Low-Calorie Sweeteners: Disturbing the Energy Balance Equation in Adolescents?

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Objective: The aim of this study was to investigate the relationship between low-calorie sweeteners (LCSs), energy intake, and weight in US youth.

Methods: Data were collected from individuals aged 2 to 19 years who participated in the National Health and Nutrition Examination Survey (NHANES) 2009-2010 (n = 3,296), 2011-2012 (n = 3,139), and 2013-2014 (n = 3,034). Logistic regression, unadjusted and adjusted for age, sex, race/ethnicity, income, energy intake, and physical activity, was used to estimate the odds of obesity in LCS consumers versus nonconsumers, both overall and across product categories (foods vs. beverages) and sociodemographic subgroups.

Results: Among adolescents, the odds of obesity were 55% and 70% higher in LCS beverage consumers than in nonconsumers in unadjusted and adjusted models, respectively. Energy intakes did not differ based on LCS consumption. In contrast, associations between LCS consumption and obesity risk were not statistically significant among children (2-11 y old), except in boys and those who self-identified as Hispanic.

Conclusions: LCS consumption is associated with increased odds of obesity among adolescents. This relationship is strikingly independent of total energy intake. Although findings should be interpreted cautiously because of the limitations of self-reported dietary intake and the cross-sectional nature of this analysis, the observational analysis in this study supports the need to investigate the mechanisms by which LCS may influence body weight, independently of changes in energy intake.

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Introduction

The consumption of low-calorie sweeteners (LCSs) is increasingly prevalent among youth (1). Beverages are the predominant contributors to LCS intake in children, although LCSs are also found widely in foods, condiments, and sweetener packets (1). Although LCSs offer a lower-calorie alternative to added sugars, their role in weight management and metabolic health is unclear (2).

Epidemiologic studies report positive associations between LCSs and body weight in children and adults (3). However, little is known about whether LCS consumption correlates with energy intake, especially in youth. In adults, LCS consumers have a higher discretionary calorie intake (4), purchase more snack foods, and consume more calories (5) than sugar-sweetened beverage consumers. A recent analysis also reported that adults with overweight and obesity who consume LCS beverages have a higher calorie intake compared with individuals with similar weight who consume sugar-sweetened beverages (6). Despite the growing body of epidemiologic literature connecting LCS intake to higher body weight in adults (7), causality cannot be inferred from observational analyses, and the majority of randomized controlled trials in adults demonstrate that LCS may be a useful tool for modest weight loss in the context of intensive lifestyle interventions (8,9). Meanwhile, population-level relationships among LCS consumption, energy intake, and obesity in youth have not been evaluated. We investigated this relationship in youth by using data from three cycles (2009–2014) of the National Health and Nutrition Examination Survey (NHANES).
TABLE 1 Characteristics of child and adolescent NHANES 2009-2014 participantsa, overall and stratified by weight status categoriesb

|                      | Children (2-11 y) | Adolescents (12-19 y) |
|----------------------|-------------------|-----------------------|
|                      | All (n = 5,590)   | Underweight (n = 214) | Healthy (n = 3,609) | Overweight (n = 845) | Obesity (n = 922) | P  |
| Total                | 100%              | 3.8%                  | 66.2%               | 15.3%               | 14.7%              |    |
| Gender, n (%)        |                   |                       |                     |                     |                    |    |
| Male                 | 2,842 (61.1)      | 110 (48.3)            | 1,823 (60.6)        | 422 (51.1)          | 487 (54.0)         | 0.5132 |
| Female               | 2,748 (48.9)      | 104 (51.7)            | 1,786 (49.4)        | 423 (48.9)          | 435 (46.0)         |    |
| Race/ethnicity, n (%)c |                   |                       |                     |                     |                    |    |
| White                | 1,552 (53.2)      | 56 (53.0)             | 1,096 (56.6)        | 215 (51.6)          | 185 (39.7)         | < 0.0001 |
| Black                | 1,376 (13.8)      | 53 (12.6)             | 877 (13.2)          | 195 (12.6)          | 251 (18.3)         |    |
| Hispanic             | 1,949 (24.0)      | 58 (19.5)             | 1,130 (20.9)        | 352 (28.7)          | 409 (34.3)         |    |
| Age, n (%)           |                   |                       |                     |                     |                    | < 0.0001 |
| 2-5 y                | 2,270 (39.3)      | 100 (34.5)            | 1,593 (42.6)        | 310 (38.0)          | 267 (27.2)         |    |
| 6-11 y               | 3,320 (60.7)      | 114 (65.5)            | 2,016 (57.4)        | 535 (62.0)          | 655 (72.8)         |    |
| Income, n (%)d       |                   |                       |                     |                     |                    | 0.0011 |
| 1st tertile          | 2,491 (35.5)      | 80 (26.0)             | 1,586 (34.3)        | 377 (36.79)         | 448 (42.42)        |    |
| 2nd tertile          | 1,587 (33.0)      | 63 (34.4)             | 1,000 (32.7)        | 251 (33.6)          | 273 (33.2)         |    |
| 3rd tertile          | 1,134 (31.4)      | 55 (39.5)             | 795 (32.9)          | 155 (29.6)          | 129 (24.4)         |    |
| LCS consumer, n (%)  | 1,785 (34.6)      | 59 (26.7)             | 1,108 (34.2)        | 274 (34.9)          | 344 (37.8)         | 0.0684 |
| LCS beverage use, n (%) | 1,451 (28.3)  | 45 (20.1)             | 895 (27.9)          | 223 (28.2)          | 288 (32.3)         | 0.0558 |
| LCS food use, n (%)  | 484 (10.0)        | 18 (7.6)              | 309 (10.2)          | 76 (10.1)           | 81 (9.3)           | 0.7168 |
| Physical activity (d/wk) | 6.1 ± 0.0        | 6.1 ± 0.2             | 6.3 ± 0.0           | 6.1 ± 0.1           | 5.7 ± 0.1          | < 0.001 |
| Energy intake (kcal/day) | 1,756.3 ± 9.4 | 1,674.6 ± 40.7        | 1,743.5 ± 10.9      | 1,753.5 ± 25.7      | 1,837.5 ± 28.3     | 0.005 |

aIn reflects the number of participants in the samples, whereas percentages are weighted to account for the complex NHANES survey design.

bDefined based on standard BMI (kg/m²) cutoffs (13,14).
cRespondents reporting “other” for race (n = 713 children, n = 496 adolescents), including multiracial respondents, are included in overall estimates but are not shown separately.
dDefined based on tertiles of poverty-to-income ratio; 378 children and 301 adolescents were missing data for income.

<Because of the small sample size (n < 30), these estimates may be unreliable and should be interpreted with caution.

In children 2-11 y, physical activity was assessed as number of days per week physically active at least 60 min. 11 children were missing data for physical activity.

In adolescents 12-19 y, physical activity was assessed as MET minutes of moderate and vigorous activity per week, which was derived using NHANES recommended MET score; 110 adolescents were missing data for physical activity.

MET, metabolic equivalent.
Methods

Data source

NHANES is a continuous cross-sectional study of the US population, with data released in 2-year cycles. NHANES sampling and data collection methods are described elsewhere (10). The current analyses used data collected from individuals aged 2 to 19 years who participated in NHANES 2009-2010, 2011-2012, and 2013-2014, providing a sample of 9,469 individuals. NHANES response rates were 75% for the age groups studied in all three survey cycles (10). Demographic and anthropometric data were collected, categorized, and analyzed as detailed previously (1). Consistent with prior analyses (1), those with missing weight (n = 177) or implausible energy intake (n = 31) were excluded, providing a final sample of 9,261. Participants with missing data for any characteristic were excluded only from the subgroup comparison for which information was missing. Because assessment of physical activity in NHANES (see “Physical activity”) differs for younger children (2-11 y) and adolescents (12-19 y), all analyses were conducted separately for children (2-11 y) and adolescents (12-19 y).

LCS consumption

LCS use was also identified and categorized in accordance with our prior publications (1,11). Briefly, food and beverage items containing LCSs reported during the 24-hour recalls were identified by using food descriptions provided in the Food and Nutrient Database for Dietary Studies version 5.0 and version 2011-2012, in NHANES 2009-2010 and NHANES 2011 to 2014, respectively. Food codes containing the terms “diet,” “dietetic,” “low-calorie,” “no sugar added,” “light,” “sugar-free,” “sugar substitute,” “low-calorie sweetener,” or “no-calorie sweetener” were extracted. After confirming that food codes extracted did indeed reflect the presence of LCSs (e.g., a food such as light mayonnaise does not contain LCSs despite being labeled “light”) by using publicly available ingredient information, each code was then categorized as an LCS beverage or an LCS food. Any participant who completed one (n = 1,299) or both (n = 8,170) dietary recalls was included in the analysis. Children who reported consuming ≥ 1 food or beverage containing LCSs during at least one of their two dietary recalls were defined as LCS consumers.

Table 2

|                     | Children 2-11 y | Adolescents 12-19 y |
|---------------------|----------------|--------------------|
|                     | Consumers     | Nonconsumers       | P       | Consumers | Nonconsumers | P       |
| Gender, n (%)       |               |                    |         |           |             |         |
| Male                | 876 (48.7)    | 1,966 (52.4)       | 0.0157  | 435 (46.2) | 1,454 (53.1) | 0.0031  |
| Female              | 909 (51.3)    | 1,839 (47.6)       |         | 437 (53.8) | 1,345 (46.9) |         |
| Race/ethnicity, n (%)<sup>a</sup> |               |                    |         |           |             |         |
| White               | 550 (58.3)    | 1,002 (50.6)       | 0.0011  | 312 (66.6) | 696 (52.5)   | <0.0001 |
| Black               | 409 (12.2)    | 967 (14.7)         |         | 198 (10.7) | 729 (15.8)   |         |
| Hispanic            | 623 (22.1)    | 1,326 (25.0)       |         | 269 (16.6) | 971 (22.5)   |         |
| Age, n (%)<sup>a</sup> |               |                    |         |           |             |         |
| 2-5 y               | 627 (33.5)    | 1,643 (42.4)       | <0.001  | N/A       | N/A          |         |
| 6-11 y              | 1,158 (66.5)  | 2,162 (57.6)       |         | N/A       | N/A          |         |
| Income, n (%)<sup>b</sup> |               |                    |         |           |             |         |
| 1st tertile         | 730 (31.4)    | 1,761 (37.8)       | 0.0066  | 302 (24.3) | 1,119 (32.7) | 0.0009  |
| 2nd tertile         | 524 (33.6)    | 1,063 (32.7)       |         | 276 (34.4) | 837 (33.5)   |         |
| 3rd tertile         | 431 (34.9)    | 703 (29.5)         |         | 234 (41.3) | 602 (33.8)   |         |
| Weight status, n (%)<sup>c</sup> |               |                    |         |           |             |         |
| Underweight         | 59 (2.9)      | 155 (4.2)          | 0.0684  | 23 (2.3)<sup>f</sup> | 92 (3.4)   | 0.0125  |
| Healthy             | 1,108 (65.5)  | 2,501 (66.5)       |         | 496 (58.9) | 1,697 (62.8) |         |
| Overweight          | 274 (15.5)    | 571 (15.2)         |         | 149 (14.7) | 462 (15.9)   |         |
| Obesity             | 344 (16.1)    | 578 (14.0)         |         | 204 (24.1) | 548 (17.9)   |         |
| Physical activity (d/wk)<sup>d</sup> | 6.1 ± 0.1     | 6.2 ± 0.1          | 0.6318  | 2,192 ± 88.7 | 2,244 ± 66.7 | 0.6064  |
| Energy intake (kcal/d) | 1,789 ± 15.5  | 1,739 ± 9.9        | 0.0046  | 2,032 ± 33.3 | 2,051 ± 24.8 | 0.6338  |

<sup>a</sup>Each n reflects the number of participants in the sample, whereas percentages are weighted to account for the complex NHANES survey design.

<sup>b</sup>Respondents reporting “other” race (n = 713 children, n = 496 adolescents), including multiracial respondents, are included in overall estimates but are not shown separately.

<sup>c</sup>N/A indicates that age subgroup comparisons were not performed for adolescents.

<sup>d</sup>Defined based on tertiles of poverty-to-income ratio.

<sup>e</sup>Defined based on standard BMI (kg/m²) cutoffs (13,14).

<sup>f</sup>Because of the small sample size (<30), these estimates may be unreliable and should be interpreted with caution.

<sup>g</sup>In children 2-11 y, physical activity was assessed as the number of days per week physically active for at least 60 min.

<sup>h</sup>In adolescents 12-19 y, physical activity was assessed as MET minutes of moderate and vigorous activity per week, which was derived by using NHANES recommended MET score.

MET, metabolic equivalent; N/A, not applicable.
### Table 3: Unadjusted and adjusted odds of obesity by LCS consumption among NHANES 2009-2014 participants

|                      | Any LCS, OR (95% CI) | LCS beverages, OR (95% CI) | LCS foods, OR (95% CI) |
|----------------------|----------------------|-----------------------------|------------------------|
|                      | Unadjusted           | Adjusted<sup>a</sup>        | Unadjusted             | Adjusted<sup>a</sup>  |
| **Children (2-11 y)**|                      |                             |                        |
| All (n = 5,590)      | 1.18 (0.97-1.44)     | 1.19 (0.97-1.46)            | 1.25 (1.01-1.56)       | 1.24 (0.98-1.56)      | 0.91 (0.68-1.23) | 0.99 (0.73-1.34) |
| **Race/ethnicity**   |                      |                             |                        |
| Male (n = 2,842)     | 1.21 (0.93-1.59)     | 1.24 (0.94-1.63)            | 1.42 (1.08-1.88)       | 1.45 (1.09-1.93)      | 0.79 (0.50-1.23) | 0.87 (0.55-1.37) |
| Female (n = 2,748)   | 1.16 (0.89-1.51)     | 1.13 (0.84-1.52)            | 1.09 (0.81-1.47)       | 1.02 (0.74-1.42)      | 1.06 (0.70-1.63) | 1.13 (0.75-1.72) |
| **Age group**        |                      |                             |                        |
| 2-5 y (n = 2,270)    | 1.33 (0.96-1.87)     | 1.28 (0.92-1.79)            | 1.48 (1.00-2.18)       | 1.35 (0.89-2.05)      | 0.84 (0.47-1.52) | 0.87 (0.47-1.61) |
| 6-11 y (n = 3,320)   | 1.05 (0.85-1.28)     | 1.13 (0.91-1.41)            | 1.09 (0.87-1.37)       | 1.17 (0.91-1.50)      | 0.94 (0.65-1.37) | 1.03 (0.72-1.49) |
| **Adolescents (12-19 y)** |                |                             |                        |
| All (n = 3,671)      | 1.45 (1.15-1.83)     | 1.57 (1.23-2.01)            | 1.55 (1.17-2.06)       | 1.71 (1.31-2.23)      | 1.12 (0.64-1.97) | 1.10 (0.61-1.96) |
| **Race/ethnicity**   |                      |                             |                        |
| Male (n = 1,889)     | 1.86 (1.32-2.64)     | 1.92 (1.35-2.72)            | 1.94 (1.28-2.95)       | 2.03 (1.33-3.08)      | 1.74 (0.98-3.09) | 1.66 (0.90-3.05) |
| Female (n = 1,782)   | 1.14 (0.88-1.49)     | 1.32 (1.01-1.73)            | 1.25 (0.95-1.66)       | 1.46 (1.13-1.89)      | 0.73 (0.34-1.57) | 0.73 (0.31-1.71) |
| **Income**           |                      |                             |                        |
| White (n = 1,008)    | 1.81 (1.26-2.60)     | 1.95 (1.35-2.82)            | 1.99 (1.33-2.99)       | 2.17 (1.50-3.15)      | 1.14 (0.50-2.60) | 1.12 (0.47-2.67) |
| Black (n = 927)      | 0.99 (0.68-1.43)     | 1.01 (0.68-1.49)            | 1.06 (0.70-1.62)       | 1.17 (0.78-1.75)      | 0.81 (0.42-1.58) | 0.69 (0.37-1.28) |
| Hispanic (n = 1,240) | 1.27 (0.85-1.89)     | 1.34 (0.88-2.06)            | 1.17 (0.80-1.72)       | 1.23 (0.82-1.85)      | 1.53 (0.65-3.60) | 1.69 (0.69-4.10) |
| **Adolescents (12-19 y)** |                |                             |                        |
| All (n = 3,671)      | 1.48 (1.03-2.12)     | 1.39 (0.97-2.01)            | 1.46 (1.05-2.04)       | 1.35 (0.96-1.83)      | 1.42 (0.59-3.41) | 1.35 (0.61-3.00) |
| **Race/ethnicity**   |                      |                             |                        |
| Male (n = 1,113)     | 1.61 (0.96-2.70)     | 1.77 (1.08-2.91)            | 1.83 (1.04-3.24)       | 1.99 (1.13-3.49)      | 0.93 (0.44-1.98) | 0.99 (0.47-2.06) |
| Female (n = 836)     | 1.46 (0.86-2.47)     | 1.71 (0.99-2.93)            | 1.69 (1.00-2.87)       | 1.95 (1.14-3.33)      | 0.96 (0.31-2.96) | 1.13 (0.36-3.50) |

Values in bold are statistically significant. Values were rounded to the nearest hundredth.

<sup>a</sup>Adjusted model included the following covariates: age, sex, race/ethnicity, income, total energy intake, and physical activity.

### Obesity

BMI percentile was then calculated based on measured height and weight and weight status subgroups (underweight, normal weight, overweight, or obesity) that were determined using standard cut-offs. Obesity was defined as having a BMI at or above the sex-specific 95th percentile of BMI for age, based on the 2000 Centers for Disease Control and Prevention growth charts (12,13).

### Physical activity

For children (2-11 y), physical activity was assessed as number of days per week physically active for at least 60 minutes. This was assessed based on the question, “During the past 7 days, on how many days was the participant physically active for a total of at least 60 min/d?” For adolescents (12-19 y), physical activity was assessed as metabolic equivalent minutes of moderate and vigorous activity per week, which was derived by using the NHANES recommended metabolic equivalent score. This was assessed based on the question, “In a typical week, on how many days do you do moderate- or vigorous-intensity sports, fitness, or recreational activities, and how much time do you spend doing vigorous-intensity sports, fitness, or recreational activities on a typical day?”

### Covariates

Covariates included the participant’s age (categorized as child or adolescent), sex, socioeconomic status (coded as low, middle, or high, determined by using tertiles of family income to poverty ratio), and self-reported race/ethnicity (coded as non-Hispanic white, non-Hispanic black, Hispanic, or other), energy intake, and physical activity.
Statistical analysis
SAS version 9.4 (SAS Institute, Cary, North Carolina; 2013) was used to account for the complex sampling design. Sample weights were used to generate national-level estimates of consumption. Differences in sociodemographic characteristics across weight categories were examined by $F$ test. Logistic regression, unadjusted and adjusted for age, sex, race/ethnicity, income, energy intake, and physical activity, was used to estimate the obesity odds in LCS consumers versus nonconsumers. All $P$ values were two-sided and $P < 0.05$ was considered statistically significant. Values are presented as odds ratios with 95% confidence intervals or percentages, as appropriate.

Results
Sociodemographic characteristics by weight status and reported LCS consumption are presented in Table 1 and Table 2, respectively. Odds ratios of obesity overall and by product category are shown in Table 3. LCS packet use was not separately analyzed because of the low prevalence of LCS packet use in youth.

Among adolescents, obesity odds were 55% and 70% higher in LCS beverage consumers than in nonconsumers in unadjusted and adjusted models, respectively. This pattern was observed across sex and income strata. In contrast, LCS food consumption was not associated with obesity odds, and daily energy intakes did not differ based on LCS consumption (Table 3 and Supporting Information Table S1).

Associations between LCS consumption and obesity were not consistently observed in children 2 to 11 years, except in male and Hispanic participants, before and after adjustment. Energy intakes did not differ with LCS consumption in any subgroup (Supporting Information Table S1).

Discussion
LCS beverage consumption is associated with obesity in US adolescents, even after adjustment for relevant covariates, including energy intake. This finding is also supported by recent data in adults, in which BMI was found to be consistently higher with increasing diet beverage consumption, despite similar reported daily energy intakes (14). Although the observed associations do not imply causation, these results underscore the need to investigate the mechanisms by which LCS may independently influence weight. LCSs have been shown to upregulate adipogenesis and inhibit lipolysis in vitro and alter gut microbiota in rodents (15). Augmentation of insulin is reported in humans (16) and is particularly relevant for adolescents, given the physiological insulin resistance of puberty (17).

The lack of an association observed between consumption of LCS foods and obesity risk across sociodemographic subgroups is noteworthy. Although likely explained by the low prevalence of LCS foods among children and adolescents, it is also possible that LCS foods are used differently in the diet than are LCS beverages and thus may be associated with different dietary patterns or lifestyle habits.

The lack of consistent associations in younger children is likely multifactorial. Because obesity is much more prevalent in children above the age of 6 years than in 2- to 5-year-olds (18), combining data from young and school-aged children may be misleading. In addition, if LCSs are determined to be causally related to the development of obesity, it may occur gradually and will thus be observable only in older children. In addition, LCS consumption is much more common in adolescents, and thus, greater exposure may be necessary to observe an association (1). Heightened susceptibility to LCS consumption’s effects on insulin secretion (e.g., insulin resistance of puberty) may also be necessary (17).

Limitations of the current investigation include analysis of self-reported dietary recall data, which is subject to systematic bias and susceptible to misreporting of energy intake, specifically among individuals with obesity (19,20). In addition, as the observational nature of our study is not sufficient to establish causation, the observed effects may be in part explained by reverse causality and residual confounding. Furthermore, it is not possible to distinguish between different LCSs using NHANES dietary data, and potential misclassification of consumers is possible with self-reported dietary assessment.

Conclusion
Taken together, our observational findings emphasize the need to determine whether chronic LCS ingestion is causally related to the development of obesity. It is also important to consider race/ethnicity, gender, age, and other factors when evaluating the potential effects of LCS consumption on body weight, as heterogeneity in associations was observed across sociodemographic subgroups.

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