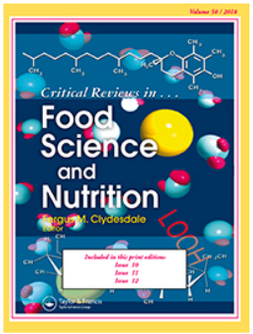

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Metabolic effects of aspartame in adulthood: A systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Data about harms or benefits associated with the consumption of aspartame, a nonnutritive sweetener worldwide consumed, are still controversial. This systematic review and meta-analysis of randomized controlled clinical trials aimed to assess the effect of aspartame consumption on metabolic parameters related to diabetes and obesity. The search was performed on Cochrane, LILACS, PubMed, SCOPUS, Web of Science databases, and on a gray literature using Open Grey, Google Scholar, and ProQuest Dissertations & Theses Global. Searches across all databases were conducted from the earliest available date up to April 13, 2016, without date and language restrictions. Pooled mean differences were calculated using a random or fixed-effects model for heterogeneous and homogenous studies, respectively. Twenty-nine articles were included in qualitative synthesis and twelve, presenting numeric results, were used in meta-analysis. Fasting blood glucose (mmol/L), insulin levels (μU/mL), total cholesterol (mmol/L), triglycerides concentrations (mmol/L), high-density lipoprotein cholesterol (mmol/L), body weight (kg), and energy intake (MJ) were considered as the main outcomes in subjects that consumed aspartame, and results were presented as mean difference; % confidence interval, range. Aspartame consumption was not associated with alterations on blood glucose levels compared to control (−0.03 mmol/L; 95% CI, −0.21 to 0.14) or to sucrose (0.31 mmol/L; 95% CI, −0.05 to 0.67) and on insulin levels compared to control (0.13 μU/mL; 95% CI, −0.69 to 0.95) or to sucrose (2.54 μU/mL; 95% CI, −6.29 to 11.37). Total cholesterol was not affected by aspartame consumption compared to control (−0.02 mmol/L; 95% CI, −0.31 to 0.27) or to sucrose (−0.24 mmol/L; 95% CI, −0.89 to 0.42). Triglycerides concentrations were not affected by aspartame consumption compared to control (0.00 mmol/L; 95% CI, −0.04 to 0.05) or to sucrose (0.00 mmol/L; 95% CI, −0.09 to 0.09). High-density lipoprotein cholesterol serum levels were higher on aspartame compared to control (−0.03 mmol/L; 95% CI, −0.06 to −0.01) and lower on aspartame compared to sucrose (0.05 mmol/L; 95% CI, 0.02 to 0.09). Body weight did not change after aspartame consumption compared to control (5.00 kg; 95% CI, −1.56 to 11.56) or to sucrose (3.78 kg; 95% CI, −2.18 to 9.74). Energy intake was not altered by aspartame consumption compared to control (−0.49 MJ; 95% CI, −1.21 to 0.22) or to sucrose (−0.17 MJ; 95% CI, −2.03 to 1.69). Data concerning effects of aspartame on main metabolic variables associated to diabetes and obesity do not support a beneficial related to its consumption.

KEYWORDS

Aspartame; blood glucose; insulin; energy intake; lipid profile; systematic review; meta-analyze

Abbreviations: ADA: American Dietetic Association; ALA: alanine; APM, aspartame; BDD: Balanced Deficit Diet; BMI: body mass index; CI, confidence interval; CMW: carbonated mineral water; DSD: diet soft drink; FDA: Food and Drug Administration; GRADE: Grading of Recommendation Assessment Development, and Evaluation; HbA1c: glycated hemoglobin; HDL-c: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model of assessment insulin resistance; IGT: impaired glucose tolerance; LDL: low-density lipoprotein; NGT: normal glucose tolerance; PHE: phenylalanine; PICOS: Population, Intervention, Comparison, Outcome, Study design; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SD: standard deviation; RCTs: randomized clinical trials

Background

Aspartame (L-aspartyl-L-phenylalanine methyl ester) was discovered in 1965 by James Schlatter and approved for use in foods by Food and Drug Administration (FDA) in 1981. It is a noncaloric sweetener composed by two amino acids, phenylalanine (50%), and aspartic acid (40%), linked to a methanol molecule (10%) (Humphries et al., 2008). Aspartame is a compound 200 times sweeter than sugar, considered as a low-calorie sweetener (4 kcal/g), that is consumed by over 200 million people around the world and it is used in over 6,000 products, such as soft drinks, yoghurts, and pharmaceuticals (Grembecka

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and Szefer, 2012). Unlike other sweeteners, aspartame can be rapidly metabolized in the human body by esterases and peptidases. The absorption of metabolites occurs in the lumen of the gastrointestinal tract followed by entry into systemic circulation (Magnuson et al., 2007; Yang, 2010; Mourad and Noor, 2011). According to the American Dietetic Association (ADA), the use of artificial sweeteners such as aspartame can bring benefits to consumers, for example, by reducing the caloric intake and aid in the control of chronic diseases as diabetes and obesity (Whitehouse et al., 2008).

Obesity is characterized as abnormal or excessive fat accumulation that can be directly related to the intake of high calorie diets and high-glycemic index foods (Roberts, 2015). The consumption of these foods can cause an increase on glucose levels and postprandial insulin (Anton et al., 2010). It was reported in a meta-analysis of prospective cohort studies that increased body mass index (BMI) and abdominal circumference is closely associated with diabetes type 2 as well as with metabolic syndrome (Guh et al., 2009; Swithers, 2013).

Many studies have been conducted in order to make the association between the consumption of sugar-sweetened beverages or foods and the risk of overweight and the development of obesity in adults, since it is known that sugar is able to promote an increase in carbohydrate absorption rate, which leads to an excessive increase in energy intake and weight gain (Basu et al., 2014; Schulze et al., 2004; Saris and Tarnopolsky, 2003). De la Hunty et al. showed that aspartame consumption was effective to reduce energy intake and to maintain or lose weight (De la Hunty et al., 2006). On the other hand, some epidemiological studies suggest that the attempt to change the eating habits, with the inclusion of low-calorie or no-calorie sweeteners in the diet, is not playing a crucial role in reducing rates of obesity and overweight, which continue to grow in populations worldwide (Yang, 2010). Rogers et al. performed a systematic review of animal studies, human observational and human interventions studies to joint information about the impact of low-energy sweeteners (LES) consumption on energy intake (EI) and body weight (BW) and reached the conclusion that the consumption of LES instead of sugar is associated with a decrease on EI and BW (Rogers et al., 2016). When different kinds of LES are considered together, there is a positive association between its consumption and reduced values of EI and BW (Rogers et al., 2016). However, there is no evidence that these effects occur when each kind of LES is considered individually. Besides, there is the need to show the effects of sweeteners not only in relation to EI and BW, but also its effects on other parameters that are important to be considered when the concern is diabetes and obesity. Therefore, this systematic review aims to evaluate and summarize information of randomized clinical trials (RCTs) performed with subjects who consumed aspartame to analyze its influence on clinical parameters related to diabetes and obesity.

Methods

Protocol and registration

This systematic review was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Checklist (Moher et al., 2010). The review protocol was registered at the International Prospective Register of Systematic Reviews PROSPERO (registration number: CRD42016038073).

Eligibility criteria

A systematic review of RCTs was undertaken to summarize studies that evaluate the metabolic effects of aspartame consumption on adulthood.

Inclusion criteria

Studies conducted in order to analyze the consequence of aspartame consumption in some metabolic aspects, such as glycemic control and obesity, of adults were included. Only studies published in Latin (Roman) alphabet were accepted. The search was conducted without time and language restrictions. The PICOS (population, intervention, comparison, outcome, study design) format was used to construct the research question with the following inclusion criteria: (i) population: adults who consume aspartame; (ii) intervention: consumption of aspartame; (iii) comparison: adults who did not consume aspartame; (iv) primary outcome: glycemic control (blood glucose levels), obesity (BMI, fat mass); (v) secondary outcome: glycemic control (glucose tolerance test, homeostatic model of assessment insulin resistance [HOMA-IR], hyperglycemia and glycated hemoglobin [HbA1c]), obesity (overweight, energy intake, HDL-c, low-density lipoprotein [LDL], triglycerides); (vi) study design: RCTs.

Exclusion criteria

The following exclusion criteria were applied: (1) studies that did not fit PICOS strategy; (2) reviews, letters, personal opinions, book chapters, and conference abstracts; (3) studies that full paper copy were not available.

Information sources and search strategies

A criteria search was performed using the following electronic bibliographic databases: Cochrane, LILACS, PubMed, Scopus and Web of Science. A gray literature search was performed using Open Grey, Google Scholar and ProQuest Dissertations & Theses Global. More information regarding the search strategies is provided in Appendix Table 1 in Supplemental File 1. In addition, reference lists of selected articles were hand screened for potential relevant studies that could have been missed during the electronic database searches. Searches across all databases were conducted from the earliest available date up to April 13, 2016. Duplicated references were removed by reference manager software (EndNote®, Thomson Reuters). Furthermore, the references were manually curated to remove further remained duplicated references.

Study selection

Articles were selected in two phases. In phase 1, two reviewers independently (NCS and LMA) reviewed the titles and

abstracts of all identified electronic database citations. A third author (MSC) was involved when required to make a final decision. Any studies that appeared not to fulfill the inclusion criteria were discarded. In phase 2, the same selection criteria were applied to the full articles to confirm their eligibility, what was evaluated by the same two reviewers (NCS and LMA) independently. Any disagreement in either phase was resolved by discussion and mutual agreement between the three reviewers. Final selection was always based on the full-text of the publication.

Data collection process

The data were extracted independently by two reviewers (NCS and LMA) and disagreements were solved by consensus or by a third reviewer (MSC). Data extracted from eligible articles included name of first author, publication year, country, study design, samples size, demographic characteristics of the participants, outcome measures, results, and key conclusions.

Risk of bias in individual studies

To assess the risk of bias of the included RCTs, it was applied the Cochrane Collaboration Risk of Bias Tool (Higgins et al., 2011). Study quality assessment included adequate random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, selective reporting and other sources of bias. The risk of bias was assessed as low, high or unclear. The risk of bias was independently evaluated by two reviewers (NCS and LMA) and disagreements were solved by consensus or by a third reviewer (MSC).

Summary measures

Fasting blood glucose levels (mmol/L), body weight (Kg), energy intake (MJ) and insulin (μU/mL), cholesterol (mmol/L), HDL (mmol/L), triglyceride concentrations (mmol/L), were considered as the main outcomes in subjects that consumed aspartame. The values of mean $\pm$ standard deviation were considered for each outcome.

Synthesis of results

The influence of aspartame consumption on the outcomes was evaluated through a meta-analysis following the appropriate Cochrane Guidelines (Deeks et al., 2011). Review Manager® 5.2 program (Rev-Man 5.2, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to construct the forest plots as part of the meta-analysis.

Risk of bias across studies

Clinical heterogeneity (by comparing variability among the participant's characteristics and outcomes studied), methodological heterogeneity (by comparing the variability in study design and risk of bias), and statistical heterogeneity were considered.

Confidence in cumulative evidence

The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) instrument (Balshem et al., 2011; Schünemann et al., 2013) assessed evidence quality and grading of recommendation strength in the 12 studies included in quantitative synthesis. This assessment was based on study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. Evidence quality was characterized as high, moderate, low, or very low instrument. The GRADE was assessed using its website (Balshem et al., 2011; Schünemann et al., 2013).

Results

Study selection

The exhaustive review included 1,367 articles identified across the five databases. After removing the duplicates, 1,050 articles remained. Out of them, 979 were excluded after a comprehensive assessment of the title and the abstract. The first hundred references obtained from Google Scholar search were chosen by title and abstracts examination. Two articles were included from Google Scholar search and four additional articles were identified from the reference lists of the selected studies and were allocated to in-depth review. Consequently, 77 full-text manuscripts have been extensively reviewed of which 29 have been considered of interest for descriptive analysis. Twelve of them presented enough numerical data with standard deviation to be used in meta-analysis. A flow chart detailing the process of identification, inclusion, and exclusion of the studies is shown in Figure 1 and Appendix Table 2 in Supplemental File 1.

Study characteristics

The 29 RCTs included were published in English. Seventeen of the 29 included studies were published before the 2000s (Black et al., 1991; Black et al., 1993; Blackburn et al., 1997; Bruce et al., 1987; Colagiuri et al., 1989; Horwitz et al., 1988; Kanders et al., 1988; Lapierre et al., 1990; Lavin et al., 1997; Leon et al., 1989; Melanson et al., 1999; Moller, 1991; Nehrling et al., 1985; Rodin, 1990; Ryan-Harshman et al., 1987; Singleton et al., 1999; Stern et al., 1976), and the other 12 were published after the year 2000 (Bryant et al., 2014; Coppola et al., 2004; Flood et al., 2006; Kuzma et al., 2015; Maersk et al., 2012a; Maersk et al., 2012b; Reid et al., 2007; Sathyapalan et al., 2015; Siegler et al., 2012; Smeets et al., 2005; Steinert et al., 2011; Temizkan et al., 2015).

Six of the studies presented a group that consumed aspartame and another group that consumed glucose, sucrose, or other kind of sweetener (Blackburn et al., 1997; Bryant et al., 2014; Colagiuri et al.,1989; Coppola et al., 2004; Kuzma et al., 2015; Reid et al., 2007), 12 studies compared groups which consumed aspartame or a control substance (water or placebo without sweetener or sugar) (Black et al., 1991; Black et al., 1993; Bruce et al., 1987; Kanders et al., 1988; Lapierre et al., 1990; Leon et al., 1989; Moller, 1991; Nehrling et al., 1985; Ryan-Harshman et al., 1987; Sathyapalan et al., 2015; Stern

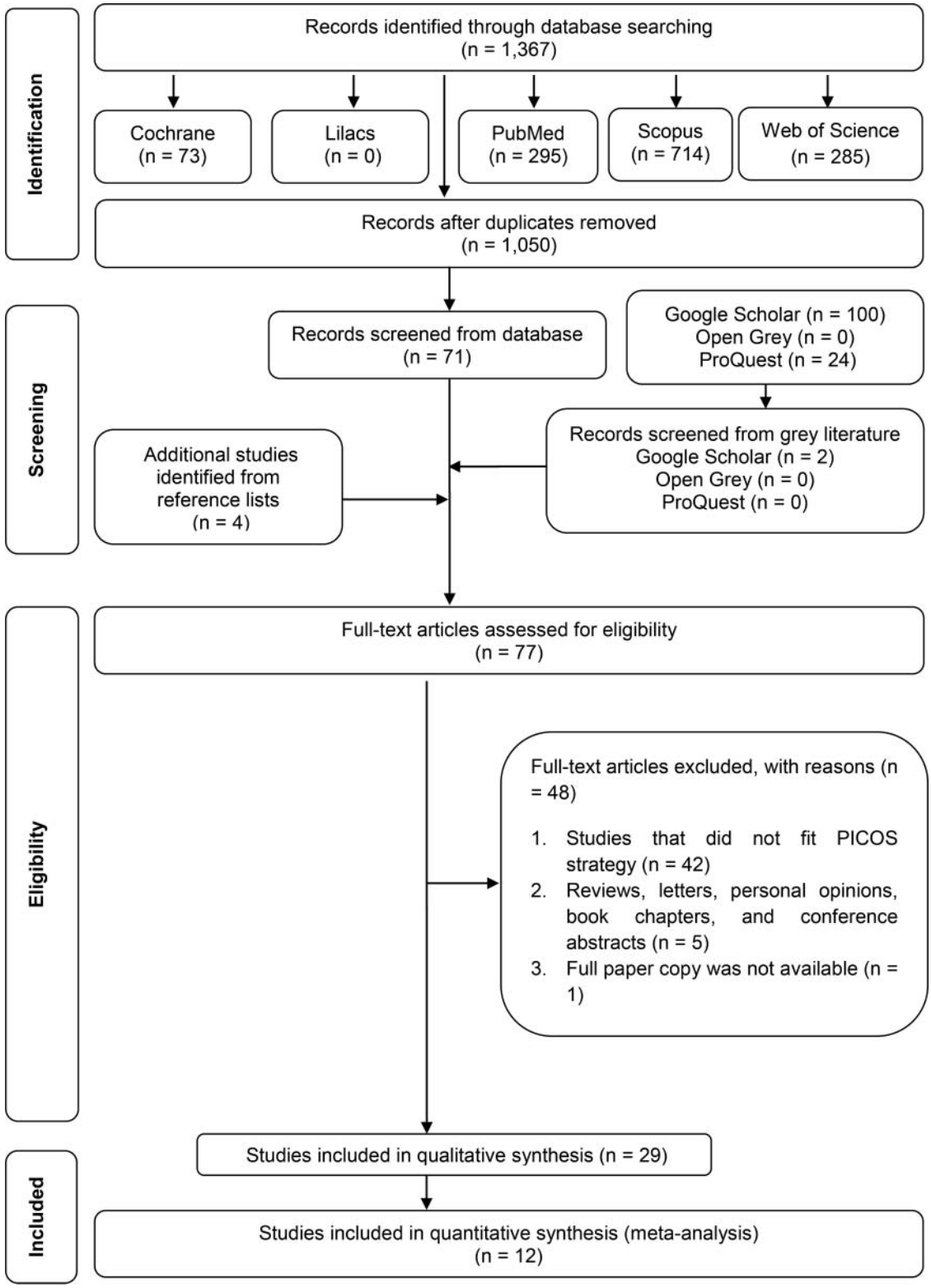

Figure 1. Flow diagram of literature search and selection criteria. Adapted from PRISMA (Moher et al., 2010).

et al., 1976), and 11 studies presented groups that consumed either aspartame, or a kind of sweetener or a control substance (Flood et al., 2006; Horwitz et al., 1988; Lavin et al., 1997; Maersk et al., 2012a; Maersk et al., 2012b; Rodin, 1990; Siegler et al., 2012; Singleton et al., 1999; Smeets et al., 2005; Steinert et al., 2011; Temizkan et al., 2015). All of the studies reported leastwise one of the outcomes described as a primary or secondary outcome at PICOS strategy. Together, the included studies had a total of 1,044 participants. Nineteen trials were performed exclusively in healthy participants (Black et al., 1991; Black et al., 1993; Bruce et al., 1987; Bryant et al., 2014; Coppola et al., 2004; Flood et al., 2006; Kuzma et al., 2015; Lapierre et al., 1990; Lavin et al., 1997; Leon et al., 1989; Melanson et al., 1999; Moller, 1991; Reid et al., 2007; Ryan-Harshman

et al., 1987; Sathyapalan et al., 2015; Siegler et al., 2012; Singleton et al., 1999; Smeets et al., 2005; Steinert et al., 2011), whereas one trial was conducted in healthy and overweight participants (Rodin, 1990), four trials were conducted in overweight or obese participants (Blackburn et al., 1997; Kanders et al., 1988; Maersk et al., 2012a; Maersk et al., 2012b), two trials were conducted in healthy and diabetic participants (Horwitz et al., 1988; Temizkan et al., 2015), and three trials were conducted with insulin-dependent diabetes mellitus or noninsulin-dependent diabetes mellitus participants (Colagiuri et al., 1989; Nehrling et al., 1985; Stern et al., 1976). A summary of the descriptive characteristics for the included studies is depicted in Table 1.

Risk of bias within studies

Among the 29 included studies, six presented low risk of bias at random sequence generation, 21 were classified as unclear, and two were classified as high risk of bias. Considering allocation concealment, eight studies presented low risk of bias, 21 were classified as unclear or with a high risk of bias, respectively. In relation to blinding of participants and personnel, 15 presented low risk of bias at random sequence generation, 11 were classified as unclear and 3 were classified as high risk of bias. Two of studies were classified as low risk of bias and 27 were classified as unclear at blinding of outcome data. All studies were classified as low risk of bias in relation to incomplete outcome data and selective reporting. Seven of studies presented low risk of other sources of bias and 22 were classified as unclear (Fig. 2) according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials criteria (Appendix Table 3 in Supplemental File 1). The risk of bias summary, according to judgments of the review authors about each risk of bias item for each included study is shown in Appendix Figure 1 in Supplemental File 2.

Results of individual studies

Nine studies showed no significant effect of aspartame consumption on blood glucose or in insulin values in normal healthy subjects (Bruce et al., 1987; Bryant et al., 2014; Coppola et al., 2004; Lapierre et al., 1990; Moller, 1991; Sathyapalan et al., 2015; Singleton et al., 1999; Smeets et al., 2005; Steinert et al., 2011). Studies that compared healthy participants with subjects with diabetes mellitus showed no adverse changes in blood glucose concentration after aspartame consumption (Colagiuri et al., 1989; Horwitz et al., 1988; Nehrling et al., 1985; Temizkan et al., 2015). Conversely, one study showed different changes on blood glucose levels after aspartame ingestion with a decline in 40% of subjects, increases in 20%, or stability in 40% (Melanson et al., 1999). Decrease on blood glucose levels were shown by Moller study (Moller, 1991). Siegler et al. showed that aspartame consumed with carbohydrate lowered insulin levels during exercise when compared to consumption of carbohydrate alone (Siegler et al., 2012). Six studies did not show changes in energy intake of subjects who consumed aspartame (Black et al., 1991; Black et al., 1993; Flood et al., 2006; Maersk et al., 2012a; Rodin, 1990; Ryan-Harshman et al., 1987).

Results of one study showed that aspartame consumption was positively correlated with weight loss and helped in the long-term maintenance of reduced body weight in obese women that participated of a weight-control program (Blackburn et al., 1997). In other study, overweight or obese participants who consumed hypocaloric diet plus aspartame presented a higher weight loss when compared to control group that consumed only hypocaloric diet (Kanders et al., 1988). One study found that acute ingestion of aspartame does not have any detectable metabolic effects in humans (Sathyapalan et al., 2015). Maersk et al. showed that the effect of a beverage sweetened with aspartame on fatness, ectopic fat, and metabolic factors is mainly neutral and very similar to that of water (Maersk et al., 2012b). Leon et al. and Stern et al. did not find difference in mean body weight of participants who ingested aspartame compared to control groups that ingested placebo (Leon et al., 1989; Stern et al., 1976). Only one study showed an increase in energy intake after aspartame consumption when compared with control groups that received sucrose or carbonated mineral water (Lavin et al., 1997).

Synthesis of results

Meta-analysis was conducted with data from articles where participants consumed aspartame compared to a control group that received water or placebo without sweetener or sugar, or consumed aspartame compared to a sucrose group. Studies that showed results in graph or did not show standard deviation values were excluded from meta-analysis as well as studies that presented results measured by area under the curve due the difference of times considered in the measurement. The forest plots were constructed for consumption of aspartame *versus* control (Fig. 3) and consumption of aspartame *versus* sucrose (Fig. 4).

Twelve studies had enough data to be included in the quantitative analysis (meta-analysis) (Black et al., 1991; Blackburn et al., 1997; Bruce et al., 1987; Colagiuri et al., 1989; Lavin et al., 1997; Maersk et al., 2012a; Maersk et al., 2012b; Melanson et al., 1999; Reid et al., 2007; Ryan-Harshman et al., 1987; Sathyapalan et al., 2015; Siegler et al., 2012) (Figs. 3 and 4). Eight of the studies included in meta-analysis were conducted with healthy subjects (Black et al., 1991; Bruce et al., 1987; Lavin et al., 1997; Melanson et al., 1999; Reid et al., 2007; Ryan-Harshman et al., 1987; Sathyapalan et al., 2015; Siegler et al., 2012), whereas three of them were conducted with overweight or obese subjects (Blackburn et al., 1997; Maersk et al., 2012a; Maersk et al., 2012b) and one was conducted with noninsulin-dependent diabetes mellitus subjects (Colagiuri et al., 1989). The studies were grouped and the meta-analysis was performed individually for each metabolic parameter.

Fasting blood glucose levels results showed moderate heterogeneity between studies with an inconsistency (I^2) of 68%. There was no significant difference between the group that consumed aspartame compared to control group ($p = 0.71$, $n = 119$) (Fig. 3A). For comparison between consumption of aspartame or sucrose there was a moderate heterogeneity with an I^2 of 56%. There was no difference between the group that

Table 1. Summary of descriptive characteristics of included articles ($n = 29$).

First Author, Year, Country	Study Design	Sample size, Gender, Age	Population Mean or Range of BMI (kg/m^2)	Intervention	Main outcomes to APM consumption	Main conclusion
Black, 1991; Canada	RCT	20 healthy men; age: 19–25 years	22–29	(1) 280 mL of CMW; (2) 280 mL DSD (160–170 mg APM)	(1) Food intake: no difference between all preload types	The consumption of aspartame-sweetened beverages did not increase short-term subjective hunger or food intake
Black, 1993; Canada	RCT	18 men; age: 19–25 years	21–25	(1) 280 mL of CMW; (2) 280 mL of CMW with 340 mg of encapsulated APM; (3) 560 mL of CMW; (4) 560 mL of an APM-sweetened soft drink (340 mg APM)	(1) Total caloric intake: consuming 340 mg APM as a sweetener significantly increased all four measures of subjective hunger and subjective appetite	APM treatment does not have a significant effect on total caloric intake at the lunchtime meal
Blackburn, 1997; United States	Stratified, two-arm, open parallel design	APM group 82 obese women; age: 42.5 ± 9.3[1] No APM group; 81 obese women; age: 43.0 ± 10.2	APM group (37.4 ± 5.1) No APM group (37.2 ± 4.6)	(1) Food and drinks sweetened with APM; (2) use of sugar or honey as sweetener	(1) Body weight: mean weight loss of 5.1 kg (5.1%)	APM facilitated long-term maintenance of a reduced body weight and a greater weight loss in a weight-control program
Bruce, 1987; Australia	RCT	Seventeen healthy normal subjects; age: 19 to 32 years	—	Study 1: dextrose; study; (2) noncaloric artificial sweetener APM + dextrose or water + dextrose; study; (3) APM or water.	(1) Blood glucose: no significant changes (Study 1 and Study 3) and decrease (Study 2); (2) plasma insulin levels: no significant changes (Study 1 and Study 3) and increase (Study 2)	The administration of APM alone had no effect on blood glucose or serum insulin when compared with water
Bryant, 2014; United Kingdom and United States	RCT	6 men and 4 women; age: 18 to 24 years	21.8 ± 1.8	(1) Glucose; (2) glucose + APM; (3) glucose + saccharin; (4) glucose + acesulfame-K	(1) Blood glucose: no difference between intervention 2 and others	The administration of APM with glucose did not alter glycemic response when compared to glucose alone
Colagiuri, 1989; Australia	Double-blind, cross-over design	8 men and 1 woman noninsulin-dependent diabetes mellitus; age: 66 ± 5	26.4 ± 2.1	(1) APM; (2) sucrose	(1) Blood glucose: no difference compared with pretreatment values; (2) body weight: mean increase of 1.2 kg on eight subjects during the sucrose period, loss of 4 kg on one subject during the APM period; (3) insulin levels: no difference with pretreatment values	APM did not alter blood glucose and insulin levels and has no specific advantage over sucrose when used solely as a sweetening agent
Coppola, 2004; Italy	RCT	10 men and 10 women with (NGT); age: 68 ± 8 and 10 men and 10 women with (IGT); age: 69 ± 1.1	NGT = 26.4 ± 3 IGT = 27 ± 3.6	(1) APM; (2) glucose	(1) Blood glucose levels: no change after APM intake; (2) insulin levels: no change after APM intake	The APM treatment was not able to alter blood glucose and insulin levels
Flood, 2006; United States	Crossover design	18 women; age: 22.0 ± 0.2; and 15 men; age: 23.3 ± 0.3	Women 22.6 ± 0.3 and men 24.4 ± 0.3	(1) Cola; (2) diet cola; (3) water	(1) Energy intake: Increase at lunch for caloric beverage consumption compared with noncaloric beverage	Ingestion of APM sweetened beverages can be an effective strategy for decreasing energy intake
Horwitz, 1988; United States	Crossover design	20 normal subjects; age: 28 ± 8; 10 diabetic subjects; age: 57 ± 8	—	(1) Unsweetened cherry-flavored Kool-Aid; (2) APM; and (3) Saccharin	(1) Glucose levels: no significant changes	Ingestion of APM in the absence of food appears to cause no adverse changes in blood glucose concentration in normal subjects or subjects with noninsulin-dependent diabetes mellitus
Kanders, 1988; United States	Open two arms parallel design	13 men and 46 women; 26.5 to 60.7	Control group: 36–38 and experimental group: 37–38	(1) BDD; (2) BDD + foods and beverages sweetened with APM	(1) Body weight: loss of 1.68 kg in experimental group	APM may facilitate compliance to a hypocaloric diet

Kuzma, 2015; United States	Controlled, double-blind crossover design	10 healthy normal-weight adults; age: 18–25 years	22.7 ± 1.3	(1) APM; (2) fructose; (3) glucose	(1) Body weight: no difference between three diet periods; (2) energy intake: lower in APM period compared with others	APM-sweetened beverages do not alter body weight and decrease energy intake
Lapierre, 1990; United Kingdom	Double-blind, placebo controlled crossover design	6 men and 4 women; age: 26.3	—	(1) Capsules with 300 mg of APM; (2) placebo capsules	(1) Glucose levels: no difference in comparison to placebo	Treatment with APM was not able to significantly alter plasma glucose levels
Lavin, 1997; United Kingdom	RCT	14 healthy normal-weight women	—	(1) APM; (2) sucrose; (3) mineral water	(1) Energy intake: higher when compared with interventions 2 and 3	The replacement of sucrose-sweetened drinks by APM-sweetened drinks does not automatically reduce total energy intake
Leon, 1989; United States	Double-blind, placebo-controlled, parallel-group design	101 healthy; age: 18–62 years	—	(1) Capsules with 300 mg of APM; (2) placebo capsules composed of 300 mg of microcrystalline cellulose and 0.9 mg of silicon dioxide	(1) Body weight: no significant change in the APM group; (2) lipoprotein cholesterol: no significant changes	APM consumption is not associated with any significant changes in clinical measures or adverse experiences in healthy adults
Maersk, 2012; Denmark	Open crossover design	24 subjects overweight or obese; age: 33.5 ± 9.2 years	31.4 ± 3.11	(1) Diet cola; (2) semiskimmed milk; (3) cola; (4) water	(1) Peak glucose concentration: higher after regular cola compared with interventions 1, 2, and 3; (2) insulin levels (AUC): no significant difference between diet cola and water; (3) energy intake: higher after regular cola compared with diet cola and water	APM-sweetened diet cola does not increase appetite or energy intake when compared with water
Maersk, 2012a; Denmark	Open four arms parallel intervention study	47 nondiabetic subjects; age: 20–50 years	26 – 40	(1) Diet cola; (2) cola; (3) semiskim milk; (4) mineral water	(1) Body weight: no significant difference between the four groups; (2) glucose levels: no significant difference between the four groups; (3) insulin levels: no significant difference between the four groups; (4) total fat mass: no significant difference between the four groups	Effect of APM sweetened diet cola on fatness, ectopic fat, and metabolic factors is mainly neutral and very similar to that of water
Melanson, 1999; Netherlands and United States	RCT	10 healthy weight-stable men	23.4 ± 1.9	(1) APM drinks; (2) simple carbohydrate drinks; (3) high-fat drinks	(1) Blood glucose: no difference was found; (2) energy intake: no compensation after APM preload ingestion	APM did not alter blood glucose and did not lead to energy intake compensation after its consumption
Moller, 1991; Denmark	RCT	6 healthy men; age: 22–37	—	(1) APM; (2) bovine albumin; (3) water	(1) Glucose levels: decrease relative to control; (2) insulin levels: not significantly affected	APM consumption by healthy men did not affect plasma insulin but had a significant dose effect on plasma glucose
Nehrling, 1985; United States	Placebo-controlled, double-blind experimental design	62 subjects insulin-dependent or noninsulin-dependent diabetes; age: 18–65	—	(1) Capsules with 300 mg of APM; (2) placebo capsules composed of 200 mg of corn starch	(1) Glucose levels: no difference from placebo treated groups	The use of APM as a low-calorie sweetener does not adversely affect glycemic control of persons with diabetes
Reid, 2007; United Kingdom	Counter-balanced design, one open group, one single-blind group	133 women; age: 31.8 ± 9.1	22.5 ± 2.8	(1) APM drinks; (2) sucrose drinks	(1) Body weight: loss on APM group; (2) energy intake: lower than baseline at week 1 and week 4	APM consumption was related to weight loss and lower energy intake when compared to sucrose drinks consumption

(*Continued on next page*)

Table 1. (*Continued*)

First Author, Year, Country	Study Design	Sample size, Gender, Age	Population Mean or Range of BMI (kg/m^2)	Intervention	Main outcomes to APM consumption	Main conclusion
Rodin, 1990; United States	Completely balanced, within-subjects design	6 normal-weight men, 6 normal-weight women, 6 overweight men, 6 overweight women	—	Preload: (1) APM; (2) fructose; (3) glucose; (4) water	(1) Glucose levels: lower when compared to fructose and glucose; (2) energy intake: no difference from water; (3) insulin levels: lower when compared to fructose and glucose	APM does not appear to have stimulating effect on food intake
Ryan-Harshman, 1987; Canada	Double-blind placebo controlled	13 healthy men; 23.1 ± 3.8	—	(1) ALA placebo; (2) APM (5.04 g) + ALA (5.04 g); (3) APM (10.08 g) + PHE (10.08 g)	(1) Energy intake: APM did not affect mean energy intake	APM in doses up to 10 g failed to alter food intake or hunger, mood, and arousal in normal weight adult males
Sathyapalan, 2015; United Kingdom and Ireland, Qatar	Double blind crossover design	Sensitive $n = 48$ 50.53 ± 16.24 and control $n = 48$ 52.42 ± 15.38	Sensitive 30.14 ± 5.71 and control 28.87 ± 5.9	(1) Cold pressed cereal bars with 100 mg of APM; (2) Cold pressed cereal bars without APM	(1) Biochemical or metabolic measures: no difference compared to control	Acute ingestion of APM does not have any detectable psychological or metabolic effects in humans
Siegler, 2012; Australia	Double-blind crossover design	9 men; age: 22 ± 2	—	(1) Carbohydrate maltodextrin + sucrose; (2) APM + maltodextrin + sucrose; (3) APM + maltodextrin; (4) water	(1) Insulin levels: decrease comparing intervention 2 *versus* 1 and no difference comparing intervention 3 *versus* 4	APM with carbohydrate significantly lowered insulin levels during exercise *versus* carbohydrate alone
Singleton, 1999; Italy and United States	RCT	12 men and 10 women; age: 27.36	25.3 ± 4.5	(1) Dairy cream + 1 g of APM; (2) dairy cream + 30 g of fructose; (3) dairy cream + 17.5 g of glucose; (4) dairy cream	(1) Glucose levels: no changes; (2) insulin levels: no changes; (3) total cholesterol: no changes	APM did not alter insulin, glucose, total cholesterol, HDL cholesterol, or LDL cholesterol concentrations
Smeets, 2005; the Netherlands	Crossover design single blind	5 men; age: 20.4	21.7 ± 1.1	(1) Water; (2) water + glucose; (3) water + APM; (4) water + maltodextrin	(1) Insulin levels: no changes	APM solutions failed to trigger an insulin response
Steinert, 2011; Switzerland	Placebo controlled, double-blind, six-way cross-over trial	6 men and 6 women; age: 23·3 ± 0.7	23.0 ± 0.5	(1) APM; (2) acesulfame K; (3) glucose; (4) fructose; (5) sucralose; (6) water	(1) Glucose levels: no change; (2) insulin levels: no change; (3) plasma glucagon: no change	APM had a minimal effect on appetite and did not affect blood glucose concentration and plasma glucagon. No significant insulin response was observed.
Stern, 1976; United States	Double-blind, placebo controlled, parallel two arms	Noninsulin-dependent diabetic subjects, 12 men and 57 women; age: 21–70	—	(1) APM capsules; (2) placebo capsules	(1) Diabetic control: no difference between APM and placebo; (2) LDH: higher in placebo group	APM did not improve diabetic control
Temizkan, 2015; Turkey	Single-blinded	4 men and 4 women, type 2 diabetic patients; age: 51.5 ± 9.2; and 4 men and 4 women, healthy; age: 45.0 ± 4.1	Diabetic patients 33.7 ± 5.4; Healthy 30.3 ± 4.5	(1) APM + water; (2) sucralose + water	(1) Glucose levels: no difference between APM and water; (2) insulin levels: no difference between APM, sucralose and water	APM did not alter glucose and insulin levels compared with water and sucralose

Abbreviations: ALA, alanine, APM, aspartame; BDD, Balanced Deficit Diet; CMW, carbonated mineral water; DSD, diet soft drink; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; PHE, phenylalanine; SD, standard deviation.
[1]Mean ± SD (all such values).

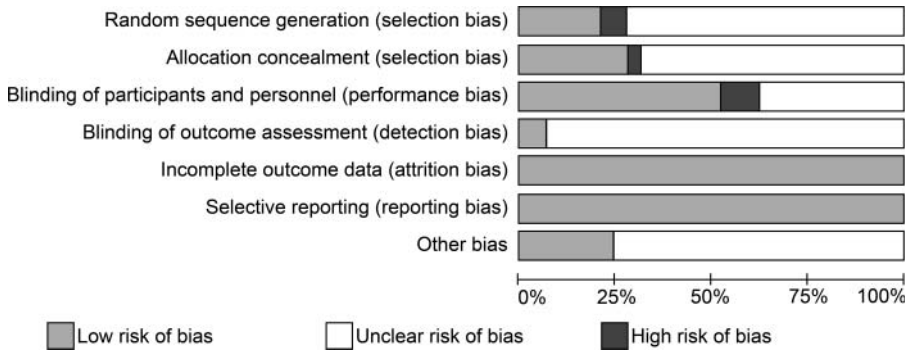

Figure 2. Risk of bias summary. Review authors' judgments about each risk of bias item presented as percentages across all included studies by applying the Cochrane Collaboration Risk of Bias Tool (Higgins et al., 2011).

consumed aspartame compared to sucrose group ($p = 0.09$, $n = 58$) (Fig. 4A). A random model was chosen for both comparisons due to the heterogeneity between studies.

Insulin levels results showed moderate heterogeneity between the studies comparing consume of aspartame *versus* control, with an I^2 of 49%. There was no difference between the groups ($p = 0.76$, $n = 101$) (Fig. 3B). The comparison of aspartame consumption *versus* sucrose consumption showed a high heterogeneity between studies with an I^2 of 92%. There was no difference between the group that consumed aspartame compared to sucrose group ($p = 0.57$, $n = 40$) (Fig. 4B). A random model was chosen for both comparisons.

Total cholesterol results showed high heterogeneity with an I^2 of 94% for the comparison between aspartame consumption and control. There was no difference between the groups ($p = 0.92$, $n = 91$) (Fig. 3C). For the comparison between groups that consumed aspartame compared to sucrose, there was a high heterogeneity between studies with an I^2 of 97%. There was no difference between the group that consumed aspartame compared to sucrose group ($p = 0.48$, $n = 40$) (Fig. 4C). A random model evaluated both comparisons.

Triglycerides concentrations results showed low heterogeneity between studies with an I^2 of 0% for comparisons between aspartame consumption *versus* control and aspartame consumption *versus* sucrose consumption. There was no significant difference between the group that consumed aspartame compared to control group ($p = 0.90$, $n = 91$) (Fig. 3D). There was no difference between the group that consumed aspartame compared to that consuming sucrose ($p = 1.00$, $n = 40$) (Fig. 4D). A fixed model was used for both comparisons due to low heterogeneity between studies evaluated.

HDL-c serum levels results showed low heterogeneity between the studies with an I^2 of 0% and were different between aspartame group and control group favoring subjects who consumed aspartame ($p = 0.01$, $n = 91$) (Fig. 3E). The comparison of aspartame and sucrose consumption showed low heterogeneity between studies with I^2 of 0% and the results were different between groups that consumed aspartame or sucrose favoring subjects who consumed sucrose ($p = 0.005$, $n = 40$) (Fig. 4E). A fixed model evaluated both comparisons.

Body weight results showed high heterogeneity between studies with an I^2 of 97%. There was no difference between aspartame group and control group ($p = 0.13$, $n = 179$) (Fig. 3F). The comparison of aspartame and sucrose consumption showed high heterogeneity between studies with I^2 of 94%. There was no difference between aspartame group and sucrose group ($p = 0.21$, $n = 40$) (Fig. 4F). A random model was chosen for both comparisons.

Energy intake results showed high heterogeneity between studies comparing consumption of aspartame *versus* control, with an I^2 of 92%. There was no difference between the groups ($p = 0.18$, $n = 195$) (Fig. 3G). The comparison of aspartame and sucrose consumption showed high heterogeneity between studies with I^2 of 95%. There was no difference between aspartame group and sucrose group ($p = 0.86$, $n = 201$) (Fig. 4G). A random model was chosen for both comparisons.

Risk of bias across studies

The included studies used similar methodology, which reduced the possibility of misinterpretation. All studies selected were considered to be relatively homogeneous, since all of them were RCTs studies. Besides this particular issue, in the meta-analysis, high heterogeneity was found in the selected studies possible due to different treatment patterns for aspartame and for sucrose or control.

Confidence in cumulative evidence

Overall, the quality of the evidence from the outcomes evaluated by the GRADE system was assessed as moderate (Appendix Table 4 in Supplemental File 1), suggesting moderate confidence in the estimated effect from the outcomes assessed. The heterogeneity was the main factor responsible for the limited quality of the evidence from studies evaluated.

Discussion

Summary of evidence

Aspartame is a nonnutritive sweetener present in more than 6,000 products and is worldwide consumed as substitute for sugar due not only to its sweetening power, which is about two hundred times higher than sugar, but also to its negligible contribution to caloric content of beverages and foods (Bellisle and Drewnowski, 2007; Butchko et al., 2002; Fernstrom, 2015). Aspartame use has increased by diabetic and obese individuals with the aim of comply with dietary requirements (Butchko et al., 2002). However, concerns have been emerging since its

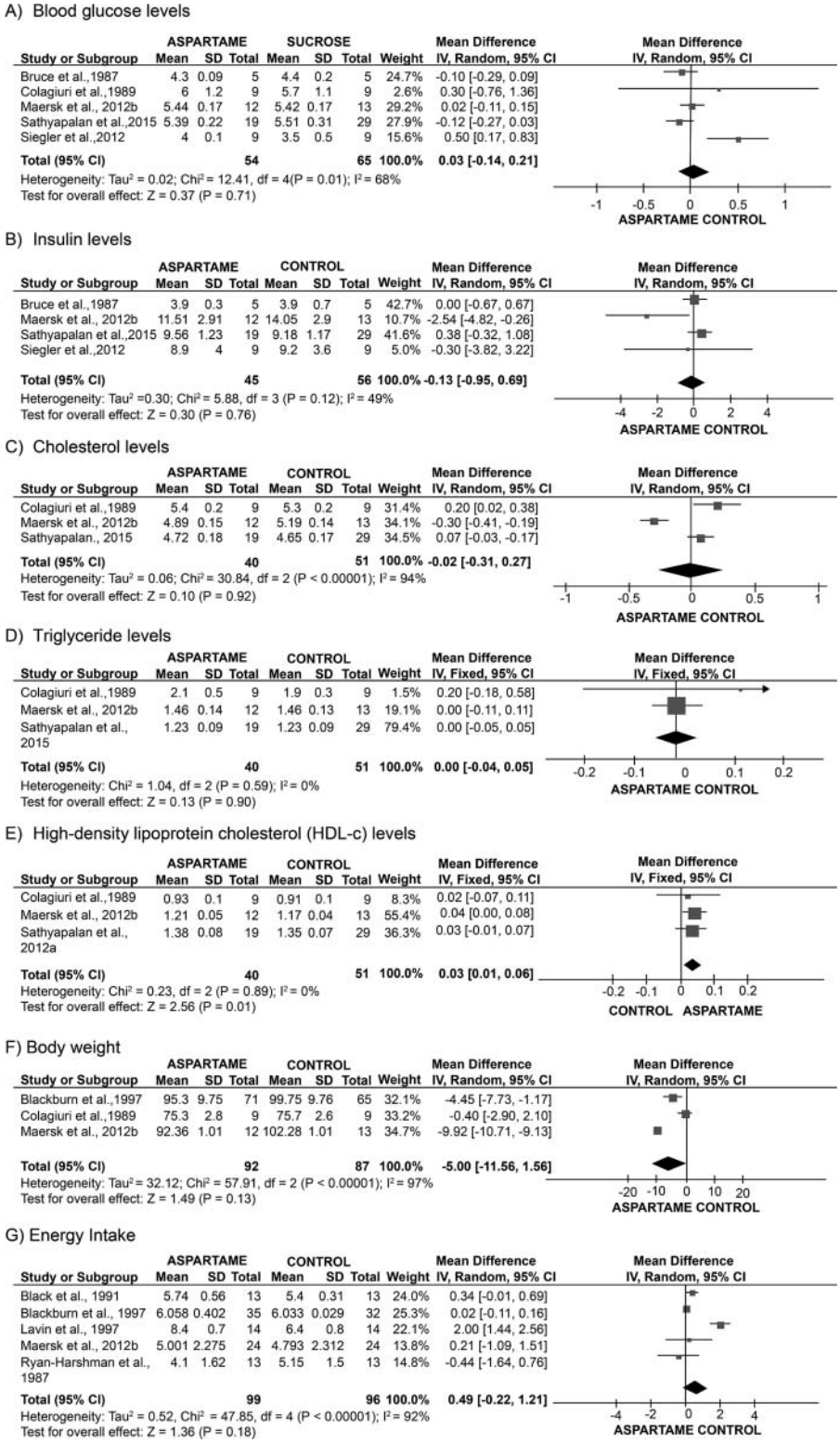

Figure 3. Forest plot of comparison control *versus* aspartame. (A) Blood glucose levels (mmol/L), (B) insulin levels (mU/mL), (C) cholesterol (mmol/L), (D) triglyceride (mmol/L), (E) high-density lipoprotein cholesterol (HDL-c) serum levels (mmol/L), (F) body weight (kg), and (G) energy Intake (MJ).

approval in the 1980s including a large anecdotal database reporting severe symptoms that can be triggered by this sweetener (Sathyapalan et al., 2015). The finding that the consumption of nonnutritive artificial sweeteners, both in mice and humans, can change the gut microbiota affecting weight, insulin resistance, and diabetes type 2 lately raised doubts about the benefits of their use (Suez et al., 2014). In this systematic review, it was examined the existing evidence supporting or refuting a link between aspartame use and changes in metabolic parameters in adulthood.

This systematic review and meta-analysis of RCTs demonstrates that aspartame consumption does not appear to influence blood glucose or insulin levels since there were no significant difference between groups that consumed aspartame

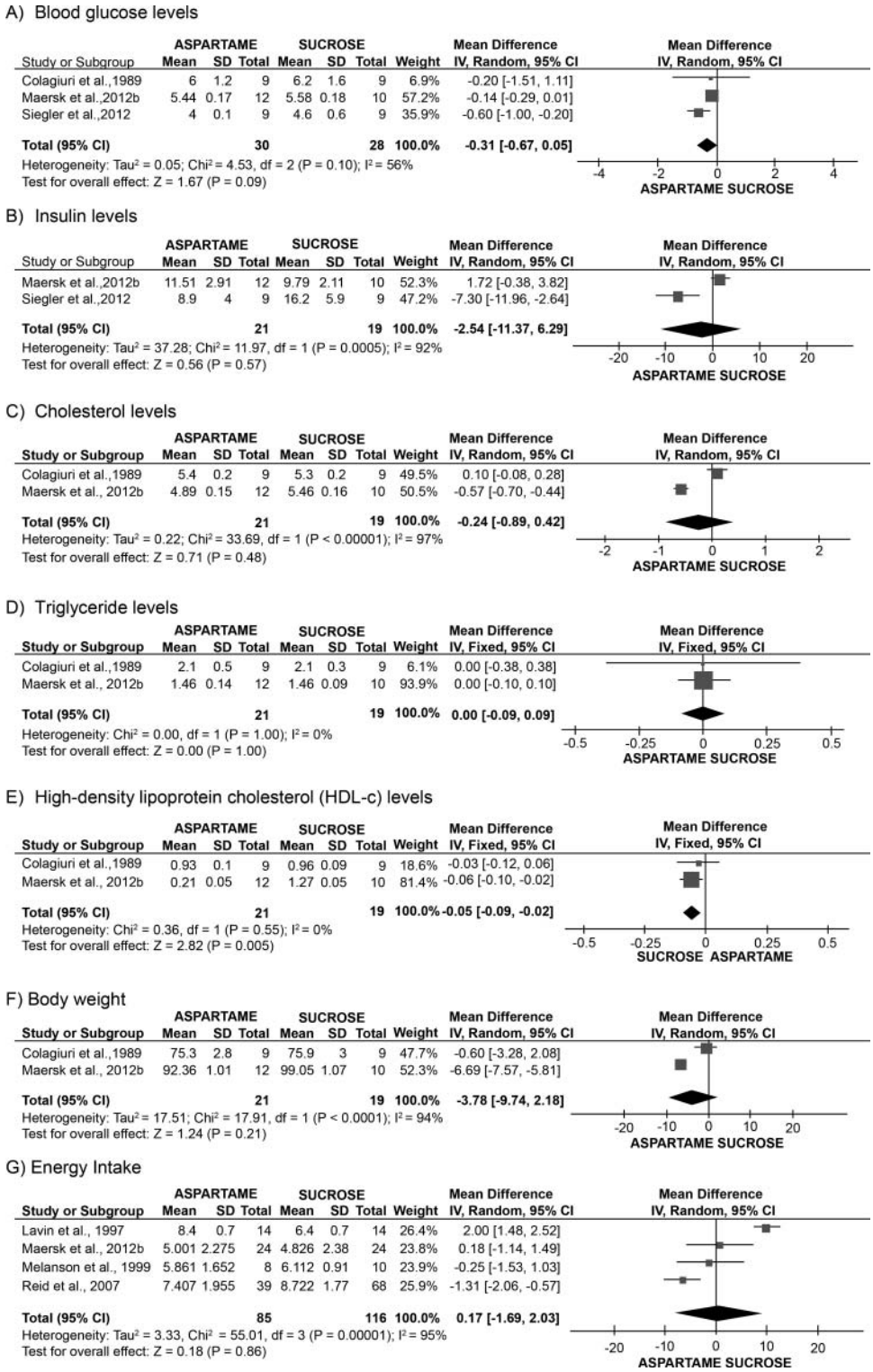

Figure 4. Forest plot of comparison sucrose *versus* aspartame. (A) Blood glucose levels (mmol/L), (B) insulin levels (mU/mL), (C) cholesterol (mmol/L), (D) triglyceride (mmol/L), (E) high-density lipoprotein cholesterol (HDL-c) serum levels (mmol/L), (F) body weight (kg), and (G) energy Intake (MJ).

compared with either control or sucrose groups. It can be attributed to the moderate to high heterogeneity among studies, which had different protocols for aspartame consumption ranging from a single dose (Bruce et al., 1987) to two years follow-up interventions (Blackburn et al., 1997) and included a variable set of subjects who were healthy, diabetic, or obese (Bruce et al., 1987; Colagiuri et al., 1989; Maersk et al., 2012b; Sathyapalan et al., 2015; Siegler et al., 2012). Therefore, according to the results jointed in this systematic review, there is no evidence of benefits or harm related to the consumption of products containing aspartame on blood glucose and insulin responses and it is insufficient to establish the recommendation of aspartame use to help on glycemic control.

Considering the lipid profile (total cholesterol, HDL cholesterol, and triglycerides) only HDL cholesterol serum levels showed statistically significant difference between results being

higher on aspartame groups compared with control and lower than levels found on sucrose group (Colagiuri et al., 1989; Maersk et al., 2012b; Sathyapalan et al., 2015). However, the studies evaluated in this meta-analysis for the lipid profile are limited in function of the number of individuals included in each group (aspartame, $n = 40$ and control, $n = 51$) and sucrose (aspartame, $n = 21$ and sucrose $n = 19$). Despite the statistical significant difference showed on quantitative analysis, the changes observed on means of HDL cholesterol levels values possibly does not represent a clinical benefit when aspartame consumption is compared with the consumption of beverages and foods which does not contain aspartame or are sweetened with sucrose, since the mean differences are minimal with a mean of 0.03 [0.01 to 0.06] mmol/L for the comparison between aspartame group *versus* control group and a mean of −0.05 [−0.09 to −0.02] mmol/L for the comparison between aspartame group *versus* sucrose group.

Among the clinical trials studied, aspartame use did not promote weight gain and in some cases produced a modest weight loss, consistent with the caloric reduction associated with their presence in the diet. The study of Kanders et al. which included overweight and obese subjects who participated on a 12-week weight loss program, showed that weight loss was higher in the group consuming aspartame sweetened beverages and foods (Kanders et al., 1988). Other study including obese woman, who participated of a multidisciplinary weight-loss program, showed higher weight loss and better weight maintenance on group that consumed aspartame-sweetened food and beverages compared to group abstaining the use of this sweetener (Blackburn et al., 1997). On the other hand, an observational study published in 2008 by Fowler et al. showed positive dose–response relationship between artificial sweetener beverage consumption and long-term weight gain (Fowler et al., 2008). Additionally, the collection of data from 381 nondiabetic individuals (44% men and 56% women; age 43.3 ± 13.2) ongoing clinical nutritional study showed that artificial sweeteners consumption was correlated with alterations on metabolic-syndrome-related parameters including increase on body weight and impairment of glycemic response leading to an increase on fast blood glucose, glycosylated hemoglobin, and impaired glucose tolerance (Suez et al., 2014).

The meta-analysis did not show significant difference between body weight comparing individuals that ingested aspartame either to nonsweetened control or to sucrose. These results are different from the obtained by De la Hunty study, which showed significant reduction on body weight and energy intake when ingestion of aspartame was compared to all types of control except when it was compared with ingestion of non-sucrose controls, such as water (De la Hunty, 2006). That study considered RCTs that evaluated both aspartame alone and combined with others sweeteners while the present meta-analysis only included studies wherein aspartame were evaluated alone to clarify the specific effect of this sweetener without interference of results obtained due the consumption of others sweeteners. The meta-analysis of Rogers et al. showed that consumption of LES in place of sugars is consistently found to reduce energy intake on short and sustained interventions and there are a reduction of body weight on the last one (Rogers et al., 2016). However, when aspartame as an LES is considered separately in studies performed in adults, there were no alterations either on body weight or on energy intake. The difference between the results found in this meta-analysis when compared with results showed by Rogers et al. (2016) may be due to the differences between the kinds of studies included in the quantitative analysis. Whereas this systematic review considered RCTs performed with adults who consumed aspartame, the study of Rogers et al. (2016) included studies performed with adults, children, and all kinds of LES, not only aspartame. These results highlight the importance of investigating whether there are some benefits on the blend of sweeteners in a formulation instead of use of just one sweetener, with the aim to improve the control of parameters related to diabetes and obesity.

The results relative to energy intake showed a high degree of heterogeneity. Only the work of Lavin et al. showed significant increase on energy intake after the aspartame-sweetened lemonade compared with both sucrose-sweetened lemonade and the water (Lavin et al., 1997). The authors attributed this effect to an increase in the amount of carbohydrate consumed that resulted in a higher overall energy intake. Swithers supposed that consuming drinks with artificial sweeteners contributed for overweight due to changes on the signs of neural modulation responsible for energy balance and consequently indicating that more sugar should be consumed (Swithers, 2013).

Taken as a whole, the evidences for the effect of aspartame on metabolic variables associated to diabetes and obesity are limited and do not support or refute a beneficial or harm related to consumption of this sweetener.

Limitations

The moderate quality of the evidences from the outcomes was mainly due to the heterogeneity between studies, except for HDL results analysis, that showed homogeneity between the studies, but with a low number of participants. The included studies showed variations in their design and study population by including healthy, diabetic, and obese people. In addition, the intervention duration varied widely, ranging from one day to two years of intervention, as well as on type of control. Some studies did not aim to primarily study aspartame consumption effects, but it was used as a control and for this reason these studies were included in this work.

Conclusion

This systematic review and meta-analysis found considerable evidences that do not support beneficial effects of aspartame on metabolic variables associated to diabetes and obesity. Although there were no found deleterious effects associated with aspartame consumption on variables studied, there is no support for the recommendation of aspartame consumption as a sweetener with the aim of comply dietary requirements on diabetes and obesity control according to studies evaluated. Further research is needed to assess whether the ingestion of aspartame is innocuous to adulthood.

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Declarations

Competing interests

The authors state that they have no competing interests.

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Authors' contributions to the article

All of the authors designed the review protocol. NCS and LMA selected articles and extracted data; NCS, LMA, and MSC conducted research; NCS and LMA analyzed data; NCS, LMA, GDLC, and ENSG performed statistical analysis; NCS, LMA, MSC, and MFB wrote the paper; NCS and LMA had primary responsibility for final content; MSC, MFB, GDLC, and ENSG critically reviewed the paper. All authors read and approved the final version of the manuscript.

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