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**Impact of sucralose on postprandial
glycemic and insulinemic responses
and GLP-I secretion in adults: a
systematic review and meta-analysis**

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Impacto da sucralose na resposta pós-prandial glicémica e insulinémica e na secreção de GLP-1 em adultos: revisão sistemática e meta-análise

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This is just the end of a beginning...

Abstract

Background and Objectives: The metabolic neutrality of non-nutritive sweeteners (NNS) remains inconsistent. This systematic review and meta-analysis evaluated the acute effects of sucralose, alone or with carbohydrates, on postprandial glycemic, insulinemic, and glucagon-like peptide-1 (GLP-1) responses in adults.

Methods: Following PRISMA guidelines, the search was conducted across PubMed and Web of Science up to November 1, 2025, for randomized controlled trials (RCTs) assessing glycemic and insulinemic responses and GLP-1 secretion. Risk of bias was evaluated via Cochrane RoB 2.0, and random-effects meta-analyses were performed.

Results: Seventeen RCTs (424 participants) were included, with eight suitable for quantitative analysis. In healthy adults, sucralose demonstrated showed no statistically significant overall effect. Conversely, in obesity or insulin resistance, oral sucralose modulated insulin kinetics, showing up to a 20% increase in insulin incremental area under the curve (iAUC) and decreased insulin sensitivity. GLP-1 responses and gastrointestinal infusions yielded no variations (except under complex matrices), while sham-feeding suggested, without statistical confirmation, a role for cephalic oral signaling.

Conclusion: Sucralose is not uniformly inert. While neutral in healthy individuals, it acts as an endocrine modulator in populations with metabolic vulnerabilities, depending on host phenotype, cephalic oral engagement, and nutrient co-ingestion.

Keywords: Sucralose; Cephalic Phase; Glucagon-Like Peptide-1; Glycemic Response; Insulin Secretion.

Resumo

Introdução e Objetivos: A neutralidade metabólica dos adoçantes não-nutritivos (ANN) permanece inconsistente. Esta revisão sistemática e meta-análise avaliou os efeitos agudos da sucralose, isolada ou com hidratos de carbono, nas respostas pós-prandiais glicémica, insulinémica e do peptídeo semelhante ao glucagon-1 (GLP-1) em adultos.

Métodos: Seguindo as diretrizes PRISMA, a pesquisa foi realizada na PubMed e Web of Science até 1 de novembro de 2025 por ensaios clínicos randomizados (ECRs) para avaliar as respostas glicémicas e insulinémicas e a secreção do GLP-1. O risco de viés foi avaliado via Cochrane RoB 2.0 e realizaram-se meta-análises de efeitos aleatórios.

Resultados: Foram incluídos dezassete ECRs (424 participantes), sendo oito adequados para análise quantitativa. Em adultos saudáveis, a sucralose não demonstrou um efeito global estatisticamente significativo. Contudo, na obesidade ou resistência à insulina, a sucralose oral modificou a cinética da insulina, com aumentos de até 20% na área incremental sob a curva (iAUC) e menor sensibilidade à insulina. As respostas ao GLP-1 e as infusões gastrointestinais não revelaram variações (exceto em matrizes complexas), enquanto o *sham-feed* sugeriu, sem confirmação estatística, um papel da sinalização oral cefálica.

Conclusão: A sucralose não é uniformemente inerte. Embora seja neutra em indivíduos saudáveis, atua como modulador endócrino em populações com vulnerabilidades metabólicas, dependendo do fenótipo, do envolvimento oral e da coingestão de nutrientes.

Palavras-Chave: Sucralose; Fase Cefálica; Glucagon-Like Peptide-1; Resposta Glicémica; Secreção de Insulina.

Index

Acknowledgments	ii
Abstract.....	iv
Keywords	iv
Resumo	v
Palavras-Chave	v
List of Abbreviations.....	viii
List of Figures.....	x
1. Introduction.....	1
2. Aims	4
3. Methods.....	4
3.1. Eligibility Criteria	4
3.2. Search Strategy and Selection Process.....	5
3.3. Outcomes and Data Extraction.....	6
3.4. Risk of Bias Assessment	7
3.5. Quantitative and Qualitative Synthesis	8
4. Results	9
4.1. Study Selection	9
4.2. Characteristics of the Included Studies.....	10
4.3. Risk of Bias Assessment	11
4.4. Postprandial Glycemic Responses	12
4.5. Postprandial Insulinemic Responses	13

4.6.	Postprandial GLP-1 Secretion	14
4.7.	Mechanistic Pathways: Oral Signaling versus Direct Intestinal Exposure	14
4.8.	Meta-Analysis and Heterogeneity Framework	15
4.8.1.	Standard Oral Ingestive Pathways	16
4.8.2.	Sensory-Isolated and Mechanistic Protocols (Sham-Feeding)	19
4.8.3.	Methodological Scope and Descriptive Certainty Reporting	20
5.	Discussion	21
5.1.	Principal Findings	21
5.2.	Influence of Baseline Metabolic Phenotype	22
5.3.	Oral Sensory Signalling and Intestinal Exposure	23
5.4.	Effects of Nutrient Co-Ingestion on GLP-1 Response.....	25
5.5.	Methodological Sources of Heterogeneity	25
5.6.	Strengths and Limitations.....	26
6.	Conclusion.....	28
	Bibliography.....	30
	Supplementary Material.....	36
	Appendix I - Systematic Literature Search Strategies	36
	Appendix II - Characteristics of Included Studies.....	37
	Appendix III - Methodological Risk of Bias Assessment (RoB 2.0)	38

List of Abbreviations

ADI - Acceptable Daily Intake

ANN - Adoçantes Não-Nutritivos

AUC - Area Under the Curve

BMI - Body Mass Index

CPIR - Cephalic Phase Insulin Response

DPP-4 - Dipeptidyl Peptidase-4

ECRs - Ensaios Clínicos Randomizados

EFSA - European Food Safety Authority

FAO - Food and Agriculture Organization

FDA - Food and Drug Administration

GIP - Glucose-Dependent Insulinotropic Polypeptide

GLP-1 - Glucagon-Like Peptide-1

HOMA-IR - Homeostatic Model Assessment of Insulin Resistance

iAUC - Incremental Area Under the Curve

JECFA - Joint FAO/WHO Expert Committee on Food Additives

MeSH - Medical Subject Headings

NNS - Non-Nutritive Sweeteners

OGTT - Oral Glucose Tolerance Test

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PYY - Peptide YY

RCTs - Randomized Controlled Trials

RoB 2.0 - Risk of Bias 2.0

SGLT-1 - Sodium Glucose Cotransporter 1

T1R - Type 1 Taste Receptors

T1DM - Type 1 Diabetes Mellitus

T2DM - Type 2 Diabetes Mellitus

WHO - World Health Organization

List of Figures

Figure 1. PRISMA 2020 flow diagram of the study selection process.....	11
Figure 2. Forest plot of glucose incremental area under the curve (iAUC) following acute oral sucralose ingestion preceding a glycemic or carbohydrate challenge	17
Figure 3. Forest plot of peak postprandial glucose concentrations following acute oral sucralose ingestion.....	18
Figure 4. Forest plot of insulin incremental area under the curve (iAUC) following acute oral sucralose ingestion.....	18
Figure 5. Forest plot of peak postprandial insulin concentrations following acute oral sucralose ingestion	19
Figure 6. Forest plot of GLP-1 incremental area under the curve (iAUC) following acute oral sucralose ingestion.....	19
Figure 7. Forest plot of cephalic-phase glucose iAUC during sensory-isolated sham-feeding protocols	20
Figure 8. Forest plot of cephalic-phase insulin iAUC during sensory-isolated sham-feeding protocols	21

1. Introduction

Excess intake of free sugars is a well-established contributor to excess daily energy intake and to the growing burden of non-communicable diseases, including obesity, type 2 diabetes mellitus (T2DM), and the metabolic syndrome⁽¹⁻⁸⁾. To response to these public health concerns, the World Health Organization (WHO) has recommended, since 2015, that free sugar intake should be limited to less than 10% of total daily energy intake^(9, 10). More recently, the 2026-2031 Dietary Guidelines for Americans introduced even more stringent boundaries by shifting the focus toward acute metabolic management, proposing a maximum threshold of 10 grams of added sugars per single meal occasion to mitigate postprandial glycemic excursions⁽¹¹⁾. These recommendations have encouraged the food industry to reformulate products by reducing sugar content and replacing them with non-nutritive sweeteners (NNS), also referred to as low- or zero-calorie sweeteners^(5, 12-15). This strategy is widely discussed as a key intervention for mitigating the obesity epidemic and improving public health outcomes by preserving sweet palatability while lowering the energy density of traditionally high-sugar products⁽¹⁶⁻¹⁸⁾.

Among NNS, sucralose (1,6-dichloro-1,6-dideoxy- β -D-fructofuranosyl-4-chloro-4-deoxy- α -D-galactopyranoside) is one of the most widely used additives in "zero-sugar," "sugar-free," or "diet" products⁽¹⁹⁻²¹⁾. Sucralose is an organochlorine derivative of sucrose with an estimated sweetening power approximately 600 times greater than that of sucrose. Because of its chemical stability, including resistance to heat and to a wide range of pH conditions, sucralose is extensively used in processed foods and beverages and across multiple food matrices^(16, 21-24). It is currently approved as a food additive (E955) by major regulatory authorities,

including the Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (JECFA), the U.S. Food and Drug Administration (FDA), and the European Food Safety Authority (EFSA)⁽²⁴⁻²⁷⁾. The current acceptable daily intake (ADI) established by WHO is 15 mg/kg body weight⁽²⁷⁻²⁹⁾.

The physiological response to sucralose begins in the oral cavity, where sweet taste is detected through Type 1 taste receptors (T1R2/T1R3) coupled to G-protein α -gustducin⁽³⁰⁻³²⁾. Activation of these pathways may contribute to cephalic-phase responses, which represent anticipatory neuroendocrine signals that prepare the organism for nutrient ingestion. These responses may influence not only early insulin secretion and incretin signaling, but also central pathways involved in appetite regulation, reward processing, and food-related behavior⁽³³⁻³⁸⁾.

In addition, sweet taste receptors are also expressed in extraoral tissues, including the gastrointestinal tract and the pancreas, where they have been proposed to function as metabolic sensors^(31, 39-41). In the intestinal lumen, sucralose may stimulate incretin secretion, particularly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) and may interact with transport systems such as sodium glucose cotransporter 1 (SGLT-1), thereby potentially modifying carbohydrate absorption dynamics^(32, 36, 39, 42-44). At the pancreatic level, sucralose has also been suggested to act directly on β -cells through locally expressed sweet taste receptors, thereby modulating insulin secretion^(40, 41).

However, findings from human studies remain inconsistent⁽⁴⁵⁻⁴⁸⁾. Some studies have reported that sucralose may impair insulin sensitivity, alter postprandial glucose and insulin responses, or influence the gut microbiota in

healthy individuals⁽⁴⁹⁻⁵¹⁾, whereas others have found no significant acute metabolic effects⁽⁵²⁻⁵⁴⁾. These inconsistencies may reflect substantial heterogeneity in study populations, dosing regimens, administration routes, comparator conditions, and measured outcomes. For this reason, a systematic synthesis of the available evidence is needed to clarify the acute metabolic effects of sucralose in humans⁽⁵⁵⁻⁵⁷⁾.

From a pharmacokinetic perspective, most ingested sucralose is not absorbed. Approximately 84% passes through the gastrointestinal tract unchanged and is excreted in the feces^(58, 59). This fraction is generally considered metabolically inert during intestinal transit. The remaining fraction is absorbed in the upper small intestine, undergoes minimal biotransformation, and is excreted primarily in the urine⁽⁵⁸⁻⁶⁰⁾. However, although sucralose is mostly eliminated within a relatively short time frame, some evidence suggests that a small, absorbed fraction may persist in systemic circulation or accumulate in adipose tissue, raising questions about possible long-term metabolic effects^(58, 59, 61).

Historically, NNS have been promoted as useful dietary tools to support glycemic control and body weight management, particularly in individuals with obesity or diabetes^(34, 62, 63). However, their long-term health effects remain controversial. Observational evidence has linked frequent NNS consumption with adverse cardiometabolic outcomes, including obesity, dysglycemia, metabolic syndrome, and possibly all-cause mortality, although causality remains uncertain^(4, 64-67). Moreover, most existing reviews either assess NNS as a single group or focus on compounds other than sucralose, such as aspartame^(68, 69), steviol glycosides⁽⁷⁰⁻⁷²⁾ or blends of acesulfame-K⁽⁷³⁾. Because each NNS has a distinct

chemical structure, receptor-binding pattern, and pharmacokinetic profile, pooling different sweeteners may obscure compound-specific effects.

Therefore, a dedicated and systematic synthesis focusing exclusively on this sweetener is warranted to address the current gaps in literature. The specific aims and clinical questions addressed by this work are detailed in the following section.

2. Aims

The primary aim of this systematic review and meta-analysis is to synthesize the acute metabolic effects of sucralose in adults. Specifically, this study evaluates the acute impact of sucralose—administered either in isolation or co-ingested with carbohydrates—on postprandial glycemic, insulinemic, and GLP-1 responses, relative to placebos, water, caloric controls, or alternative sweeteners.⁽⁵⁵⁾

3. Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement⁽⁷⁴⁾. As this project comprised a systematic review and meta-analysis of previously published literature, formal institutional ethical approval was not required. The comprehensive review protocol, outlining the core objectives, precise eligibility criteria, and planned analytical workflows, was registered in the PROSPERO database on January 5, 2026 (Registration ID: CRD420251270273)⁽⁵⁵⁾.

3.1. Eligibility Criteria

Studies were considered eligible if they evaluated the acute postprandial metabolic effects of sucralose exposure in adult cohorts. Studies were included if

sucralose was administered alone (e.g., dissolved in plain water) or co-administered with food, carbohydrate challenges, or alternative sweeteners, without restrictions on dosage or vehicle formulation (including liquids, tablets, capsules, or complex solid meals). Eligible comparators encompassed inert placebos (defined as an identical vehicle devoid of sucralose), water controls, caloric references (such as sucrose, glucose, or fructose), and alternative non-nutritive sweeteners.

The eligible population included adults of either sex or any ethnic background. For descriptive and stratifying purposes, participants were categorized based on baseline metabolic phenotypes into three major groups: healthy (normal-weight or overweight individuals with a body mass index [BMI] < 30 kg/m²), individuals with obesity (BMI ≥ 30 kg/m²), or patients diagnosed with type 1 (T1DM) and/or type 2 diabetes mellitus (T2DM), whenever such baseline details were reported.

To meet inclusion criteria, clinical trials were required to report at least one of the following postprandial parameters: glycemic response, insulinemic response, or GLP-1 secretion kinetics. Eligibility was strictly restricted to human randomized controlled trials (RCTs). Consequently, case reports, case series, scientific commentaries, editorials, narrative reviews, observational designs, and all animal or in vitro experimental models were excluded.

3.2. Search Strategy and Selection Process

A systematic literature search was executed across PubMed (MEDLINE) and Web of Science from database inception through November 1, 2025. The operational search strings combined controlled vocabulary terms (such as MeSH) and free-text

keywords including sucralose, non-nutritive sweeteners, glycemic response, insulin excursions, and GLP-1 kinetics (the full search strategies across databases are detailed in Appendix I). Furthermore, official public repositories from the European Food Safety Authority (EFSA) and the U.S. Food and Drug Administration (FDA) were consulted for regulatory context, and the reference lists of all eligible papers were manually screened to capture missing reports.

No language or publication year restrictions were applied. Following the automated removal of duplicate records, two reviewers (M.J. and N.B.) independently screened all retrieved titles and abstracts. Potentially eligible studies were subsequently subjected to independent full-text evaluation. Any interpersonal disagreements during the selection process were resolved via structured consensus or, when necessary, through arbitration by a third senior reviewer (P.T.). Articles not accessible via institutional subscriptions were requested directly from the corresponding authors.

3.3. Outcomes and Data Extraction

The primary outcomes of interest were:

- Postprandial glycemic response, assessed via incremental area under the curve (iAUC), total area under the curve (AUC total), and peak glucose concentration.
- Postprandial insulinemic response, assessed via iAUC, AUC total, and peak insulin concentration.

The secondary outcome of interest was the postprandial GLP-1 response, captured through cumulative area metrics or peak concentrations.

Two reviewers (M.J. and N.B.) independently extracted data using a standardized, pre-piloted spreadsheet. The following variables were systematically collected (Appendix II): first author and publication year; study design; sample size per treatment arm; participant baseline characteristics (including age, sex, BMI, and metabolic status); intervention and comparator characteristics (dose, vehicle, molecular formulation, and administration route); duration and granularity of postprandial sampling; and main metabolic outcomes (glucose, insulin, and GLP-1 profiles).

Whenever outcome data was presented exclusively within graphics, numerical values were extracted from high-resolution vectors using Plot Digitizer software (version 2.5.1) and statistically recalculated following standard validated methods. All extracted data points were converted into International System (SI) units prior to statistical synthesis.

3.4. Risk of Bias Assessment

Two reviewers (M.J. and N.B.) independently evaluated the risk of bias for each included trial using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool⁽⁷⁵⁾. Methodological evaluations were performed at the outcome level, assessing glycemic, insulinemic, and incretin parameters independently across five structural domains:

1. Bias arising from the randomization process;
2. Bias due to deviations from intended interventions;
3. Bias due to missing outcome data;
4. Bias in measurement of the outcome;
5. Bias in selection of the reported result.

Each operational domain was classified as "low risk of bias", "some concerns", or "high risk of bias" following official RoB 2.0 implementation guidelines. Inter-reviewer discrepancies were resolved by consensus or through adjudication by a third author (P.T.). Summary plots and domain visualizations were generated using the 'robvis' package (Appendix III).

3.5. Quantitative and Qualitative Synthesis

Meta-analytic calculations were performed using JASP (Version 0.19.1; JASP Team). Random-effects models were used throughout, since the included trials differed in sucralose dose, delivery vehicle, and the metabolic phenotype of participants. For continuous postprandial outcomes, effect sizes were expressed as standardized mean differences (SMD) utilizing Hedges' g with corresponding 95% confidence intervals (CIs) to effectively minimize small-sample inflation bias (trials with 8 to 30 participants per arm).

Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic, using the conventional 50% threshold to flag moderate-to-high inconsistency. A minimum of three independent treatment arms ($n \geq 3$) was required before an outcome was pooled quantitatively, to avoid unstable pooled estimates and severe bias in variance or heterogeneity estimates; below that threshold, findings were reported via descriptive narrative synthesis, since pooled variance and heterogeneity estimates become unreliable with so few data points.

Two further rules governed which comparisons could enter the same pooled model. First, only trials using an inert reference condition – water, saline, or a matched placebo vehicle – were combined; trials that instead compared sucralose against an active caloric comparator addressed a different clinical question and

were kept out of the quantitative pooling. This ruled out Dhillon et al.⁽⁷⁶⁾, where sham-fed sucralose was compared against sham-fed sucrose rather than water, and Wu et al.⁽⁷⁷⁾, where sucralose itself served as the reference condition against glucose, tagatose/isomalt, and TIM preloads. Neither trial produced a sucralose-versus-inert-control effect size, so both were retained only in the narrative synthesis. Second, when a single crossover trial tested more than one sucralose dose against the same control group, only one dose was carried into each pooled model, to avoid entering that control arm more than once and artificially shrinking the between-study variance. This applied to Sylvetsky et al.⁽⁷⁸⁾, where the 68 mg dose was selected for being closest to the range used across the remaining trials (24-52 mg).

Encapsulated or intragastric/intraduodenal delivery – which bypasses oral and cephalic-phase exposure altogether – was treated as mechanistically distinct from both standard oral ingestion and sham-feeding. Mezitis et al.⁽⁷⁹⁾ was the only eligible trial using this route, and with just two treatment arms it fell short of the pooling threshold; findings from this study are therefore reported narratively.

Evidence certainty was judged qualitatively, drawing on the RoB 2.0 ratings, the degree of statistical inconsistency (I^2), and the imprecision associated with small sample sizes. A formal GRADE assessment was not conducted.

Three subgroup dimensions were considered wherever the data allowed a meaningful split: baseline metabolic phenotype (healthy, obese, or diabetic), route of exposure (oral ingestion, sham-feeding, or direct gastrointestinal infusion/encapsulation), and nutrient context (sucralose alone versus co-ingested with a carbohydrate load).

Publication bias assessment via funnel plot asymmetry and Egger's regression test was reserved for pooled analyses with at least ten treatment arms included. None of the outcomes evaluated in the present work reached this threshold, so these tests were not applied.

4. Results

4.1. Study Selection

The database search identified 3072 records. After removal of 2174 duplicates, 898 titles and abstracts were screened. Fifty full-text articles were assessed for eligibility, of which 17 randomized controlled trials met the inclusion criteria and were included in the qualitative synthesis. Eight of these studies provided data suitable for quantitative pooling. A PRISMA 2020 flow diagram summarizing the study selection process and reasons for exclusion at the full-text stage is presented in Figure 1⁽⁷⁴⁾.

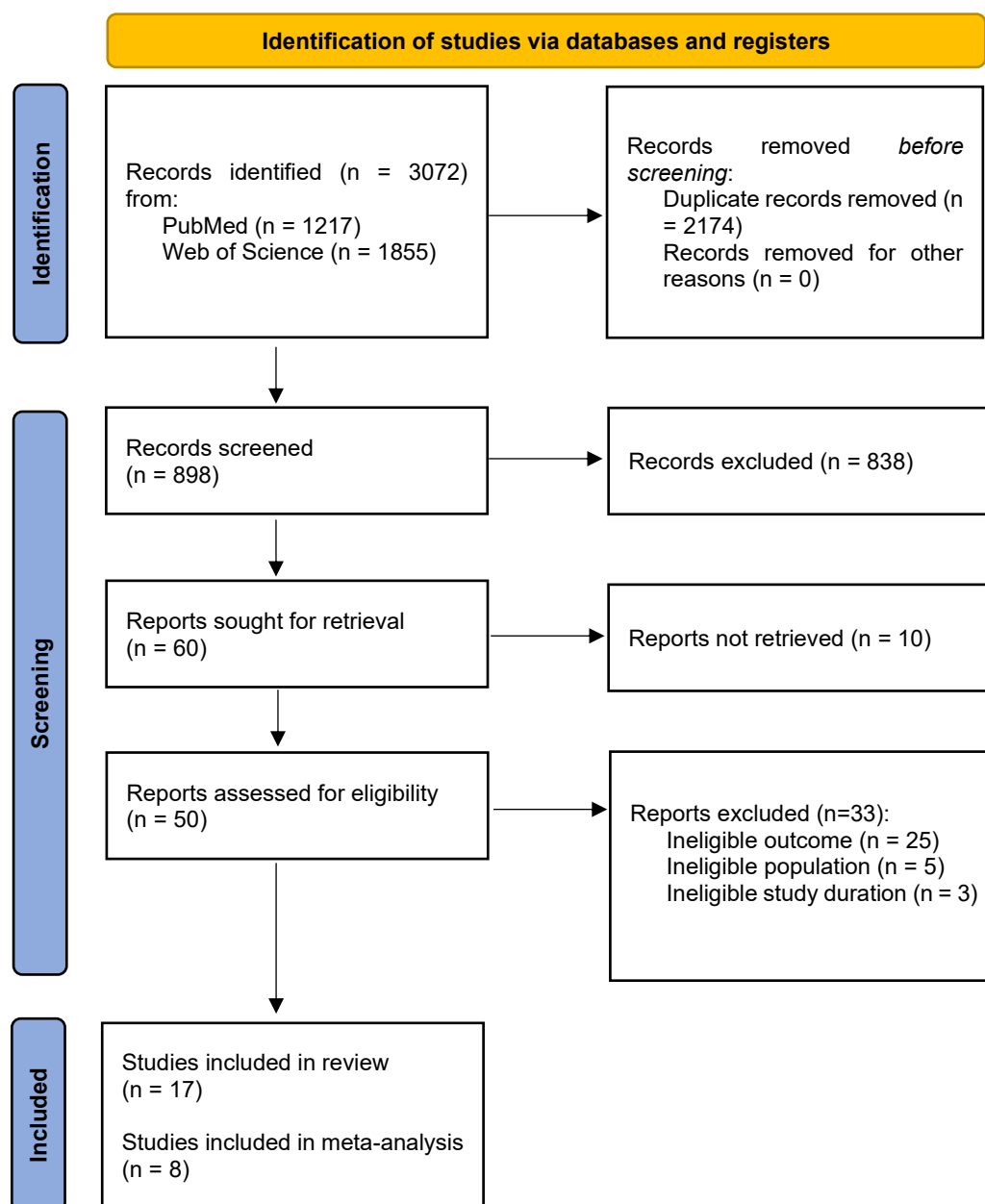


Figure 1. PRISMA 2020 flow diagram of the study selection process.

4.2. Characteristics of the Included Studies

The 17 included randomized controlled trials were published between 1996 and 2021 and comprised a total of 424 adult participants. Sixteen studies used a crossover design, whereas one study⁽⁸⁰⁾ used a parallel-group placebo-controlled design. Sample sizes ranged from 7 participants⁽⁸¹⁾ to 74 participants⁽⁸²⁾.

Most studies enrolled healthy normal-weight adults. One trial⁽⁸³⁾ focused specifically on adults with severe obesity, and others included mixed cohorts spanning healthy-weight, overweight, and obese individuals^(76, 82, 84, 85). Two trials enrolled participants with diabetes mellitus: Mezitis et al. (1996)⁽⁷⁹⁾ included both type 1 and type 2 diabetes, and Temizkan et al. (2015)⁽⁸⁶⁾ compared healthy adults with newly diagnosed type 2 diabetes.

The administered dose of sucralose varied markedly across studies, ranging from 24 mg⁽⁸⁶⁾ to 1000 mg⁽⁷⁹⁾. The most frequently used physiological dose was 48 mg in 50-60 mL of water^(80, 83, 85, 87). Sucralose was administered orally in most studies, generally in aqueous solutions, although capsules⁽⁷⁹⁾, solid matrices such as muffins⁽⁸⁴⁾, and sweetened gelatin⁽⁷⁶⁾ were also used. Three trials investigated direct intestinal exposure using intragastric or intraduodenal infusion^(81, 88, 89), thereby bypassing oral sensory stimulation.

Comparators included water or placebo vehicle in most studies, as well as caloric comparators such as sucrose, glucose, or fructose, and other non-nutritive sweeteners including aspartame and acesulfame-K. Postprandial follow-up ranged from 120 minutes^(86, 87, 89) to 300 minutes⁽⁸³⁾ or 5 h with intensive sampling⁽⁸⁵⁾, depending on study design. A detailed summary of study characteristics is presented in Appendix II.

4.3. Risk of bias assessment

Risk of bias was assessed using the Cochrane RoB 2.0 tool at the outcome level. Most studies were judged as having "some concerns" overall, mainly because of insufficient detail regarding randomization procedures or absence of a publicly available protocol to assess selective reporting. Most studies were considered low

risk in the domains of missing outcome data and outcome measurement, reflecting the objective nature of biochemical outcomes. No study was judged at high overall risk of bias. Detailed risk-of-bias assessments are presented in Appendix III.

4.4. Postprandial Glycemic Responses

Postprandial glycemic response was evaluated in all 17 included trials, most commonly through glucose iAUC and peak glucose concentration. Across the majority of studies involving healthy normal-weight adults, sucralose did not significantly alter postprandial glycemia compared with water or placebo, regardless of the administered dose or food vehicle^(77-82, 87-92).

In direct comparisons with caloric sweeteners, sucrose and glucose consistently produced larger glycemic excursions than sucralose, as expected. However, a small number of studies reported deviations from overall glycemic neutrality. Pepino et al. (2013)⁽⁸³⁾, in a cohort of insulin-sensitive adults with severe obesity (BMI 41.0 ± 1.5 kg/m²), found that sucralose administered before a 75-g oral glucose tolerance test (OGTT) increased the incremental peak glucose concentration compared with water (4.8 ± 0.3 vs. 4.2 ± 0.2 mmol/L; $P = 0.03$), although the total glycemic iAUC did not differ significantly. Nichol et al. (2019)⁽⁸⁵⁾ reported that ingested sucralose increased glucose iAUC by approximately $30\% \pm 10\%$ ($P = 0.03$) relative to water in both lean and obese adults during a five-hour dual-tracer OGTT, whereas sham-fed sucralose did not produce this effect.

In contrast, Temizkan et al. (2015)⁽⁸⁶⁾ observed a lower glucose AUC (385 vs. 787 mmol/L·120 min, $P = 0.002$) after 24 mg of sucralose compared with water in healthy adults undergoing 75-g OGTT, although this effect was not observed in participants with type 2 diabetes. Mezitis et al. (1996)⁽⁷⁹⁾, using a high-dose (1000

mg) encapsulated sucralose intervention, found no effect on glycemic response in adults with either type 1 or type 2 diabetes.

4.5. Postprandial Insulinemic Responses

Insulin or C-peptide responses were evaluated in 16 of the 17 included trials. In healthy normal-weight adults, most studies found no significant effect of sucralose on insulin or C-peptide iAUC, whether administered alone or with carbohydrate^(77-79, 81, 82, 86, 87, 89, 90, 92).

However, in adults with obesity or in mixed-metabolic-status cohorts, several studies suggested that sucralose may alter postprandial insulin kinetics. Pepino et al. (2013)⁽⁸³⁾ reported that a 48 mg oral sucralose preload before a 75-g OGTT led to a significantly greater insulin iAUC ($20 \pm 8\%$; $P < 0.03$), increased peak insulin secretion rate ($22 \pm 7\%$; $P < 0.02$), reduced insulin clearance ($7 \pm 4\%$; $P = 0.04$), and lower estimated insulin sensitivity ($23 \pm 20\%$; $P = 0.01$) compared with water in adults with severe obesity. Nichol et al. (2019)⁽⁸⁵⁾ also reported phenotype-dependent insulin effects, with lower early insulin concentrations (initial 40 min) in normal-weight adults, but higher late insulin concentrations (between 90 and 140 min) in adults with obesity following ingested sucralose. Gómez-Arauz et al. (2019)⁽⁸⁰⁾ observed significantly higher insulin concentrations at 30 min (1.3-fold, $P = 0.041$), 45 min (1.4-fold, $P = 0.046$), and 180 min (2-fold, $P = 0.048$) following 48 mg of sucralose in healthy young adults relative to water, despite no significant difference in glucose. Gallagher et al. (2016)⁽⁸⁴⁾ found that a sucralose-sweetened solid meal (muffin) co-ingested with a high-fat solid meal, elicited a higher insulin response than an isocaloric fructose-sweetened

comparator ($P = 0.041$), although the difference relative to sucrose was not statistically significant.

4.6. Postprandial GLP-1 Secretion

GLP-1 response was assessed in nine included trials. In protocols where sucralose was administered alone in water, no significant stimulation of GLP-1 secretion was observed in most studies involving healthy adults^(78, 81-83, 87, 89, 92). Similarly, no effect was reported by Wu et al. (2012)⁽⁷⁷⁾ when 60 mg of sucralose was administered 15 minutes before a solid meal.

One study, Temizkan et al. (2015)⁽⁸⁶⁾, reported a significantly higher GLP-1 AUC after 24 mg of sucralose compared with water during an OGTT in healthy adults (3192 vs. 2463 pmol/L·120 min, $P = 0.04$), but not in participants with type 2 diabetes. Sylvetsky et al. (2016)⁽⁷⁸⁾ observed that two commercial diet sodas significantly augmented the GLP-1 response to an OGTT ($P = 0.04$ and $P = 0.07$, respectively), whereas a matched sucralose plus acesulfame-K solution in plain seltzer did not, suggesting that other beverage components rather than sucralose itself may have contributed to the observed effect.

4.7. Mechanistic Pathways: Oral Signaling vs. Direct Intestinal Exposure

Several studies were specifically designed to distinguish between oral sensory stimulation and direct gastrointestinal exposure. Dhillon et al. (2017)⁽⁷⁶⁾, using a sham-feeding design in adults with overweight or obesity, identified a subgroup of participants in whom sham-fed sucralose elicited a cephalic phase insulin response (CPIR) comparable in magnitude to sucrose. This response was more frequently observed when sucralose was delivered in solid rather than liquid form,

suggesting that oral contact time and mastication may enhance cephalic signaling. Nichol et al. (2019)⁽⁸⁵⁾ showed that sham-fed sucralose lowered early insulin concentrations within the first 60 minutes in both normal-weight and obese cohorts, whereas ingested sucralose produced a different, phenotype-dependent response pattern. In contrast, Ford et al. (2011)⁽⁸⁷⁾ found no cephalic-phase rise in insulin, GLP-1, or PYY following either ingested or sham-fed sucralose in healthy normal-weight adults.

Studies bypassing the oral cavity by intragastric or intraduodenal infusion found no meaningful metabolic effect of sucralose. Ma et al. (2009)⁽⁸¹⁾ reported that intragastric infusion of 80 mg or 800 mg of sucralose did not alter glucose, insulin, GLP-1, GIP, or gastric emptying. Steinert et al. (2011)⁽⁸⁹⁾ similarly found no effect of intragastric sucralose on GLP-1, PYY, ghrelin, insulin, glucose, or appetite with intragastric infusion of 62 mg of sucralose. Ma et al. (2010)⁽⁸⁸⁾, using 150-min intraduodenal co-infusion of sucralose with glucose and 3-O-methylglucose, found no evidence that sucralose enhanced glucose absorption, altered blood glucose, or stimulated GLP-1 release. Overall, these findings suggest that direct intestinal exposure to sucralose alone is insufficient to consistently activate acute glycemic or incretin responses in humans.

4.8. Meta-Analysis and Heterogeneity Framework

Random-effects meta-analyses were performed for each distinct physiological endpoint where at least three independent treatment arms met the inclusion criteria described in Section 3.5. Effect sizes were expressed as Hedges' g , and heterogeneity was assessed with Cochran's Q test and the I^2 statistic.

4.8.1. Standard Oral Ingestive Pathways

Across the outcomes examined under standard oral ingestion, sucralose showed no consistent effect on glycemic, insulinemic, or incretin responses, with one exception in the glycemic domain discussed below.

For glucose iAUC, pooling six independent treatment arms produced a small, non-significant reduction relative to control (Pooled Effect = -0.09, 95% CI: [-0.90, 0.72], $t(5) = -0.27$, $p = 0.796$). This estimate came with substantial heterogeneity ($Q(5) = 12.26$, $p = 0.031$; $I^2 = 63.89\%$, 95% CI: [0.00, 96.45]), driven largely by Temizkan et al.⁽⁸⁶⁾ in the healthy subgroup, whose effect ($g = -1.92$) diverged sharply from the remaining five arms, all of which clustered close to zero. This finding may reflect the clinical variation of the underlying participant phenotypes.

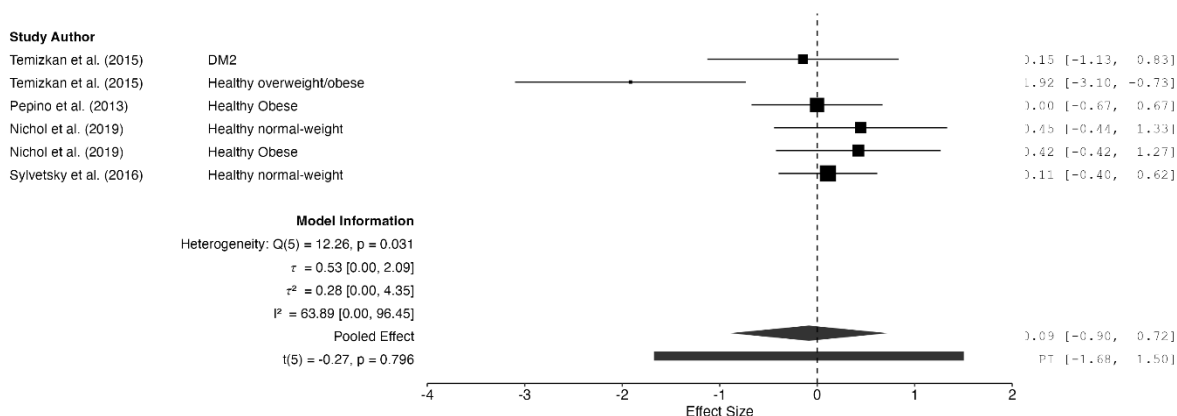


Figure 2. Forest plot of glucose incremental area under the curve (iAUC) following acute oral sucralose ingestion preceding a glycemic or carbohydrate challenge.

Peak glucose concentrations, pooled across four arms, showed a small positive trend that did not reach significance (Pooled Effect = 0.20, 95% CI: [-0.24, 0.64], $t(3) = 1.43$, $p = 0.247$), with no detectable heterogeneity ($Q(3) = 1.92$, $p = 0.588$; $I^2 = 0.00\%$).

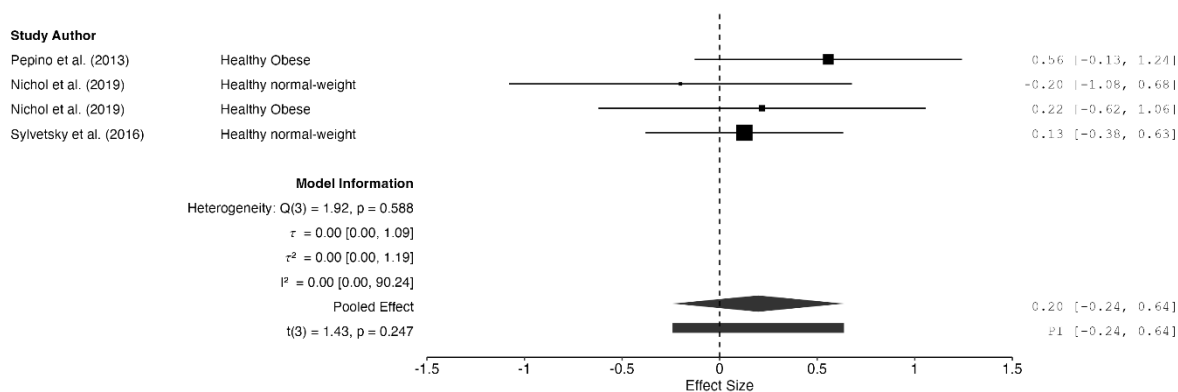


Figure 3. Forest plot of peak postprandial glucose concentrations following acute oral sucralose ingestion.

Insulin iAUC, pooled across the same six treatment arms, produced a pooled effect close to zero (Pooled Effect = 0.04, 95% CI: [-0.33, 0.41], $t(5) = 0.31, p = 0.771$) under complete homogeneity ($Q(5) = 4.30, p = 0.507; I^2 = 0.00\%$).

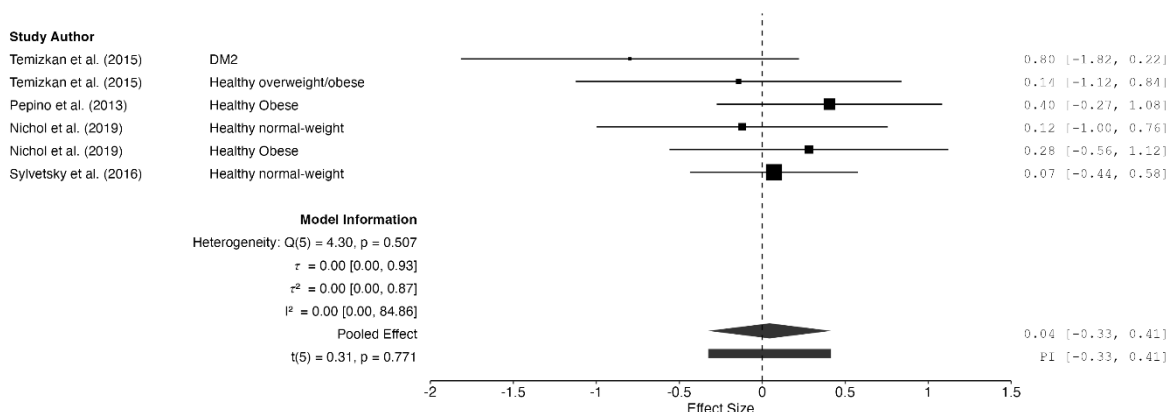


Figure 4. Forest plot of insulin incremental area under the curve (iAUC) following acute oral sucralose ingestion.

Peak insulin concentrations followed the similar pattern across four arms (Pooled Effect = 0.06, 95% CI: [-0.38, 0.51], $t(3) = 0.46, p = 0.679; Q(3) = 1.95, p = 0.583; I^2 = 0.00\%$).

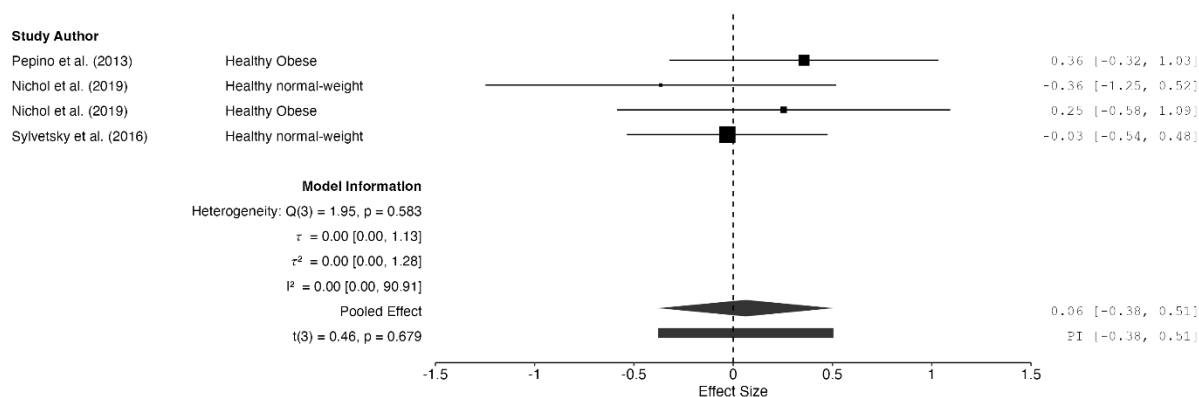


Figure 5. Forest plot of peak postprandial insulin concentrations following acute oral sucralose ingestion.

Finally, GLP-1 iAUC pooled across four treatment arms, showed no evidence of an independent incretin effect (Pooled Effect = 0.05, 95% CI: [-0.49, 0.59], $t(3) = 0.30, p = 0.782$; $Q(3) = 2.72, p = 0.437$; $I^2 = 0.00\%$).

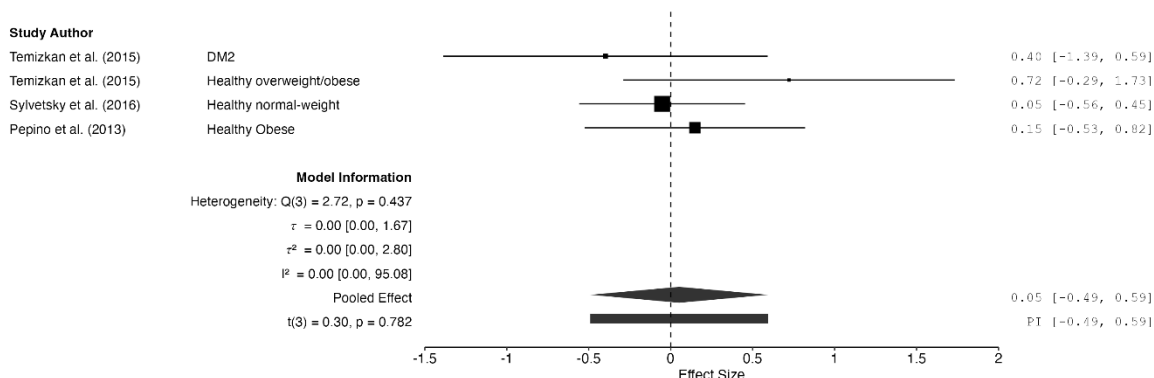


Figure 6. Forest plot of GLP-1 incremental area under the curve (iAUC) following acute oral sucralose ingestion.

4.8.2. Sensory-Isolated and Mechanistic Protocols (Sham-Feeding)

To separate the cephalic-phase reflex from downstream gastrointestinal exposure, glucose and insulin iAUC were pooled separately for the three trials using sham-feeding against a water or inert control.

Cephalic-phase glucose iAUC, pooled across three arms, produced a small-to-moderate positive trend that stopped short of statistical significance (Pooled Effect = 0.34, 95% CI: [-0.24, 0.93], $t(2) = 2.54$, $p = 0.126$), with no heterogeneity across the dataset ($Q(2) = 0.50$, $p = 0.778$; $I^2 = 0.00\%$). All three arms pointed the same direction, which is worth noting given how rarely that happens by chance with a genuinely null effect.

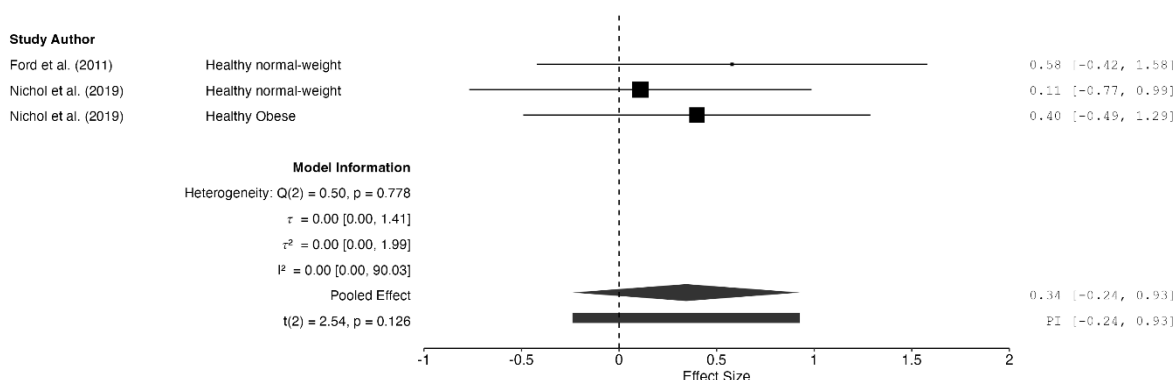


Figure 7. Forest plot of cephalic-phase glucose iAUC during sensory-isolated sham-feeding protocols.

Cephalic-phase insulin iAUC demonstrated a different effect. The pooled estimate crossed zero and moved in the negative direction (Pooled Effect = -0.29, 95% CI: [-1.69, 1.11], $t(2) = -0.88$, $p = 0.470$), with mild heterogeneity ($Q(2) = 2.76$, $p = 0.251$; $I^2 = 23.22\%$) attributable mainly to Ford et al.⁽⁸⁷⁾, whose effect ($g = -1.01$) sat apart from the two Nichol et al.⁽⁸⁵⁾ arms, both close to zero. The wide confidence interval reflects the small sample behind the Ford et al.⁽⁸⁷⁾ estimate ($n = 8$) and should temper any reading of this result as genuine cephalic-phase insulin suppression.

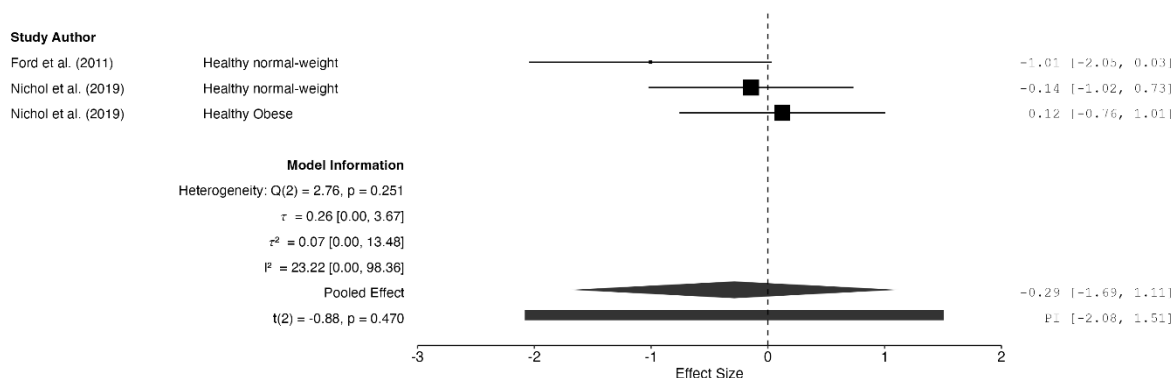


Figure 8. Forest plot of cephalic-phase insulin iAUC during sensory-isolated sham-feeding protocols.

4.8.3. Methodological Scope and Descriptive Certainty Reporting

Several outcomes could not be pooled quantitatively because too few eligible trials remained after applying the comparator and unit-of-analysis rules set out in Section 3.5. GLP-1 peak concentration under oral ingestion was treated narratively, since only two arms (Sylvetsky et al.⁽⁷⁸⁾ and Pepino et al.⁽⁸³⁾) met the inclusion criteria. The same applied to peak glucose, peak insulin, and GLP-1 concentrations under sham-feeding, to trials using intragastric or intraduodenal infusion, and to Mezitis et al.⁽⁷⁹⁾, the only eligible trial using an encapsulated, oral-bypass route (where $n \leq 2$ trials per outcome). Pooling fewer than three arms was judged likely to produce unstable variance estimates rather than a meaningful synthesis, so these findings are addressed narratively in Sections 4.5 to 4.7 instead.

Certainty of evidence for the oral ingestion outcomes was considered moderate-to-high overall, given the consistent absence of heterogeneity across four of the five pooled endpoints; the exception, glucose iAUC, is discussed above and warrants a more cautious reading. Certainty around the cephalic-phase

findings remains lower, constrained by the small number of eligible sham-feeding trials and by sample sizes that rarely exceed ten participants per arm — precisely the gap that future mechanistic interventions on sucralose should target.

5. Discussion

5.1. Principal Findings

This systematic review of 17 randomized controlled trials suggests that the acute metabolic effects of sucralose in humans are context-dependent rather than uniformly neutral or uniformly adverse. In healthy normal-weight adults, acute sucralose exposure was metabolically neutral in most studies, with no consistent effects on postprandial glycemia, insulinemia, or GLP-1 secretion^(77-79, 81, 82, 87, 89, 90, 92). This apparent neutrality was not entirely uniform at the pooled level, however: glucose iAUC showed significant heterogeneity ($I^2 = 63.89\%$) driven primarily by a single healthy-cohort trial, a divergence discussed further in Section 5.5. However, in individuals with obesity or impaired insulin sensitivity, a subset of studies suggests that sucralose may augment insulin secretion, alter insulin clearance, and modify postprandial metabolic responses^(83, 85). Sucralose is not the metabolically inert additive it is often assumed to be — its neutrality holds in some contexts and breaks down in others.

5.2. Influence of Baseline Metabolic Phenotype

A central finding across the evidence base is the apparent importance of baseline metabolic phenotype. Studies conducted in healthy adults generally reported no significant metabolic perturbation after acute sucralose exposure, whereas trials involving participants with obesity reported greater insulin

responses or altered insulin kinetics^(83, 85). These findings suggest that the metabolic response to sucralose depends on the individual's baseline metabolic status.

Possible mechanisms driving this phenotype-dependent response include underlying hyperinsulinemia, altered hepatic or peripheral insulin clearance, or differences in enteroendocrine sensitivity in the presence of excess adiposity⁽⁸³⁾. From a clinical perspective, the observed magnitude of these effects in individuals with obesity appears modest rather than profound; for instance, Pepino et al. (2013)⁽⁸³⁾ reported a 20% increase in insulin iAUC and a minor elevation in peak glucose (4.8 vs. 4.2 mmol/L), while insulin clearance was reduced by only 7%. In our meta-analysis, this study showed one of the largest positive effect sizes for peak glucose (Hedges' $g = 0.56$). However, when this phenotype-specific response is pooled with data from metabolically healthy participants, its effect is attenuated (Pooled Effect = 0.20, 95% CI: [-0.24, 0.64], $p = 0.247$, $I^2 = 0.00\%$). These findings indicate that pooling data from metabolically heterogeneous populations may attenuate phenotype-specific effects, without establishing a clinically relevant disruption of glucose-insulin kinetics. Furthermore, findings of increased postprandial insulin after a single sucralose exposure in healthy young adults raise the possibility that an acute regulatory threshold might be lower than previously assumed in specific cohorts⁽⁸⁰⁾. Conversely, this modulatory capacity appears to reach a state of desensitization or downregulation in established clinical states, as evidenced by no significant effect in patients with type 1 or type 2 diabetes⁽⁷⁹⁾.

5.3. Oral Sensory Signalling and Intestinal Exposure

Another important observation is that the route of administration drastically influences the acute metabolic response. Studies bypassing the oral cavity via direct intragastric or intraduodenal infusion consistently failed to detect any effects of sucralose on glucose absorption, gastric emptying, GLP-1, or insulin secretion^(81, 88, 89). These findings do not support the direct translation of classical rodent intestinal sweet-taste data to human physiology.

In contrast, studies incorporating oral sensory stimulation suggest that cephalic-phase and oral taste signaling shape the metabolic response, even without any nutrient reaching the gut. This dependence on oral stimulation is illustrated by sham-feeding paradigms, where oral exposure to sucralose elicited a significant CPIR in a subgroup of overweight or obese adults, an effect that was more pronounced when sucralose was delivered in a solid food matrix rather than a liquid beverage⁽⁷⁶⁾. Our meta-analytic aggregation of sham-feeding trials assessing glucose iAUC lends some support to this mechanism: pooling across three treatment arms produced a small-to-moderate positive trend that did not reach statistical significance (Pooled Effect = 0.34, 95% CI: [-0.24, 0.93], $p = 0.126$), with no heterogeneity across the dataset ($I^2 = 0.00\%$, $p = 0.778$) and all three arms pointing in the same direction. This consistency across otherwise independent trials is suggestive, even if the pooled estimate itself falls short of significance, and points to isolated stimulation of oral sweet-taste receptors (TAS1R2/TAS1R3) as a plausible driver of subtle postprandial glucose changes through cephalic-phase mechanisms. Larger, adequately powered mechanistic trials are needed before this can be considered more than a signal.

The corresponding insulin data tells a less coherent story. Pooled cephalic-phase insulin iAUC crossed the null value and trended negative (Pooled Effect = -0.29, 95% CI: [-1.69, 1.11], $p = 0.470$), with mild heterogeneity across the three arms ($I^2 = 23.22\%$, $p = 0.251$). This was driven largely by Ford et al.⁽⁸⁷⁾, whose small sample ($n = 8$) produced a comparatively large negative effect that pulled against two Nichol et al.⁽⁸⁵⁾ arms sitting close to zero. Rather than pointing to a genuine suppressive cephalic-phase insulin response, this pattern more plausibly reflects the imprecision of pooling very small, mechanistically similar trials, and argues for caution in over-interpreting any single sham-feeding insulin result. Bypassing the oral cavity entirely through encapsulation likewise produced no significant effect⁽⁷⁹⁾. Taken together, these findings support the broader hypothesis that the oral-gastrointestinal axis, rather than isolated intestinal exposure alone, underlies any acute endocrine response to sucralose, and that the sensory-metabolic relationship depends on both the delivery vehicle and the host phenotype^(87, 89).

5.4. Effects of Nutrient Co-Ingestion on GLP-1 Response

The evidence regarding the secondary outcome of GLP-1 secretion is particularly context-dependent. Most studies found no effect of sucralose alone on GLP-1 secretion when administered in plain water^(78, 81-83, 87, 89, 92). However, isolated trials reported an augmented GLP-1 response when sucralose was administered prior to an oral glucose load⁽⁸⁶⁾. Methodological analyses suggest that a temporal lead — such as administering a preload 15 minutes before the carbohydrate challenge — is a key factor that allows sufficient time for the pre-activation of gastrointestinal receptors before glucose enters the duodenum⁽⁸⁶⁾.

Furthermore, diet soda studies demonstrate that commercial beverage matrices or co-ingredients may significantly contribute to these observed incretin responses, whereas equimolar doses of pure sucralose in plain seltzer do not⁽⁷⁸⁾. Overall, current human evidence does not support a consistent independent incretin effect of sucralose per se, nor does it support acute, independent upregulation of enterocyte glucose transport⁽⁸⁸⁾. Our aggregated meta-analysis did not detect a stand-alone signal on GLP-1 secretion following acute exposure, with a global effect size close to absolute zero (Pooled Effect = 0.05, 95% CI: [-0.49, 0.59], $p = 0.782$) and low heterogeneity across the evidence base ($Q(3) = 2.72$, $p = 0.437$; $I^2 = 0.00\%$). Instead, any modulatory capacity is limited to complex commercial formulations or highly specific, timing-dependent synergy with co-ingested carbohydrates^(78, 86).

5.5. Methodological Sources of Heterogeneity

Several methodological factors may explain the statistical and clinical crosscurrents observed across literature. A primary source of divergence rests upon host-related physiological variations, most notably baseline glucose tolerance, habitual non-nutritive sweetener consumption, and individual taste-receptor genetics. Humans exhibit wide genetic polymorphisms in the TAS1R2 and TAS1R3 sweet-taste receptor genes, which inherently modulate individual sensitivity and downstream cephalic-phase responsivity to intensely sweet non-caloric ligands.

Direct comparison across the literature is also structurally compromised by procedural mismatches in experimental design. The field lacks standardization regarding sucralose dosages, the metabolic nature of the co-ingested

carbohydrate vehicle, and the precise temporal resolution of postprandial blood draws. For instance, glycemic metrics vary significantly between trials, with some reporting total area under the curve (AUC total) and others utilizing incremental area (iAUC), two distinct models that can obscure or artificially amplify subtle physiological responses.

Finally, a major biochemical confounding layer involves substantial variation in incretin tracking. Most trials fail to distinguish between total GLP-1 peptide concentration and the active, intact fraction (GLP-1 7-36 amide) that escapes immediate dipeptidyl peptidase-4 (DPP-4) degradation. Because different commercially available immunoassays target different epitopes of the hormone, this introduces methodological variability that may obscure localized acute endocrine responses in the proximal gut.

5.6. Strengths and Limitations

A major strength of this review is its compound-specific eligibility criteria. By deliberately restricting our analysis to a single molecule (sucralose), rather than grouping structurally, chemically and metabolically distinct non-nutritive sweeteners together, we were able to evaluate its effects independently of other sweeteners. Additionally, our rigorous categorization of distinct delivery systems—ranging from simple oral solutions and encapsulated vehicles to complex solid food matrices and direct intestinal infusions—facilitated a unique, detailed investigation of the oral-gastrointestinal axis that human syntheses have rarely attempted. Methodological quality was strengthened by independent dual-reviewer workflows and an outcome-level risk assessment via the Cochrane RoB 2.0 framework.

A few limitations should be acknowledged. First, although PubMed and Web of Science were systematically searched, Embase and the Cochrane CENTRAL database were not included. Consequently, some relevant randomized controlled trials may have been missed, introducing a potential risk of study selection bias.

An additional methodological limitation concerns protocol registration. Although the review protocol was registered in PROSPERO, registration occurred after completion of the literature search. Therefore, the review was not prospectively registered, which may increase the theoretical risk of selective outcome reporting.

The available evidence was also characterized by generally small sample sizes, limiting statistical power to detect subtle postprandial endocrine responses. Furthermore, only two trials included participants with diagnosed diabetes mellitus, limiting the applicability of the findings to individuals with established metabolic disease. Formal influence diagnostics, such as leave-one-out re-estimation, were not conducted for the outcome showing significant heterogeneity (glucose iAUC); the disproportionate contribution of a single trial was identified narratively but not statistically quantified, and this result should accordingly be interpreted with some caution.

Clinical protocols also differed considerably with respect to carbohydrate co-ingestion and postprandial monitoring schedules, contributing to methodological heterogeneity. In addition, the review evaluated only acute interventions; therefore, these findings cannot be extrapolated to the long-term physiological adaptations associated with chronic sucralose consumption.

Finally, most included studies were conducted in high-income Western countries and enrolled participants predominantly of European or North American

ancestry. Consequently, the generalizability of these findings to other ethnic, geographical, and dietary populations remains uncertain.

6. Conclusion

This systematic review of 17 randomized controlled trials suggests that, under acute exposure conditions, sucralose is not uniformly metabolically inert in humans. In healthy, normal-weight adults, a single dose of sucralose was not associated with statistically significant changes in postprandial glucose, insulin or GLP-1 responses in the available studies. Conversely, in populations presenting elevated adiposity or impaired insulin sensitivity, acute sucralose consumption may influence endocrine responses, including increased postprandial insulin secretion and altered insulin kinetics in susceptible individuals. The acute metabolic effect of sucralose is therefore not a universal phenomenon but depends on a combination of interacting factors: the host's baseline metabolic phenotype, oral sensory engagement during the cephalic phase, the structural matrix of delivery (solid versus liquid), and the timing of carbohydrate co-ingestion. Current evidence does not demonstrate consistent stimulation of GLP-1 secretion following isolated intestinal exposure, nor does it support increased glucose transporter activity in humans.

These findings may have implications for clinical practice and future recommendations. Current recommendations regarding sucralose may require more cautious and nuanced framing, particularly for individuals with obesity, insulin resistance, or metabolic syndrome, in whom alterations in postprandial endocrine responses cannot be excluded. These conclusions should be interpreted considering that the certainty of evidence was moderate-to-high for most oral

ingestion outcomes, with the notable exception of glucose iAUC, where substantial study heterogeneity was observed; certainty was substantially lower for mechanistic subgroup analyses owing to the limited number of trials and small sample sizes.

To resolve current clinical uncertainties, future research should prioritize:

- **Long-term longitudinal interventions:** Randomized controlled trials of at least 12 weeks' duration evaluating chronic exposure in populations at high metabolic risk;
- **Phenotype-stratified mechanistic designs:** Well-controlled clinical studies designed to clarify individual phenotypic susceptibility, incorporating microbiome-informed frameworks;
- **Dose-response evaluations:** Analyses spanning the full spectrum of habitual and pharmacological human exposure limits;
- **Genetic and molecular investigation:** Exploration of inter-individual variability and polymorphisms within the TAS1R2/TAS1R3 sweet-taste receptor signaling cascade and downstream endocrine pathways.
- **Sensory-isolated protocols (mouth rinsing):** Exploration of oral-only exposure through mouth-rinsing paradigms—akin to protocols utilized in sports science—to isolate cephalic-phase responses from gastrointestinal exposure, thereby elucidating the independent role of oral sweet-taste receptors on acute metabolic outcomes.

Until such consistent evidence becomes available, clinical and regulatory guidelines may need to differentiate between exposure scenarios in metabolically healthy and metabolically compromised populations, rather than assuming a uniform biological neutrality across all consumers.

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Supplementary Material:

Appendix I - Systematic Literature Search Strategies

("Sucralose" OR sucralose[tiab] OR "E955"[tiab] OR Splenda[tiab] OR "artificial sweetener*" [tiab] OR "non-nutritive sweetener*" [tiab] OR "non nutritive sweetener*" [tiab] OR nonnutritive sweetener* [tiab] OR "non-caloric sweetener*" [tiab] OR noncaloric sweetener* [tiab] OR "non caloric sweetener*" [tiab] OR "low-calorie sweet*" [tiab] OR "low calorie sweet*" [tiab] OR "low-caloric sweet*" [tiab] OR "low caloric sweet*" [tiab] OR "zero-calorie" [tiab] OR "zero calorie" [tiab] OR "low-energy sweet*" [tiab] OR "low energy sweet*" [tiab] OR "nonsugar sweet*" [tiab] OR "non-sugar sweet*" [tiab] OR "non sugar sweet*" [tiab] OR "artificially-sweetened" [tiab] OR "artificially sweetened" [tiab] OR "low-calorie-sweetened" [tiab] OR "diet beverage*" [tiab] OR "diet drink*" [tiab] OR "diet soda*" [tiab] OR NNS[tiab] OR NSS[tiab]) AND ("Blood Glucose"[Mesh] OR "Glycemic Index"[Mesh] OR glucose[tiab] OR "blood glucose" [tiab] OR glycemia[tiab] OR glycaemia[tiab] OR glycemic[tiab] OR glycaemic[tiab] OR postprandial[tiab] OR "post-prandial" [tiab] OR "post prandial" [tiab] OR "postprandial glucose" [tiab] OR "postprandial insulin" [tiab] OR "Oral Glucose Tolerance Test" OR OGTT[tiab] OR "glucose tolerance" [tiab] OR "area under the curve" [tiab] OR AUC[tiab] OR "incremental area under the curve" [tiab] OR iAUC[tiab] OR "peak glucose" [tiab] OR Cmax[tiab] OR Tmax[tiab] OR "test meal" [tiab] OR "mixed meal" [tiab] OR "meal challenge" [tiab] OR "Insulin"[Mesh] OR insulin[tiab] OR insulinemia[tiab] OR insulinemic[tiab] OR "Insulin Secretion"[Mesh] OR "Glucagon-Like Peptide 1"[Mesh] OR "glucagon like peptide-1" [tiab] OR "glucagon like peptide 1" [tiab] OR "glucagon-like peptide 1" [tiab] OR GLP-1[tiab] OR "GLP 1" [tiab] OR incretin*[tiab])

Study	Design	Population & Baseline Characteristics	Intervention & Challenge Protocol	Comparator(s)	Follow-up	Main Metabolic Findings
Gómez-Arauz (2019)	Parallel-group, RCT	Healthy, non-insulin-resistant young adults (n=45; placebo: 8 F / 12 M with 24.6 ± 3.6 kg/m ² and intervention: 8 females / 17 males with 23.7 ± 2.9 kg/m ²)	48 mg oral dose in 60 mL water, followed 15 min later by a 75 g OGTT	Water	180 min	• Insulin: Significantly higher at 30, 45, and 180 min (P<0.05) • Glucose: No statistically significant overall effect • Induced imbalances in monocyte subpopulations.
Wu (2013)	Single-blind, randomized crossover	Healthy normal-weight males (n=10 males; BMI: 25.5 ± 1.0 kg/m ²)	52 mg sucralose alone or 46 mg sucralose mixed with 26 mg ace-K, oral dose, 10 min prior to a 75 g oral glucose load	Water	240 min	• Complete neutrality across all conditions. • No significant differences in glucose, insulin, or total GLP-1 AUC. • Gastric emptying rates (T50) remained unaffected.
Ma (2009)	Single-blind, randomized crossover	Healthy normal-weight adults (n=7; BMI: 21.6 ± 1.2 kg/m ²)	Intragastric infusion of 80 mg (0.4 mM) or 800 mg (4 mM) in 500 mL saline	Saline solution; Sucrose (50g)	240 min	• Isolated intestinal exposure demonstrated no statistically significant overall effect • No significant rise in glucose, insulin, GLP-1, or GIP curves.
Wu (2012)	Single-blind, randomized crossover	Healthy normal-weight adults (n=10; 3 F / 7 M; BMI: 25.5 ± 1.5 kg/m ²)	60 mg oral preload in water, administered 15 min before a carbohydrate-dense mashed-potato meal	Water; glucose; 3-OMG; tagatose/isomalt mixture	240 min	• Glucose & Insulin: Excursions were significantly lower compared to the active caloric control (glucose load). • GLP-1: Preload failed to stimulate or alter incretin iAUC.
Ford (2011)	Single-blind, randomized crossover	Healthy normal-weight adults (n=8; 7 F / 1 M; BMI range: 18.8 – 23.9 kg/m ²)	41.5 mg oral ingestion in 50 mL water, with or without a 200 mL sham-feeding (taste and expectorate)	Water; maltodextrin + sucralose; sham-fed sucralose	120 min	• Sweetener ingestion in fasting states showed no statistically significant overall effect • No changes in GLP-1, PYY, insulin, glucose, or subjective appetite scores.
Mezitis (1996)	Double-blind, randomized crossover	Adults with Type 1 (n=13; 40% F / 60% M; BMI: 23.7 ± 0.9 kg/m ²) and Type 2 diabetes (n=13; 40% females / 60% males; BMI: 32.0 ± 1.9 kg/m ²)	1000 mg pharmacological dose administered via opaque capsules, followed by a 360-kcal liquid breakfast	Placebo capsules	240 min	• Complete metabolic neutrality across both clinical cohorts. • Bypassing the oral cavity resulted in no significant alterations in glucose or C-peptide AUC.
Ma (2010)	Single-blind, randomized crossover	Healthy normal-weight adults (n=10; 2 F / 8 M; BMI: 23.4 ± 0.8 kg/m ²)	150-min intraduodenal infusion of 4 mM sucralose in saline, co-administered with glucose and 3-OMG	Saline solution	150 min	• Direct local intestinal exposure did not alter postprandial parameters. • No differences observed in blood glucose, GLP-1 release, or intestinal glucose absorption kinetics.
Pepino (2013)	Randomized crossover	Adults with Class III obesity (n=17; 15 F / 2 M; BMI: 41.0 ± 1.5 kg/m ² ; insulin-sensitive: HOMA ≤ 2.6; non-NNS users)	48 mg oral dose in 60 mL water, administered 10 min prior to a standardized 75 g OGTT	Water	300 min	• Insulin: Significantly increased insulin iAUC (+20 ± 8%) and peak secretion rate (+22 ± 7%). • Glucose: Elevated incremental peak glucose (4.8±0.3 vs. 4.2±0.2 mmol/L). • Sensitivity: Reduced whole-body insulin sensitivity (SI: -23 ± 20%) and reduced metabolic clearance.
Temizkan (2015)	Single-blind, randomized crossover	Healthy overweight/obese adults (n=8; BMI: 30.3 ± 4.5 kg/m ²) vs. drug-naïve, newly diagnosed T2DM patients (n=8; BMI: 33.7 ± 5.4 kg/m ²)	24 mg oral dose in 200 mL water, administered 15 min prior to a 75 g OGTT	Water; 72 mg Aspartame	120 min	• Healthy Group: Sucralose significantly lowered glucose total AUC (P=0.002) and augmented GLP-1 total AUC (P=0.04). • T2DM Group: Showed no statistically significant overall effect
Sylvetsky (2016)	Randomized crossover	Healthy adults with mixed BMI (Arm 1: n=30, BMI: 25.8 ± 4.2 kg/m ² ; Arm 2: n=31, BMI: 26.3 ± 7.5 kg/m ²)	Pure doses (68, 170 or 250 mg sucralose) in water (Arm 1) vs. commercial diet sodas containing NNS blends (Arm 2), paired with an OGTT	Water; Seltzer; Commercial diet sodas	130 min	• Pure Sucralose: Demonstrated absolute neutrality over all metabolic parameters. • Diet Sodas: Significantly augmented GLP-1 AUC (P=0.039), showing matrix-dependent confounding effects.
Yunker (2021)	Randomized crossover	Healthy young adults with mixed BMI (n=74; 43 F / 31 M; range: 19.18 – 40.27 kg/m ²)	Sweetness-matched doses (179, 239 or 358 mg) in 300 mL water, administered in fasting state	Water; Sucrose (75g)	120 min	• Compared with sucrose, sucralose was associated with lower postprandial glucose, insulin, and GLP-1 responses, alongside differential neural food-cue reactivity. • Identified neural reactivity and subsequent ad libitum intake differences mediated by sex and obesity status.
Nichol (2019)	Randomized crossover	Healthy lean adults (n=10; 7 F / 3 M; BMI: 22.8 ± 0.9 kg/m ²) vs. adults with obesity (n=11; 10 females / 1 male; BMI: 37.7 ± 5.5 kg/m ² ; HOMA-IR ≤ 3)	48 mg oral dose in 60 mL water (administered as normal ingestion or sham-fed) 10 min prior to a 75 g OGTT, integrated into a continuous IV [6,6-2H ₂]glucose infusion and a [U-13C ₆] labeled tracer protocol	Water (ingested or sham-fed), paired with the same dual-tracer protocol.	300 min	• Ingestion: Increased glucose iAUC by 30 ± 10% across both groups (P<0.05). • Insulin Kinetics: Modulations followed a weight-stratified and phenotype-dependent trajectory. • Sham-fed sucralose did not reproduce the glycemic increase observed with ingested sucralose.
Brown AW (2011)	Single-blind, randomized crossover	Healthy normal-weight females (n=8; BMI: 22.16 ± 1.71 kg/m ²)	6 g granular Splenda blend in 355 mL water, followed by a standardized breakfast meal	Water; 50g Sucrose; 50g Sucrose + 6g granular Splenda	120 min	• Metabolic parameters differed exclusively between sucrose-containing arms. • Granular formulation vehicle showed no statistically significant overall effect, behaving similarly to the water control.
Steinert (2011)	Double-blind, randomized crossover	Healthy normal-weight adults (n=12; 6 F / 6 M; BMI range: 20.5–24.7 kg/m ²)	Intragastric infusion of 62 mg in 250 mL water, administered alone in a fasting state	Water; Caloric controls (glucose or fructose); Other NNS (169 mg aspartame or 220 mg ace-k)	120 min	• Bypassing the oral cavity via infusion yielded complete gastrointestinal neutrality. • Failed to induce changes in GLP-1, PYY, ghrelin, insulin, or subjective appetite metrics.
Gallagher (2016)	Randomized crossover	Healthy cohorts spanning normal-weight, overweight, and obesity (n=29; 18 F / 11 M; BMI: 26.3 ± 5.4 kg/m ²)	100 mg of pure sucralose incorporated into a solid food matrix (muffin), co-ingested with a high-fat load	Sucrose muffin (65g); Fructose muffin (52g)	240 min	• Glucose: Glycemic excursions did not differ significantly relative to the sucrose muffin control. • Insulin: Altered by muffin composition; insulin was higher in the sucralose condition compared to fructose (P=0.041).
Sae lab (2020)	Randomized crossover	Healthy young adults with mixed BMI (n=10; 5 F / 5 M; BMI range: 19 – 37 kg/m ²)	0.007% w/v oral solution in 300 mL water, administered as a preload 45 min prior to an ad libitum meal	Water; Sucrose; Maltodextrin	105 min	• Sucralose did not produce the glucose rise observed with maltodextrin in male participants; authors interpreted this as consistent with cephalic-phase signaling. • Non-sweet control vehicles (maltodextrin) led to significantly higher glycemic values in males.
Dhillon (2017)	Randomized crossover	Healthy overweight and obese adults with high body fat percentage (n=64; 41 F / 23 M; BMI range: 24 - 37 kg/m ²)	Sham-fed (taste and expectorate) sucralose preload delivered via either a solid matrix (gelatin cubes) or a liquid beverage	Sham-fed sucrose-sweetened solid or beverage preload	121 min	• Cephalic Response: Identified a reproducible subgroup of CPIR "responders". • Matrix Effect: Cephalic insulin surges were significantly enhanced by the solid mastication vehicle.

Abbreviations: F, Female; M, Male; ace-K, acesulfame-potassium; AUC, area under the curve; BMI, body mass index; CPIR, cephalic phase insulin response; iAUC, incremental area under the curve; NNS, non-nutritive sweetener; OGTT, oral glucose tolerance test; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PYY, peptide YY; RCT, randomized controlled trial; SI, insulin sensitivity index; 3-OMG, 3-O-Methylglucose; HOMA-IR, homeostatic model assessment of insulin resistance; IV, intravenous

Appendix III - Methodological Risk of Bias Assessment (RoB 2.0)

Intention-to-treat	Unique ID	D1	D2	D3	D4	D5	Overall		
	Pepino et al., 2013_Glycemia	!	+	+	+	!	!	+	Low risk
	Pepino et al., 2013_Insulinemia	!	+	+	+	!	!	!	Some concerns
	Pepino et al., 2013_GLP-1	!	+	+	+	!	!	-	High risk
	Ford et al., 2011_Glycemia	!	+	+	+	!	!		
	Ford et al., 2011_Insulinemia	!	+	+	+	!	!	D1	Randomisation process
	Ford et al., 2011_GLP-1	!	+	+	+	!	!	D2	Deviations from the intended interventions
	Wu et al., 2013_Glycemia	!	+	+	+	!	!	D3	Missing outcome data
	Wu et al., 2013_Insulinemia	!	+	+	+	!	!	D4	Measurement of the outcome
	Wu et al., 2013_GLP-1	!	+	+	+	!	!	D5	Selection of the reported result
	Ma et al., 2009_Glycemia	!	+	+	+	!	!		
	Ma et al., 2009_Insulinemia	!	+	+	+	!	!		
	Ma et al., 2009_GLP-1	!	+	+	+	!	!		
	Wu et al., 2012_Glycemia	!	+	+	+	!	!		
	Wu et al., 2012_Insulinemia	!	+	+	+	!	!		
	Wu et al., 2012_GLP-1	!	+	+	+	!	!		
	S. Temizkan et al. (2015)_Glycemia	!	+	+	+	!	!		
	S. Temizkan et al. (2015)_Insulinemia	!	+	+	+	!	!		
	S. Temizkan et al. (2015)_GLP-1	!	+	+	+	!	!		
	Gómez-Arauz et al., 2019_Glycemia	!	+	+	+	!	!		
	Gómez-Arauz et al., 2019_Insulinemia	!	+	+	+	!	!		
	Dhillon et al., 2017_Glycemia	!	+	+	+	+	!		
	Dhillon et al., 2017_Insulinemia	!	+	+	+	+	!		
	Steinert et al., 2011_Glycemia	!	+	+	+	!	!		
	Steinert et al., 2011_Insulinemia	!	+	+	+	!	!		
	Steinert et al., 2011_GLP-1	!	+	+	+	!	!		
	Nichol et al. (2019)_Glycemia	!	+	+	+	+	!		
	Nichol et al. (2019)_Insulinemia	!	+	+	+	+	!		
	Yunker et al., 2021_Glycemia	!	+	+	+	+	!		
	Yunker et al., 2021_Insulinemia	!	+	+	+	+	!		
	Yunker et al., 2021_GLP-1	!	+	+	+	+	!		
	Sylvetsky et al. (2016)_Glycemia	!	+	+	+	+	!		
	Sylvetsky et al. (2016)_Insulinemia	!	+	+	+	+	!		
	Sylvetsky et al. (2016)_GLP-1	!	+	+	+	+	!		
	Mezitis et al., 1996_Glycemia	!	+	+	+	!	!		
	Ma et al., 2010_Glycemia	!	+	+	+	!	!		
	Ma et al., 2010_Insulinemia	!	+	+	+	!	!		
	Ma et al., 2010_GLP-1	!	+	+	+	!	!		
	Sae lab T et al., 2020_Glycemia	!	+	+	+	!	!		
	Sae lab T et al., 2020_Insulinemia	!	+	+	+	!	!		
	Brown AW et al., 2011_Glycemia	!	+	+	+	!	!		
	Brown AW et al., 2011_Insulinemia	!	+	+	+	!	!		
	Gallagher C et al., 2016_Glycemia	!	+	+	+	!	!		
	Gallagher C et al., 2016_Insulinemia	!	+	+	+	!	!		

