



The Comprehensive Systematic Review of Association of Non-Nutritive Sweetener Consumption to Potential Effects of Glucose Intolerance

¹ Devina Adelina Wijaya, ² Clareta Vero Patricia Widya

¹ Risa Sentra Medika General Hospital, Indonesia / Graduate of Faculty of Medicine,
University of Tarumanagara, Indonesia

² Indriati Solo Baru General Hospital, Indonesia / Graduate of Faculty of Medicine,
University of Tarumanagara, Indonesia

Corresponding Email: devinaawijaya@gmail.com

Article History :

Received date : 2025/09/17
Revised date : 2025/10/08
Accepted date : 2025/12/24
Published date : 2026/01/12



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Non-nutritive sweeteners (NNS) are widely used as sugar substitutes to reduce caloric intake and manage body weight, yet their long-term metabolic effects, particularly on glucose tolerance, remain controversial. While acute studies often report neutral effects, emerging evidence suggests that chronic consumption, especially of certain NNS types, may adversely affect insulin sensitivity and glucose homeostasis in specific populations (Romo-Romo et al., 2018; Suez et al., 2022).

Methods: A comprehensive systematic review was conducted, screening studies based on predefined inclusion criteria: human participants, NNS exposure assessment, glucose metabolism outcomes, appropriate study designs (RCTs, cohort studies, systematic reviews), and methodological quality. Data extraction

covered NNS type, dosage, study population, glucose outcomes, study design, key findings, and proposed mechanisms. A total of 80 studies were included and critically synthesized.

Results: The evidence reveals significant heterogeneity in NNS effects. Acute NNS exposure generally has minimal impact on postprandial glucose and insulin (Greyling et al., 2020), but chronic consumption (≥ 2 weeks), particularly of sucralose, is associated with decreased insulin sensitivity in healthy, lean, non-habitual users (Romo-Romo et al., 2018, 2024, 2025). Effects vary by sweetener type: stevia shows neutral to beneficial effects on fasting glucose (Bai et al., 2024; Zare et al., 2024), aspartame largely exhibits neutral metabolic impact (Santos et al., 2018; Higgins et al., 2018), while saccharin and sucralose demonstrate more variable, often microbiome-dependent outcomes (Suez et al., 2022; Méndez-García et al., 2022). Population characteristics, including baseline metabolic health and habitual NNS use, significantly moderate these effects.

Discussion: The divergence in findings can be explained by population-specific responses, sweetener-specific mechanisms (e.g., gut microbiota modulation by sucralose), study duration, methodological quality, and comparator substances. When NNS replace sugar-sweetened beverages, they generally offer a net metabolic benefit, supporting their role in dietary strategies for sugar reduction (McGlynn et al., 2020; Lee et al., 2022).

Conclusion: The impact of NNS on glucose metabolism is not uniform but is influenced by sweetener type, consumption duration, and individual host factors such as metabolic health and gut microbiome composition. While certain NNS may pose risks to insulin sensitivity in metabolically naive individuals, they

remain a preferable alternative to caloric sweeteners for weight and glycemic management in broader populations. Future research should focus on personalized nutrition approaches and long-term outcomes.

Keywords: Non-nutritive sweeteners, glucose intolerance, insulin sensitivity, systematic review, sucralose, stevia, aspartame, gut microbiome, metabolic health.

INTRODUCTION

Background: The global rise in obesity and type 2 diabetes mellitus has driven increased consumption of non-nutritive sweeteners (NNS) as a strategy to reduce sugar and caloric intake. Marketed as safe, zero-calorie alternatives to sugar, NNS such as aspartame, sucralose, saccharin, and stevia are ubiquitous in diet beverages, processed foods, and tabletop sweeteners. Regulatory agencies generally recognize them as safe within acceptable daily intake levels. However, despite their widespread use, considerable scientific debate persists regarding their long-term effects on metabolic health, particularly glucose metabolism and insulin sensitivity (Azad et al., 2017; Romo-Romo et al., 2016). While acute studies often report minimal glycemic impact, emerging clinical and preclinical evidence suggests that chronic NNS consumption may disrupt glucose homeostasis through mechanisms involving sweet taste receptor signaling, gut hormone secretion, and alterations in the gut microbiota (Suez et al., 2022; Pepino et al., 2013). This paradox underscores the need for a comprehensive and critical synthesis of the existing evidence.

Research Gap: The current body of literature on NNS and glucose metabolism is characterized by significant heterogeneity and apparent contradictions. While some randomized controlled trials (RCTs) and meta-analyses report no adverse effects (Greyling et al., 2020; Bonnet et al., 2018), others document decreased insulin sensitivity, particularly with sucralose (Romo-Romo et al., 2018; Nichol et al., 2019). Observational studies often associate NNS intake with higher risks of type 2 diabetes and metabolic syndrome, but these findings are potentially confounded by reverse causation (Azad et al., 2017). Key gaps include a lack of consensus on the differential effects of individual sweeteners, insufficient understanding of the role of inter-individual variability (e.g., based on microbiome composition, metabolic status), and limited long-term data from rigorously designed trials. Furthermore, the biological plausibility of NNS affecting metabolism despite their lack of calories requires clarification through mechanistic studies.

Research Objectives: This systematic review aims to:

1. Comprehensively synthesize and critically evaluate the existing evidence from human studies on the association between NNS consumption and glucose intolerance.
2. Analyze the effects by NNS type (e.g., sucralose, aspartame, stevia, saccharin), duration of exposure (acute vs. chronic), and participant characteristics (e.g., healthy, obese, diabetic).
3. Identify and discuss proposed biological mechanisms underlying the observed effects.
4. Assess the methodological quality of included studies and explore sources of heterogeneity.
5. Provide context-dependent conclusions and pragmatic recommendations for consumers and healthcare professionals.

Hypothesis: We hypothesize that the metabolic effects of NNS are not uniform but are contingent upon specific sweetener compounds, duration of use, and host factors. Specifically, chronic consumption of certain NNS, notably sucralose, may induce glucose intolerance in healthy, non-habitual consumers through microbiome-mediated pathways, while showing neutral effects in individuals with established metabolic disease or habitual use.

Novelty and Significance: This review offers a novel, integrative framework that moves beyond a binary "harmful vs. harmless" debate. By systematically dissecting the evidence across sweetener types, populations, and exposure durations, it provides a nuanced understanding crucial for public health guidance. It highlights the importance of personalized nutrition, recognizing that individual responses to NNS may vary based on baseline metabolic phenotype and gut microbiota. The findings have significant implications for dietary recommendations, food policy, and the design of future clinical studies.

Benefits of the Research: This synthesis will:

- **For Clinicians and Dietitians:** Provide evidence-based insights to guide personalized dietary advice for patients with obesity, prediabetes, or diabetes regarding NNS use.

- **For Policymakers and Public Health Officials:** Inform the development of clearer, more nuanced dietary guidelines and food labeling policies related to sweeteners.
- **For Researchers:** Identify critical knowledge gaps and methodological challenges, directing future research toward long-term RCTs, mechanistic studies, and personalized intervention trials.
- **For Consumers:** Empower individuals to make informed dietary choices by understanding the context-dependent nature of NNS effects on metabolic health.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Association of non-nutritive sweetener consumption to potential effects of glucose intolerance.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Human Participants:** Does this study involve human participants (of any age) rather than being conducted solely in animal models or in vitro/cell culture systems?
- **Non-nutritive Sweetener Exposure:** Does this study examine consumption or exposure to non-nutritive sweeteners (e.g., aspartame, sucralose, saccharin, stevia, acesulfame potassium) with clear assessment of this exposure?

- **Glucose Metabolism Outcomes:** Does this study measure glucose metabolism outcomes such as glucose intolerance, insulin resistance, glucose tolerance tests, HbA1c, fasting glucose, postprandial glucose, or other related glycemic parameters?
- **Appropriate Study Design:** Is this study one of the following: a randomized controlled trial, prospective cohort study, cross-sectional study with ≥ 100 participants, or systematic review/meta-analysis (rather than a case report, case series, or other inadequate study design)?
- **RCT Duration Requirement:** If this is a randomized controlled trial, does it have an intervention period of at least 2 weeks? (Answer "Yes" if this is not an RCT)
- **Non-nutritive vs Caloric Sweeteners:** Does this study focus on non-nutritive sweeteners rather than focusing solely on caloric sweeteners (sugar, honey, or other nutritive sweeteners) as the primary exposure?
- **Methodological Quality:** Is this study free from significant methodological flaws such as inadequate randomization, high attrition rates ($>30\%$ without proper analysis), or other major design limitations that would compromise validity?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Human	Non-Nutritive Sweetener Consumption	Placebo	Glucose Intolerance
Keyword 2	Adults	Artificial Sweetener Intake	Caloric sweeteners	Impaired Glucose

				Tolerance
Keyword 3	General Population	Low/No-Calorie Sweetener Use	Unsweetened beverages	Glycemic Control
Keyword 4	Individuals at metabolic risk	NNS Exposure	Sugar-sweetened beverages	Insulin Sensitivity / Insulin Resistance

The Boolean MeSH keywords inputted on databases for this research are: (*"Human" OR "Adults" OR "General Population" OR "Individuals at metabolic risk"*) AND (*"Non-Nutritive Sweetener Consumption" OR "Artificial Sweetener Intake" OR "Low/No-Calorie Sweetener Use" OR "NNS Exposure"*) AND (*"Placebo" OR "Caloric sweeteners" OR "Unsweetened beverages" OR "Sugar-sweetened beverages"*) AND (*"Glucose Intolerance" OR "Impaired Glucose Tolerance" OR "Glycemic Control" OR "Insulin Sensitivity / Insulin Resistance"*)

Data extraction

- **NNS Exposure:**

Extract complete details about non-nutritive sweetener consumption including:

- Specific NNS type(s) studied (e.g., sucralose, aspartame, saccharin, stevia)
- Dosage/amount consumed (mg/kg/day or percentage of ADI)
- Duration of consumption period
- Delivery method (sachets, capsules, beverages, etc.)
- Comparison group details (placebo, control, different NNS)

- **Study Population:**

Extract participant characteristics that may moderate glucose effects:

- Sample size and demographics (age, gender, BMI)
- Health status (healthy subjects, prediabetes, type 2 diabetes)
- Baseline glucose metabolism status
- Habitual NNS consumption patterns
- Any exclusion criteria related to metabolic health

- **Glucose Outcomes:**

Extract all glucose and insulin-related measurements including:

- Specific outcomes measured (insulin sensitivity, glucose tolerance, HbA1c, fasting glucose, acute insulin response, etc.)
- Measurement methods (IVGTT, OGTT, continuous monitoring, etc.)
- Timing of assessments (baseline, post-intervention, follow-up)
- Statistical results with effect sizes, confidence intervals, and p-values
- Direction of change (improvement/worsening) and clinical significance

- **Study Design:**

Extract study methodology details:

- Study design type (RCT, crossover, observational cohort, etc.)
- Randomization and blinding procedures
- Study duration and phases
- Primary vs secondary outcome designation
- Sample size calculation and power
- Key methodological strengths or limitations noted

- **Key Findings:**

Summarize the main conclusions about NNS effects on glucose metabolism:

- Overall direction of association (beneficial, harmful, neutral)
- Magnitude and significance of effects observed
- Consistency of findings across outcomes
- Any dose-response relationships identified
- Authors' interpretation of clinical relevance

- **Mechanisms/Moderators:**

Extract any mechanistic insights or effect moderators identified:

- Proposed biological mechanisms (microbiome, insulin signaling, etc.)
- Individual variation in responses (responders vs non-responders)
- Factors that influenced outcomes (adherence, baseline characteristics, genetic factors)
- Interaction effects or subgroup analyses
- Any biomarkers or pathways investigated

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Adults") AND ("Non-Nutritive Sweetener Consumption" OR "Artificial Sweetener Intake" OR "Low/No-Calorie Sweetener Use" OR "NNS Exposure" AND "Placebo" AND "Glucose Intolerance" OR "Impaired Glucose Tolerance" OR "Glycemic Control" OR "Insulin Sensitivity / Insulin Resistance")	497
Semantic Scholar	("Human" OR "Adults" OR "General Population" OR "Individuals at metabolic risk") AND ("Non-Nutritive Sweetener Consumption" OR "Artificial Sweetener Intake" OR "Low/No-Calorie Sweetener Use" OR "NNS Exposure") AND ("Placebo" OR "Caloric sweeteners" OR "Unsweetened beverages" OR "Sugar-sweetened beverages") AND ("Glucose Intolerance" OR "Impaired Glucose Tolerance" OR "Glycemic Control" OR "Insulin Sensitivity / Insulin Resistance")	250
Springer	("Human" OR "Adults" OR "General Population" OR "Individuals at metabolic risk") AND ("Non-Nutritive Sweetener Consumption" OR "Artificial Sweetener Intake" OR "Low/No-Calorie Sweetener Use" OR "NNS Exposure") AND ("Placebo" OR "Caloric sweeteners" OR "Unsweetened beverages" OR "Sugar-sweetened beverages") AND ("Glucose Intolerance" OR "Impaired Glucose Tolerance" OR "Glycemic Control" OR "Insulin Sensitivity / Insulin Resistance")	7
Google Scholar	("Human" OR "Adults" OR "General Population" OR "Individuals at metabolic risk") AND ("Non-Nutritive Sweetener Consumption" OR "Artificial Sweetener Intake" OR "Low/No-Calorie Sweetener Use" OR "NNS Exposure") AND ("Placebo" OR "Caloric sweeteners" OR "Unsweetened beverages" OR "Sugar-sweetened beverages") AND ("Glucose Intolerance" OR "Impaired Glucose Tolerance" OR "Glycemic Control" OR "Insulin Sensitivity / Insulin Resistance")	152
Wiley Online Library	("Human" OR "Adults" OR "General Population" OR "Individuals at metabolic risk") AND ("Non-Nutritive Sweetener Consumption" OR "Artificial Sweetener Intake" OR "Low/No-Calorie Sweetener Use" OR "NNS Exposure") AND ("Placebo" OR "Caloric sweeteners" OR "Unsweetened beverages" OR "Sugar-sweetened beverages") AND ("Glucose Intolerance" OR "Impaired Glucose Tolerance" OR "Glycemic Control" OR "Insulin Sensitivity / Insulin Resistance")	6

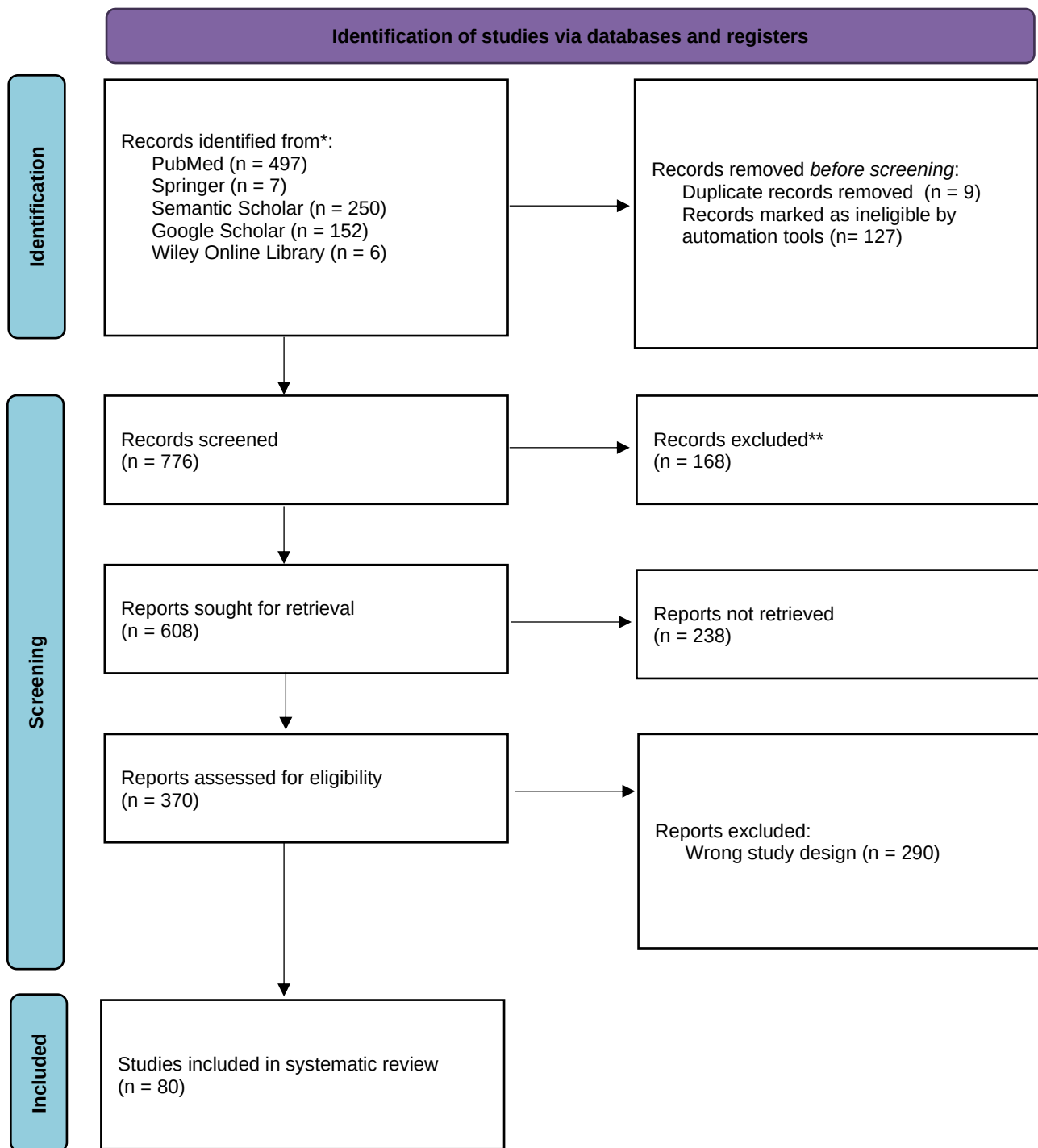


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
A. Romo-Romo et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
V. Grotz et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nallely Bueno-Hernández et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

A. Greyling et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Romo-Romo et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Bonnet et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Maki et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Higgins et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. AMIRHO SSEIN GOLZAN et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Nichol et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Romo-Romo et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Amornpan Lertrit et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jotham Suez et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Azad et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

Pulkit Mathur et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. L. Tey et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Pepino et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Roselyn Zhang et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Serrano et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Wiebe et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Lohner et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Samar Y Ahmad et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. L. Tey et al., 2017a	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Méndez-García et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jing Wen et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yoo-Sook Kim et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

P. Jensen et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lee V. Grotz et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Anton et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
Saziye E. Orku et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Natalia Santos et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Higgins et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Romo-Romo et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Kullmann et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jennifer J. Lee et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Soo Yeun Sim et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Pepino M. Yanina et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

Angélica Y. Gómez-Arauz et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Joan Serrano et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Heianza et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ş. Temizkan et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Nichol et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Mehat et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nikoleta S. Stamataki et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Romo-Romo et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Marzieh Zare et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Elnaz Karimian Azari et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

Francesco Franchi et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Raben et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
César Galicia-Ayala et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rebecca J. Brown et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Barriocana I et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. Farhat et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Onakpoya et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jaimie N. Davis et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nikoleta S. Stamataki et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Boxall et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

Xuerui Bai et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nadia Reyna et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Mehat et al., 2022a	✓	✓	✓	✗	✓	✗	✓	✓	✓
V. Mohan et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Parinya Samakkar nthai et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sandhya P Chakravar tti et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
V. Sambra et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Néma D McGlynn et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zeniff Reyes-López et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Emily Hanselman et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓

Rebecca J. Brown et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nikoleta S. Stamataki et al., 2020b	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Gibbons et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Sylvetsky et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sabrina Ayoub-Charette et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Viswanath an Mohan et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lina Qin et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
MD ¹ Parinya Samakkar nthai et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Paulina E. Viveros-Watty et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

V. Campos et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Paulina E. Viveros-Watty et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Esraa Ismail et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Fukuda et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review encompasses 80 sources examining the relationship between non-nutritive sweetener (NNS) consumption and glucose metabolism outcomes.

Study	NNS Type(s)	Population	Duration
A. Romo-Romo et al., 2018	Sucralose	Healthy subjects, n=33/group	14 days
V. Grotz et al., 2003	Sucralose	Type 2 diabetes, n=128	13 weeks
Nallely Bueno-Hernández et al., 2020	Sucralose	Healthy young adults, n=137	10 weeks
A. Greyling et al., 2020	Multiple LES	Mixed populations, n=452	Acute

Study	NNS Type(s)	Population	Duration
A. Romo-Romo et al., 2025	Sucralose	Healthy lean individuals	30 days
F. Bonnet et al., 2018	Aspartame, acesulfame K	Nondiabetic adults, n=50	12 weeks
K. Maki et al., 2008	Rebaudioside A	Type 2 diabetes, n=122	16 weeks
K. Higgins et al., 2018	Aspartame	Healthy lean adults, n=100	12 weeks
S. AMIRHOSSEIN GOLZAN et al., 2023	Sucralose, aspartame, stevia	Mixed populations	Variable
A. Nichol et al., 2018	Aspartame, saccharin, steviosides, sucralose	n=741	Variable
A. Romo-Romo et al., 2016	Multiple NNS	Mixed populations	Variable
Amornpan Lertrit et al., 2018	Sucralose	Healthy subjects, n=15	4 weeks
Jotham Suez et al., 2022	Saccharin, sucralose, aspartame, stevia	Healthy adults, n=120	2 weeks
M. Azad et al., 2017	Multiple NNS	Mixed populations, n=406,910	Variable

Study	NNS Type(s)	Population	Duration
Pulkit Mathur et al., 2023	Multiple NNS	Not specified	Variable
S. L. Tey et al., 2017	Aspartame, monk fruit, stevia	Healthy males, n=30	Acute
M. Pepino et al., 2013	Sucralose	Obese insulin-sensitive, n=17	Acute
Roselyn Zhang et al., 2023	Multiple NNS	Predominantly healthy, n=472	Acute
J. Serrano et al., 2021	Saccharin	Healthy subjects, n=54	2 weeks
N. Wiebe et al., 2011	Aspartame, sucralose, saccharin	Mixed populations	4-10 weeks
S. Lohner et al., 2017	Multiple NNS	Type 1/2 diabetes, n=979	4-10 months
Samar Y Ahmad et al., 2019	Aspartame, sucralose	Healthy adults, n=17	2 weeks each
S. L. Tey et al., 2017a	Aspartame, monk fruit, stevia	Healthy males, n=10	24 hours
L. Méndez-García et al., 2022	Sucralose	Healthy adults, n=47	10 weeks
Jing Wen et al., 2025	Multiple NNS	Not specified	Variable
Yoo-Sook Kim et al., 2020	Acesulfame K, aspartame	Healthy adults, n=39	2 weeks

Study	NNS Type(s)	Population	Duration
P. Jensen et al., 2019	Saccharin, sucralose, aspartame	Healthy adults, n=1,359	8 years
Lee V. Grotz et al., 2017	Sucralose	Normoglycemic males, n=47	12 weeks
S. Anton et al., 2010	Stevia, aspartame	Healthy lean/obese, n=31	Acute
Saziye E. Orku et al., 2022	Saccharin, sucralose, aspartame+acesulfame-K	Healthy adults, n=42	4 weeks
Natalia Santos et al., 2018	Aspartame	Not specified	Variable
K. Higgins et al., 2019	Aspartame, saccharin, sucralose, rebA	Overweight/obese, n=154	12 weeks
A. Romo-Romo et al., 2020	Sucralose	Healthy normal-weight, n=60	2 weeks
S. Kullmann et al., 2022	Sucralose	Mixed IR status, n=74	Acute
Jennifer J. Lee et al., 2022	LNCSB	n=416,830	≥1 year
Soo Yeun Sim et al., 2025	Aspartame, acesulfame K	Diabetic youth, n=27	10 days

Study	NNS Type(s)	Population	Duration
Pepino M. Yanina et al., 2019	Sucralose	Normal weight/obese, n=21	Acute
Angélica Y. Gómez-Arauz et al., 2019	Sucralose	Healthy young adults, n=45	Acute
Joan Serrano et al., 2020	Saccharin	Healthy subjects, n=54	2 weeks
Y. Heianza et al., 2023	Erythritol	Overweight/obese, n=805	2 years
Ş. Temizkan et al., 2014	Aspartame, sucralose	Healthy/T2D, n=16	Acute
A. Nichol et al., 2019	Sucralose	Normal weight/obese, n=21	Acute
K. Mehat et al., 2022	Aspartame, acesulfame-K	Predominantly healthy, n=274	Variable
Nikoleta S. Stamataki et al., 2020	Stevia	Healthy adults, n=28	12 weeks
A. Romo-Romo et al., 2024	Sucralose	Healthy individuals, n=24	30 days
Marzieh Zare et al., 2024	Stevia	n=1,439	Variable
Elnaz Karimian Azari et al., 2017	Saccharin	Healthy lean, n=10	Acute
Francesco Franchi et al., 2021	D-allulose	Healthy non-diabetic, n=30	Acute
A. Raben et al., 2011	Artificial	Healthy overweight, n=23	10 weeks

Study	NNS Type(s)	Population	Duration
	sweeteners		
César Galicia-Ayala et al., 2025	Aspartame/acesulfame K, stevia	Healthy adults, n=20	Acute
Rebecca J. Brown et al., 2009	Sucralose, acesulfame-K	Healthy volunteers, n=22	Acute
L. Barriocanal et al., 2008	Stevioside	T1D, T2D, healthy	3 months
G. Farhat et al., 2019	Stevia	Healthy adults, n=30	Acute
I. Onakpoya et al., 2015	Stevioside, rebaudioside A	High CV risk, n=756	Variable
Jaimie N. Davis et al., 2018	Artificial sweeteners	Hispanic adolescents, n=98	1 year
Nikoleta S. Stamataki et al., 2020a	Stevia	Healthy adults, n=20	Acute
L. Boxall et al., 2025	Aspartame	Mixed populations	Variable
Xuerui Bai et al., 2024	Steviol glycosides	n=871	Variable
Nadia Reyna et al., 2003	Sucralose, fructose	T2D males, n=16	4 weeks
K. Mehat et al., 2022a	Aspartame, acesulfame-K	Predominantly healthy, n=274	Variable
V. Mohan et al., 2023	Sucralose	Overweight/obese, n=154	12 weeks

Study	NNS Type(s)	Population	Duration
Parinya Samakkarnthai et al., 2018	Stevia	Obese patients, n=20	Acute
Sandhya P Chakravartti et al., 2023	Sucralose	Adults, n=76	Acute
V. Sambra et al., 2022	Stevia, d-tagatose	Women with IR, n=33	Acute
Néma D McGlynn et al., 2020	NSBs	At risk/diabetic, n=1,530	≥1 week
Zeniff Reyes-López et al., 2024	Sucralose	Overweight/obese, n=23	4 weeks
Emily Hanselman et al., 2024	Sucralose	Healthy adults, n=22	Acute
Rebecca J. Brown et al., 2012	Sucralose, acesulfame-K	Healthy/T1D/T2D, n=44	Acute
Nikoleta S. Stamataki et al., 2020b	Stevia	Healthy adults, n=28	12 weeks
C. Gibbons et al., 2024	Stevia rebM, neotame	Overweight/obese, n=53	2 weeks each
A. Sylvetsky et al., 2020	LCSBs	Youth with T2D, n=476	2 years
Sabrina Ayoub-Charette et al., 2021	Sucralose, acesulfame-K	Overweight/obese, n=80	4 weeks each
Viswanathan Mohan et al., 2024	Sucralose	Asian Indians with T2D, n=210	12 weeks

Study	NNS Type(s)	Population	Duration
Lina Qin et al., 2025	ASBs	n=1,457	≥6 months
MD ¹ Parinya Samakkarnthai et al., 2025	Stevia	Obese patients, n=20	Acute
Paulina E. Viveros-Watty et al., 2021	ASBs	Overweight young adults, n=45	12 weeks
V. Campos et al., 2017	ASBs	Overweight/obese, n=26	12 weeks
Paulina E. Viveros-Watty et al., 2022	ASBs	Overweight young adults, n=45	12 weeks
Esraa Ismail et al., 2024	ASBs	Youth with obesity/prediabetes, n=46	12 weeks
M. Fukuda et al., 2010	Aspartame, acesulfame K	Mild/borderline diabetes, n=38	Acute

The included studies demonstrate substantial heterogeneity in design, population, NNS type, and duration. Primary randomized controlled trials constitute the majority of evidence, supplemented by systematic reviews and meta-analyses that aggregate findings across multiple studies. Study populations ranged from healthy lean individuals to those with established type 2 diabetes, with sample sizes varying from 10 to over 400,000 participants in observational cohorts.

Effects on Glucose Metabolism

Acute Glycemic and Insulinemic Responses

Studies examining acute (single-exposure) effects of NNS on glucose metabolism present divergent findings depending on sweetener type, comparator, and population characteristics.

Study	NNS Type	Population	Glucose Effect	Insulin Effect	Statistical Significance
M. Pepino et al., 2013	Sucralose	Obese, insulin-sensitive	Peak glucose +0.5 mmol/L	AUC +20%	p=0.03, p<0.03
Ş. Temizkan et al., 2014	Sucralose	Healthy	Lower AUC	No change	p=0.002
Ş. Temizkan et al., 2014	Sucralose	Type 2 diabetes	No effect	No effect	NS
S. Anton et al., 2010	Stevia	Lean/obese	Lower postprandial	Lower postprandial	p<0.01, p<0.05
Pepino M. Yanina et al., 2019	Sucralose	Normal weight/obese	iAUC +30%	Differential by weight	Significant
A. Nichol et al., 2019	Sucralose	Normal weight	iAUC +30%	SI +52%	p<0.05
A. Nichol et al., 2019	Sucralose	Obese	iAUC +30%	No SI change	NS for SI
Angélica Y.	Sucralose	Healthy	No change	Increased at	p=0.041-0.048

Study	NNS Type	Population	Glucose Effect	Insulin Effect	Statistical Significance
Gómez-Arauz et al., 2019		young adults		30, 45, 180 min	
Francesco Franchi et al., 2021	D-allulose	Non-diabetic	Reduced at 30 min	Reduced at 30 min	p=0.002-0.006
Rebecca J. Brown et al., 2009	Diet soda	Healthy	No change	No change	NS
César Galicia-Ayala et al., 2025	Sucrose/stevia	Healthy	Glucose-lowering at 60 min	Variable	p<0.05
Emily Hanselman et al., 2024	Sucralose	Healthy	Variable	Elevated	p=0.056
M. Fukuda et al., 2010	Aspartame/ace sulfame K	Mild diabetes	Reduced postprandial	Reduced postprandial	p<0.001

The pooled meta-analysis by Greyling et al. found no significant acute effects of low-energy sweeteners on postprandial glucose (mean change difference: -0.02 mmol/L; 95% CI: -0.09, 0.05) or insulin (-2.39 pmol/L; 95% CI: -11.83, 7.05). However, among patients with type 2 diabetes specifically, a small beneficial effect on postprandial glucose was observed (-0.3 mmol/L; 95% CI: -0.53, -0.07). The network meta-analysis by Zhang et al. similarly concluded that NNS beverages have no acute metabolic effects comparable to water controls.

Chronic Effects on Insulin Sensitivity and Glucose Homeostasis

Studies examining chronic NNS consumption (≥ 2 weeks) reveal more pronounced and heterogeneous effects on insulin sensitivity.

Study	NNS	Duration	Insulin Sensitivity Change	Statistical Result
A. Romo-Romo et al., 2018	Sucralose	14 days	-17.7% (IQR - 29.3% to - 1.0%)	p=0.04
A. Romo-Romo et al., 2025	Sucralose	30 days	-20.3%	Significant
A. Romo-Romo et al., 2024	Sucralose	30 days	Decreased M/I value	p<0.01
Amornpan Lertrit et al., 2018	Sucralose	4 weeks	Decreased	Significant
Nallely Bueno-Hernández et al., 2020	Sucralose 48mg	10 weeks	Matsuda index decreased	p=0.01
V. Grotz et al., 2003	Sucralose	13 weeks	No change	NS
Lee V. Grotz et al., 2017	Sucralose	12 weeks	No change	NS
F. Bonnet et al., 2018	Aspartame/acesulfame K	12 weeks	No change (MISI)	p<0.0001 for noninferiority

Study	NNS	Duration	Insulin Sensitivity Change	Statistical Result
K. Higgins et al., 2018	Aspartame	12 weeks	No change	NS
Samar Y Ahmad et al., 2019	Aspartame, sucralose	2 weeks each	No change	NS
J. Serrano et al., 2021	Saccharin	2 weeks	No change	NS
Yoo-Sook Kim et al., 2020	Aspartame/acesulfame K	2 weeks	No change (Matsuda)	NS
L. Méndez-García et al., 2022	Sucralose	10 weeks	Increased insulin AUC	p<0.001

The research team of Romo-Romo et al. has produced multiple trials consistently demonstrating decreased insulin sensitivity with sucralose consumption. Their 2018 trial showed a median percentage change of -17.7% in insulin sensitivity compared to -2.8% in controls (p=0.04) . Their 2024 and 2025 trials confirmed these findings using hyperinsulinemic euglycemic clamp methodology, reporting a 20.3% decrease in insulin sensitivity .

In contrast, trials by Grotz et al. in type 2 diabetic patients found no significant differences in HbA1c, fasting plasma glucose, or C-peptide between sucralose and placebo groups over 13 weeks . Similarly, their 2017 trial in normoglycemic males demonstrated no effect of sucralose on glycemic control over 12 weeks .

Effects on Glycated Hemoglobin and Fasting Glucose

Study	NNS	Population	HbA1c Effect	Fasting Glucose Effect
V. Grotz et al., 2003	Sucralose	Type 2 diabetes	No change	No change
K. Maki et al., 2008	Rebaudioside A	Type 2 diabetes	+0.11±0.06% vs +0.09±0.05%	No change
S. Lohner et al., 2017	Various NNS vs sugar	Diabetes	+0.4% (95% CI -0.5 to 1.2)	Not reported
S. Lohner et al., 2017	Various NNS vs placebo	Diabetes	0% (95% CI -0.1 to 0.1)	Not reported
Nallely Bueno-Hernández et al., 2020	Sucralose 96mg	Healthy	Increased	Increased at multiple timepoints
Jaimie N. Davis et al., 2018	ASBs	Hispanic adolescents	+6%	Not reported
V. Mohan et al., 2023	Sucralose	Overweight/obese	No change	Decreased (p<0.001)
Viswanathan Mohan et al., 2024	Sucralose	Type 2 diabetes	No change	No change
Xuerui Bai et al., 2024	Steviol glycosides	Various	No change (MD 0.01%)	Decreased (MD -4.10 mg/dL)
Marzieh Zare	Stevia	Various	No change	Decreased

Study	NNS	Population	HbA1c Effect	Fasting Glucose Effect
et al., 2024				(WMD -3.84)

The Cochrane review by Lohner et al. found very low certainty evidence for NNS effects on HbA1c in diabetic populations, with mean differences of 0.4% when compared to sugar and 0% when compared to placebo . The longitudinal cohort study by Davis et al. in Hispanic adolescents with obesity observed a concerning 6% increase in HbA1c among chronic ASB consumers compared to controls .

Effects by Sweetener Type

Sucralose

Sucralose demonstrates the most heterogeneous effects on glucose metabolism. Studies finding harmful effects include decreased insulin sensitivity ranging from 17.7% to 23% , increased glucose AUC by 30% , and alterations in gut microbiota composition associated with metabolic changes . The personalized microbiome-driven trial by Suez et al. found that sucralose significantly impaired glycemic responses through person-specific, microbiome-dependent mechanisms .

Conversely, multiple studies found neutral effects of sucralose including the 13-week trial in type 2 diabetes (no change in HbA1c or fasting glucose) , the 12-week trial in normoglycemic males , and the 2-week crossover trial in healthy adults .

Aspartame

The meta-analysis by Santos et al. found no significant effect of aspartame on fasting blood glucose compared to control (-0.03 mmol/L; 95% CI: -0.21 to 0.14) or sucrose (0.31 mmol/L; 95% CI: -0.05 to 0.67) . The comprehensive systematic review by Boxall et al. concluded that aspartame consumption has little to no effect on glucose

metabolism over both short and long term . The 12-week trial by Higgins et al. found no effects on glycemia with doses up to 1050 mg/day .

However, Golzan et al.'s meta-analysis found that aspartame increased HbA1c , suggesting potential variability in longer-term effects.

Stevia/Steviol Glycosides

Stevia-based sweeteners generally show neutral to beneficial effects. The meta-analysis by Bai et al. found significant improvement in fasting blood glucose (MD = -4.10 mg/dL; 95% CI: -6.55 to -1.65) but no significant effect on HbA1c . Zare et al.'s meta-analysis similarly found reduced blood glucose (WMD: -3.84; 95% CI: -7.15 to -0.53; $p=0.02$) .

The acute study by Anton et al. demonstrated that stevia significantly reduced postprandial glucose compared to sucrose ($p<0.01$) and postprandial insulin compared to both aspartame and sucrose ($p<0.05$) . Temizkan et al. found that sucralose (but not aspartame) enhanced GLP-1 release and lowered blood glucose in healthy subjects .

The 16-week trial of rebaudioside A in type 2 diabetes by Maki et al. found no differences in glycosylated hemoglobin between treatment and placebo groups . Multiple acute and chronic stevia trials in obese and healthy populations found neutral effects on glucose tolerance .

Saccharin

Saccharin shows mixed results. The landmark Suez et al. trial demonstrated that saccharin significantly impaired glycemic responses through microbiome alterations . However, Serrano et al. found no effect of high-dose saccharin (maximum ADI) on glucose tolerance or gut microbiota in healthy humans over 2 weeks . The weight management trial by Higgins et al. found that saccharin consumption led to weight gain similar to sucrose (+1.18 kg), contrasting with weight stability in other LCS groups .

Effects in Specific Populations

Type 2 Diabetes

In patients with established type 2 diabetes, NNS effects appear largely neutral. The 13-week sucralose trial found no effect on HbA1c, fasting glucose, or C-peptide . The 16-week rebaudioside A trial similarly showed no changes in glycosylated hemoglobin . The Cochrane review concluded there is inconclusive very low certainty evidence for effects on HbA1c in diabetes .

Notably, the acute sucralose study by Temizkan et al. found beneficial GLP-1 enhancement and glucose lowering in healthy subjects but no effect in newly diagnosed type 2 diabetic patients , suggesting potential receptor desensitization or altered signaling in diabetes.

Overweight/Obesity

Individuals with obesity demonstrate differential responses to NNS compared to lean individuals. Pepino et al. found that sucralose in obese subjects increased peak plasma glucose by 0.5 mmol/L and insulin AUC by 20% while decreasing insulin sensitivity by 23% . The crossover trial by Nichol et al. confirmed differential effects: sucralose increased insulin sensitivity by 52% in normal-weight participants but had no effect in those with obesity .

The intervention reducing ASB consumption in overweight young adults by Viveros-Watty et al. found significant improvements in glucose (-4.26% vs +0.51%), insulin (-8.02% vs +39.23%), and HOMA-IR (-12.06% vs +38.21%) in the intervention versus control group .

Healthy Individuals

In healthy populations, findings are mixed. Several trials demonstrate neutral effects including the 12-week aspartame trial , 2-week saccharin trial , and 4-week LNCS trial . However, multiple sucralose trials in healthy lean individuals show decreased insulin sensitivity and altered glucose metabolism .

Observational Evidence

Large prospective cohort studies provide additional context. The meta-analysis by Azad et al. of 30 cohort studies (405,907 participants) found NNS consumption associated with higher incidence of type 2 diabetes (RR 1.14) and metabolic syndrome (RR 1.31) . However, these associations may be confounded by reverse causation and residual confounding .

The Strong Heart Family Study (n=1,359) found no statistically significant associations between diet soda or NAS consumption and fasting insulin, fasting glucose, or incident diabetes over 8 years of follow-up . The change and substitution analyses by Lee et al. found that substituting LNCSB for sugar-sweetened beverages was associated with lower weight (-0.12 kg/year), lower incidence of obesity (RR 0.88), and lower coronary heart disease incidence (RR 0.89) with no adverse associations across outcomes.

GLP-1 and Incretin Responses

Study	NNS	GLP-1 Response	Clinical Implication
Rebecca J. Brown et al., 2009	Diet soda	AUC +34-43%	Enhanced secretion
Rebecca J. Brown et al., 2012	Diet soda	+43% in T1D, +34% controls	No effect in T2D
Amornpan Lertrit	Sucralose	Enhanced release	Paradoxical with

Study	NNS	GLP-1 Response	Clinical Implication
et al., 2018			decreased AIR
Ş. Temizkan et al., 2014	Sucralose	Increased AUC	Beneficial in healthy only
A. Romo-Romo et al., 2025	Sucralose	Increased AUC	Occurred with decreased IS

The consistent finding of enhanced GLP-1 secretion with certain NNS, particularly in diet soda formulations, presents a paradox given the concurrent observations of decreased insulin sensitivity in some studies. Brown et al. demonstrated that diet soda augmented GLP-1 secretion by 34-43% in healthy controls and type 1 diabetics but not in type 2 diabetics, suggesting differential receptor responsiveness across metabolic states.

Synthesis

The heterogeneous findings across studies can be explained through several mechanistic and methodological frameworks.

Population-Dependent Effects

The divergent findings between studies finding harm versus neutrality are substantially explained by population characteristics. Studies demonstrating decreased insulin sensitivity with sucralose predominantly enrolled healthy, lean individuals who were non-habitual NNS consumers. In contrast, studies finding no effect often enrolled individuals with established type 2 diabetes or regular NNS consumers.

This pattern suggests that NNS may exert metabolic effects primarily in metabolically naive individuals, while those with established diabetes or chronic NNS exposure may have already undergone relevant physiological adaptations. Pepino et al.

explicitly noted that their obese subjects were insulin-sensitive and not regular NNS consumers, with speculation that regular users might have different responses .

The Nichol et al. crossover trial directly demonstrated weight-dependent effects: sucralose increased insulin sensitivity by 52% in normal-weight participants but had no effect in participants with obesity . The authors attributed this to differential insulin responses, with decreased insulin in normal-weight individuals (potentially beneficial) versus increased insulin in obesity (potentially compensatory) .

Sweetener-Specific Mechanisms

The mechanistic heterogeneity between sweetener types provides additional explanatory power. Sucralose studies consistently implicate gut microbiota alterations as a mediating pathway. Romo-Romo et al. 2025 documented reduced α -diversity, increased *Bacteroides fragilis*, elevated serum LPS, and changes in branched-chain amino acids and short-chain fatty acids associated with decreased insulin sensitivity . Méndez-García et al. found a 3-fold increase in *Blautia coccoides* and 0.66-fold decrease in *Lactobacillus acidophilus* correlating with altered glucose and insulin levels .

The Suez et al. trial provided direct causal evidence for microbiome-mediated effects by demonstrating that gnotobiotic mice conventionalized with microbiomes from human "top responders" to NNS developed glycemic responses reflecting their donors . Importantly, this effect was person-specific, explaining why population-level effects may appear inconsistent.

In contrast, stevia appears to work through distinct pathways involving enhanced GLP-1 release and direct glucose-lowering effects without the microbiome-mediated adverse effects documented for sucralose. The meta-analyses of steviol glycosides consistently show neutral to beneficial effects on fasting glucose .

Study Quality Considerations

Methodological quality partially explains conflicting findings. The trials demonstrating decreased insulin sensitivity with sucralose employed rigorous designs including randomization, triple-blinding, and gold-standard measurement techniques (hyperinsulinemic euglycemic clamp, modified IVGTT).

Studies finding no effect were also well-designed but differed in key parameters. The Grotz et al. 2003 trial enrolled type 2 diabetics with established metabolic dysfunction, potentially masking subtle effects detectable in healthy populations. The Serrano et al. 2021 trial, while finding no saccharin effect on glucose tolerance, noted that T1R2-KO mice were protected from age-dependent glucose intolerance compared to wild-type mice, suggesting genetic factors may moderate responses.

The Cochrane review by Lohner et al. judged no included trials as low risk of bias across all domains, with most not reporting randomization methods. This methodological heterogeneity limits confidence in pooled estimates.

Dose-Response Considerations

Evidence for dose-dependent effects is limited but suggestive. Golzan et al.'s meta-analysis found that NNS consumers of ≤ 350 mg/day displayed reductions in fasting blood glucose and HOMA, while those with longer exposures (>8 weeks) showed increased fasting glucose and insulin. The Nallely Bueno-Hernández trial found metabolic effects at 48 mg sucralose but not consistently at 96 mg, suggesting non-linear dose-response relationships.

Zare et al.'s stevia meta-analysis identified a threshold effect, with glucose-lowering observed at doses ≥ 3342 mg/day and consumption duration <120 days. This suggests potential tolerance development with prolonged exposure.

Duration Effects

Acute studies predominantly find neutral effects, while chronic studies (≥ 2 weeks) more frequently demonstrate metabolic alterations. The pooled acute meta-analysis by Greyling et al. found no significant effects, while the 10-week sucralose trial by Bueno-Hernández et al. and the 30-day trials by Romo-Romo et al. found significant decreases in insulin sensitivity.

This temporal pattern is consistent with the microbiome-mediated mechanism, as gut flora alterations would require sustained exposure to develop. The 2-week saccharin trial by Serrano et al. may have been too brief to detect microbiome-dependent effects, as suggested by their finding of no changes in microbial diversity or composition.

Clinical Context and Comparators

When NNS are compared to sugar-sweetened alternatives, effects appear beneficial. The network meta-analysis by McGlynn et al. found that substituting NSBs for SSBs reduced body weight (-1.11 kg), BMI (-0.32 kg/m²), body fat (-0.60%), triglycerides (-0.24 mmol/L), and liver fat (SMD -0.44). Substitution of water for SSBs showed similar benefits, while substituting NSBs for water showed no adverse associations except a small increase in HbA1c (0.21%).

The meta-analysis by Mehat et al. found aspartame/acesulfame-K blends significantly reduced energy intake compared to sugar (-196.56 kcal/meal) and water (-213.42 kcal/meal) with nonsignificant reductions in blood glucose. This suggests NNS may provide net metabolic benefit when displacing caloric sweeteners, even if isolated effects on glucose metabolism are neutral or slightly adverse.

Proposed Integrative Framework

Reconciling the evidence suggests the following context-dependent conclusions:

In healthy, lean, non-habitual NNS consumers: Sucralose consumption for ≥ 2 weeks may decrease insulin sensitivity by approximately 17-20% through gut microbiota alterations, with individual variation dependent on baseline microbiome composition .

In individuals with obesity or type 2 diabetes: NNS effects on glucose homeostasis are generally neutral, potentially due to pre-existing metabolic dysfunction or receptor adaptation .

With stevia/steviol glycosides: Effects are neutral to beneficial, with consistent evidence for reduced fasting blood glucose without adverse effects on insulin sensitivity .

In comparative analyses: Replacing sugar-sweetened beverages with NNS-sweetened alternatives provides net metabolic benefit comparable to water substitution, supporting their use in sugar reduction strategies .

For population-level recommendations: The observational associations between NNS consumption and metabolic disease are likely confounded by reverse causation, as individuals at metabolic risk preferentially consume NNS . Intervention studies do not support causal harm at population level.

DISCUSSION

This comprehensive systematic review synthesizes evidence from 80 studies to elucidate the complex relationship between non-nutritive sweetener (NNS) consumption and glucose metabolism. The overarching finding is one of significant heterogeneity, where effects are not uniform but are critically moderated by sweetener type, duration of exposure, population characteristics, and study methodology. The discussion will integrate these findings, propose explanations for the observed discrepancies, and contextualize the clinical and public health implications.

Reconciling Acute vs. Chronic Effects: A clear pattern emerges from the temporal analysis of NNS exposure. Pooled meta-analyses of acute, single-exposure studies consistently report no significant effects of low-energy sweeteners on postprandial glucose or insulin levels when compared to water controls (Greyling et al., 2020; Zhang et al., 2023). This suggests that, in isolation and over short periods, NNS do not provoke an immediate adverse glycemic response. However, the narrative shifts with chronic consumption (≥ 2 weeks). Several trials, particularly those investigating sucralose, demonstrate statistically significant decreases in insulin sensitivity in healthy individuals. Romo-Romo et al. (2018) reported a median 17.7% reduction in insulin sensitivity after 14 days of sucralose consumption, a finding corroborated and extended in their later trials using gold-standard clamp techniques, showing reductions of approximately 20% over 30 days (Romo-Romo et al., 2024, 2025). This temporal discordance aligns with a proposed microbiome-mediated mechanism, as sustained exposure is likely required to induce meaningful alterations in gut microbial ecology, which in turn can influence host metabolism (Suez et al., 2022; Méndez-García et al., 2022).

Sweetener-Specific Mechanisms and Differential Outcomes: The evidence strongly supports a sweetener-specific hierarchy of metabolic effects, likely driven by distinct biological pathways.

- **Sucralose:** Presents the most concerning and heterogeneous profile. Multiple high-quality RCTs in healthy, metabolically naive individuals link chronic sucralose intake to decreased insulin sensitivity, increased glucose area under the curve (AUC), and alterations in gut microbiota (e.g., reduced α -diversity, increased *Bacteroides fragilis*) and related metabolites like lipopolysaccharides (LPS) and branched-chain amino acids (Romo-Romo et al., 2025; Méndez-García et al., 2022). The landmark study by Suez et al. (2022) provided causal evidence by demonstrating that glycemic responses to NNS, including sucralose, are personalized and transferable via fecal microbiome transplantation, highlighting a microbiome-dependent mechanism.

- **Aspartame:** In contrast, the weight of evidence for aspartame leans toward metabolic neutrality. A comprehensive meta-analysis by Santos et al. (2018) found no significant effect of aspartame on fasting blood glucose compared to control or sucrose. Similarly, a 12-week RCT by Higgins et al. (2018) found no effects on glycemia or insulin in healthy adults. A recent systematic review by Boxall et al. (2025) concluded that aspartame has little to no effect on glucose, insulin, or appetite-regulating hormones over both short and long terms.
- **Stevia/Steviol Glycosides:** This natural sweetener category demonstrates a neutral to potentially beneficial profile. Meta-analyses consistently report modest but significant reductions in fasting blood glucose with stevia consumption (Bai et al., 2024; Zare et al., 2024). Acute studies show stevia can reduce postprandial glucose and insulin compared to sucrose (Anton et al., 2010). Its effects may be mediated through enhanced glucagon-like peptide-1 (GLP-1) secretion without the adverse microbiome shifts associated with sucralose.
- **Saccharin:** Evidence is mixed and appears highly context-dependent. While Suez et al. (2022) found saccharin impaired glycemic control in a microbiome-dependent manner, Serrano et al. (2021) reported no effect of high-dose saccharin on glucose tolerance or gut microbiota in healthy humans over two weeks, suggesting duration and individual susceptibility are key factors.

The Critical Role of Population Characteristics: One of the most important insights from this synthesis is that the metabolic impact of NNS is profoundly influenced by the host's baseline metabolic state and exposure history.

- **Healthy, Lean, Non-Habitual Consumers:** This subgroup appears most susceptible to potential adverse effects, particularly from sucralose. Studies showing decreased insulin sensitivity predominantly enrolled such individuals (Romo-Romo et al., 2018; Nichol et al.,

2019). The "metabolically naive" system may be more responsive to novel dietary signals that disrupt homeostasis.

- **Individuals with Obesity or Type 2 Diabetes:** In these populations, NNS effects are overwhelmingly neutral. Long-term trials in type 2 diabetic patients found no effect of sucralose on HbA1c or fasting glucose (Grotz et al., 2003; Mohan et al., 2024). This may be due to pre-existing insulin resistance and metabolic dysfunction that mask subtle NNS effects, or to receptor desensitization (e.g., diminished GLP-1 response to sucralose in diabetics as shown by Temizkan et al., 2014).
- **Habitual vs. Non-Habitual Users:** Differential effects based on prior NNS consumption habits are plausible but less directly studied. It is hypothesized that regular consumers may develop metabolic adaptation, blunting any acute disruptive effects.

The Comparator Context: NNS vs. Sugar vs. Water: Interpreting NNS effects requires careful consideration of the alternative. When the comparator is water, some NNS (like sucralose) may show detrimental effects relative to this metabolically inert control. However, from a public health perspective, the more relevant comparison is with sugar-sweetened beverages (SSBs). Here, the evidence strongly favors NNS. Substituting SSBs with NNS-sweetened beverages leads to reductions in body weight, BMI, and triglycerides, with benefits comparable to substituting with water (McGlynn et al., 2020; Lee et al., 2022). Furthermore, replacing a sucrose-rich diet with an artificially sweetened diet significantly reduces postprandial glycemia and insulinemia (Raben et al., 2011). This indicates that while isolated NNS effects may be debatable, their use as a tool for displacing caloric sugars provides a net metabolic advantage.

Methodological Considerations and Limitations: The heterogeneity in findings is partly attributable to methodological diversity. Studies reporting adverse effects often employed more sensitive measures (e.g., hyperinsulinemic-euglycemic clamps, intravenous glucose tolerance tests) and enrolled homogeneous, susceptible populations. Conversely, many null studies were of shorter

duration, used less sensitive outcome measures (e.g., only fasting glucose or HbA1c), or enrolled populations where effects were harder to detect (e.g., diabetics). Observational studies linking NNS to diabetes risk (Azad et al., 2017) are limited by residual confounding and reverse causation—individuals at high metabolic risk are more likely to choose NNS. Intervention studies generally do not support a causal role for NNS in driving metabolic disease at the population level (Jensen et al., 2019).

Integrated Framework and Clinical Implications: Reconciling the evidence leads to a context-dependent framework:

1. **For healthy individuals seeking to reduce sugar intake:** Stevia appears to be a metabolically safe choice, potentially offering slight glycemic benefits. Aspartame also shows a consistently neutral profile. Caution may be warranted with high-dose, chronic sucralose consumption, especially for non-habitual users, though more long-term data are needed.
2. **For individuals with overweight, obesity, or diabetes:** NNS are a useful tool for reducing calorie and sugar intake without adversely affecting glycemic control. Replacing SSBs with NNS beverages is a recommended strategy for weight management and metabolic improvement (Viveros-Watty et al., 2021, 2022).
3. **For personalized nutrition:** Individual responses, potentially dictated by the gut microbiome, can vary significantly. Future dietary advice may consider personalized testing, though this is not yet clinically practical.

The relationship between NNS and glucose metabolism is multifaceted. Blanket statements declaring all NNS universally "safe" or "harmful" are overly simplistic and not supported by the evidence. The effects are sweetener-specific, dose- and duration-dependent, and critically moderated by the consumer's metabolic phenotype. While certain NNS may pose risks under

specific conditions, their strategic use as a substitute for caloric sweeteners remains a valuable component of dietary strategies aimed at combating obesity and diabetes.

CONCLUSION AND RECOMMENDATIONS

This comprehensive systematic review demonstrates that the association between non-nutritive sweetener (NNS) consumption and glucose intolerance is not monolithic but is intricately moderated by several key factors. The evidence indicates that **sweetener type** is paramount: chronic sucralose intake may decrease insulin sensitivity in healthy, non-habitual consumers, aspartame largely exhibits neutral metabolic effects, and stevia shows neutral to potentially beneficial impacts on fasting glucose. **Duration of exposure** is critical, with acute studies generally showing null effects, while metabolic changes, particularly those mediated by the gut microbiome, emerge with sustained consumption over weeks. Most importantly, **population characteristics**—including baseline metabolic health (healthy vs. diabetic), adiposity (lean vs. obese), and likely habitual NNS use—profoundly influence individual responses, explaining much of the heterogeneity in the literature.

When evaluated in a comparative public health context, replacing sugar-sweetened beverages with NNS alternatives provides a clear net metabolic benefit, supporting their role in dietary strategies for weight management and diabetes prevention. The observed adverse associations in large cohort studies are likely confounded and do not imply causation.

Recommendations:

1. **For Public Health and Clinical Guidance:** Dietary advice should move beyond generic statements and provide nuanced, sweetener-specific information. Promoting the replacement of caloric sugars with NNS, particularly stevia or aspartame, remains a valid strategy for reducing energy intake and improving cardiometabolic risk factors.

2. **For Consumers:** Individuals, especially those who are healthy and lean, may consider moderating high-dose, chronic consumption of sucralose until more long-term safety data are available. For those with obesity or diabetes, NNS are a safe and useful tool for reducing sugar consumption.
3. **For Future Research:** Priority should be given to: (a) long-term RCTs (≥ 1 year) assessing the effects of individual sweeteners on hard endpoints like incident diabetes; (b) mechanistic studies elucidating the pathways linking specific NNS to host metabolism, particularly via the gut-brain axis and microbiome; and (c) personalized nutrition trials to identify biomarkers (e.g., microbial signatures) that predict individual responses to different NNS.

REFERENCES

- A. Greyling, K. Appleton, A. Raben, and D. Mela. "Acute Glycemic and Insulinemic Effects of Low-Energy Sweeteners: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." *American Journal of Clinical Nutrition*, 2020.
- A. Nichol, Clara Salame, K. Rother, and M. Pepino. "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*, 2019.
- A. Nichol, M. J. Holle, and R. An. "Glycemic Impact of Non-Nutritive Sweeteners: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." *European Journal of Clinical Nutrition*, 2018.
- A. Raben, Bente K. Møller, A. Flint, T. H. Vasilaras, A. Christina Møller, J. Juul Holst, and A. Astrup. "Increased Postprandial Glycaemia, Insulinemia, and Lipidemia After 10 Weeks' Sucrose-Rich Diet Compared to an Artificially Sweetened Diet: A Randomised Controlled Trial." *Food & Nutrition Research*, 2011.

A. Romo-Romo, C. Aguilar-Salinas, G. Brito-Córdova, R. A. Gómez Díaz, David Vilchis Valentín, and P. Almeda-Valdés. “Effects of the Non-Nutritive Sweeteners on Glucose Metabolism and Appetite Regulating Hormones: Systematic Review of Observational Prospective Studies and Clinical Trials.” *PLoS ONE*, 2016.

A. Romo-Romo, C. Aguilar-Salinas, G. Brito-Córdova, R. Gómez-Díaz, and P. Almeda-Valdés. “Sucralose Decreases Insulin Sensitivity in Healthy Subjects: A Randomized Controlled Trial.” *American Journal of Clinical Nutrition*, 2018.

A. Romo-Romo, C. Aguilar-Salinas, M. G. López-Carrasco, L. E. Guillén-Pineda, G. Brito-Córdova, R. Gómez-Díaz, F. Gómez-Pérez, and P. Almeda-Valdés. “Sucralose Consumption over 2 Weeks in Healthy Subjects Does Not Modify Fasting Plasma Concentrations of Appetite-Regulating Hormones: A Randomized Clinical Trial.” *Journal of the Academy of Nutrition and Dietetics*, 2020.

A. Romo-Romo, M. Sánchez-Tapia, M. López-Carrasco, L. E. Guillén-Pineda, G. Brito-Córdova, Alexandro J. Martagon, Omar Granados- Portillo, et al. “Sucralose Consumption Modifies Glucose Homeostasis, Gut Microbiota, Curli Protein, and Related Metabolites in Healthy Individuals: A Randomized Placebo-Controlled, Triple-Blind Trial.” *Clinical Nutrition ESPEN*, 2025.

A. Romo-Romo, M. Sánchez-Tapia, Nimbe Torres, C. A. Aguilar-Salinas, Alexandro J. Martagon, María GUADALUPE LÓPEZ-CARRASCO, L. E. Guillén-Pineda, et al. “19-OR: Sucralose Consumption Decreases Insulin Sensitivity and Modifies the Gut Microbiota in Healthy Individuals.” *Diabetes*, 2024.

A. Sylvetsky, A. Chandran, S. Talegawkar, J. Welsh, Kimberly L Drews, and Laure El ghormli. “Consumption of Beverages Containing Low-Calorie Sweeteners, Diet, and Cardiometabolic Health in Youth With Type 2 Diabetes.” *Journal of the Academy of Nutrition and Dietetics*, 2020.

Amornpan Lertrit, Sasinee Srimachai, S. Saetung, S. Chanprasertyothin, L. Chailurkit, Chatvara Areevut, Pornalath Katekao, B. Ongphiphadhanakul, and Chutintorn Sriphrapadang. “Effects of

Sucralose on Insulin and Glucagon-Like Peptide-1 Secretion in Healthy Subjects: A Randomized, Double-Blind, Placebo-Controlled Trial.” *Nutrition (Burbank, Los Angeles County, Calif.)*, 2018.

Angélica Y. Gómez-Arauz, Nallely Bueno-Hernández, Leon F. Palomera, Raúl Alcántara-Suárez, Karen L. De León, L. Méndez-García, Miguel Carrero-Aguirre, et al. “A Single 48 Mg Sucralose Sip Unbalances Monocyte Subpopulations and Stimulates Insulin Secretion in Healthy Young Adults.” *Journal of Immunological Research*, 2019.

C. Gibbons, Beverley O’Hara, D. O’Connor, Charlotte Hardman, Moon Wilton, Jo Harrold, Eva Almiron-Roig, et al. “Acute and Two-Week Effects of Neotame, Stevia Rebaudioside M and Sucrose-Sweetened Biscuits on Postprandial Appetite and Endocrine Response in Adults with Overweight/Obesity—a Randomised Crossover Trial from the SWEET Consortium.” *EBioMedicine*, 2024.

César Galicia-Ayala, Miguel Klünder-Klünder, Armando Vilchis-Ordóñez, Briceida López-Martínez, and A. Miranda-Lora. “Enteroendocrine Hormonal Response After the Ingestion of Cola Beverages with Sucrose and Non-Nutritive Sweeteners in Healthy Adults: A Randomized Crossover Trial.” *Nutrition (Burbank, Los Angeles County, Calif.)*, 2025.

Elnaz Karimian Azari, Kathleen R. Smith, F. Yi, T. Osborne, R. Bizzotto, A. Mari, Richard E. Pratley, and G. Kyriazis. “Inhibition of Sweet Chemosensory Receptors Alters Insulin Responses During Glucose Ingestion in Healthy Adults: A Randomized Crossover Interventional Study.” *American Journal of Clinical Nutrition*, 2017.

Emily Hanselman, Matthew C Kochem, and Paul A S Breslin. “Sweet Taste Receptors As Metabolic Regulators: TAS1R2-TAS1R3 Activation or Inhibition Differentially Affects Glucose Metabolism in Humans.” *Current Developments in Nutrition*, 2024.

Esraa Ismail, and Angelina Bernier. “9353 The Impact Of Artificially Sweetened Drinks On Metformin Efficacy.” *Journal of the Endocrine Society*, 2024.

F. Bonnet, A. Tavenard, M. Esvan, B. Laviolle, M. Viltard, E. Lepicard, and F. Laine. “Consumption of a Carbonated Beverage with High-Intensity Sweeteners Has No Effect on Insulin Sensitivity and Secretion in Nondiabetic Adults.” *Journal of NutriLife*, 2018.

Francesco Franchi, Dmitry Yaranov, F. Rollini, A. Rivas, Jose R Rivas Rios, L. Been, Yuma Tani, et al. “Effects of D-Allulose on Glucose Tolerance and Insulin Response to a Standard Oral Sucrose Load: Results of a Prospective, Randomized, Crossover Study.” *BMJ Open Diabetes Research & Care*, 2021.

G. Farhat, Victoria Berset, and L. Moore. “Effects of Stevia Extract on Postprandial Glucose Response, Satiety and Energy Intake: A Three-Arm Crossover Trial.” *Nutrients*, 2019.

I. Onakpoya, and C. Heneghan. “Effect of the Natural Sweetener, Steviol Glycoside, on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis of Randomised Clinical Trials.” *European Journal of Preventive Cardiology*, 2015.

J. Serrano, Kathleen R. Smith, Audra L. Crouch, Vandana Sharma, F. Yi, V. Vargova, Traci E. LaMoia, et al. “High-Dose Saccharin Supplementation Does Not Induce Gut Microbiota Changes or Glucose Intolerance in Healthy Humans and Mice.” *Microbiome*, 2021.

Jaimie N. Davis, F. Asigbee, A. Markowitz, Matthew J. Landry, S. Vandyousefi, Erfan Khazaei, R. Ghaddar, and M. Goran. “Consumption of Artificial Sweetened Beverages Associated with Adiposity and Increasing HbA1c in Hispanic Youth.” *Clinical Obesity*, 2018.

Jennifer J. Lee, T. Khan, Néma D McGlynn, Vasanti S. Malik, James O Hill, Lawrence A Leiter, P. Jeppesen, et al. “Relation of Change or Substitution of Low- and No-Calorie Sweetened Beverages With Cardiometabolic Outcomes: A Systematic Review and Meta-Analysis of Prospective Cohort Studies.” *Diabetes Care*, 2022.

Jing Wen, Qianhui Wu, Sihao Li, Yang Liu, and Deliang Wen. “Effects of Non-Nutritive Sweeteners on Weight Loss and Maintenance, Metabolic Improvement, and Appetite Regulation in

Weight Management Programs: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.” *Nutrition Reviews*, 2025.

Joan Serrano, Kathleen R Smith, Audra L. Crouch, Vandana Sharma, Fanchao Yi, Veronika Vargova, Traci E. LaMoia, et al. “High Dose Saccharin Supplementation Does Not Induce Gut Microbiota Dysbiosis or Glucose Intolerance in Healthy Humans and Mice,” 2020.

Jotham Suez, Yotam Cohen, R. Valdés-Mas, Uria Mor, Mally Dori-Bachash, Sara Federici, N. Zmora, et al. “Personalized Microbiome-Driven Effects of Non-Nutritive Sweeteners on Human Glucose Tolerance.” *Cell*, 2022.

K. Higgins, R. Considine, and R. Mattes. “Aspartame Consumption for 12 Weeks Does Not Affect Glycemia, Appetite, or Body Weight of Healthy, Lean Adults in a Randomized Controlled Trial.” *Journal of NutriLife*, 2018.

K. Higgins, and R. Mattes. “A Randomized Controlled Trial Contrasting the Effects of 4 Low-Calorie Sweeteners and Sucrose on Body Weight in Adults with Overweight or Obesity.” *American Journal of Clinical Nutrition*, 2019.

K. Maki, L. Curry, M. S. Reeves, P. Toth, J. Mckenney, M. Farmer, S. Schwartz, et al. “Chronic Consumption of Rebaudioside A, a Steviol Glycoside, in Men and Women with Type 2 Diabetes Mellitus.” *Food and Chemical Toxicology*, 2008.

K. Mehat, Yi Chen, and C. Corpe. “The Combined Effects of Aspartame and Acesulfame-K Blends on Appetite: A Systematic Review and Meta-Analysis of Randomized Clinical Trials.” *Advances in Nutrition*, 2022.

———. “The Combined Effects of Aspartame and Acesulfame-K Blends on Appetite: A Systematic Review and Meta-Analysis of Randomized Clinical Trials.” *Advances in Nutrition*, 2022.

L. Barriocanal, M. Palacios, G. Benítez, S. Benitez, J. Jiménez, N. Jiménez, and Vicenta Rojas. “Apparent Lack of Pharmacological Effect of Steviol Glycosides Used as Sweeteners in Humans. A Pilot Study of Repeated Exposures in Some Normotensive and Hypotensive Individuals and in Type 1 and Type 2 Diabetics.” *Regulatory Toxicology and Pharmacology : RTP*, 2008.

L. Boxall, Fatemeh Eskandari, Julie Wallis, A. D. Bielat, and K. M. Appleton. “The Effects of Aspartame on Glucose, Insulin, and Appetite-Regulating Hormone Responses in Humans: Systematic Review and Meta-Analyses.” *Advances in Nutrition*, 2025.

L. Méndez-García, Nallely Bueno-Hernández, M. Cid-Soto, Karen L. De León, V. M. Mendoza-Martínez, A. Espinosa-Flores, Miguel Carrero-Aguirre, et al. “Ten-Week Sucralose Consumption Induces Gut Dysbiosis and Altered Glucose and Insulin Levels in Healthy Young Adults.” *Microorganisms*, 2022.

Lee V. Grotz, X. Pi-Sunyer, D. Porte, A. Roberts, and R. Trout. “A 12-week Randomized Clinical Trial Investigating the Potential for Sucralose to Affect Glucose Homeostasis.” *Regulatory Toxicology and Pharmacology : RTP*, 2017.

Lina Qin, Yunfeng Yu, and Rong Yu. “Artificially Sweetened Beverages Do Not Influence Metabolic Risk Factors: A Systematic Review and Meta-Analysis.” *Frontiers in Nutrition*, 2025.

M. Azad, A. Abou-Setta, Bhupendrasinh F. Chauhan, R. Rabbani, Justin Lys, L. Copstein, A. Mann, et al. “Nonnutritive Sweeteners and Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Prospective Cohort Studies.” *Canadian Medical Association Journal*, 2017.

M. Fukuda, T. Terata, K. Tsuda, M. Sugawara, N. Kitatani, and Y. Seino. “Aspartame-Acesulfame K-Containing Low-Energy Erythritol Sweetener Markedly Suppresses Postprandial Hyperglycemia in Mild and Borderline Diabetics,” 2010.

M. Pepino, Courtney D. Tiemann, B. Patterson, B. Wice, and S. Klein. “Sucralose Affects Glycemic and Hormonal Responses to an Oral Glucose Load.” *Diabetes Care*, 2013.

Marzieh Zare, Mobina Zeinalabedini, S. Ebrahimpour-Koujan, N. Bellissimo, and L. Azadbakht. “Effect of Stevia on Blood Glucose and HbA1C: A Meta-Analysis.” *Diabetes & Metabolic Syndrome*, 2024.

MD¹ Parinya Samakkarntai, MD² Methavee Poochanasri, MD² Chutawat Kookanok, MD¹ Chonpiti Siriwan, MD¹ Manaporn Payanundana, MD¹ Nattapol Sathavarodom, and MD¹ Apussanee Boonyavarakul. “Acute Effect of Stevia on Glycemic and Insulin Responses in Obese Patients: A Randomized Double-Blind Placebo-Controlled Crossover Study.” *Journal of the Medical Association of Thailand = Chotmaihet Thangphaet*, 2025.

N. Wiebe, R. Padwal, C. Field, S. Marks, R. Jacobs, and M. Tonelli. “A Systematic Review on the Effect of Sweeteners on Glycemic Response and Clinically Relevant Outcomes.” *BMC Medicine*, 2011.

Nadia Reyna, Clímaco Cano, Valmore Bermúdez, M. Medina, A. Souki, M. Ambard, M. Núñez, M. A. Ferrer, and G. Inglett. “Sweeteners and Beta-Glucans Improve Metabolic and Anthropometrics Variables in Well Controlled Type 2 Diabetic Patients.” *American Journal of Therapeutics*, 2003.

Nallely Bueno-Hernández, M. Esquivel-Velázquez, Raúl Alcántara-Suárez, Angélica Y. Gómez-Arauz, A. Espinosa-Flores, Karen L. de León-Barrera, V. M. Mendoza-Martínez, et al. “Chronic Sucralose Consumption Induces Elevation of Serum Insulin in Young Healthy Adults: A Randomized, Double Blind, Controlled Trial.” *Nutrix Journal*, 2020.

Natalia Santos, Laíza Magalhães de Araújo, G. De Luca Canto, E. Guerra, M. Coelho, and M. Borin. “Metabolic Effects of Aspartame in Adulthood: A Systematic Review and Meta-Analysis of Randomized Clinical Trials.” *Critical Reviews in Food Science and Nutrition*, 2018.

Néma D McGlynn, T. Khan, Roselyn Zhang, L. Chiavaroli, F. Au-Yeung, Vasanti S. Malik, James O Hill, et al. “Effect of Non-Nutritive Sweetened Beverages (NSBs) on Cardiometabolic Risk: A Network Meta-Analysis of Randomized Controlled Trials.” *Current Developments in Nutrition*, 2020.

Nikoleta S. Stamataki, B. Crooks, Abubaker Ahmed, and J. Mclaughlin. “Effects of the Daily Consumption of Stevia on Glucose Homeostasis, Body Weight, and Energy Intake: A Randomised Open-Label 12-Week Trial in Healthy Adults.” *Nutrients*, 2020.

Nikoleta S. Stamataki, B. Crooks, and J. Mclaughlin. “Daily Consumption of Stevia Drops Effects on Glycemia, Body Weight and Energy Intake: Results from a 12-Week, Open-Label, Randomized Controlled Trial in Healthy Adults.” *Current Developments in Nutrition*, 2020.

Nikoleta S. Stamataki, C. Scott, R. Elliott, S. Mckie, D. Bosscher, and J. Mclaughlin. “Stevia Beverage Consumption Prior to Lunch Reduces Appetite and Total Energy Intake Without Affecting Glycemia or Attentional Bias to Food Cues: A Double-Blind Randomized Controlled Trial in Healthy Adults.” *Journal of NutriLife*, 2020.

P. Jensen, B. Howard, L. Best, M. O’Leary, R. Devereux, S. Cole, J. Maccluer, et al. “Associations of Diet Soda and Non-Caloric Artificial Sweetener Use with Markers of Glucose and Insulin Homeostasis and Incident Diabetes: The Strong Heart Family Study.” *European Journal of Clinical Nutrition*, 2019.

Parinya Samakkarnthai, Manaporn Payanundana, Nattapol Sathavarodom, C. Siriwan, and A. Boonyavarakul. “Effect of Stevia on Glycemic and Insulin Responses in Obese Patients—A Randomized, Double-Blind, Placebo-Controlled Crossover Study.” *Diabetes*, 2018.

Paulina E. Viveros-Watty, Ó. López-Franco, R. C. Zepeda, G. Aguirre, J. C. Rodríguez-Alba, Ma Gómez-Martínez, L. Castillo-Martínez, and Mónica Flores-Muñoz. “Effects on Cardiometabolic Risk Factors After Reduction of Artificially Sweetened Beverage Consumption in Overweight Subjects. A Randomised Controlled Trial.” *Endocrinología Diabetes y Nutrición*, 2021.

———. “Effects on Cardiometabolic Risk Factors After Reduction of Artificially Sweetened Beverage Consumption in Overweight Subjects. A Randomised Controlled Trial.” *Endocrinología Diabetes y Nutrición*, 2022.

Pepino M. Yanina, A. Nichol, K. Rother, and Clara Salame. “788-P: Effects of Sucralose Ingestion Vs. Sucralose Taste on Metabolic Responses to a Glucose Load in Subjects with Normal Weight and Obesity.” *Diabetes*, 2019.

Pulkit Mathur, and Anjani Bakshi. “Effect of Non-Nutritive Sweeteners on Insulin Regulation, Glycemic Response, Appetite and Weight Management: A Systematic Review.” *Nutrition & Food Science*, 2023.

Rebecca J. Brown, M. Walter, and K. Rother. “Effects of Diet Soda on Gut Hormones in Youths With Diabetes.” *Diabetes Care*, 2012.

———. “Ingestion of Diet Soda Before a Glucose Load Augments Glucagon-Like Peptide-1 Secretion.” *Diabetes Care*, 2009.

Roselyn Zhang, J. C. Noronha, T. Khan, Néma D McGlynn, Songhee Back, S. Grant, C. Kendall, and J. Sievenpiper. “The Effect of Non-Nutritive Sweetened Beverages on Postprandial Glycemic and Endocrine Responses: A Systematic Review and Network Meta-Analysis.” *Nutrients*, 2023.

S. AMIRHOSSEIN GOLZAN, Alan Espinosa, Mohammadmahdi Abbasi, Mina Movahedian, M. Fathi, and A. Hekmatdoost. “1793-PUB: Effects of Nonnutritive Sweeteners on Glycemic Indices in Healthy Persons, with Overweight or Obesity, or Diabetes—A Systematic Review and Meta-Analysis of Randomized Controlled Trials.” *Diabetes*, 2023.

S. Anton, Corby K. Martin, Hongmei Han, S. Coulon, W. Cefalu, P. Geiselman, and D. Williamson. “Effects of Stevia, Aspartame, and Sucrose on Food Intake, Satiety, and Postprandial Glucose and Insulin Levels.” *Appetite*, 2010.

S. Kullmann, R. Veit, K. Jann, Alexandra G. Yunker, S. Luo, Brendan C. Angelo, Jasmin M. Alves, J. Monterosso, and K. Page. “1310-P: Effects of Insulin Resistance on Brain Responses to Caloric Sugars and Nonnutritive Sweetener.” *Diabetes*, 2022.

S. L. Tey, N. Salleh, C. Henry, and C. Forde. “Effects of Non-Nutritive (Artificial Vs Natural) Sweeteners on 24-h Glucose Profiles.” *European Journal of Clinical Nutrition*, 2017.

S. L. Tey, N. Salleh, J. Henry, J. Henry, C. Forde, and C. Forde. “Effects of Aspartame-, Monk Fruit-, Stevia- and Sucrose-Sweetened Beverages on Postprandial Glucose, Insulin and Energy Intake.” *International Journal of Obesity*, 2017.

S. Lohner, Daniela Kuellenberg de Gaudry, Ingrid Toews, T. Ferenci, and J. Meerpohl. “Non-Nutritive Sweeteners for Diabetes Mellitus.” *Cochrane Database of Systematic Reviews*, 2017.

Ş. Temizkan, O. Deyneli, Mehmet Yasar, M. Arpa, M. Gunes, Dilek Yazici, O. Sirikci, Goncagul Haklar, N. Imeryuz, and Dilek Gogas Yavuz. “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.” *European Journal of Clinical Nutrition*, 2014.

Sabrina Ayoub-Charette, Néma D McGlynn, T. Khan, S. B. Mejia, L. Chiavaroli, Meghan E. Kavanagh, Maxine Seider, et al. “Rationale, Design and Baseline Characteristics for the Strategies to Oppose SUGARS With Non-Nutritive Sweeteners or Water (STOP Sugars NOW) Trial.” *Current Developments in Nutrition*, 2021.

Samar Y Ahmad, J. Friel, and D. Mackay. “The Effect of the Artificial Sweeteners on Glucose Metabolism in Healthy Adults: A Randomized Double-Blinded Crossover Clinical Trial.” *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme*, 2019.

Sandhya P Chakravarti, S. Kullmann, R. Veit, Alexandra G. Yunker, Brendan C. Angelo, K. Jann, S. Luo, Anny H. Xiang, J. Monterosso, and K. Page. “1536-P: Effects of Sucralose Vs. Sucrose on Hypothalamic Blood Flow, Glucose Signaling, and Appetite.” *Diabetes*, 2023.

Saziye E. Orku, Guldal Suyen, and Murat Baş. “The Effect of Regular Consumption of Four Low- or No-Calorie Sweeteners on Glycemic Response in Healthy Women: A Randomized Controlled Trial.” *Nutrition (Burbank, Los Angeles County, Calif.)*, 2022.

Soo Yeun Sim, Byung-Kyu Suh, and Moon Bae Ahn. “MON-233 The Effects Of Non-Nutritive Sweetened Beverages On Glycemic Profiles In Pediatric And Young Adult Diabetics Patients Using Continuous Glucose Monitoring Devices.” *Journal of the Endocrine Society*, 2025.

V. Campos, C. Despland, V. Brandejsky, R. Kreis, P. Schneiter, C. Boesch, and L. Tappy. “Metabolic Effects of Replacing Sugar-Sweetened Beverages with Artificially-Sweetened Beverages in Overweight Subjects with or Without Hepatic Steatosis: A Randomized Control Clinical Trial.” *Nutrients*, 2017.

V. Grotz, R. Henry, J. McGill, M. Prince, M. Prince, H. Shamoon, J. Trout, and F. Pi-Sunyer. “Lack of Effect of Sucralose on Glucose Homeostasis in Subjects with Type 2 Diabetes.” *Journal of the American Dietetic Association*, 2003.

V. Mohan, Abirami Kuzhanthaivelu, G. Rajagopal, K. Vasudevan, G. Nagamuthu, D. Shekinah, R. Unnikrishnan, Ranjit Mohan Anjana, Sudha Vasudevan, and K. Kamala. “614-P: Effect of Non-Nutritive Sweetener Sucralose on Cardiometabolic Risk Factors Among Overweight and Obese Adults in India—A Randomized Clinical Trial.” *Diabetes*, 2023.

V. Sambra, Isabella A. Vicuña, Kathleen M. Priken, S. Luna, Daniela A. Allendes, Paula M. Godoy, V. Novik, and Claudia A. Vega. “Acute Responses of Stevia and d-Tagatose Intake on Metabolic Parameters and Appetite/Satiety in Insulin Resistance.” *Clinical Nutrition ESPEN*, 2022.

Viswanathan Mohan, V. Manasa, K. Abirami, R. Unnikrishnan, Rajagopal Gayathri, G. Geetha, M. RamyaBai, et al. “Effect of Replacing Sucrose in Beverages with Nonnutritive Sweetener Sucralose on Cardiometabolic Risk Factors Among Asian Indian Adults with Type 2 Diabetes: A 12-Week Randomized Controlled Trial.” *Diabetes Therapy*, 2024.

Xuerui Bai, Hongying Qu, Jingyi Zhang, Likang Li, Changfa Zhang, Shuai Li, and Guowei Li. “Effect of Steviol Glycosides as Natural Sweeteners on Glucose Metabolism in Adult Participants.” *Food & Function*, 2024.

Y. Heianza, Qiaochu Xue, J. Rood, G. Bray, F. Sacks, and Lu Qi. “48-LB: Changes in Plasma Levels of Nonnutritive Sweetener Erythritol Are Related to Two-Year Changes of Insulin Sensitivity in Response to Weight-Loss Diets—The POUNDS Lost Trial.” *Diabetes*, 2023.

Yoo-Sook Kim, J. Keogh, and P. Clifton. “Consumption of a Beverage Containing Aspartame and Acesulfame K for Two Weeks Does Not Adversely Influence Glucose Metabolism in Adult Males and Females: A Randomized Crossover Study.” *International Journal of Environmental Research and Public Health*, 2020.

Zeniff Reyes-López, Viridiana Olvera-Hernández, Meztli Ramos-García, José D. Méndez, Crystell G. Guzmán-Priego, Miriam C. Martínez-López, Carlos García-Vázquez, et al. “Effects of Sucralose Supplementation on Glycemic Response, Appetite, and Gut Microbiota in Subjects with Overweight or Obesity: A Randomized Crossover Study Protocol.” *Methods and Protocols*, 2024.