Health outcomes of non-nutritive sweeteners: analysis of the research landscape

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Abstract

Background: Food products containing non-nutritive sweeteners (NNSs) instead of sugar have become increasingly popular in the last decades. Their appeal is obviously related to their calorie-free sweet taste. However, with the dramatic increase in their consumption, it is reasonable and timely to evaluate their potential health benefits and, more importantly, potential adverse effects. The main aim of this scoping review was to map the evidence about health outcomes possibly associated with regular NNS consumption by examining the extent, range, and nature of research activity in this area.

Methods: We systematically searched Ovid MEDLINE, EMBASE and the Cochrane CENTRAL databases for studies on NNSs (artificial sweeteners or natural, non-caloric sweeteners, either used individually or in combination) using text terms with appropriate truncation and relevant indexing terms. All human studies investigating any health outcomes of a NNS intervention or exposure were eligible for inclusion. No studies were excluded based on language, study design or methodological quality. Data for each health outcome were summarized in tabular form and were discussed narratively.

Results: Finally, we included 372 studies in our scoping review, comprising 15 systematic reviews, 155 randomized controlled trials (RCTs), 23 non-randomized controlled trials, 57 cohort studies, 52 case-control studies, 28 cross sectional studies and 42 case series/case reports.

In healthy subjects, appetite and short term food intake, risk of cancer, risk of diabetes, risk of dental caries, weight gain and risk of obesity are the most investigated health outcomes. Overall there is no conclusive evidence for beneficial and harmful effects on those outcomes. Numerous health outcomes including headaches, depression, behavioral and cognitive effects, neurological effects, risk of preterm delivery, cardiovascular effects or risk of chronic kidney disease were investigated in fewer studies and further research is needed. In subjects with diabetes and hypertension, the evidence regarding health outcomes of NNS use is also inconsistent.

Conclusions: This scoping review identifies the needs for future research to address the numerous evidence gaps related to health effects of NNSs use. It also specifies the research questions and areas where a systematic review with meta-analyses is required for the proper evaluation of health outcomes associated to regular NNSs consumption.

Keywords: Non-nutritive sweetener, Artificial sweetener, Aspartame, Saccharin, Stevia, Diabetes, Cancer, Dental caries, Weight gain, Overweight, Obesity, Scoping review

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Introduction
In the last decades, growing concerns about health and quality of life have encouraged people to avoid the consumption of food rich in sugar, salt or fat [1, 2]. With increased consumer interest in reducing sugar intake, food products containing calorie-free alternatives (non-nutritive sweeteners; NNSs) have become increasingly popular [3, 4]. NNSs are generally several hundred to several thousand times sweeter than sucrose [5]. Most of them do not contain any calories while some NNSs (e.g., aspartame) contain very few [6]. Each sweetener has specific characteristics of sweetness intensity, persistence of the sweet taste, coating of the teeth and aftertaste effect [7, 8].

Most of the NNSs approved for human consumption are synthetic (artificial sweeteners; AS). However, more and more NNSs of natural origin are available on the market (natural, non-caloric sweeteners; NNCSs). The most familiar NNCSs are Stevia rebaudiana-based products. Steviol glycosides, extracted from the plant Stevia include stevioside and rebaudioside A, but also other, less common glycosides [9].

With regard to the range of approved ASs there are differences among countries. In the United States for example, there are currently six ASs which the Food and Drug Administration (FDA) has approved for consumption (Table 1; [10] acesulfame-K, aspartame, neotame, saccharin, sacralose and advantame). In the European Union meanwhile, the range of currently approved ASs is wider, also including, for example, cyclamate [11, 12]. Stevia has been used as a sweetener for decades in some countries (e.g. Japan), while it was approved as a food additive just recently by the European Food Safety Authority (EFSA) [13] and the US FDA.

Parallel to the dramatic increase in the consumption of food and beverages sweetened with NNSs, concerns have been raised about their potential adverse health effects [14–16]. Several studies investigated short-term consequences (e.g. on food intake, mood, blood pressure); others evaluated long-term health effects (e.g. on body weight, incidence of obesity, risk of cancer, risk of diabetes or dental caries) of NNSs. Overall, plenty of scientific studies have been published, postulating a wide variety of beneficial, but also negative health effects of NNSs.

Since scoping reviews are used to present a broad overview of the evidence pertaining to a topic irrespective of study quality, they can be seen as a hypothesis-generating exercise and are therefore the optimal method for examining this emerging area as a first approach [17]. The aim of this scoping review was to map the available evidence about the health outcomes possibly associated with regular NNS consumption by examining the extent, range, and nature of research activity in this area.

Objectives
Primary objectives of this scoping review were to:

- Identify all potential health outcomes associated with regular NNS consumption;
- Define the number and types of primary studies (i.e. studies that collect original data from subjects) available for each health outcome;
- Identify any gaps in the evidence base for the health outcomes of regular NNS consumption.

Secondary objective of this scoping review was to:

- Summarize available systematic reviews on the association of NNS consumption and health outcomes, compare their inclusion criteria and limitations, and determine whether a new systematic review in this area is justified.

Methods
We used the approach of a scoping review (including a process known as evidence mapping) [18, 19] to compile all relevant evidence about the health effects of NNS consumption from the scientific literature. This approach is based on a systematic literature search and the transparent assessment of the retrieved evidence for its relevance for the research question by presenting an overview of a potentially large and diverse body of literature pertaining to this broad research topic, without making restrictions based on study design and methodology. Furthermore, it seeks to provide a descriptive
Inclusion criteria
To be included, a primary study needed to meet all of the following criteria: a) a study on human beings (of any age, gender or health status); b) an intervention with or exposure to any type and any dosage of ASs (aspartame, acesulfame potassium, saccharin, sucralose, advantame, neotame, cyclamate, alitame, neohesperidin dihydrochalcone (DC)) or NNCSs (stevioside, rebaudioside A, thauatin, brazzein) or NNSs (defined as any combination of AS and NNCS); c) a study reporting health effects of any type (both health outcomes and intermediate markers of health outcomes were included); d) no restriction on study design or language.

We also included relevant systematic reviews on the association of an NNS intervention/exposure and one or more defined health outcomes (every review describing or indicating a systematic search was regarded to be a systematic review).

In this manuscript we report on relevant systematic reviews, clinical trials, cohort studies, case-control and cross-sectional studies.

Search strategy
Ovid MEDLINE (ovidsp.ovid.com), EMBASE (www.embase.com) and the Cochrane CENTRAL database (www.cochranelibrary.com) were searched from inception to October Week 2 2015 for studies on AS and to January Week 3 2016 for studies on NNCS and NNS, using text words with appropriate truncation and relevant indexing terms (MeSH). The search was in the form [terms for artificial sweeteners/ natural, non-caloric sweeteners/non-nutritive sweeteners] and [human studies]. Electronic searches were limited neither in time nor in language. Electronic searches were followed by hand searching of reference lists of relevant review articles and included primary studies. Electronic searches were updated in May Week 4 2017.

Data extraction and management
Titles and abstracts were screened for inclusion by a single reviewer (SL). Only clearly irrelevant records were excluded at this stage. All potentially relevant abstracts and full papers were screened for inclusion by two reviewers independently using an inclusion/exclusion form specifically developed for the purpose of this scoping review (SL and IT). In case of disagreement, the subject was discussed among the two reviewers until a mutual decision could be made. When this was not possible, a third reviewer (JM) was consulted. A data extraction sheet was designed and piloted. Then two reviewers (SL and IT) independently extracted the following data for each included primary study: 1) first author; 2) year of publication; 3) study location; 4) study design; 5) aim of the study; 6) main characteristics and size of the study sample; 7) main characteristics of intervention/exposure and control; 8) outcome measures with direction of effect.

Intervention studies were classified as RCTs (with either parallel, or cross-over design) or non-randomized controlled trials (non-RCTs), while observational studies were classified as prospective or retrospective cohort studies, cross-sectional studies, case-control studies, ecological studies or case reports/case series. Data sheets were compared and in case of differences in the extracted data, the relevant information was checked again in the study article and corrected.

Data for each health outcome were summarized in tabular form and were discussed narratively. Bubble charts were used to highlight the main relationship among the types of NNS used in the studies as intervention/exposure, the health effects and the study types. Bubble charts are multi-variable graphs, whose plot points along a grid where the X and Y axis are separate variables (in our case they represent the type of sweetener and health outcomes). Additionally, the different colours of the plotted points represent a third variable (in our case they show the study type).

For each included systematic review following data were extracted: 1) first author; 2) year of publication; 3) date of search; 4) databases searched 5) aim of the review; 6) study design of eligible studies; 7) main characteristics of eligible intervention/exposure; 8) outcome(s) eligible for inclusion.

Results
The flow diagram of the literature search (PRISMA Flow Diagram adapted for the scoping review process) is shown in Fig. 1. For ASs a total of 7970 articles were identified in the initial literature search, of which 669 appeared to be potentially relevant. Fifteen papers could not be retrieved; all others were available for detailed full-text assessment. Finally, 317 articles fulfilled the inclusion criteria. This search focused on studies with ASs as the intervention or exposure; however, 11 primary studies with NNCSs, 28 studies with diet beverages/diet sodas and one study with a combination of NNSs and sugar-alcohols were already identified at this stage. For NNCSs and NNSs, 3087 articles were identified in the original literature search, 112 full texts were screened for eligibility and finally 55 were included in the review. In 2017, after the update search of databases, 48 further studies were eligible for inclusion.

In total, 24 systematic reviews (Table 2), 175 randomized controlled trials (RCTs), 29 non-randomized controlled clinical trials (non-RCTs), 62 cohort studies, 52 case-control studies and 36 cross-sectional studies were included in this scoping review. We also found 42 case studies.
Health outcomes assessed in the included studies

Health outcomes by intervention as investigated in primary studies are shown in Fig. 2. We first report short-term outcomes (appetite and short-term food intake), then long-term health outcomes in healthy populations (in alphabetical order: cancer, chronic kidney disease, dental caries, diabetes, headaches, neurocognitive outcomes, obstetric outcomes, weight gain and obesity). Finally, health outcomes in non-healthy populations are described.

Short-term outcomes

Appetite and short term food intake

Eating behavior and metabolic effects due to the exposure to NNSs were investigated in five systematic reviews among other outcomes [20–24]. One review reported evidence for an appetite lowering effect of aspartame, whereas the other reviews reported conflicting evidence for the effects of Stevia and ASs in general on eating behavior.

The primary studies on short-term food intake focused on whether exposure to NNSs enhances the desire for sweet foods and drinks, leading to an increased food intake. From the included 60 primary studies, 32 were small, cross-over RCTs [25–56] with a similar design: the subjects first consumed a “preload”, a food or drink sweetened with either NNSs or with sugar (a nutritive sweetener) or a food or drink which did not contain any sweetener (e.g. water). After a time delay subjects were offered an ad libitum meal and total energy intake was measured.

No effects of NNSs on short-term food intake or subjective awareness of hunger were described in 39 studies (9 parallel RCTs [53, 57–64], 22 cross-over RCTs [25–29, 31, 33–39, 41, 43, 46, 50, 51, 53–56], 7 non-RCTs [45, 65–70] and 1 case-control study [71]); 10 studies described an increased [32, 40, 45, 47, 49, 52, 72–75], while 11 studies described a decreased food intake or appetite [30, 42, 48, 76–83] in the NNSs intervention group as compared to the sugar-receiving or placebo group.

Long-term health outcomes in healthy populations

Cancer

Berry et al. [84] systematically summarized studies on the carcinogenic potential of sucralose and concluded that sucralose does not demonstrate carcinogenic activity even when exposure levels are several orders of magnitude greater than the range of anticipated daily
| First author, publication year | Population | Intervention/ Exposure | Outcome | Included study designs | Limitations | Date of search | Searched databases |
|--------------------------------|------------|-------------------------|---------|------------------------|-------------|---------------|-------------------|
| Bernardo, 2016 [274]           | adults and children | AS use | adverse clinical effects | comparative and epidemiological studies | ND | ND | MEDLINE; EMBASE; Cochrane Library; Lilacs/Scielo |
| Berry, 2016 [84]               | ND | sucralose consumption | carcinogenic potential | ND | ND | ND | MEDLINE; TOXFILE, BIOSIS Toxline; FOODOLINE; CAB Abstracts; Food Science and Technology Abstracts; NITS; EMBASE |
| Borkum, 2016 [275]             | ND | migraine triggers (including aspartame) | oxidative stress in the brain | ND | published between 1990-2014 and in English language | ND | MEDLINE |
| Brown, 2010 [22]               | children (0–18 y) | AS consumption | metabolic health effects (food intake, weight change, diabetes, metabolic syndrome components) | ND | published in peer reviewed journals in English language | ND | MEDLINE; Web of Science, EMBASE |
| Greenwood, 2014 [157]          | generally healthy population | sugar- or artificially-sweetened beverage consumption | incident diabetes mellitus type 2 risk | prospective observational studies (min. Duration: 3 years) | published since 1990 and in English language | November 2009; updated: June 2013 | MEDLINE; EMBASE; Cochrane Library; MEOUINE; MEOUINE In-Process; EMBASE; CAB Abstracts; ISI Web of Science; BIOSIS |
| Cheungpasitporn, 2014 [135]    | ND | sugar- or artificially-sweetened soda consumption | chronic kidney disease incidence | RCTs, case-control, cross-sectional or cohort studies | provided odds ratios, relative risk, hazard ratios or standardized incidence ratios with 95% confidence intervals | June 2014 | MEDLINE; EMBASE; Cochrane Library; CENTRAL |
| Hendriksen, 2011 [276]        | ND | added sugar and intense sweeteners | beneficial and hazardous health effects | ND | written in English or Dutch language | October 2008 | ND |
| Immamura, 2016 [161]          | adults without diabetes | artificially sweetened beverages | incidence of type 2 diabetes | prospective studies | no language or time limitations | May 2013; updated: February 2014 | MEDLINE; EMBASE; Ovid; Web of Science |
| Miles, 2014 [181]              | generally healthy population | low-calorie sweeteners from foods or beverages or as tabletop sweeteners | body weight or body composition | RCTs and prospective cohort studies | a minimum study duration of 2 weeks for RCTs and 6 months for prospective cohorts | September 2013 | MEDLINE |
| Pereira, 2014 [180]            | no limitation | ASB (or sugar- sweetened beverages) consumption | body weight or body fat composition | RCTs and prospective cohort studies | observational studies min. Duration of 6 months studies in English language | March 2012 | MEDLINE |
| Pereira, 2013 [277]            | ND | DB/ASB consumption | body weight, obesity risk, type 2 diabetes, or cardiovascular disease | ND | | September 2011 | MEDLINE |
| Reid, 2016 [183]               | pregnant women, infants, or children (<12 years of age) | early life NNS exposure (all types of NNS consumption) | long-term metabolic health (BMI, birth weight, growth velocity, incidence of overweight/obesity, change in adiposity, incidence of impaired glucose tolerance, metabolic syndrome, insulin resistance or type 2 diabetes) | RCTs and prospective cohort studies | min. Study duration of 6 months | July 2015 | MEDLINE; EMBASE; Cochrane Library |
| Reference | Year | Population | Intervention | Outcomes | Study Design | Inclusion Criteria | Database Search Terms |
|-----------|------|------------|--------------|----------|--------------|-------------------|----------------------|
| Rogers, 2016 [182] | 2016 | humans and animals | low-energy sweeteners consumption | energy intake, body weight, BMI | ND | no language or time limitations | February 2015 MEDLINE, EMBASE, Web of Science |
| Romo-Romo, 2016 [24] | 2016 | adults | NNS consumption | glucose metabolism and appetite regulating hormones, development of metabolic chronic diseases | observational studies and clinical trials | follow up of at least 3 years in cohort studies | April 2015; updated March 2016 MEDLINE, Cochrane Library, Trip Database |
| Russel, 2016 [278] | 2016 | adult type 2 diabetes patients or obese subjects | nutrients (incl. Low-calorie sweeteners) | postprandial hyperglycemia | intervention trials | studies in English language | ND MEDLINE, Web of Science |
| Shankar, 2013 [279] | 2013 | ND | NNS consumption | obesity/weight gain, diabetes, cardiometabolic indicators | ND | full articles in English language | June 2015 MEDLINE, EMBASE |
| Spencer, 2016 [280] | 2016 | humans and animals | aspartame, saccharin or sucralose consumption | fermentation, absorption, gastrointestinal symptoms | clinical studies | studies in English language | May 2012 MEDLINE, Scopus |
| Timpe Behnen, 2013 [281] | 2013 | diabetes patients | acesulfame, aspartame, luo han guo, monk fruit, neotame, rebaudioside a, sucralose, stevia, and sucralose | diabetic control, including, but not limited to, blood glucose levels, postprandial blood glucose, HbA1c | | |
| Webe, 2011 [23] | 2011 | ND | a sweetener (e.g. non-caloric sweetener) | weight change, energy intake, lipids, HbA1C, insulin resistance | parallel or crossover RCT | follow up at least 1 week in duration; at least 10 participants per group, no trials with placebo control | January 2011 MEDLINE, EMBASE, Cochrane Library CENTRAL, CAB Global |
| Oliver, 2015 [85] | 2015 | ND | aspartame, ace-K, cyclamic acid and its salts, steviol glycosides, neohesperidin DC, neotame, saccharin and its salts, sucralose, aspartame-acesulfame salt, thaumatin | benefits and risks related to intense sweeteners | meta-analysis, RCTs, quasi experimental, cohort, case-control, cross-sectional studies | none | |
| Onakpoya, 2015 [21] | 2015 | adult volunteers (>18 y) | steviol glycoside | cardiovascular risk factors (blood pressure, blood sugar, cholesterol) | double-blind RCTs | No age, language or time restrictions; Studies in which steviol glycosides were combined with other dietary supplements were excluded | May 2014 MEDLINE, EMBASE, Ame, Cinahl, The Cochrane Library, Google Scholar |
| Poolsup, 2012 [282] | 2012 | patients with hypertension | stevioside | systolic and diastolic blood pressure control | RCTs | published in English language | February 2012 MEDLINE, Science Direct, Cochrane Library, Wiley Online Library |
| Ulbricht, 2010 [20] | 2010 | both adults and children | stevia | adverse effects, (pharmacology, kynetics, dosing, interactions, toxicology) | no restriction (both in vivo and in vitro studies) | no language restrictions | ND AMED, CANCERLIT, CINAHL, COSCIM, Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, MEDLINE, NAPRAELT |
| Reference          | Year | Design               | Sweeteners                         | Outcomes                                                                 | Notes                                                                 | Dates       | Databases                        |
|--------------------|------|----------------------|------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------|-------------|----------------------------------|
| Urban, 2015        | 283  | ND                   | steviol glycosides and/or stevia leaf extracts of known concentrations | allergic reactions no restriction (also animal and in vitro studies)    |                                                                       | ND October 2014 | MEDLINE, Science Direct, Google Scholar |
| Wang, 2016         | 284  | adults, pregnant women and infants (>6 mo) | FDA-approved sweeteners            | energy sensing by the brain; gut hormones that may influence energy homeostasis; satiety and preference for taste; eating behavior; body weight and composition | RCTs, non-RCT, not controlled trials, prospective cohorts English language; cancer patients were excluded | ND          | MEDLINE                          |

**Abbreviations:** ASB artificially sweetened beverage, DB diet beverage, HbA1c glycosylated haemoglobin type A1C, ND not described, RCT randomized controlled trial; y, years; mo, months.
Ingestion levels. Another, broadly focused systematic review published in 2015 [85] assessed cancer risk among several other health outcomes. Authors of this review also searched for diet beverage studies, but only narratively summarized their results and concluded that, based on the available data, it was not possible to establish a link between cancer risk and the consumption of ASs.

In total, we identified 51 primary studies assessing the association of NNS consumption and cancer risk. The investigated exposure was use of any type of ASs or use of a subtype of ASs (saccharin or aspartame) in 47 studies, while 4 studies investigated exposure to NNCSs. Cancer outcomes by type of exposure as investigated in primary studies are shown in Fig. 3.

Out of the identified 41 case-control studies reporting on the effect of NNSs on cancer, 32 assessed the relationship between NNS consumption and the risk of developing bladder cancer or urinary tract cancer. The results of these studies are controversial: 11 case-control studies describe a positive association between AS/NNS intake and bladder or urinary tract cancer risk [86–96], while 20 report no association [97–116].

Two case-control studies assessed the risk of brain cancer (no association with AS use [117, 118]), 1 study assessed the risk of colorectal cancer (significantly increased with AS use [119]), 2 studies investigated the risk of pancreatic cancer (no association with NNSs [120, 121]), 1 study investigated the risk of breast cancer (no association with AS use [122]) and 4 studies investigated the risk of any type or more types of cancer (no association with NNS use [123–126]).

Three prospective cohort studies investigated the risk of lymphomas or other hematological malignancies...
[127, 128], 1 assessed the risk of biliary tract cancer [129], 1 assessed cancer incidence in general [130], 1 assessed the risk of tumor multiplicity in treated bladder cancer patients [131], 1 investigated the 5-year survival rate in urinary bladder cancer patients [132], while 2 retrospective cohort studies assessed the risk of bladder cancer [112, 133] (no significant associations were described in either of them).

The cross-sectional study described that breast cancer survivors compared to age-matched controls had significantly lower intakes of NNSs [134].

Chronic kidney disease
In a systematic review by Cheungpasitporn et al. [135], the 4 included studies assessed the association between consumption of artificially sweetened soda and chronic kidney disease. The authors concluded that consuming artificially sweetened soda did not increase the risk of chronic kidney disease in high-risk patients.

The primary studies we found on the association of NNS consumption and the risk of developing chronic kidney disease were 3 prospective cohort studies (describing no association [136–138]), 1 case-control study (describing a significant positive association [139]) and 2 cross-sectional studies (one of them indicating a positive association [136, 140]).

Dental health (caries)
We found 16 intervention studies (14 RCTs [141–154] and 2 non-RCTs [155, 156]) on the association of an NNS intervention and dental health. Details of these studies are summarized in Table 3.

Only two of the studies mentioned above described no differences between intervention and control groups [142, 155]; all other studies described a less acidogenic (increased) oral pH after the intervention as compared to the sugar-containing control.
### Table 3: Characteristics of studies investigating the effects of non-nutritive sweeteners on dental outcomes

| First author, publication year | Study sample (n) | Intervention/Exposure | Control | Outcome | Effect |
|--------------------------------|------------------|-----------------------|---------|---------|--------|
| **Interventional studies: randomized controlled trials with parallel-group design** | | | | | |
| Beiswanger, 1998 [141] | children (1818) | sugar-free chewing gum containing AS and non-AS | no intervention | development of caries/caries prevalence | decreased development of caries |
| Lopez de Bocanera, 1999 [142] | both adults and children (32) | a solution/drink with AS | sugared solution/drink | salivary or plaque pH | no effect on pH |
| **Interventional studies: randomized controlled trials with cross-over design** | | | | | |
| Brambilla, 2014 [143] | adults (20) | a solution/drink with stevioside | sugared solution/drink | salivary or plaque pH | less acidogenic (increased) pH |
| Jawale, 2012 [144] | adults (20) | diet soft drink | sugared solution/drink | salivary or plaque pH | less acidogenic (increased) pH |
| Manning, 1993 [145] | adults (10) | sugar-free chewing gum containing AS and non-AS | sugared chewing gum | salivary or plaque pH | less acidogenic (increased) pH |
| Mendes de Santa, 2014 [146] | adults (9) | a solution/drink with a combination of NNS | sugared solution/drink | salivary or plaque pH | less acidogenic (increased) pH |
| Mentes, 2001 [147] | adults (29) | a solution/drink with AS and non-AS | sugared solution/drink | salivary or plaque pH | less acidogenic (increased) pH |
| Meyerowitz, 1996 [148] | age group not described (14) | a solution/drink with sucralose | sugared solution/drink | salivary or plaque pH | less acidogenic (increased) pH |
| Park, 1993 [149] | age group not described (5) | sugar-free chewing gum containing sucralose/ace K | another NNS | salivary or plaque pH | no difference in pH |
| Park, 1995 [150] | adults (8) | sugar-free chewing gum containing AS or non-AS | sugared chewing gum; no intervention | salivary or plaque pH | less acidogenic (increased) pH |
| Roos, 2002 [151] | children (17) | diet soft drink | sugared solution/drink | salivary or plaque pH | less acidogenic (increased) pH |
| Steinberg, 1995 [152] | age group not described (10) | a solution/drink with sucralose | sugared solution/drink | salivary or plaque pH | less acidogenic (increased) pH |
| Steinberg, 1996 [153] | age group not described (12) | a solution/drink with sucralose | sugared solution/drink | salivary or plaque pH | less acidogenic (increased) pH |
| Zanela, 2002 [154] | children (T: 200) | a solution/drink with stevioside | chlorhexidine gluconate | amount of plaque formed | less effective in decreasing the amount of plaque formed |
| **Interventional studies: non-randomized controlled trials** | | | | | |
| Mühlemann, 1985 [155] | adults (T:2) | a solution/drink with aspartame | sugared solution/drink | salivary or plaque pH | no effect on pH |
| Syrrakou, 1993 [156] | age group not described (15) | a solution/drink with sucralose | sugared solution/drink | salivary or plaque pH | less acidogenic (increased) pH |
| **Observational studies: case-control studies** | | | | | |
| Grenby, 1975 [287] | adults (24) | saccharin instead of sucrose | sugared solution/drink | amount of plaque formed | decreased amount of plaque formed |
| **Observational studies: cross-sectional studies** | | | | | |
| Serra-Majem, 1993 [288] | age group not described (893) | AS in regular diet | – | development of caries/caries prevalence | decreased development of caries |

**Abbreviations:** AS artificial sweetener, ace K acesulfame potassium, n total number of participants, non-AS a non-sugar sweetener other than NNS (e.g. sugar alcohols)
Table 4: Cohort studies on the association of AS consumption and risk of developing diabetes

| First author, publication year | Study sample | Number of participants | Exposure | Main outcome | Direction of effect |
|--------------------------------|--------------|------------------------|----------|--------------|--------------------|
| Prospective cohort studies     |              |                        |          |              |                    |
| Bhuphatiraju, 2013 [165]       | female nurses (age 30–55 y) + male health professionals (age 40–75 y) | 74,749 + 39,059 | ASB       | risk of type 2 diabetes | – |
| deKonig, 2011 [160]            | middle-aged (40–75 y) male health care providers | 40,389 | ASB       | incidence of type 2 diabetes | – |
| Fagherazzi, 2013 [162]         | women        | 66,118                 | ASB       | risk of type 2 diabetes | ↑↑ |
| Fagherazzi, 2017 [163]         | women        | 61,440                 | AS in packets or tablets | risk of type 2 diabetes | ↑↑ |
| Palmer, 2008 [285]             | women (age 21–69 y) | 43,960 | diet soft drink | risk of type 2 diabetes | – |
| Schulze, 2004 [217]            | healthy women | 91,249 | diet soft drink | risk of diabetes | ↑ |
| Sakurai, 2014 [286]            | men          | 2037                   | diet soda | risk of type 2 diabetes | ↑↑ |
| Retrospective cohort studies   |              |                        |          |              |                    |
| Armstrong, 1975 [166]          | bladder cancer patients + patients with other cancers | 18,733 + 19,709 | saccharin  | prevalence of diabetes | – |
| Case-control study             |              |                        |          |              |                    |
| The Inter Act Consortium, 2013 [164] | type 2 diabetes cases + controls | 11,684 + 15,374 | artificially sweetened soft drink | incidence of type 2 diabetes | ↑ |

Abbreviations: ASB artificially sweetened beverage consumption; y years; AS artificial sweeteners; ↑ means that a positive association was suggested in the study, but this was not significant; ↑↑ means a significant positive association; − means that there was no (significant) difference in the outcome between the intervention and control group.
Diabetes
In a systematic review published in 2014 [157], three included publications on 4 cohorts investigated the association between intake of artificially sweetened soft drinks and risk of type-2 diabetes [158–160] using additional information provided by the authors of two of the publications [158, 159]. The review reported an increased risk of diabetes when consuming 330 ml/day of artificially sweetened soft drinks; however, substantial heterogeneity was described among the cohort studies. Also, another systematic review published in 2016 [161] described a positive association between the consumption of artificially sweetened beverages and type-2 diabetes incidence; however, the authors of this review rated their findings as biased. We found 6 prospective cohort studies (4 with an AS exposure and 2 with a “diet beverage” exposure), 1 retrospective cohort study (with AS exposure) and 1 case-control study (with AS exposure) on the risk of developing diabetes. These studies are summarized in Table 4.

Among the studies investigating the exposure to AS, 2 prospective cohort studies [162, 163] and one case-control study [164] described an increased risk of type-2 diabetes, while 2 prospective [160, 165] and 1 retrospective cohort studies [166] found no association between AS consumption and risk of diabetes. There were no studies investigating diabetes risk in association with NNCS consumption.

Headaches
We found 3 RCTs [167–169] with a cross-over design and 2 cohort studies [170, 171] investigating the effect of AS on headaches. These included either healthy populations or populations with a subjectively reported sensitivity to AS or people with a history of migraines. Two of them (one RCT [168] and one cohort study [170]) described a significant positive association, in the others no significant association was found between AS consumption and headaches.

Cognitive effects, mental health
RCTs assessing the behavior and mood of essentially healthy children after they were given a preload of either an artificially sweetened or sugar-sweetened food or beverage found no consistent effect of ASs on behavior. Most of the interventional and observational studies investigating the effect of an AS preoad on cognitive abilities in healthy children and adults demonstrated that there was no association between cognitive performance, measured by an array of tests, and the intake of ASs in different forms.

Three studies (2 RCTs and 1 cohort study) investigated the effect of AS on depression and described an increased risk of developing depression symptoms or increased severity of symptoms in mood disorder patients [172–174]. In 1 case-control study, consumption of saccharin was significantly positively associated with the risk of Alzheimer’s disease [175].

Obstetric outcomes
Three cohort studies investigated the effect of AS consumption and preterm delivery [176–178], two of them describing a significant positive, while one described no association. One case-control study described no association between saccharin use before conception or during pregnancy and spontaneous abortion [179].

Weight change
We found 4 systematic reviews addressing the question whether NNS consumption has an unfavorable or favorable effect on body weight [22, 180–182]. Details of these reviews are described in Table 2. Miller et al. [181] indicated, based on data from RCTs, that substituting low-calorie sweeteners (LCS, including NNSs and sugar-alcohols) for calorically dense alternatives resulted in a modest reduction of body weight, body mass index (BMI), fat mass, and waist circumference. Rogers et al. [182] concluded, based on results of relevant RCTs, that low-energy sweetener consumption does not increase body weight. The meta-analysis of observational studies showed a significant positive association between LCS intake and slightly increased BMI, but no association with body weight or fat mass. Pereira et al. [180] concluded that results of the epidemiologic studies are highly inconsistent.

A systematic review [22] focusing on metabolic health effects of AS consumption in pediatric populations identified 3 large cohort studies with long-term follow-up, supporting the existence of an association between ASB (artificially sweetened beverage) consumption and weight gain in children, while 2 other prospective cohort studies described no or an inverse association with obesity. The identified 3 RCTs on children described no differences in weight or BMI between the NNS and the control groups.

Another systematic review [183] focusing on long-term metabolic effects of early NNS consumption concluded that the current evidence of the long-term metabolic effects of NNS exposure during gestation, infancy, and childhood is limited and inconsistent.

We found 31 interventional studies (27 RCTs [58, 61, 62, 74, 77, 184–205] and 4 non-RCTs [67, 68, 79, 206]) and 36 observational studies [158, 159, 202, 203, 207–241] on the effect of NNS consumption on BMI or weight change, including recently published studies, which were not included in the systematic reviews presented above.
Of the 27 RCTs, 14 reported a weight reduction after the intervention with NNSs or diet beverages, 2 reported an increase in weight, while in 11 RCTs no weight change was observed. After subdividing the RCTs according to the type of exposure, we found 15 RCTs with an AS intervention, 8 describing a decrease in body weight after the AS intervention as compared to the (sugar-containing or unmodified) control intervention, 1 describing an increase, while in 6 AS intervention studies no differences were observed between the two groups. There were 3 RCTs with a NNCS (stevia) intervention [187, 204, 242]. None of them described a difference in change of body weight between the intervention and control groups.

Of the 17 prospective cohort studies, 10 described a positive association (either statistically significant or a non-significant trend) between NNS or diet beverage consumption and weight gain/increased BMI [159, 207–211, 216, 218, 237, 239], 3 observed an inverse association [214, 215, 217], while in 4 prospective cohort studies no association [212, 213, 219, 220] between body weight and NNS consumption was found. When investigating the subgroup of prospective cohort studies with a clear AS intervention (8 studies), we found 7 studies describing a positive [208–210, 216, 218, 237, 239] and 1 study describing no association [219] between AS consumption and weight gain/increased BMI. There were no cohort studies with a NNCS intervention reporting on weight gain or obesity.

Of the 17 cross-sectional studies, 12 described a positive [158, 222–226, 229–233, 241], 2 a negative [227, 235] and 3 no association [221, 228, 234] between NNS or diet beverage consumption and weight gain/increased BMI.

**Health outcomes in non-healthy populations (diabetes and hypertension)**

There are two main disease groups with a relatively wide literature of NNS intervention studies. In type-1 and type-2 diabetes patients, the effects of NNS use on diabetic control, including, but not limited to, blood glucose levels, postprandial blood glucose, and glycated hemoglobin (HbA1c), are widely investigated. We found 21 interventional studies (13 RCTs [33, 198, 243–253] and 4 non-RCTs [254–257] with an AS intervention, and 4 RCTs [193, 258–260]) and 2 non-RCT with an NNCS intervention [261] on this topic. Most of the studies described no difference in diabetic patients on diabetic control between the NNS intervention and the control group. Some studies investigated the glycemic effects of NNSs in people with insulin resistance and impaired glucose tolerance [204, 206, 262].

The other disease group consists of hypertensive patients, where the role of NNSs in blood pressure control has been investigated. We found 9 RCTs [187, 193, 242, 259, 263–267], 4 prospective cohort studies [268–271], 1 case-control study [272] and 1 cross-sectional study [273] on this question, with controversial results.

**Discussion**

**Summary of findings**

Overall the evidence for health outcomes of AS is inconsistent and there are numerous gaps in the evidence base. In healthy subjects, appetite and short term food intake, risk of cancer, risk of diabetes, risk of dental caries, weight gain and risk of obesity were the most investigated health outcomes.

In case of the health outcome appetite and short term food intake, a majority of studies were short interventions with a cross-over design. A smaller part were randomized controlled trials with an intervention duration of 4 weeks up to 18 months. In case of the longer interventions, the type and dosage of the NNS was often not defined.

Bladder cancer and cancer of the urinary tract were investigated in multiple studies. For this type of cancer a systematic review may provide conclusive evidence. Most of the studies on urinary tract cancer investigated effects of artificial sweeteners in general; a smaller number investigated the effects of aspartame or saccharin. Other types of cancer were investigated in only one or a low number of studies.

We also found several studies on the role of NNS in dental caries prevention. Included studies suggested that stevia in chewing gum or NNCS beverages instead of sugar-sweetened beverages may be an effective tool for dental caries prevention. However, it has to be mentioned, that while sugar alcohols are widely used in chewing gums for caries prevention, and the literature on their effects is broad, the effects of NNCS on dental caries is investigated in a limited number of studies. In addition, in these studies, NNCSs were often combined with sugar alcohols. It would be interesting to see more comparative studies on the effectiveness of NNCS alone versus other interventions in influencing dental plaque pH; or studies with a longer intervention period and follow-up.

The effect of NNS on risk of diabetes was investigated in a limited number of cohort studies. These studies mainly focused on artificially sweetened beverage or diet beverage consumption and described different directions of effect. Further studies, focusing on special types of NNS (also including NNCS), are required.

Intervention studies on weight change focused mainly on the question whether NNS can be efficiently used in weight management. As part of weight loss intervention programs, more intervention studies would be required, to investigate the effects of NNS alone on body weight in both overweight, obese and normal-weight subjects.
This would be especially important, since it is very difficult in observational studies to evaluate causality between NNS consumption and BMI/weight change and therefore results of these studies have to be interpreted with caution. A positive association between NNS consumption and weight gain in observational studies may be the consequence of and not the reason for overweight and obesity. Moreover, other factors, such as population characteristics, may influence the results of observational studies.

In subjects with diabetes, the effects of NNS were investigated mainly on glycemic control. Because of the heterogeneous, if not contradictory results, a thorough analysis of these findings in a full-fledged systematic review including meta-analyses, subgroup and sensitivity analyses is needed and might help to resolve some of the ongoing uncertainties. Further studies on long-term patient-relevant outcomes in diabetes are required.

The effect of NNS on lowering blood pressure in hypertensive patients should also be analyzed in a high quality systematic review and meta-analysis.

Regarding NNCS, although Stevia is increasingly used as a sweetener, the number of studies on its health effects is limited as of now. Studies investigating the effects of NNCS on cancer or diabetes risk are completely lacking, while there are only few studies on weight gain and obesity risk. Clearly, there is a need for further research.

Eligible NNS not addressed by any of the included primary studies were: neotame, allitame, neohesperidin DC, thaumatin and brazzein.

**Strength and limitations of this scoping review**

The strength of our scoping review is its inclusion of all types of primary studies and systematic reviews which investigate any health effect of any NNS in any population. We are therefore able to present a comprehensive overview of the available scientific evidence on health effects of NNS.

Our scoping review might be limited by the following factors. Firstly, the literature search was conducted in three major and comprehensive databases, but we might have inadvertently missed relevant studies listed in other databases. Secondly, the title abstract screening was conducted by one reviewer who might have inadvertently excluded relevant studies at the first stage of the screening. This limitation might be evened out by conducting the literature search in two steps. In the second step, relevant references for both topics were identified and the chances for including all relevant references in our review were increased.

Detailed assessment of the study quality is not covered in a scoping review and was not conducted in the context of our scoping review. Therefore, information gathered on the health outcome includes only its direction of effect but no information on the internal or external validity of the study results.

**Discussion of findings in light of other evidence summaries**

In our scoping review we found a large number of studies of different designs, investigating effects of different types of NNS in different populations on a variety of health outcomes.

Systematic reviews to summarize the available evidence are already available (Table 2). However, they often have methodological limitations (e.g. language limitation of the search, electronic search in only one database, etc.) or a narrow scope.

There are systematic reviews, which also included key words for “diet soda” and “diet beverage” in their search strategy. There are several, primarily observational studies, where the exposure is defined as “diet”, which may indicate NNS-containing beverages, but further details are often not provided. Therefore, it is clearly a challenge when trying to synthesize the evidence to decide, how to deal with studies describing the intervention/exposure as “diet beverage”, “diet drink” or “diet soda” only. We also included such studies in this scoping review; however, it has to be mentioned that we did not include specific search terms for “diet” beverages/sodas in our search strategy, therefore the list of studies reporting on the effects of diet beverage etc. may be incomplete.

**Implications of findings for practice, policy and future research**

Current evidence demonstrates that there is a need for both further primary research and high quality comprehensive systematic reviews including meta-analyses, to inform future recommendations about the health benefits and risks of NNS to advise and support health care practice and public health decision-making.

This scoping review highlights the need for studies which investigate the long-term effects of individual sweeteners on some of the less well-researched health outcomes (e.g. headaches, depression or other mood disorders, Alzheimer’s disease, risk of preterm delivery). Future studies need to be rigorous in design and conduct, with well-defined interventions (providing information on type and dosage of the non-nutritive sweetener) and controls. Study reports should include detailed descriptions of all methodological aspects to enable proper interpretation of the results.

Systematic reviews are required for health outcomes with a large number of primary studies, but without conclusive evidence (e.g. appetite and short term food intake, risk of cancer, dental caries, risk of diabetes,
Conclusions
There are numerous gaps in evidence related to the health effects of NNS in both healthy and non-healthy populations. In healthy subjects appetite and short term food intake, risk of cancer, risk of diabetes, risk of dental caries are the most investigated health outcomes, all of them without any conclusive evidence. There is a need for well-conducted systematic reviews to quantitatively summarize results and assess their validity. Besides, there are numerous health outcomes, like incidence of headaches in association with NNS consumption, depression, Alzheimer’s disease, risk of preterm delivery, behavioural effects, cardiovascular effects or risk of chronic kidney disease, which were investigated in only few studies and further research activity is needed. A systematic review may also help to enable formulating recommendations for subjects with diabetes and hypertension on using NNS.

Abbreviations
A/S: Artificial sweeteners; EFSA: European Food Safety Authority; FDA: Food and Drug Administration; LCS: Low-calorie sweeteners; MeSH: Medical Subject Headings; NNCS: Natural, non-caloric sweetener; NNS: Of non-nutritive sweetener; RCT: Randomized controlled trial

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SL and IT developed search strategy; acquired trial reports, selected trials for inclusion and extracted data; JM supervised the work; SL prepared the first review draft. All authors read, commented and approved the final manuscript.

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References
1. Servo M, Montagnese C, Mathers JC, Soroka KR, Stephan BC, Wells JC. Sugar consumption and global prevalence of obesity and hypertension: an ecological analysis. Public Health Nutr. 2014;17:587–96.
2. Stanhope KL. Sugar consumption, metabolic disease and obesity: the state of the controversy. Crit Rev Clin Lab Sci. 2016;53:52–67.
3. Martyn DM, Nugent AP, McNulty BA, O’Reilly E, Tustos C, Walton J, Flynn A, Gibney MJ. Dietary intake of four artificial sweeteners by Irish pre-school children. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2016;33:592–602.
4. Li YE, Lopetichmar K, Drake MA. Parents’ And children’s acceptance of skim chocolate milks sweetened by monk fruit and stevia leaf extracts. J Food Sci. 2015;80:S1083–92.
5. Fujimaru T, Park JH, Lim J. Sensory characteristics and relative sweetness of tagatose and other sweeteners. J Food Sci. 2012;77:523–8.
6. Chattopadhyay S, Raychaudhuri U, Chakraborty R. Artificial sweeteners - a review. J Food Sci Technol. 2014;51:11–21.
7. Pati S, Ravi R, Saraswathi G, Prakash M. Development of low calorie snack food based on intense sweeteners. J Food Sci Technol. 2014;51:4096–101.
8. Nahon DF, Rooszen JP, de Graaf C. Sensory evaluation of mixtures of maltitol or aspartame, sucrose and an orange aroma. Chem Senses. 1998;23:59–66.
9. Cuenen S, Geuns JM. Steviol glycosides: chemical diversity, metabolism, and function. J Nat Prod. 2013;76:2101–28.
10. US Food, Drug Administration. High-Intensity Sweeteners [http://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm397716.htm (last accessed 08 May 2017)].
11. Roberts A. The safety and regulatory process for low calorie sweeteners in the United States. Physiol Behav. 2016.
12. Mortensen A. Sweeteners permitted in the European Union: safety aspects. Scand J Food Nutr. 2006;50:104–16.
13. Revised exposure assessment for steviol glycosides for the proposed uses as a food additive. [Available from: http://www.efsa.europa.eu/de/efsajournal/pub/1972].
14. Choudhary AK, Lee YY. Neuropsychological symptoms and aspartame: what is the connection? Nutr Neurosci. 2017;11–11.
15. Sylvetsky Meni AC, Swinths SE, Rother KI. Positive association between artificial sweeteners and type 2 diabetes: a systematic review and meta-analysis. Int J Environ Res Public Health. 2014;11:1478–93.
16. Schernhammer ES, Bertrand KA, Birmann BM, Sampson L, Willett WC, Colditz GA. Artificially sweetened beverage consumption and incidence of diabetes. Diabetologia. 2015;58:2455–66.
17. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Dietary intake of four artificial sweeteners by Irish pre-school children. Am J Clin Nutr. 2012;96:1419–28.
18. Smidt M, Motschall E, Van der Pas KE. Measuring sugar consumption among children: a comparison of different methods. J Clin Epidemiol. 2015;78:64–53.
19. Colquhoun HL, Levac D, O’Brien KK, Straus S, Tricco AC, Perrier L, Kastner M, Moher D. Scoping reviews: time for clarity in definition, methods, and reporting. J Clin Epidemiol. 2014;67:1291–4.
20. Ulbricht C, Isaac R, Milkin T, Poole EA, Rusie E, Grimes Serrano JM, Weissner K. Dietary intake of four artificial sweeteners by Irish pre-school children. J Food Sci Technol. 2014;51:4096–101.
21. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015;13:141–6.
22. Schmucker C, Motschall E, Antes G, Meerpohl JJ. Methods of evidence mapping. A systematic review. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2013;56:1390–7.
23. Colquhoun HL, Levac D, O’Brien KK, Straus S, Tricco AC, Perrier L, Kastner M, Moher D. Scoping reviews: time for clarity in definition, methods, and reporting. J Clin Epidemiol. 2014;67:1291–4.
24. Ulbricht C, Isaac R, Milkin T, Poole EA, Rusie E, Grimes Serrano JM, Weissner K, Windsor RC, Woods J. An evidence-based systematic review of stevia by a food additive. [Available from: http://www.efsa.europa.eu/de/efsajournal/pub/1972].
25. Choudhary AK, Lee YY. Neuropsychological symptoms and aspartame: what is the connection? Nutr Neurosci. 2017;11–11.
26. Sylvetsky Meni AC, Swinths SE, Rother KI. Positive association between artificial sweeteners and type 2 diabetes: a systematic review and meta-analysis. Int J Environ Res Public Health. 2014;11:1478–93.
27. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Dietary intake of four artificial sweeteners by Irish pre-school children. Am J Clin Nutr. 2012;96:1419–28.
28. Smidt M, Motschall E, Van der Pas KE. Measuring sugar consumption among children: a comparison of different methods. J Clin Epidemiol. 2015;78:64–53.
23. Wiebe N, Padwal R, Field C, Marks S, Jacobs R, Tonelli M. A systematic review on the effect of sweeteners on glycemic response and clinically relevant outcomes. BMC Med. 2011;9
24. Romo-Romo A, Aguilar-Salinas CA, Brito-Cordova GX, Diaz RAG, Valentín DV, Almeda-Valdes P. 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;11
25. Anderson GH, Saravis S, Schacher R, Zlotkin S, Leiter LA. Aspartame: effect on lunch-time food intake, appetite and hedonic response in children. Appetite. 1989;13:93–103.
26. Anton SD, Martin CK, Han H, Coulon S, Cefalu WT, Geiselman P, Williamson DA. Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. Appetite. 2010;55:37–43.
27. Bellisimo N, Pencharz PB, Thomas SG, Anderson GH. Effect of television viewing at mealtime on food intake after a glucose preload in boys. Ped Res. 2007;60:714–9.
28. Bellisimo N, Thomas SG, Goode RC, Anderson GH. Effect of short-duration physical activity and ventilation threshold on subjective appetite and short-term energy intake in boys. Appetite. 2007;49:644–51.
29. Beridot-Therond ME, Arts J, Fantino M, De La Guerciniere V. Short-term effects of the flavour of drinks on ingestive behaviours in man. Appetite. 1998;31:67–81.
30. Birch LL, McPhee L, Sullivan S. Children’s Food intake following drinks sweetened with sucrose or aspartame: time course effects. Physiol Behav. 1989;45:387–95.
31. Black RM, Leiter LA, Anderson GH. Consuming aspartame with and without taste: differential effects on appetite and food intake of young adult males. Physiol Behav. 1999;53:459–66.
32. Branton A, Akhavan T, Gladacan B, Pollard D, Welch J, Rossetter M, Bellisimo N. Pre-meal video game playing and a glucose preload suppress food intake in normal weight boys. Appetite. 2014;83:256–62.
33. Bryant CE, Wasse LK, Astbury N, Nandra G, McLaughlin JT. Non-nutritive sweeteners: no class effect on the glycaemic or appetite responses to ingested glucose. Eur J Clin Nutr. 2014;68:629–31.
34. Carvalho P, Sousa M, Barros R, Padrao P, Moreira P, Teixeira V. Impact of the removal of sugar from the diet. J Human Nutr Diet. 1995;8:167–81.
35. Cullen M, Nolan J, Cullen M, Moloney M, Kearney J, Lambe J, Gibney MJ. Effect of stevia and sucralose on gut hormone response and satiety. J Human Nutr Diet. 1994;59:338–48.
36. DellaValle DM, Roe LS, Rolls BJ. Does the consumption of caloric and non-caloric beverages with a meal affect energy intake? Appetite. 2005;44:187–93.
37. Flood JE, Roe LS, Rolls BJ. The effect of increased beverage portion size on energy intake at a meal. J Am Diet Assoc. 2006;106:1984–90.
38. Gadash NS, Brunstrom JM, Rogers PJ. Cross over studies underestimate energy compensation: the example of sucrose versus sucralose-containing drinks. Appetite. 2016;107:398–405.
39. Patel BP, Hamilton JK, Vien S, Thomas SG, Anderson GH. Puberal status, pre-meal drink composition, and later meal timing interact in determining children’s appetite and food intake. Appl Physiol Nutr Metab. 2016;41:924–30.
40. Sylverstyk AC, Brown RI, Blau JE, Walter M, Rother KI. Hormonal responses to non-nutritive sweeteners in water and diet soda. Nutr Metab. 2016;13:71.
41. Teey SL, Salleh NB, Henry J, Forde CG. Effects of aspartame–monk fruit–stevia–and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake. Int J Obes. 2017;41:450–7.
42. Black RM, Tanaka P, Leiter LA, Anderson GH. Soft drinks with aspartame: effect on subjective hunger, food selection, and food intake of young adult males. Physiol Behav. 1991;48:803–10.
43. Blackburn GL, Kanders BS, Lavit FT, Keller SD, Whatley J. The effect of aspartame as part of a multidisciplinary weight-control program on short- and long-term control of body weight. Am J Clin Nutr. 1997;65:409–18.
44. Canty DJ, Chan MM. Effects of consumption of caloric vs noncaloric sweet drinks on indices of hunger and food consumption in normal adults. Am J Clin Nutr. 1991;53:119–64.
45. Drewnowski A, Massen C, Louis-Sylvestre J, Fricker J, Chapelot D, Apfellbaum M. Comparing the effects of aspartame and sucrose on motivational ratings, taste preferences, and energy intakes in humans. Am J Clin Nutr. 1994;59:338–45.
46. Raben A, Moller BK, Flint A, Vasilas TH, Moller AC, Holst JJ, Astrup A. Increased postprandial glycaemia, insulinaemia, and lipidaemia after 10 weeks’ sucrose-rich diet compared to an artificially sweetened diet: a randomised controlled trial. Nutr Food Res. 2011;55.
47. Reid SJ, Hamersley R, Hill AJ, Skidmore P. Long-term dietary compensation for added sugar: effects of supplementary sucrose drinks over a 4-week period. Brit J Nutr. 2007;97:193–203.
48. Rolls BJ, Kim S, Fedoroff IC. Effects of drinks sweetened with sucrose or aspartame on hunger, thirst and food intake in men. Physiol Behav. 1990;48:189–26.
49. Ruyter JC, Olthof MO, Kuiper LJP, Liem G, Siedel JC, Katan MB. Short-term satiety and long-term weight effects of sugars and sugar-sweetened beverages in children. Obesity facts. 2013;3:63.
50. Mattes R. Effects of aspartame and sucrose on hunger and energy intake in humans. Physiol Behav. 1990;47:1037–44.
51. Ryan-Harshman M, Leiter LA, Anderson GH. Phenylnalanine and aspartame fail to alter feeding behavior, mood and arousal in men. Physiol Behav. 1987;39:247–53.
52. Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. Am J Clin Nutr. 1990;51:963–9.
53. Van Wymelbeke V, Beridot-Therond ME, De La Guerciniere V, Fantino M. Influence of repeated consumption of beverages containing sucrose or intense sweeteners on food intake. Eur J Clin Nutr. 2004;58:154–61.
54. Wilson JF. Lunch eating behavior of preschool children. Effects of age, gender, and type of beverage served. Physiol Behav. 2000;70:227–33.
55. Wilson JF. Does type of milk beverage affect lunchtime eating patterns and food choice by preschool children? Appetite. 1994;23:90–2.
56. Cullen M, Nolan J, Cullen M, Monoloy M, Keamey J, Lamb L, Gibney MJ. Effect of high levels of intense sweetener intake in insulin dependent diabetics on the ratio of dietary sugar to fat: a case-control study. Eur J Clin Nutr. 2004;58:1336–41.
171. Taheri S. To study the significance of dietary trigger factors and their exclusion in the aetiology and treatment of childhood headache disorders. Cephalalgia. 2011;31:202.

172. Lindsen GH, Coolahan SE, Petrov TV, Lindseth PD. Neurobehavioral effects of aspartame consumption. Res Nurs Health. 2014;37:185–93.

173. Guo X, Park Y, Freedman ND, Sinha R, Hollenbeck AR, Blair A, Chen H. Sweetened beverages, coffee, and tea and depression risk among older US adults. PLoS One. 2014;9:e94715.

174. Walton RG, Hudak R, Green-Walke RJ. Adverse reactions to aspartame: double-blind challenge in patients from a vulnerable population. Biol Psychiatry. 1993;34:13–7.

175. Baker FM, Jordan B, Barclay L, Schoenberg BS. Risk factors for clinically diagnosed Alzheimer's disease. Int J Geriatr Psychiatry. 1993;8:379–85.

176. Halldorsson TI, Strøm M, Petersen SB, Olsen SF. Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women. Am J Clin Nutr. 2010;92:2626–33.

177. Englund-Ogge L, Brantsaeter AL, Haugen M, Sellgpiel V, Khatibi A, Myhre R, Mykling S, Melzer HM, Kacerovsky M, Nilsen RM, Jacobsson B. Association between intake of artificially sweetened and sugar-sweetened beverages and preterm delivery: a large prospective cohort study. Am J Clin Nutr. 2012;96:552–9.

178. Petherick ES, Goran MI, Wright J. Relationship between artificially sweetened and sugar-sweetened cola beverage consumption during pregnancy and preterm delivery in a multi-ethnic cohort: analysis of the born in Bradford cohort study. Eur J Clin Nutr. 2014;68:404–7.

179. Kline J, Stein ZA, Susser M, Watanbour D. Spontaneous abortion and the use of sugar substitutes (saccharin). Am J Obstet Gynecol. 1978;130:708–11.

180. Pereira MA. Sugar-sweetened and artificially-sweetened beverages in relation to obesity risk. Adv Nutr. 2014;5:797–808.

181. Miller PE, Perez V. Low-calorie sweeteners and body weight and adolescent body weight. N Engl J Med. 2012;367:1407–14.

182. Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Rodrigo Y. Effect of decreasing the consumption of sweetened caloric and non-caloric beverages on weight, body composition and blood pressure in young adults. Eur J Prev Cardiol. 2013;1:5120.

183. Peters JC, Beck J, Cardel M, Wyatt HR, Foster GD, Pan Z, Wojtanowski AC, Vander Veur SS, Herring SJ, Brill C, Hill JO. The effects of water and non-nutritive sweetened beverages on weight loss and weight maintenance: a randomized clinical trial. Obesity. 2016;24:297–304.

184. Marisela Vazquez Duran M, Castillo Martinez L, Orea Tejada A, Tellez Olvera DA, Delgado Perez LG, Marquez Zepeda B, Pineda Juarez JA, Lopez Rodriguez Y. Effect of decreasing the consumption of sweetened caloric and non-caloric beverages on weight, body composition and blood pressure in young adults. Eur J Prev Cardiol. 2013;1:5120.

185. Raben A, Moller AC, Vasilas TH, Astrup A. A randomized 10 week trial of sucrose vs artificial sweeteners on body weight and blood pressure after 10 weeks [abstract]. Obes Res. 2001;9:896s.

186. Reid M, Hammersley R, Duffy M. Effects of sucrose drinks on macronutrient intake, body weight, and mood state in overweight women over 4 weeks. Appetite. 2010;55:130–6.

187. Reyna NY, Cano C, Bermúdez VJ, Medina MT, Souki AJ, Ambard M, Nuñez M, Ferrer MA, Inglett GE. Sweeteners and beta-glucans improve metabolic and anthropometrics variables in well controlled type 2 diabetic patients. Am J Ther. 2003;10:438–43.

188. Rodearmel SJ, Wyatt HR, Stroebel N, Smith SM, Ogden LG, Hill JO. Small changes in dietary sugar and physical activity as an approach to preventing excessive weight gain: the America on the move family study. Obes Res. 2007;15:869–79.

189. Sørensen LB, Vasilas TH, Astrup A, Raben A. Sucrose compared with artificial sweeteners: a clinical intervention study of effects on energy intake, appetite, and energy expenditure after 10 wk of supplementation in overweight subjects. Am J Clin Nutr. 2014;100:363–45.

190. Williams CL, Strobinova BA, Brotanek J. Weight control among obese adolescents: a pilot study. Int J Food Sci Nutr. 2007;58:217–30.

191. French SA, Sherwood NE, Jaffa MM, Haapala J, Ebbeling CB, Ludwig DS. Physical changes in the home environment to reduce television viewing and sugar-sweetened beverage consumption among 5- to 12-year-old children: a randomized pilot study. Pediatric Obesity. 2016;11:e12–e5.

192. Markey O, Le Jeune J, Lovegrove JA. Energy compensation following consumption of sugar-reduced products: a randomized controlled trial. Eur J Nutr. 2016;55:2137–49.

193. Kari EN, Landis G, Pavalka A, Lambrou G, Mantzou E, Androutsakis I, Giannakou A, Panapiploou E, Chrousos GP. Long-term effects of stevia rebaudiana on glucose and lipid profile, adipokines, markers of inflammation and oxidation status in patients with metabolic syndrome. Endocr Dev. 2016;37.

194. Vazquez-Duran M, Orea-Tejada A, Castillo-Martinez L, Cano-Garcia A, Tellez-Olvera L, Leims-Davis C A. A randomized control trial for reduction of caloric and non-sweetened beverages in young adults: effects in weight, body composition and blood pressure. Nutr Hosp. 2016;33:1372–8.

195. Shin DH, Lee JH, Kang MS, Kim TH, Jeong SJ, Kim CH, Kim SS, Kim U. Glycemic effects of rebaudioside a and erythritol in people with glucose intolerance. Diabetes Metab J. 2016;40:283–9.

196. Berkley CS, Rockett HR, Field AE, Gillman MW, Colditz GA. Sugar-added beverages and adolescent weight change. Obes Res. 2004;12:778–88.

197. Chen L, Appel LJ, Loria C, Champagne CM, Elmer PJ, Ard JD, Mitchell D, Batch BC, Svetkey LP, Caggiula AR, Cappo PD. Reduction in consumption of sugar-sweetened beverages is associated with weight loss: the PREMIER randomized controlled trial. Am J Clin Nutr. 2009;89:1299–306.

198. Colditz GA, Willett WC, Stampfer MJ, Spiegelman D, Manson JE, Colditz GA. Sugar-added beverages and adolescent weight change. Obes Res. 2002;10:326–36.

199. Fowler SP, Williams K, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. Obes Res. 2000;8:161894–900.

200. Jackson CL, Treadway MD, Stensland LD, Stalling YM, Moore RM, Faith MS. Beverage consumption patterns of children born at different risk of obesity. Pediatrics. 2008;161:1802–8.

201. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. Lancet. 2001;357:505–8.
260. Gregersen S, Jeppesen PB, Holt JI, Hermansen K. Antihyperglycemic effects of stevioside in type 2 diabetic subjects. Metab Clin Exp. 2004;53:73–6.

261. Ritu M, Nandini J. Nutritional composition of Stevia Rebaudiana, a sweet herb, and its hypoglycaemic and hypolipidemic effect on patients with non-insulin dependent diabetes mellitus. J Sci Food Agric. 2016;96:4231–4.

262. Kassi E, Landis G, Pavlaki A, Lambrou G, Mantzou E, Andreoukis I, Giannakou A, Papankolou E, Chrousos GP. Acute effects of stevia rebaudiana extract on postprandial glucose metabolism in patients with metabolic syndrome. Endocr Rev. 2016;37.

263. Raben A, Vasilas TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. In Clin Nutr. 2016;35:2022-2031.

264. Chan P, Tomlinson B, Chen YJ, Liu JC, Hsieh MH, Cheng JT. A double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension. Br J Clin Pharmacol. 2000;50:215–20.

265. Memon M, MacDonald I, Bennett T. Effect of mental stress on cardiovascular function at rest and after ingestion of fructose or sucralose in healthy, white European males. Turku J Med Sci. 2013;43:913–8.

266. Ferri LAF, Alves-Do-Prado W, Yamada SS, Gazola S, Batista MR, Bazotte RB. Effects of steviol glycosides on cardiac and cerebrovascular function in a young healthy population. J Clin Nutr. 2013 Dec;98(6):1599. Am J Clin Nutr. 2013;95:555–63.

267. Borkum JM. Migraine triggers and oxidative stress: a narrative review and primer for gastroenterologists. J Neurogastroenterol Motil. 2016;22:168–80.

268. Urban JD, Carakostas MC, Taylor SL. Steviosol glycoside safety: are highly purified steviosol glycoside sweeteners food allergens? Food Chem Toxicol. 2015;75:71–8.

269. Wang DD, Shams-White M, Bright DJ, Parrott JS, Chung M. Creating a literature database of low-calorie sweeteners and health studies: evidence mapping. BMC Med Res Methodol. 2016;16:1.

270. Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. Arch Int Med. 2008;163:847–92.

271. Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K, Nagasawa S, Morikawa Y, Iwashita M, Kido T, Naruse Y, et al. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men. Eur J Nutr. 2014;53:251–8.

272. Nandini J, Ritu M, Niu X, Verheggen P, Aiyer S, Panigrahi SK, Renwick AG. Caffeine and theanine present in tea reduce sex differences in blood glucose regulation. Crit Rev Food Sci Nutr. 2016;56:541–51.

273. Kassi E, Landis G, Pavlaki A, Lambrou G, Mantzou E, Andreoukis I, Giannakou A, Papankolou E, Chrousos GP. Acute effects of stevia rebaudiana extract on postprandial glucose metabolism in patients with metabolic syndrome. Endocr Rev. 2016;37.

274. Ritu M, Nandini J. Nutritional composition of Stevia Rebaudiana, a sweet herb, and its hypoglycaemic and hypolipidemic effect on patients with non-insulin dependent diabetes mellitus. J Sci Food Agric. 2016;96:4231–4.

275. Borkum JM. Migraine triggers and oxidative stress: a narrative review and primer for gastroenterologists. J Neurogastroenterol Motil. 2016;22:168–80.

276. Urban JD, Carakostas MC, Taylor SL. Steviosol glycoside safety: are highly purified steviosol glycoside sweeteners food allergens? Food Chem Toxicol. 2015;75:71–8.

277. Wang DD, Shams-White M, Bright DJ, Parrott JS, Chung M. Creating a literature database of low-calorie sweeteners and health studies: evidence mapping. BMC Med Res Methodol. 2016;16:1.

278. Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. Arch Int Med. 2008;163:847–92.

279. Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K, Nagasawa S, Morikawa Y, Iwashita M, Kido T, Naruse Y, et al. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men. Eur J Nutr. 2014;53:251–8.

280. Grenby TH. Dental plaque, dental caries and sugar intake. The effects on the plaque of a low-calorie sweetener used in beverages in place of ordinary sugar. Brit Dent J. 1975;139:129–34.

281. Serra-Majem L, Garcia Glosas R, Ramon JM, Manau C, Cuenca E, Krasse B. Dietary habits and dental caries in a population of Spanish schoolchildren with low levels of caries experience. Caries Res. 2003;37:488–94.

282. Serra-Majem L, Bassas L, Garcia-Glosas R, Ribas L, Ingles C, Casals I, Saavedra P, Renwick AG. Cyclic amine intake and cycloexyamine excretion are not related to male fertility in humans. Food Addit Contam. 2003;20:1097–104.

283. Petersen SB, Rasmussen MA, Olsen SF, Vestergaard P, Mølgaard C, Haldorsen TI, Strom M. Maternal dietary patterns during pregnancy in relation to offspring forearm fractures: prospective study from the Danish National Birth Cohort. Nutrients. 2015;7:2382–400.

284. Samant SS, Wilkes K, Odek Z, Seo HS. Tea-induced calmness: sugar-sweetened tea calms consumers exposed to acute stressor. Sci Rep. 2016;6:36537.

285. Thakkar P, Arora K, Goyal K, Das RR, Javadekar B, Ayer S, Panigrahi SK. To evaluate and compare the efficacy of combined sucrose and non-nutritive sucking for analgesia in newborns undergoing minor painful procedure: a randomized controlled trial. J Perinatol. 2016;36:67–70.

286. Pagani-Hill A, Kavas CH, Corrada MM. Non-alcoholic beverage and caffeine consumption and mortality: the leisure world cohort study. Prev Med. 2007;44:305–10.