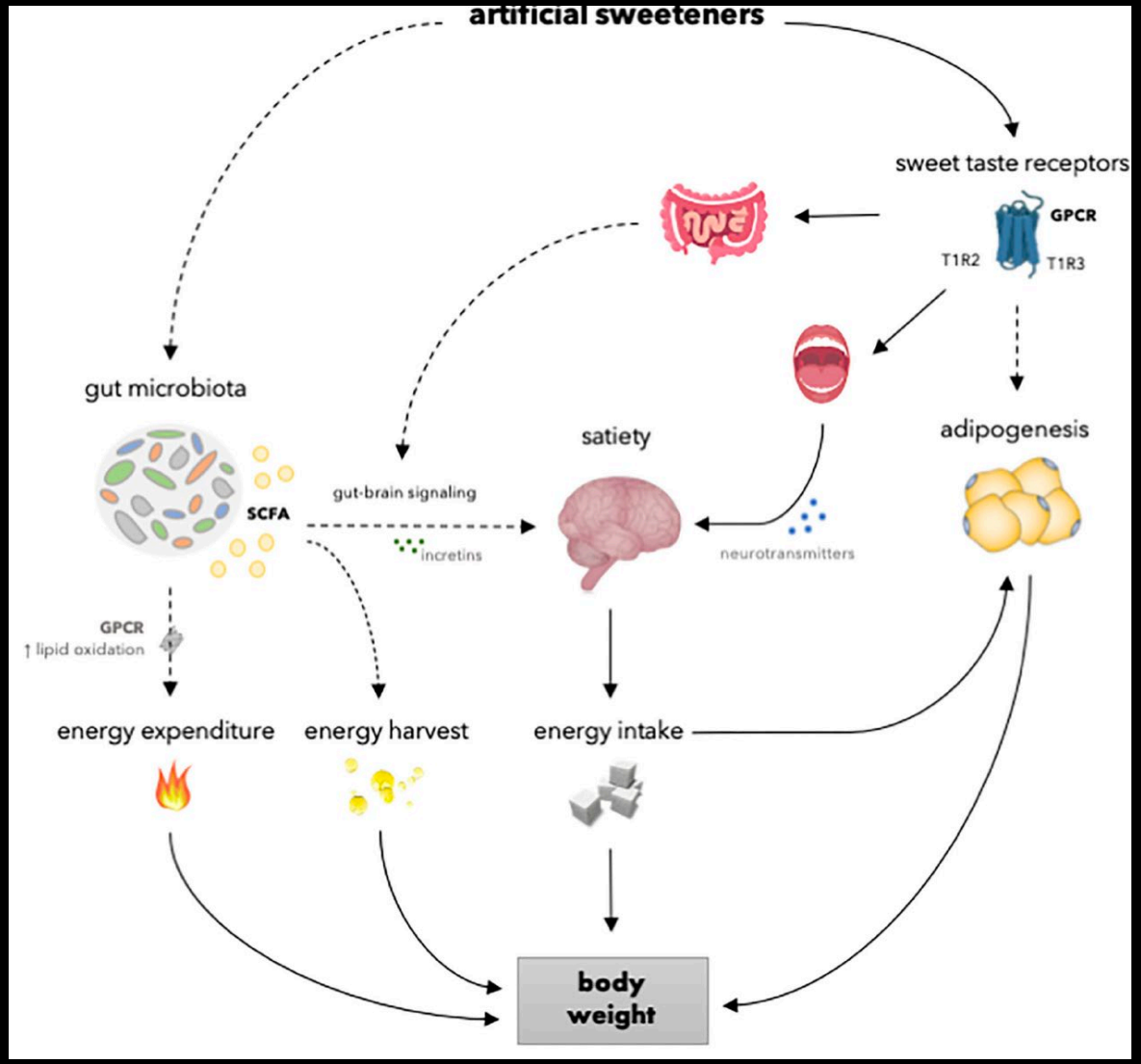
- Steviol glycoside is fermented by the gut microbiota to form steviol, which is absorbed into the liver and excreted in the urine.



Artificial sweeteners: overview

They have a different effect on body weight and glucose homeostasis because of underlying physiological mechanisms such as

1. Gut microbiota
2. Reward system
3. Adipogenesis
4. Insulin secretory capability
5. Intestinal glucose absorption
6. Insulin resistance



Front Nutr. (2021) 7:598340. doi: 10.3389/fnut.2020.598340

Artificial sweeteners: overview

- Many people turn to NNS as a means to reduce their daily calorie intake, manage weight, and maintain a healthy diet.

Recent research has indicated that the use of NNS may:

- Disrupt the balance of gut microbiota
- Lead to impaired glucose tolerance in healthy individuals
- Potentially contributing to the development of T2DM.

Nutrients. (2019) 11:644. doi: 10.3390/nu11030644

Artificial sweeteners	Brand name	No. of calorie (kcal)	Relative sweetness to sucrose	Acceptable daily intake (mg/kg bw/d)	Reaction to heat	Bitter after taste	Application in food industry
Saccharin (39, 41)	Sweet and Low®, Sweet Twin®, Sweet'N Low®, Necta Sweet®	0	300	5	Stable	Yes	Beverages, bases, and mixes for many food products, table sugar substitute
Acesulfame potassium (39, 41)	Sunett®, Sweet One®	0	200	15	Stable	Yes	Beverages, candy, frozen desserts, baked goods. Heat stable so it can be used in baking
Aspartame (39, 41)	Nutrasweet®, Equal®, Sugar Twin®	4	180–200	50	Not stable	No	Soft drinks, chewing gum, pudding, cereals, instant coffee. Also distributed as a "General Purpose Sweetener"

Artificial sweeteners	Brand name	No. of calorie (kcal)	Relative sweetness to sucrose	Acceptable daily intake (mg/kg bw/d)	Reaction to heat	Bitter after taste	Application in food industry
Neotame (39, 41)	Newtame®	0	7,000–13,000	18	Stable	No	Beverages, candy gum
Advantame (39, 41)	N/A	0	20,000	32.8	Stable	No	Baked goods, beverages, frozen desserts, frosting, chewing gum, candy, pudding, jelly and jam, gelatin
Sucralose (39, 41)	Splenda®	0	600	5	Stable	No	Milk, beverages, dairy products, chewing gum and ice cream.

Consumption of NNS can influence energy balance as well as metabolic functions through various mechanisms such as the peripheral and central systems, implying that NNS are not inert substances.

Physiol Behav. (2015) 152:381– 8. doi: 10.1016/j.physbeh.2015.05.036

NNS and their impact on glucose dynamics

The consumption of dietary sugars has been linked to a range of health issue such as excess weight, CVDs, and T2DM.

As an alternative, ASs are used as alternatives to added sugars.

An increasing body of experimental studies suggests that these sweeteners **may not be as safe as previously assumed**.

Clin Nutr ESPEN. (2017) 18:1–8. doi: 10.1016/j.clnesp.2017.01.004

Systematic review by WHO

- Recently, WHO conducted a systematic review and meta-analysis examining the relationships between ASs and health outcomes.

- The WHO's findings indicated potential associations between ASs and conditions such as obesity, CVD, and mortality, positive links with T2DM.

- Level of confidence in these associations was considered to be low.

Available online at: https://www.who.int/publications-detail-redirect/ 9789240046429

NNS and other concerns

- There are concerns regarding an increased risk of cancer and kidney disease Hepatotoxicity and MASLD associated with sweetener consumption.

- ASs are often found in Ultra Processed Foods, a category of food products that has been shown to have associations with the development of T2DM.

Indian Heart J. (2018) 70:197–9. doi: 10.1016/j.ihj.2018.01.020

Clin J Am Soc Nephrol. (2019) 14:49–56. doi: 10.2215/CJN.06380518

PLOS Med. (2022) 19:e1003950. doi: 10.1371/journal.pmed.1003950

RESEARCH ARTICLE

Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study

PLOS Medicine | https://doi.org/10.1371/journal.pmed.1003950 March 24, 2022

What did the researchers do and find?

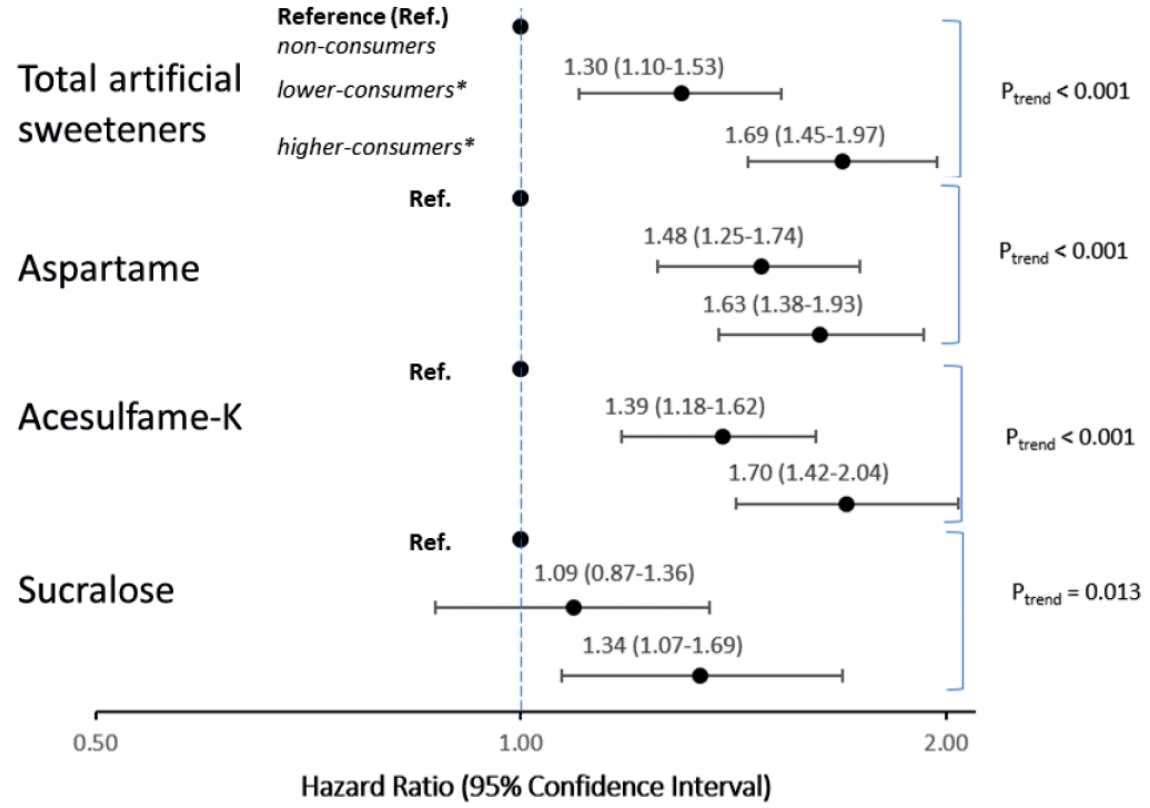
- In this large cohort of 102,865 French adults, artificial sweeteners (especially aspartame and acesulfame-K) were associated with increased overall cancer risk (hazard ratio [HR] for higher consumers compared to non-consumers = 1.13 [95% CI 1.03 to 1.25], *P*-trend = 0.002).
- More specifically, aspartame intake was associated with increased breast (HR = 1.22 [95% CI 1.01 to 1.48], *P* = 0.036) and obesity-related (HR = 1.15 [95% CI 1.01 to 1.32], *P* = 0.026) cancer risks.

Diabetes Care
American Diabetes Association

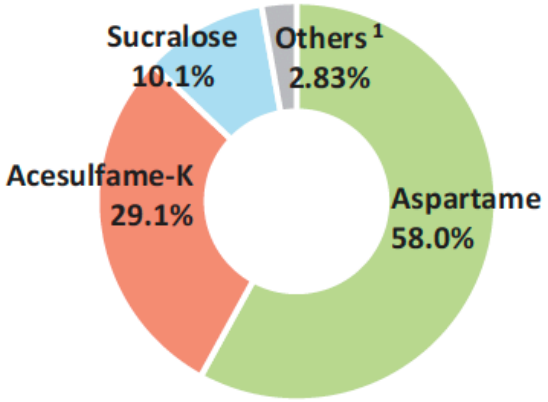
Artificial Sweeteners and Risk of Type 2 Diabetes in the Prospective NutriNet-Santé Cohort

- NutriNet-Santé cohort France, 2009-2022
- *N* = 105,588 participants
- Mean age at baseline 42.5 ± 14.6 years; 79.2% female
- Repeated 24 hour dietary records with brand-specific information and quantitative assessment of food additive exposures
- Multi-adjusted Cox models, including sensitivity analyses to limit reverse causality
- 9.1-year median follow-up
- 972 incident type 2 diabetes (T2D)
- 37.1% of participants consumed artificial sweeteners
- Mean intake = 42.3 mg/day
  equivalent to 100 ml/day of artificially sweetened beverages (ASB)

Associations between artificial sweeteners and risk of type 2 diabetes

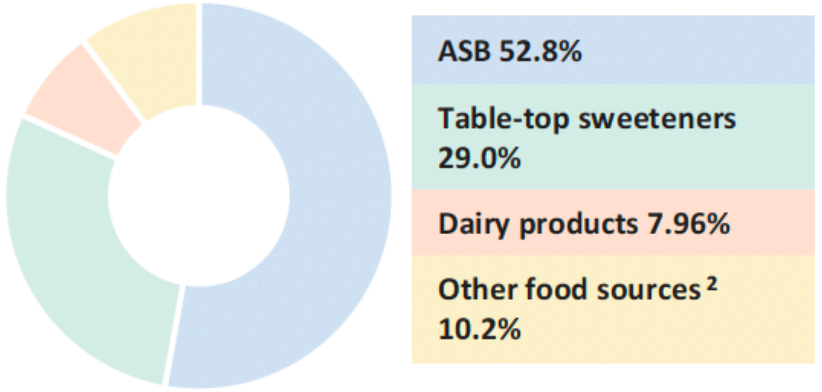


Contribution of each artificial sweetener to total intake



[1] *cyclamates, saccharin, thaumatin, neohesperidine dihydrochalcone, steviol glycosides, aspartame-acesulfame salt*

Contribution of food groups to artificial sweetener intake



[2] *soft drinks, fruit-based purées, high protein substitutes, sugary foods, cookies, biscuits, cakes, pastries, breakfast cereals, sauces, savoury foods, ultra-processed fish products*

- **Higher intakes of artificial sweeteners were associated with increased risk of T2D** (compared with nonconsumption)
- Important and novel information in the context of **ongoing re-evaluation of artificial sweeteners by health authorities** *(World Health Organization, European Food Safety Authority)*

Highlights

- Added sugars are risk factors for chronic diseases, including T2D, leading manufacturers toward using **artificial sweeteners** in thousands of foods/beverages consumed by millions daily.

- Deleterious effect of artificially sweetened beverages on T2D is suspected, but the level of evidence remains low.

- We observed higher T2D risk with total artificial sweeteners, aspartame, acesulfame-K, and sucralose.

- In the context of on-going reevaluation of artificial sweeteners by health authorities worldwide, our findings provide important information to strengthen the evidence.

EPIC cohort

- These findings differed from a study conducted within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

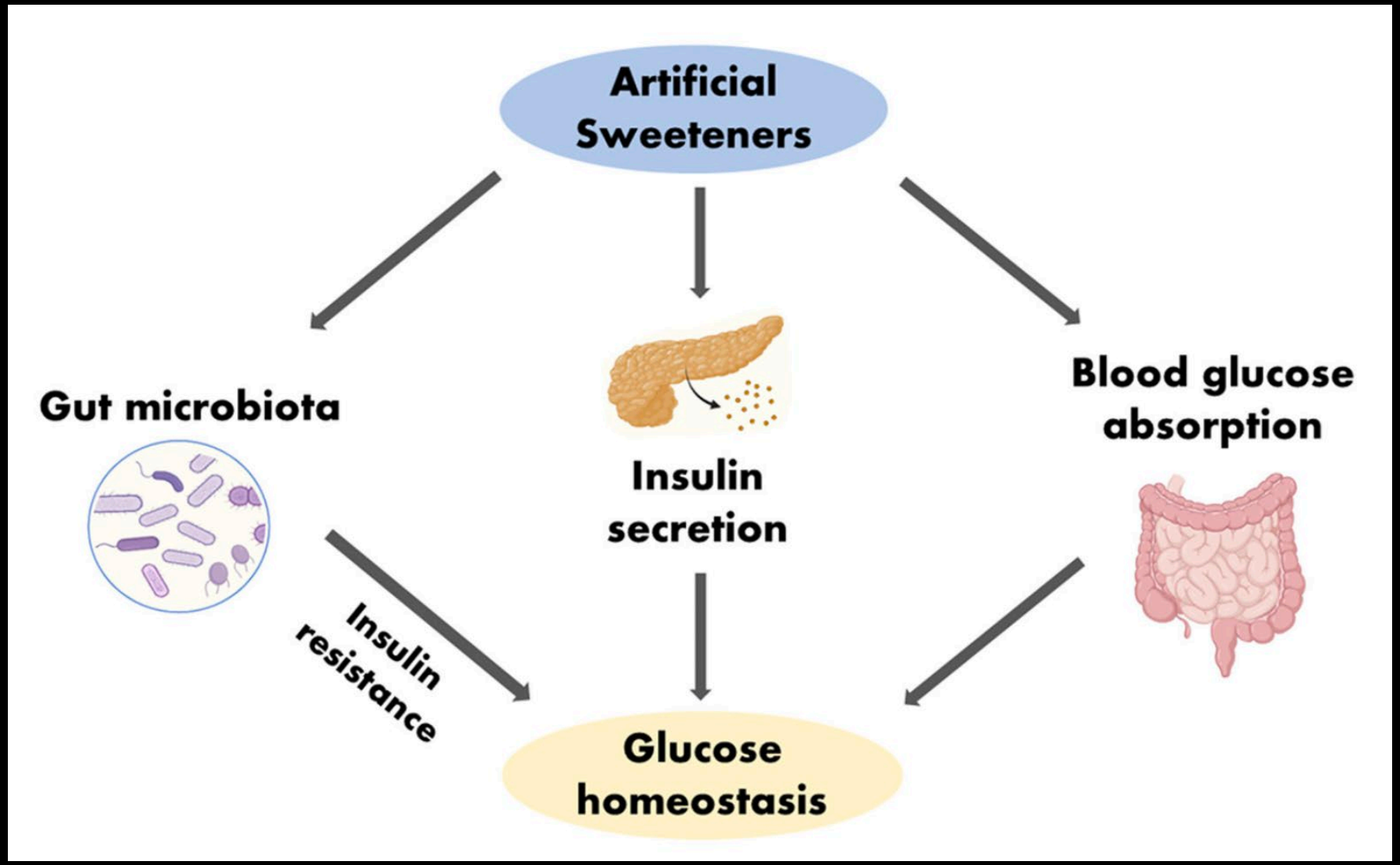
- increase in daily consumption of artificially sweetened beverages (ASBs) by one can was linked to a higher risk of T2DM; however, when adjusted for BMI, this association lost statistical significance

Other Cohorts & ASS and risk of DM

- Likewise, in other cohorts such as EPIC Norfolk, Health Professionals Follow-Up Study (HPFS), and Black Women's Health Study (BWHS), no significant associations were found between ASBs and T2D after accounting for BMI.

J Nutr. (2016) 146:290–7. doi: 10.3945/jn.115.220194

Impact of ASs in glucose homeostasis



1- Artificial sweeteners and blood glucose

- The outcomes of systematic reviews and meta-analyses investigating the link between ASs consumption and glucose regulation or the risk of developing T2DM have produced contradictory results.

- According to Daher et al. the majority of these systematic reviews and meta-analyses, which drew from RCTs or prospective cohort studies involving healthy individuals, did not yield definitive evidence supporting the idea that Ass heighten the risk of T2DM.

Diabetes Res Clin Pract. (2019) 155:107786–107786.

1-Artificial sweeteners and blood glucose

Intervention studies in both healthy individuals and patients with diabetes did not identify any significant effects of ASs on factors related to glucose regulation, such as glucose and insulin levels .

.

Table 3 – Interventional studies describing the association between NNS consumption and T2D risk.

Reference	Type of study (Sample size)	Duration	Type and source of NNS in the experimental group	Control group	No difference between NNS and control	Beneficial effect of NNS on T2D risk
Tey et al. [32]	Randomized cross-over double blind (30 healthy normal weight males aged between 21 and 50 years)	6 h each test session for 4 sessions	Aspartame (artificial sweetener), stevia and monk-fruit (natural sweetener) from a test beverage	sucrose sweetened beverages	X	
Tey et al. [33]	Randomized cross-over double blind (10 healthy normal weight males aged between 21 and 50 years)	1 day each test for 4 sessions	Aspartame (artificial sweetener), stevia and monk-fruit (natural sweetener) from a test beverage	sucrose sweetened beverages	X	
Raben et al. [34]	Randomized controlled trial (23 healthy overweight participants aged between 20 and 50 years)	10 weeks	Artificial sweeteners from food and beverages	Sucrose from food and beverages		X
Lertrit et al. [35]	Randomized cross over double blind (15 healthy participants aged > 18 years)	4 weeks each phase for 2 phases	Sucralose pills	Placebo (empty pills)		
Ma et al. [36]	Randomized single blind (7 healthy normal weight participants aged 24 ± 2 years)	4 h each session for 4 sessions	Intragastric infusion of sucralose in normal saline (80 g and 800 mg)	normal saline or 50 g of sucrose in water		
Grotz et al. [37]	Randomized double blind (46 healthy males)	20 weeks	Sucralose pills	Placebo (cellulose)	X	

Diabetes Res Clin Pract. (2019) 155:107786–107786

1- Artificial sweeteners and blood glucose

Should we ring the bell?

- systematic reviews and meta-analyses that relied on prospective cohort studies involving healthy individuals revealed a positive association between ASs consumption and the occurrence of T2DM, even after accounting for factors such as body adiposity (although this association was somewhat weakened after adjusting for BMI).

Table 4 – Systematic reviews describing the association between NNS consumption and T2D risk.

Reference	Type of study (Sample size)	NNS and T2D risk		
		No conclusive evidence	↑ the risk for T2D	Not beneficial in risk prevention
Lohner et al. [38]	Scoping review (15 SR, 155 RCT, 23 non-randomized controlled trials, 57 cohort, 52 case-control, 28 cross-sectional, 42 case series/case reports)	X		
Bruyère et al. [39]	Systematic review and meta-analysis (383 studies)	X		
Romo-Romo et al. [40]	Systematic review (14 prospective studies, 28 clinical trials and 2 meta-analysis)	X		
Wiebe et al. [41]	Systematic review and meta-analysis (53 RCT)	X		
Tucker and Tan [42]	Systematic review (41 interventional studies)			X
Greenwood et al. [43]	Systematic review and meta-analysis (11 prospective studies)		X	
Imamura et al. [44]	Systematic review and meta-analysis 21 prospective studies		X	

Diabetes Res Clin Pract. (2019) 155:107786–107786

283 studies RCT, prospective cohort studies , case–control studies assessing cancer

Cohort/case–control studies

Adiposity
- ↑ Incident obesity HR 1.76 *(low)*
- ↑ BMI +0.14 kg/m² *(very low)*
- Ø Other measures

Type 2 diabetes
- ↑ Disease (beverage) HR 1.23 *(low)*
- ↑ Disease (tabletop) HR 1.34 *(low)*
- ↑ High fasting glucose HR 1.21 *(low)*
- Ø Other measures

All-cause mortality
- ↑ Mortality HR 1.12 *(very low)*

Cardiovascular diseases
- ↑ CVD mortality HR 1.19 *(low)*
- ↑ CV events HR 1.32 *(low)*
- Ø CHD *(very low)*
- ↑ Stroke HR 1.19 *(low)*
- ↑ Hypertension HR 1.13 *(low)*

Cancer
- Ø Mortality *(very low)*
- Ø Incidence: any type *(very low)*
- ↑ Bladder cancer OR 1.31 *(very low)* — Mostly in saccharin

Total energy intake (kJ/day)
No data

Sugars intake (g/day)
No data

Pregnancy
- ↑ Preterm birth HR 1.25 *(low)*

Randomized controlled trials

Adiposity
- ↓ Body weight –0.71 kg *(low)*
- ↓ BMI –0.14 kg/m² *(low)*

Mostly in NSS→sugars

- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 (*moderate*)
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

Total energy intake (kJ/day)
- ↓ Energy intake –569 *(low)* — Mostly in NSS→sugars

Sugars intake (g/day)
- ↓ Sugars intake –38 *(low)*

Pregnancy
No data

1- Artificial sweeteners and blood glucose

- NNS consumption in both mice and humans **enhances the risk of glucose intolerance**

- These adverse metabolic effects are mediated by modulation of the composition and function of the microbiota.

Front Nutr. (2021) 7:598340. doi: 10.3389/fnut.2020.598340

Nature. (2014) 514:181–6. doi: 10.1038/nature13793

2-Effect of NNS on insulin resistance

- The consumption of nutrients involves a wide range of sensory signals that allow the human body to prepare for the digestion and utilization of these substances.

- Even before ingestion, exposure to sweet-tasting sugars triggers physiological responses aimed at regulating blood glucose , such as the release of insulin or incretin hormones.

- ASs do not elicit the same preparatory responses in GI tract for the digestion and utilization of nutrients as natural sugars do.

Front Nutr. (2021) 7:598340. doi: 10.3389/fnut.2020.598340

Am J Clin Nutr. (2005) 82:1011–6. doi: 10.1093/ajcn/82.5.1011

Original Article

Effect of artificial sweeteners on insulin resistance among type-2 diabetes mellitus patients

Kushagra Mathur[1], Rajat Kumar Agrawal[1], Shailesh Nagpure[2], Deepali Deshpande[3]

- ASs, may surprisingly influence blood sugar levels.

- In research by Mathur et al.it was observed that T2DM patients from Group A, who consumed ASs, exhibited greater insulin resistance compared to individuals in Group B, who didn't intake these sweeteners.

J Fam Med Prim Care. (2020) 9:69–71. doi: 10.4103/jfmpc.jfmpc_329_19

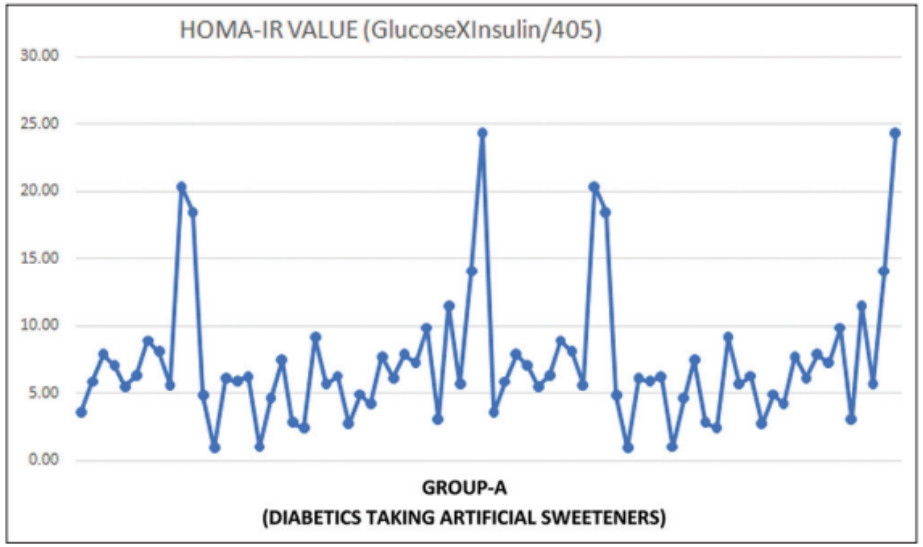


Figure 1: Graphical representation of patients receiving artificial sweeteners

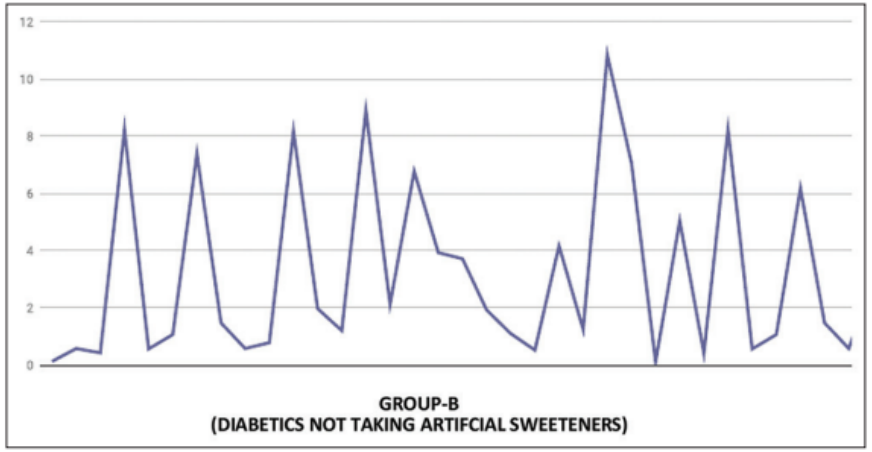


Figure 2: Graphical representation of patients not taking artificial sweeteners

Cephalic insulin response to aspartame & sucralose

- In a randomized crossover study involving 5 healthy individuals, Sleeths and colleagues (2005) with FMRI

1. Tasting glucose resulted in an early increase in insulin

2. Tasting **aspartame** did not lead to a cephalic insulin response

- Another randomized crossover study in healthy individuals reported no cephalic response when tasting **sucralose**. (No increase plasma GLP-1 or PYY

Am J Clin Nutr. (2005) 82:1011–6. doi: 10.1093/ajcn/82.5.1011

Eur J Clin Nutr. (2011) 65:508–13. doi: 10.1038/ejcn.2010.291

3- Effect of NNS on insulin secretion

- Natural sugars stimulate the secretion of incretin hormones, which in turn stimulate beta cells to release insulin

- Ass do not **directly** induce the secretion of incretins, as this response appears to be dependent on the presence of nutrients.

Molecular effects of artificial sweeteners on glucose and insulin signaling

sucralose, acesulfame K, aspartame, and saccharin

Influencing glucose assimilation and modulating the secretion of insulin and incretins.

Molecular effects of artificial sweeteners on glucose and insulin signaling

- ASs lead to diverse effects on metabolic health, attributed to the unique ways in which they are processed by the body and their distinct impacts on biological functions, including :

1. Composition of gut bacteria
2. Release of insulin
3. Uptake of glucose.

Molecular effects of artificial sweeteners on glucose and insulin signaling

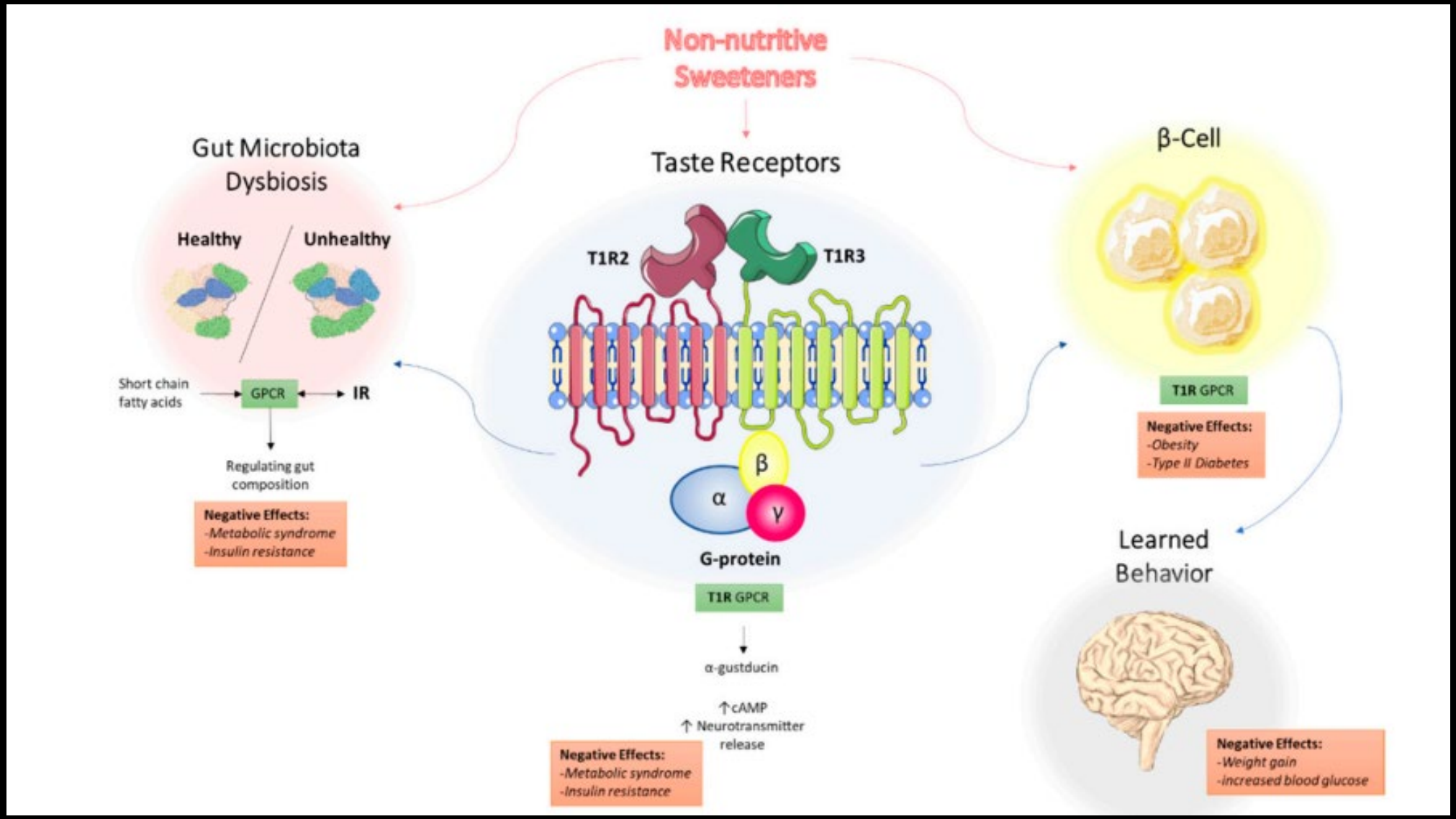
findings of Liauchonak et al.

Potential for NNS consumption to

1. disrupt the balance of gut microbiota
2. affect the activity of miRNAs
3. changes in the gene expression of glucose metabolism and signaling of insulin
4. May interfere with the regulation of glucose and sensitivity to insulin.

ASs could play a role in the onset of metabolic syndrome and T2DM.

Nutrients. (2019) 11:644. doi: 10.3390/nu11030644



Effect of NNS on body weight
Stevia

- Stamataki et al. reported that the effects of daily Stevia consumption for 3 months in doses similar to real-life consumption on body weight in healthy adults with a normal BMI did not significantly alter their body weight from baseline, and also did not demonstrate the weight gain that occurred in the control group

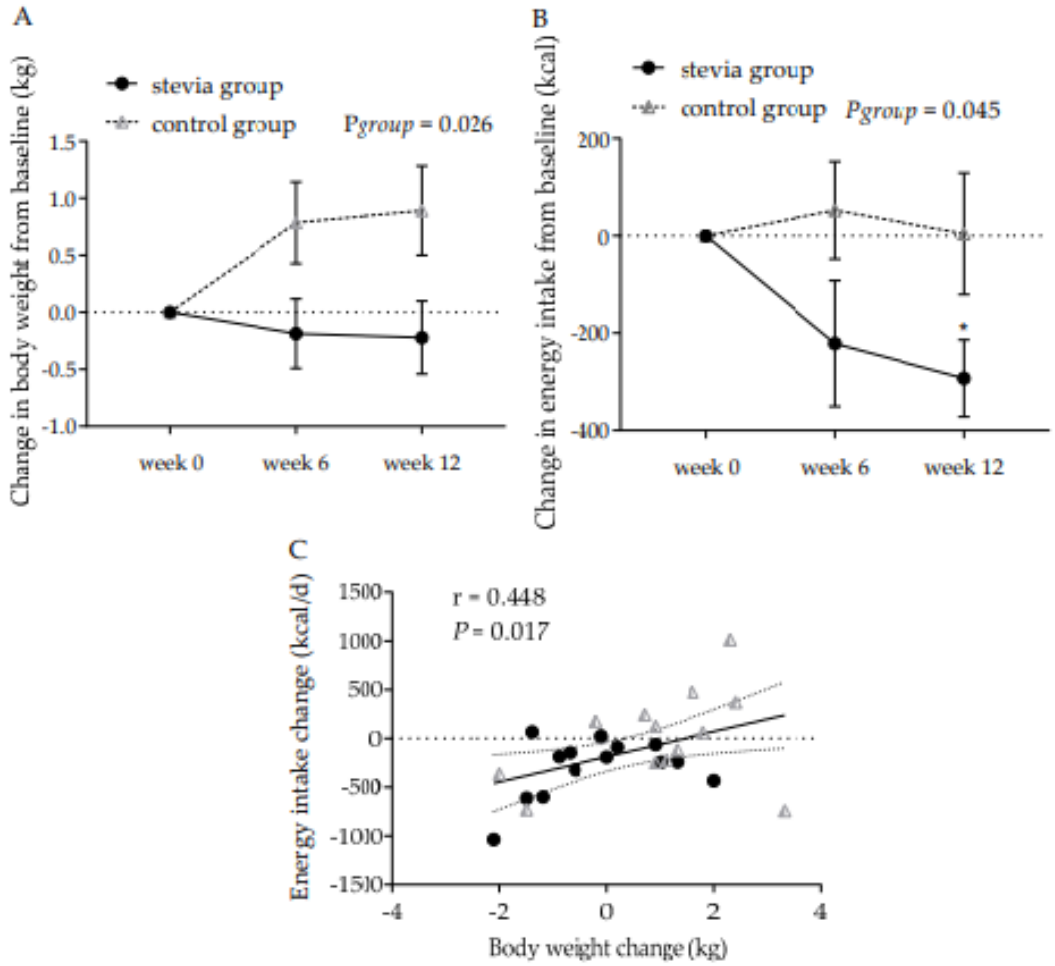
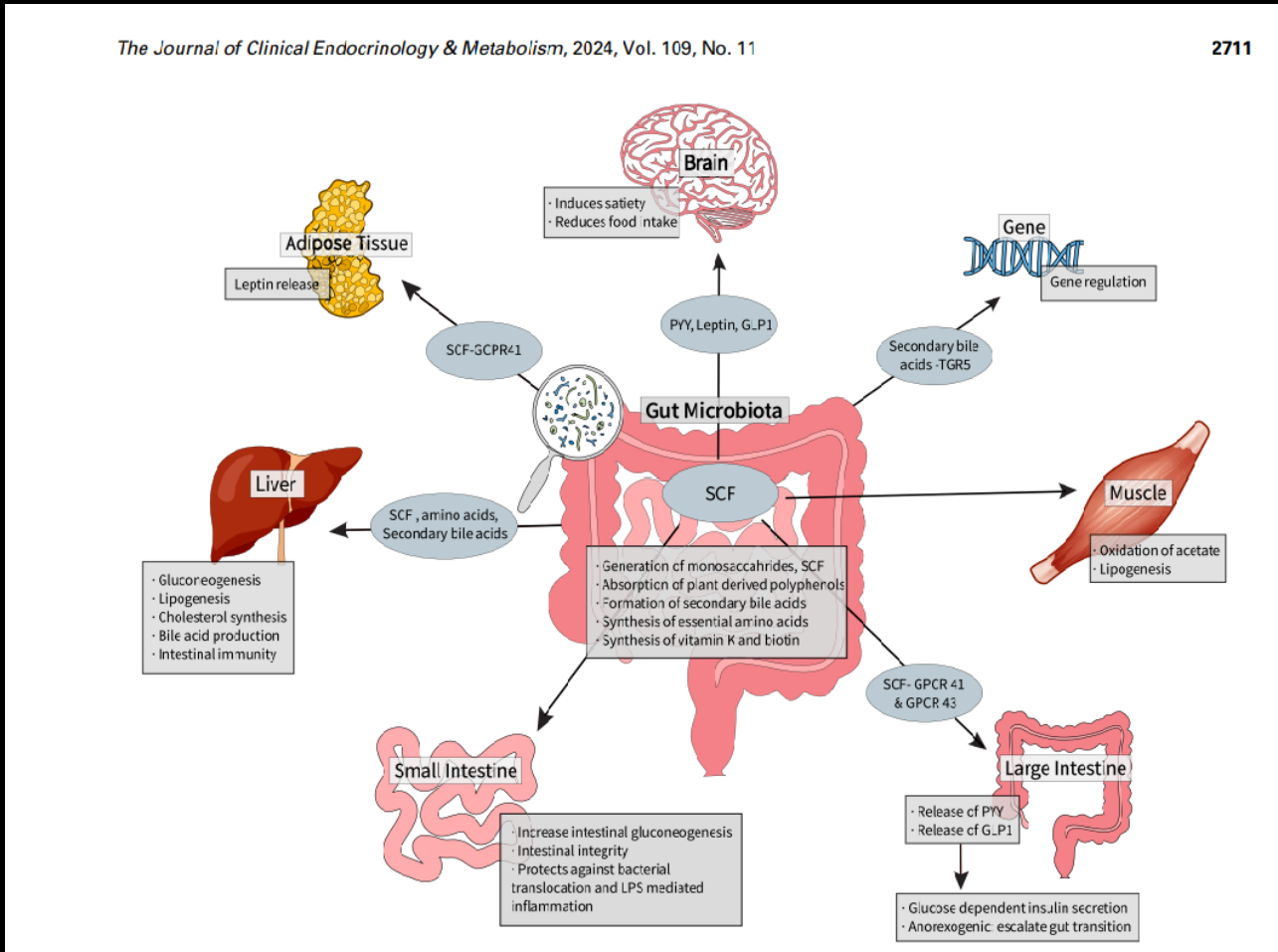


Figure 3. Change in body weight (**A**) and energy intake (**B**) in the stevia and control groups over 12 weeks (n = 14 in each group). Differences in body weight were correlated with changes in energy intake (**C**). Data are expressed as means ± SE. * p = 0.003.

Nutrients. (2020) 12:3049. doi: 10.3390/nu12103049

Effect of NNS on gut microbiota

- The human intestinal tract houses a large assembly of over 100 trillion microbial cells.
- This ecosystem serves critical functions in regulating metabolism.
- By engaging in mutually beneficial relationships with the host, the gut microbiome has the capacity to influence energy metabolism.
- there is a belief that the gut microbiome is linked to metabolic disorders in both humans and animals.



J Obes Metab Syndr. (2020) 29:114–23. doi: 10.7570/jomes19079

Effect of NNS on gut microbiota

- In a study by Ahmad et al. evaluated the influence of sucralose and aspartame intake on the gut microbiota using practical doses of NNS.

This double-blind, randomized crossover trial engaged 17 healthy participants

- Aged 18 and 45
- BMI 20 and 25.

- The findings revealed that in these healthy subjects, the ingestion of aspartame and sucralose didn't lead to notable changes in the composition of the gut microbiota .

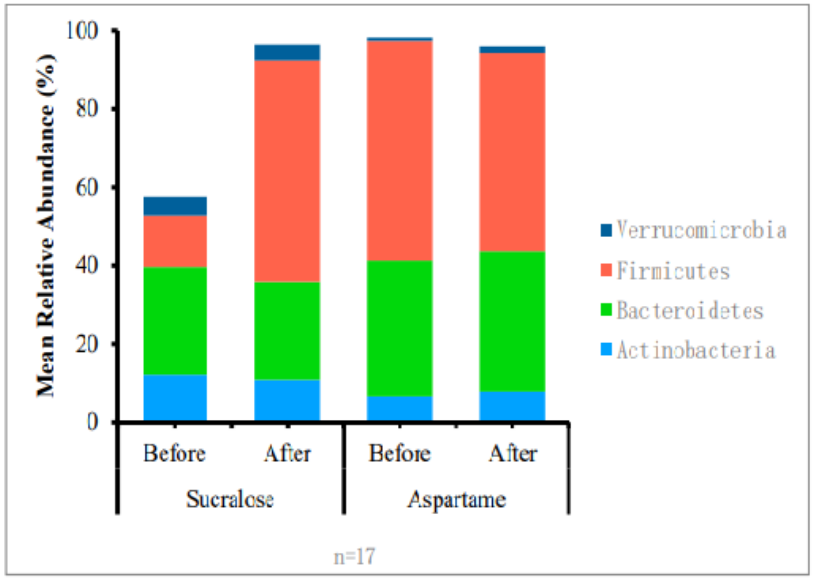


Figure 3. Mean relative abundance of the four dominant microbiota phyla of the human gut by treatment group before and after the administration of aspartame or sucralose drinks.

Nutrients. (2020) 12:3408. doi: 10.3390/nu12113408

Effect of NNS on gut microbiota

- In research by Méndez-García et al. it was found that daily intake of 48 mg of sucralose over a span of ten weeks led to an imbalance in the gut microbiome.

This was evident by an

- increase in Blautia coccoides
- Decrease in Lactobacillus acidophilus among healthy young adults who were not insulin resistant .

Microorganisms. (2022) 10:434. doi: 10.3390

Effect of NNS on gut microbiota

- In a separate research conducted by Suez et al., it was demonstrated that three non-sugar sweeteners, saccharin, sucralose, and aspartame, influenced an elevation in glucose levels by altering the makeup of the gut microbiota .

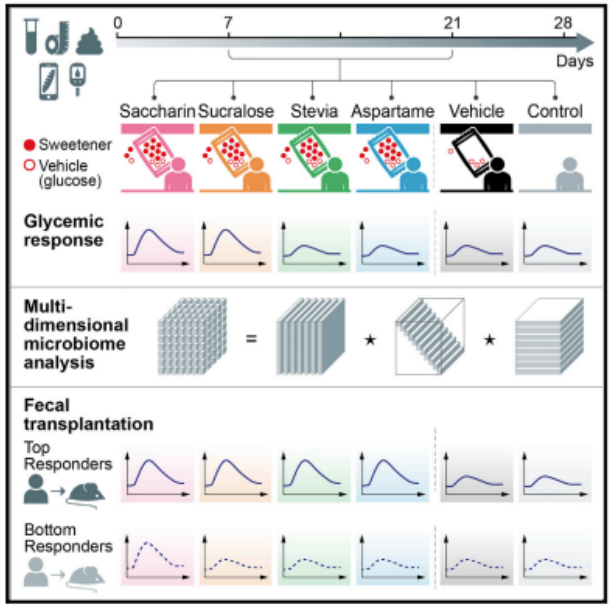
Cell. (2022) 185:3307–28.e19. doi: 10.1016/j.cell.2022. 07.016

Cell

Article

Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance

Graphical abstract



Authors

Jotham Suez, Yotam Cohen, Rafael Valdés-Mas, ..., Christoph K. Stein-Thoeringer, Eran Segal, Eran Elinav

Correspondence

jsuez1@jhu.edu (J.S.), eran.segal@weizmann.ac.il (E.S.), eran.elinav@weizmann.ac.il (E.E.)

In brief

A study of the effects of non-nutritive sweeteners on human metabolism as well as their microbiomes reveals how these can induce individual-specific, microbiome-dependent changes to glycemic responses, warranting follow-up clinical studies to understand long-term impact.

Highlights

- Randomized-controlled trial on the effects of non-nutritive sweeteners in humans
- Sucralose and saccharin supplementation impairs glycemic response in healthy adults
- Personalized effects of non-nutritive sweeteners on microbiome and metabolome
- Impacts on the microbiome are causally linked to elevated glycemic response

Effect of NNS on gut microbiota

Researchers at the Weizmann Institute of Science

- Their findings suggest that NNS consumption disrupts the composition of intestinal microbiota in mice, which, in turn, could potentially lead to metabolic imbalances like glucose intolerance

Sci Transl Med. (2009). 1. doi: 10.1126/scitranslmed.3000322

Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort

Charlotte Debras,[1,2] Eloi Chazelas,[1,2] Laury Sellem,[1,2] Raphaël Porcher,[3,4] Nathalie Druesne-Pecollo,[1,2] Younes Esseddik,[1] Fabien Szabo de Edelenyi,[1] Cédric Agaësse,[1] Alexandre De Sa,[1] Rebecca Lutchia,[1] Léopold K Fezeu,[1,2] Chantal Julia,[1,5] Emmanuelle Kesse-Guyot,[1,2] Benjamin Allès,[1] Pilar Galan,[1,2] Serge Hercberg,[1,2,5] Mélanie Deschasaux-Tanguy,[1,2] Inge Huybrechts,[2,6] Bernard Srour,[1,2] Mathilde Touvier[1,2]

Participants

103 388 participants of the web based NutriNet-Santé cohort
mean age 42.2±14.4
79.8% female
904 206 person years
Dietary intakes and consumption of artificial sweeteners were assessed by repeated 24 h dietary records, including brand names of industrial products.

Main outcomes measures
Associations between sweeteners an CVD risk, assessed by multivariable adjusted Cox hazard models

RESULTS

Total artificial sweetener intake was associated with increased risk of cardiovascular diseases (1502 events, hazard ratio 1.09, 95% confidence interval 1.01 to 1.18, P=0.03); absolute incidence rate in higher consumers (above the sex specific median) and non-consumers was 346 and 314 per 100 000 person years, respectively. Artificial sweeteners were more particularly associated with cerebrovascular disease risk (777 events, 1.18, 1.06 to 1.31, P=0.002; incidence rates 195 and 150 per 100 000 person years in higher and non-consumers, respectively). Aspartame intake was associated with increased risk of cerebrovascular events (1.17, 1.03 to 1.33, P=0.02; incidence rates 186 and 151 per 100 000 person years in higher and non-consumers, respectively), and acesulfame potassium and sucralose were associated with increased coronary heart disease risk (730 events; acesulfame potassium: 1.40, 1.06 to 1.84, P=0.02; incidence rates 167 and 164; sucralose: 1.31, 1.00 to 1.71, P=0.05; incidence rates 271 and 161).

- Controversy exists about their health impacts on body weight and glucose homeostasis.

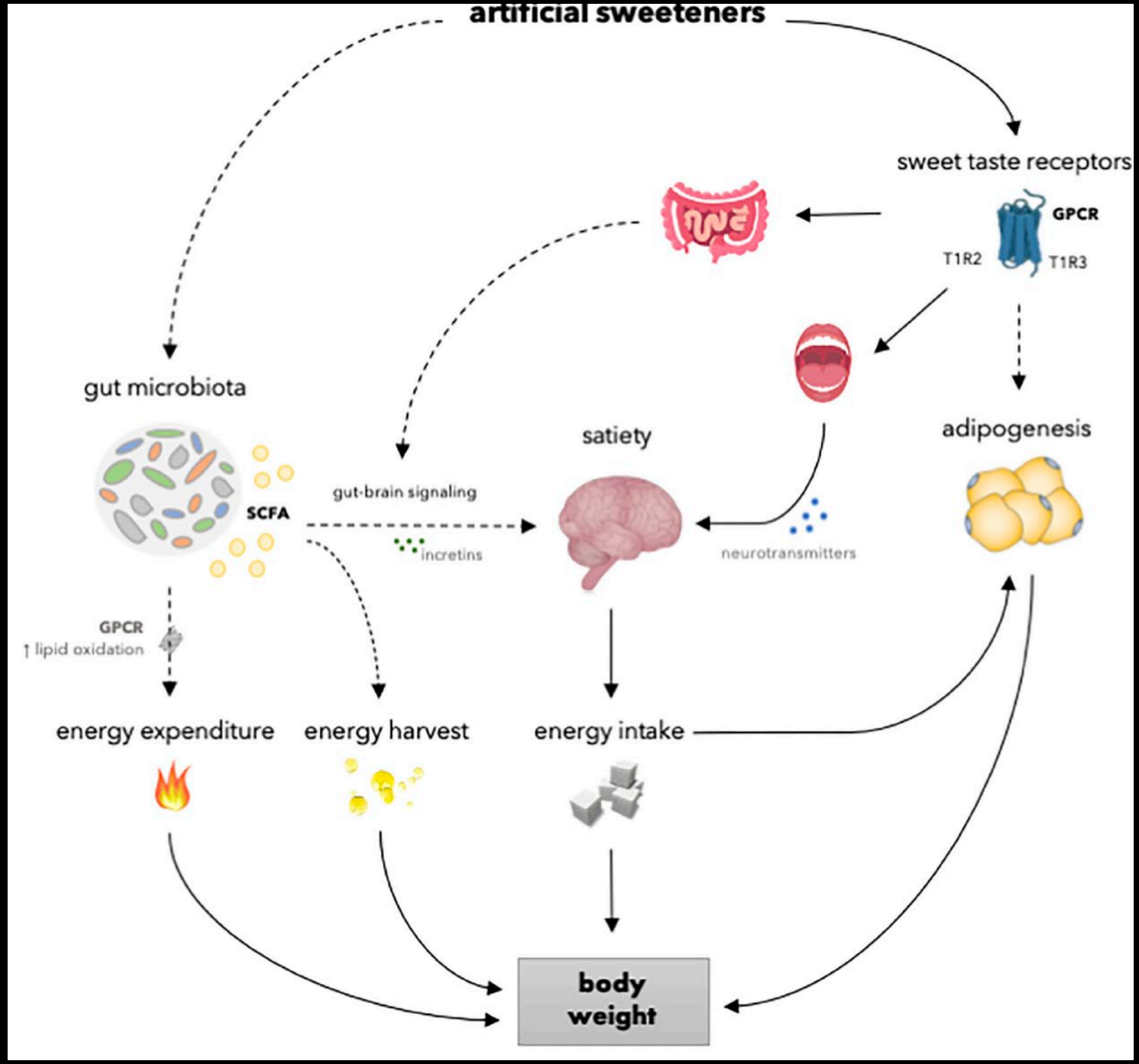
AS differ in sweetness, metabolic fate, and impact on health.

Based on Pang et al., 2021

Characteristics of human studies investigating the effect of specific artificial sweeteners on body weight or adiposity

References	Study type	Duration	Participants	Dosage artificial sweetener	Comparator	Adiposity measure	Statistical significance
Aspartame							
(34)	Meta-analysis	Acute—16 weeks	Obese, T2DM	162 mg, *ad libitum*, or 500 ml beverage	Sucrose or water	Body weight	N.S.
(34)	Meta-analysis	Acute	Obese, T2DM	162 mg or 500 ml beverage	Sucrose	Body weight	N.S.
Steviol glycoside							
(35)	Meta-analysis	90 days—2 years	Healthy, T1DM, T2DM	3.75–1,500 mg/day	Placebo (talcum, maize starch or unspecified)	BMI	N.S.
Saccharin							
(36)	RCT	12 weeks	Overweight, obese	1.25–1.75 L/daily	Sucrose	Body weight	N.S.
Sucralose							
(37)	RCT	7 days	Healthy	780 mg/day	Placebo (calcium carbonate)	Body weight	N.S.
(38)	RCT	14 days	Healthy	36 mg/day in commercial sachets	Control group	Body weight and BMI	N.S.

Mechanisms of how artificial sweeteners may affect physiological processes involved in body weight regulation.



Effects on Body Weight

- Mixed evidence:
- Meta-analyses of RCTs: Neutral or beneficial effects.
- Rodent studies: Some AS linked to weight gain at high doses.
- -AS may help reduce caloric intake without full compensation.

Interaction between artificial sweeteners, reward, and adiposity

Reward

Energy intake

Adipogenesis

Interaction between artificial sweeteners, gut microbiota, and energy balance

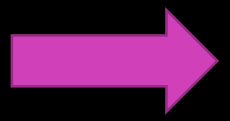
Alteration in Gut Microbiota

Gut –Brain signaling

Energy- Expenditure

Glucose homeostasis IR , Insulin secretion

Interaction between artificial sweeteners, reward, and adiposity

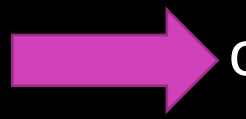
Reward  less reward compared to natural sugars

Energy intake

Adipogenesis

Interaction between artificial sweeteners, reward, and adiposity

Reward

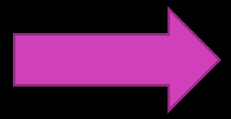
Energy intake  compensatory energy intake dose not occur

Adipogenesis

Interaction between artificial sweeteners, reward, and adiposity

Reward

Energy intake

Adipogenesis  inconsistent

Interaction between artificial sweeteners, gut microbiota, and energy balance

Alteration in Gut Microbiota

Gut –Brain signaling

Energy- Expenditure

Glucose homeostasis IR , Insulin secretion

Intestinal glucose absorption

Interaction between artificial sweeteners, gut microbiota, and energy balance

Alteration in Gut Microbiota → Alters

Gut –Brain signaling

Energy- Expenditure

Glucose homeostasis IR , Insulin secretion

Intestinal glucose absorption

Interaction between artificial sweeteners, gut microbiota, and energy balance

Alteration in Gut Microbiota

Gut –Brain signaling → no human studies

Energy- Expenditure

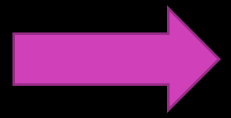
Glucose homeostasis IR , Insulin secretion

Intestinal glucose absorption

Interaction between artificial sweeteners, gut microbiota, and energy balance

Alteration in Gut Microbiota

Gut –Brain signaling

Energy- Expenditure.  needs further studied

Glucose homeostasis IR , Insulin secretion

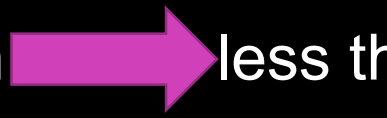
Intestinal glucose absorption

Interaction between artificial sweeteners, gut microbiota, and energy balance

Alteration in Gut Microbiota

Gut –Brain signaling

Energy- Expenditure

Glucose homeostasis IR , Insulin secretion  less than natural sugars

Intestinal glucose absorption

Interaction between artificial sweeteners, gut microbiota, and energy balance

Alteration in Gut Microbiota

Gut –Brain signaling

Energy- Expenditure

Glucose homeostasis IR , Insulin secretion less than natural sugars

Intestinal glucose absorption → no significant effects

Conclusion

- ASs have significant benefits for diabetes care, particularly in terms of weight control and blood glucose level stabilization.
- Their connection with gut health, cellular aging, and insulin sensitivity, is still controversial.
- The extant literature has a dichotomy of findings, with some indicating potential health advantages and others indicating caution.
- While ASs are useful according to several scientific reports, they should be used with caution until more definite research into their broader health effects is available.
- Future research is critical for navigating the complex environment of ASs health effects that will ultimately give a clearer guidelines for individuals and healthcare professionals involved in diabetes management.