Acute glycemic and insulinemic effects of low energy sweeteners: A systematic review and meta-analysis of randomized controlled trials[1-2]

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Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

Abbreviations:

Ace K: Acesulfame potassium

BNR: Blinding not reported

CI: Confidence interval

CO: Cross-over study design

D: Double-blind

iAUC: Incremental area under the curve

LES: Low energy sweeteners

NR: Not reported

O: Open label

PPG: Postprandial glucose response

PPI: Postprandial insulin response

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

S: Single-blind

SD: Standard deviations

SE: Standard Error

RoB: Risk of bias

T1D: Type-1 diabetes mellitus

T2D: Type-2 diabetes mellitus

Abstract

Background: It has been suggested that low energy sweeteners (LES) may be associated with an increased risk of metabolic diseases, possibly due to stimulation of glucose-responsive mechanisms.

Objective: We conducted a systematic review and meta-analysis of human intervention studies examining the acute effect of LES intake on postprandial glucose (PPG) and insulin (PPI) responses, in order to comprehensively and objectively quantify these relationships.

Methods: We systematically searched Medline, OVID FSTA and SCOPUS databases until January 2020. Randomized controlled trials comparing acute postprandial effects on PPG and/or PPI after exposure to LES; either alone, with a meal or other nutrient-containing preloads to the same intervention without LES were eligible for inclusion. PPG and PPI responses were calculated as mean incremental area under the curve divided by time. Meta-analyses were performed using random effects models with inverse variance weighing.

Results: Twenty-six papers (34 PPG trials and 29 PPI trials) were included. There were no differences in the effect of LES on PPG and PPI responses compared to control interventions. Pooled effects of LES intake on the mean change difference in PPG and PPI were -0.02 mmol/l [95% CI -0.09, 0.05] and -2.39 pmol/l [95%CI -11.83, 7.05] respectively. The results did not appreciably differ by the type or dose of LES consumed, co-intervention type or fasting glucose and insulin levels. Among patients with type 2 diabetes, the mean change difference indicated a smaller PPG response after exposure to LES *vs.* control (-0.3 mmol/l [95% CI -0.53, -0.07]).

Conclusions: Ingestion of LES, administered alone or in combination with a nutrient-containing preload, has no acute effects on the mean change in postprandial glycemic or insulinemic responses compared to a control intervention. Apart from a small beneficial effect on PPG (-0.3 mmol/l) in studies enrolling patients with type 2 diabetes, the effects did not differ by type or dose of LES, or fasting glucose or insulin levels.

Keywords: Non-caloric sweeteners; Non-nutritive sweeteners; Artificial sweeteners; Postprandial; Glucose; Insulin; Diabetes

Introduction

Low-energy sweeteners (LES) are often used to replace sugars in food and beverage formulations because they can provide sweet taste with little or no energy contribution or cariogenicity. As such, a range of different LES are common in the global food supply (1), and frequently used by manufacturers providing lower calorie or sugar alternatives to various food and beverage products. In the United Sates National Health and Nutrition Examination Survey 2007–2012, about 50% of respondents reported consuming LES-containing products over a 2-day period (2).

Despite extensive safety evaluations of these compounds by regulatory bodies (3-5), there is an ongoing debate regarding potential detrimental health effects of LES intake (6, 7). Concerns have been expressed, mainly based on selected animal and human observational studies, that LES consumption may increase risks of metabolic disease, especially obesity and type 2 diabetes (8-11). It has been suggested that this might arise in part as a result of LES stimulation of gut or systemic mechanisms responsive to sweet stimuli and glucose (5, 11, 12). However, while LES stimulation of such systems has mainly been demonstrated *in vitro* and with animal models, it is uncertain whether these effects are physiologically relevant in humans (13, 14). Furthermore, a substantial body of human intervention data suggests that overall, LES intake has no significant acute or chronic effects on measures of glucose homeostasis (10, 15-18).

A key question underpinning the putative link between LES and metabolism is the presence and magnitude of an effect of LES, ingested as part of a non-caloric or caloric (nutrient-containing) preload, on glycemic responses. To date there has been no reported quantitative meta-analysis of the effects of LES intake on two-hour (120 min)

55 postprandial glucose (PPG) and insulin (PPI) responses, which is a standard way of
56 testing for and expressing the systemic glycemic and insulinemic exposures induced by
57 meals. Dietary patterns giving higher post-meal glycemic excursions are associated
58 with increased risk of type 2 diabetes (19, 20), whereas drugs lowering PPG have been
59 shown to reduce the risk of progression from pre-diabetes to diabetes (19, 21). Our
60 objective was therefore to perform an up-to-date systematic review with meta-analysis
61 of controlled human intervention studies investigating the acute effects of LES intake on
62 PPG and PPI responses.

63 # Methods

64 The protocol for this systematic review and meta-analysis was registered in the
65 international prospective register of systematic reviews (PROSPERO, registration
66 number: CRD42018099608), and conducted and reported in accordance with the
67 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
68 statement guidelines (22).

69 **Search strategy**

70 To qualify for inclusion, trials had to meet the pre-defined inclusion criteria outlined
71 in **Table 1**.

72 PubMed/Medline, OVID FSTA, and SCOPUS were searched (from the date of
73 inception until January 2020) to identify potentially relevant studies conducted in
74 human participants and published in English. Titles, abstracts and keywords were
75 searched for variations and combinations of the following terms: *Artificial sweetener(s),*
76 *non-nutritive sweetener(s), low calorie sweetener(s), low energy sweetener(s),*

77 *sucralose, aspartame, stevia, steviol, saccharin(e), acesulfame, erythritol, diet(beverage*
78 *OR drink OR soda), low calorie(beverage OR drink OR soda)), low-energy(beverage*
79 *OR drink OR soda), glucose, insulin and glyc(a)emic* (full PubMed search syntax in the
80 Supplementary Methods). Bibliographies from obtained publications were also screened
81 for additional potentially relevant studies.

82 **Screening and selection of trials**

83 A two-step screening and selection process was followed. During the first step,
84 titles, abstracts and keywords of publications were screened separately by two of the
85 authors (AG & DJM) to identify potentially eligible studies. During the second step,
86 the full texts of these publications were examined to gauge eligibility based on the
87 stated inclusion criteria. In cases of inter-reviewer disagreement, questions on study
88 eligibility were resolved through consensus and consultation with the other co-authors
89 (KMA & AR).

90 **Data extraction and quantification**

91 The following information was extracted from eligible publications by means of a
92 predefined data extraction file: 1) publication details (author, year of publication,
93 country); 2) study design characteristics (crossover or parallel, blinding); 3) subject
94 characteristics (age, gender and health status); 4) intervention and control treatment
95 characteristics (type and dosage of LES, presence and type of meal/nutrient-containing
96 preload, type of control); 5) postprandial glucose and insulin incremental area under the
97 curve (iAUC) and associated measures of variance; 6) risk of bias indicators. If no
98 iAUC values were reported, postprandial data per measured timepoint were extracted
99 (either from tables and text or from figures by means of a web-based plot digitizing tool

100 (23)). Data were extracted by 2 independent reviewers (AG, DJM) and differences
101 resolved by consensus.

102 **Data synthesis and statistical analysis**

103 Where postprandial data at individual timepoints were extracted, the iAUC was
104 calculated by the trapezoidal method (24). The variances of these iAUCs were based on
105 the standard deviations (SD) of the respective individual timepoints and, calculated by
106 means of matrix algebra involving a covariance matrix with the assumed correlation
107 structure being compound symmetry (25). For this purpose, the correlation between
108 timepoints was assumed to be 0.75 for glucose and 0.5 for insulin. These assumptions
109 were based on PPG and PPI measurements at repeated timepoints in previous studies
110 conducted by our group (26-29).

111 Prior to meta-analysis, all glucose and insulin data were transformed into SI units
112 (mmol/l for glucose (= 0.0555*mg/dl) and pmol/l for insulin (= 6*μU/ml)). The
113 outcomes were expressed as mean postprandial changes by dividing the iAUCs by the
114 duration of the postprandial measurement period (120 min). When measures of
115 variance were not reported, they were imputed using variance data from the other
116 studies included in the meta-analysis (30).

117 For both glucose and insulin, the principal effect measure was the difference in the
118 mean postprandial changes between LES and control interventions. Pairwise analyses
119 were applied to all crossover trials as described by Elbourne et al (31). The weighted
120 effect estimates and corresponding 95% confidence intervals (CI) were calculated using
121 random effects models with inverse variance weighting (32) using the PROC MIXED
122 procedure in SAS (SAS v9.4, SAS Institute, Cary, NC, USA).. Pooled effects

123 calculated by means of fixed effects models served as sensitivity analyses. Several
124 trials included in the meta-analyses included two or more different comparisons (e.g.
125 different doses or types of LES) in the same subjects (33-41). To ensure that these trials
126 did not contribute a disproportionate weight to the meta-analyses due to double counting
127 of the same subjects, the weight of each comparison was divided by the total number of
128 included comparisons in the respective trial (42).

129 Influence analyses were conducted by systematically excluding one study at a time
130 and re-analyzing the remaining data to determine whether a specific study was exerting
131 excessive influence on the overall outcomes. Where enough data were available, the
132 potential effects of pre-defined covariates on the overall outcomes were assessed by
133 means of subgroup (minimum of 4 comparisons per subgroup) and weighted meta-
134 regression analyses (minimum of 10 comparisons per covariate) (43, 44). The pre-
135 defined covariates were: LES type, health status (healthy; having type 2 diabetes), co-
136 exposure type (i.e. LES consumed in a fasted state; LES consumed with a meal or other
137 nutrient-containing preload), baseline fasting glucose and insulin and LES dose.

138 **Risk of bias assessment**

139 Assessment of the risk of bias (RoB) in the included studies was done by means of
140 the Cochrane Collaboration's tool for assessing RoB (45). For this purpose, seven
141 different domains were considered (random sequence generation, allocation
142 concealment, blinding of participants and personnel, blinding of outcome assessment,
143 incomplete outcome data, selective reporting and other sources of bias). The
144 assessments were carried out independently by 2 authors (AG and DJM), and
145 differences resolved by consensus.

Publication bias was evaluated by means of visual inspection of funnel plots (constructed by plotting inverse SE against the respective weighted mean difference in glucose and insulin iAUC for each trial) and Egger's regression test (with $P<0.1$ indicating asymmetry) (46).

Heterogeneity was assessed by means of the Cochran's Q statistic (significant at $P<0.1$) and quantified by the I^2-statistic (with values of 25%, 50% and 75% considered to be low-, moderate- and high-level heterogeneity respectively) (47). In the absence of a enough studies with head-to-head comparisons of the PPG and PPI effects of the different LES types included in the review, a post-hoc frequentist network meta-analysis was conducted in order to study any potential heterogeneity (or informative lack thereof) in this regard. Analyses were conducted using the netmeta package on the R statistical software (48).

Results

Included trial characteristics

The systematic searches retrieved a total of 5,105 potentially relevant papers after removal of duplicates (**Figure 1**). After exclusion of those that did not meet the pre-defined inclusion criteria, 26 papers remained that were included in the quantitative synthesis (meta-analysis) (33-41, 49-65). The 26 included papers reported on 34 trials (experiments) with information on PPG responses (yielding 55 comparisons) and 29 trials with information on PPI responses (yielding 50 comparisons). The characteristics of these trials are summarized in **Table 2**. Additionally, 18 papers (66-83) that reported

glucose and/or insulin responses for time periods <120 minutes post-prandially were included in the qualitative synthesis, and are summarized in **Supplementary Table 1**.

A total of 452 individual participants took part in the 55 comparisons for PPG, and 394 participants in 50 comparisons provided data for PPI. The number of participants per comparison ranged from 6 to 31. Mean age ranged from 18 to 66 years. Forty-one comparisons included healthy lean participants. The remaining 14 comparisons were comprised of patients with diabetes (n = 9 type 2 diabetes and n = 1 type 1 diabetes) and participants with obesity but no other health condition (n = 4).

In all comparisons, participants started from a fasting baseline. In 12 comparisons, LES was administered to participants in a non-caloric vehicle (capsules, water, "diet" beverage or intragastric infusion). In the remaining comparisons, LES was administered either in conjunction with a standardized carbohydrate-containing meal (n = 23) or a 75g glucose load (n = 20). The types of LES administered were: sucralose (13 comparisons), l-arabinose (n = 10), aspartame (n = 9), saccharin (n = 5), erythritol (n = 3), stevia/steviosides (n = 3), acesulfame potassium (n = 4) and combinations of sucralose and acesulfame potassium (n = 6), and sucralose, acesulfame potassium and aspartame (n = 1). The types of control treatments administered were: water or other unsweetened beverage (31 comparisons), iso-caloric (and iso-carbohydrate) meals or beverages without LES (n = 21), saline (n = 2), and corn starch placebo capsules (n = 1).

Effects of LES intake on PPG and PPI responses

In the primary meta-analyses using random effects models, there were no statistically significant effects of LES intake on the mean change differences in PPG and PPI

responses (-0.02 mmol/l mean PPG [95% CI -0.09, 0.05] and -2.39 pmol/l mean PPI [95%CI -11.83, 7.05] respectively) (**Figure 2 and 3**). In meta-analyses using fixed effects models, the overall estimates of PPG and PPI mean change differences remained similar (-0.01 mmol/l mean PPG [95% CI -0.04, 0.02] and -1.41 pmol/l mean PPI [95%CI -4.12, 1.29] respectively).

Meta-regression and subgroup analyses

Meta-regression analyses found no statistically significant influence of baseline fasting glucose and insulin or dose of LES used, on the mean change differences in PPG and PPI responses to LES (**Table 3**). However, sub-group analyses of health status (**Table 4**), indicated a statistically significant difference in the mean change difference in PPG response to LES when comparing healthy participants and those with type 2 diabetes: thus, there was a small statistically significant reduction in mean PPG for LES *vs* control in the type 2 diabetes subgroup (-0.3 mmol/l [95% CI -0.53, -0.07]) whereas no change was evident in the healthy subgroup (-0.01 mmol/l [95%CI -0.07, 0.06]). No further influences on PPG or PPI mean change differences were evident when dividing studies by LES type or co-exposure type (LES consumed in a non-caloric *vs* a meal or nutrient-containing preload).

Influence analyses, assessment of potential biases and heterogeneity

Influence analyses conducted by omitting any single study from the meta-analyses did not materially affect results for PPG or PPI (Supplementary Table 2). Overall, all studies had some risk of bias, most notably regarding blinding (most studies were single blind as participants could not be blinded due to the nature of the interventions), as well as unclear reporting of random sequence generation and allocation concealment

(Supplementary Table 3). To evaluate potential effects of (lack of) blinding, a post-hoc analysis including only the seven trials (16 comparisons)(34, 36, 38, 63, 64) reported as being double-blind was conducted. The outcomes of both random and fixed effect meta-analyses were similar to those of the main analyses (Supplementary Table 4).

Both PPG and PPI mean change differences showed low to moderate heterogeneity (P value for Q statistic <0.01; I^2 = 44.7% and P <0.01, I^2 = 48.3% respectively) between studies. Egger's linear regression test did not indicate the potential presence of publication bias (P value of intercept = 0.48 and 0.83 for PPG and PPI respectively). In addition, visual inspection of the funnel plots did not confirm an obvious presence of publication bias, with the PPG and PPI changes scattered relatively uniformly around the overall estimates (**Figure 4 A and B**).

The network meta-analyses produced similar results to the main analyses. For PPG and PPI mean change differences, there were no direct evidence of an effect of the different LES types versus each other or the control intervention. For each outcome, the posterior between-study SD was below 0, suggesting low heterogeneity and (Supplementary material, Network meta-analysis section). For stevia, indirect evidence suggested a smaller PPG response compared to control -0.79 mmol/l [95%CI -1.56; -0.02], sucralose -0.81 mmol/l [95%CI -1.59; -0.02], aspartame -0.82 mmol/l [95%CI -1.60; -0.04], erythritol -0.87 mmol/l [95%CI -1.65; -0.09] and the combination of sucralose and aspartame -0.89 mmol/l [95%CI -1.73;-0.05].

Discussion

This meta-analysis quantifying evidence from 34 randomized controlled intervention trials found that intake of LES had no statistically significant effects on the mean change differences in acute post-prandial glucose or insulin responses compared with a control intervention. Our findings for LES in a non-caloric (e.g. water) vehicle are in accordance with the outcome of a recent meta-analysis that found no acute effects on PPG measured over a range of postprandial time periods (15), as well as another recent systematic review of PPG responses to LES (84). This is now confirmed based on a standard 120 min postprandial period of analysis for glucose and for insulin as well. A somewhat older network meta-analysis that compared the effects of different caloric and non-caloric sweeteners on 120 min PPG responses, concluded that the data were inconclusive (85); however, many relevant trials have been published since that analysis, which included only two of the 34 trials here.

LES are often consumed in conjunction with caloric nutrients i.e. protein, fat and carbohydrates. As such, for the first time, our meta-analysis also included studies where LES were administered along with standardized mixed meals, carbohydrate-containing beverages or a 75g glucose preload. In this regard, sub-group analyses found a similar absence of effect of LES on the mean change differences in PPG and PPI when consumed either with or without a carbohydrate or nutrient containing preload. This suggests that nutrient and/or food matrix interactions probably do not play a role in determining potential effects of LES intake on acute glycemic responses.

The outcomes of the 18 studies in which glucose and/or insulin responses were measured for time periods <120 minutes postprandially, are mostly consistent with the

results of our meta-analyses. Most studies reported no effects (67, 69-78, 83) or very small changes (70, 74, 76) in PPG and PPI responses after LES ingestion.

The findings of the few included trials of immediate cephalic phase responses were inconsistent, with four of these (66, 68, 79, 82) reporting no effects on glucose or insulin, and two (80, 81) reporting increased cephalic phase PPI responses but no effects on PPG. This is noteworthy since, although effects of sweetness itself have been suggested (86, 87), it would seem that sweet taste stimuli alone are not sufficient to elicit meaningful acute glycemic responses. A recent systematic review of studies utilizing pre-ingestive sweet taste stimulation designs, also suggested that oral sweet taste activation from LES has limited effects on human glucose homeostasis (84).

Meta-analyses of data from some observational studies suggest an association between LES intake and an increased risk of developing metabolic diseases, particularly type 2 diabetes (8, 9). However, difficulties in the accurate assessment of LES exposure and problems with reverse causality and confounding factors raise concerns regarding the reliability and interpretation of associations from observational studies (88-90). Conversely, our meta-analysis and other reviews (15, 84), show that data from human intervention studies suggest no effects of LES intake on postprandial glucose responses.

We note, however, that among patients with type 2 diabetes, the mean change difference indicated a smaller PPG response after exposure to LES *vs.* control. Similar effects were also noted in the meta-analysis of Nichol et al. (15). This might suggest a potential direct glucose-lowering benefit of LES intake for these individuals. However, effect sizes are small and were found from only 9 comparisons, all of which were judged to be of high risk of performance bias and included only 86 individuals. Moreover, it is uncertain

whether the 0.3 mmol/l reduction in PPG response is truly replicable or would be of any long-term clinical relevance in diabetes management. A number of longer-term trials of LES show no significant effects on glycemic control in this population (16). We have no obvious explanation or hypothesis for any differential response in the short term, although this could be related to the poorer glycemic control in people with diabetes.

Several limitations of this meta-analysis should be noted. Firstly, we did not have an *a priori* hypothesis that different types of LES would differ in their effects on the mean change in PPG or PPI responses. We therefore assumed that it was appropriate to pool the effects of different LES types in the same meta-analysis. Concerns have however been raised that different LES types might differ in the physiological effects (91). As such, a network meta-analysis might therefore have been a more appropriate approach. Network meta-analysis allows for the pooling of outcomes derived from direct and indirect evidence across multiple different treatments while preserving the benefits of randomized comparisons within each trial. We did conduct a post hoc network meta-analysis to study any potential informative (lack of) heterogeneity in this regard. The outcomes were in line with our main analyses, suggesting no direct evidence of a difference in PPG or PPI effects for the different LES types versus each other or a control treatment. The outcome of this analysis should be interpreted with caution however, since it was conducted after the studies, data and outcomes of the main analyses were known.

Secondly, most of the included studies had relatively small sample sizes, potentially obscuring possible intervention effects due to a lack of statistical power. However, small study biases are generally associated with the erroneous overestimation of effect size and statistical significance (92, 93). Thirdly, as a result of the sweet tasting nature

306 of the interventions, only a small number of the included studies that had specific design
307 considerations (i.e. administration via capsules/gastric infusion or concomitantly with
308 glucose/sucrose) were double-blinded. It is possible that detection bias has occurred in
309 studies where the participants and, in some cases, the investigators were not blinded as
310 to the treatments. However, a post-hoc analysis including only the studies reported as
311 being double-blind had outcomes similar to those of the main analyses. This suggests
312 that potential performance bias was likely not an issue in this case. Regarding the
313 subgroup and post-hoc analyses, another potential limitation is that many aspects of the
314 studies covary. For example, all of the double-blind studies were conducted in healthy
315 subjects whereas all of the studies in subjects with type 2 diabetes were not blinded
316 (potentially high risk of performance bias), and all of the sucralose and l-arabinose
317 studies are relatively recent whereas most of the aspartame and saccharin studies are
318 older. As such, the outcomes of the sub-group analyses should be interpreted with
319 caution. Lastly, most of the studies included in this meta-analysis investigated the
320 effects of a single LES administered alone. No differences were found based on LES
321 type, but many current food and beverage products contain combinations of two or more
322 types of LES. We only had enough data to perform a sub-group analysis on one
323 potential combination (acesulfame potassium + sucralose). Our conclusions in this
324 regard can, therefore, not be extrapolated to other combinations of LES. There is,
325 however, currently no evidence or reasonable explanatory hypothesis as to why the
326 intake of a combination of LES would have different effects on glucose homeostasis
327 compared with a single LES alone.

328 In conclusion, this review provides an up-to-date overview of controlled human
329 intervention studies on the effects of LES consumption on acute postprandial glycemic

and insulinemic responses. Our analyses indicate that under acute conditions, whether administered alone or in combination with a nutrient-containing load, LES do not exert an independent effect on the mean change in postprandial blood glucose or insulin responses compared to a control intervention. Some small reductions in PPI, based on limited studies, were found in studies enrolling patients with type 2 diabetes, but overall the null results do not seem to differ appreciably by the type of LES consumed, dose of LES, or fasting glucose or insulin levels. A post-hoc network meta-analysis suggested no direct evidence of a difference in PPG or PPI effects for the different LES types versus each other or a control treatment. In light of concerns that different LES types may differ in their physiological effects, future work adopting an *a priori* network meta-analysis approach is recommended.

Author contributions

The authors' responsibilities were as follows—DJM and AG: conceived and designed the study, conducted the literature review, and drafted the manuscript; AG: conducted the statistical analysis; and KMA and AR: amended and approved the protocol, provided critical revision and important intellectual content. All of the authors made significant contributions to this manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Trial selection criteria.

Inclusion	Exclusion
Participants/population	
Human children (3-10 years of age), adolescents (10-18 years of age) and adults (≥18 years of age);	
Healthy participants and those with impaired glucose homeostasis (i.e. prediabetes, diabetes type 1 or 2, impaired glucose tolerance and overweight or obese individuals)	Hospitalized/critically ill patients
Intervention	
Acute exposure to LES; either alone, in water, as diet beverage or intragastric infusion, or with a meal or other nutrient-containing preloads	Co-intervention with insulin or drugs affecting glucose homeostasis
Comparators	
The same intervention without inclusion of LES	
Outcomes	
Acute postprandial blood glucose response (defined as incremental Area Under the Curve) after exposure to LES or Control	Trials measuring postprandial blood glucose or insulin responses for < 120 min (for quantitative meta-analysis only)
Acute postprandial insulin response (defined as incremental Area Under the Curve) after exposure to LES or Control	

Table 2. Characteristics of studies included in the meta-analysis

First author, year [country]	Study design	N	Mean Age (years)	Health status	LES type	LES dose (mg)	Control	Meal test	Meal carbohydrate content (g)	Outcome
Ahmad, 2018 (49) [Pakistan]	CO, S	20	24.1	Healthy	Stevia	3000	Isocaloric meal	Mixed meal	50	PPG
Azari, 2017 (50) [US]	CO, S	10	33.5	Healthy	Saccharin	18	Water	75g glucose	75	PPG, PPI
Brown, 2009 (51) [US]	CO, BNR	22	18.5	Healthy	Sucralose + Acesulfame K	45.6; 25.9	Carbonated water	75g glucose	75	PPI
Brown, 2012 (52) [US]	CO, BNR	25	18.8	Healthy	Sucralose + Acesulfame K	45.6; 25.9	Carbonated water	75g glucose	75	PPG
		9	18.2	T1D						
		10	17.9	T2D						
Burns, 1991 (33) [US]	CO, BNR	8	26.1	Healthy	Aspartame	500	Unsweetened beverage	100g sucrose None	100 0	PPG, PPI
Cooper, 1988 (53) [Australia]	CO, BNR	17	62.2	T2D	Saccharin	93*	Isocaloric meal	Mixed meal	47	PPG, PPI
Ford, 2011 (54) [UK]	CO, S	8	22-27	Healthy	Sucralose	41.5	Water	None	0	PPG, PPI

First author, year [country]	Study design	N	Mean Age (years)	Health status	LES type	LES dose (mg)	Control	Meal test	Meal carbohydrate content (g)	Outcome
Gregersen, 2004 (55) [Denmark]	CO, BNR	12	65.8	T2D	Stevioside	1000	Corn starch	Mixed meal	55	PPG, PPI
Halschou-Jensen, 2015 (34) [Denmark]	CO, D	17	22.5	Healthy	L-Arabinose	2900 5900	Isocaloric meal	Mixed meal	68	PPG, PPI
						2500 4900			72	
		6	23.3	Healthy	L-Arabinose	10200	Isocaloric meal	Solid mixed meal Semi-solid mixed meal	72	
						15000		Liquid mixed meal	75	
Helou, 2019 (64) [Lebanon]	CO, D	15 15	20.1 21.7	Healthy Obese	Acesulfame K	3500 3500	Isocaloric meal	Mixed meal	116	PPG, PPI

First author, year [country]	Study design	N	Mean Age (years)	Health status	LES type	LES dose (mg)	Control	Meal test	Meal carbohydrate content (g)	Outcome
Horwitz 1988, (35) [US]	CO, O	12	28	Healthy	Aspartame Saccharin	400 135	Unsweetened beverage	Fasted	0	PPG, PPI
		10	57	T2D	Aspartame Saccharin	400 135				
Krog-Mikkelsen, 2011 (36) [Denmark]	CO, D	15	25	Healthy	L-Arabinose	1000 2000 3000	Isocaloric beverage	75g sucrose	75	PPG, PPI
Ma, 2009 (37) [Australia]	CO, S	7	24	Healthy	Sucralose	800 80	Saline	Fasted	0	PPG, PPI
Nichol, 2020 (65) [US]	CO, BNR	10 11	27 29.5	Healthy Obese	Sucralose	48	Water	75g glucose	75	PPG, PPI
Overduin, 2016 (56) [UK]	CO, S	10 10	33.4 33.6	Healthy Obese	Erythritol	8000	Isocaloric meal	Mixed meal	NR	PPG, PPI
Parimalavalli, 2011 (57) [India]	CO, BNR	6	NR	T2D	Stevia	2000	Isocaloric meal	Mixed meal	50	PPG

First author, year [country]	Study design	N	Mean Age (years)	Health status	LES type	LES dose (mg)	Control	Meal test	Meal carbohydrate content (g)	Outcome
Pepino, 2013 (58) [US]	CO, BNR	17	35.1	Obese	Sucralose	48	Water	75g glucose	75	PPG, PPI
Prat-Larquemin, 2000 (59) [France]	CO, BNR	24	23.2	Healthy	Aspartame	270	Isocaloric meal	Mixed meal	90	PPG, PPI
Slama, 1984 (60) [France]	CO, BNR	12	51-57	T2D	Saccharin	40	Isocaloric meal	Mixed meal	70	PPG, PPI
Solomi, 2019 (61) [UK]	CO, BNR	10	27.2	Healthy	Aspartame + Acesulfame K (Diet Coke)	55.9; 38.5†	Water	25g glucose	25	PPG
Steinert, 2011 (38) [Switzerland]	CO, D	12	23.3	Healthy	Acesulfame K Aspartame Sucralose	220 169 62	Water	Fasted	0	PPG, PPI

First author, year [country]	Study design	N	Mean Age (years)	Health status	LES type	LES dose (mg)	Control	Meal test	Meal carbohydrate content (g)	Outcome
Sylvetsky, 2016 (39) [US]	CO, BNR	30	29.7	Healthy	Sucralose	68 170 205	Water	75g glucose	75	PPG, PPI
		31	27.4	Healthy	Sucralose + Acesulfame K (Diet Rite Cola) Sucralose + Acesulfame K + Aspartame (Diet Mountain Dew) Sucralose + Acesulfame K	68; 41 18; 18; 57 68; 41	Carbonated water	75g glucose	75	PPG, PPI
Temizkan, 2015 (40) [Turkey]	CO, S	8	45	Healthy	Aspartame Sucralose	72 24	Water	75g glucose	75	PPG, PPI
		8	51.5	T2D	Aspartame Sucralose	72 24				

First author, year [country]	Study design	N	Mean Age (years)	Health status	LES type	LES dose (mg)	Control	Meal test	Meal carbohydrate content (g)	Outcome
Wolf-Novak, 1990 (62) [US]	CO, BNR	7	27	Healthy	Aspartame	200	Isocaloric beverage	Beverage	60	PPG, PPI
Wölnerhanssen, 2016 (63) [Switzerland]	CO, D	20	25.9	Healthy	Erythritol	75000	Water	Fasted	0	PPG, PPI
Wu, 2016 (41) [Australia]	CO, S	10	33.6	Healthy	Acesulfame K	200	Water	75g glucose	75	PPG, PPI
					Sucralose + Acesulfame K	46; 26				
					Sucralose	52				

*dose not given but reported as equivalent sweetness to 28g sucrose; dose calculated considering a sweetness equivalence of 300:1

†dose not reported; estimated according to content of Aspartame + Acesulfame K in commercially sold diet cola

BNR: Blinding not reported; CO: Cross-over study design; D: Double-blind; PPG: Postprandial glucose; PPI: Postprandial insulin; LES: Low energy sweetener; NR: Not reported; O: Open-label; S: Single-blind; T1D: Type-1 diabetes mellitus; T2D: Type-2 diabetes mellitus

Table 3. Impact of continuous covariates on PPG and PPI responses to LES

Covariates	Mean change difference in PPG			Mean change difference in PPI		
	β	SE	P	β	SE	P
Baseline fasting glucose (per 1 mmol/l increase)	-0.059	0.04	0.15	2.17	2.87	0.45
Baseline fasting insulin (per 1 pmol/l increase)	-0.001	0.001	0.32	-0.04	0.11	0.75
Sucralose dose (per 10 mg increase)	0.004	0.003	0.22	0.08	0.19	0.66
L-Arabinose dose (per 1000 mg increase)	0.001	0.024	0.96	0.96	3.93	0.81

PPG: Postprandial glucose; PPI: Postprandial insulin

Table 4. Mean change difference in PPG and PPI after LES intake within different subgroups.

	Mean change difference in PPG								Mean change difference in PPI							
Subgroup	No. of studies	Effect (mmol/l)	95% CI	P within subgroup	I^2	Chi^2	df	P between subgroups	No. of studies	Effect (pmol/l)	95% CI	P within subgroup	I^2	Chi^2	df	P between subgroups
LES type						7.11	6	0.31						2.57	6	0.86
Sucralose	13	0.05	-0.07, 0.18	0.40	33.45				13	-3.58	-21.06; 13.90	0.69	12.99			
L-Arabinose	10	-0.03	-0.22, 0.16	0.77	34.91				10	-6.90	-32.63; 18.83	0.60	45.41			
Aspartame	9	0.05	-0.09, 0.20	0.46	0				9	1.82	-13.27; 16.92	0.81	49.51			
Sucralose + Ace K	6	0.12	-0.14, 0.38	0.36	0				4	25.32	-24.28; 74.92	0.32	0			
Saccharin	5	-0.04	-0.20, 0.13	0.66	0				5	-0.29	-17.03; 16.44	0.97	0			
Ace K	4	-0.12	-0.29, 0.05	0.16	0				4	2.74	-21.07; 26.54	0.82	0			
Co-exposure						0.48	1	0.48						0.09	1	0.77
Without nutrient preload	12	0.02	-0.11, 0.15	0.76	44.8				12	-0.57	-15.85, 14.71	0.94	0			
With nutrient preload	43	-0.03	-0.11, 0.04	0.40	41.46				38	-3.48	-15.38, 8.42	0.57	56.31			
Health status						5.56	1	0.02*						0.45	1	0.5
Healthy	41	-0.01	-0.07, 0.06	0.80	36.31				39	-2.86	-12.01, 6.30	0.54	56.31			
Type 2 diabetes	9	-0.30	-0.53, -0.07	0.01*	32.69				7	4.87	-15.63, 25.37	0.64	18.67			

Ace K: Acesulfame potassium; Df: degrees of freedom; PPG: Postprandial glucose; PPI: Postprandial insulin

Figure legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection procedure.

Figure 2. Forest plot showing mean change difference in PPG after LES intake. Horizontal lines represent 95% confidence intervals. The diamond represents the pooled estimate determined using a random effects model.

Figure 3. Forest plot showing mean change difference in PPI after LES intake. Horizontal lines represent 95% confidence intervals. The diamond represents the pooled estimate determined using a random effects model.

Figure 4. Funnel plot used to assess risk of publication bias for (A) PPG and (B) PPI. Weights ($1/SE^2$) are plotted against the changes in PPG (*A*) and PPI (*B*) from a total of 55 comparisons (452 individual participants) for PPG and 50 comparisons for PPI (394 individual participants) respectively. Both PPG and PPI effects showed moderate heterogeneity (P value for Q statistic <0.01; $I^2 = 59.5\%$ and P <0.01, $I^2 = 61.2\%$ respectively) between studies.