Circulation

AHA SCIENCE ADVISORY

Low-Calorie Sweetened Beverages and Cardiometabolic Health

A Science Advisory From the American Heart Association

The American Diabetes Association supports this AHA Science Advisory and considers the clinical document to be of educational value.

ABSTRACT: In the United States, 32% of beverages consumed by adults and 19% of beverages consumed by children in 2007 to 2010 contained low-calorie sweeteners (LCSs). Among all foods and beverages containing LCSs, beverages represent the largest proportion of LCS consumption worldwide. The term LCS includes the 6 high-intensity sweeteners currently approved by the US Food and Drug Administration and 2 additional high-intensity sweeteners for which the US Food and Drug Administration has issued no objection letters. Because of a lack of data on specific LCSs, this advisory does not distinguish among these LCSs. Furthermore, the advisory does not address foods sweetened with LCSs. This advisory reviews evidence from observational studies and clinical trials assessing the cardiometabolic outcomes of LCS beverages. It summarizes the positions of government agencies and other health organizations on LCS beverages and identifies research needs on the effects of LCS beverages on energy balance and cardiometabolic health. The use of LCS beverages may be an effective strategy to help control energy intake and promote weight loss. Nonetheless, there is a dearth of evidence on the potential adverse effects of LCS beverages relative to potential benefits. On the basis of the available evidence, the writing group concluded that, at this time, it is prudent to advise against prolonged consumption of LCS beverages by children. (Although water is the optimal beverage choice, children with diabetes mellitus who consume a balanced diet and closely monitor their blood glucose may be able to prevent excessive glucose excursions by substituting LCS beverages for sugar-sweetened beverages [SSBs] when needed.) For adults who are habitually high consumers of SSBs, the writing group concluded that LCS beverages may be a useful replacement strategy to reduce intake of SSBs. This approach may be particularly helpful for persons who are habituated to a sweet-tasting beverage and for whom water, at least initially, is an undesirable option. Encouragingly, self-reported consumption of both SSBs and LCS beverages has been declining in the United States, suggesting that it is feasible to reduce SSB intake without necessarily substituting LCS beverages for SSBs. Thus, the use of other alternatives to SSBs, with a focus on water (plain, carbonated, and unsweetened flavored), should be encouraged.

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With the emergence of strong research evidence linking consumption of sugar-sweetened beverages (SSBs) to weight gain and adverse cardiometabolic health over the past decade, some people are choosing beverages with low-calorie sweeteners (LCSs) as alternatives. In contrast to SSBs, which are the largest source of added sugars in the American diet, LCS beverages contain few to no calories, which makes them a potentially appealing substitute for SSBs from a public health perspective. However, the replacement of SSBs with LCS beverages has been debated because of potential safety concerns[1,2] and inconsistent findings regarding their health effects in observational studies and intervention trials.[3–6]

AMERICAN HEART ASSOCIATION'S PUBLISHED STATEMENTS AND ADVISORIES ON NONNUTRITIVE SWEETENERS, ADDED SUGARS, AND OVERALL DIET

The American Heart Association (AHA) recommends limiting the intake of added sugars to the equivalent of no more than 100 calories (25 g) per day in women and 150 calories (37.5 g) per day in men,[7] equivalent to 6 teaspoons (2 tablespoons) and 9 teaspoons (3 tablespoons), respectively. The AHA also recommends that children and adolescents aged 2 to 18 years should limit their intake of added sugars to <100 calories (25 g) per day,[8] or <6 teaspoons (2 tablespoons). For children <2 years of age, added sugars should not be included in the diet.[8] These recommendations are based on a robust body of evidence demonstrating that diets high in added sugars are linked to risk factors for cardiovascular disease (CVD), including obesity, dyslipidemia, elevated blood pressure, and chronic inflammation.[7,8] Of additional concern, foods and beverages high in added sugars often displace nutrient-containing foods in the diet and are associated with excess energy intake. Limiting intake of added sugars can help reduce energy intake and facilitate achieving or maintaining a healthy body weight.[7,8]

In 2012, an expert review conducted by the AHA in collaboration with the American Diabetes Association concluded that when used judiciously, nonnutritive sweeteners (NNSs) may facilitate reductions in added sugars and energy intake, help people achieve and maintain a healthy body weight, and lower the risk of CVD and type 2 diabetes mellitus.[9] However, it stressed that these potential benefits will not be fully realized if there is a compensatory increase in energy intake from other sources. The expert reviewers also found that scientific evidence was limited and inconclusive about whether the benefits of substituting NNSs for added sugars in foods and beverages was effective for reducing added sugars and energy intakes.[9]

LCS TERMINOLOGY

The AHA/American Diabetes Association 2012 statement used the term *nonnutritive sweeteners* to refer to LCSs,[9] which included sweeteners that have a higher intensity of sweetness per gram than caloric sweeteners such as sucrose, corn syrups, and fruit juice concentrates. At that time, 5 NNSs (aspartame, acesulfame-K, neotame, saccharin, and sucralose) were classified as food additives and subsequently given Generally Recognized as Safe status by the US Food and Drug Administration. Stevia had not received any determination regarding its Generally Recognized as Safe status, but the US Food and Drug Administration issued no objection letters for a number of Generally Recognized as Safe notifications for stevia sweeteners.[10] Since then, new sugar substitutes have been introduced. Some are NNSs, whereas others are reduced-energy sweeteners. Hence, in this AHA science advisory, the term *low-calorie sweeteners* is used to refer to both zero- and reduced-energy food additives. The term *low-calorie sweeteners* includes the 6 high-intensity sweeteners currently approved by the US Food and Drug Administration (saccharin, aspartame, acesulfame-K, sucralose, neotame, and advantame) and 2 additional high-intensity sweeteners: steviol glycosides, obtained from the leaves of the stevia plant (*Stevia rebaudiana*), and extracts obtained from *Siraitia grosvenorii* Swingle fruit, also known as *luo han guo* or monk fruit.[10] Other common terms for LCSs include *nonnutritive sweeteners*, *artificial sweeteners*, *sugar substitutes*, and *low-energy sweeteners*. The term *low-calorie sweetened beverages* includes beverages marketed as "diet" or "sugar-free," including liquids, powdered drink mixes, and liquid concentrates. The term *low-calorie sweetened beverages* does not include beverages sweetened with sugar substitutes such as fruit juice concentrate (eg, apple or grape) or beverages that contain a mix of added sugars and LCSs. Of note, LCSs and LCS beverages in the food supply are an evolving landscape.

NEED FOR FOCUSED UPDATE ON LCS BEVERAGES

Among all foods and beverages containing LCSs, beverages represent the largest proportion of LCS consumption worldwide.[11] In the United States in 2007 to 2010, LCS beverages constituted 19% and 32% of all beverages consumed by children and adults, respectively.[12] Consumer demand for products that are lower in sugar is increasing. Beverage companies are making efforts to reduce sugar in their beverages as consumers seek lower-calorie options,[13] particularly as the new Nutrition Facts label is phased in, which requires mandatory information for added sugars content. Thus, there is a need for this AHA science advisory to clarify the existing science on the relationship between LCS beverages and cardiometabolic health. Because of a lack of data, this science advisory does not distinguish among the different types of LCSs. Furthermore, it does not address foods sweetened with LCSs.

POSITIONS OF GOVERNMENTAL AGENCIES AND NONGOVERNMENTAL HEALTH ORGANIZATIONS FOR LCSs

Every 5 years, the Secretaries for Health and Human Services and the US Department of Agriculture update the *Dietary Guidelines for Americans*, guidelines that must be adhered to by federally supported food and nutrition programs. The 2015 Dietary Guidelines Advisory Committee reviewed the evidence to inform its conclusions about the relationship between LCS intake and body weight/obesity and type 2 diabetes mellitus.[14] The committee concluded that (1) "moderate and generally consistent evidence from short-term RCTs [randomized controlled trials] conducted in adults and children supports that replacing sugar-containing sweeteners with low-calorie sweeteners reduces calorie intake, body weight, and adiposity"; (2) "long-term observational studies conducted in children and adults provide inconsistent evidence of an association between low-calorie sweeteners and body weight as compared to sugar-containing sweeteners"; and (3) "long-term observational studies conducted in adults provide inconsistent evidence of an association between low-calorie sweeteners and risk of type 2 diabetes."

Two of the 5 primary 2015 to 2020 *Dietary Guidelines for Americans* specifically address added sugars. One is to "limit calories from added sugars and saturated fats and reduce sodium intake." The other is to "shift to healthier food and beverage choices" such that <10% of calories per day are from added sugars. Strategies to promote a shift in dietary intake include choosing beverages with no added sugars, such as water, in place of SSBs.

Several nongovernmental health agencies have also provided guidance relevant to LCS consumption. The American Dental Association recommends for oral health that consumers avoid a steady diet of foods and beverages with a low pH because research indicates that this is the primary determinant of a beverage's potential to erode tooth enamel.[15] Low-pH–level acidic foods include carbonated diet sodas, but the recommendations do not provide specific information or recommended quantities for these products.[15,16]

Although the American Academy of Pediatrics (AAP) has stated that it has no recommendations regarding the use of LCSs, recent statements and reports provide some guidance.[17] A 2015 AAP policy statement, coauthored by the AAP's Council on School Health and Committee on Nutrition, suggested several LCSs have been accepted by the US Food and Drug Administration as safe and could be used as a tool to assist with lowering caloric intake if they are used to replace added sugars.[18] However, this AAP policy, which was published in March 2015, also noted "data are scarce on long-term benefits for weight management in children and adolescents or on the consequences of long-term consumption."[18,19] A clinical report from the AAP Committee on Nutrition, published in July 2015,[20] described the use of LCS beverages as controversial for children and adolescents and an area of ongoing research and debate because they could (1) lead to taste preferences for and habitual consumption of sweetened beverages, (2) lead to reduced awareness of calorie intake, (3) be substituted for healthier beverages, and (4) alter gut microbiota or increase glucose intolerance.[20] This clinical report stated that "there is no evidence of benefits of these products over plain water, and artificially sweetened beverages currently have a limited place in a child's diet."[20]

A 2012 review by the American Medical Association's Council on Science and Public Health addressed the evidence for both the benefits and adverse effects of consumption of LCS beverages.[21] The American Medical Association concluded that there could be modest benefits of LCS beverages as an aid for weight loss and weight regulation. The report cited the following potential adverse effects of LCS beverages: they contribute to the perception that individuals can consume more calories from other foods, foster a taste preference for sweet foods, make naturally sweetened foods less appealing, and adversely alter feelings of hunger and fullness. The report noted mixed evidence for the link between diet beverage consumption and increased risks of metabolic syndrome, type 2 diabetes mellitus, and vascular events (stroke, myocardial infarction, and vascular death). The report stated that children could be at increased risk of these harmful effects because of their size and cautioned that other ingredients in LCS beverages, such as caffeine and artificial colors, could also be of concern. More recently, the American Medical Association called for continued research into the safety of long-term consumption of LCS beverages, particularly in children and adolescents.[22]

In a 2013 position statement and in the 2018 medical care standards for diabetes, the American Diabetes Association stated that "the use of nonnutritive sweeteners has the potential to reduce overall calorie and carbohydrate intake if substituted for caloric sweeteners and without compensation by intake of additional calories from other food sources."[23,24] Furthermore, the American Diabetes Association found that substituting LCS beverages for SSBs might help reduce increases in blood glucose levels associated with high intakes of SSBs in people with diabetes mellitus.[24]

In 2012, the Academy of Nutrition and Dietetics conducted a comprehensive review of the scientific literature to date for the use of LCSs.[25] For aspartame, the weight of the evidence indicated that consumption of aspartame in food products had little effect on appetite, food intake, or a wide range of adverse effects. The position paper concluded that in association with a weight loss or maintenance plan, aspartame could help improve weight loss and potentially be useful in long-term weight maintenance.[25] Little evidence was identified on its effects in children or other special populations. For both saccharin and sucralose, the review found the evidence to be limited for either benefits or adverse effects. The review identified no studies on the relationships between saccharin or sucralose and energy density, nutrient quality, or behavior/cognitive effects and no evidence about its effects in children. The review concluded that "non-nutritive sweeteners, when substituted for nutritive sweeteners, may help consumers limit carbohydrate and energy intake as a strategy to manage blood glucose or weight."

CONSUMPTION TRENDS AND USE PATTERNS OF LCS BEVERAGES: NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY DATA

Data from the 2009 to 2012 National Health and Nutrition Examination Survey (NHANES) were used to assess the prevalence of LCS consumption.[26] On at least 1 of the 2 days of dietary recall, among children, 25% reported consuming LCSs, and 19% reported consuming LCS beverages. Among adults, 41% reported consuming LCSs, and 31% reported consuming LCS beverages. Females were more likely to consume LCS beverages than males, as were people with high family incomes. People with overweight or obesity were more likely to consume LCSs than people at a healthy (normal) weight. People of non-Hispanic white race/ethnicity reported higher consumption than people of non-Hispanic black race and Hispanic ethnicity. People with diabetes mellitus were more likely to report consuming LCSs than people without diabetes mellitus.

Trends in self-reported consumption of LCSs in beverages and foods have been analyzed in several studies. Among Americans ≥2 years of age, consumption of NNSs in both beverages and foods increased over the period from 1965 to 2004.[27] Trends in self-reported consumption of diet soda, LCS carbonated water, and LCS fruit drinks were assessed using NHANES data from 1999 to 2014 (Tables 1 and 2; Figure 1). LCS beverages include these beverages, and thus, the self-reported intake of diet soda, LCS carbonated water, and LCS fruit drinks in NHANES was used as a proxy measure for LCS beverages. One serving was defined as 8 oz of the beverage. Among adults, consumption of LCS beverages peaked in 2005 to 2006, with a mean self-reported intake of 0.70 servings per day (5.6 oz/d), and declined to a low of 0.48 servings per day (3.8 oz/d) in 2013 to 2014. Among children and adolescents, mean self-reported intake declined from its level in 1999 to 2000 (0.11 servings per day) to a low of 0.07 servings per day (0.56 oz/d) in 2013 to 2014. By comparison, in 1999 to 2000, mean self-reported intake of SSBs was 2.03 servings per day (16.2 oz/d) among adults and 2.37 servings per day (19.0 oz/d) among children and adolescents. In 2013 to 2014, this declined to a low of 1.05 servings per day (8.4 oz/d) among adults and 1.07 servings per day (8.6 oz/d) among children and adolescents (Table 3; Figure 2).

The decreasing trends in SSB consumption in children and adolescents were previously reported in other studies using NHANES conducted from 1999 to 2010.[28–30] The present analysis is an update to these previous findings. In addition, similar decreasing time trends in SSB consumption were observed in another nationally representative survey, the Youth Risk Behavior Surveys, in which the prevalence of daily soda consumption decreased from 33.8% to 20.4% in high school students from 2007 through 2015.[31] Interestingly, the Youth Risk Behavior Surveys found an accelerated decreasing trend in SSB consumption in younger participants (grade 9) in more recent years (2011–2015). However, for LCS beverages, to the best of our knowledge, the present analysis is the first report of time trends in US children and adolescents. There could be biases attributable to changes in dietary assessment methods in NHANES. For example, only 1-day 24-hour recall was used before 2003, whereas a second 24-hour recall was added after 2003; however, this change would not explain our findings, because the observed trends were generally linear.

LCS BEVERAGES AND CARDIOMETABOLIC RISK: OBSERVATIONAL EVIDENCE

LCS Beverages and Body Weight/Adiposity

Some cross-sectional and prospective cohort studies have found positive associations between LCS beverage intake and weight gain. A meta-analysis of 9 prospective cohort studies evaluated LCS use in foods and beverages. Seven of the 9 cohorts examined intakes of LCS beverages, whereas the other 2 cohorts investigated intakes of only 1 type of LCS (saccharin). The intake of LCSs was not associated with body weight or fat mass but was significantly associated with a small increase in body mass index (BMI) (0.03 kg/m^2; 95% confidence interval, 0.01–0.06 kg/m^2).[32] Similarly, a systematic review of 14 prospective cohort studies evaluating the relationship of intake of LCS beverages with risk of obesity, metabolic syndrome, and type 2 diabetes mellitus found that the majority of studies reported positive associations. However, for most studies, the associations were attenuated and became nonsignificant after adjustment for BMI.[28,29] Another review of 30 cohort studies found a positive association between LCS intake and body weight, waist circumference, obesity, hypertension, metabolic

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Table 1. Self-Reported Consumption of LCS Beverages (8-oz Servings/Day) in NHANES 1999 to 2014

	1999–2000	2001–2002	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	*P* for Trend
Adults (>19 y)									
n	4232	4736	4447	4519	5416	5759	4800	5042	
Mean (95% CI)	0.60 (0.49–0.71)	0.58 (0.45–0.70)	0.68 (0.54–0.81)	0.70 (0.63–0.78)	0.62 (0.53–0.72)	0.57 (0.51–0.64)	0.52 (0.45–0.60)	0.48 (0.41–0.55)	0.002
Children and adolescents (2–19 y)									
n	3828	4286	3825	4029	3105	3279	3134	3019	
Mean (95% CI)	0.11 (0.09–0.14)	0.09 (0.06–0.11)	0.14 (0.10–0.17)	0.11 (0.09–0.14)	0.11 (0.07–0.14)	0.11 (0.08–0.15)	0.08 (0.05–0.12)	0.07 (0.06–0.09)	0.004
Male adults									
n	1975	2247	2135	2163	2661	2788	2394	2410	
Mean (95% CI)	0.56 (0.42–0.71)	0.59 (0.45–0.72)	0.68 (0.48–0.88)	0.70 (0.60–0.80)	0.63 (0.52–0.74)	0.59 (0.48–0.69)	0.51 (0.40–0.63)	0.48 (0.40–0.55)	0.02
Female adults									
n	2257	2489	2312	2356	2755	2971	2406	2632	
Mean (95% CI)	0.63 (0.53–0.74)	0.57 (0.43–0.70)	0.67 (0.57–0.78)	0.70 (0.59–0.82)	0.61 (0.49–0.74)	0.56 (0.49–0.64)	0.53 (0.43–0.64)	0.48 (0.38–0.57)	0.003
Male children and adolescents									
n	1937	2130	1902	1983	1610	1711	1586	1520	
Mean (95% CI)	0.11 (0.07–0.14)	0.07 (0.05–0.09)	0.13 (0.10–0.17)	0.12 (0.09–0.15)	0.09 (0.05–0.13)	0.10 (0.07–0.12)	0.07 (0.05–0.09)	0.06 (0.04–0.08)	<0.001
Female children and adolescents									
n	1891	2156	1923	2046	1495	1568	1548	1499	
Mean (95% CI)	0.12 (0.09–0.16)	0.10 (0.06–0.14)	0.14 (0.09–0.19)	0.11 (0.08–0.13)	0.12 (0.07–0.17)	0.13 (0.08–0.18)	0.10 (0.05–0.15)	0.09 (0.07–0.11)	0.20
2–5 y									
n	663	856	763	902	830	861	836	678	
Mean (95% CI)	0.04 (0.02–0.06)	0.03 (0.01–0.05)	0.04 (0.01–0.06)	0.03 (0.01–0.05)	0.02 (0.01–0.03)	0.02 (0.01–0.02)	0.02 (0.00–0.03)	0.02 (0.01–0.03)	0.008
6–11 y									
n	960	1136	900	1012	1120	1153	1146	1047	
Mean (95% CI)	0.08 (0.04–0.11)	0.08 (0.06–0.11)	0.09 (0.05–0.13)	0.12 (0.07–0.16)	0.08 (0.06–0.10)	0.09 (0.05–0.12)	0.04 (0.03–0.06)	0.06 (0.03–0.09)	0.03
12–19 y									
n	2205	2294	2162	2115	1155	1265	1152	1294	
Mean (95% CI)	0.18 (0.14–0.22)	0.11 (0.08–0.15)	0.21 (0.15–0.27)	0.15 (0.12–0.18)	0.16 (0.10–0.23)	0.18 (0.12–0.23)	0.14 (0.07–0.22)	0.10 (0.07–0.12)	0.05
20–39 y									
n	1481	1732	1535	1747	1749	1927	1713	1745	
Mean (95% CI)	0.48 (0.38–0.58)	0.49 (0.38–0.60)	0.57 (0.42–0.72)	0.55 (0.44–0.65)	0.50 (0.39–0.62)	0.48 (0.38–0.58)	0.38 (0.32–0.45)	0.32 (0.25–0.38)	<0.001
40–59 y									
n	1217	1484	1251	1376	1721	1934	1586	1732	
Mean (95% CI)	0.83 (0.61–1.05)	0.74 (0.56–0.92)	0.90 (0.65–1.15)	0.99 (0.87–1.11)	0.83 (0.65–1.01)	0.74 (0.60–0.87)	0.69 (0.54–0.84)	0.65 (0.51–0.80)	0.02
>59 y									
n	1534	1520	1661	1396	1946	1898	1501	1565	
Mean (95% CI)	0.46 (0.31–0.60)	0.40 (0.30–0.51)	0.46 (0.38–0.53)	0.45 (0.39–0.51)	0.48 (0.40–0.55)	0.46 (0.39–0.53)	0.47 (0.36–0.57)	0.45 (0.37–0.52)	0.79

LCS beverages included diet soft drinks (all types), LCS carbonated water, and LCS fruit-flavored drinks.
CI indicates confidence interval; LCS, low-calorie sweetener; and NHANES, National Health and Nutrition Examination Survey.

Table 2. NHANES/USDA Food Codes Used to Determine Data Provided in Table 1 and Figure 1

USDA Food Code	Description	Includes
92400100	Soft drink, NFS, diet	Sugar free
92410250	Carbonated water, sweetened, with low-calorie or no-calorie sweetener	All flavors sugar-free, low-calorie water, diet tonic water, Clearly Canadian Zero
92410320	Soft drink, cola, diet	Diet Coke, Diet Pepsi, Tab, Coke Zero, Pepsi One, not specified as to caffeine, Pepsi Max, sugar free
92410350	Soft drink, cola, decaffeinated, diet	Caffeine-free Diet Coke, caffeine-free Diet Pepsi, Diet Rite Cola, sugar free
92410370	Soft drink, pepper type, diet	Diet Dr. Pepper, Dr. Pepper Ten, Pibb Zero, sugar free
92410400	Soft drink, pepper type, decaffeinated, diet	Caffeine-free Diet Dr. Pepper, sugar free
92410420	Soft drink, cream soda, diet	Sugar free
92410520	Soft drink, fruit flavored, diet, caffeine free	Diet Slice, Diet Sprite, Diet 7-Up, Fresca, Diet 7-Up, not specified as to caffeine, Diet Cherry 7-Up, Sierra Mist Free, Sprite Zero, diet fruit-flavored soda, all flavors, Fanta Zero, Diet Tropicana Twister soda, sugar free
92410560	Soft drink, fruit flavored, caffeine containing, diet	Diet Mountain Dew, Diet Sunkist Orange, Diet Inca Kola, Diet Cheerwine, sugar free
92410620	Soft drink, ginger ale, diet	Sugar free
92410720	Soft drink, root beer, diet	Sugar free
92410820	Soft drink, chocolate flavored, diet	Canfield's Diet Chocolate Fudge Soda, sugar free
92411610	Soft drink, cola, fruit or vanilla flavored, diet	Sugar free, Diet Cherry Coke, Diet Pepsi Wild Cherry, Vanilla Coke Zero
92411620	Soft drink, cola, chocolate flavored, diet	Caffeine free, sugar free

NFS indicates not further specified; NHANES, National Health and Nutrition Examination Survey; and USDA, US Department of Agriculture.

syndrome, type 2 diabetes mellitus, and cardiovascular events.[33] However, this review had a number of limitations, including potential reverse causation bias, different outcome measures, different types of LCSs, and different lengths of follow-up times, which resulted in too much variability to pool the results.[34] Findings from these observational studies may be confounded by related diet factors and lifestyle behaviors or bias attributable to reverse causation whereby people trying to control their weight consume LCS beverages as one strategy, with an overall approach to weight control that is typically unsuccessful.[6]

To reduce the possibility of potential reverse causation, some prospective studies with repeated measurements of diet and body weight have used "change of change" analysis strategies to examine the association between changes in intake of LCS beverages and changes in body weight. For example, weight gain in women who reported increasing their LCS soft drink intake from 1991 to 1995 (1.59 kg) was significantly lower than that for women who reported decreasing their LCS soft drink intake (4.25 kg), after adjustment for changes in other dietary factors. This finding was the opposite of the pattern of change observed for SSBs and weight gain reported previously.[35] In a large pooled analysis of 3 cohorts of US men and women with repeated measurements of diet and body weight over 4-year intervals between 1986 and 2006, an increase of 1 serving per day of LCS soda during each 4-year period was associated with 0.11 lb less weight gain, whereas increasing the same amount of SSBs was associated with a 1.00-lb greater weight gain.[36] It was estimated that substituting 1 serving per day of LCS beverages for the same amount of SSBs was associated with 0.47 kg less weight gain within each 4-year period.[37]

LCS Beverages and Type 2 Diabetes Mellitus

A meta-analysis of 10 prospective studies concluded that consumption of 1 serving per day of LCS beverages was associated with a 25% increased risk of type 2 diabetes mellitus.[38] The association was attenuated to 8% after adjustment for adiposity, which implies that most of the association between LCS beverages and type 2 diabetes mellitus might be attributable to concurrent high adiposity. This suggests that overweight and obese adults might preferentially report consuming more LCS beverages or might have switched from SSBs to LCS beverages before the survey data were collected. Substantial heterogeneity among the cohorts and potential publication bias were detected in this meta-analysis, further complicating interpretation of the results.[38] Investigators examined the relation of plain-water intake and the substitution of plain water for SSBs and fruit juices with incident type 2 diabetes mellitus in the Nurses' Health Study. Replacement of SSBs with LCS beverages was related to a 7% lower risk of type 2 diabetes mellitus, and the replacement of SSBs with plain water, coffee, or low-fat milk was associated with the same or greater magnitude of reduction in risk of diabetes mellitus.[39]

LCS Beverages and Type 1 Diabetes Mellitus

Limited research exists on the association of LCSs with CVD risk markers and obesity in people with type 1 diabetes mellitus, although concern about the prevalence of obesity in people with type 1 diabetes mellitus is sim-

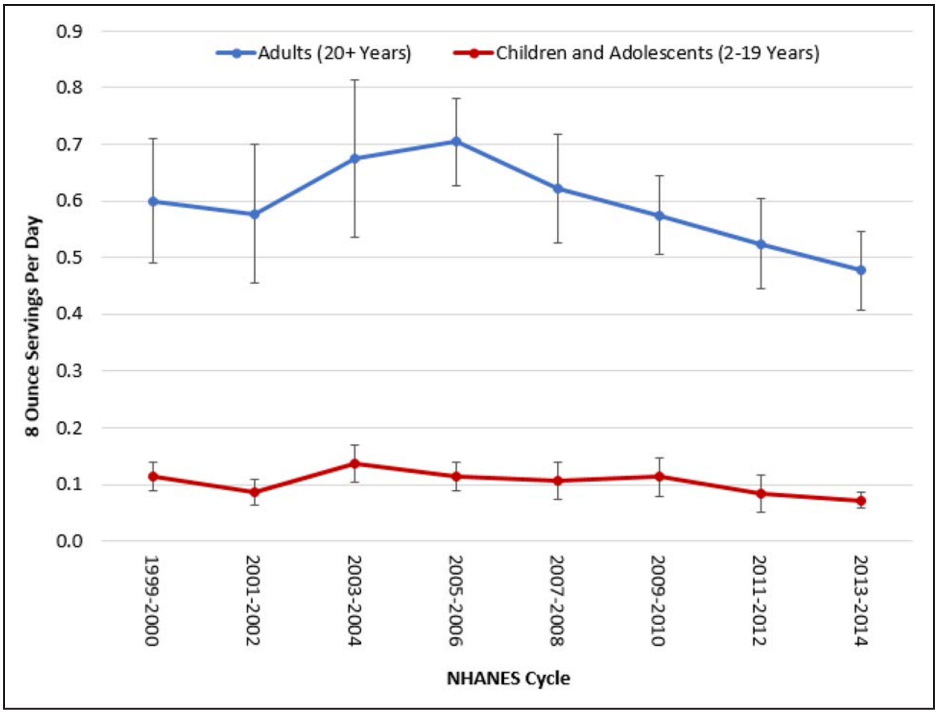

Figure 1. Self-reported consumption of low-calorie sweetened (LCS) beverages (8-oz servings per day, mean and 95% confidence interval) from 1999 through 2014.
LCS beverages included diet soft drinks (all types), LCS carbonated water, and LCS fruit-flavored drinks. NHANES indicates National Health and Nutrition Examination Survey.

ilar to that of the general population.[40–42] Bortsov et al[42] examined the relationship between LCS beverages and metabolic parameters in 1806 youth 10 to 22 years of age with type 1 diabetes mellitus, of which 22% were of a minority race/ethnicity (10% Hispanic, 8% blacks, 4% other races) and 48% were female. Higher intake of LCS beverages was associated with higher hemoglobin A1c, total cholesterol, low-density lipoprotein cholesterol, and triglycerides. These associations were partially confounded by BMI, saturated fat, and total fiber intake. Higher consumption of LCS beverages was also associated with lower overall diet quality, and the authors concluded that LCS beverage intake might have been a marker for an unhealthy lifestyle, which in turn was associated with worse metabolic and glycemic control and CVD risk profile in these youth.

LCS Beverages, CVD, and Brain/Cognitive Outcomes

To date, 2 large prospective studies[43,44] with decades of follow-up concluded that consumption of LCS beverages was not associated with risk of coronary heart disease[43,44] or related biomarkers.[43] Conversely, SSBs have been associated with increased risk of coronary heart disease, which implies a need to find healthy substitutes for SSBs.[7]

Three prospective analyses in 4 cohorts[45] have shown an association between LCS beverages and risk of vascular events, notably stroke. An analysis of the Nurse's Health Study, a prospective cohort study of 84 085 women followed up for 28 years (1980–2008), and the Health Professionals Follow-Up Study, a prospective cohort study of 43 371 men followed up for 22 years (1986–2008), showed that low-calorie soda consumption was associated with incident stroke (pooled relative risk of total stroke for ≥1 serving of low-calorie soda per day versus none, 1.16; 95% confidence interval, 1.05–1.28). Adjustment for diabetes mellitus and hypertension attenuated the association (1.09; 95% confidence interval, 1.04–1.14). Similarly, in the Northern Manhattan Study,[46] a positive association was observed between baseline daily intake of diet soft drinks and risk of incident vascular events, including stroke, myocardial infarction, and vascular death. Although the authors attempted several sensitivity analyses to reduce potential reverse causation, the analyses were underpowered. Thus, they were not able to rule out reverse confounding or indication bias. For instance, people at increased risk of vascular events because of preexisting vascular conditions might have been advised to switch from SSBs to LCS beverages.[46] Finally, a recent analysis of the Framingham Heart Study Offspring cohort suggested that LCS beverage consumption was associated with a higher risk of ischemic stroke, all-cause dementia, and Alzheimer dementia.[47] Compared with daily intake of LCS beverages of 0 per week (reference category), the hazard ratios for drinking ≥1 LCS beverage per day were 2.96 for ischemic stroke,

Table 3. Self-Reported Consumption of SSBs (8-oz Servings/Day) in NHANES 1999 to 2014

	1999–2000	2001–2002	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	*P* for trend
Adults (>19 y)									
n	4232	4736	4447	4519	5416	5759	4800	5042	
Mean (95% CI)	2.03 (1.79–2.28)	1.92 (1.74–2.11)	1.80 (1.65–1.95)	1.61 (1.49–1.72)	1.57 (1.36–1.77)	1.41 (1.31–1.51)	1.19 (1.11–1.27)	1.05 (0.93–1.17)	<0.001
Children and adolescents (2–19 y)									
n	3828	4286	3825	4029	3105	3279	3134	3019	
Mean (95% CI)	2.37 (2.13–2.61)	2.21 (2.06–2.37)	2.13 (1.98–2.27)	1.90 (1.73–2.07)	1.74 (1.58–1.89)	1.50 (1.10–1.60)	1.23 (1.12–1.34)	1.07 (0.97–1.18)	<0.001
Male adults									
n	1975	2247	2135	2163	2661	2788	2394	2410	
Mean (95% CI)	2.43 (2.16–2.70)	2.42 (2.15–2.69)	2.29 (2.10–2.49)	2.15 (1.99–2.31)	1.99 (1.73–2.26)	1.79 (1.66–1.93)	1.43 (1.33–1.54)	1.28 (1.12–1.43)	<0.001
Female adults									
n	2257	2489	2312	2356	2755	2971	2406	2632	
Mean (95% CI)	1.66 (1.39–1.93)	1.47 (1.32–1.61)	1.34 (1.20–1.48)	1.11 (1.00–1.21)	1.18 (1.01–1.35)	1.06 (0.97–1.16)	0.97 (0.89–1.05)	0.85 (0.73–0.96)	<0.001
Male children and adolescents									
n	1937	2130	1902	1983	1610	1711	1586	1520	
Mean (95% CI)	2.72 (2.45–3.00)	2.57 (2.33–2.80)	2.45 (2.23–2.67)	2.23 (1.98–2.48)	1.94 (1.73–2.15)	1.72 (1.57–1.87)	1.40 (1.25–1.54)	1.26 (1.10–1.43)	<0.001
Female children and adolescents									
n	1891	2156	1923	2046	1495	1568	1548	1499	
Mean (95% CI)	2.00 (1.79–2.21)	1.85 (1.68–2.02)	1.80 (1.64–1.96)	1.56 (1.41–1.72)	1.53 (1.37–1.68)	1.26 (1.17–1.35)	1.05 (0.95–1.16)	0.88 (0.79–0.96)	<0.001
2–5 y									
n	663	856	763	902	830	861	836	678	
Mean (95% CI)	1.12 (0.87–1.37)	1.20 (1.07–1.32)	1.02 (0.88–1.16)	0.84 (0.71–0.97)	0.79 (0.68–0.90)	0.74 (0.64–0.84)	0.66 (0.56–0.76)	0.49 (0.39–0.59)	<0.001
6–11 y									
n	960	1136	900	1012	1120	1153	1146	1047	
Mean (95% CI)	1.96 (1.76–2.15)	1.76 (1.57–1.95)	1.81 (1.61–2.00)	1.45 (1.28–1.61)	1.54 (1.38–1.70)	1.23 (1.14–1.33)	1.11 (1.00–1.22)	0.94 (0.83–1.06)	<0.001
12–19 y									
n	2205	2294	2162	2115	1155	1265	1152	1294	
Mean (95% CI)	3.25 (2.90–3.60)	3.00 (2.72–3.29)	2.79 (2.62–2.96)	2.67 (2.44–2.90)	2.30 (2.06–2.55)	2.04 (1.88–2.20)	1.57 (1.40–1.75)	1.37 (1.17–1.57)	<0.001
20–39 y									
n	1481	1732	1535	1747	1749	1927	1713	1745	
Mean (95% CI)	3.18 (2.73–3.63)	2.89 (2.58–3.20)	2.69 (2.39–2.99)	2.35 (2.13–2.57)	2.23 (1.91–2.55)	2.06 (1.82–2.30)	1.66 (1.49–1.82)	1.48 (1.36–1.60)	<0.001
40–59 y									
n	1217	1484	1251	1376	1721	1934	1586	1732	
Mean (95% CI)	1.47 (1.27–1.66)	1.62 (1.42–1.82)	1.58 (1.42–1.75)	1.41 (1.29–1.53)	1.51 (1.28–1.75)	1.33 (1.15–1.51)	1.16 (1.02–1.30)	0.97 (0.73–1.21)	<0.001
>59 y									
n	1534	1520	1661	1396	1946	1898	1501	1565	
Mean (95% CI)	0.78 (0.70–0.87)	0.68 (0.57–0.79)	0.64 (0.60–0.69)	0.75 (0.64–0.87)	0.65 (0.58–0.72)	0.61 (0.55–0.66)	0.61 (0.53–0.70)	0.59 (0.50–0.69)	0.004

SSBs included soft drinks, fruitades, sports drinks and other sugary beverages (fruit drinks, sweetened water, smoothie drinks, Frappuccino), and reduced-sugar colas (half weight).

CI indicates confidence interval; NHANES, National Health and Nutrition Examination Survey; and SSBs, sugar-sweetened beverages.

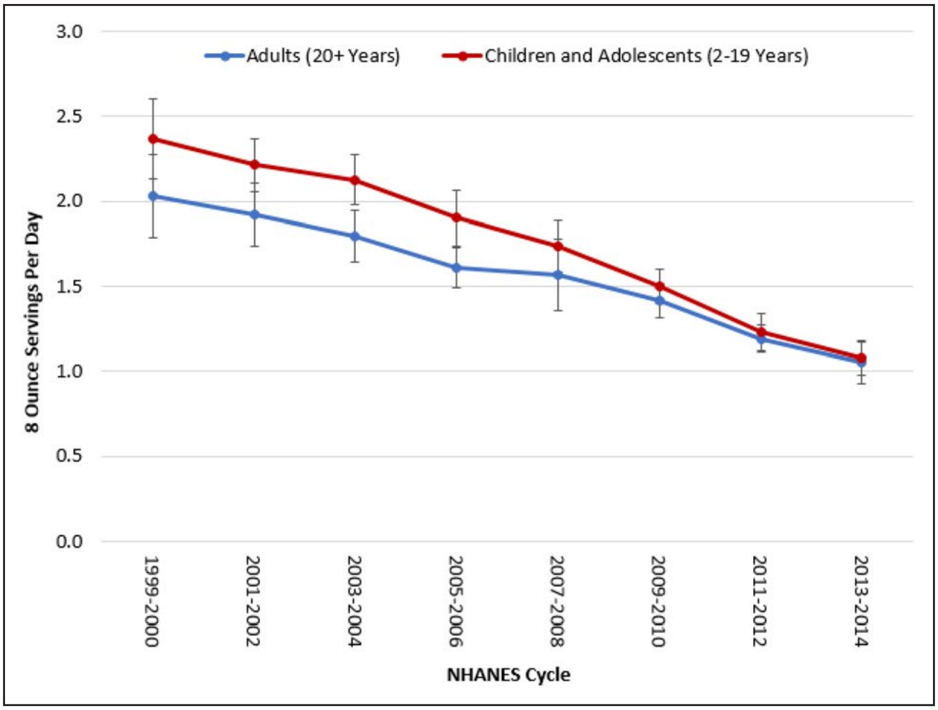

Figure 2. Self-reported consumption of sugar-sweetened beverages (SSBs) (8-oz servings per day, mean and 95% confidence interval) from 1999 through 2014.
SSBs included soft drinks, fruitades, sports drinks and other sugary beverages (fruit drinks, sweetened water, smoothie drinks, Frappuccino), and reduced-sugar colas (half weight). NHANES indicates National Health and Nutrition Examination Survey.

2.47 for all-cause dementia, and 2.89 for Alzheimer dementia, after adjustment for age, sex, total caloric intake, systolic blood pressure, treatment of hypertension, prevalent CVD, atrial fibrillation, left ventricular hypertrophy, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes mellitus, and waist-to-hip ratio. The authors were cautious in interpreting these findings because of concerns about residual confounding and reverse causality. In this cohort, diabetes mellitus and other CVD risk factors were more prevalent in those who regularly consumed LCS beverages. Hence, it was not clear whether LCS beverages increased the risk of stroke and dementia through diabetes mellitus or whether people with diabetes mellitus were more likely to consume LCS beverages. In addition, this study had few ethnic minorities, which limits its generalizability.

Summary of Observational Evidence

Taken together, some observational data suggest a positive association between long-term consumption of LCS beverages with risk of type 2 diabetes mellitus and CVD; however, reverse causality and adiposity cannot be ruled out as driving factors in the observations. The positive association between LCS beverages and stroke risk was more consistent across cohorts. However, as stressed by the investigators, these results need to be interpreted cautiously because of methodological concerns with regard to unmeasured or residual confounding and reverse causation. More research is needed on the relationship between LCS beverages and brain health outcomes. Little is known about the effects of substituting LCS beverages for SSBs in people with type 1 diabetes mellitus and hyperglycemia associated with excess SSB intake.

LCS BEVERAGES AND CARDIOMETABOLIC RISK: CLINICAL TRIALS

There are few randomized controlled trials (RCTs) relevant to LCS beverages and CVD. The majority of these trials used LCS beverages as a replacement for SSBs. None of the trials had sufficient sample size and patient characteristics to examine cardiovascular outcomes as end points. Therefore, RCTs reported to date have examined CVD risk factors such as body weight, adiposity indices, and blood lipids.

LCS Beverages and Body Weight

The effect of LCS beverages was assessed in 641 children from 4 to 11 years of age.[48] Participants were randomly assigned to receive one 8-oz can per day of an LCS beverage or SSB for a period of 18 months. At the end of the intervention period, the BMI *Z* score increased by 0.15 SD units in the SSB group (body weight increase of 7.37 kg or ≈16 lb) and by 0.02 SD in the LCS beverage group (body weight increase of 6.35 kg or ≈14 lb).

Other adiposity indices (skinfold thicknesses, waist-to-height ratio, fat mass) were also significantly higher in the SSB group compared with the LCS beverage group.

The effect of LCS beverages was also assessed in 224 overweight or obese adolescents who reported regular SSB consumption. Participants were randomized to a 1-year intervention to decrease SSB consumption (intervention group) or no intervention (control group). The primary outcomes were rate of weight gain after the 1-year intervention and after the 1-year postintervention follow-up period.[49] The intervention group received home delivery every 2 weeks of bottled water and LCS beverages, monthly parental motivational telephone calls, and 3 check-in visits. Intake of SSBs was significantly reduced in the intervention compared with the control group at year 1 and remained lower than in the control group at the end of the 1-year postintervention follow-up period. However, although the rate of gain in BMI was significantly lower in the intervention group than in the control group at the end of the 1-year intervention period, the change in BMI was similar between the 2 groups at the end of the 1-year postintervention follow-up. Although it was not possible to precisely decipher the respective contributions of substituting water versus LCS beverages in place of SSBs to the changes in body weight observed at the end of the 1-year intervention period, the investigators posited that the change in intake of added sugars was the only variable that could have contributed to the observed differences.

A systematic review[50] and a meta-analysis[32] of trials of relatively short duration and small sample size generally concluded that LCS beverages could contribute to a modest weight loss and could therefore be a useful tool to help control body weight/fat, but longer follow-up studies are critically needed. Another review of 7 RCTs found no significant effect of LCSs on BMI and no consistent effects on other measures of body composition[33]; however, these results should be treated with caution because of a number of limitations. The RCTs had great variability in exposure and outcome variables and a small number of participants, which increased the possibility that the results occurred by chance. In addition, the trials were rated as having a high risk of bias because the participants were not blinded to the intervention and dropout rates were not provided.[34]

A secondary analysis of a large RCT conducted in the Netherlands[40] concluded that the children who benefited most from substituting LCS beverages for SSBs were those who at baseline were above the median BMI value, which suggests that children most susceptible to excess weight gain were those who benefited the most from reducing their intake of SSBs.[42] In a 6-month RCT involving 318 overweight and obese adults, it was found that replacing SSBs with noncaloric beverages such as LCS beverages or water resulted in similar average weight losses for the 2 groups: 2.5% and 2%, respectively.[51] The study found no evidence that LCS beverages promoted a preference for sugary food or drinks. These findings were consistent with those reported for a 12-week randomized behavioral weight loss treatment program that concluded that water was not superior to LCS beverages in inducing weight loss within the context of a comprehensive behavioral weight loss program.[52] These results did not support the position that LCS beverages promote the consumption of other foods with a high energy content.[27,53] Of note, in multifaceted behavioral weight loss treatment programs, it is difficult to isolate the contribution of LCS beverages per se from other changes in energy balance that lead to weight loss.

LCS Beverages and Visceral Adiposity and Ectopic Fat

Imaging studies have shown that visceral adipose tissue accumulation, particularly when accompanied by ectopic fat deposition in liver, heart, and skeletal muscle, elevates CVD risk profiles in overweight and obese individuals.[54,55] Therefore, a relevant question is whether long-term overconsumption of SSBs contributes to visceral or ectopic fat accumulation. In overweight or obese adults, long-term overconsumption of fructose SSBs, provided as 25% of energy for 10 weeks, increased de novo lipogenesis, induced atherogenic dyslipidemia, increased circulating insulin levels, and increased visceral adiposity.[56] Although the relevance of this study to the consumption patterns of a large segment of the population has been questioned because of the extremely high fructose content of the diet and its short duration, the results of this trial suggested that body weight might not be the optimal metric to fully appreciate the changes in cardiometabolic risk and body composition that result from manipulating dietary added sugar.

A 6-month RCT assessed the effects of replacing 1 serving of SSB per day with an isocaloric amount of milk, LCS beverages, or water.[57] Liver fat, visceral adipose tissue, and skeletal muscle fat were all significantly higher in the SSB group, although total body fat was similar among the groups. LCS beverages were similar to water in minimizing the accumulation of visceral or ectopic fat. Replacing SSBs with either milk or an LCS beverage resulted in lower blood pressure than in the SSB group. Another imaging study examined the effect of substituting LCS beverages for SSBs in high consumers of SSBs (at least 22 oz/d).[58] At the end of the 12-week intervention period, replacing SSBs with LCS beverages resulted in a decrease in liver fat content.

Gut Microbiota

One concern raised with the use of LCS beverages is that they could have a negative impact on the gut microbiota and that such changes could have a deleterious effect on glucose tolerance.[31,59] Little evidence on this topic is available in humans.[60]

Summary of Clinical Trial Evidence

In summary, there is a lack of RCT evidence on the long-term effects of consumption of LCS beverages on clinical outcomes including cardiometabolic diseases and mortality. It is notable that the longest RCT available provided LCS beverages to children 4 to 11 years of age for 18 months.[48] There is some short-term evidence that suggests that replacement of SSBs with LCS beverages could help in the management of overweight and obesity, particularly among high-risk overweight or obese individuals with harmful levels of visceral or ectopic fat.

LCS BEVERAGES AND CARDIOMETABOLIC RISK: EXPERIMENTAL ANIMAL MODEL EVIDENCE

The putative mechanisms that might explain the effects of LCSs on body weight have been addressed in several reviews primarily focused on animal models.[61–64] These include altered cephalic response to an energy load, increased food consumption, elevated rate of weight gain, increased percent body fat, lower postprandial thermogenesis, altered glucose homeostasis that includes glucose dysregulation and insulin resistance, changes in gut microbiota,[64] and reduction of the cephalic response to a caloric load in animal models.[62,65] Although animal studies are informative, they are not generalizable to humans. Nonetheless, animal studies can be useful for hypothesis testing in human studies.

Reports on the effect of LCSs on body weight in rodents have been inconsistent. A systematic review[63] of 47 rodent studies of LCSs (compared with sugars or unsweetened alternatives) concluded that body weight significantly decreased in 22 studies, did not change in 21 studies, and increased in 4 studies.[63] Differences among the studies included the LCS evaluated, route of administration, and duration of the treatment. In addition, there could have been a repeat exposure effect, wherein animals exposed repetitively to either glucose or LCSs were more likely to gain weight.[63]

Summary of Animal Model Evidence

Collectively, the experimental animal evidence indicates that LCSs might have multiple biological effects that alter energy intake and trigger insulin response. Interpretation of the animal model data for LCSs relative to potential human outcomes or mechanisms of action is challenging because of the scarcity of information on the equivalency of responses. This is of particular concern because intake patterns in animals do not replicate the day-to-day variation of humans. Thus, caution is suggested before drawing conclusions with regard to whether these findings, primarily conducted in rodents, are applicable to humans.

DATA GAPS AND RESEARCH NEEDS

Two major areas where additional research is needed were identified by the 2015 Dietary Guidelines Advisory Committee: (1) identify sources and names of LCSs used in the food supply and quantify their consumption levels and trends in the US diet and (2) conduct prospective research on the association of LCS with health outcomes including clinical markers of CVD, with strong experimental designs and multiple measures of LCS consumption. This would enhance the development of evidence-based recommendations regarding the use of LCS beverages in place of SSBs for the promotion of optimal cardiometabolic health.

Additional work is needed to determine the mechanisms of action of LCSs to gain a better understanding of any causal role they might play in CVD. Further prospective cohort studies and short-term RCTs, particularly in children, are needed to elucidate the associations between substituting SSBs with LCS beverages and the development of risk factors for future CVD. It will be important to include analyses of beverage change patterns or beverage substitution analyses in new research.

There is a continuing need to examine the changing patterns of consumption of SSBs and LCS beverages, including a focus on exploring the patterns of consumers with chronically high intakes versus those whose consumption declines. Additionally, there is a need to address consumers' increasing concerns about excess sugars intake and their demand for lower-sugar foods and beverages.

SUMMARY AND CONCLUSIONS

In the United States, LCS beverages make up 32% and 19% of the beverages adults and children report consuming, respectively. There is a scarcity of long-term RCTs of sufficient sample size and duration to adequately document the efficacy and safety of LCS beverages, particularly relative to SSBs, as a tool to help maintain energy balance, control cardiometabolic risk factors, and reduce risk of cardiovascular events. This lack of evidence does not mean that LCS beverages are or are not efficacious. The use of LCS beverages may be an effective strategy to help control energy intake and promote weight loss. Nonetheless, there is a dearth of evidence on the potential adverse effects of LCS beverages relative to potential benefits. On the basis of the available evidence, the writing group concluded that, at this time, it is prudent to advise against prolonged consumption of LCS beverages by children. (Although water is the optimal beverage choice, children with diabetes mellitus who consume a balanced diet and closely monitor their blood glucose may be able to prevent excessive glucose excursions by substituting LCS beverages for SSBs when needed.) For adults who are habitually high consumers of SSBs, the writing group concluded that LCS beverages may be a useful replacement strategy to reduce intake of SSBs. This approach may be particularly helpful for persons who are habituated to a sweet-tasting beverage and for whom water, at least initially, is an undesirable option. Encouragingly, self-reported consumption of both SSBs and LCS beverages has been declining in the United States, suggesting that it is feasible to reduce SSB intake without necessarily substituting LCS beverages for SSBs. Thus, the use of other alternatives to SSBs, with a focus on water (plain, carbonated, and unsweetened flavored), should be encouraged. The potential benefits from LCS beverages as replacements for SSBs will not be fully realized if their use is accompanied by a compensatory increase in energy intake from other sources. Additionally, an overall healthful dietary pattern rich in vegetables, fruits, whole grains, nonfat or low-fat milk and dairy products, seafood, legumes, and nuts and low in red and processed meats, added sugars (not more than 10% of total energy), saturated fat, sodium, and refined grains is advised.[66] It is clear that there is a need for further research on the effects of LCS beverages as they pertain to energy balance, cardiometabolic risk factors, and risk of CVD and other chronic diseases.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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Barbara V. Howard	MedStar Health Research Institute	None	None	None	None	None	None	None
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*Modest.

†Significant.

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