

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

3

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

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19 **ABSTRACT**

20 Previous meta-analyses of intervention studies have come to different conclusions about  
21 effects of consumption of low-calorie sweeteners (LCS) on body weight. The present review  
22 included 60 articles reporting 88 parallel-groups and cross-over studies  $\geq 1$  week in duration  
23 that reported either body weight (BW), BMI and/or energy intake (EI) outcomes. Studies  
24 were analysed according to whether they compared (1) LCS with sugar, (2) LCS with water or  
25 nothing, or (3) LCS capsules with placebo capsules. Results showed an effect in favour of LCS  
26 vs sugar for BW (29 parallel-groups studies, 2267 participants: BW change, -1.06 kg,  
27 95%CI -1.50 to -0.62,  $I^2 = 51\%$ ), BMI and EI. Effect on BW change increased with 'dose' of  
28 sugar replaced by LCS, whereas there were no differences in study outcome as a function of  
29 duration of the intervention or participant blinding. Overall, results showed no difference in  
30 effects of LCS vs water/nothing for BW (11 parallel-groups studies, 1068 participants: BW  
31 change, 0.10 kg, 95%CI -0.87 to 1.07,  $I^2 = 82\%$ ), BMI and EI; and inconsistent effects for LCS  
32 consumed in capsules (BW change: -0.28 kg, 95%CI -0.80 to 0.25,  $I^2 = 0\%$ ; BMI change: 0.20  
33 kg/m<sup>2</sup>, 95%CI 0.04 to 0.36,  $I^2 = 0\%$ ). Occurrence of adverse events was not affected by the  
34 consumption of LCS. The studies available did not permit robust analysis of effects by LCS  
35 type. In summary, outcomes were not clearly affected when the treatments differed in  
36 sweetness, nor when LCS were consumed in capsules without tasting; however, when  
37 treatments differed in energy value (LCS vs sugar), there were consistent effects in favour of  
38 LCS. The evidence from human intervention studies supports the use of LCS in weight  
39 management, constrained primarily by the amount of added sugar that LCS can displace in  
40 the diet.

41 **INTRODUCTION**

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

56 A variety of RCTs investigating the effects of sustained (long-term) exposure to LCS  
57 on BW have been carried out. Two systematic reviews that included meta-analyses found  
58 combined evidence in favour of a beneficial effect (relatively lower BW) of LCS  
59 consumption<sup>10,11</sup>, with our earlier review concluding that “Overall, the balance of evidence  
60 indicates that use of low-energy sweeteners in place of sugar, in children and adults, leads  
61 to reduced energy intake and body weight, and possibly also when compared with water” (p  
62 381<sup>10</sup>). In contrast, two subsequent meta-analytic reviews<sup>12,13</sup> concluded that there was no  
63 clear evidence of a difference between the effects on BW of consumption of LCS vs control.  
64 In planning the present review, we set out to resolve these different conclusions in the light  
65 of the comparisons made between LCS and different controls and the recent publication of  
66 further relevant RCTs.

67 Specifically, we framed our literature search strategies and data analyses according  
68 to three questions concerning potential effects of LCS on BW<sup>14</sup>: the effects of (1) LCS  
69 compared with sugar (i.e., when there is a difference in energy content of the target  
70 beverages and/or foods consumed, while taste is controlled); (2) LCS compared with water  
71 or nothing given to the comparator group (i.e., where there is no meaningful difference in  
72 energy content between treatments, while there is a difference in sweet taste); and (3) LCS  
73 in capsules vs placebo capsules (i.e., where there is no meaningful difference in energy  
74 content between treatments, nor a difference in taste). The first of these questions bears on  
75 a primary intended use of LCS, namely the effects of reduction in sugar and energy content  
76 of beverages and foods. The second question concerns the effects of exposure to sweet  
77 taste, which might be to increase or help satisfy desire for sweetness, or to have no  
78 effect.<sup>8,9,15</sup> The third question concerns the possibility that LCS have effects on appetite, or  
79 even energy expenditure, via post-ingestive actions in the gut or post-absorptively.<sup>14,16</sup> We  
80 included studies that exposed participants to LCS and one or more of the relevant  
81 comparators for  $\geq 1$  week and measured BW, BMI and/or daily EI. We included EI as an  
82 outcome, as effects of LCS on BW and BMI can be expected to occur primarily via effects on  
83 EI.<sup>14,17</sup> Although only small changes in body weight can be expected to result from

84 consumption of LCS for one week, assessment of EI during part or all of that period will  
85 likely predict the effect on BW of longer-term consumption of LCS.

86

## 87 **METHODS**

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

95

### 96 *Definitions*

97 For the purposes of this review, we defined LCS as sweeteners and blends of sweeteners  
98 that, by virtue of their highly intense sweet taste (high potency), contribute sweetness but  
99 zero or negligible energy to a food or beverage product. This group of chemically diverse,  
100 sweet-tasting compounds includes aspartame which has an energy value of 17 kJ/g, but for  
101 humans is 180-200 times sweeter than sucrose. So, for example, where aspartame replaces  
102 50 g of sugar in a beverage it contributes 4 kJ vs 837 kJ. Essentially, therefore, aspartame  
103 like truly zero-calorie intense sweeteners such as acesulfame-K, saccharin and sucralose,  
104 provides 'sweetness without calories'.<sup>19</sup> We defined sugar as monosaccharides and  
105 disaccharides, typically sucrose, fructose, glucose, glucose syrup and high-fructose syrup.<sup>20</sup>  
106 Both this definition of sugar<sup>20</sup>, and the definition of LCS, excludes sugar alcohols (polyols)  
107 such as erythritol.

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

116

### 117 *Search strategy*

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

127

### 128 *Study Inclusion*

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

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

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

163

#### 164 *Data extraction*

165 Searches were undertaken by PJR. All search results were first screened for study inclusion  
166 via titles and abstracts independently by both authors, and all potentially relevant articles  
167 were obtained. All these articles were screened independently by both authors. Articles  
168 were only discarded if they were clearly considered unsuitable for inclusion in the review by  
169 both authors. Discordances were resolved by discussion. Data on methodological aspects of  
170 each study, all relevant available outcomes and risk of bias (ROB) were subsequently  
171 extracted, independently by both authors, for each relevant study, using a data extraction  
172 form developed specifically for the work. Data were collated by study rather than by article,  
173 to guard against overinclusion of some original studies that contributed to several reports.  
174 Where we considered that details of methods that would allow or preclude inclusion in the

175 review were required, we attempted to contact authors requesting the relevant  
176 information. Study authors were also contacted if published data were unclear in relation to  
177 our research question, or were partial. Studies were subsequently included or excluded  
178 based on this information. The instances where data were obtained and included in the  
179 present analyses are noted in the SI Details of Included Studies file, column AE.

180  
181 *Risk of bias assessment*

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

190  
191 *Data synthesis and analysis*

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

208 Data, corrected to ensure comparable direction in the measures, were analysed as  
209 standardized mean difference (SMD) (Cohen's d) with 95% confidence intervals (95%CI),  
210 using intention-to-treat (ITT) data (based on number of participants at study entry), where  
211 possible, or as Odds Ratios (Mantel-Haenszel estimations).<sup>35,36</sup> Estimates were made using  
212 random effects models primarily, due to likely heterogeneity between studies. Fixed effect  
213 models were also applied as sensitivity analyses.<sup>35,36</sup> Where research included multiple  
214 treatment or comparator groups, each treatment or comparator group was treated as an  
215 independent study, and numbers involved in single comparison groups were divided.  
216 Missing standard deviations (SDs) at end of intervention were carried forward from  
217 available baseline data or imputed using the mean of SDs available from other similar

218 studies.<sup>37</sup> For  $\Delta$ BW for parallel groups studies, missing SDs were calculated from the results  
219 of simple linear regression analysis predicting SD from study duration (SI p 6).

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

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

236

## 237 RESULTS

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

243

244 Figure 1 about here.

245

### 246 (1) LCS vs sugar

247 *Included Studies.* A total of 51 studies compared LCS with sugar: 37 parallel-groups studies<sup>21-</sup>  
248 <sup>26,28-30,41-58</sup> (one of these<sup>21</sup> was partly reported earlier in<sup>59</sup>) and 14 cross-over studies<sup>60-68</sup>.

249 Children were participants in 11 studies<sup>41,45,49,64</sup>, and adults were participants in 40 studies<sup>21-</sup>  
250 <sup>24,26,28-30,42-44,46,50-63,65-68</sup>. In 13 studies, all the participants were people with overweight

251 and/or obesity.<sup>21-24,26,28,29,52,53,60</sup> Studies also included participants with type 1 diabetes<sup>63</sup>,

252 type 2 diabetes<sup>44,61</sup>, or gall stones<sup>62</sup>. In two studies, the interventions were incorporated

253 into an otherwise identical weight loss programme.<sup>24,26</sup> Five articles reported research on

254 exclusively female participants<sup>26,28-30,55</sup>, and one article reported research on exclusively

255 male participants<sup>66</sup>. All other articles included both female and male participants (or gender

256 was not specified<sup>46,47</sup>), with results reported separately for females and males in three

257 articles<sup>54,58,65</sup>. In 33 studies the LCS vs sugar intervention involved beverages only<sup>21-24,28-</sup>  
258 <sup>30,41,42-46,48,50,52,55-58,60,65,67,68</sup>, and in 18 studies it involved beverages and foods<sup>26,49,51,53,54,61-</sup>

259 <sup>64,66</sup>. The LCS was aspartame in 24 studies<sup>21-23,26,28-30,49,55-58,61,64,65</sup>, sucralose in six

260 studies<sup>23,44,45,50,51</sup>, saccharin in four studies<sup>23,62,64</sup>, stevia/rebaudioside A in three

261 studies<sup>23,51,68</sup> and cyclamate in one study<sup>63</sup>. The type of LCS was mixed<sup>41,53,54,60,66,67</sup> or not

262 specified<sup>24,42,43,46-48,52</sup> in 13 studies. For the parallel-groups studies the median duration of  
263 the interventions was 12 weeks (1 to 78 weeks; mean = 16.5 weeks), and for the cross-over  
264 studies it was 3 weeks (1 to 6 weeks; mean = 3.2 weeks). Articles reporting 30 parallel-  
265 groups studies<sup>21-24,26,28-30,41-43,45,46,50-53,55-58</sup> and 13 cross-over studies<sup>60-62,64,65-67,68</sup> provided  
266 data on sugar dose: parallel-group studies mean = 1272 kJ/d (median = 1308 kJ/d), cross-  
267 over studies mean = 1542 kJ/d (median = 1591 kJ/d). The studies were carried out  
268 predominantly in the USA (28 studies) and Europe (16 studies).

269 Assessments of ROB are summarised in SI Table 1a. Judgements of low ROB for use  
270 of ITT analysis were given to 22 studies<sup>23,24,28,41,49,53,60-64,66,68</sup>, and judgements of low ROB for  
271 low drop out were given to 34 studies<sup>24,28,30,42,43,45,48-53,57,58,60-64,66-68</sup>. For 35 studies, the  
272 authors report that participants were blinded to the intervention<sup>23,28-  
273 30,41,44,45,49,53,55,57,58,60,61,64-67</sup>, although in three of these some participants correctly guessed  
274 their treatment allocation<sup>23,41,53</sup>. Twenty-two studies received funding from industry<sup>24,26,28,29,  
275 44,45,49,50,53,54,60,62,64</sup>, 21 did not<sup>21,23,30,41,42,43,51,52,57,61,65,67,68</sup>, and funding source was not  
276 reported for eight studies<sup>46,48,55,56,58,63,66</sup>.

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

283

284 Table 1 about here.

285

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

293 Eleven studies using a parallel-groups design provided BMI data that could be  
294 combined<sup>21-23,41,45,48,52,53</sup>. They show an effect in favour of LCS for  $\Delta$ BMI (Table 1 and Figure  
295 2). Two cross-over studies<sup>60,68</sup> provided BMI data. Both found small, non-significant effects  
296 on BMI.

297 There is moderate heterogeneity in the results for  $\Delta$ BW and  $\Delta$ BMI, and some funnel  
298 plot asymmetry (SI p 17). Effects are comparable, however, to those found in BWend and  
299 BMIend analyses. Furthermore, comparable but somewhat smaller effects were found in all  
300 sensitivity analyses.

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

305

306 Figure 2 about here

307



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

313

314 *Adverse events.* Eight studies provided data on adverse events.<sup>26,41-43,48,49</sup> There was no  
315 difference in the occurrence of adverse events for LCS vs sugar.

316

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

321

322 (2) LCS vs water/nothing

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

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

354

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

365  
366 *Energy Intake.* Ten parallel-groups studies<sup>21,24,25,27,42,43,48,70,74,75</sup> and three cross-over  
367 studies<sup>65,77</sup> provided EI data that could be combined. Analyses showed higher EI for LCS in  
368 parallel-groups studies, but lower EI for LCS in cross-over studies (Table 1). Within these two  
369 sets of studies there is low heterogeneity in results, and some funnel plot asymmetry (SI p  
370 18). Similar effects were found in all sensitivity analyses that could be conducted (SI Tables  
371 2a-2d).

372  
373 *Adverse events.* Results for adverse events were reported for four studies.<sup>43,48,74</sup> In total,  
374 thirteen adverse events were recorded for the LCS groups, mainly in two studies<sup>74</sup>, while  
375 zero adverse events were recorded for the water/nothing treatment groups.

376  
377 *Other anthropometric measures:* Eight studies provided data on other anthropometric  
378 measures: fat mass<sup>21,22,42,43,72</sup>, fat-free mass<sup>21,22,72</sup>, waist circumference<sup>24,27,48,69,70,77</sup> hip  
379 circumference<sup>48</sup>. Results for these measures do not differ clearly from the pattern of results  
380 for BW and BMI.

381  
382 Figure 3 about here

383  
384 (3) LCS capsules vs placebo capsules

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

396 Assessments of ROB are summarised in SI Table 1c. All articles reported that the  
397 studies were carried out double blind, except for one single-blind study.<sup>83</sup> Three studies  
398 were judged low ROB for conducting ITT analyses<sup>83,88,90</sup>. All studies were judged low ROB for  
399 drop out. The studies were carried out in the USA (six studies), South America (six studies)

400 and Asia (four studies). Five studies received funding from industry<sup>72,81,82,85,88</sup>, eight did  
401 not<sup>80,83,84,87,89,90</sup>. Funding source was not reported for three studies<sup>78,79,86</sup>.

402

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

412

413 *Energy Intake.* Narrative results on EI were provided for two studies<sup>88,90</sup>. The authors report  
414 no effect of LCS vs placebo.

415

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

420

421 Figure 4 about here

422

#### 423 Exploratory Analyses

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

425

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

429

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

436

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

441

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

445

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

449  
450 Excluded studies

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

455  
456 **DISCUSSION**

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

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

472  
473 LCS vs sugar

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

478 The magnitude of effects in favour of LCS, for example, 1.06 kg for  $\Delta$ BW in the  
479 parallel-groups studies, might be regarded as modest, nonetheless theoretically the effects  
480 on BW should be influenced by the energy difference between the LCS and sugar  
481 interventions (i.e., sugar dose) and the duration of the intervention. For the parallel-groups  
482 studies mean sugar dose was 1272 kJ/d and median intervention duration was 12 weeks.  
483 The results of our exploratory analyses support an effect of sugar dose. This effect of sugar  
484 dose is consistent with reduced EI being the primary means by which LCS reduces BW. For  
485 the parallel-groups studies in which it was measured, the mean difference in EI was 941 kJ/d  
486 (Table 1). Plausibly, the 26% difference in sugar dose and measured difference in EI is  
487 explained by increased EI from the rest of the diet which partially, but not fully,  
488 compensates for the lower energy content of the LCS-sweetened foods and/or  
489 beverages.<sup>10,17,91</sup> The absence of an effect of duration of these studies may in part reflect

490 diminishing adherence to interventions over time, and to a lower intensity (including lower  
491 sugar dose) of the intervention in longer-duration studies. Nevertheless, difference in BW in  
492 favour of LCS (-0.53 kg for  $\Delta$ BW) was smaller for the shorter duration cross-over studies  
493 (median duration 3 weeks).

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

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

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

512

513 LCS vs water or nothing

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

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

532

533 LCS in capsules vs placebo

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

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

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

560

#### 561 Comparison with other reviews

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

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

576 Closer examination reveals important differences in the numbers of studies included  
577 in each of the reviews, and/or how studies are grouped for analysis. For example, Toews et

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

593

#### 594 Limitations

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

605

#### 606 Conclusions and future directions

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

620

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

622

623 **POTENTIAL CONFLICTS OF INTEREST**

624 In connection with research on LCS and sugar, PJR has received funding for research from  
625 Sugar Nutrition UK; provided consultancy services for Coca-Cola Great Britain; received  
626 speaker's fees from the International Sweeteners Association, the Global Stevia Research  
627 Institute, ILSI-Brasil, ILSI-Europe and ILSI-India; and received honoraria from ILSI-Europe.  
628 KMA has received funding for relevant research from Unilever R&D Vlaardingen, NL; has  
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630 Association, US, Cargill, US, Dutch Knowledge Centre for Sugar, NL, Firmenich, CH, the  
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634

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645

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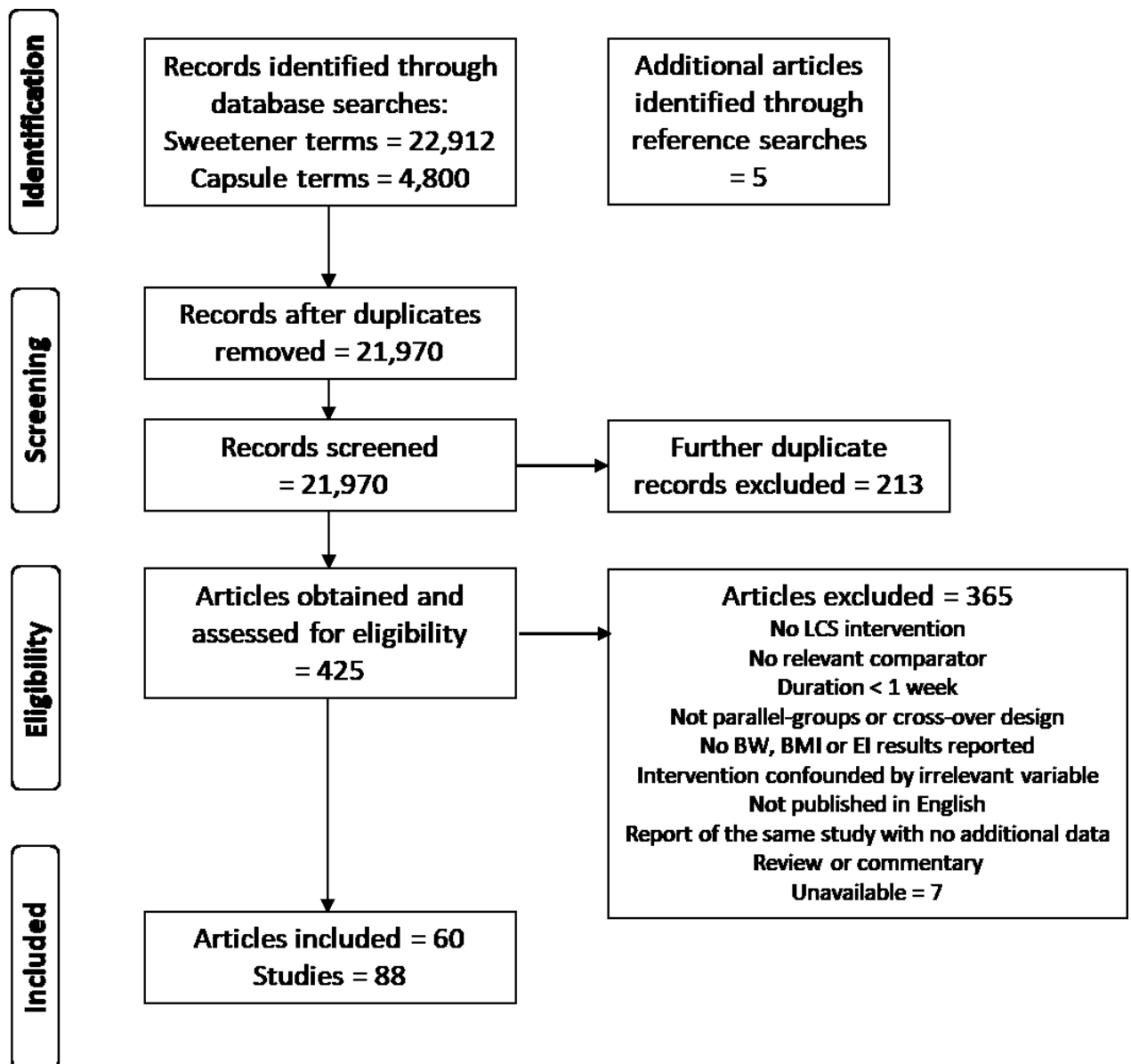
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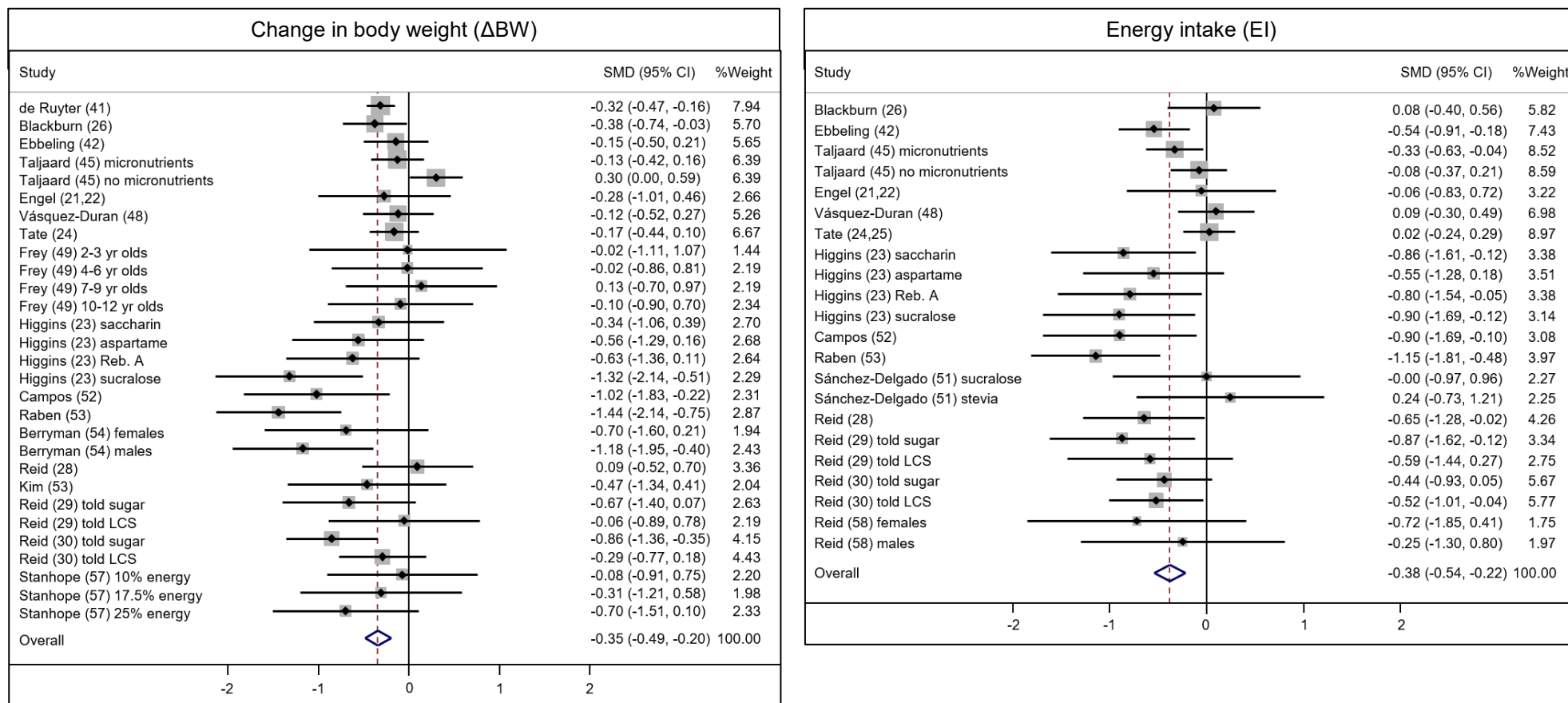
Figure 1. PRISMA flow diagram depicting the study selection procedures.



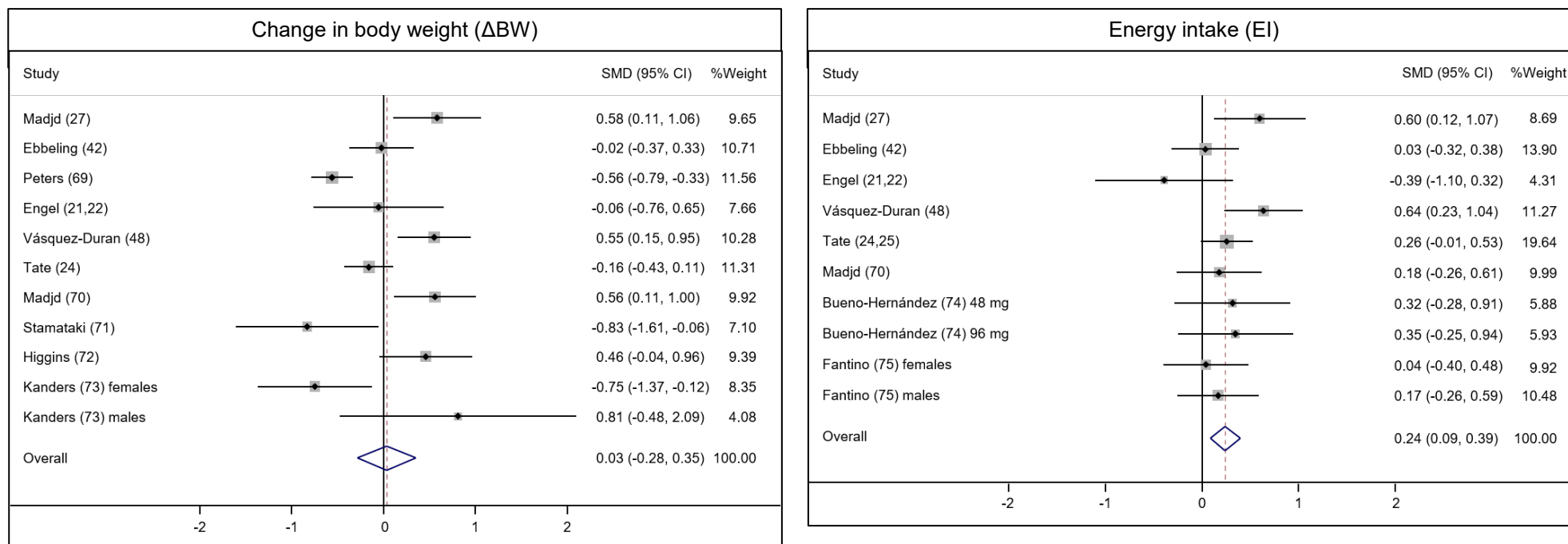
**Table 1.** Summary of the results of the meta-analyses (random effects models), estimates converted to relevant units

Outcome	Parallel groups studies				Cross-over studies			
	N <sup>a</sup>	N <sup>b</sup>	SMD estimates converted to relevant units <sup>c</sup>	I <sup>2</sup> <sup>d</sup>	N <sup>a</sup>	N <sup>b</sup>	SMD estimates converted to relevant units, <sup>c</sup>	I <sup>2</sup> <sup>d</sup>
<i>LCS vs sugar</i>								
ΔBW, kg <sup>e</sup>	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 <sup>2</sup>	11	1348	-0.35 (-0.58, -0.12)**	70	2			
BMIend, kg/m <sup>2</sup>	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			
<i>LCS vs water/nothing</i>								
ΔBW, kg <sup>e</sup>	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 <sup>2</sup>	8	431	0.20 (-0.10, 0.51)	64	0			
BMIend, kg/m <sup>2</sup>	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			
<i>LCS capsules vs placebo capsules</i>								
ΔBW, kg <sup>e</sup>	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 <sup>2</sup>	8	486	0.20 (0.04, 0.36)*	0	0			
BMIend, kg/m <sup>2</sup>	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			

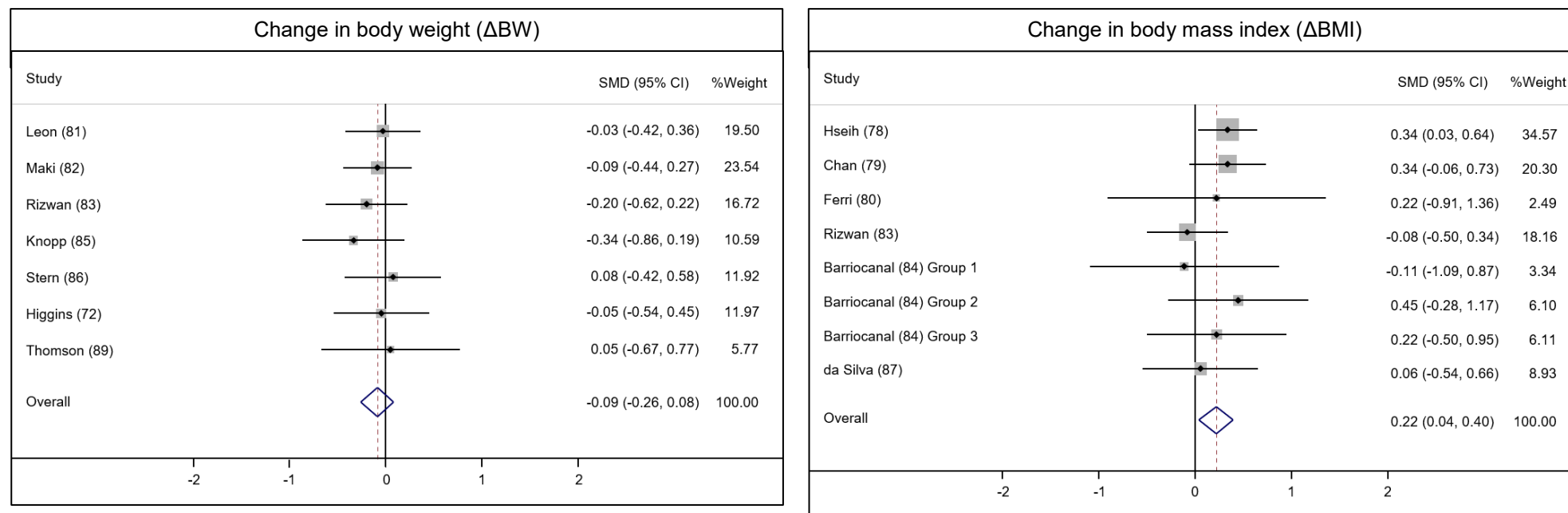
Abbreviations: LCS, low-calorie sweeteners; ΔBW, change in body weight; BWend, body weight at the end of the intervention; ΔBMI, change in body mass index; BMIend, body mass index at the end of the intervention; OR, odds ratio. <sup>a</sup>number of studies providing data suitable for analysis and included in the analysis; <sup>b</sup>number of participants in the analysis; <sup>c</sup>standardised mean difference and (95% CIs), converted to relevant units. A minus sign shows an effect in favour of LCS. <sup>d</sup>measure of heterogeneity in the results (%). <sup>e</sup>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. \*\* $P \leq .01$ , \* $P < .05$ . 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 standardized mean differences (SMD) for the effects of LCS vs sugar for  $\Delta$ BW 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  $\Delta$ BW 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  $\Delta$ BW 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  $\Delta$ BW 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  $\Delta$ BW and  $\Delta$ BMI 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  $\Delta$ BW the overall result can be converted to -0.28 (-0.80, 0.25) kg, and for  $\Delta$ BMI the overall result can be converted to 0.20 (0.04, 0.36) kg/m<sup>2</sup>. 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.