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Review

Effect of non-nutritive sweeteners on body weight and composition: a systematic review and meta-analysis

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Abstract. *Background:* Obesity has become a worldwide health problem, which has been recognized as a global epidemic by World Health Organization. It can lead to obesity-associated comorbidities, such as type 2 diabetes mellitus, osteoarthritis, hypertension and coronary heart disease. Non-nutritive sweeteners (NNS) were designed as a sugar substitute to solve obesity and its subsequent outcomes. The effect of NNS on body weight is not sure. *Methods:* We performed the search of Embase (Ovid), Medline (Ovid), Web of science, VIP, CNKI, CBM, and Cochrane with the Mesh terms and keywords, and then according to inclusion and exclusion criteria screened the literature. We completed data extraction and statistical analysis using the R package meta. *Result:* In total 16 studies included in data analyses, 1427 people were enrolled with varying body weight at baseline. We found that individuals using NNS had weight loss compared to not using NNS individuals (SMD=-0.33; 95%CI -0.55 to -0.1; p<0.01). 8 studies (n=650) showed that compared with the control group, the BMI of the experimental group also decreased (SMD=-0.61,95%CI -1.35 to 0.31), and the I^2 was 95%. *Conclusions:* Data suggest that application of non-nutritive sweeteners can reduce body weight, but long-term application may lead to weight gain and metabolic disorders.

Key words: Non-nutritive sweeteners; body weight; obesity; systematic review

Introduction

Obesity has become a worldwide health problem, which has been recognized as a global epidemic by World Health Organization (1). It can lead to obesity-associated comorbidities, such as type 2 diabetes mellitus, osteoarthritis, hypertension and coronary heart disease (2). The prevalence of obesity increased from 3.2% to 10.8% in adult men and from 6.4% to 14.9% in adult women from 1975 to 2014 (3).

Sweeteners are one of the most commonly used food additives, which are extracted from plants or manufactured by chemical synthesis. They were grouped as nutritive and nonnutritive, nutritive sweeteners contain carbohydrates and provide energy, such as sucrose, maltose, and Corn-based sweetener. Non-nutritive sweeteners (NNS) offer little to no energy, such as aspartame, neotame, sucralose, Acesulfame-K, stevia, and saccharin (4). The consumption of non-nutritive sweeteners has increased dramatically in the past two decades as they are beneficial substitutes for sucrose and other sugar. A study in 2017 showed that 25.1% of children and 41.4% of adults reported consumption of NNS, and consumption was higher in obese individuals than overweight and normal-weight individuals (5).

Non-nutritive sweeteners are designed as a sugar substitute to solve obesity and its subsequent outcomes, including metabolic syndrome, diabetes, and cardiovascular disease. NNS can be several hundred to thousands of times sweeter than sucrose with negligible caloric value, making them favorable health tools in attempts to control caloric intake and assist in weight loss (6). Currently, some studies have suggested that non-nutritive sweeteners can help weight loss. On the contrary, other studies indicated that the use of non-nutritive sweeteners can lead to weight gain (7) and metabolic disorders (8). The use of NNS is still controversial, we want to provide scientific data for its use. Therefore, the purpose of this study is to assess the effect of NNS on body weight and body composition through a systematic review and meta-analysis of randomised controlled trials.

Methods

Search strategy

This systematic review and meta-analysis adhere to the scheme of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). We performed the search of Embase (Ovid), Medline (Ovid), Web of Science, VIP, CNKI, CBM, and Cochrane from the date of incorporation until February 5, 2021. Pre-defined search terms included MeSH terms and keywords for 'Non-Nutritive Sweeteners', 'high intensity sweetener', 'non calor sweetener', 'sugar substitute', 'aspartame', 'saccharin', 'stevia', 'cyclamates', 'advantame', 'neotame', 'thaumatin', 'Sodium Saccharin', 'overweight', 'obesity' and 'weight loss'. Search restrictions in English and Chinese. The search strategy was constructed by a medical information specialist. The complete search strategy showed in Supplemental 1.

Study selection

Two independent co-authors screened all the studies by title and abstract. A third reviewer resolved the discrepancy between the two authors. For this systematic review, we used the following inclusion criteria: 1. Randomized controlled trials (RCTs). 2. Individuals with obesity, overweight or obese are defined as a body mass index (BMI) greater than or equal to 24 kg/m^2, trials should ideally describe diagnostic criteria. 3. Types of interventions: 1) Any type of NNS, either alone or in combination with another NNS. 2) NNS plus a behavior-changing intervention such as diet, exercise, or both. 4. RCTs in which the intervention had a minimum duration of four weeks. 5. The patients' age >18 years. The protocol was registered at the international prospective register of systematic reviews. (PROSPERO: CRD4202124587)

Data extraction and quality assessment

A standardized data extraction form was used to record data for the included studies, with data entered from 15 March 2021 to 29 March 2021. Two independent reviewers extracted the data and assessed the quality of the studies. The following data were extracted: study characteristics (first author, publication year, country), study design (study setting, age, sample size), the time of intervention, the intervention of experimental group and controls, the changes of body weight or BMI in the experimental group and the control group, the secondary outcome such as the change of blood pressure or blood glucose or blood lipid. The control group was defined as not using non-nutritive sweeteners. The quality assessment of studies used the Cochrane Risk of Bias Tool for RCTs(*9*). It includes (1) arising from the randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; (5) selection of the reported result; (6) overall bias. We used the Cochrane Handbook recommendations to regard the overall risk of bias.

Summary results and statistical methods

The changes of weight and BMI during the trial were the main outcomes to be analyzed. However, some studies only reported weight or BMI at the beginning and end of the study, and when some studies did not report weight differences, we calculated the weight difference between the intervention and control groups using the formula in the Cochrane Handbook (10). Effect size was expressed as the standardized mean difference (SMD), the random-effects model was used in meta-analysis, and the main results were represented by forest plots. The I^2 was calculated for heterogeneity verification, and heterogeneity across studies was defined by an I^2 of >50%. The significance level was $\alpha = 0.05$. Subgroup analysis was performed according to different intervention times and methods, which were done to interpret the heterogeneity. The meta-analysis and the forest plots were created using the package of meta in R 3.5.2.

Results

Description of included studies and assessment of potential bias

A total of 4,154 literatures were obtained by initial examination, and 3,043 literatures were obtained from the duplicate examination. After reading the title and abstract, we excluded 2,875 articles that were inconsistent with the research type, intervention measures, and research objects. After further reading the full text rescreening, we excluded 44 articles that were inconsistent with the intervention measures and outcome indicators. 16 articles were included. All articles were written in English. The literature screening process is shown in Figure 1. Descriptive characteristics of the included studies were shown in Table 1.

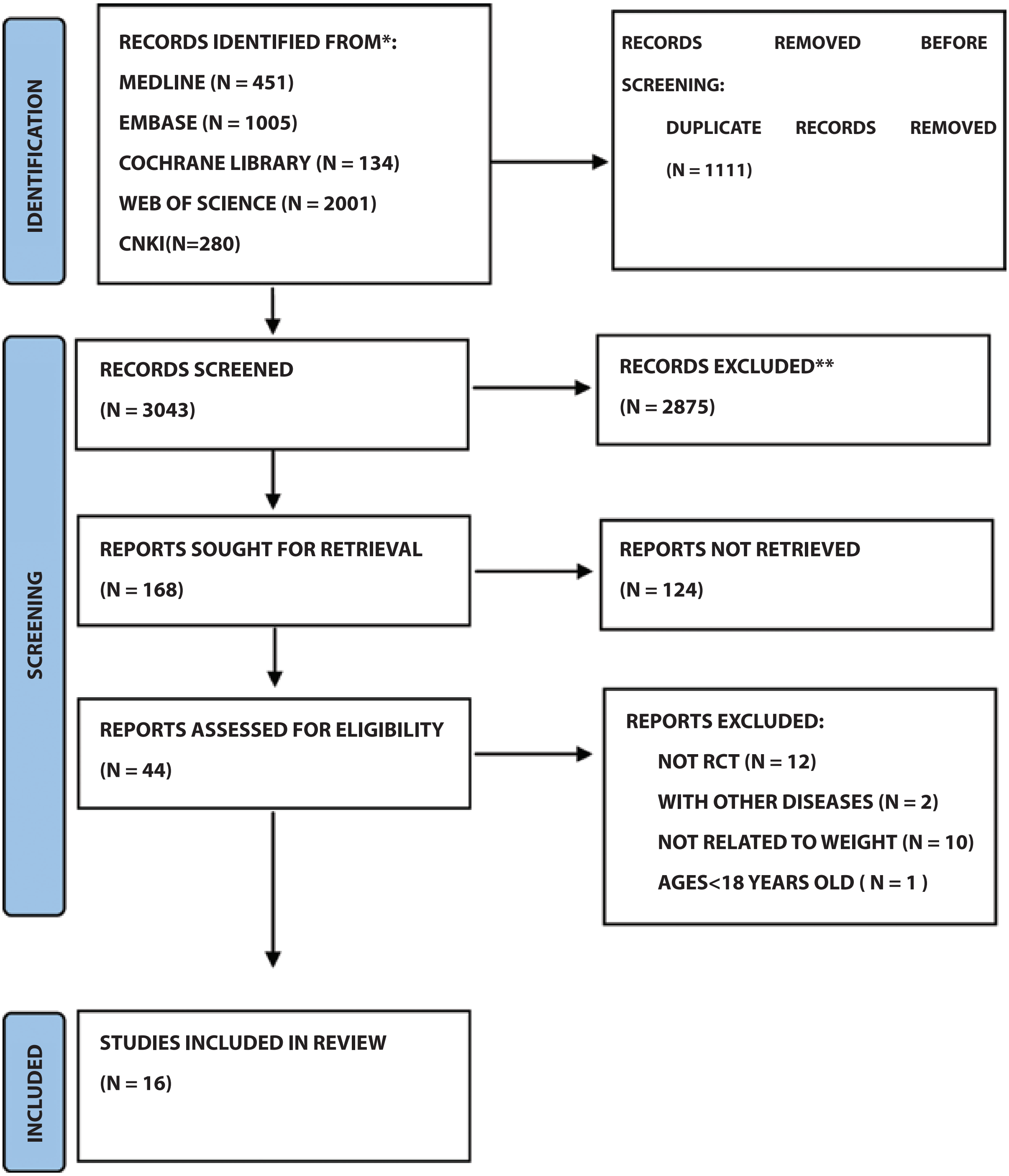

Figure 1. Selection process for the systematic review and meta-analysis.

Table 1. Characteristics of studies entered the study.

	Study Duration, wk	Population	The type of NNS	NNS Consumers	Comparison	Controls	Behavior-changing intervention	Weight Changes[c]
George et al. 1997	16	Overweight/ obesity	Aspartame	82	Sucrose	81	With Behavior-changing intervention	-9.9kg
Deborah et al. 2012	24	Overweight/ obesity	Diet beverages[a]	105	Water	108	With Behavior-changing intervention	-2.6kg
Anne et al. 2002	10	Overweight/ obesity	Mixture[b]	20	Sucrose	21	With Behavior-changing intervention	-1kg
Kelly et al. 2019	4	Overweight/ obesity	Aspartame	30	Sucrose	39	Without Behavior-changing intervention	0.73kg
Ameneh et al. 2015	24	Overweight/ obesity	Diet beverages	32	Water	30	With Behavior-changing intervention	-7.6kg
Fabrice et al. 2018	24	Overweight/ obesity	Aspartame	30	Water	30	Without Behavior-changing intervention	-0.25kg
Youngji et al. 2018	12	Overweight/ obesity	D-allulose	40	sucralose	40	Without Behavior-changing intervention	-0.98kg
John et al. 2014	12	Overweight/ obesity	Mixture	142	Water	134	With Behavior-changing intervention	-5.95kg
Kelly et al. 2018	12	Healthy	Aspartame	31	PABA Sucrose	31	Without Behavior-changing intervention	0.2kg
Robert et al. 2009	13	Overweight/ obesity	Aspartame	22	Lactose	33	With Behavior-changing intervention	-6.88kg
Madjd et al. 2018	77	Overweight/ obesity	diet beverages	36	Water	35	Without Behavior-changing intervention	-7.8kg
Marie et al. 2007	4	Healthy	Aspartame	133	Water	68	Without Behavior-changing ntervention	-0.2kg
Maria et al. 2012	24	Overweight/ obesity	Aspartame	12	Water	13	Without Behavior-changing intervention	-0.24kg/ m^2
Vanessa et al. 2015	12	Overweight/ obesity	Mixture	14	Sucrose	13	Without Behavior-changing intervention	-1.4kg
Marie Reid et al. 2013	4	Overweight/ obesity	Aspartame	21	Sucrose	20	Without Behavior-changing intervention	-0.31kg

[a]Diet beverages refers to Beverages sweetened with SWEETENING AGENTS that are synthetic or artificial as opposed to naturally-occurring. [b]Mixture of NNS refers to an intervention with several NNS. [c]Weight changes refers to the difference of NNS in body weight after the intervention.

Quality assessment results showed that 8 studies had a high risk of bias, 6 studies had an unclear risk of bias, and 2 studies had a low risk of bias. The detailed risk of bias was shown in Figure 2. The Egger method showed there was no publication bias (Supplement 2).

The 16 studies included in data analyses enrolled 1,427 participants of varying weight at baseline, ranging from 65kg to 100kg. The mean age of the subjects ranged from 18 to 48. In the majority of studies, the baseline characteristics of participants assigned to the intervention and control groups were generally comparable. One study had an unequal distribution of sex between the groups, then they used the relative change in gender and baseline adjustment for analysis. The mean age in one study was statistically significant, but the difference did not have a statistically significant effect on height or weight.

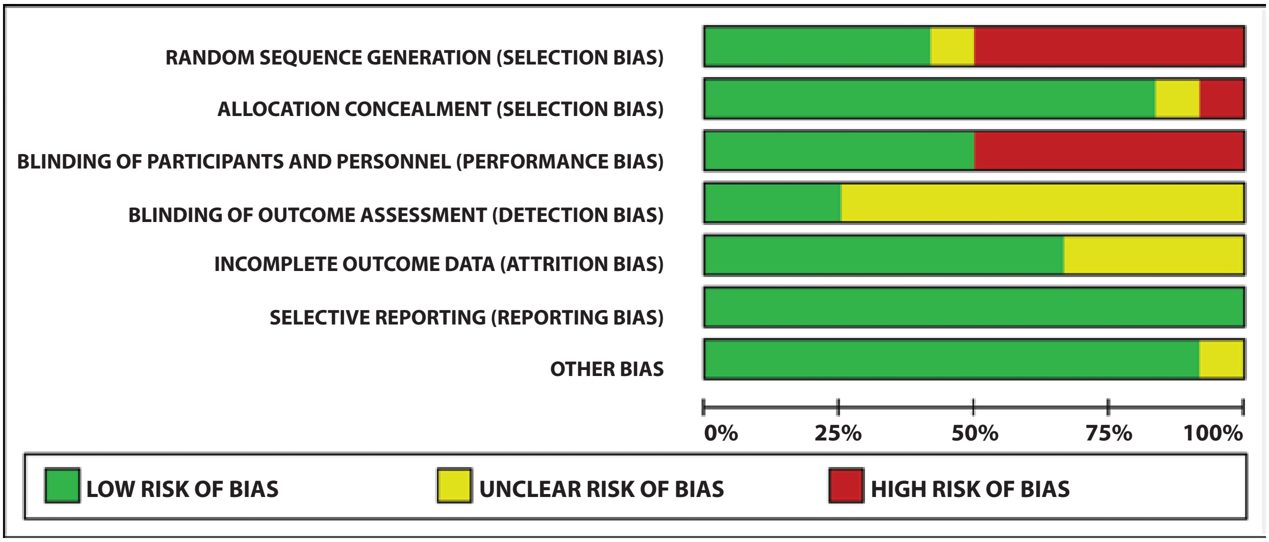

Figure 2. Assessment of risk of bias of the included studies.

Weight and BMI changes

Considering that two studies' outcomes missing, 14 studies were included in the meta-analyses. We found that individuals who used NNS lost weight greater compared to not used NNS individuals (SMD = -0.33; 95% CI -0.55 to -0.1; $p < 0.01$) shown in Figure 3. The I^2 denotes a heterogeneity as high as 75%. In secondary outcomes, 8 studies were included to assess the differences in BMI. Compared with the control group, the change in BMI in the experimental group also showed significantly greater BMI differences (SMD = -0.61, 95% CI -1.35 to 0.31), and the I^2 was 95%. (Supplement 3)

Subgroup analysis by the type of the comparator

Subgroups were analyzed according to different type of control group, when compared NNS with sucrose group(*11-16*), the outcome revealed significant differences (SMD = -0.71; 95% CI -1.19 to -0.24, I^2 = 78%, $p < 0.01$). Compared with water group(*17-19*), we found the effect of NNS on body weight was similar (SMD = -0.81; 95% CI -0.64 to 0.29, I^2 = 85%, $p < 0.01$). Compared with the low-calorie beverage group(*20, 21*), the result was no overall effect (SMD = 0.03; 95% CI -0.74 to 0.81; I^2 = 81%) (Figure 4). Compared with the placebo group(*22-24*), the weight of NNS decreased slightly, but the difference was not statistically significant. (SMD = -0.15; 95% CI -0.38 to 0.08) (Figure 4)

Subgroup analysis by the different populations

In two studies, participants were adults with normal BMI. All participants in the remaining study were obese or overweight adults(22,25). Subgroup analysis of different populations found that the effect of NNS on weight loss is better in obese or overweight patients. Compared with control group, the intervention group showed greater weight differences, (SMD = -0.38; 95% CI -0.65 to -0.12; I^2 = 77%). On the contrary, studies on healthy populations found the differences to be statistically insignificant. (SMD = -0.08; 95% CI -0.40 to 0.23; I^2 = 27%). (Supplement 4)

Subgroup analysis by the duration

Considering that the duration of each experiment is different, subgroup analysis was performed to assess the influence of intervention time. We set the intervention time dividing line at 6 months. The group that experimental intervention time less than 6 months found weight loss (SMD = -0.47; 95% CI -0.73 to -0.22; I^2 = 70%); but the experimental intervention time more

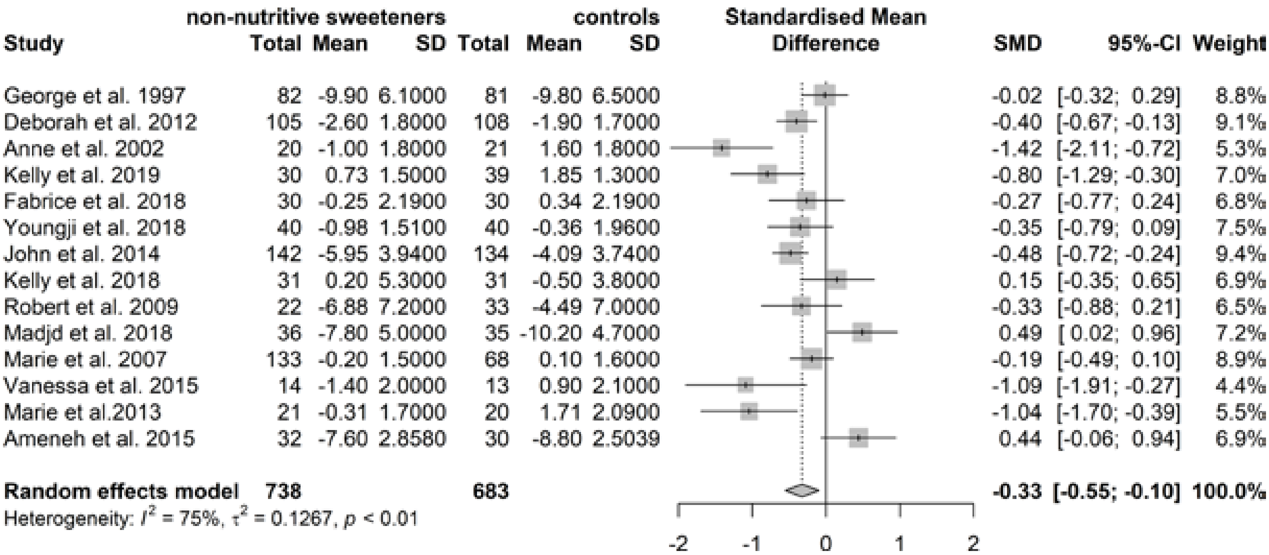

Figure 3. Forest plot on the comparison of weight differences between non-nutritive sweeteners and control group.

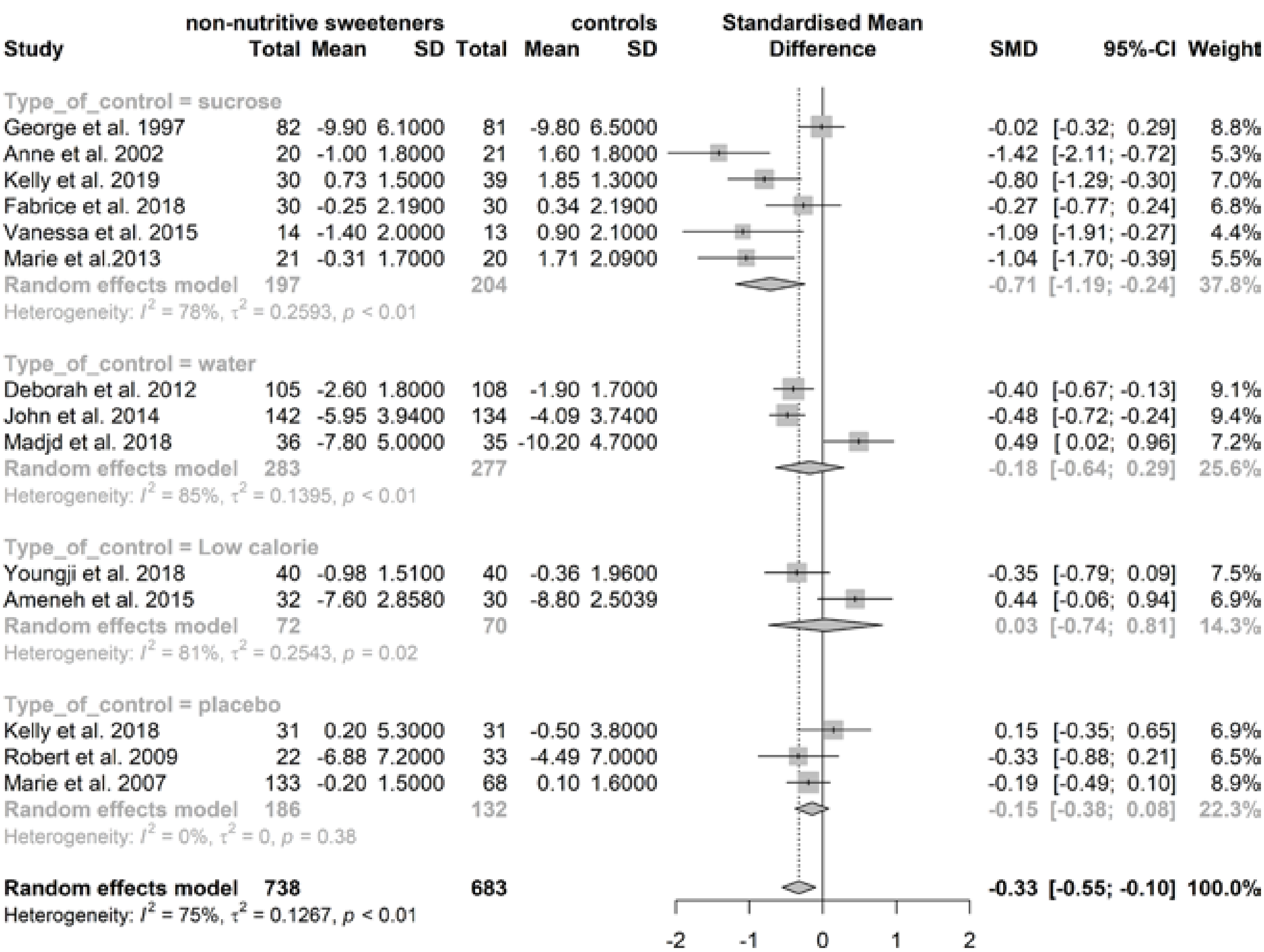

Figure 4. Forest plot on the comparison of weight differences between non-nutritive sweeteners and control group according to the type of the comparator.

than 6 months can lead to weight gain (SMD = 0.05; 95% CI -0.44 to 0.53; I^2 = 81%). (Figure 5)

Subgroup analysis by the intervention

When considering studies that set behavior-changing interventions such as diet, exercise, or both, the subgroups were divided into calorie restriction and non-calorie restriction groups. The weight differences of calorie restriction group (SMD = -0.33; 95% CI -0.66 to 0.01; I^2 = 79%) and non-calorie restriction group (SMD = -0.34; 95% CI -0.67 to 0.00; I^2 = 74%) showed no significant weight effect. (Figure 6)

Safety evaluation

Only two studies (26,27) reported adverse reactions including neurogenic bladder, severe right calf pain, bowel change, menstrual change, febrile illnesses, and back spasms, none of which were considered relevant to research.

Studies assessed NNS consumption vs control in total cholesterol, high-density lipoprotein, and low-density lipoprotein showed no significant effect. Conversely, triglyceride significantly increased in the NNS group. (Supplement 5)

Discussion

The main purpose of this article is to explore whether NNS can reduce weight in obese or overweight patients. Of the 14 RCT studies we included, two studies showed weight gain, the total effect size was weight loss. The heterogeneity of this paper is a little high, which may be related to the duration of the study, the initial weight of the participants, and whether the diet was controlled.

Meanwhile, we performed subgroup analyses respectively. In the subgroup analysis of intervention time, we found that short-term intervention of NNS would lead to weight loss, and long-term intervention would result in weight gain; one study included

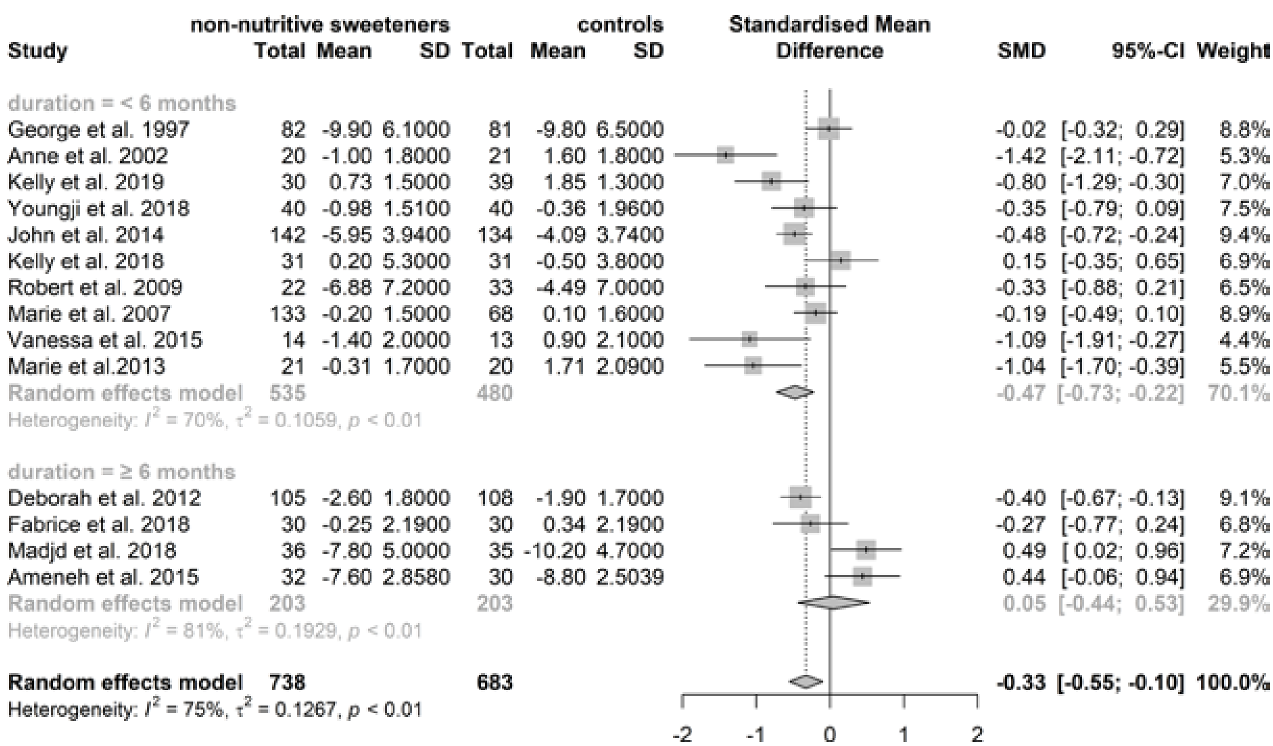

Figure 5. Forest plot on the comparison of weight differences between non-nutritive sweeteners and control group according to the duration.

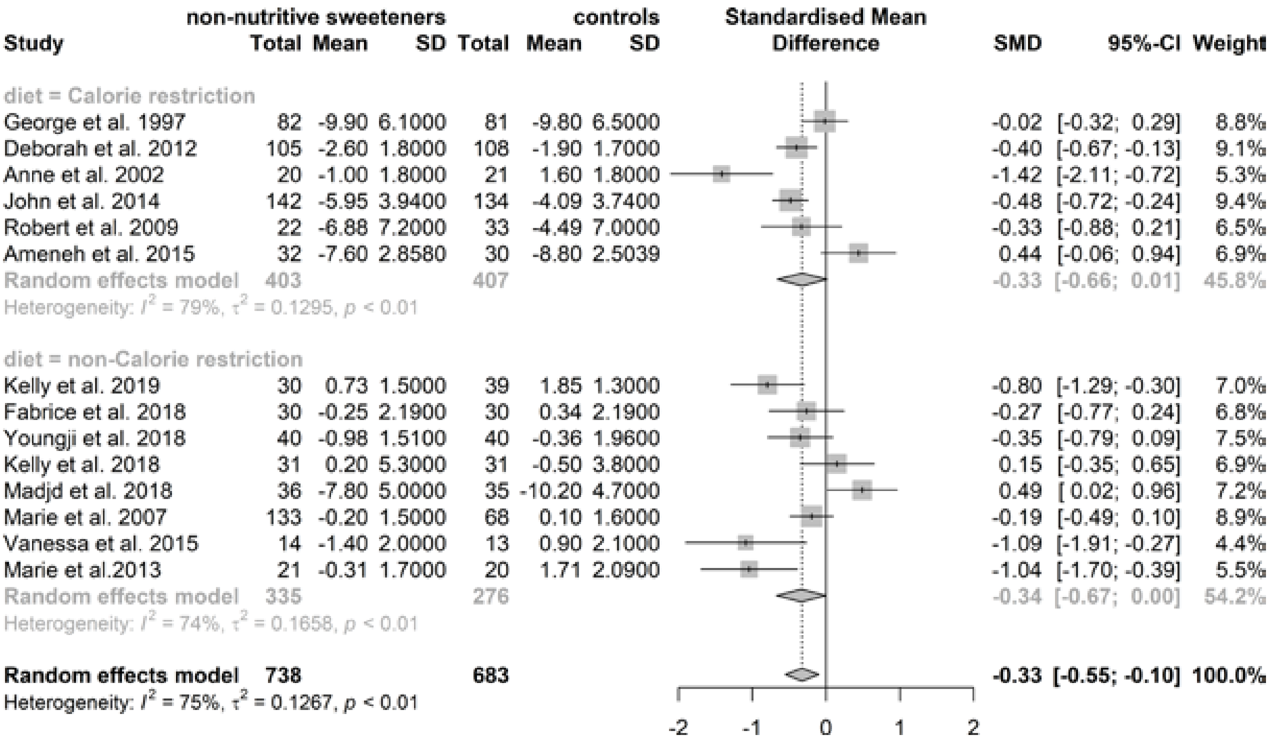

Figure 6. Forest plot on the comparison of weight differences between non-nutritive sweeteners and control group according to the intervention.

30 cohort studies which had 405,907 participants, and the median follow-up was 10 years also found that consumption of non-nutritive sweeteners was associated with a moderate increase in BMI (mean correlation 0.05, 95% CI 0.03 to 0.06; I^2 = 0%)(*28*).

Compared with obese or overweight patients, the effect of NNS on weight loss in healthy individuals is not evident. It may be related to the fact that in our study, NNS was used to replace calorie beverages and the calorie intake of participants was controlled, healthy people may use fewer calorie beverages, and their eating habits are relatively healthy and reasonable. Also, the baseline weight of obese or overweight patients was greater than healthy people.

The included studies were divided into calorie restriction and non-calorie restriction groups, we found two studies in which weight gain was in the no-calorie restriction group, which showed that using NNS together with calorie restriction reduces weight better. In our study, there was no difference between the two groups. However, the number of people we included is not enough, and some trials are not double-blind, which may affect the diet of the participant.

We also found that NNS can significantly reduce body weight compared with sucrose, but the weight loss is not obvious when compared with water. So, it is may advisable to replace sugar with NNS, but considering the possible side effects of NNS, it is not recommended to replace water with NNS.

In addition, we also analyzed other secondary outcomes. Firstly, we analyzed the effect of NNS on waist circumference; a total of 7 studies (n=879) were included, and the results showed that the consumption of NNS increases waist circumference.

Secondly, considering that glucose metabolism may affect lipid metabolism, we made a statistical analysis of blood lipid indexes. We found that the use of NNS did not increase total cholesterol, high-density lipoprotein, and low-density lipoprotein, but it can lead to triglyceride increased. However, because the number of people we included is not very large, it is questionable whether the results are true.

In addition, we found a decrease in diastolic blood pressure, systolic blood pressure, and fasting blood glucose in participants, but these indicators were not monitored for a long period and were only measured at the beginning and end of the experiment. Given that the results were subject to chance, we did not conduct statistical analyses.

In assessing adverse reactions in the included literature, only two articles reported adverse reactions. It was assumed that the occurrence of adverse reactions was not directly related to NNS. However, some studies suggest that long-term application of NNS may lead to metabolic abnormalities, so what are the mechanisms by which non-nutritive sweeteners may affect metabolism?

The sweet taste receptor, a G-protein-coupled receptor, has two 7-transmembrane subunits T1R2/T1R3(*29*). Information from activated sweet taste receptor cells is communicated to the brain by stimulating presynaptic cells in afferent cranial nerve fibers (30). Functional sweet taste receptors have been identified in various tissues, such as the brain, pancreas, mouth, and intestine. These receptors are involved in metabolic processes, such as hormone secretion and glucose control (31). Studies have shown that in vitro application of caloric sweeteners and NNS to intestinal endocrine cells can induce secretion of the proliferators glucagon-like peptide 1 (GLP-1) and glucose-dependent insulin-like peptide (GIP) by these cells through a T1R3-dependent mechanism (32). GLP-1 interacts with afferent fibers of the vagus nerve to mediate appetite. It causes the hypothalamus to increase satiety signals and attenuate hunger signals, thereby increasing satiety and reducing caloric intake. Given the combined effects of these hormones, it is likely that they are involved in the pathogenesis of metabolic diseases, including obesity and type 2 diabetes.

Disruption or imbalance of the microbiota is associated with many metabolic disease states, including obesity, insulin resistance and cardiovascular disease (33). Several studies have demonstrated that low-calorie sweeteners such as sucralose, aspartame, and saccharin have been shown to disrupt the balance and diversity of the gut microbiota. One study showed that this disruption can lead to impaired glucose tolerance (34). Changes in the gut microbiota or short-chain fatty acids induced by low-calorie sweetener consumption may also propagate downstream in the gut, affecting bile acid metabolism, gene expression, sweet taste receptors, satiety, and secretion of peptide YY (PYY) and the proliferators GLP-1 and GIP, all of which may affect glucose regulation (35,36).

The brain plays an important regulatory role in directing energy balance and eating behavior (37). Sweet taste receptors have also been identified in several areas of the brain, including the hypothalamus, which may be directly involved in glucose homeostasis. Glucose intake affects neuronal activity and functional connectivity in areas involved in reward and eating behavior throughout the brain (38). Anna M found that non-nutritive sweeteners appear to have only a small effect on eating behavior, both in terms of satiety and reward (38), so long-term consumption may affect brain responses associated with eating behavior.

Conclusions

The addition of non-nutritive sweeteners to foods and beverages is becoming increasingly common in the modern food environment. The application of non-nutritive sweeteners currently appears to reduce body weight, but long-term application may lead to weight gain and metabolic disorders and may affect food digestion and metabolism.

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Statement of Ethics: An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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