endocrines

MDPI

Systematic Review

Sucralose Intake and Cardiometabolic Outcomes in Healthy Adults: A Systematic Review of Randomized Controlled Trials

María Pérez Sendino [1,2], Vicente Ávila Gandía [1] and Juan Pablo Rey-López [3,*]

[1] Departamento de Fisiología del Ejercicio, UCAM—Universidad Católica de Murcia, 30107 Murcia, Spain; mperez938@ext.ucam.edu (M.P.S.); vavila@ucam.edu (V.Á.G.)
[2] Programa de Doctorado en Ciencias de la Salud, UCAM—Universidad Católica de Murcia, 30107 Murcia, Spain
[3] Facultad de Deporte, UCAM—Universidad Católica de Murcia, 30107 Murcia, Spain
* Correspondence: jprey@ucam.edu

Abstract

Background/Objectives: Sucralose is a cheap, non-nutritive sweetener commonly used by the food industry. Although it seems a healthy alternative to sugar, it remains unclear whether the habitual consumption of sucralose may impair cardiometabolic health in healthy participants. **Methods:** A systematic review of randomized controlled trials evaluating the effects of sucralose on cardiometabolic outcomes was performed (using PubMed and Web of Science, since inception to May 2026). **Results:** A total of 23 randomized trials were selected (12 acute studies versus 11 studies with 7 or more days of intervention). From the latter, contradictory findings (null effects and harmful effects) of sucralose on glucose metabolism (higher insulin or glucose levels) were found. In contrast, most trials did not find short-term statistically significant changes in ghrelin, peptide YY, leptin, GLP-1 or GIP. **Conclusions:** Our systematic review shows emerging experimental evidence that habitual sucralose consumption in humans may impair glucose metabolism. The present findings raise doubts about the safety of sucralose for human consumption, and a precautionary approach indicates that sucralose intake should be reduced as part of a healthy lifestyle.

Keywords: sucralose; artificial sweeteners; glucose; insulin; microbiota

1. Introduction

Cardiometabolic diseases represent the leading cause of mortality worldwide [1,2]. Regular physical exercise (mainly endurance) lowers the risk of cardiovascular disease (CVD), reducing blood pressure and improving glycemic and lipid metabolism [3]. However, endurance athletes need sport supplements for performance reasons, which may contain high amounts of sugar, such as energy gels or rehydration beverages [4,5]. While sport supplements are essential for optimal athletic performance, the chronic consumption of high doses of sport supplements might lead to adverse metabolic responses and oral health changes. For example, the prevalence of dental caries is between 20% and 84% in elite athletes, a factor that may impair sport performance and general health [6]. Low-calorie sweeteners (LCSs) and non-nutritive sweeteners (NNSs) may help to reduce the intake of added sugars in foods and beverages, maintaining a sweet taste with minimal or no caloric load [7,8]. Nevertheless, the World Health Organization (WHO) recently examined the impact of NNSs on health through a systematic review of the literature, including randomized controlled trials (RCTs), prospective cohort studies and case–control studies [9]. Long-term prospective cohort studies suggested an association between NNS consumption

Check for updates

Academic Editor: Alessandro Delitala

Received: 22 June 2026
Revised: 3 August 2026
Accepted: 17 August 2026
Published: 28 August 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

and increased body weight, risk of type 2 diabetes, and cardiovascular disease. In contrast, some short-term RCTs reported reductions in body weight and body mass index (BMI) of participants when they consumed NNSs [10].

Although various types of NNSs exist, sucralose is the most widely used artificial sweetener worldwide [7]. Sucralose, manufactured by McNeil Specialty Products (a subsidiary of Johnson & Johnson, of Brunswick, New Jersey, USA) was approved by the Food and Drug Administration (FDA) in April 1998. With zero caloric load and being 600 times sweeter than sugar, this NNS is widely used by the food and beverage industry [11]. In fact, sucralose (also known as Splenda in USA) has been approved for use in baked goods, baking mixes, non-alcoholic beverages, chewing gum, coffee and tea products, confections and frostings, fats and oils, frozen dairy desserts, fruit and water ices, gelatins, puddings and fillings, jams and jellies, milk products, processed fruits and fruit juices, sweet sauces, toppings and syrups. In addition, sucralose is currently used in sport supplements (for example, pre-training supplements and energy gels).

The FDA and the European Food Safety Authority (EFSA) established an acceptable daily intake of up to 5–15 mg/kg/day, considering this range safe for human consumption [12]. Despite this, the safety of sucralose for human consumption has been disputed by independent scientists. Concerns included that the majority of safety studies initially approved by the FDA were conducted in animal models and had short durations. Moreover, human studies were only conducted by the manufacturer of sucralose [13].

Recent clinical trials in humans using sucralose showed harmful effects on gut microbiota integrity and the abundance of beneficial fecal microbiota [14–16]. A healthy microbiome is linked to gut health and metabolic health. Nevertheless, the challenge in distinguishing causation from correlation between gut microbiome and cardiometabolic health is still presented in the literature because most published studies are cross-sectional.

Therefore, the objective of this review is to evaluate the available experimental evidence in humans on the effects of sucralose consumption on biomarkers of cardiometabolic health (glycemic metabolism, lipid profiles, insulin sensitivity, gut microbiota, and cardiovascular health). This information may be critical for re-evaluating the safety of sucralose in the food system in general, as well as its use in the sport supplement industry.

2. Materials and Methods

2.1. Literature Search

In Web of Science and PubMed, we searched for studies involving randomized controlled trials (RCT) examining the effects of NNSs on cardiometabolic outcomes, published up to 17 May 2026. All researchers designed the search strategy for systematic review. One researcher (M.P.S.) oversaw the first identification of the literature, building the search strategy and exporting the files from Web of Science and PubMed to software for systematic reviews.

The search strategy consisted of combining Boolean operators (AND, OR) and keywords as follows: (Sucralose OR E955 OR chlorinated sucralose) AND (microbiota OR gut microbiome OR intestinal microbiota Or gut dysbiosis OR glucose OR blood glucose OR glucose tolerance OR hyperglycemia OR type 2 diabetes OR metabolic syndrome OR GLP-1 OR T1R3 OR leptin OR pancreatic function OR insulin OR insulin sensitivity OR total cholesterol OR inflammatory markers OR low-grade inflammation OR incretin OR glucagon OR sport supplement OR transaminases OR ALT OR AST OR liver enzymes OR hepatic function OR triglycerides OR lipid profile OR dyslipidemia OR dietary supplement OR sports nutrition OR protein supplement OR pre-workout OR bloating OR flatulence OR abdominal pain OR diarrhea OR gut motility OR intestinal permeability OR nausea OR digestive symptoms OR cardiometabolic health OR cardiometabolic risk OR metabolic

syndrome OR cardiovascular risk OR blood pressure OR hypertension OR endothelial function OR oxidative stress OR body weight OR obesity OR waist circumference OR visceral fat OR adiposity OR HbA1c).

The PRISMA 2020 guideline was used to describe the results of the literature search [17]. In addition, a PRISMA checklist is included in the Supplementary Material Section.

2.2. Eligibility Criteria

We selected randomized controlled trials that evaluated the effects of sucralose on cardiometabolic outcomes. Eligible studies were performed in adult populations (aged over 18 years), including participants of both sexes, in which sucralose was administrated orally as the primary intervention (exposure). Studies were required to assess at least one cardiometabolic outcome, including traditional risk factors (e.g., blood lipids, glucose, insulin or adiposity measures), inflammatory biomarkers (e.g., interleukins), markers of hepatic function, or gastrointestinal alterations. We excluded studies in which sucralose was co-administered simultaneously with other artificial sweeteners, (thereby preventing the isolation of its independent effect), pilot studies and study protocols without available results. Studies evaluating sucralose exposure from non-intervention studies (i.e., cross-sectional or cohort) or those using indirect assessment methods were not considered eligible. Studies conducted in populations with diagnosed diseases at baseline, or participants under regular use of medications, or pregnant or lactating individuals were also excluded.

Two researchers (M.P.S. and J.P.R.-L.) independently screened the articles by title and abstract using the software Rayyan (https://www.rayyan.ai, accessed on 22 March 2026) and read full-text articles for the selection stage. A third author (V.Á.G.) settled disagreements among researchers.

2.3. Data Extraction

Two researchers (M.P.S. and J.P.R.-L.) independently extracted the following data: (1) first author name and year of publication, (2) study design, (3) sample size, population main characteristics, comparison group, (4) characteristics of intervention, duration, dose of sucralose, (5) outcome variable, (6) record of sweetener consumption before the intervention, and (7) the main results of the RCTs.

If responses were inconsistent between authors, they discussed the original data again to reach a consensus.

3. Results

3.1. Identification of RCTs

From 246 records initially identified from databases, and after duplicates were removed, we screened a total of 230 records for titles and abstracts. After discarding irrelevant studies, 30 full-text articles were read to verify whether they were eligible or not. Finally, a total of 23 studies were selected for the systematic review [14–16,18–37] (Figure 1).

Table 1 shows descriptive data and characteristics of the 23 selected RCTs. A total of 797 participants were examined, with a mean age of 25.5 ± 6.3 years. Four studies included exclusively female [25,34] or male participants [20,28], and the rest included both sexes. Study durations varied from acute intervention (one dose of sucralose) representing 43.5% (n = 10) [18,19,21,22,26,29–31,34,37] to interventions lasting from 7 days to 14 weeks, representing 56.5% (n = 13) [14–16,20,23–25,27,28,32,33,35,36]. RCTs were conducted in the following countries: Mexico (n = 6), the United States, (n = 6), Canada (n = 2), Turkey (n = 2), the United Kingdom (n = 1), Germany (n = 1), Thailand (n = 1), Austria (n = 1), Israel (n = 1), Chile (n = 1) and Australia (n = 1).

Table 1. Main descriptive data of the randomized controlled trial studies that evaluated the effect of sucralose on cardiometabolic outcomes in healthy adults.

Author	Study Design	Sample Size	Population Main Characteristics	Intervention-Duration and Dose	Outcome	A Low Artificially Sweetener Diet Before the Intervention?	Main Results
Chakravartti et al. 2025 [37]	Randomized, blinded, crossover trial	N = 75	Males and females; aged 18–35 years; BMI 27.16 ± 5.17 kg/m^2	Acute intervention (single exposure sessions); 300 mL drinks containing either 75 g sucrose, sucralose (sweetness-matched to sucrose), or water	Hypothalamic blood flow (fMRI), hunger ratings, glucose levels, functional connectivity	No	Sucralose increased hypothalamic blood flow (marker of hunger) compared to sucrose and water and increased hunger vs. sucrose; sucralose altered brain connectivity in reward/motivation regions
Thomson et al. 2019 [20]	Parallel, double-blind, placebo-controlled trial	N = 34 sucralose (n = 17) placebo (n = 17)	Males; aged 18–50 years; BMI 20–30 kg/m^2; no regular engagement in intense physical activity	7 days; 780 mg/day (3 capsules × 260 mg/day); 75% of the ADI (acceptable daily intake) for a 70 kg individual	Glycemic control; insulin response; insulin resistance/sensitivity; gut microbiome composition	No	No changes were observed in glycemic control or insulin resistance. No modifications in gut microbiome composition were detected
Dalenberg et al. 2020 [32]	Randomized, double-blind, controlled clinical trial	N = 39 LCS (n = 13); Sugar (n = 13); Combo (n = 13)	Males and females; mean age 27.79 ± 3.96 years; mean BMI 23.72 ± 3.13 kg/m^2	10 days; 7 beverages of 355 mL consumed over 2 weeks (≈1 every 1–2 days); containing 0.06 g sucralose or 30.38 g sucrose or 0.06 g sucralose + 31.83 g maltodextrin	Glucose tolerance and insulin response (OGTT); insulin sensitivity/resistance; brain response to taste (fMRI); taste perception and preference.	Yes; habitual non-consumers of sweeteners	Co-ingestion of sucralose with carbohydrates impaired glucose metabolism and reduced insulin sensitivity; this effect was not observed with sucralose or sucrose administered alone
Romo-Romo et al. 2018 [24]	Open-label, parallel-group, randomized clinical trial	N = 61 intervention group (n = 30); control group (n = 31)	Males and females: intervention group (n = 24), control group (n = 25); aged 18–55 years; median age 23 years	14 days; 15% of the ADI (15 mg/kg/day) (3 commercial sachets/day)	Insulin sensitivity; acute insulin response to glucose; disposition index; glucose effectiveness	Yes; low habitual NNS consumption (<5 servings/week) in the 24 h preceding the study	Sucralose consumption showed a significant decrease in insulin sensitivity and increased insulin response, suggesting impaired glucose metabolism in healthy adults
Nichol et al. 2020 [26]	Randomized crossover design	N = 21 normal weight (n = 10); obesity (n = 11)	Males and females	Acute (single dose); participants were evaluated at three visits with one week apart; 48 mg sucralose in 60 mL	Glucose and insulin responses (OGTT, AUC); insulin sensitivity (SI); β-cell function; glucose kinetics (rate of appearance, endogenous glucose production)	Yes; habitual non-consumers of sweeteners (<1 serving/week)	Sucralose increased the glucose area under the curve. Sucralose did not affect glucose rates of appearance or β-cell function in either weight group
Yunker et al. 2021 [18]	Randomized, within-participant crossover trial	N = 74 water (beverage 1) and sucrose (beverage 2) (n = 73); water (beverage 1); sucrose (beverage 2); and sucralose (beverage 3) (n = 72)	Males and females; age 23.40 ± 3.96 years; BMI range 19.18–40.27 kg/m^2	Acute (single dose); participants were evaluated at three separate study visits; 300 mL with sucralose at an individually adjusted concentration to match the sweetness of 75 g sucrose	Neural response to food cues; endocrine responses (glucose, insulin, GLP-1, ghrelin, PYY, leptin); eating behavior; appetite ratings	No	Sucrose vs. sucralose increased glucose, insulin and GLP-1 and suppressed ghrelin, whereas sucralose alone did not stimulate endocrine responses; no overall differences in brain responses in the whole cohort

Table 1. *Cont.*

Author	Study Design	Sample Size	Population Main Characteristics	Intervention-Duration and Dose	Outcome	A Low Artificially Sweetener Diet Before the Intervention?	Main Results
Orku et al. 2022 [25]	Single-center, randomized, single-blind, controlled parallel-group study	N = 42 saccharin (n = 11); sucralose (n = 11); Asp + Ace−K (n = 11); control (n = 10)	Females; age 21.24 ± 2.26 years; BMI 20.65 ± 2.88 kg/m^2	4 weeks; 330 mL water with 140 mg saccharin or 66 mg sucralose or 88 mg aspartame + 88 mg acesulfame-K (Asp + Ace−K), or water	Glycemic response (fasting glucose and OGTT values, AUC); insulin levels (fasting and AUC); insulin sensitivity; GLP-1 concentrations; HbA1c; anthropometric measures	Yes; habitual non-consumers of sweeteners (<1 time/week)	Regular consumption of LNCS-sweetened water at doses comparable to daily-life intake over 4 weeks had no significant effect on glycemic response, insulin sensitivity, GLP-1 release, or body weight
Ford et al. 2011 [30]	Randomized, single-blind crossover design	N = 8: sucralose (S); maltodextrin + sucralose (MD); cephalic sucralose/oral rinse (WS); water (W)	Males and females (n = 7); aged 22–27 years; BMI 18.8–23.9 kg/m^2	Acute (single dose); four separate study visits; S: 50 mL of 0.083% sucralose solution; WS: 50 mL water ingested + oral rinse with 200 mL of 0.083% sucralose for 1 min (expectorated); MD: 50% w/v maltodextrin + 0.083% sucralose	Gut hormone responses (GLP-1, PYY); insulin and glucose concentrations; cephalic phase responses (insulin, GLP-1); subjective appetite ratings; energy intake at ad libitum meal	No	Oral ingestion of sucralose did not increase plasma GLP-1 or PYY concentrations. Oral stimulation with sucralose had no effect on GLP-1, insulin, or appetite
Temizkan et al. 2014 [21]	Single-blind randomized trial	N = 16: healthy (n = 8), T2DM (n = 8)	Males and females, healthy subjects: 45.0 ± 4.1 years, mean BMI 30.3 ± 4.5 kg/m^2; males and females, T2DM: 51.5 ± 9.2 years, mean BMI 33.7 ± 5.4 kg/m^2	Acute (single dose); three sessions on separate days; 200 mL water with 72 mg aspartame or 24 mg sucralose	Blood glucose levels (time points and AUC during OGTT); insulin and C-peptide levels (AUC); GLP-1 concentrations (AUC); metabolic response to sweeteners	No	Total GLP-1 AUC was significantly higher in the sucralose condition. Total glucose AUC was statistically significantly lower in the sucralose condition compared with the water condition
Brown et al. 2011 [34]	Randomized crossover clinical trial	N = 8	Females; 21.75 ± 2.25 years; BMI 22.16 ± 1.71 kg/m^2	Acute (single dose); four visits separated by 2–5 days; 355 mL water with 6 g granular Splenda (~360–480 mg sucralose), 50 g sucrose, or 50 g sucrose + 6 g Splenda	Glucose homeostasis markers (glucose, insulin, glucagon); acylated ghrelin; triacylglycerols; subjective hunger and well-being (VAS); short-term metabolic and appetite responses	No	No significant differences were detected in subjective responses, circulating triacylglycerol, or glucagon concentrations over time. Artificial sweetener ingestion (sucralose + acesulfame-K) before OGTT increased GLP-1 secretion
Staltner et al. 2023 [22]	Randomized, placebo-controlled, single-blind crossover study	N = 11	Males and females; 26.2 ± 0.8 years; BMI 21.9 ± 0.5 kg/m^2	Acute (single dose); three visits with ≥ 1week washout; 1 L water with: 180 mg sucralose or 110 g sucrose or 180 mg sucralose + 110 g maltodextrin	Postprandial endotoxemia (plasma endotoxin levels); blood glucose and lipid profile; intestinal permeability markers (xylose permeation, endotoxin translocation); intestinal damage marker (iFABP)	Yes; participants were instructed to abstain from sweeteners for 3 weeks prior to the study	Intake of a sucralose-sweetened beverage at a physiological dose had no effect on intestinal barrier function in healthy young adults

Table 1. *Cont.*

Author	Study Design	Sample Size	Population Main Characteristics	Intervention-Duration and Dose	Outcome	A Low Artificially Sweetener Diet Before the Intervention?	Main Results
Wu et al. 2012 [19]	Single-blind randomized trial	N = 10	Males and females; 28.8 ± 4.0 years; BMI 25.5 ± 1.5 kg/m^2	Acute (single dose); four sessions separated by ≥3 days; 400 mL water with 40 g glucose, 40 g 3-OMG, 40 g TIM, or 60 mg sucralose	Gut hormone responses (GLP-1, GIP); blood glucose and insulin responses; gastric emptying rate (T50); postprandial glycemic response (iAUC); subjective appetite ratings (hunger, fullness, desire to eat)	No	Preloads of 3-OMG and TIM slowed gastric emptying and induced satiety compared with sucralose. No effect of sucralose alone on the GLP-1 response to a subsequent glucose load was demonstrated.
Ahmad et al. 2020 [36]	Randomized, controlled, double-blinded, crossover design	N = 17	Males and females; 24 ± 6.8 years; BMI 22.9 ± 2.5 kg/m^2	Two 14-day treatment periods separated by a minimum of a 4-week washout period; 1000 mL water with either 0.136 g sucralose (~20% ADI) or 0.425 g aspartame (~14% ADI)	Glucose, insulin, active GLP-1, leptin (fasting and OGTT AUC); insulin sensitivity indices (HOMA-IR, HOMA-%B, HOMA-%S)	Yes; participants were not regular NNS users and avoided NNS during the study	No significant differences vs. baseline in glucose, insulin, GLP-1 or leptin concentrations (fasting or OGTT AUC); no changes in insulin sensitivity or secretion (HOMA indices); small non-significant AUC variations observed but not statistically meaningful
Ahmad et al. 2020 [35]	Randomized, double-blind crossover controlled clinical trial Secondary outcomes	N = 17	Males and females; 24 ± 6.8 years; BMI 22.9 ± 2.5 kg/m^2	Two 14-day treatment periods separated by a four-week washout period; 500 mL water with 14% of the ADI for aspartame (~0.425 g) and 20% of the ADI for sucralose (~0.136 g)	Glucose metabolism (glucose, insulin, OGTT responses); gut microbiota composition and diversity; fecal short-chain fatty acids (acetate, propionate, butyrate)	Yes; abstention from any NNS during the study period was an inclusion criterion	No significant differences were observed in the median relative proportions of the most abundant bacterial taxa before and after NNS. Microbiota community structure showed no marked differences. No significant differences in fecal SCFAs were detected following NNS consumption
Romo-Romo et al. 2025 [14]	Parallel-group, triple-blind, placebo-controlled, randomized clinical trial	N = 40: placebo (n = 20), sucralose (n = 19)	Males and females; aged 20–45 years; BMI 18.5–24.9 kg/m^2	30 days; 30% of the sucralose ADI; 90 mg pure sucralose per capsule (3 capsules/day)	Glucose homeostasis (glucose, insulin, C-peptide responses and iAUC during MMTT); insulin sensitivity (Matsuda index, HOMA-IR); gut hormones (GLP-1, ghrelin, PYY); gut microbiota composition (16S sequencing, diversity); inflammatory markers (LPS, CRP, TNF-α, IL-6); metabolites (SCFA, BCAA, fatty acid profile, Curli protein)	Yes; low habitual NNS consumption (<5 products/week)	Pro-inflammatory markers, BCAAs, acetate, and fecal Curli protein were increased, whereas serum glutamic acid and fecal butyrate were decreased following sucralose consumption. Sucralose consumption in healthy lean individuals for 30 days resulted in a statistically significant 20.3% decrease in insulin sensitivity
Méndez-García et al. 2022 [16]	Open-label, randomized clinical trial	N = 40: sucralose (n = 20), control (n = 20)	Males and females; aged 18–35 years; BMI 18.5–29.9 kg/m^2	10 weeks; 60 mL water with 48 mg sucralose; <15% of the ADI	Gut microbiota composition (relative abundance of bacterial species); glucose and insulin responses during OGTT (time points and AUC); associations between microbiota and metabolic parameters	Yes; low habitual NNS consumption	Sucralose intake altered the abundance of Firmicutes without affecting Actinobacteria or Bacteroidetes. Long-term sucralose ingestion induced gut dysbiosis associated with altered insulin and glucose levels during an OGTT

Table 1. *Cont.*

Author	Study Design	Sample Size	Population Main Characteristics	Intervention-Duration and Dose	Outcome	A Low Artificially Sweetener Diet Before the Intervention?	Main Results
Romo-Romo et al. 2020 [23]	Open-label, parallel-group, randomized clinical trial	N = 61: intervention group (n = 30), control group (n = 31)	Males and females: intervention group (n = 24), control group (n = 25); aged 18–55 years; median age 23 years	14 days; 15% of the ADI (15 mg/kg/day)	Fasting appetite-regulating hormones (GLP-1, PYY, ghrelin, leptin); fasting glucose and insulin concentrations; insulin resistance (HOMA-IR)	Yes; low habitual NNS consumption (<5 servings/week) in the 24 h preceding the study	Sucralose intake was not associated with changes in fasting concentrations of glucagon-like peptide-1, ghrelin, peptide YY, or leptin
Grotz et al. 2017 [28]	Double-blind, parallel-group, randomized clinical trial	N = 47: sucralose (n = 24), control (n = 23)	Males; sucralose: 28.92 ± 6.60 years; BMI 23.72 ± 2.23 kg/m^2; control: 29.04 ± 5.20 years, BMI 23.42 ± 2.69 kg/m^2	12 weeks; ~333 mg sucralose × 3 times/day with meals (~1000 mg/day; ~13.2 mg/kg/day)	Glucose homeostasis (fasting glucose, HbA1c, glucose AUC during OGTT); insulin and C-peptide (fasting levels and AUC); changes from baseline in glycemic and hormonal parameters	No	No clinically meaningful differences were observed between groups in glucose, insulin, or C-peptide responses to OGTTs. Results were consistent with sucralose contributing no caloric intake to the diet
Lertrit et al. 2018 [27]	Randomized, double-blind crossover study	N = 15	Males and females (n = 11); 31.9 ± 10 years; BMI 23.1 ± 3 kg/m^2	4 weeks; 200 mg sucralose in capsules	Glucose response during OGTT (AUC); insulin secretion (acute insulin response, insulinogenic index); insulin sensitivity (Matsuda index, HOMA-IR); GLP-1 response (AUC); beta-cell function indices	Yes; low habitual NNS consumption (<1 diet beverage/day or <1 tsp NNS/week)	Sucralose reduced the acute insulin response (AIR), decreased insulin sensitivity, and enhanced GLP-1 release in healthy subjects
Suez et al. 2022 [15]	Randomized, open-label, multi-arm controlled trial	N = 120: aspartame (n = 20), sucralose (n = 20), saccharin (n = 20), stevia (n = 20), glucose (n = 20), NSC (n = 20)	Males and females; median age 29.95 years (IQR 26.93–35.23)	7-day baseline period; 14-day intervention period; 7-day follow-up period; aspartame, saccharin, sucralose, and stevia at 8%, 20%, 34%, and 75% of the ADI, respectively	Glycemic response (OGTT incremental AUC using continuous glucose monitoring); gut microbiome composition and function (metagenomic sequencing); plasma metabolome; personalized glycemic responses; microbiome-mediated effects (fecal transplantation experiments)	Yes; complete NNS abstainers at enrollment	Sucralose (and saccharin) was associated with a significant increase in glycemic responses (impaired glucose tolerance) during the intervention period; responses were variable across individuals; observed changes were associated with alterations in the gut microbiome and metabolome
Gómez-Arauz et al. 2019 [29]	Randomized, parallel-group, placebo-controlled clinical trial	N = 45: sucralose (n = 25), control (n = 20)	Males and females; aged 18–35 years	Acute (single dose); 60 mL water with 48 mg sucralose	Glucose and insulin responses during OGTT (time points); serum insulin concentrations; monocyte subpopulations (classical, intermediate, nonclassical); immune markers (CD11c, CD206 expression); associations between insulin and immune cell changes	No	Sucralose was associated with significant increases in serum insulin at 30, 45, and 180 min, whereas blood glucose values showed no significant differences. Sucralose ingestion increased serum insulin and disrupted monocyte subpopulations expressing CD11c and CD206

Table 1. *Cont.*

Author	Study Design	Sample Size	Population Main Characteristics	Intervention-Duration and Dose	Outcome	A Low Artificially Sweetener Diet Before the Intervention?	Main Results
Eckstein et al. 2022 [31]	Single-center, randomized, double-blind crossover controlled trial	N = 12	Males and females; 25.4 ± 2.5 years; BMI 23.7 ± 1.7 kg/m^2	Acute (single dose); visits separated by ≥48 h; 300 mL water with 1 g/kg glucose, 1 g/kg fructose, 1 g/kg glucose-fructose, or 0.2 g sucralose	Cardiac autonomic function (HRV: SDNN, RMSSD, LF/HF); electrocardiographic parameters (QT, QTc, PQ, QRS intervals); heart rate response and heart rate turn point (HRTP) during CPET; effects of glucose, fructose and sucralose supplementation	No	Sucralose did not produce significant changes in HRV, ECG, or cardiac autonomic response compared with glucose or fructose; cardiac responses were comparable across all conditions
Bueno-Hernández et al. 2020 [33]	Randomized, parallel-group, double-blind, placebo-controlled trial	N = 95: 48 mg sucralose (n = 30), 96 mg sucralose (n = 31), control (n = 34)	Males and females; aged 18–35 years	10 weeks; 48 mg or 96 mg sucralose in 60 mL	Glucose and insulin concentrations during OGTT; AUC of glucose and insulin; insulin sensitivity; peak glucose and insulin responses; HbA1c; overall glycemic and insulinemic response	Yes; low habitual NNS consumption was an inclusion criterion	Significant changes in insulin concentrations, insulin AUCs, and glucose AUCs were observed in the 48 mg sucralose intervention group at week 10

LCS: low-calorie sweeteners; NNS: non-nutritive sweeteners; ADI: Acceptable daily intake; BMI: Body mass index; AUC: area under the curve; T2DM: Type 2 diabetes mellitus; 3OMG: 3-O-methyglucose; TIM: tagatose/isomalt mixture; OGTT: oral glucose tolerance test; NSC: No supplement control.

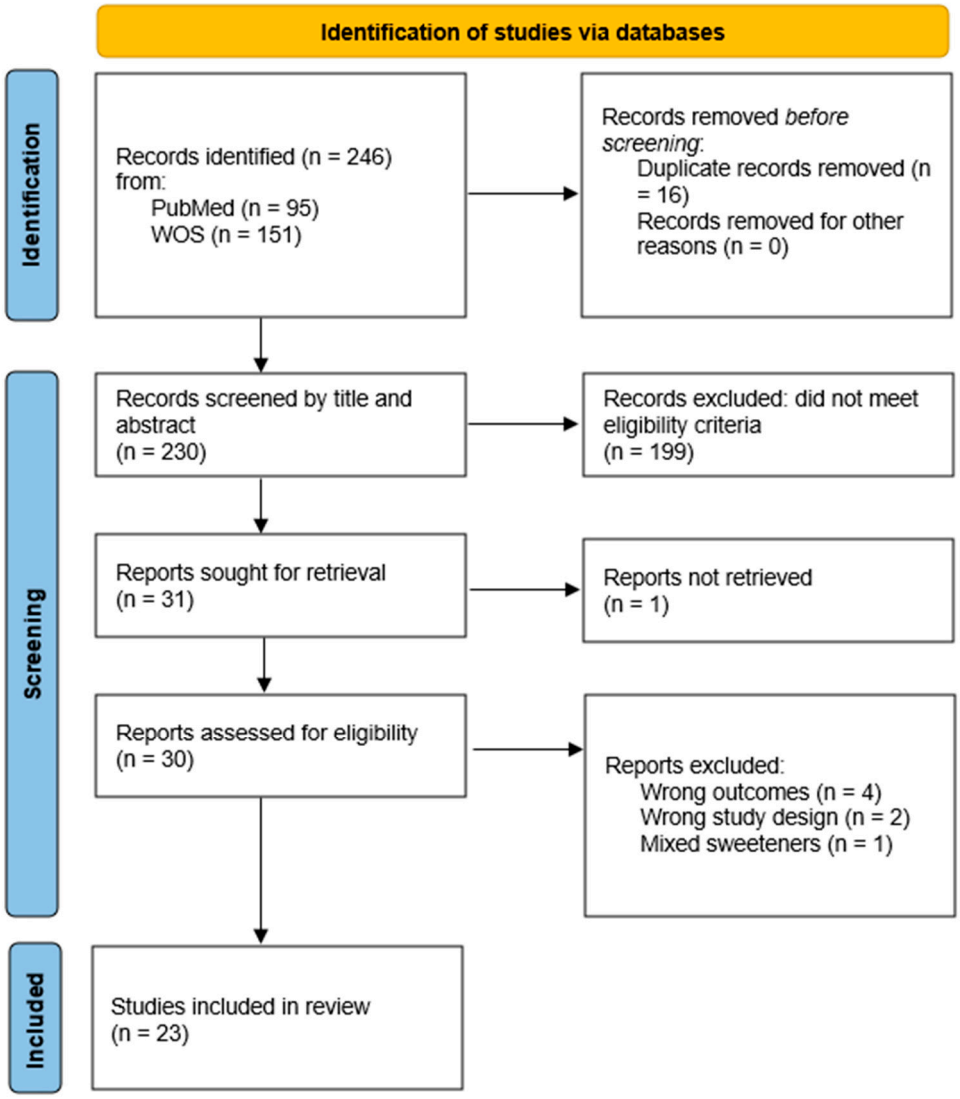


Figure 1. PRISMA 2020. Identification of randomized controlled trials of sucralose and cardiometabolic outcomes.

3.2. Glucose Homeostasis and Insulin Sensitivity

Trials involving an acute sucralose intervention (single dose) showed opposite results on fasting glucose levels or glucose AUC values or insulin AUC values. Administration of a lower dose of sucralose (24 mg) resulted in a reduction in glucose AUC compared with the group that consumed only water or aspartame [21]. No effects were observed on glucose [18,21] on glucose AUC or insulin levels [30] after a sucralose, or sucralose plus maltodextrin beverage was administered (respectively). In contrast, glucose AUC was increased in other acute trials after sucralose intake [26,30]. In one trial using the commercial product Splenda, a sweetener that combines maltodextrin with sucralose, a significant increase in glucose levels was found after 30 min and 90 min of consumption at breakfast [34].

In trials with at least 7 days of intervention, harmful effects on insulin metabolism were observed. After consumption of 15% of the ADI of sucralose for two weeks, the insulin sensitivity index decreased by 17.7% [24] and by 20.3% in a 30-day intervention study [14]. In a similar way, a statistically significant increase in glycemic responses by a glucose tolerance test (GTT-iAUC) was found with a daily intake of 34% of the ADI of sucralose after 14 days [15]. A trial with a duration of 10 days reported no effects of acute

sucralose on insulin sensitivity. However, when it was combined with a carbohydrate source (maltodextrin), a decrease in insulin sensitivity was observed [32].

In contrast, other trials did not show changes in fasting glucose levels, serum insulin, or markers of insulin resistance (HOMA-IR) [20,25,36] after sucralose intake.

3.3. Incretins and Appetite Regulating Hormones

Incretins, primarily glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), play a crucial role in the regulation of glucose homeostasis by mediating part of postprandial insulin secretion. Some studies show that acute sucralose intake does not influence levels of active ghrelin (hunger hormone), peptide YY (a satiety hormone), leptin, GLP-1 or GIP after consumption of sucralose alone or prior to a glucose load in a single administration [18,19,30,32,34], or in longer-duration interventions [14,23]. When subjective hunger sensation was assessed using data collected on the visual analogue scale (VAS), short-term sucralose consumption did not appear to increase the desire to eat compared with sucrose [34].

In contrast, other trials found changes in gut hormones. A single intake of 24 mg of sucralose significantly increased GLP-1 AUC compared with water ($p = 0.04$), with no differences under aspartame conditions [21]. After 30 days of a daily dose of 270 mg of sucralose, GLP-1 values were increased [14]. This increase was confirmed in a 4-week study [27].

The only study that assessed hypothalamic blood flow found that the intake of beverages sweetened with a dose of sucralose equivalent in sweetness to 75 g of sucrose produced a marked increase in hypothalamic blood flow, a marker associated with hunger, compared with sucrose and water in individuals with a healthy body weight [37].

3.4. Gut Microbiome Composition and Intestinal Barrier Function

Of the 23 selected studies, a total of five trials (with intervention periods of seven days or longer), assessed the composition of the human gut microbiota following sucralose consumption [14–16,20,35].

Some short-term trials, administering 20% (0.136 g) of the ADI of sucralose, did not detect statistically significant changes in intestinal bacterial diversity or evenness in fecal samples, nor in fecal metabolites such as acetate, butyrate, or propionate [20,35]. In one acute study no effects of sucralose intake on the intestinal barrier integrity was reported [22].

Opposite findings were, however, reported in three trials where sucralose intake changed the composition and functionality of the gut microbiota [14–16]. Suez et al. [15] gave four artificially sweetened products over a 14-day period, showing an impairment of the functional capacity of the human microbiome depending on the specific sweetener. These effects were observed primarily in the composition of the fecal microbiota, as well as the oral cavity [15]. Consistent with these findings, a reduction in Alpha diversity and an increased relative abundance of Gram-negative bacteria were documented. Furthermore, alterations in the metabolic profile were reported. In another trial, short-chain fatty acids (SCFAs)—particularly butyrate—were reduced, while excessive expression of the pro-inflammatory Curli protein was observed, accompanied by elevated markers of low-grade inflammation [14]. Sucralose changed the abundance of firmicutes after 10 weeks of 48 mg intake per day [16], as well as a significant reduction in beneficial bacterial species involved in the regulation of insulin and glucose levels, such as *Lactobacillus acidophilus*, as well as genera including *Prevotella o Ruminococcus*, alongside an increase in *Blautia coccoides*. Regarding the immune system, one study demonstrated that single 48 mg dose of sucralose increased the proportion of classical monocytes while reducing the levels of nonclassical monocytes [33].

3.5. Cardiac Function

One study evaluated the effect of a single dose of sucralose on cardiac function in healthy young adults during vigorous physical exercise. Analysis of heart rate variability (HRV) data showed no significant changes at any point during the assessment. When heart rate turns points (HRTP) and the time required to reach it, as determined by a cardiopulmonary exercise test (CPET), were compared with HRMTP data obtained following sucralose intake, no significant differences were found. Baseline electrocardiogram (ECG) parameters remained within normal clinical ranges [31].

4. Discussion

The main findings of the present systematic review show emerging experimental evidence that sucralose consumption in humans may impair glucose metabolism.

For example, when we restricted the synthesis of results to randomized controlled trials with at least 7 days of intervention, five trials found that sucralose intake had harmful effects on glucose metabolism [14,15,24,32]. Consistent with this experimental evidence, a recent large cohort study from France found that individuals who habitually consumed a high amount of sucralose (mean intake of 7.15 mg/day) exhibited a 34% increased risk of developing type 2 diabetes after 9 years of follow-up [38]. In contrast, three trials found non statistically significant differences on glucose levels among groups [20,25,36], with one trial reporting inconsistent effects [32], and another trial presenting wrong conclusions [36].

The mechanisms that explain the rapid deleterious changes in glucose metabolism (and a potential higher risk of type 2 diabetes) with sucralose intake in some individuals enrolled in clinical trials are not clear. Interventions exhibited substantial variation in dosage of sucralose, ranging from 24 mg/day to 1000 mg/day, which could partially explain the heterogenous results among trials. Nonetheless, Suez et al. [39] suggested an upregulation of pathways involved in lipopolysaccharide biosynthesis leading to low-grade systemic inflammation that blocks insulin signals and raises blood glucose levels.

Regarding the effects of sucralose on the gut microbiome, a scarce number of studies were identified with opposite findings. Therefore, it remains unclear whether and how sucralose may change the composition and functional capabilities of the microbiome. However, because some trials have found rapid low-grade inflammatory responses (lower butyrate, higher Curli protein expression), a regular consumption of sucralose should be avoided as a precautionary approach.

The effects of isolated sucralose on the secretion of appetite-regulating hormones appear to be minimal following acute exposure. The absence of significant effects on ghrelin and peptide YY levels may be attributed to the lack of caloric load provided by the artificial sweetener. Nevertheless, some studies found an increased secretion of glucagon-like peptide-1 (GLP-1) after several weeks of intervention. Moreover, it is intriguing that sucralose may produce direct changes in the brain. For example, repeated exposure to sweet stimuli that is not accompanied by corresponding caloric intake may interfere with hypothalamic signaling pathways that regulate hunger, altering the way in which the brain evaluates nutrient value [40]. Similarly, when the perceived sweetness substantially exceeds the associated caloric content, the body seems unable to generate an appropriate metabolic response [41]. This phenomenon, referred to as uncoupling, may explain why acute ingestion of sucralose has been shown to significantly increase hypothalamic blood flow.

5. Limitations

This systematic review has several limitations that should be considered when interpreting its findings. Many interventions were acute (one dose), which is less informative for researchers and policymakers when determining the health effects of short-term sucralose consumption. Additionally, the reduced number of selected studies did not allow us to run a meta-analysis or evaluate the risk of bias of each trial. Sensitivity analysis in meta-analysis requires a minimum of ten studies to produce informative results. Undue influence (commercial biases) in some research studies of sucralose cannot be discarded because this is a common bias in nutritional studies. The effect of heterogeneity in the formulations used across the trials (doses and mode: powder, capsules, or commercially available preparations) should be investigated in future meta-analysis. Another limitation observed in some experimental studies was the lack of measurement of habitual NNSs before the intervention studies. Researchers should exclude participants with a regular consumption of sucralose of future trials. Finally, future studies will need to evaluate additional cardiometabolic parameters beyond glycemia and insulin sensitivity, such as immune and inflammatory markers associated with diabetes or cardiovascular disease.

6. Conclusions

The systematic review shows emerging experimental evidence in humans that habitual sucralose consumption may have rapid harmful effects on glucose metabolism. However, further well-designed randomized controlled trials are needed to understand how sucralose is impacting human metabolic health. The mechanisms that explain why sucralose intake leads to reduced insulin sensitivity and higher glucose and insulin levels remain unknown, but sucralose might be involved in low-grade inflammation pathways that may impair metabolic health. Although it must be recognized that there are still very few well-designed clinical trials of sucralose and health studies in humans to promote food regulations, a precautionary approach indicates that sucralose intake should be reduced as part of healthy lifestyle. However, what defines a healthy gut requires a non-reductionist approach because there are a broad range of environmental factors that influence microbiota (for example, antibiotics, pollution and chemicals, food emulsifiers, dietary lipids, diets low in fiber and polyphenols, mental stress, lack of physical exercise) [42].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/endocrines7030049/s1, Table S1: PRISMA 2020 Check List.

Author Contributions: Conceptualization, J.P.R.-L.; methodology, M.P.S.; validation, J.P.R.-L., M.P.S. and V.Á.G.; investigation, J.P.R.-L. and M.P.S.; resources, J.P.R.-L. and M.P.S.; writing—original draft preparation, M.P.S.; writing—review and editing, J.P.R.-L.; supervision, V.Á.G.; project administration, J.P.R.-L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CVD	Cardiovascular disease
LCSs	Low-calorie sweeteners
NNSs	Non-nutritive sweeteners
WHO	World Health Organization
RCTs	Randomized controlled trials
BMI	Body mass index
FDA	Food and Drug Administration
EFSA	European Food Safety Authority
fMRI	Functional magnetic resonance imaging
MRI	Pulsed arterial spin labeling perfusion
NSC	No supplement control
OGTT	Oral glucose tolerance test
ADI	Acceptable daily intake
SI	Insulin sensitivity
T2DM	Type 2 diabetes mellitus
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulinotropic polypeptide
PYY	Peptide tyrosine
AUC	Area under the curve
iAUC	Incremental area under the curve
HbA1c	Glycated hemoglobin
VAS	Visual analogue scale
3-OMG	3-O-methyglucose
TIM	Tagatose/isomalt mixture
SCFAs	Fecal short-chain fatty acids (SCFA)
MMTT	Mixed meal tolerance test
LPS	Lipopolysaccharide
CRP	C- reactive protein
TNF-α	Tumor necrosis factor alpha
IL-6	Interleukin 6
SCFA	Short chain fatty acids
BCAA	Branched chain amino acids
HRV	Heart rate variability
HRTP	Heart rate turn points
SDNN	Standard deviation of R-R intervals
RMSSD	Differences between normal heartbeats
LF/HF	Low frequency/high frequency
CPET	Cardiopulmonary exercise testing
ECG	Electrocardiogram

References

1. World Health Organization (WHO). Cardiovascular Diseases (CVDs). 2025. Available online: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed on 27 November 2023).
2. Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators. Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators. Global, Regional, and National Burden of Cardiovascular Diseases and Risk Factors in 204 Countries and Territories, 1990–2023. *J. Am. Coll. Cardiol.* **2025**, *86*, 2167–2243. [CrossRef] [PubMed]
3. Masmoum, M.D.; Khan, S.; Usmani, W.A.; Chaudhry, R.; Ray, R.; Mahmood, A.; Afzal, M.; Mirza, M.S.S. The Effectiveness of Exercise in Reducing Cardiovascular Risk Factors Among Adults: A Systematic Review and Meta-Analysis. *Cureus* **2024**, *16*, e68928. [CrossRef] [PubMed]

4. Burd, N.A.; Jeukendrup, A.; Reid, M.B.; Burke, L.M.; Stear, S.J.; Castell, L.M. A–Z of nutritional supplements: Dietary supplements, sports nutrition foods and ergogenic aids for health and performance—Part 26. *Br. J. Sports Med.* **2011**, *45*, 1163–1164. [CrossRef] [PubMed]
5. Burke, L.M.; Jeukendrup, A.E.; Jones, A.M.; Mooses, M. Contemporary Nutrition Strategies to Optimize Performance in Distance Runners and Race Walkers. *Int. J. Sport Nutr. Exerc. Metab.* **2019**, *29*, 117–129. [CrossRef] [PubMed]
6. Schulze, A.; Busse, M. Sports Diet and Oral Health in Athletes: A Comprehensive Review. *Medicina* **2024**, *60*, 319. [CrossRef] [PubMed]
7. Risdon, S.; Battault, S.; Romo-Romo, A.; Roustit, M.; Briand, L.; Meyer, G.; Almeda-Valdes, P.; Walther, G. Sucralose and Cardiometabolic Health: Current Understanding from Receptors to Clinical Investigations. *Adv. Nutr. Int. Rev. J.* **2021**, *12*, 1500–1513. [CrossRef] [PubMed]
8. Rose, B.D.; Kreuch, D.; Wu, T.; Horowitz, M.; Rayner, C.K.; Page, A.J.; Miller, C.L.; Young, R.L. Glycemic Impact of Non-Nutritive Sweeteners in Health and Type 2 Diabetes. *Nutr. Rev.* **2026**, nuaf313. [CrossRef] [PubMed]
9. World Health Organization. *Health Effects of the Use of Non-Sugar Sweeteners: A Systematic Review and Meta-Analysis*, 1st ed.; World Health Organization: Geneva, Switzerland, 2022.
10. World Health Organization. *Use of Non-Sugar Sweeteners: WHO Guideline Summary*; World Health Organization: Geneva, Switzerland, 2023.
11. Aguayo-Guerrero, J.A.; Méndez-García, L.A.; Solleiro-Villavicencio, H.; Viurcos-Sanabria, R.; Escobedo, G. Sucralose: From Sweet Success to Metabolic Controversies—Unraveling the Global Health Implications of a Pervasive Non-Caloric Artificial Sweetener. *Life* **2024**, *14*, 323. [CrossRef] [PubMed]
12. FDA Food and Drug Administration; US Department of Health and Human Services; Public Health Services; Food Chemical News. FDA Approved New High-Intensity Sweetener Sucralose. UCSF Industry Documents Library, CSPI Collection, Center for Science in the Public Interest 1992 March 16. Available online: https://www.industrydocuments.ucsf.edu/docs/hjxd0229/ (accessed on 7 June 2026).
13. EFSA Panel on Food Additives and Flavourings (FAF); Castle, L.; Andreassen, M.; Aquilina, G.; Bastos, M.L.; Boon, P.; Fallico, B.; FitzGerald, R.; Fernandez, M.J.F.; Grasl-Kraupp, B.; et al. Re-evaluation of sucralose (E 955) as a food additive and evaluation of a new application on extension of use of sucralose (E 955) in fine bakery wares. *EFSA J.* **2026**, *24*, e9854. [CrossRef] [PubMed]
14. Romo-Romo, A.; Sánchez-Tapia, M.; López-Carrasco, M.G.; Guillén-Pineda, L.E.; Brito-Córdova, G.X.; Martagón, A.J.; Granados-Portillo, O.; Walther, G.; Gómez-Pérez, F.J.; Aguilar-Salinas, C.A.; et al. Sucralose consumption modifies glucose homeostasis, gut microbiota, Curli protein, and related metabolites in healthy individuals: A randomized placebo-controlled, triple-blind trial. *Clin. Nutr. ESPEN* **2025**, *69*, 733–744. [CrossRef] [PubMed]
15. Suez, J.; Cohen, Y.; Valdés-Mas, R.; Mor, U.; Dori-Bachash, M.; Federici, S.; Zmora, N.; Leshem, A.; Heinemann, M.; Linevsky, R.; et al. Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. *Cell* **2022**, *185*, 3307–3328.e19. [CrossRef] [PubMed]
16. Méndez-García, L.A.; Bueno-Hernández, N.; Cid-Soto, M.A.; De León, K.L.; Mendoza-Martínez, V.M.; Espinosa-Flores, A.J.; Carrero-Aguirre, M.; Esquivel-Velázquez, M.; León-Hernández, M.; Viurcos-Sanabria, R.; et al. Ten-Week Sucralose Consumption Induces Gut Dysbiosis and Altered Glucose and Insulin Levels in Healthy Young Adults. *Microorganisms* **2022**, *10*, 434. [CrossRef] [PubMed]
17. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef] [PubMed]
18. Yunker, A.G.; Alves, J.M.; Luo, S.; Angelo, B.; DeFendis, A.; Pickering, T.A.; Monterosso, J.R.; Page, K.A. Obesity and Sex-Related Associations With Differential Effects of Sucralose vs Sucrose on Appetite and Reward Processing. *JAMA Netw. Open* **2021**, *4*, e2126313. [CrossRef] [PubMed]
19. Wu, T.; Zhao, B.R.; Bound, M.J.; Checklin, H.L.; Bellon, M.; Little, T.J.; Young, R.L.; Jones, K.L.; Horowitz, M.; Rayner, C.K. Effects of different sweet preloads on incretin hormone secretion, gastric emptying, and postprandial glycemia in healthy humans. *Am. J. Clin. Nutr.* **2012**, *95*, 78–83. [CrossRef] [PubMed]
20. Thomson, P.; Santibañez, R.; Aguirre, C.; Galgani, J.E.; Garrido, D. Short-term impact of sucralose consumption on the metabolic response and gut microbiome of healthy adults. *Br. J. Nutr.* **2019**, *122*, 856–862. [CrossRef] [PubMed]
21. Temizkan, S.; Deyneli, O.; Yasar, M.; Arpa, M.; Gunes, M.; Yazici, D.; Sirikci, O.; Haklar, G.; Imeryuz, N.; Yavuz, D.G. Sucralose enhances GLP-1 release and lowers blood glucose in the presence of carbohydrate in healthy subjects but not in patients with type 2 diabetes. *Eur. J. Clin. Nutr.* **2014**, *69*, 162–166. [CrossRef] [PubMed]

22. Staltner, R.; Sánchez, V.; Bergheim, I.; Baumann, A. Acute Intake of Sucrose but Not of the Intense Sweetener Sucralose Is Associated with Post-Prandial Endotoxemia in Healthy Young Adults—A Randomized Controlled Trial. *Nutrients* **2023**, *15*, 4038. [CrossRef] [PubMed]
23. Romo-Romo, A.; Aguilar-Salinas, C.A.; López-Carrasco, M.G.; Guillén-Pineda, L.E.; Brito-Córdova, G.X.; Gómez-Díaz, R.A.; Gómez-Pérez, F.J.; Almeda-Valdes, P. Sucralose Consumption over 2 Weeks in Healthy Subjects Does Not Modify Fasting Plasma Concentrations of Appetite-Regulating Hormones: A Randomized Clinical Trial. *J. Acad. Nutr. Diet.* **2020**, *120*, 1295–1304. [CrossRef] [PubMed]
24. Romo-Romo, A.; Aguilar-Salinas, C.A.; Brito-Córdova, G.X.; Gómez-Díaz, R.A.; Almeda-Valdes, P. Sucralose decreases insulin sensitivity in healthy subjects: A randomized controlled trial. *Am. J. Clin. Nutr.* **2018**, *108*, 485–491. [CrossRef] [PubMed]
25. Orku, S.E.; Suyen, G.; Bas, M. The effect of regular consumption of four low- or no-calorie sweeteners on glycemic response in healthy women: A randomized controlled trial. *Nutrition* **2022**, *106*, 111885. [CrossRef] [PubMed]
26. Nichol, A.D.; Salame, C.; Rother, K.I.; Pepino, M.Y. Effects of Sucralose Ingestion versus Sucralose Taste on Metabolic Responses to an Oral Glucose Tolerance Test in Participants with Normal Weight and Obesity: A Randomized Crossover Trial. *Nutrients* **2020**, *12*, 29. [CrossRef] [PubMed]
27. Lertrit, A.; Srimachai, S.; Saetung, S.; Chanprasertyothin, S.; Chailurkit, L.-O.; Areevut, C.; Katekao, P.; Ongphiphadhanakul, B.; Sriphrapradang, C. Effects of sucralose on insulin and glucagon-like peptide-1 secretion in healthy subjects: A randomized, double-blind, placebo-controlled trial. *Nutrition* **2018**, *55–56*, 125–130. [CrossRef] [PubMed]
28. Grotz, V.L.; Pi-Sunyer, X.; Porte, D., Jr.; Roberts, A.; Trout, J.R. A 12-week randomized clinical trial investigating the potential for sucralose to affect glucose homeostasis. *Regul. Toxicol. Pharmacol.* **2017**, *88*, 22–33. [CrossRef] [PubMed]
29. Gómez-Arauz, A.Y.; Bueno-Hernández, N.; Palomera, L.F.; Alcántara-Suárez, R.; De León, K.L.; Méndez-García, L.A.; Carrero-Aguirre, M.; Manjarrez-Reyna, A.N.; Martínez-Reyes, C.P.; Esquivel-Velázquez, M.; et al. A Single 48 mg Sucralose Sip Unbalances Monocyte Subpopulations and Stimulates Insulin Secretion in Healthy Young Adults. *J. Immunol. Res.* **2019**, *2019*, 6105059. [CrossRef] [PubMed]
30. Ford, H.E.; Peters, V.; Martin, N.M.; Sleeth, M.L.; Ghatei, M.A.; Frost, G.S.; Bloom, S.R. Effects of oral ingestion of sucralose on gut hormone response and appetite in healthy normal-weight subjects. *Eur. J. Clin. Nutr.* **2011**, *65*, 508–513. [CrossRef] [PubMed]
31. Eckstein, M.L.; Zimmermann, P.; Erlmann, M.P.; Wachsmuth, N.B.; Haupt, S.; Zimmer, R.T.; Schierbauer, J.; Herz, D.; Aberer, F.; Sourij, H.; et al. Glucose and Fructose Supplementation and Their Acute Effects on Electrocardiographic Time Intervals during Anaerobic Cycling Exercise in Healthy Individuals: A Secondary Outcome Analysis of a Double-Blind Randomized Crossover-Controlled Trial. *Nutrients* **2022**, *14*, 3257. [CrossRef] [PubMed]
32. Dalenberg, J.R.; Patel, B.P.; Denis, R.; Veldhuizen, M.G.; Nakamura, Y.; Vinke, P.C.; Luquet, S.; Small, D.M. Short-Term Consumption of Sucralose with, but Not without, Carbohydrate Impairs Neural and Metabolic Sensitivity to Sugar in Humans. *Cell Metab.* **2020**, *31*, 493–502.e7. [CrossRef] [PubMed]
33. Bueno-Hernández, N.; Esquivel-Velázquez, M.; Alcántara-Suárez, R.; Gómez-Arauz, A.Y.; Espinosa-Flores, A.J.; de León-Barrera, K.L.; Mendoza-Martínez, V.M.; Medina, G.A.S.; León-Hernández, M.; Ruiz-Barranco, A.; et al. Chronic sucralose consumption induces elevation of serum insulin in young healthy adults: A randomized, double blind, controlled trial. *Nutr. J.* **2020**, *19*, 32. [CrossRef] [PubMed]
34. Brown, A.W.; Brown, M.M.B.; Onken, K.L.; Beitz, D.C. Short-term consumption of sucralose, a nonnutritive sweetener, is similar to water with regard to select markers of hunger signaling and short-term glucose homeostasis in women. *Nutr. Res.* **2011**, *31*, 882–888. [CrossRef] [PubMed]
35. Ahmad, S.Y.; Friel, J.; Mackay, D. The Effects of Non-Nutritive Artificial Sweeteners, Aspartame and Sucralose, on the Gut Microbiome in Healthy Adults: Secondary Outcomes of a Randomized Double-Blinded Crossover Clinical Trial. *Nutrients* **2020**, *12*, 3408. [CrossRef] [PubMed]
36. Ahmad, S.Y.; Friel, J.K.; MacKay, D.S. The effect of the artificial sweeteners on glucose metabolism in healthy adults: A randomized, double-blinded, crossover clinical trial. *Appl. Physiol. Nutr. Metab.* **2020**, *45*, 606–612. [CrossRef] [PubMed]
37. Chakravartti, S.P.; Jann, K.; Veit, R.; Liu, H.; Yunker, A.G.; Angelo, B.; Monterosso, J.R.; Xiang, A.H.; Kullmann, S.; Page, K.A. Non-caloric sweetener effects on brain appetite regulation in individuals across varying body weights. *Nat. Metab.* **2025**, *7*, 574–585. [CrossRef] [PubMed]
38. Debras, C.; Deschasaux-Tanguy, M.; Chazelas, E.; Sellem, L.; Druesne-Pecollo, N.; Esseddik, Y.; de Edelenyi, F.S.; Agaësse, C.; De Sa, A.; Lutchia, R.; et al. Artificial Sweeteners and Risk of Type 2 Diabetes in the Prospective NutriNet-Santé Cohort. *Diabetes Care* **2023**, *46*, 1681–1690. [CrossRef] [PubMed]
39. Suez, J.; Korem, T.; Zeevi, D.; Zilberman-Schapira, G.; Thaiss, C.A.; Maza, O.; Israeli, D.; Zmora, N.; Gilad, S.; Weinberger, A.; et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* **2014**, *514*, 181–186. [CrossRef] [PubMed]
40. Veldhuizen, M.G.; Babbs, R.K.; Patel, B.; Fobbs, W.; Kroemer, N.B.; Garcia, E.; Yeomans, M.R.; Small, D.M. Integration of Sweet Taste and Metabolism Determines Carbohydrate Reward. *Curr. Biol.* **2017**, *27*, 2476–2485.e6. [CrossRef] [PubMed]

41. Ouyang, K.; Nayak, S.; Lee, Y.; Kim, E.; Wu, M.; Tallarida, C.S.; Rawls, S.M. Behavioral effects of Splenda, Equal and sucrose: Clues from planarians on sweeteners. *Neurosci. Lett.* **2017**, *636*, 213–217. [CrossRef] [PubMed]
42. Van Hul, M.; Cani, P.D.; Petitfils, C.; De Vos, W.M.; Tilg, H.; El-Omar, E.M. What defines a healthy gut microbiome? *Gut* **2024**, *73*, 1893–1908. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.