Associations of Diet Soda and Non-Caloric Artificial Sweetener Use with Markers of Glucose and Insulin Homeostasis and Incident Diabetes: the Strong Heart Family Study

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Author Contributions
PNJ drafted the manuscript, analyzed the data, had full access to the data in the study, and had final responsibility for the decision to submit for publication. LB, MO, RBD, SAC, JWM, TA, ETL, FLY and JY contributed to the interpretation of results and critically reviewed the manuscript. JU and BVH contributed to the conception and design of the study, the acquisition of data, and critically reviewed the manuscript. AMF contributed to the conception and design of the study, the data analysis, and critically reviewed the manuscript. All authors approved of the final version and agree to be accountable for all aspects of the work.

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data Statement
Due to privacy agreements with the tribal communities involved in this study, access to study data are restricted. Further information can be found at https://strongheartstudy.org/
Abstract

**Background/Objectives:** Non-caloric artificial sweeteners (NAS) are marketed as healthier alternatives to sugar, but the relationship between consumption of NAS and development of diabetes is unclear. This study assessed the associations of diet soda and NAS consumption with: (1) early markers of insulin and glucose homeostasis (cross-sectionally); and (2) incident diabetes (over an average of 8 years of follow-up) among American Indians, a population with high rates of obesity.

**Subjects/Methods:** The study population included Strong Heart Family Study participants without cardiovascular disease or diabetes who participated in the 2007-2009 study exam (n=1,359). Diet soda and NAS consumption were assessed using a Block food frequency questionnaire and supplemental NAS questionnaire at the study exam. Fasting plasma glucose and insulin were measured during the study exam after a 12-hour overnight fast. Participants were followed for incident diabetes through December 2017 using a single phone interview and medical record review; diabetes was identified by self-report and confirmed by documentation in medical records. Associations of diet soda and NAS consumption with fasting insulin, glucose and incident diabetes were assessed using generalized estimating equations (fasting insulin and glucose analyses) and parametric survival models with Weibull distributions (incident diabetes analyses).

**Results:** Just under half of participants reported regularly consuming diet soda (40%) or using NAS to sweeten their beverages (41%). During an average 8 years of follow-up, we identified 98 cases of incident diabetes. After correction for multiple comparisons, there were no statistically significant associations of reported diet soda and NAS consumption with fasting insulin, fasting glucose, or incident diabetes.

**Conclusions:** Although reported consumption of diet soda and NAS were high, neither were associated with diabetes risk.

Keywords

Artificial sweeteners; aspartame; diabetes; diet; diet soda; insulin; glucose; saccharin; sucralose

Introduction

The consumption of sugar-sweetened beverages (SSBs) is associated with the development of obesity and type 2 diabetes. Non-caloric artificial sweeteners (NAS) are currently being
recommended in weight loss programs as healthy alternatives to sugar, and the availability and consumption of beverages and foods containing NAS is rising.\textsuperscript{5} However, the relationship between consumption of NAS and metabolic outcomes is unclear.\textsuperscript{6-15} The goal of this analysis was to determine whether diet soda or NAS consumption is associated with early markers of insulin and glucose homeostasis and diabetes risk among American Indians (AIs) who participated in the Strong Heart Family Study (SHFS).

**Materials/Subjects and Methods**

**Study Setting**

The SHFS is a family-based longitudinal study of the genetics and risk factors for cardiovascular disease (CVD) in 12 AI communities in Arizona, Oklahoma, and North and South Dakota. Details of the study design have been described previously.\textsuperscript{16} Institutional review boards from each Indian Health Service region and all participating communities approved the study, and written informed consent was obtained from all participants; this research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**Dietary Questionnaire**

During the study examination in 2007–2009, participants completed an interviewer-administered Block Food Frequency Questionnaire (FFQ) to assess usual diet over the past year. The Block FFQ is a widely used FFQ, and it has demonstrated reliability and validity.\textsuperscript{17} In addition to food items on the standard Block FFQ, participants answered the following three questions about NAS consumption: (1) how often do you drink diet drinks, like diet Coke, in the past week (never, once a week, twice a week, 3–4 times a week, to 5–6 a week, everyday, more than once a day)?; (2) How often do you use artificial sweeteners to sweeten your drinks (never, occasionally, often always)?; (3) If you ever use artificial sweeteners, what type do you use (saccharin, sucralose, aspartame, other—identified by brand name and color of packet: Sweet N’ Low (pink packet), Splenda (yellow packet), Equal (blue packet), NutraSweet (white packet), or Sunett (purple packet)?)

**Measures of Glucose Homeostasis and Incident Diabetes**

Blood samples were collected after a 12-hour overnight fast at the 2007–2009 examination. Plasma insulin was measured using a modified version of the Morgan and Lazarof radioimmunoassay and plasma glucose was measured using a glucose oxidase method.\textsuperscript{18} Surveillance for incident diabetes for all participants continued through December 2017 using a single phone interview and medical record review; diabetes was identified by self-report and confirmed by documentation in medical records.

**Statistical Analysis**

Of the 2,481 participants who completed the study examination, we excluded participants with prevalent diabetes (n=634), CVD (n=176), and those with missing or unrealistic diet data (<2512 kJ per day, or >25,116 kJ per day for women and >33,488 kJ per day for men) (n=312). Additionally, for the incident diabetes analyses, participants whose medical records were not available for review were excluded (n=217). In total, 1,142 participants comprised
the prospective analyses of diet soda and NAS consumption with incident diabetes and 1,359 participants comprised the analytic cohort for the cross-sectional analyses of diet soda and NAS consumption with fasting glucose and insulin. Parametric survival models with Weibull distributions and robust standard errors were used to assess associations of reported diet soda and NAS consumption with incident diabetes. Parametric-Weibull models were selected for prospective analyses to account for interval-censored incident diabetes, while accounting for family clustering. Generalized estimating equations (GEE) with robust standard errors were used to evaluate cross-sectional associations of reported diet soda and NAS consumption with fasting insulin and glucose levels. Because the SHFS is comprised of large families, GEE models with an independence working correlation were fit to account for family clustering. Due to right-skewed distributions, insulin values were log-transformed and geometric mean ratios (GMR) are presented. Models included adjustment for age, sex, study site, BMI, education (years), physical activity (steps per day; measured using Accusplit AE120 pedometers (Yamax, Japan) over 3–7 days), smoking (never, former, current), self-reported quality of life (Likert scale), total energy intake, and intake of saturated fat (percent calories), fruit and vegetables (servings per day), processed meat (servings per day), fiber (grams/4186 kJ), and sugar-sweetened beverages (SSB) (servings per day). Missing values for physical activity (n=304) were estimated using multiple imputation by chained equations. A Bonferroni correction was used to adjust for multiple comparisons; the significance threshold used was p=0.01 (based on 2 exposures (i.e., reported diet soda and NAS consumption) and 3 outcomes (i.e., fasting insulin, fasting glucose, and incident diabetes) (p= 0.05/6 =0.01). Tests for trend were evaluated with intake categories for diet soda and NAS entered as ordinal variables. All statistical analyses were conducted using R version 3.4.3 (R Core Team, Vienna, Austria).

**Results**

The mean age of participants was 42 years and 62% were women. There were 50% of participants with BMI of 30 or greater, and 41% accumulated less than 5,000 steps per day of physical activity. In total, 40% of participants reported consuming diet soda at least once a week (17% 1–2 days per week; 10% 3–6 days per week; 13% every day) and 41% of participants reported using NAS to sweeten their beverages (20% occasionally; 8% often; and 12% always). Among those who reported use of NAS, 56% used saccharin, 39% used sucralose, and 31% used aspartame. Additionally, 44% of study participants reported consuming at least one sugar-sweetened beverage per day, of which 22% reported consuming sugar-sweetened soda daily.

Baseline characteristics of study participants according to reported intake of diet soda are shown in Table 1. Briefly, participants who reported consuming at least one diet soda per day were older, had higher BMI, and consumed fewer calories per day than those who reported consuming diet soda less than once per week.

Of the 1,126 participants with available follow-up data (8,510 person-years of follow-up; average follow-up: 8 years), 98 developed diabetes. Results suggest no statistically significant associations of reported consumption of diet soda or NAS with incident diabetes after correction for multiple comparisons. Ignoring multiple comparisons, any consumption
(versus none) of diet soda or NAS was associated with a higher risk of diabetes (borderline significance) (Table 2).

In cross-sectional analyses among participants with measures of diet soda, NAS, fasting glucose, and fasting insulin (n=1,359), we observed no association of any diet soda or NAS consumption with fasting insulin or glucose levels. However, among participants who reported no consumption of saccharin, participants who reported any use of saccharin had slightly higher insulin levels (GMR: 1.11 (95% CI, 1.02, 1.21)) - although this finding was of borderline significance after accounting for multiple comparisons. There were no associations of the other types of artificial sweeteners (i.e., sucralose, aspartame) with fasting insulin or glucose levels (Table 2).

**Discussion**

Results of this study, which contains detailed information on diet, NAS consumption, and cardio-metabolic risk factors in a large cohort of AIs, indicate that consumption of diet soda and NAS is high. Results also suggest that diet soda and NAS consumption is not associated with early markers of insulin or glucose homeostasis or diabetes risk after correction for multiple testing.

Animal studies have suggested several metabolic pathways by which NAS consumption may influence glucose or insulin homeostasis; in mice, NAS consumption alters intestinal microbiota and induces glucose intolerance, promotes intestinal absorption of glucose, increases appetite and promotes weight gain.\(^{20, 21}\) However, evidence of these associations in humans is limited, and results from studies that have assessed the relationship of NAS consumption with incident diabetes have been inconsistent; some studies report that higher intake of diet soda and/or NAS consumption is associated with higher risk of diabetes, while others find no association.\(^{4, 7-15, 22}\)

To our knowledge, no published studies have assessed the relationship of NAS consumption with markers of insulin or glucose homeostasis or with diabetes risk among AIs, a population with a high burden of obesity. These data indicate no statistically significant associations of diet soda or NAS consumption with fasting insulin, fasting glucose, or incident diabetes. However, there are several reasons why this area warrants further. The study population comprised AIs who reside in largely rural communities, and results may not be generalizable to other populations. Further, the limited distribution of many risk factors for diabetes, including diet, across study participants may have limited power to assess associations. Assessment of diet soda and NAS consumption were based on self-report; participants may not have accurately recalled type or frequency of diet soda or NAS consumed. Additionally, participants may have altered consumption of diet soda or NAS in response to previous medical advice or knowledge of cardio-metabolic risk.\(^{23-25}\) For instance, participants with a higher underlying risk of diabetes may have been more likely to consume diet soda or NAS as an alternative to sugar-sweetened beverages — known obesogenic and diabetogenic drinks. Although we adjusted analyses for health behaviors, morbidity, self-reported health status, and BMI, residual confounding by unmeasured factors is possible. Finally, we utilized a Bonferroni correction to account for multiple comparisons.
As the reported outcomes were not independent, use of the threshold \( p < 0.01 \) may be conservative. On the other hand, ignoring multiple comparisons—even with correlated outcomes—may increase the likelihood of type 1 error.

In conclusion, in this large cohort of AIs, reported consumption of diet soda and NAS was high, but neither were associated with diabetes risk. Given that SSB consumption reduction is widely considered a public health priority, more studies are needed to confirm these findings and build an evidence-base for nutrition recommendations related to use of diet soda and NAS.

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Table 1.
Baseline Characteristics of Strong Heart Family Study Participants According to Reported Intake of Diet Soda (n=1,359)

| Diet Soda Consumption | None (n=804) | 1-2 per week (n=228) | 3-6 per week (n=139) | ≥1 per day (n=169) |
|-----------------------|-------------|---------------------|---------------------|-------------------|
| Mean or % SD          | Mean or % SD | Mean or % SD        | Mean or % SD        | Mean or % SD      |
| Age                   | 41 16       | 41 16               | 45 13               | 46 14             |
| Male                  | 41% 28%     | 41% 28%             | 41% 33%             | 33%               |
| Highest education     |             |                     |                     |                   |
| Less than HS          | 13%         | 13%                 | 10%                 | 11%               |
| HS graduate           | 54%         | 46%                 | 46%                 | 45%               |
| Some College          | 23%         | 31%                 | 22%                 | 22%               |
| BA/BS or greater      | 10%         | 10%                 | 21%                 | 21%               |
| Body Mass Index       |             |                     |                     |                   |
| <25                   | 21%         | 11%                 | 13%                 | 10%               |
| 25-29.9               | 29%         | 29%                 | 26%                 | 25%               |
| 30-34.9               | 27%         | 26%                 | 31%                 | 32%               |
| ≥35                   | 23%         | 34%                 | 29%                 | 33%               |
| Waist circumference (cm) | 102 17     | 108 17              | 104 15              | 105 15            |
| Smoking               |             |                     |                     |                   |
| Never                 | 37%         | 43%                 | 42%                 | 39%               |
| Past                  | 21%         | 24%                 | 29%                 | 27%               |
| Current               | 42%         | 33%                 | 28%                 | 34%               |
| Physical Activity Level|            |                     |                     |                   |
| Sedentary             | 41%         | 38%                 | 33%                 | 41%               |
| Low-active            | 25%         | 25%                 | 30%                 | 28%               |
| Somewhat active       | 17%         | 20%                 | 18%                 | 19%               |
| Active                | 17%         | 16%                 | 18%                 | 13%               |
| Daily consumption     |             |                     |                     |                   |
| Fruit servings        | 0.9         | 0.8                 | 1.1                 | 1.0               |
| Vegetable servings    | 2.3         | 1.6                 | 2.3                 | 2.0               |
| Processed meat servings| 0.7         | 0.9                 | 0.7                 | 0.6               |
| Saturated Fat (g)     | 33          | 19                  | 30                  | 31                |
| Fiber (g)             | 16          | 9                   | 16                  | 11                |
| Total kJ              | 2460        | 1297                | 2237                | 2363              | 2195 1180 |
Table 2.
Associations of Reported Intake of Diet Soda and Non-Caloric Artificial Sweeteners with Incident Diabetes Risk and Fasting Insulin and Glucose Levels among Strong Heart Family Study Participants

|                                | Incident Diabetes (N=1,142) | Insulin (N=1,359) | Glucose (N=1,359) |
|--------------------------------|-------------------------------|-------------------|-------------------|
|                                | % No. cases | HR (95% CI) | p-value | GMR (95% CI) | p-value | beta (95% CI) | p-value |
| Any consumption a              |                |             |         |             |         |               |         |
| Diet soda b                    | 39% 52        | 1.74 (1.11, 2.75) | 0.02    | 0.94 (0.87, 1.01) | 0.08 | 0.53 (−0.96, 2.02) | 0.48 |
| Supplemental NAS b             | 41% 52        | 1.68 (1.05, 2.69) | 0.03    | 1.06 (0.97, 1.16) | 0.19 | 0.79 (−0.33, 1.91) | 0.17 |
| Frequency of consumption       |                |             |         |             |         |               |         |
| Diet Soda b                    |                |             |         |             |         |               |         |
| None c                         | 61% 46        | 1.00 (−, −) | 0.06d | 1.00 (−, −) | 0.11 | 0.00 (−, −) | 0.73d |
| 1-2 days per week              | 16% 20        | 1.71 (0.94, 3.12) | 0.08    | 0.97 (0.87, 1.07) | 0.51 | 1.57 (−0.38, 3.52) | 0.12 |
| 3-6 days per week              | 10% 17        | 2.22 (1.19, 4.16) | 0.01    | 0.92 (0.82, 1.03) | 0.16 | 0.47 (−1.60, 2.53) | 0.66 |
| 7 days per week                | 13% 15        | 1.41 (0.7, 2.8) | 0.33    | 0.92 (0.80, 1.05) | 0.21 | −0.90 (−2.59, 0.79) | 0.30 |
| Supplemental NAS b             |                |             |         |             |         |               |         |
| None c                         | 59% 46        | 1.00 (−, −) | 0.03d | 1.00 (−, −) | 0.39d | 0.00 (−, −) | 0.59d |
| Occasionally                   | 20% 23        | 1.54 (0.86, 2.78) | 0.15    | 1.08 (0.99, 1.19) | 0.10 | 1.42 (0.03, 2.81) | 0.05 |
| Often                          | 9% 13         | 1.85 (0.9, 3.81) | 0.09    | 1.00 (0.87, 1.14) | 0.96 | −0.34 (−2.49, 1.81) | 0.75 |
| Always                         | 12% 16        | 1.79 (0.93, 3.44) | 0.08    | 1.07 (0.91, 1.24) | 0.41 | 0.52 (−1.56, 2.60) | 0.62 |
| Supplemental NAS type          |                |             |         |             |         |               |         |
| None c                         | 59% 28        | 1.00 (−, −) |          |             |         |               |         |
| Saccharin b                    | 23% 29        | 1.38 (0.8, 2.37) | 0.25    | 1.11 (1.02, 1.21) | 0.01 | 0.85 (−0.51, 2.21) | 0.22 |
| Sucralose b                    | 16% 24        | 1.55 (0.91, 2.66) | 0.11    | 0.91 (0.80, 1.03) | 0.13 | −0.36 (−2.13, 1.41) | 0.69 |
| Aspartame b                    | 13% 17        | 1.45 (0.83, 2.54) | 0.19    | 1.01 (0.89, 1.15) | 0.86 | 0.47 (−1.41, 2.36) | 0.62 |

Models include adjustment for age, sex, study site, BMI, education, steps per day, smoking, self-reported quality of life, total calories consumed per day, % total calories from saturated fat, fruit and vegetable servings per day, processed meat servings per day, total fiber consumed per day, and SSB consumption. Significance evaluated at a p < 0.01 threshold to account for multiple comparisons.

a Analyses of any diet soda or supplemental NAS evaluated relative to no reported diet soda or supplemental NAS use
b Represents a separate model
c Referent category: analyses of saccharin, sucralose, and aspartame evaluated use of each type of NAS relative to no NAS use
d P-value for trend across frequency of consumption categories

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