The evidence to support these conclusions comes from three SRs/MA published between January 2010 and August 2014.1-3 In total, 39 articles were considered in these reviews, of which six were included in two or more reviews. Experimentally, the protocols described in the 39 articles included RCTs and prospective cohort studies. Although results from both experimental designs were carefully assessed, the DCAC deemed evidence from RCTs to be scientifically stronger and used it as the foundation for conclusions pertaining to body weight.

Among prospective cohort studies, LCS intake was not associated with body weight or fat mass, but was significantly associated with slightly higher BMI (0.03; 95% CI = 0.01 to 0.06).2 These findings should be viewed with caution, however, because of the high risk of reverse causality and the possibility that people with higher body weights would consume more LCS-containing foods and beverages as a weight-control strategy.

Evidence from short-term RCTs consistently indicated that LCSs (vs. sugar-containing foods and beverages) modestly reduces body weight in adults. When evidence from adults and children were combined, LCSs modestly reduced BMI, fat mass, and waist circumference. The primary research articles used by Miller and Perez for the MA contained findings from both adults (n=5 cohorts) and children (n=4 cohorts).2 The results of interventions lasting 3 to 78 weeks indicated that LCSs reduced body weight in adults (-0.72 kg; 95% CI = -1.15 to -0.30) and children (-1.06 kg; 95% CI = -1.17 to -0.56). Age-specific results were not provided for BMI, fat mass, or waist circumference, but data from both age groups were pooled to show the impact of LCSs vs. sugar-containing foods/beverages on these outcomes.
In contrast, Brown et al. summarized that very limited evidence from three short-term (12 to 25 week) RCTs, which suggested that consumption of LCS does not influence body weight or BMI in predominantly pre-teenage and teenage youth (ages 10 to 21 years), compared to sugar-sweetened beverage or placebo. The authors cautioned that insufficient data exist to assess causality of LCS on body weight. The evidence reported in this 2010 publication was obtained from very heterogeneous experimental designs and interventions. One study tested the effects of encapsulated aspartame vs. placebo during weight loss; another allowed subjects to exchange sugar-sweetened beverages with either LCS beverages or water (precluding assessment of LCS beverages specifically); and a third was described as a “pilot study.”

Collectively, evidence is mixed on the impact of LCSs vs. sugar-containing foods/beverages on body weight in children. However, the DGAC deemed evidence presented by Miller and Perez to be stronger than from Brown et al. because it culminated from a larger, more recent research base and include both systematic review and meta-analysis assessment and evaluation techniques.

Table 1. Summary of existing reports, systematic reviews, and meta-analyses examining the relationship between the intake of low-calorie sweeteners (LCS) and body weight or risk of obesity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Publication Type</th>
<th>AMSTAR Rating*</th>
<th>Low-calorie Sweeteners (LCS) Considered</th>
<th>Outcomes Considered</th>
<th>Date Range Searched</th>
<th>Included Studies** (Number and Design)</th>
<th>Recommendations, Evidence/Conclusion Statements, and/or Main Results from Existing Report/ SR/ MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown, 2010</td>
<td>Systematic Review</td>
<td>AMSTAR: 8/11</td>
<td>“Artificial sweeteners” identified by the following terms: artificial sweeteners, sweetening agent, sweetener, sugar substitute, nonnutritive sweetener, intense sweetener, sucralose, aspartame, saccharin, sugar free, metabolic health effects, such as food intake, weight change, diabetes, and metabolic health effects, such as food intake, weight change, diabetes, and metabolic syndrome components; and provide original data. Articles published solely in abstract form were omitted.</td>
<td>No date restriction (published in 2010) Studies were required to: be published in peer reviewed journals in the English language, include pediatric subjects age 0 to 18; specifically address artificial sweetener consumption in association with metabolic health effects, such as food intake, weight change, diabetes, and metabolic syndrome components; and provide original data. Articles published solely in abstract form were omitted.</td>
<td>18 studies (included 3 RCTs, 6 prospective cohort studies, 3 cross-sectional studies, and 6 food intake studies)</td>
<td>Conclusion: Presently, there is no strong clinical evidence for causality regarding artificial sweetener use and metabolic health effects, but it is important to examine possible contributions of these common food additives to the global rise in pediatric obesity and diabetes. <strong>Main Results:</strong> General trend from 6 food intake studies is that artificial sweeteners may reduce total caloric intake when consumed between meals, but when consumed with meals, children may compensate for low-calorie snacks or drinks by increasing meal-associated calories. Data from the 6 epidemiologic studies support the existence of an association between artificially-sweetened beverage consumption and weight gain in children. The few small, randomized controlled trials conducted in children did not find an association between artificial sweetener consumption and weight change.</td>
<td></td>
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</tbody>
</table>
## Appendix E-2.47: LCS and Body Weight Evidence Portfolio

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Methods</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Miller, 2014</strong>&lt;br&gt;Systematic Review and Meta-Analysis</td>
<td>All individual LCS (generic and name brands) approved for use globally; food and beverage sources of LCS such as &quot;diet soda&quot;; and sweeteners with different names such as &quot;intense sweetener&quot; or &quot;polyol&quot;&lt;br&gt;At least one measure of body weight or composition</td>
<td>Up to September 16, 2013&lt;br&gt;Prospective cohorts and RCTs were eligible if study population was generally healthy (not hospitalized or acutely ill); dose or intake data for at least one LCS (nonnutritive sweetener or polyol) or delivery vehicle of LCS were provided; the effect of LCS, compared with the control arm, could be examined independently of other intervention components; and outcome data for at least one measure of body weight or composition were available</td>
<td>15 RCTs and 9 prospective cohort studies</td>
<td>The meta-analysis of observational studies showed a small positive association between LCS intake and BMI, but no association with body weight or fat mass. On the other hand, data from RCTs, which provide the highest quality of evidence for examining the potentially causal effects of LCS intake on body weight, indicate that substituting LCS for calorically dense alternatives results in a modest reduction of body weight, BMI, fat mass and waist circumference. Conclusion: The meta-analysis of observational studies showed a small positive association between LCS intake and BMI, but no association with body weight or fat mass. On the other hand, data from RCTs, which provide the highest quality of evidence for examining the potentially causal effects of LCS intake on body weight, indicate that substituting LCS for calorically dense alternatives results in a modest reduction of body weight, BMI, fat mass and waist circumference.</td>
</tr>
<tr>
<td><strong>Wiebe, 2011</strong>&lt;br&gt;Systematic Review</td>
<td>High-intensity caloric sweeteners that are functionally non-caloric</td>
<td>1950 – January 2013&lt;br&gt;Parallel or crossover RCTs comparing sweeteners in generally healthy, overweight/obese and/or diabetic adults (≥ 16 years old). Trials had to have at least two groups comparing different sweeteners</td>
<td>3 RCTs (of the 13 trials looking at weight management, blood glucose and blood lipids, three trials compared a non-caloric sweetener to sucrose; 10 trials compared a saccharide to a different</td>
<td>Conclusion: Although data suggest that non-caloric sweeteners may lead to clinically relevant weight loss through reduced energy consumption; this conclusion was driven by a single trial with a total of 41 participants. Main Results: Two of the three trials reported change in BMI. A four-week trial in healthy participants did not find a significant loss in BMI in non-caloric sweetener recipients (-0.3 kg/m², 95% CI: -1.1 to 0.5). A 10-week trial in 41 overweight participants found a...</td>
</tr>
</tbody>
</table>
and at least one week of follow-up. Trials with less than 10 participants were excluded.

| saccharide) | significantly greater loss in BMI in participants consuming the non-caloric sweetener (-0.9 kg/m², 95% CI: -1.5 to -0.4). One crossover trial in 10 type 1 diabetic participants found no difference in weight loss between groups over four weeks (0.8 kg, 95% CI: -3.3 to 4.9).

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* A measurement tool for the ‘assessment of multiple systematic reviews’ (AMSTAR)

**Reference overlap: Of the 39 articles included in total across the reviews, 6 were included in two or more reviews.

**References Included in Review**


Supplementary Information:

(Note: One search for low-calorie sweeteners and body weight, type 2 diabetes, cardiovascular disease, and dental caries was conducted. Only reviews on body weight and type 2 diabetes were identified and are presented below.)

Methodology

This question was answered using existing SRs/MA published from January 2010 to August 2014.

Search Strategy for Existing Systematic Reviews/Meta-Analyses

PubMed:

(Non-caloric sweeten* OR non caloric sweeten* OR "Non-Nutritive Sweeteners"[Mesh] OR Non-Nutritive Sweetener*[tiab] OR Non Nutritive Sweetener*[tiab] OR low calorie sweeten* OR (artificial* sweeten*) OR “sugar free” OR sugar-free OR saccharin OR aspartame OR acetasulfame OR sucralose OR trichlorosucrose OR neotame OR erythritol OR rebaudioside* OR rebiana OR diet soda* OR diet drink* OR (intense* sweeten*[tiab])) pooled analysis* OR systematic[sb] OR systematic review* OR meta-analys* OR meta analys* OR lim to SR/MA

Embase:

(Non-caloric NEXT/1 sweeten*) OR ("non caloric" NEXT/1 sweeten*) OR (Non-Nutritive NEXT/1 Sweeten*) OR “Non-Nutritive” NEXT/1 Sweeten* OR "Non Nutritive" NEXT/1 Sweeten* OR “low calorie” NEXT/1 sweeten* OR (artificial* NEXT/1 sweeten*) OR “sugar free” OR sugar-free OR saccharin OR aspartame OR acetasulfame OR sucralose OR trichlorosucrose OR neotame OR erythritol OR rebaudioside* OR rebiana OR diet soda* OR diet drink* OR (intense* NEXT/1 sweeten*) OR advantame OR (sugar NEXT/1 substitute*) OR stevia OR cyclamate* OR (monk NEXT/1 fruit*)
'systematic review'/exp OR 'meta analysis'/exp OR pooled NEXT/1 analysis* OR “systematic review” OR meta NEXT/1 analys*

Cochrane:

(Non-caloric NEXT/1 sweeten*) OR ("non caloric" NEXT/1 sweeten*) OR (Non-Nutritive NEXT/1 Sweeten*) OR “Non-Nutritive” NEXT/1 Sweeten* OR "Non Nutritive" NEXT/1 Sweeten* OR “low calorie” NEXT/1 sweeten* OR (artificial* NEXT/1 sweeten*) OR “sugar free” OR sugar-free OR saccharin OR aspartame OR acetasulfame OR sucralose OR trichlorosucrose OR neotame OR erythritol OR rebaudioside* OR rebiana OR diet soda* OR diet drink* OR (intense* NEXT/1 sweeten*) OR advantame OR (sugar NEXT/1 substitute*) OR stevia OR cyclamate* OR (monk NEXT/1 fruit*)
Inclusion Criteria

Date Range:
- Published between January 2010 and August 2014 (in English in a peer-reviewed journal)

Study Design:
- Systematic review and/or meta-analysis that included randomized controlled trials and/or prospective cohort studies

Study Subjects:
- Reviews that included studies from high or very high human development (2012 Human Development Index)
- Healthy or at elevated chronic disease risk

Intervention/Exposure:
- Low-calorie sweetener - The Committee approached this topic broadly, including sweeteners labeled as low-calorie sweeteners, non-caloric sweeteners, non-nutritive sweeteners, artificial sweeteners, and diet beverages.

Outcome:
- Body weight: Body mass index, body weight, percent body fat, waist circumference, incidence of overweight or obesity
- Type 2 diabetes: Glucose intolerance, insulin resistance, or incidence of type 2 diabetes

Quality:
- Reviews rated 8-11 on AMSTAR (A measurement tool for the ‘assessment of multiple systematic reviews’)

Search Results

Excluded Articles with Reason for Exclusion


(prospective analysis to examine associations between SSBs and ASBs with self-reported incident hypertension)


dental carries not included as outcome; review focused on comparisons with no chewing gum as a control


