The effects of low-calorie sweeteners on energy intake and body weight: a systematic review and meta-analyses of sustained intervention studies

Running title: Effects of LCS on energy intake and body weight

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ABSTRACT

Previous meta-analyses of intervention studies have come to different conclusions about effects of consumption of low-calorie sweeteners (LCS) on body weight. The present review included 60 articles reporting 88 parallel-groups and cross-over studies ≥ 1 week in duration that reported either body weight (BW), BMI and/or energy intake (EI) outcomes. Studies were analysed according to whether they compared (1) LCS with sugar, (2) LCS with water or nothing, or (3) LCS capsules with placebo capsules. Results showed an effect in favour of LCS vs sugar for BW (29 parallel-groups studies, 2267 participants: BW change, -1.06 kg, 95%CI -1.50 to -0.62, I^2 = 51%), BMI and EI. Effect on BW change increased with 'dose' of sugar replaced by LCS, whereas there were no differences in study outcome as a function of duration of the intervention or participant blinding. Overall, results showed no difference in effects of LCS vs water/nothing for BW (11 parallel-groups studies, 1068 participants: BW change, 0.10 kg, 95%CI -0.87 to 1.07, I^2 = 82%), BMI and EI; and inconsistent effects for LCS consumed in capsules (BW change: -0.28 kg, 95%CI -0.80 to 0.25, I^2 = 0%; BMI change: 0.20 kg/m^2, 95%CI 0.04 to 0.36, I^2 = 0%). Occurrence of adverse events was not affected by the consumption of LCS. The studies available did not permit robust analysis of effects by LCS type. In summary, outcomes were not clearly affected when the treatments differed in sweetness, nor when LCS were consumed in capsules without tasting; however, when treatments differed in energy value (LCS vs sugar), there were consistent effects in favour of LCS. The evidence from human intervention studies supports the use of LCS in weight management, constrained primarily by the amount of added sugar that LCS can displace in the diet.

INTRODUCTION

Low-calorie sweeteners (LCS), for example acesulfame-K, aspartame, cyclamate, saccharin, steviol glycosides and sucralose, provide the pleasure of sweetness without calories. As such, use of LCS can be expected to contribute to the goals of international recommendations to reduce intake of sugar and to reduce the prevalence of overweight and obesity.[1] The role of LCS in healthy weight management, however, has been disputed on both empirical and theoretical grounds. This includes evidence from observational studies[e.g.2,3], the proposal that exposure to sweetness without calories disrupts appetite control[3-5] and a concern that exposure to sweetness increases preference for sweet, energy-containing items in the diet.[6,7] In relation to the latter claims, there is little compelling support for either the 'sweet taste confusion' or 'sweet tooth' hypotheses.[8,9] Furthermore, observational studies, including prospective cohort studies, are subject to confounding and reverse causation[10], which leaves intervention studies, that is, randomised controlled trials (RCTs), as the primary source of evidence concerning the effects of LCS on body weight (BW) and body mass index (BMI).

A variety of RCTs investigating the effects of sustained (long-term) exposure to LCS on BW have been carried out. Two systematic reviews that included meta-analyses found combined evidence in favour of a beneficial effect (relatively lower BW) of LCS consumption[10,11], with our earlier review concluding that "Overall, the balance of evidence indicates that use of low-energy sweeteners in place of sugar, in children and adults, leads to reduced energy intake and body weight, and possibly also when compared with water" (p 381[10]). In contrast, two subsequent meta-analytic reviews[12,13] concluded that there was no clear evidence of a difference between the effects on BW of consumption of LCS vs control. In planning the present review, we set out to resolve these different conclusions in the light of the comparisons made between LCS and different controls and the recent publication of further relevant RCTs.

Specifically, we framed our literature search strategies and data analyses according to three questions concerning potential effects of LCS on BW[14]: the effects of (1) LCS compared with sugar (i.e., when there is a difference in energy content of the target beverages and/or foods consumed, while taste is controlled); (2) LCS compared with water or nothing given to the comparator group (i.e., where there is no meaningful difference in energy content between treatments, while there is a difference in sweet taste); and (3) LCS in capsules vs placebo capsules (i.e., where there is no meaningful difference in energy content between treatments, nor a difference in taste). The first of these questions bears on a primary intended use of LCS, namely the effects of reduction in sugar and energy content of beverages and foods. The second question concerns the effects of exposure to sweet taste, which might be to increase or help satisfy desire for sweetness, or to have no effect.[8,9,15] The third question concerns the possibility that LCS have effects on appetite, or even energy expenditure, via post-ingestive actions in the gut or post-absorptively.[14,16] We included studies that exposed participants to LCS and one or more of the relevant comparators for ≥ 1 week and measured BW, BMI and/or daily EI. We included EI as an outcome, as effects of LCS on BW and BMI can be expected to occur primarily via effects on EI.[14,17] Although only small changes in body weight can be expected to result from consumption of LCS for one week, assessment of EI during part or all of that period will likely predict the effect on BW of longer-term consumption of LCS.

METHODS

The protocol for this systematic review and meta-analyses was registered in the international prospective register of systematic reviews (PROSPERO registration number: CRD42019135483). Differences between this protocol and our final methods are reported on Supplementary Information (SI) p 2. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[18] All research, analysis and writing for this review was undertaken solely by the two named authors.

Definitions

For the purposes of this review, we defined LCS as sweeteners and blends of sweeteners that, by virtue of their highly intense sweet taste (high potency), contribute sweetness but zero or negligible energy to a food or beverage product. This group of chemically diverse, sweet-tasting compounds includes aspartame which has an energy value of 17 kJ/g, but for humans is 180-200 times sweeter than sucrose. So, for example, where aspartame replaces 50 g of sugar in a beverage it contributes 4 kJ vs 837 kJ. Essentially, therefore, aspartame like truly zero-calorie intense sweeteners such as acesulfame-K, saccharin and sucralose, provides 'sweetness without calories'.[19] We defined sugar as monosaccharides and disaccharides, typically sucrose, fructose, glucose, glucose syrup and high-fructose syrup.[20] Both this definition of sugar[20], and the definition of LCS, excludes sugar alcohols (polyols) such as erythritol.

Throughout this review we use the term 'study' to refer to a comparison between LCS and either (1) sugar, (2) water/nothing, or (3) placebo. In some instances, the research compared participants randomised to LCS, sugar or water[e.g.21,22] thereby contributing two studies, namely LCS vs sugar, and LCS vs water. In another example the research compared participants randomised to saccharin, aspartame, rebaudioside A, sucralose and sucrose[23], contributing four studies: each LCS vs sucrose. Overall, therefore, the number of studies exceeds the number of articles, even though for some studies information for the same study was taken from more than one article.[e.g.24,25]

Search strategy

Four academic databases: MEDLINE, EMBASE and Web of Science and the Cochrane Library were searched using two separate searches which included: 1) a 'sweetener' term combined with a 'body weight' term or an 'energy intake' term; or 2) a 'sweetener' term combined with the terms 'capsule' or 'capsules'. Specific search terms are reported on SI pp 3-4. Terms were searched for in 'title' and 'abstract' fields, for all years of records. Searches were limited to include studies in humans where possible. Only the published literature, including abstracts and trial registrations, was considered. We also searched the reference lists of included articles and searched the issues of journals that contained identified articles. Our intention was to include as much of the relevant published literature as possible.

Study Inclusion

Studies were considered suitable for inclusion in the review if they: included exposure to LCS; for ≥ 1 week; included a relevant comparator; reported results for BW, BMI and/or EI;

and used a parallel-groups or a within-subjects design. Studies were included regardless of mode of LCS delivery, including the use of instructions to consume LCS, to continue consuming foods and/or beverages containing LCS, or to consume capsules containing LCS. To allow inclusion of as many studies as possible where effects on BW and/or EI may be found, exposure to LCS was required for ≥ 1 week, where the intervention period was considered to be the total period for which LCS exposure was manipulated or requested. Suitable comparators were exposure to, or instructions to consume or to continue to consume equivalent foods and/or beverages without LCS (foods and/or beverages containing sugar, or equivalent unsweetened foods and/or beverages (e.g., water)), to consume no additional foods or beverages (e.g., usual diet, wait-list control), or to consume placebo (presumably inert) capsules. Studies in which LCS exposure was part of an intervention strategy that included other elements (e.g., other dietary advice) were included provided those other elements were also present in the comparator group.[e.g.24,26,27] We included five studies from three articles where information or misinformation was provided to participants.[28-30] For these studies we compared groups provided with the same information on the basis that only sweetener (LCS vs sugar) and not information differed between groups (we considered these studies to be blinded). We did not include studies in which the LCS treatment was confounded with another treatment (i.e., which was not controlled for in the comparator group).[e.g.31-33]

Studies were included if they included a measure of BW and/or BMI before and at the end of the intervention, a measure of EI during and/or at the end of the intervention, and/or a change in BW and/or BMI over the intervention period. Our primary outcomes were BW/BMI from baseline to the end of the intervention (longest period reported) and adverse events during the intervention. Secondary outcomes were EI during or at the end of the intervention and, where available, measures of anthropometry, such as waist circumference. We only considered BW and BMI where these outcomes were measured objectively (self-reported BW or BMI measures were not accepted), and for EI where it was measured using diet diaries or dietary recall. The methods for EI measurement are detailed in the SI Details of Included Studies file, column K. Measures of anthropometry were only investigated in studies that also assessed BW or BMI. Studies were included regardless of gender, age, weight status or health status of the population studied, and regardless of study setting, context or location.

Data extraction

Searches were undertaken by PJR. All search results were first screened for study inclusion via titles and abstracts independently by both authors, and all potentially relevant articles were obtained. All these articles were screened independently by both authors. Articles were only discarded if they were clearly considered unsuitable for inclusion in the review by both authors. Discordances were resolved by discussion. Data on methodological aspects of each study, all relevant available outcomes and risk of bias (ROB) were subsequently extracted, independently by both authors, for each relevant study, using a data extraction form developed specifically for the work. Data were collated by study rather than by article, to guard against overinclusion of some original studies that contributed to several reports. Where we considered that details of methods that would allow or preclude inclusion in the review were required, we attempted to contact authors requesting the relevant information. Study authors were also contacted if published data were unclear in relation to our research question, or were partial. Studies were subsequently included or excluded based on this information. The instances where data were obtained and included in the present analyses are noted in the SI Details of Included Studies file, column AE.

Risk of bias assessment

ROB was assessed using the six domains recommended by the Cochrane collaboration[34]: randomization; allocation concealment; blinding of participants and researchers; use of ITT analysis; drop out; incomplete outcome reporting; and other. For each domain, ROB was judged independently by both authors, as 'low', 'high' or 'unclear' (or, additionally for blinding only, 'not possible'), based on published information. Criteria for ROB judgements are given in SI p 5. Discordances were discussed and resolved, and judgements tabulated. Funding source (partly or solely funded by industry vs no industry funding) was recorded but did not contribute to judgments of ROB.

Data synthesis and analysis

All studies were considered per research question and per study design (parallel-groups and cross-over designs). Studies are ordered in all results tables and figures below by intervention length (longest first) and then date of publication (most recent first). BW, BMI, EI and adverse events data were subsequently combined using meta-analysis. Analyses were conducted separately on studies using parallel-groups and cross-over designs to allow an adjustment for the reduced within-study variance in studies using a cross-over design. Analyses were conducted separately for change in BW (ΔBW) and change in BMI (ΔBMI) over the longest period of the intervention, BW and BMI at the end of the intervention (BWend and BMIend, respectively). Because BW is a cumulative effect of EI and energy expenditure, we analysed EI during the intervention averaged across all available time points, or solely at the end of the intervention if those were the only data available. Adverse events occurring during the intervention (reported as number of participants or number of events) were included in analyses, as reported. Too few studies reporting other anthropometric measures were found for the results to be combined for analysis. Analyses beyond the end of the intervention, that is, at longest follow-up, were not conducted because too few studies provided such results.

Data, corrected to ensure comparable direction in the measures, were analysed as standardized mean difference (SMD) (Cohen's d) with 95% confidence intervals (95%CI), using intention-to-treat (ITT) data (based on number of participants at study entry), where possible, or as Odds Ratios (Mantel-Haenszel estimations).[35,36] Estimates were made using random effects models primarily, due to likely heterogeneity between studies. Fixed effect models were also applied as sensitivity analyses.[35,36] Where research included multiple treatment or comparator groups, each treatment or comparator group was treated as an independent study, and numbers involved in single comparison groups were divided. Missing standard deviations (SDs) at end of intervention were carried forward from available baseline data or imputed using the mean of SDs available from other similar studies.[37] For ΔBW for parallel groups studies, missing SDs were calculated from the results of simple linear regression analysis predicting SD from study duration (SI p 6).

Heterogeneity between studies was investigated using Higgins' I^2 statistic.[38,39] Possible sources of heterogeneity were identified *a-priori* to include publication bias, and ROB. Possible publication bias was investigated using funnel plot asymmetry.[40] Where sufficient data (≥ four studies) were available, the impact of ROB was assessed using sensitivity analyses which included only the studies judged to be low ROB as assessed using measures based on the use of ITT analyses and measures based on low (< 20%) drop out. These domains were selected as those considered most likely to influence study results. Exploratory analyses (meta-regression or subgroup analyses) were also conducted on LCS vs sugar parallel-groups studies to investigate the relationship between ΔBW and BWend and (1) duration of study, (2) sugar 'dose' (i.e., difference in energy value of the sugar treatment minus LCS treatment), (3) whether participants were or were not blinded to their group allocation (LCS vs sugar), (4) whether LCS were provided in beverages or beverages and foods, and (5) funding source. Insufficient studies per subgroup were available for these exploratory analyses in cross-over studies, or studies investigating LCS vs water/nothing or LCS vs placebo.

Analyses were undertaken in Stata (StataCorp LLC, Texas, USA).

RESULTS

Database searches were undertaken on 14th June, 2019 and updated on 2nd June 2020. A summary of the total number of records identified, through the selection of articles, to the number of studies included in the review is presented in Figure 1. Details of studies and data extracted are included in SI (Details of studies file). Results are presented per research question below.

Figure 1 about here.

(1) LCS vs sugar

Included Studies. A total of 51 studies compared LCS with sugar: 37 parallel-groups studies[21-26,28-30,41-58] (one of these[21] was partly reported earlier in[59]) and 14 cross-over studies[60-68]. Children were participants in 11 studies[41,45,49,64], and adults were participants in 40 studies[21-24,26,28-30,42-44,46,50-63,65-68]. In 13 studies, all the participants were people with overweight and/or obesity.[21-24,26,28,29,52,53,60] Studies also included participants with type 1 diabetes[63], type 2 diabetes[44,61], or gall stones[62]. In two studies, the interventions were incorporated into an otherwise identical weight loss programme.[24,26] Five articles reported research on exclusively female participants[26,28-30,55], and one article reported research on exclusively male participants[66]. All other articles included both female and male participants (or gender was not specified[46,47]), with results reported separately for females and males in three articles[54,58,65]. In 33 studies the LCS vs sugar intervention involved beverages only[21-24,28-30,41,42-46,48,50,52,55-58,60,65,67,68], and in 18 studies it involved beverages and foods[26,49,51,53,54,61-64,66]. The LCS was aspartame in 24 studies[21-23,26,28-30,49,55-58,61,64,65], sucralose in six studies[23,44,45,50,51], saccharin in four studies[23,62,64], stevia/rebaudioside A in three studies[23,51,68] and cyclamate in one study[63]. The type of LCS was mixed[41,53,54,60,66,67] or not specified[24,42,43,46-48,52] in 13 studies. For the parallel-groups studies the median duration of the interventions was 12 weeks (1 to 78 weeks; mean = 16.5 weeks), and for the cross-over studies it was 3 weeks (1 to 6 weeks; mean = 3.2 weeks). Articles reporting 30 parallel-groups studies[21-24,26,28-30,41-43,45,46,50-53,55-58] and 13 cross-over studies[60-62,64,65-67,68] provided data on sugar dose: parallel-group studies mean = 1272 kJ/d (median = 1308 kJ/d), cross-over studies mean = 1542 kJ/d (median = 1591 kJ/d). The studies were carried out predominantly in the USA (28 studies) and Europe (16 studies).

Assessments of ROB are summarised in SI Table 1a. Judgements of low ROB for use of ITT analysis were given to 22 studies[23,24,28,41,49,53,60-64,66,68], and judgements of low ROB for low drop out were given to 34 studies[24,28,30,42,43,45,48-53,57,58,60-64,66-68]. For 35 studies, the authors report that participants were blinded to the intervention[23,28-30,41,44,45,49,53,55,57,58,60,61,64-67], although in three of these some participants correctly guessed their treatment allocation[23,41,53]. Twenty-two studies received funding from industry[24,26,28,29,44,45,49,50,53,54,60,62,64], 21 did not[21,23,30,41,42,43,51,52,57,61,65,67,68], and funding source was not reported for eight studies[46,48,55,56,58,63,66].

Meta-analyses (using random effects models) were conducted for ΔBW, BWend, ΔBMI, BMIend, EI and AE, with results subsequently converted to meaningful units. These results are summarised in Table 1. All original results (SMD, 95%CIs), together with results of all sensitivity analyses where missing SDs were imputed from means using fixed effects models and using only the studies of low risk of attrition bias (ITT analyses and drop out), are presented in SI Tables 2a-2d.

Table 1 about here.

BW and BMI. Twenty-nine LCS vs sugar studies using a parallel-groups design provided BW data that could be combined[21-24,25,26,28-30,41,42,43,45,48,49,52,53,54,56,57], as did eight studies using a cross-over design[60-63,66,68]. Table 1 and Figure 2 show that for both types of study there was an effect on ΔBW in favour of LCS (i.e., consumption of LCS resulted in greater weight loss, or lower weight gain, than did consumption of sugar). Results for BWend show similar effects. The effects were smaller in the cross-over studies, and were not significant for BWend.

Eleven studies using a parallel-groups design provided BMI data that could be combined[21-23,41,45,48,52,53]. They show an effect in favour of LCS for ΔBMI (Table 1 and Figure 2). Two cross-over studies[60,68] provided BMI data. Both found small, non-significant effects on BMI.

There is moderate heterogeneity in the results for ΔBW and ΔBMI, and some funnel plot asymmetry (SI p 17). Effects are comparable, however, to those found in BWend and BMIend analyses. Furthermore, comparable but somewhat smaller effects were found in all sensitivity analyses.

Six studies using a parallel-groups design[44,46,47,50,55,58] provided only narrative BW data, and two parallel-groups design[51] and two cross-over studies[67] provided BW data only as medians and IQR. These studies reported no statistically significant differences in BW between LCS and sugar groups.

Figure 2 about here

Energy Intake. Twenty-two studies using a parallel groups design[21-24,26,28-30,42,43,45,48,51-53,58], and 12 studies using a crossover design[60,62,63,64-67] provided EI data that could be combined. In these studies EI was lower for LCS vs sugar (Figure 2). There is some heterogeneity, and some funnel plot asymmetry (SI p 17), but comparable effects were found in all sensitivity analyses.

Adverse events. Eight studies provided data on adverse events.[26,41-43,48,49] There was no difference in the occurrence of adverse events for LCS vs sugar.

Other anthropometric measures. Eleven studies provided data on other anthropometric measures: skinfold thickness[41], waist-hip ratio ratio[41], fat mass[21-23,41,42,43,52], fat-free mass[21-23,52], waist circumference[24,41,48,60] and hip circumference[46]. Results were similar in direction to the effects found in the analyses of BW and BMI data.

(2) LCS vs water/nothing

Included Studies: In the LCS vs water/nothing category, we included 21 studies: 17 parallel-groups[21,22,24,25,27,42,43,46-48,55,69-75] and four cross-over studies[,65,76,77]. All studies were conducted with solely adult participants. In seven studies, all the participants were people with overweight and/or obesity[22,24,25,27,69,70,73], and in two studies, the participants were people with type 2 diabetes[70] or pre-diabetes[76]. In seven studies, the interventions were incorporated into an otherwise identical weight loss programme[24,25,27,69,70,73,76]. Three articles reported research on solely female participants[27,55,70], for one study the gender of participants was not reported[71], while all other articles included both female and male participants, with results reported separately for females and males in three articles[65,73,75]. The intervention involved consumption of LCS beverages ranging from 250 ml/d 5 days per week[27,70] to 1.2 L/d[61]. Eighteen studies involved the consumption of LCS in beverages[21,22,24,25,27,42,43,48,55,65,69-72,74,75,77], two studies included consumption of both LCS-sweetened beverages and foods[73], while in another study participants sucked two tablets containing aspartame before meals[76]. In 14 studies water, either still and/or carbonated, or unsweetened beverages were the comparators[21,2224,27,42,43,46,48,55,69,70,74,76,77], and in 7 studies 'nothing' was the comparator (i.e., the comparator was the omission of the LCS treatment[65,71,72,73,76]). The LCS was aspartame in eight studies[21,22,55,65,72,73,76], sucralose in two studies[74], aspartame and acesulfame-K in one study[77], acesulfame-K, aspartame and sucralose in one study[75], stevia in one study[71], and was not specified for the other studies[24,27,42,43,46,48,69,70]. The minimum duration of the interventions was 3 weeks[65] and the maximum was 77 weeks[27] (median duration = 12 weeks). The studies were carried out predominantly in the USA (10 studies) and Europe (five studies).

Assessments of ROB are summarised in SI Table S1b. Judgements of low ROB for use of ITT analyses were given to six studies[24,70,71,75,76], and judgements of low ROB for low drop out were given to 13 studies[24,27,42,43,48,70-73,75-77]. For ten studies[24,27,42,43,48,65,70,74,77] the authors report that the researchers and/or analysts were blinded to the intervention allocated to respective participants. Blinding was not possible for participants due to the nature of the intervention. There was no researcher/analyst blinding in one study[21], and blinding was not reported for the other studies[46,55,69,71,72,73,76]. Eight studies received funding from industry[24,69,72,73,75,77], nine did not[21,27,42,43,65,70,71,74], and funding source was not reported for four studies[47,48,55,76].

BW and BMI. Eleven parallel-groups studies that compared LCS with water/nothing provided BW data that could be combined[21,22,24,27,42,43,48,69-73], as did four studies using a cross-over design[65,76,77]. Eight parallel-groups studies[21,22,27,48,70,73,74], but no cross-over studies, provided data for BMI that could be combined. Analyses showed no effect of LCS vs water/nothing for BW or BMI (Table 1 and Figure 3). These analyses also revealed considerable heterogeneity in results, and some funnel plot asymmetry (SI p 18). Some different effects were found in the sensitivity analyses using fixed effect models, possibly due to differing effects in larger studies[24,69], and in sensitivity analyses for ROB where these could be conducted (SI Tables 2a-2d). Three studies provided data that could not be analysed.[46,55,75] The authors report no effect of LCS vs water on body weight.

Energy Intake. Ten parallel-groups studies[21,24,25,27,42,43,48,70,74,75] and three cross-over studies[65,77] provided EI data that could be combined. Analyses showed higher EI for LCS in parallel-groups studies, but lower EI for LCS in cross-over studies (Table 1). Within these two sets of studies there is low heterogeneity in results, and some funnel plot asymmetry (SI p 18). Similar effects were found in all sensitivity analyses that could be conducted (SI Tables 2a-2d).

Adverse events. Results for adverse events were reported for four studies.[43,48,74] In total, thirteen adverse events were recorded for the LCS groups, mainly in two studies[74], while zero adverse events were recorded for the water/nothing treatment groups.

Other anthropometric measures: Eight studies provided data on other anthropometric measures: fat mass[21,22,42,43,72], fat-free mass[21,22,72], waist circumference[24,27,48,69,70,77] hip circumference[48]. Results for these measures do not differ clearly from the pattern of results for BW and BMI.

Figure 3 about here

(3) LCS capsules vs placebo capsules

Included Studies. Of the 16 included capsule studies, 15 used a parallel-groups design[72,78-89] and one a cross-over design[90]. All studies, except one[89] (males only), included both male and female participants, with type 2 (non-insulin-dependent) diabetes[82,84,86], hypertension[78-80], type 1 diabetes[84], chronic kidney disease[83], hyperlipidemia[87], or participants who were healthy[72,81,84,88-90], including some individuals with overweight/obesity[85]. One study[85] included participants aged 10 to 21 y. All other studies were conducted with solely adult participants. The capsulated LCS was stevia/rebaudioside A (10 studies[78-80,82-84,87,88], 200 mg/d to 1.5 g/day), aspartame (four studies[72,81,85,86], 700 mg/d to 5 g/d), or sucralose (two studies[89,90], 200 and 780 mg/d). The comparators were placebo capsules. The minimum duration of the interventions was 7 days[89] and the maximum was 2 years[78] (median duration = 13 weeks).

Assessments of ROB are summarised in SI Table 1c. All articles reported that the studies were carried out double blind, except for one single-blind study.[83] Three studies were judged low ROB for conducting ITT analyses[83,88,90]. All studies were judged low ROB for drop out. The studies were carried out in the USA (six studies), South America (six studies) and Asia (four studies). Five studies received funding from industry[72,81,82,85,88], eight did not[80,83,84,87,89,90]. Funding source was not reported for three studies[78,79,86].

BW and BMI. Seven studies provided data for BW that could be combined[72,81-83,85,86,89], and eight (predominantly different) studies provided data for BMI that could be combined[78,79,80,83,84,87]. Taken together, results of the analyses show no effect of LCS capsules vs placebo capsules for BW or BMI (Table 1 and Figure 4). A small effect was found in favour of placebo for ΔBMI, but limited original SD data were available to conduct this analysis. Heterogeneity for these results is low, and funnel plot asymmetry is low (SI p 19). Comparable effects were found using fixed effect models. In all studies drop out was reported to be low, but ITT analysis was reported for only a minority of studies. Two studies provided narrative results on BW.[88,90] The authors reported no effect of LCS vs placebo.

Energy Intake. Narrative results on EI were provided for two studies[88,90]. The authors report no effect of LCS vs placebo.

Adverse events. Thirteen studies provided data on adverse events[78-82,84-89] There was no difference in the occurrence of adverse events for LCS vs placebo (Table 1). Heterogeneity for these results is low, but there is considerable funnel plot asymmetry. Similar effects were found in the sensitivity analyses based on ROB (SI Tables 2a-2d).

Figure 4 about here

Exploratory Analyses

The analyses below are for LCS vs sugar parallel-groups studies (random effects models).

Duration of study. Results of meta-regression analyses show no association between duration (weeks) of intervention and ΔBW (29 studies) or BWend (26 studies): largest coefficient = 0.005 (-0.002, 0.011), $P = 0.15$).

Sugar dose. Results of meta-regression analyses show an association between sugar dose replaced by LCS (MJ) and ΔBW: 22 studies, coefficient = -0.344 (-0.535, -0.152), $P < 0.01$. Results show a similar effect for BWend: coefficient = -0.126 (-0.263, 0.010), $P = 0.07$. The magnitude of this effect is such that for every 1 MJ of energy replaced by LCS, ΔBW decreases by 0.344 SDs or approximately 1.06 kg in adults assuming a mean ΔBW SD of 3.07 kg.

Blinding. Twenty-six studies provided information on whether participants were or were not blinded to the intervention. Results of subgroup analyses show no difference in the effect of the intervention as a function of blinding for either ΔBW or BWend: participants categorised as blinded, not blinded and unintentionally not blinded: largest $\chi^2(2) = 1.59$, $P = 0.45$.

LCS provision in beverages or in foods and beverages. Twenty-nine studies provided data on LCS provision. Subgroup analyses for ΔBW and BWend show no differences between the subgroups: largest: $\chi^2(1) = 0.74$, $P = 0.39$.

Funding source. Twenty-five studies provided information on funding source. Subgroup analyses show no differences between industry-funded and non-industry-funded studies in the effect of the intervention on ΔBW and BWend: largest: $\chi^2(1) = 0.02$, $P = 0.89$.

Excluded studies

Five articles[49,50,54,56,67] that reported studies that we analysed also reported other studies that did not meet our inclusion criteria. In two cases[49,54] this was because participants in the intervention group consumed LCS in foods/beverages and in capsules, while the comparator group consumed neither.

DISCUSSION

This review and meta-analyses sought to address three questions concerning the potential effects of LCS on BW, BMI and EI: (1) the effects of LCS compared with sugar (i.e., when there is a difference in energy content of the target beverages and/or foods consumed, while taste is controlled); (2) the effects of LCS compared with water or nothing (i.e., where there is no meaningful difference in energy content between treatments, while there is a difference in taste); and (3) the effects of LCS consumed in capsules vs placebo capsules (i.e., where there is no meaningful difference in energy content between treatments, and no difference in taste).

Our searches identified a considerable number of studies overall, and sufficient studies to answer each of the three questions. Almost all studies relevant to the first two questions were designed deliberately to test effects of LCS on BW, BMI and/or EI, in real life settings. A majority manipulated LCS consumption solely via beverages. A large majority of all studies was conducted with adult participants, and included individuals with healthy weight, overweight and/or obesity, and/or health conditions such as diabetes. In some studies, the intervention was superimposed on a weight loss programme.

LCS vs sugar

Consistent with the primary intended use of LCS, the results for both parallel-groups and cross-over studies showed that BW, BMI and EI were reduced by consumption of LCS compared with sugar. More limited data showed no difference in occurrence of adverse events between the LCS and sugar interventions.

The magnitude of effects in favour of LCS, for example, 1.06 kg for ΔBW in the parallel-groups studies, might be regarded as modest, nonetheless theoretically the effects on BW should be influenced by the energy difference between the LCS and sugar interventions (i.e., sugar dose) and the duration of the intervention. For the parallel-groups studies mean sugar dose was 1272 kJ/d and median intervention duration was 12 weeks. The results of our exploratory analyses support an effect of sugar dose. This effect of sugar dose is consistent with reduced EI being the primary means by which LCS reduces BW. For the parallel-groups studies in which it was measured, the mean difference in EI was 941 kJ/d (Table 1). Plausibly, the 26% difference in sugar dose and measured difference in EI is explained by increased EI from the rest of the diet which partially, but not fully, compensates for the lower energy content of the LCS-sweetened foods and/or beverages.[10,17,91] The absence of an effect of duration of these studies may in part reflect diminishing adherence to interventions over time, and to a lower intensity (including lower sugar dose) of the intervention in longer-duration studies. Nevertheless, difference in BW in favour of LCS (-0.53 kg for ΔBW) was smaller for the shorter duration cross-over studies (median duration 3 weeks).

A further result was that there was no difference in the effect on BW between studies in which participants were blinded vs not blinded to their allocation to LCS or sugar. This is consistent with other evidence for a lack of 'conscious EI compensation' with consumption of LCS foods and/or drinks.[8] It is also worth noting that, in common with all weight management interventions, the long term effect of consuming LCS in place of (some) sugar in the diet will be further limited by the increase in appetite and decrease in energy expenditure that occurs with weight loss.[17,92,93]

Difference in results across studies (heterogeneity) was mostly low to moderate. In addition to sugar dose, study duration and participant blinding, other analyses of potential sources of heterogeneity revealed no effects of consumption of LCS in beverages vs beverages and foods, or funding source (industry vs non-industry funding).

Sensitivity analyses using fixed effect models suggested low bias due to the inclusion of some large studies, but funnel plots provided evidence of biases associated with study size, including possible publication bias. Sensitivity analyses using only the studies judged to be low in attrition bias also suggest some impact of attrition. In this respect, the effects of LCS on BW and EI were smaller when only studies with low drop out were considered. These findings perhaps indicate an effect related to the acceptability or other aspects of the intervention.

LCS vs water or nothing

Overall, there was no effect of LCS vs water/nothing on BW or BMI. Results for parallel-groups studies showed higher EI with LCS than with water/nothing, but the cross-over studies showed an effect in the opposite direction. Furthermore, there was inconsistency in results (considerable heterogeneity) for effects on ΔBW and BMI within the parallel-groups studies, and for the effect on ΔBW within the cross-over studies. Taken together, these results are consistent with the zero difference in energy content of the LCS and comparator treatments in these studies, and with a lack of effect of dietary exposure to sweetness on intake of sweet foods and beverages observed in other studies.[9]

The explanation for large differences in results between studies comparing LCS vs water is uncertain. There was some evidence for biases associated with study effect size, such as publication bias. Furthermore, relatively few studies were available, and they varied widely in procedural details. The study[69] of this type with the largest number of participants enrolled consumers of LCS beverages to a behavioural weight loss programme including randomisation to continue to consume LCS beverages or water. It found an effect on BW in favour of LCS. In contrast, two studies[27,70], also involving a weight loss programme, in which participants were permitted to consume only one LCS beverage 5 d per week, showed an effect on BW, and on EI, in favour of water over LCS. It is unknown why this pattern of consumption of LCS should be disadvantageous to weight loss.

LCS in capsules vs placebo

Taken together, the results from these studies show no effect of LCS consumed in capsules compared to the consumption of (presumably inert) placebo capsules. This indicates that, beyond the effect due to reduced sugar intake, there is no meaningful post-ingestive effect on overall energy balance of the LCS tested, namely aspartame, stevia and sucralose.

For BW and for BMI, differences in results across studies (heterogeneity) was low. Across measures, however, results were inconsistent. For ΔBMI there was a statistically significant effect in favour of placebo, whereas the pattern of effects for ΔBW change, BWend and BMIend was, if anything, in favour of LCS. What accounts for these different results is unclear. Relatively few studies were available, and they largely reported BW *or* BMI, so the different outcomes may reflect different study procedures or differences in effects of different LCS. Stevia was the LCS in all the studies[78-80,83,84,87] reporting BMI as an outcome, whereas aspartame was the LCS in four[72,81,85,86] of the seven studies reporting BW as an outcome. However, BW was also measured in two stevia studies[82,83] both of which showed small effects (non-significant) for ΔBW favouring stevia over placebo. Two studies found no effects of sucralose vs placebo on BW[89,90], and one no effect on EI[90]. Therefore, in relation to energy balance, the available studies provide information about the (lack of) post-ingestive effects of three LCS. Notably, there was no difference in occurrence of adverse events between the LCS and placebo interventions, even in studies in which unusually high doses of LCS were consumed.[78,85,86]

While there is great diversity in the molecular structure of different LCS[16], currently there is limited evidence on whether different LCS differ in their effects on energy balance[16,23]. Their common feature is that they provide sweetness with zero or essentially zero energy, which is likely to be the primary reason why they reduce EI, BW and BMI compared with sugar. Further capsule studies on a wider range of LCS, and further studies like that of Higgins and Mattes[23] comparing the effects of different LCS (or even different combinations of LCS) vs sugar, would be informative, but a large undertaking.

Comparison with other reviews

Five systematic reviews with meta-analyses of the effects of LCS on BW have been published previously.[10-13,94] The most recent of these reviews[94] included fewer studies overall than the present review, and it did not investigate effects on EI. It also included two studies[31,32] that we excluded the grounds that the LCS intervention was confounded with other strategies for reducing sugar-sweetened beverage intake.

In agreement with the results of the present review, three of the previous reviews found clear evidence that consumption of LCS reduces BW compared with the consumption of sugar[10,11,94]. The other two[12,13], however, are equivocal about the effect of LCS consumption on BW; for example, "Evidence from RCTs does not clearly support the intended benefits of nonnutritive sweeteners for weight management" (p E937[12]). On the face of it these different conclusions are puzzling, especially as these two reviews are relatively recent and so had access to most of the studies we have included here. Furthermore, all these reviews include some of the same studies included in other reviews that conclude that intake of free sugars increases BW.[e.g.95]

Closer examination reveals important differences in the numbers of studies included in each of the reviews, and/or how studies are grouped for analysis. For example, Toews et al.[13] included only five studies in their meta-analysis of effects of LCS on BW. Among their criteria for inclusion of studies was that LCS "type was sufficiently specified", but arguably this is unnecessarily restrictive. It led, for example, to the exclusion of a large study (n=210)[24] in which participants were provided with "any combination of noncaloric sweetened beverages of their choice" (p 556[24]), so various types of LCS would have been consumed. Critically, however, in relation to potential effects on BW, what the beverages in this study had in common was sweetness and zero sugar and energy content. In contrast, the largest study (n = 122) included by Toews et al.[13] in their BW meta-analysis, compared the effect of LCS capsules vs placebo capsules.[82] This comparison is not relevant to the intended use of LCS as a replacement for sugar in foods and beverages. The inappropriate inclusion of this study with its null effect had a substantial effect on the overall result. As discussed by other authors[96], similar issues of the selection and combination of studies are present in the review by Azad et al.[12] To arrive at valid conclusions about the effects of LCS consumption on BW it is necessary to frame research questions and hypotheses in terms of plausible biological and behavioural mechanisms.[14] This is the approach we have taken here.

Limitations

While there were a substantial number of LCS vs sugar studies, our review is limited by the smaller number of studies available to address our second and third research questions. Our funnel plots show asymmetry, suggesting possible publication bias within the set of studies included and the reduced effects in the analyses of studies with low attrition bias indicate the presence of other biases. Many studies also failed to report SDs for ΔBW or ΔBMI, thus requiring imputation, and none of the cross-over studies reported a correlation between conditions for individual participants, requiring estimations in our analyses of cross-over studies. Our searches were confined to articles published in English. We did, however, allow the inclusion of conference abstracts and trial registrations, resulting in the inclusion of some studies that have not been included in other similar reviews.

Conclusions and future directions

The results of this review show that consumption of LCS vs sugar decreases BW, and that it does so via decreasing daily EI. The studies available to test these effects included adults and children, with healthy weight, overweight and obesity, and consumption of LCS or sugar in beverages, or in beverages and foods. In contrast, there was no clear evidence of effects on BW or EI of LCS compared with the consumption of water/nothing. There were, however, substantial differences in results across studies, so further research on this question would be valuable. At least one such study is in progress.[97] Relatedly, further studies that randomise high consumers of sugar-sweetened beverages to LCS beverages, water, or no change in beverage consumption will strengthen the evidence base for recommendations for this group of consumers. There was also no evidence overall of an effect of LCS consumed in capsules vs placebo capsules, indicating that, beyond the effect of reduced sugar intake, there is no meaningful post-ingestive effect of LCS on energy balance. Occurrence of adverse events did not differ between LCS and comparator interventions.

Supplementary information is available at International Journal of Obesity's website.

POTENTIAL CONFLICTS OF INTEREST

In connection with research on LCS and sugar, PJR has received funding for research from Sugar Nutrition UK; provided consultancy services for Coca-Cola Great Britain; received speaker's fees from the International Sweeteners Association, the Global Stevia Research Institute, ILSI-Brasil, ILSI-Europe and ILSI-India; and received honoraria from ILSI-Europe. KMA has received funding for relevant research from Unilever R&D Vlaardingen, NL; has current funding from TIFN, NL (in collaboration with Arla Foods, DK, American Beverage Association, US, Cargill, US, Dutch Knowledge Centre for Sugar, NL, Firmenich, CH, the International Sweeteners Association, BE, SinoSweet, China, Unilever, NL), and from the International Sweeteners Association; and has received speaker's expenses from the International Sweeteners Association, PepsiCo and ILSI-North America.

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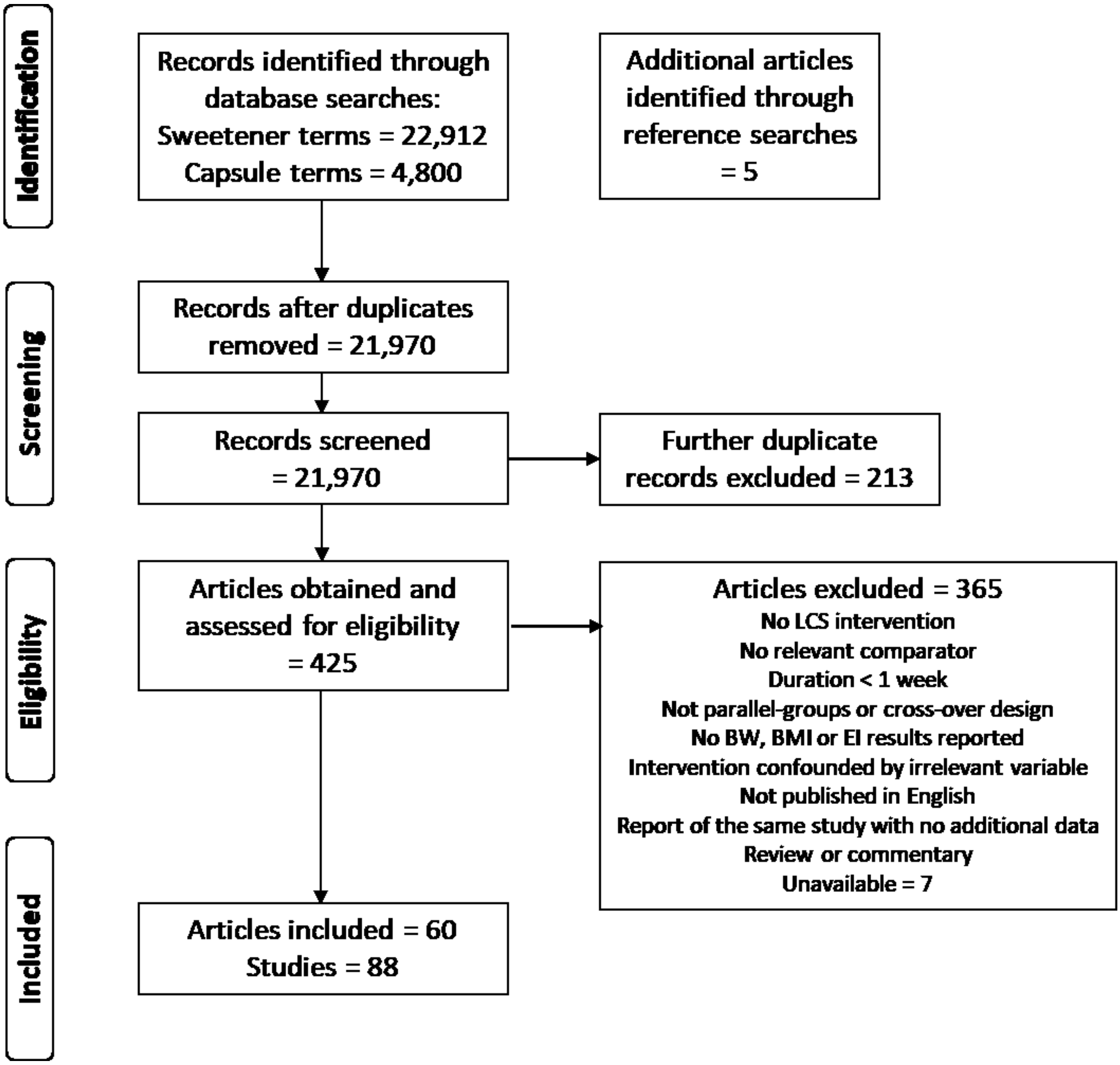

Figure 1. PRISMA flow diagram depicting the study selection procedures.

Table 1. Summary of the results of the meta-analyses (random effects models), estimates converted to relevant units

Outcome	Parallel groups studies				Cross-over studies			
	N[a]	N[b]	SMD estimates converted to relevant units[c]	I^2 [d]	N[a]	N[b]	SMD estimates converted to relevant units, [c]	I^2 [d]
LCS vs sugar								
ΔBW, kg[e]	29	2267	-1.06 (-1.50, -0.62)**	51	8	123	-0.53 (-1.01, -0.05)*	0
BWend, kg	26	2196	-1.45 (-2.50, -0.41)*	0	8	123	-0.55 (-5.34, 4.25)	0
ΔBMI, kg/m^2	11	1348	-0.35 (-0.58, -0.12)**	70	2			
BMIend, kg/m^2	11	1348	-0.27 (-0.63, 0.10)	0	2			
Energy intake, kJ	22	1397	-941 (-1341, -541)**	45	12	149	-1304 (-2118, -489)**	0
Adverse events (OR)	8	1064	0.99 (0.64, 1.53)	0	0			
LCS vs water/nothing								
ΔBW, kg[e]	11	1068	0.10 (-0.87, 1.07)	82	4	134	-0.45 (-0.91, 0.00)*	0
BWend, kg	10	1040	-0.01 (-1.55, 1.53)	3	4	134	-0.05 (-0.50, 0.39)	0
ΔBMI, kg/m^2	8	431	0.20 (-0.10, 0.51)	64	0			
BMIend, kg/m^2	8	431	0.23 (-0.40, 0.87)	0	0			
Energy intake, kJ	9	756	676 (267, 1085)**	19	3	80	-431 (-1711, 850)*	0
Adverse events (OR)	3				2			
LCS capsules vs placebo capsules								
ΔBW, kg[e]	7	521	-0.28 (-0.80, 0.25)	0	0			
BWend, kg	7	521	-0.82 (-2.94, 1.30)	0	0			
ΔBMI, kg/m^2	8	486	0.20 (0.04, 0.36)*	0	0			
BMIend, kg/m^2	8	486	-0.47 (-1.07, 0.13)	0	0			
Energy intake, kJ	0				0			
Adverse events (OR)	10	786	0.83 (0.64, 1.07)	0	0			

Abbreviations: LCS, low-calorie sweeteners; ΔBW, change in body weight; BWend, body weight at the end of the intervention; ΔBMI, change in body mass index; BMIend, body mass index at the end of the intervention; OR, odds ratio. [a]number of studies providing data suitable for analysis and included in the analysis; [b]number of participants in the analysis; [c]standardised mean difference and (95% CIs), converted to relevant units. A minus sign shows an effect in favour of LCS. [d]measure of heterogeneity in the results (%). [e]For parallel-groups studies simple linear regression with study duration as the predictor variable was used to estimate missing SDs. For cross-over studies and all other variables, missing SDs were imputed using mean SD. ***P* ≤ .01, **P* < .05. Results are for energy intake and adverse events measured during the intervention. Where cells are empty no analyses were undertaken due to insufficient numbers of studies.

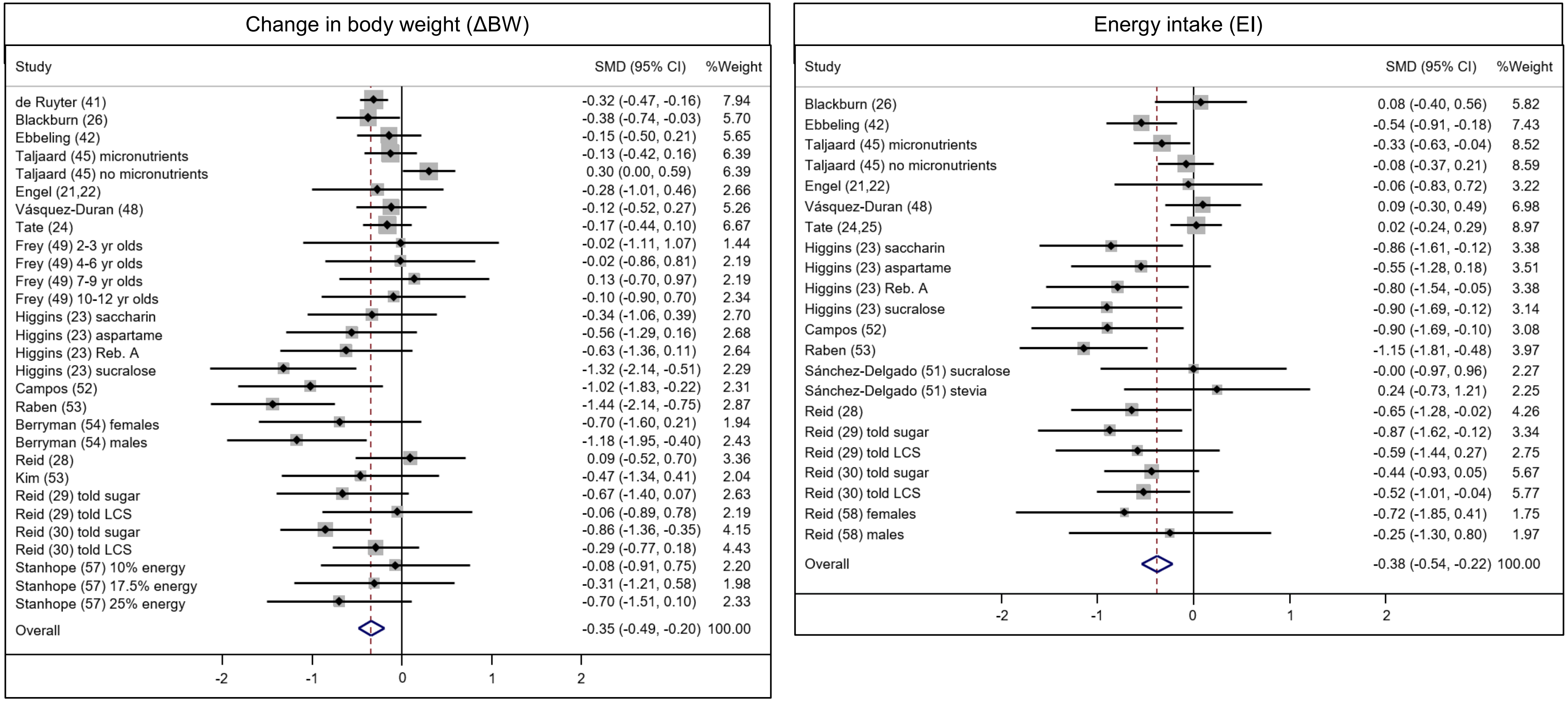

Figure 2. Forest plots showing individual and overall standardised mean differences (SMD) for the effects of LCS vs sugar for ΔBW and EI measured in parallel-groups studies (random effects models). Diamonds represent SMDs, square size represents the weight of the study (% contribution of the study to the overall result) and the horizontal lines represent the 95%CIs. Also shown is I^2 (together with its p-value), which is a measure of differences in results between studies (heterogeneity). Studies are ordered by duration of study (longest first), then date of completion (most recent first). Results to the left of the 0 line are in favour of LCS and results to the right of the line are in favour of sugar. For ΔBW the overall result can be converted to -1.06 (-1.50, -0.62) kg, and for EI the overall result can be converted to -941 (-1341, -541) kJ/d. Numbers in parentheses are study article reference numbers. Participants in studies (41), (45) and (49) were children. All other studies were conducted solely with adult participants.

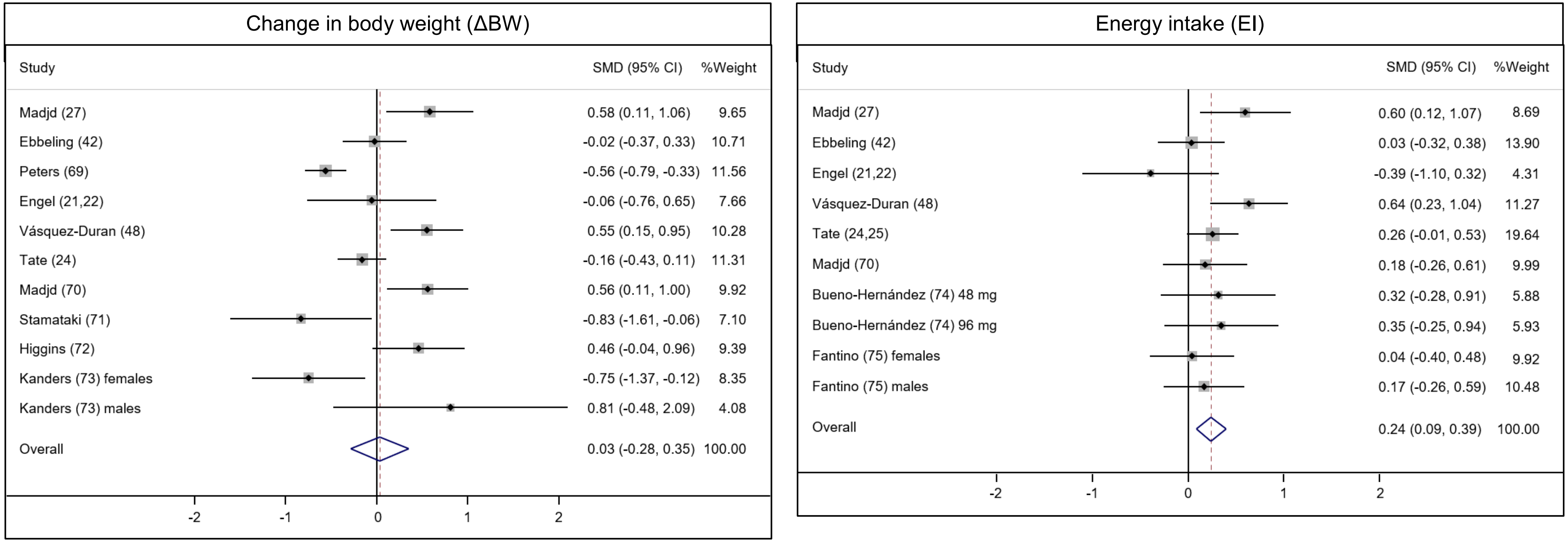

Figure 3. Forest plots showing individual and overall standardised mean differences (SMD) for the effects of LCS vs water/nothing for ΔBW and EI measured in parallel-groups studies (random effects models). Diamonds represent SMDs, square size represents the weight of the study (% contribution of the study to the overall result) and the horizontal lines represent the 95%CIs. Also shown is I^2 (together with its p-value), which is a measure of differences in results between studies (heterogeneity). Studies are ordered by duration of study (longest first), then date of completion (most recent first). Results to the left of the 0 line are in favour of LCS and results to the right of the line are in favour of sugar. For ΔBW the overall result can be converted to 0.10 (-0.87, 1.07) kg, and for EI the overall result can be converted to 676 (267, 1085) kJ/d. Numbers in parentheses are study article reference numbers.

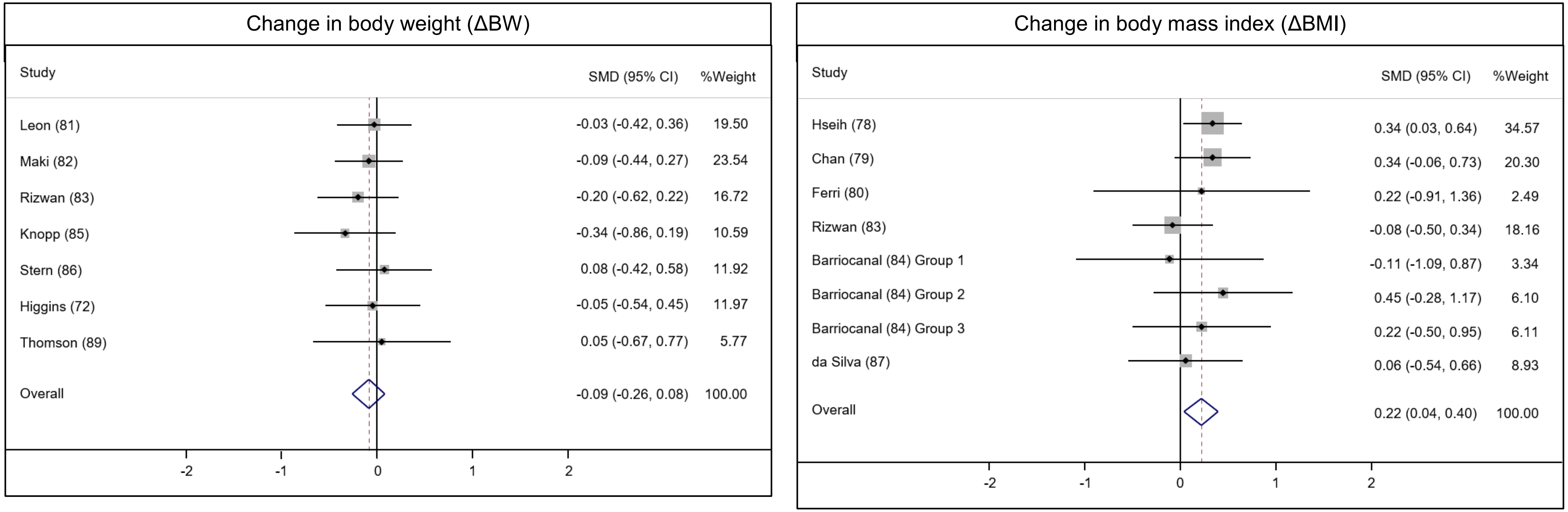

Figure 4. Forest plots showing individual and overall standardised mean differences (SMD) for the effects of LCS capsules vs placebo capsules for ΔBW and ΔBMI measured in parallel-groups studies (random effects models). Diamonds represent SMDs, square size represents the weight of the study (% contribution of the study to the overall result) and the horizontal lines represent the 95%CIs. Also shown is I^2 (together with its p-value), which is a measure of differences in results between studies (heterogeneity). Studies are ordered by duration of study (longest first), then date of completion (most recent first). Results to the left of the 0 line are in favour of LCS and results to the right of the line are in favour of sugar. For ΔBW the overall result can be converted to -0.28 (-0.80, 0.25) kg, and for ΔBMI the overall result can be converted to 0.20 (0.04, 0.36) kg/m^2. Numbers in parentheses are study article reference numbers. Participants in study (85) were aged 10-21 years. All other studies were conducted solely with adult participants.