Appendix E.2.48: Evidence Portfolio

Part D. Chapter 6: Cross-Cutting Topics of Public Health Importance

What is the relationship between the intake of low-calorie sweeteners (LCS) and risk of type 2 diabetes?

**Conclusion Statement:** Long-term observational studies conducted in adults provide inconsistent evidence of an association between LCS and risk of type 2 diabetes.

**DGAC Grade:** Limited

**Review of Evidence**

Evidence to address the impact of LCSs (specifically artificially sweetened soft drinks, ASSD) on risk of type 2 diabetes comes from two SRs/MA published between January 2010 and August 2014.\(^1\),\(^2\) The data from one of the reviews also is represented in the second review.

Greenwood et al. reported that higher consumption of ASSD predicts increased risk of type 2 diabetes.\(^1\) The summary RR for ASSD on type 2 diabetes risk was 1.13 (95% CI = 1.02 to 1.25, p<0.02) per 330 ml/day, based on four analyses from three prospective observational studies. Although the finding indicates a positive association between ASSD and type 2 diabetes risk, the trend was not consistent and may indicate an alternative explanation, such as confounding by lifestyle factors or reverse causality (e.g., individuals with higher BMI at baseline may use ASSD as a means to control weight).

Romaguera et al. also reported that higher consumption of ASSD was associated with increased risk of type 2 diabetes.\(^2\) In adjusted models, one 336 g (12 oz) daily increment in ASSD consumption was associated with a hazard ratio for type 2 diabetes of 1.52 (95% CI = 1.26 to 1.83). High consumers of ASSD showed almost twice the hazard ratio of developing type 2 diabetes compared with low consumers (adjusted HR = 1.93; 95% CI = 1.47 to 2.54; p for trend <0.0001). However, the association was attenuated and became statistically not significant when BMI was included in the model (HR = 1.13, 95% CI = 0.85 to 1.52; p for trend = 0.24). The authors offered these interpretations of the findings: “In light of these findings, we have two possible explanations of the association between artificially sweetened soft drinks and diabetes: (1) the observed association is driven by reverse causality and residual confounding, given that the underlying health of people consuming artificially sweetened soft drinks may be compromised and their risk of type 2 diabetes increased; or (2) the association between artificially sweetened soft drinks and type 2 diabetes is mediated through increased BMI.” The authors argued that explanation 1 is more likely correct based on reverse causality, but new research would be needed to clarify the issue.
Collectively, both studies report a positive association between ASSD and type 2 diabetes risk that was confounded by baseline BMI. The experimental designs of the studies included in these reviews analyzed associations, but precluded the assessment of cause and effect relationships, and future experimental studies should examine the relationship between ASSD and biomarkers of insulin resistance and other diabetes biomarkers.

**Table 1.** Summary of existing reports, systematic reviews, and meta-analyses examining the relationship between the intake of low-calorie sweeteners (LCS) and risk of type 2 diabetes

<table>
<thead>
<tr>
<th>Author, Year Publication Type</th>
<th>Low-calorie sweeteners (LCS) Definition</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>Greenwood, 2014 Systematic Review and Meta-Analysis AMSTAR: 8/11</td>
<td>Carbonated artificially sweetened soft drinks (ASSD) Converted consumption to ml/d to explore linear &amp; non-linear dose-response trends Incidence of T2D</td>
<td>1990 to Nov 2009, with an update in June 2013 PCSs; English language; original research article; at least 3 yr duration; differentiated between sugar and artificially sweetened beverages; participants from a generally healthy population</td>
<td>3 publications on 4 cohorts examined association of artificially sweetened soft drink (ASSD) intake and T2D risk. A pooled estimate of RR from linear dose-response meta-analysis was also produced.</td>
<td>Conclusion: ASSD conclusion: Included studies were observational, thus results should be interpreted cautiously. Meta-analyses demonstrate positive association of ASSD intake and T2D risk. Association was stronger and more consistent for sugar-sweetened beverages than for ASSD and together with the effect of adjusting for BMI (attenuation), may indicate an alternative explanation for observed association such as lifestyle or reverse causality. <strong>Main Results:</strong> ASSD pooled estimate of relative risk from linear dose-response meta-analysis was 1.13 (95% CI: 1.02 to 1.25)/330 ml ASSD (p=0.02). Substantial heterogeneity between cohort studies (I²=87%); few studies available to explore sources of heterogeneity. Some evidence of mild nonlinearity in the dose-response curve; number of included studies was small</td>
</tr>
<tr>
<td>Romaguera, 2013 (Note: Included in Greenwood, 2014) Meta-Analysis of eight cohorts from the EPIC study AMSTAR: N/A</td>
<td>Artificially sweetened soft drink (ASSD) Incidence of T2D</td>
<td>N/A Excluded those with evidence of T2D and those within the lowest and highest 1% of the cohort distribution of the ratio of reported total energy intake: energy requirement and those with missing information on diet, physical activity, level of education, smoking status, or BMI</td>
<td>Eight cohorts of the EPIC study</td>
<td>Conclusion: Study reported association between ASSD and T2D that disappears when models are adjusted for baseline BMI. <strong>Main Results:</strong> High consumers of ASSD showed almost twice the hazard ratio (HR) of developing T2D compared with low consumers (adjusted HR 1.93, 95% CI: 1.47 to 2.54; p for trend &lt; 0.0001); association was attenuated and became statistically not significant when BMI was included in the model (HR 1.13, 95% CI: 0.85 to 1.52; p for trend 0.24). Adjusted HR of T2D associated with 12 oz. increment in consumption of ASSD was 1.52 (95% CI: 1.26 to 1.83), which was attenuated and not significant after adjustment for body adiposity measurement. Significant interaction (p=0.03) between consumption of</td>
</tr>
</tbody>
</table>
ASSD and BMI category on T2D incidence.

In stratified analyses, ASSD consumption was sig. assoc. with T2D incidence in normal weight subjects and was unchanged with adjustment for BMI: HR: 1.43, 95% CI: 1.05 to 1.95). Borderline significance among overweight; no association among obese.

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

References Included in the 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 acutosulfame 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 acutosulfame 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 acutosulfame 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


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


