Low-calorie sweeteners and weight – a systematic review of human and animal studies

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Disclosures

• I have received funding for research from Sugar Nutrition UK, provided consultancy services for Coca-Cola Great Britain and received speaker’s fees from the International Sweeteners Association and the Global Stevia Research Institute.

• I will be referring to a systematic review and meta-analyses of effects of low-calorie sweeteners on energy intake and body weight. This review was initiated by ILSI-Europe, who also provided administrative support, hosted meetings of the authors, and paid the academic authors travel expenses and honoraria. Two of the eleven authors of the review are food industry employees, and one was an ILSI-Europe employee.
Theoretically, low-calorie sweeteners ought help reduce body weight because:

• By replacing all or some sugar, low-calorie sweeteners reduce the energy content of foods and especially drinks

• And reduced energy intake in a meal or snack is not fully compensated for by increased energy intake at the next or subsequent meals or snacks

Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies

P J Rogers, P S Hogenkamp, K de Graaf, S Higgs, A Lluch, A R Ness, C Penfold, R Perry, P Putz, M R Yeomans and D J Mela

International Journal of Obesity (2016) 40, 381-394
Effects of low-calorie sweeteners consumption on body weight: **animal studies**

- BW gain when LCS added to food or drink, compulsorily or voluntarily consumed compared with BW gain on the food or drink without LCS:

  68 studies: 22↓  37→  9↑

Effects of low-calorie sweeteners consumption on body weight: animal studies

• BW gain when LCS added to food or drink, compulsorily or voluntarily consumed compared with BW gain on the food or drink without LCS:
  68 studies: 22↓ 37→ 9↑

• BW gain when LCS added to a dietary supplement compared with BW gain when glucose added to the same dietary supplement:
  22 studies: 0↓ 3→ 19↑

Rogers et al. (2016) International Journal of Obesity, 40, 381-394
Sweet taste as a predictor of food energy (sugar) content

Unsweetened yogurt 3 d/wk
Sweetened yogurt 3 d/wk
Non-predictive (of additional calories) = Saccharin
OR
Predictive (of additional calories) = Glucose

Rat chow ad libitum

Fig. 2. Total caloric intake tended to be greater in rats given access to saccharin-sweetened yogurt diet supplements in which sweet taste did not predict increased calories (Non-Predictive group) compared to animals given glucose-sweetened yogurt diet supplements (Predictive group) in which sweet taste did reliably predict increased calories (ns = 8-9 per group).
Sweet taste as a predictor of food energy (sugar) content

Swithers et al. (2010) *Physiology and Behavior, 100*, 55-62

Boakes et al. (2016) *Appetite, 105*, 105-128
Low-calorie sweeteners consumption and BMI: prospective cohort studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Follow-up (months)</th>
<th>Sample size</th>
<th>Weight (%)</th>
<th>Change in BMI [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fowler et al, 2008 (M+F, adult)</td>
<td>96</td>
<td>3371</td>
<td>6.4</td>
<td>0.20 [0.12, 0.29]</td>
</tr>
<tr>
<td>Chen et al, 2009 (M+F, adult)</td>
<td>18</td>
<td>810</td>
<td>4.0</td>
<td>-0.13 [-0.25, -0.01]</td>
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<tr>
<td>Vanselov et al, 2009 (M+F, adult)</td>
<td>60</td>
<td>2294</td>
<td>7.3</td>
<td>0.01 [-0.07, 0.09]</td>
</tr>
<tr>
<td>Pan et al, 2013 (F, adult) - NHS</td>
<td>48</td>
<td>50013</td>
<td>20.7</td>
<td>-0.04 [-0.05, -0.03]</td>
</tr>
<tr>
<td>Pan et al, 2013 (F, adult) - NHS II</td>
<td>48</td>
<td>52987</td>
<td>20.4</td>
<td>-0.03 [-0.04, -0.02]</td>
</tr>
<tr>
<td>Pan et al, 2013 (M, adult) - HPS</td>
<td>48</td>
<td>21988</td>
<td>20.4</td>
<td>-0.04 [-0.05, -0.03]</td>
</tr>
<tr>
<td><strong>RE estimate for sub-group</strong></td>
<td></td>
<td></td>
<td></td>
<td>-0.02 [-0.05, 0.01]</td>
</tr>
<tr>
<td>Sig. test of ES = 0: Z = -1.493, p = 0.135</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Het.: p &lt; 0.001, I² = 85.6 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berkey et al, 2004 (M, children)</td>
<td>12</td>
<td>5067</td>
<td>5.7</td>
<td>0.12 [0.02, 0.21]</td>
</tr>
<tr>
<td>Berkey et al, 2004 (F, children)</td>
<td>12</td>
<td>6688</td>
<td>8.4</td>
<td>0.05 [-0.02, 0.12]</td>
</tr>
<tr>
<td>Striegel-Moore et al, 2006 (F, children)</td>
<td>120</td>
<td>2371</td>
<td>6.0</td>
<td>-0.04 [-0.13, 0.05]</td>
</tr>
<tr>
<td>Laska et al, 2012 (M, children)</td>
<td>24</td>
<td>276</td>
<td>0.3</td>
<td>-0.09 [-0.56, 0.38]</td>
</tr>
<tr>
<td>Laska et al, 2012 (F, children)</td>
<td>24</td>
<td>286</td>
<td>0.3</td>
<td>0.10 [-0.35, 0.55]</td>
</tr>
<tr>
<td><strong>RE estimate for sub-group</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.04 [-0.02, 0.11]</td>
</tr>
<tr>
<td>Sig. test of ES = 0: Z = 1.298, p = 0.194</td>
<td></td>
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<tr>
<td>Het.: p = 0.229, I² = 28.9 %</td>
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<tr>
<td><strong>Overall RE estimate</strong></td>
<td></td>
<td></td>
<td></td>
<td>-0.01 [-0.03, 0.02]</td>
</tr>
<tr>
<td>Sig. test of ES = 0: Z = -0.397, p = 0.692</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Het.: p &lt; 0.001, I² = 80.2 %</td>
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</tbody>
</table>

Change in BMI (kg/m^2)
Cause or effect?
Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies

P J Rogers, P S Hogenkamp, K de Graaf, S Higgs, A Lluch, A R Ness, C Penfold, R Perry, P Putz, M R Yeomans and D J Mela

International Journal of Obesity (2016) 40, 381-394

5506 articles identified from Medline and Embase via OVID interface and Web of Science

Excluded articles: 3251
- Duplicates: 1512
- In vitro: 218
- Plants: 146
- Reviews/summaries: 292
- Other: 1083

2255 articles for further examination by subgroups

Animal studies
- Articles through database search: 1426
  - excluded: 1369
  - included: 57
- Through searching reviews and reference lists: 5
- Total: 62 articles (90 studies)
  - Compulsory consumption studies: 45 articles (47 studies)
  - Voluntary consumption studies: 10 articles (21 studies)
  - Learning studies: 7 articles (22 studies)

Observational (prospective cohort) studies
- Articles through database search: 459
  - excluded: 452
  - included: 7
- Through searching reviews and reference lists: 3
- Total: 10 articles reporting 12 studies

Short-term intervention studies/RCTs
- Articles through database search: 243
  - excluded: 200
  - included: 43
- Through searching reviews and reference lists: 13
  - Total: 56 articles reporting 218 comparisons

Sustained intervention studies/RCTs
- Articles through database search: 127
  - excluded: 115
  - included: 12
- Through searching reviews and reference lists: 1
  - Total: 13 articles reporting 15 comparisons
Short-term effects of low-calorie sweeteners on energy intake

Short-term effects of low-calorie sweeteners on energy intake

Short-term effects of low-calorie sweeteners on energy intake

Details of short-term intervention studies results: ‘compensation’ (COMPX) scores

Preload, test-meal studies showed:

- Reduced energy intake versus sugar (70% compensation in children)
- (43% compensation in adults)
- (50% compensation overall)

Rogers et al. (2016)
*International Journal of Obesity, 40, 381-394*
Preload, test-meal studies showed:

- Reduced energy intake after LCS versus sugar
- No effect on energy intake after LCS versus water
Sustained intervention studies: effects of low-calorie sweeteners versus sugar on body weight

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Follow-up (months)</th>
<th>Sample size</th>
<th>Weight (%)</th>
<th>WMD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanders et al, 1988 (M+F)</td>
<td>3</td>
<td>59</td>
<td>7.4</td>
<td>-0.40 [-2.75, 1.95]</td>
</tr>
<tr>
<td>Blackburn et al, 1997 (F)</td>
<td>40</td>
<td>163</td>
<td>11.5</td>
<td>-5.10 [-6.29, -3.91]</td>
</tr>
<tr>
<td>Raben et al, 2002 (M+F)</td>
<td>2.5</td>
<td>41</td>
<td>11.8</td>
<td>-2.60 [-3.71, -1.49]</td>
</tr>
<tr>
<td>Reid et al, 2007 (F)</td>
<td>1.25</td>
<td>66</td>
<td>12.4</td>
<td>-0.45 [-1.39, 0.49]</td>
</tr>
<tr>
<td>Nijke et al, 2009 (M+F)</td>
<td>6</td>
<td>77</td>
<td>13.9</td>
<td>-0.09 [-0.49, 0.31]</td>
</tr>
<tr>
<td>Reid et al, 2010 (M+F)</td>
<td>1.25</td>
<td>53</td>
<td>11.9</td>
<td>-0.49 [-1.58, 0.60]</td>
</tr>
<tr>
<td>Tate et al, 2012a (M+F)</td>
<td>6</td>
<td>210</td>
<td>11.8</td>
<td>-0.80 [-1.90, 0.30]</td>
</tr>
<tr>
<td>Maersk et al, 2012a (M+F)</td>
<td>6</td>
<td>22</td>
<td>5.6</td>
<td>-1.20 [-4.25, 1.85]</td>
</tr>
<tr>
<td>RE estimate for adult subgroup</td>
<td></td>
<td></td>
<td></td>
<td>-1.41 [-2.62, -0.20]</td>
</tr>
<tr>
<td>Sig. test of ES = 0: Z = -2.280, p = 0.023</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Het.: p &lt; 0.001, I^2 = 90.5 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Ruyter et al, 2012 (M+F)</td>
<td>18</td>
<td>641</td>
<td>13.7</td>
<td>-1.02 [-1.52, -0.52]</td>
</tr>
<tr>
<td>Overall RE estimate for LES vs sugar-sweetened beverages</td>
<td></td>
<td></td>
<td></td>
<td>-1.35 [-2.28, -0.42]</td>
</tr>
<tr>
<td>Sig. test of ES = 0: Z = -2.854, p = 0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Het.: p &lt; 0.001, I^2 = 89.2 %</td>
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</tbody>
</table>

Sustained intervention studies: effects of low-calorie sweeteners versus water on body weight

Does consumption of low-calorie sweeteners increase or decrease desire for sweetness?

Effect of consuming sweet drinks on sweet and savoury food intake

Participants consumed the drink with a sandwich and with the subsequently presented Doritos (savoury) and chocolate chip cookies (sweet)

*\(p<.05\), **\(p<.01\), vs water

Rogers et al., in preparation
Does diet-beverage intake affect dietary consumption patterns? Results from the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial\textsuperscript{1–3}

Carmen Piernas, Deborah F Tate, Xiaoshan Wang, and Barry M Popkin

Participants randomised to water (n=106) or diet beverages (n=104) in place of sugar-sweetened beverages for 6 months

Conclusions: Participants in both intervention groups showed positive changes in energy intakes and dietary patterns. The DB group showed decreases in most caloric beverages and specifically reduced more desserts than the water group did. Our study does not provide evidence to suggest that a short-term consumption of DBs, compared with water, increases preferences for sweet foods and beverages. This trial was registered at clinicaltrials.gov as NCT01017783. \textit{Am J Clin Nutr} 2013;97:604–11.
Other meta-analysis reviews

• Miller & Perez (2014) *American Journal of Clinical Nutrition* 100, 765-777
  ‘RCTs indicate that substituting LCS options for their regular-calorie versions results in modest weight loss and may be a useful dietary tool to improve compliance with weight loss or weight maintenance plans.’ (p 765)

• Azad et al. (2017) *Canadian Medical Association Journal* 189, E929-939
  ‘Evidence from RCTs does not clearly support the intended benefits of nonnutritive sweeteners for weight management.’ (p E929)
Why do Azad et al. (2017) come to a different conclusion?

<table>
<thead>
<tr>
<th>Study, country</th>
<th>No. of participants randomly assigned (% completed)</th>
<th>Sex</th>
<th>Population</th>
<th>Age, mean ± SD; yr</th>
<th>BMI, mean ± SD; kg/m²</th>
<th>Duration, mo</th>
<th>Type and source of NNS</th>
<th>Daily dose of NNS</th>
<th>Comparator(s)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackburn et al. 1997,28 USA</td>
<td>163 (53)</td>
<td>F</td>
<td>Obese, on weight-loss program</td>
<td>44 ± 10</td>
<td>37 ± 5</td>
<td>16</td>
<td>Aspartame ASB, packets, foodstuffs</td>
<td>Participants’ discretion</td>
<td>Aspartame avoidance</td>
<td>⬤</td>
</tr>
<tr>
<td>Hsieh et al. 2003,36 China</td>
<td>174 (97)</td>
<td>M, F</td>
<td>Mild hypertension</td>
<td>52 ± 7</td>
<td>23 ± 3</td>
<td>24</td>
<td>Stevioside capsules</td>
<td>1500 mg</td>
<td>Placebo</td>
<td>⬤</td>
</tr>
<tr>
<td>Ferri et al. 2006,27 Brazil</td>
<td>14 (86)</td>
<td>M, F</td>
<td>Mild hypertension</td>
<td>45 ± 7</td>
<td>27 ± 3</td>
<td>6</td>
<td>Stevioside capsules</td>
<td>3 phases: 3.8, 7.5, 15.0 mg/kg</td>
<td>Placebo</td>
<td>⬤</td>
</tr>
<tr>
<td>Tate et al. 2012,24 USA</td>
<td>213 (86)</td>
<td>M, F</td>
<td>Overweight, on weight-loss program</td>
<td>42 ± 11</td>
<td>36 ± 6</td>
<td>6</td>
<td>Unspecified ASB</td>
<td>Recommended ≥ 2 servings</td>
<td>Water, attention control†</td>
<td>⬤ ⬤</td>
</tr>
<tr>
<td>Maersk et al. 2012,25 Denmark</td>
<td>33 (76)</td>
<td>M, F</td>
<td>Overweight</td>
<td>39 ± 8</td>
<td>33 ± 4</td>
<td>6</td>
<td>Aspartame ASB</td>
<td>1 L of diet cola</td>
<td>Water</td>
<td>⬤</td>
</tr>
<tr>
<td>Peters et al. 2016,19 USA</td>
<td>308 (72)</td>
<td>M, F</td>
<td>Overweight, on weight-loss program</td>
<td>48 ± 11</td>
<td>34 ± 4</td>
<td>12</td>
<td>Unspecified ASB</td>
<td>At least 710 mL</td>
<td>Water with ASB avoidance</td>
<td>⬤</td>
</tr>
<tr>
<td>Madjd et al. 2015,20 Iran</td>
<td>71 (87)</td>
<td>F</td>
<td>Overweight, on weight-loss program</td>
<td>32 ± 7</td>
<td>34 ± 3</td>
<td>6</td>
<td>Unspecified ASB</td>
<td>250 mL</td>
<td>Water</td>
<td>⬤</td>
</tr>
</tbody>
</table>

Risk of bias: High, Low, Unclear
Why do Azad et al. (2017) come to a different conclusion?

- They **excluded** 6 out of 9 studies, representing 1,313 out of 1,708 participants, included in Rogers et al. (2016)
  
  Grounds for exclusion were study duration (<6 months) and participant age (≤12 y)

- **Comparator was water** (rather than sugar) in 4 out of 7 studies included

- 2 of the other 3 studies included compared LCS in capsules versus placebo capsules

- **One study (Madjd et al. 2015)** included was published after Rogers et al (2016) accepted for publication
  
  In this study, participants consumed water or LCS after lunch on 5 days a week
  
  Those consuming LCS lost less weight on a calorie-controlled diet

Conclusions

• Rogers et al. (2016) *International Journal of Obesity* 40, 381-394
  ‘Overall, the balance of evidence clearly indicates that the consumption of low-energy sweeteners in place of sugar, in children and adults, leads to reduced energy intake and body weight, and possibly also compared with water.’ (p 381)

Summary

• No reliable evidence that LCS disrupt the learned control of energy intake
• Reduced energy intake from a LCS drink is not fully compensated for in subsequent eating
• If anything, consumption of LCS in the short term reduces desire for and intake of sweet foods.
• Comprehensive systematic reviews of randomised controlled trials show that LCS versus sugar reduces body weight
Sweet taste as a predictor of food energy (sugar) content

(1) ‘We reasoned that if sweet tastes are normally valid predictors of increased caloric outcomes,* [THIS IS NOT TRUE]

(2) then exposing rats to sweet taste that is not associated with these outcomes should degrade this predictive relationship

(3) and impair energy intake and body weight regulation.’

*‘In nature, and throughout most of our evolutionary history, sweetness has been a reliable predictor of the energy content of food.’ (Swithers et al., 2010, p 56)

Swithers et al. (2010) Physiology and Behavior, 100, 55-62
Sweet taste predicts the sugars but not the energy content of foods and drinks

*Correlations between sweetness and sugar and energy content of foods and drinks in three studies*

<table>
<thead>
<tr>
<th>Country</th>
<th>Sugar</th>
<th>Energy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>.70</td>
<td>-.08</td>
<td>1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>.67</td>
<td>not reported</td>
<td>2</td>
</tr>
<tr>
<td>United States</td>
<td>.70</td>
<td>.11</td>
<td>3</td>
</tr>
</tbody>
</table>

3. van Langveld et al. (2017) *Food Quality and Preference*, 57, 1-7
Sugar content does not predict the energy content of ‘natural’ foods

*Energy, sugar and total carbohydrate content per 100 g of some ‘natural’ (i.e., minimally processed) carbohydrate-rich foods*

<table>
<thead>
<tr>
<th></th>
<th>Energy, kcal</th>
<th>Sugar, g</th>
<th>Total CHO, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh fruits and berries, n=7</td>
<td>58</td>
<td>10.3</td>
<td>14.4</td>
</tr>
<tr>
<td>Roots and tubers, n=8</td>
<td>78</td>
<td>3.1</td>
<td>17.9</td>
</tr>
<tr>
<td>Grains, n=4</td>
<td>121</td>
<td>1.0</td>
<td>25.2</td>
</tr>
</tbody>
</table>

*Some individual fruits, per 100 g*
- Strawberry = 5 g sugar, 33 kcal
- Blueberry = 10 g sugar, 57 kcal
- Grape = 16 g sugar, 67 kcal
Does consumption of low-calorie sweeteners increase or decrease desire for sweetness?

Effect of consuming a non-sweet drink (water) versus sweet drink (low-calorie blackcurrant squash) on desire to consume apple juice, fresh apple and apple pie.

Effect of Drink, p=.003
Effect of Stimulus, p=.002
Drink x Stimulus, F<1

Rogers et al., in preparation